Stell and Maran's
Textbook of Head and Neck Surgery and Oncology
Primum non nocere (first, do no harm).

Hippocrates (c.460–377bc)

Every surgeon carries about him a little cemetery, in which from time to time he goes to pray, a cemetery of bitterness and regret, of which he seeks the reason for certain of his failures.

René Leriche (1951)
Stell and Maran's
Textbook of Head and Neck Surgery and Oncology

Fifth edition

Edited by

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JCW: I wish to thank my secretary, Angela Roberts, for her help and patience during the writing of this book. To my patients for their understanding, and to Ralph Gilbert for his enduring friendship and unlimited help during all stages of the book's transition. As ever, to my parents and grandparents for their wisdom and understanding and lastly to Esmé, Helen and William since without their ongoing love and support, none of this would have been worthwhile.

RWG: I wish to thank John Watkinson for the vision and ability to pull together this most recent edition of Stell and Maran. I would also like to thank all my mentors who have contributed so greatly to my passion for head and neck surgery and taught me so many of the secrets of this subspecialty. Among these, I would like to especially acknowledge Professor Patrick Gullane, my mentor and friend, without whom I would not be involved in the writing and editing of this book. Finally to my family Anita, Richard and Emily for their love, support and understanding of my passion and commitment to this profession.

Get ahead Charitable Trust
A cancer charity fighting all head & neck diseases
Registered charity No. 1118326

A proportion of the royalties from the sales of this book will be donated to the Get A-Head Charitable Trust, which fights head and neck diseases (including cancer) by funding research, promoting education and providing state-of-the-art equipment.
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When this book was first published 40 years ago, the late Philip Stell and I had completed eight head and neck surgery courses. The book was, essentially, ‘The Book of the Course’. By dint of including every fact ever known about head and neck cancer surgery we managed to fill 453 A5 pages in the form of 19 chapters. Each of us had completed a Head and Neck Fellowship in the United States and we brought back the right product at the right time. Although throat surgery was labelled as an integral part of ENT, the soft tissue surgical skills of a generation had been dulled by the repeatable success of first, the fenestration and then the stapedectomy operations, the results of which were spectacular.

When Stell and I started trying to make head and neck surgery an integral part of the specialty of otolaryngology, it was not difficult because it was being performed half-heartedly by general surgeons, variably by plastic surgeons and badly by singly qualified oral surgeons. Although our otolaryngological colleagues welcomed the introduction of the subspecialty onto their surgical menu, it was only nurtured as a subspecialty (through cross-referrals) in a few centres. As Professor Stell was wont to say, ‘Amateurs teaching amateurs to be amateurs’.

Little wonder then that well-trained oral and maxillofacial surgeons entered the scene bringing in new levels of expertise. If there is anything remaining that gives me a sense of pride, it is the fact that I oiled the collegiate wheels to create a Specialty Fellowship for doubly qualified oral surgeons, a step which caused a quantum leap in standards. They, together with a new generation of oncologists, form part of the multidisciplinary teams around the country that make life so much better for the unfortunate patients on whom we pioneers had little alternative other than the performance of often very mutilating resections. At low points I always remembered what the famous pioneer John Conley once said to me, ‘If you don’t do the operation, the tumour will!’ Those who suffered these gross ministrations might, were they alive, have the satisfaction of knowing that their suffering has made life much better for today’s patients who are unfortunate enough to have a head and neck cancer.

I am grateful first to my colleague Professor Janet Wilson for persuading me to resurrect the book for a third edition in 1993 and to Dr Mark Gaze who ‘introduced’ radiotherapy to the book. But my biggest thanks is to John Watkinson, who carried on the Stell and Maran tradition of head and neck courses with international contributors and who has had enough belief in the need for the book to shepherd it through two subsequent editions. His hard work and focus has culminated in the magnificently illustrated book you are now holding and of which he and his contributors can be justly proud.

I feel certain that were he alive, Philip Stell would echo these sentiments.

Arnold Maran
2011
The latest edition of this landmark textbook is a great credit to John Watkinson and his team of experts. While losing nothing of the essentials of the craft of head and neck surgery, the book has expanded steadily in terms of scope and insight. The well-chosen introductory chapters set the scene of the twenty-first century head and neck disease knowledge base. This review is then set against key concerns on the overall management strategy and clinical decision-making which underpin every successfully treated head and neck condition. These considerations run through the majority of the book and make it essential reading, not just for surgeons but for all professional groups involved in the challenging yet rewarding management of this complex area.

It was inevitable that as basic science knowledge expanded, patient-focused considerations emerged, and techniques of assessment and reconstructive surgery became ever more complex, that the size of Stell and Maran would increase over the years. Nonetheless, the editors have worked extremely hard to ensure that the finished work retains the manageable size which has always made it so appealing both to trainees at the start of their career and to experts seeking a comprehensive update.

Excitingly, the publication of the present edition coincides with what appear to be the first real-world examples of allowing patient-specific biological factors to optimize treatment schedules. Furthermore, at a time when many anticipated a welcome fall in the incidence of squamous cancer due to international efforts to curtail cigarette smoking, in fact the growth of virally induced, particularly oropharyngeal lesions has led to a disease increase. Certain countries are also experiencing a considerable increase in disorders of the thyroid gland – and endocrine disease now comprises an important and substantial section of the book.

As the knowledge has undergone exponential growth over the decades, so the painstaking selection of key material by John Watkinson and his team has become all the more valuable. The reader picking up this beautifully illustrated volume draws on the combined wisdom and surgical expertise of an impressively well-informed international team. The book is a joy to own, a pleasure to read and, above all, a powerful force to advance treatment standards in the huge variety of head and neck conditions.

I regard it as a great pleasure and privilege to have been associated with Stell and Maran for over 20 years.

Janet Wilson

2011
Arnold Maran: a personal perspective

‘I do not believe, however, that what I’ve described is the sort of thing that one human being should inflict on another’. This was said to me and others who were attending a course given in New York in 1966 by the outstanding head and neck surgeon of my generation, the suave, urbane Dr John Conley. He was referring to the application of the operation that he had just described to us, the total glossolaryngectomy.

As a young, aspiring head and neck surgeon, I was disappointed to hear this from the master of so many ‘big, big operations’ for which he was famous; these were the days when the extent and complexity of the surgery performed was also a measure of the man. It was a time when surgeons were still labelled courageous even though it was their patients who were taking all the risks. But even for the great John Conley, exenteration of the entire mouth and throat was a step too far. It took both the late Philip Stell and me another quarter of a century to start sharing the same philosophy and ask ourselves, ‘What on earth are we doing to people?’

So why is this new much enhanced edition of our original slim volume now being produced thirty-four years after its birth? Why is there still such a specialty as Head and Neck Surgery? The reason, of course, is that between the first edition of the book in 1972 and now we have not developed an effective alternative. Neither radiotherapy nor chemotherapy have, on their own, been deemed to be the cure of squamous carcinoma apart from certain small tumours. The truth remains that if the surgeon does not operate and the patient is left with no treatment then the tumour will ‘do the operation’.

No-one who reads this book believes in their heart that cancer is a surgical disease, but until the ‘magic bullet’ is discovered the head and neck surgeon has a role. In practising this subspecialty we are unlike other cancer surgeons. They are usually able to leave the patient with only a scar that can be hidden by clothes, even though they may have a catheter and a bag, a cough and a weak voice or an ostomy bag into which their bowels empty near their trouser pocket. Such can, however, on the whole be disguised and physiological and anatomical problems are compatible with attending a dinner party without discomfiting the other guests. We, on the other hand, interfere with very visible anatomy and can affect, in turn, the physiology of speech, swallowing, chewing and breathing in such a way that is impossible to disguise and may attract unwanted attention from onlookers.

Since I started to practise head and neck surgery, however, things have improved enormously because of the cascade of reconstructive procedures; so much so that the specialty is now virtually unrecognizable to that which we practised in the 1960s.

People have been operating on the head and neck for centuries. Anecdotes of the Egyptians, Greeks and Chinese making holes in heads and throats do not, however, form any part of the evolution of our specialty and they should be relegated to the realms of history and archaeology. Nineteenth-century surgeons sliced off cancers of the face or lip and cauterized the base, because that was the repertoire of almost all of surgery – cutting and cauterizing. Surgeons could do this in the mouth and, for a long time, the larynx, where it was attractive to perform a tracheostomy and excise bits of the larynx opened by a laryngofissure, in between the patient’s swallows and coughs. Although survival figures were published, or rather claimed, in order to enhance the reputation of the surgeon, these were the days of eminence-based rather than evidence-based surgery and it is doubtful if there were any survivors other than from superficial verrucous tumours. The cause of death was always infection and/or haemorrhage.

The man who resurrected the specialty was Dr Hayes Martin who was the original Head of Service at the Memorial Hospital, New York. He was armed with the lessons he had learned from war, namely the control of sepsis by wide debridement, penicillin and delayed primary closure. He had learned the basic steps of the new specialty of plastic surgery and used tubed pedicle flaps. He also had access to stored blood and plasma, and was able to keep patients alive after major procedures. His three surgical pillars were total laryngectomy, the combined mandibular and oral cavity resection (COMANDO) operation and the radical neck dissection (or rather the avoidance of ‘nit picking’ nodes out of a neck showing signs of metastatic disease). There was virtually no reconstruction. Patients may have been cured of their cancers but many were left with considerable impediments.

Things had improved by the time Stell and I started; we had the Wookey flaps and the forehead flap introduced by the late Ian McGregor. It was a start, but for every Wookey flap that worked, five became unusable over a period of months as they progressively shrank before application. While the forehead flap was robust, it did leave the patient with the uncomfortable task of explaining that it was a surgical procedure rather than an unfortunate accident that had caused his facial deformity.

The early head and neck surgeons of the 1960s and 1970s were able to do far more operations than today because there were fewer of us operating. We developed good judgement as to what was and what was not possible. The problem for the patients, however, is that good judgement comes from experience, and experience is learned from bad judgement. Stell and I learned how to deal with carotid blow-outs before we learned not to make vertical incisions in irradiated necks. We learned that if a patient could not eat then he has to be fed parenterally with enough calories to encourage healing. We learned how to avoid creating raised intracranial pressure after watching patients die of it. We were able to learn slowly by a thing that is no longer fostered during surgical education, at least in the UK – a learning curve.

The single biggest factor that improved head and neck surgery was the discovery of the blood supply to the skin. It is astonishing that we had to wait until the 1970s before an apparently simple thing like the way blood supplies skin was
explained. Once it was revealed, however, the cascade of reconstruction began. The deltopectoral flap became the workhorse of reconstruction and things further improved with the advent of the pectoralis myocutaneous flap. We turned a blind eye to its incommodious bulk because of its unfailing reliability. Larger defects were closed with the latissimus dorsi flap, but we still had not solved the problem of replacing the mandible. We used free bone grafts carved to shape and wired into place, although many free bone grafts to the jaw failed and the mechanism by which those who did survive remained uncertain. All that was to end with the advent of the free flap.

The key to this was learning a new technology, namely small vessel anastomosis. Up until now, the learning curve of reconstruction had been incremental, by which I mean that it was not difficult to move from Wookey, to forehead, to deltopectoral and to myocutaneous. However, to learn small vessel anastomosis took time, patience, a steady hand and good eyesight. If the technique was learned, however, the surgeon could not only do better cancer surgery but could also close any hole with tissue that was thin, that survived and that functioned.

The introduction of this new technology did wonders for the surgical civil war that had raged over the ‘ownership’ of head and neck surgery for the previous fifty years. The only surgeons who could perform the whole repertoire on their own became those who could join blood vessels together – the rest had to call on help or do the fashionable thing and ‘work in teams’. There is, of course, nothing to be criticized about team working, in fact it is the tenet of modern surgery and the patient benefits because the tired surgeon makes mistakes and to perform a modern head and neck cancer excision and reconstruction solo is tiring.

The original civil war had been between the general and ENT surgeons in the United States, and between plastic surgery and ENT in the United Kingdom. In both countries, the initial ‘winners’ were the ENT surgeons who went on to change the name of their specialty to Otolaryngology–Head and Neck Surgery (not one that would have been recommended by a marketing man). I was not alone in deploring this change because a surgeon cannot make his reputation by a name, only by ability.

Maxillofacial surgeons had always had an interest in the specialty, but were handicapped because their leaders had not bitten the bullet and demanded dual qualification. When their specialty association finally made the brave decision in the early 1980s that all oral and maxillofacial consultants should be dually qualified the Royal College of Surgeons of Edinburgh co-operated by making available a specialty fellowship in maxillofacial surgery. The same demand was not made of the maxillofacial surgeons in the United States and there, head and neck surgery became the unchallenged province of the otolaryngologist. However, it then became ‘unfashionable’, or rather non-remunerative, especially in the United States. The advent of managed health care relegated head and neck surgery to the poor earner category. The patients were mostly from deprived communities, poor, smoking and drinking to excess and incompetent in the area of self-care and help. The rewards for doing emotionally and technically demanding surgery became unattractive for most newly qualified American otolaryngologists and so there is now a dearth of head and neck surgeons, both in academic and private practice. To a newly qualified resident, the gentle art of otology, facial plastic surgery or endoscopic rhinology proved greater attractions.

In the United Kingdom, there is not a dearth of surgeons but a dearth of experience. Cancer of the head and neck in the UK has the same prevalence as cancer of the pancreas, which is considered inoperable unless it is in the tail. But while cancer of the pancreas only occurs in one site, head and neck cancers occur in eight different sites. Some are seen first by the dentists, some by the otolaryngologists, some by the plastic surgeons and some by the generalists. Until recently, this has been the greatest problem both for the practitioners and the patients.

The volume–outcome curve in any form of surgery is unimportant after a hundred or so operations, but it is vital in the first fifty. There are many head and neck surgeons in the UK today who have, in their repertoire, operations in which they are basically ‘inexperienced’ because the condition is so rare, but they are nonetheless able to offer to operate on patients in spite of the recommendations of the Bristol Inquiry by Professor Kennedy. I therefore welcome the move taken by the Senate of Surgery a few years ago when they decided to sanction training for only a few. The original specialty, whether it is plastics, ENT or maxillofacial, is unimportant because the further specialist training will be tailored to their specific needs.

I have concentrated in this brief review of the history of the subspecialty on the surgical aspects. It is salutary to go back to the writings of Hayes Martin who foresaw the end of the surgical side of the specialty with the ‘new’ radiotherapy. ‘New’ technologies that are successful, such as the polio vaccine, antibiotics for specific infections and surgery for the drainage of abscesses are immediate, obvious and beneficial. We are seeing the same false hopes raised by every new ‘add-on’ to radiotherapy as our predecessors saw in the 1930s and 1940s. The ‘magic bullet’ will not be radiotherapy or even a variant, but, like surgery, it is for the moment the best we can offer patients.

The newer chemotherapy drugs do seem to show some benefit. In the 1960s and 1970s, when the drugs used for the treatment of mesodermal tumours were applied to squamous carcinomas, there were only two outcomes – ill patients became more ill and hirsute patients became smooth. There were no cures and if one is permitted to quote Dr Conley again, ‘If your treatment is worse than the disease then you become the disease’.

So what can readers of this book learn from the past?

- Follow the Oslerian principle of not creating harm.
- In the local situation, work with your colleagues and do not compete, because the only loser will be the patient.
- Audit and believe the results.
- And, finally, be holistic and ask whether what you plan for a particular patient would be what you would do to a relative.

If you do these things you will not make the mistake of not learning from history and you will be a good head and neck ‘doctor’.

Arnold Maran
2011
Having been interested in head and neck oncology for nearly 30 years, we are both proud to have been involved in this fifth edition of *Stell and Maran's Textbook of Head and Neck Surgery and Oncology*. Since the last edition was published ten years ago, significant advances have been made in both the diagnosis and treatment of head and neck diseases and cancer. The aim of this book is to update colleagues on recent developments in molecular biology, highlight changes in methods for pathological diagnosis to include the emerging importance of the human papilloma virus, advances in chemoradiation together with technological developments to include minimally invasive surgery, nerve monitoring, the harmonic scalpel and the robot. Side by side, we were keen to include new techniques in reconstruction, as well as covering audit and quality of life.

The main changes in the book from the last edition include division into sections on benign and malignant disease, treatments with both radiotherapy and chemotherapy, as well as an endocrine section and one on reconstruction. Each section has its own editors and within the sections, most chapters are written by at least two authors chosen for their recognized expertise in each specific field. Selected editors, subeditors and chapter authors bring a significant international flavour to this historically well-established British textbook.

The scope of head and neck cancer management ranges from laboratory science to palliative care, and within this is included treatment with surgery (as well as reconstruction), clinical oncology and subsequent rehabilitation with emphasis on quality of life. Subspecialization is now the norm and therefore some might question the continued wisdom of producing a one volume concise text attempting to address this unique discipline. However, we still believe that the way this book is written providing concise approaches with treatment plans and key points for the specific sites within head and neck cancer continues to be as valid today as it was nearly 40 years ago, when the book was first conceived by Professors Philip Stell and Arnold Maran.

We hope that in its current form, the book will continue to be a major resource not only for trainees but established practitioners in otolaryngology, maxillofacial surgery, plastic surgery, as well as endocrine surgery and clinical oncology whose specific work includes a major head and neck practice, but also for those professions allied to medicine, such as speech and language therapy, head and neck oncology and Macmillan nurses, as well as dieticians. The algebraic sum of care includes all these disciplines in one form or another, and the care for patients with these diseases continues to evolve. Best practice we feel is represented in this book, and the *UK Effective Head and Neck Cancer Management Guidelines* (second edition) can be found on the website of the British Association of Otolaryngologists (www.entuk.org).

We gratefully acknowledge all the authors (and in particular the section editors) in this book for their time, effort and expertise in making it such a wonderful source of information for patients with head and neck disease.

Ralph W Gilbert
John C Watkinson
2011
## List of abbreviations used

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>3D CRT</td>
<td>three-dimensional conformal radiotherapy</td>
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<td>3D</td>
<td>three-dimensional</td>
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<td>adenoid cystic carcinoma</td>
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<td>adult comorbidity evaluation</td>
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<td>adrenocorticotropic hormone</td>
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<td>ADC</td>
<td>apparent diffusion coefficient</td>
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<td>alcohol dehydrogenase; antidiuretic hormone</td>
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<td>amine precursor and uptake decarboxylase</td>
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<td>ASSIDS</td>
<td>Assessment of Intelligibility of Dysarthric Speech</td>
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<td>ATLS</td>
<td>Advanced Trauma Life Support</td>
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<td>British Association of Endocrine and Thyroid Surgeons</td>
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<td>bismuth and iodoform paraffin paste</td>
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<td>CADCAM</td>
<td>computer-aided design, computer-aided manufacture</td>
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<td>College of American Pathologists</td>
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<td>complete blood count</td>
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<td>Charlson comorbidity index</td>
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<td>Creutzfeldt–Jakob disease</td>
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<td>cranial nerve</td>
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<td>Children's Oncology Group</td>
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<td>COPD</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>chemoradiotherapy</td>
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<td>CSA</td>
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<td>CSCCHN</td>
<td>cutaneous SCC of the head and neck</td>
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<td>CSF</td>
<td>cerebrospinal fluid</td>
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<td>CSR</td>
<td>calcium-sensing receptor</td>
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<td>computed tomography</td>
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<td>chemoradiation</td>
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<td>clinical target volume</td>
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<td>carcinoma of unknown primary origin</td>
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<td>CV</td>
<td>central venous</td>
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<td>central venous pressure</td>
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<td>Data for Head and Neck Oncology</td>
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<td>DAT</td>
<td>digital audiotape</td>
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<td>DCIA</td>
<td>deep circumflex iliac artery</td>
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<td>DI</td>
<td>diabetes insipidus</td>
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<td>disseminated intravascular coagulation</td>
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<td>DLBCL</td>
<td>diffuse large cell B-cell lymphoma</td>
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<td>DM</td>
<td>distant metastasis</td>
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<td>DMSA</td>
<td>dimercaptosuccinic acid</td>
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<td>DNES</td>
<td>diffuse neuroendocrine system</td>
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<td>DTC</td>
<td>differentiated thyroid carcinoma</td>
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<td>DVH</td>
<td>dose–volume histograms</td>
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<td>DVT</td>
<td>deep vein thrombosis</td>
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<td>DWI</td>
<td>diffusion-weighted imaging</td>
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<tr>
<td>Abbreviation</td>
<td>Term</td>
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<tr>
<td>EA</td>
<td>early intracellular antigen</td>
</tr>
<tr>
<td>EAC</td>
<td>external auditory canal</td>
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<tr>
<td>EAM</td>
<td>external auditory meatus</td>
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<td>EBRT</td>
<td>external beam radiation therapy</td>
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<td>EBSLN</td>
<td>external branch of the superior laryngeal nerve</td>
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<td>EBV</td>
<td>Epstein–Barr virus</td>
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<td>ECD</td>
<td>extracapsular dissection</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<td>ECOG</td>
<td>Eastern Co-operative Oncology Group</td>
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<td>ECS</td>
<td>extracapsular spread</td>
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<td>EGFR</td>
<td>epidermal growth factor receptor</td>
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<td>ELS</td>
<td>endoscopic laser surgery</td>
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<td>EMA</td>
<td>epithelial membrane antigen</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyogram; electromyography</td>
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<td>EMI</td>
<td>elective mucosal irradiation</td>
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<td>END</td>
<td>elective neck dissection</td>
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<td>ENT</td>
<td>ear, nose and throat</td>
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<td>ENoG</td>
<td>electroneuronography</td>
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<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
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<td>EPI</td>
<td>electronic portal imaging</td>
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<td>EPSTSSG</td>
<td>European Paediatric Soft Tissue Sarcoma Study Group</td>
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<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
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<td>ETA</td>
<td>European Thyroid Association</td>
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<td>ETE</td>
<td>extrathyroidal extension</td>
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<td>EUA</td>
<td>examination under anaesthesia</td>
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<td>FACT</td>
<td>Functional Assessment of Cancer Therapy</td>
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<td>FAMM</td>
<td>facial artery mucosal mucosal</td>
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<td>FAP</td>
<td>familial adenomatous polyposis</td>
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<td>FBC</td>
<td>full blood count</td>
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<td>FD</td>
<td>fibrous dysplasia</td>
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<td>FDG-PET</td>
<td>18F-fluorodeoxyglucose positron emission tomography</td>
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<td>FEES</td>
<td>flexible endoscopic evaluation of swallowing</td>
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<td>FEESST</td>
<td>flexible endoscopic evaluation of swallowing with sensory testing</td>
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<td>FESS</td>
<td>functional endoscopic sinus surgery</td>
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<td>FGF</td>
<td>fibroblast growth factor</td>
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<td>FHH</td>
<td>familial hypercalcaemic hypocalciuria; familial hypercalciuric hypercalcaemia</td>
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<td>FIHP</td>
<td>familial isolated hyperparathyroidism</td>
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<td>familial medullary thyroid cancer</td>
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<td>FNA</td>
<td>fine needle aspiration</td>
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<td>fine needle aspiration biopsy</td>
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<td>free T3</td>
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<td>free T4</td>
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<td>FTSG</td>
<td>full-thickness skin grafts</td>
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<td>free tissue transfer</td>
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<td>FTUMP</td>
<td>follicular tumour of uncertain malignant potential</td>
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<td>FVPTC</td>
<td>follicular variant of papillary thyroid carcinoma</td>
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<td>G-CSF</td>
<td>granulocyte colony-stimulating factor</td>
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<td>GBR</td>
<td>guided bone regeneration</td>
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<td>GCS</td>
<td>Glasgow Coma Score</td>
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<td>GCT</td>
<td>giant cell tumour</td>
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<td>GDNF</td>
<td>glial cell line-derived neurotrophic factor</td>
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<td>growth factor receptor</td>
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<td>GH</td>
<td>growth hormone</td>
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<td>GH-releasing hormone</td>
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<td>gastrointestinal</td>
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<td>GTV</td>
<td>gross tumour volume</td>
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<td>H&amp;E</td>
<td>haematoxylin and eosin</td>
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<td>HA</td>
<td>hydroxyapatite</td>
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<td>HBO</td>
<td>hyperbaric oxygen</td>
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<td>high-dose rate</td>
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<td>hypoxia inducible factor</td>
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<td>human immunodeficiency virus</td>
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<td>human leukocyte antigen</td>
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<td>Hodgkin’s lymphoma</td>
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<td>head and neck cancer</td>
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<td>head and neck parangangliomas</td>
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<td>head and neck squamous cell carcinoma</td>
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<td>hyperparathyroidism</td>
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<td>HPT-JT</td>
<td>hyperparathyroidism or hereditary hyperparathyroidism with jaw tumours</td>
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<tr>
<td>HRT</td>
<td>hyperparathyroidism</td>
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<td>HPV</td>
<td>human papilloma virus</td>
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<td>HRQOL</td>
<td>health-related quality of life</td>
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<td>herpes simplex virus</td>
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<td>hyalinizing trabecular adenoma</td>
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<td>HTT</td>
<td>hyalinizing trabecular tumours</td>
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<td>IAC</td>
<td>internal auditory canal</td>
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<td>ICA</td>
<td>internal carotid artery</td>
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<td>ICIDH</td>
<td>International Classification of Impairment Units and Handicaps</td>
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<td>ICRU</td>
<td>International Commission on Radiation Therapy</td>
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<td>inferior dental</td>
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<td>IG</td>
<td>image guidance</td>
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<td>insulin-like growth factors</td>
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<td>inferior laryngeal nerve</td>
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<td>internal margin</td>
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<td>internal mammary artery perforator</td>
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<td>immunoradiometric</td>
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<td>intensity-modulated radiotherapy</td>
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<td>IONM</td>
<td>intraoperative nerve monitoring</td>
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<td>upper aerodigestive tract</td>
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<td>University of Washington Quality of Life</td>
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<td>VAPP</td>
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History of head and neck surgery

RALPH W GILBERT AND JOHN C WATKINSON

Because the newer methods of treatment are good, it does not follow that the old ones were bad: for if our honourable and worshipful ancestors had not recovered from their ailments, you and I would not be here today.

Confucius, 551–478 BC

This book, the original concept of the named authors, Philip Stell and Arnold Maran, is a reflection of the modern history of head and neck surgery: continuous innovation through the integration of knowledge, imagination and teamwork of health-care professionals from a variety of disciplines committed to the treatment of head and neck tumours. The pace of change in the treatment of head and neck tumours has accelerated in the last two to three decades with a remarkable transition from predominantly ablative surgery to combined therapies focused on preservation of the form and function of the anatomic structures of the head and neck. This chapter will summarize the history of head and neck surgery, with information gleaned from published summaries of this history and original articles.¹

Some of the earliest attempts at head and neck surgery can likely be credited to Egyptian physicians who attempted ablative and reconstructive procedures of the oral cavity and lip. The 'Edwin Smith Papyrus', the origins of which are dated at approximately 3000 BCE, contains some of the first descriptions of surgical management of mandibular and nasal fractures, as well as lip tumours.

Arguably, the first documented efforts of reconstructive head and neck surgery are found in the Sanskrit texts of ancient India written approximately 2600 years ago. During this period of Indian history, reconstructive surgery of the nose and ear was highly valued, as invaders from surrounding territories would often stigmatize their victims by amputating the nose or ear. The early Hindu justice system also imposed harsh penalties on those found guilty of being unfaithful to a spouse by amputating either the genitalia or the nose. It is therefore logical that the nose, a structure of dignity and unique personal identity, would become a focus of reconstructive head and neck surgery. In his Sushruta Sanhita (Sushruta’s compendium), Sushruta, regarded as the 'father of Indian surgery' described a variety of surgical techniques for reconstruction of head and neck defects. Considerable controversy exists over the time period of his contributions with dates ranging from 600 BCE to 1000 AD. He contributed to many fields of medicine, but he is said to have laid the foundations for a variety of pedicled and rotation flaps, and was the pioneer of reconstructive nasal surgery having described more than 15 methods of nasal reconstruction, similar to many of the techniques utilized in the nineteenth and twentieth centuries.

Whether Helenistic or Roman physicians were exposed to the Indian techniques through Alexander the Great’s expedition to India in the fourth century BCE is of debate. Certainly, Roman and Hellenistic physicians described similar techniques to those described in India. Aulus Cornelius Celsus, considered to be the greatest of the Roman medical authors and surgeons, also described a variety of techniques similar to those practised in India in his medical text of the first century, De Medecina, and is credited with one of the first head and neck cancer procedures describing excision of a lip malignancy.²

The development of surgery of the head and neck certainly continued in the Middle Ages. However, following the fall of Rome in the fifth century and the diffusion of Barbarians and Christianity throughout the Middle Ages, a significant decline in the advancement of all surgery, in particular reconstruction, occurred. This decline was certainly aided by Pope Innocent III who prohibited surgical procedures of all types. It is interesting to note that physicians of the time considered surgery to be a manual skill and below their intellectual and societal stature. The development of the concept of the barber surgeon appeared and the decline of the role of surgery and surgeons began.
The period of Renaissance in the fourteenth century signalled a rebirth of science, medicine and the world of surgery. In the fifteenth century, the Branca family became prominent in wound reconstruction and the reintroduction of the Indian method of nasal reconstruction. The family apparently zealously protected the techniques they had developed from outside observers and the surgical techniques were passed down through family members. Branca's son Antonius inherited this technique and modified it through the use of a delayed skin flap from the arm. This Italian method, as it became known, was eventually transferred to other families of surgeons.

Descriptions of these various techniques may have contributed to Gasparro Tagliacozzi's interest in nasal reconstruction. Tagliacozzi, incorrectly referred to as the originator of the Italian method, made significant contributions to facial reconstructive surgery. Working in Bologna in the latter half of the sixteenth century, Tagliacozzi described and refined the use of distant pedicled flaps for a variety of head and neck reconstructions.

In the seventeenth century, Pimpernelle first described tongue surgery for malignancy. In the following 200 years, there were very few publications and developments in head and neck surgery.

The modern era was heralded by the development of the achromatic microscope, which allowed pathologists to first view tissues under magnification. In 1835, Mirault and Langenbeck described wedge excision of the tongue with ligation of the lingual artery to control bleeding; a major advance to reduce the bleeding associated with these procedures. Roux, in 1839, first described access procedures to the oral cavity. His technique was the first description of lip splitting incisions combined with mandibular osteotomy. The mid-nineteenth century was dominated by developments in the pathologic description of tumours, including those by the father of modern oncologic pathology, Virchow. In the latter part of the century, the description of various surgical access approaches to the head and neck began to appear.

Gordon Buck from New York was the first to describe the laryngosillouise approach to remove laryngeal tumours in 1851. The famous Viennese surgeon, Theodore Bilroth, introduced techniques of bilateral mandibular osteotomy for oral access in 1862 and described the first total laryngectomy in 1873. Interestingly, this operation so widely used today rapidly fell out of favour as the perioperative mortality was extremely high (one in 25 of Bilroth's patients survived one year).

In the latter part of the century, Kocher described the technique of lateral mandibular osteotomy along with the first description of the importance of neck node management in mucosal tumors of the head and neck. In 1885, Henry Butlin published his work on diseases of the tongue. He described premalignant lesions of the tongue and advocated for early diagnosis and treatment. He also described the importance of the lymph nodes of the tail of the parotid as metastatic sites for advanced oral tumours.

The early twentieth century was dominated by developing knowledge of the lymphatics of the head and neck and improvements in surgical technique. Polya in 1902, described the lymphatic drainage of the oral cavity, demonstrating that 50 per cent of the lymphatics traversed the mandibular periosteum leading to an interest in en-bloc resections and the foundations of the original composite resection for oral cancer. In 1906, the American surgeon and father of neck dissection George Crile described his approach to head and neck tumours, becoming the foundation of the present-day radical and functional approaches to neck dissection. Crile was an extremely creative surgeon developing pneumatic suits for patients to maintain their blood pressure during extensive surgical procedures. He also developed a carotid clamp that would allow reductions in carotid flow without complete occlusion. In 1913, Gluck and Sorensen described improved approaches to the creation of tracheostome and repair of the pharynx in laryngectomy. The approaches of Gluck and Sorensen arguably became the foundation of modern laryngopharyngeal ablative and reconstructive surgery.

In the 1930s, surgical techniques continued to evolve along with interest in the use of radiation therapy for the treatment of head and neck tumours. In 1932, GL Semken described radical neck dissection and en-bloc resection of the tongue and the associated lymphatic structures. In 1932, Ward performed and described the first composite resection.

A major innovation for head and neck management was described in 1934 by Hayes Martin and Ellis, that of the use of final needle aspiration cytology as a diagnostic tool; a development which would dramatically alter the treatment of head and neck malignancy and thyroid disease over the next 75 years.

The 1930s and 1940s were dominated by attempts at the treatment of head and neck tumours with radiotherapy. A renaissance of interest in surgical approaches to head and neck diseases occurred in the late 1940s and 1950s as the early and late effects of this primitive form of radiation became evident.

The 1940s and 1950s were dominated by development in surgical technique and an increasing interest in organ-preserving surgical procedures. Gluck and Portmann described the technique of vertical hemilaryngectomy to extirpate small volume laryngeal lesions and reported large series of patients with successful outcomes. In 1951, Alonso from Uruguay, one of the fathers of partial laryngeal surgery, described techniques of vertical and horizontal supraglottic laryngectomy and wrote the following prophetic statement:

Cancer is a terrible disease, but I do not accept that the surgeon's scalpel may be more destructive than the disease itself. The war against the larynx must stop, since its removal is unnecessary and ineffective in many cases. To take away the disease without excising a healthy glottis to make an effort to preserve the function of the organ, to strive not to return a disabled person to the society: that is my motto.

In 1951, Hayes Martin published his seminal work on head and neck surgery describing his techniques and outcomes for patients over the previous three decades at Memorial Sloan Kettering. In 1952, Conley and Pack extended concepts of vascular surgery to neck tumours, describing approaches to vascular tumours and malignancy involving the carotid.

Management of neck disease evolved in the 1960s and 1970s following the descriptions of selective neck dissection by Soares in South America and Bocca in Italy. The current approaches to neck dissection arose from refinements...
of approaches popularized by these authors and provided an evidence basis from work done by Shah,17 Byers,18 Medina19 and others.

The 1960s, 1970s and 1980s were dominated academically by giants in the field who literally changed the face of head and neck surgery through their enormous contributions to the evidence basis of head and neck surgery. Through their fellowship training programmes their skills were extended to other countries of the world and provided the academic foundation for the next generation of surgical leaders. A list of individuals of this era would include, but not be limited to, Dr Hayes Martin (USA), Dr John Conley (USA), Philip Stell (UK), Arnold Maran (UK), Joseph Ogura (USA), Dr Douglas Bryce (Canada), Dr M Lederman (UK), Sir Donald Harrison (UK) and Dr Richard Jesse (USA).

The 1980s and 1990s saw the continued development of surgical technique, including major innovation in the techniques of delivering radiotherapy, including 3D conformal radiation and intensity modulated radiotherapy (IMRT).

The major surgical innovations of this era were the increasing interest in minimally invasive surgery of the larynx and endoscopic endonasal and skull base surgery. Iako and colleagues from the United States and Kleinsasser from Germany influenced the developments in minimally invasive surgery of the larynx. The techniques advocated by these creative surgeons have been expanded and popularized by others. Most notable among these was Dr Wolfgang Steiner20 and his colleagues from Germany, whose systematic approach to the endoscopic laser excision of laryngeal tumours has changed the management approach to early and advanced laryngeal malignancy.

In the early 1980s, Messerklinger, Stammberger21 and colleagues from Austria introduced the concept of functional endoscopic sinus surgery providing the technical foundation for the developments in minimally invasive nasal surgery. A number of groups around the world, most notably Kassam, Carrau and Snyderman22 from the United States have extended these concepts and techniques, developing transnasal approaches to the management of skull base tumours.

The last two decades have seen an expanded interest in multimodality therapy combining surgery and radiotherapy or chemotherapy and radiation, with surgery reserved for salvage. This evolution in approach has evolved from surgeons becoming increasingly involved in clinical trials and the interest of surgeons in developing an evidentiary basis for the treatments they offer. Perhaps the most prominent of these trials have been the laryngeal organ preservation trials in the United States23 and the evolution of clinical trials evaluating the role of chemotherapy, radiation therapy, molecular targeted therapy and surgery in the United States and Europe.

The most important surgical innovations of the past 40–50 years have, however, been in the development of reconstructive approaches to ablative defects of the head and neck. In the 1960s, a number of surgical innovations changed the morbidity of head and neck reconstruction. The increasing use of axial pattern flaps made reconstruction of large oral cavity and neck defects more reliable and less costly to the patient in terms of prolonged hospitalization. Foremost among these were the descriptions of the forehead flap for oral reconstruction popularized by McGregor and McGregor24 and the deltopectoral flap described in the United States by Bakamjian and colleagues.25 In the late 1970s, the description of the pectoralis major myocutaneous flap by Arriyan26 transformed head and neck oncologic surgery as patients could be offered a single stage reliable reconstruction with minimal donor site morbidity. In addition, the ease of harvest and transfer of the pectoralis major flap made it a technique that any head and neck-trained surgeon could perform, broadening the scope of reconstructive surgery to other disciplines outside plastic surgery.

The late 1960s and early 1970s heralded the era of reconstructive microsurgery. The concept of free tissue transfer had been developed years earlier, but was limited by the quality and availability of microvascular sutures, quality instruments and magnification. Jacobsen and Suarez first described the repair of vessels under 2 mm in 1960. The first free tissue transfer of a composite of skin was performed by Taylor and Daniel in 1973.27 Subsequent developments in reconstructive microsurgery have resulted in the description of a plethora of free tissue transfers available for head and neck reconstruction championed by a number of extremely gifted reconstructive microsurgeons, including Harii, Buncke, Manktelow and many others.

The more notable among these flaps are: the free forearm flap described by Yang in 198328 and popularized for oral cavity and oromandibular reconstruction by Soutar; the free fibular transfer originally described by Taylor in 197729 and popularized by Hidalgo and Rekow for mandibular reconstruction in 1995,30 and the anterolateral thigh flap described by Song et al. in 198431 and popularized for head and neck reconstruction by Wei and colleagues in 2002.32

The community of specialties performing head and neck oncologic and reconstructive surgery has changed dramatically over the past 40 years. Head and neck oncologic surgery in the 1950s and 1960s was largely the domain of general and plastic surgeons, with the majority of reconstruction performed by plastic surgeons. In the last three decades of the twentieth century, however, major changes in the specialties treating defects of the head and neck had evolved. Increasingly in Europe and North America, otolaryngologists with subspecialty training in head and neck surgery and reconstructive microsurgery began to develop an interest and expertise in head and neck surgery that extended beyond the treatment of laryngeal cancer. At the same time in Europe, maxillofacial surgery began its evolution as a specialty and increasingly maxillofacial surgeons treated and reconstructed congenital, traumatic and oncologic defects of the head and neck.

With regard to thyroid surgery, goitre (guttur, Latin for throat) has been recognized as a discrete condition since earliest recorded times (2000BC). Normal thyroid anatomy was not generally understood until the renaissance when the gland was named glandulam thyroideam (Latin for shield shaped). The first thyroidectomy was performed in 1646, but the ten-year-old patient died and the surgeon was imprisoned. In the 1850s, mortality rates remained high (approximately 40 per cent), but following key advances in anaesthesia, the discovery of antisepsis and the development of the haemostat by Spencer Wells, surgeons such as Billroth and Kocher improved mortality rates from 12.6 per cent in the 1880s to 0.2 per cent in 1898. Kocher was a meticulous surgeon with low complication rates. He described the incision for thyroidectomy, as well as other surgical advances,
and became the first surgeon to be awarded the Nobel Prize in 1909.  
Kocher trained Halstead who subsequently trained Crile, Mayo and Lahey, who in turn trained Oliver Beahrs. In the UK, James Berry and Cecil Joll further championed one-stage near-total thyroidectomy for benign disease. Further advances regarding the anatomy of the recurrent laryngeal nerve, parathyroids (including extracapsular dissection) and the external branch of the superior laryngeal nerve allowed surgeons to further refine their techniques.  

Before 1948, the thyroid gland was the domain of the general surgeon, but following the inception of the NHS and development of ENT as a specialty, over the last 50 years head and neck surgery has been shared between otolaryngologists and general and endocrine surgeons. More and more in the United Kingdom, thyroid disease and malignancy is treated in a multidisciplinary setting by a team which includes both endocrinologists as well as surgeons from backgrounds in both general and endocrine surgery, as well as otolaryngology.

THE FUTURE

In the next ten years, further refinements will occur in the selection and application of the myriad of treatment options for head and neck malignancy. Increased characterization of genomic and proteomic profiles of tumours will allow us to better select patients for these therapies, providing a more individualized approach to head and neck cancer treatment. Surgical innovation with the introduction of more minimally invasive approaches, including robotics, will continue to develop and expand with the goal of reducing the morbidity associated with treatment. In the reconstructive arena, the major innovations are clearly in tissue engineering and transplantation. Tissue engineering may offer the potential to create composite tissue constructs that will replace the current approaches, including free tissue transfer and the associated donor site morbidity. Composite tissue allografts (CTA) or transplantation clearly have the potential to dramatically change the field of reconstructive surgery of the head and neck. Certainly, the recent experience with partial facial transplantation in France has highlighted the opportunities of this technology, as well as the ethical dilemmas associated with the technique.

REFERENCES


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Epidemiology and prevention of head and neck cancer

IAN GANLY AND SNEHAL G PATEL

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To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.

Sir William Osler (1849–1919)

INTRODUCTION

Squamous cell cancer constitutes the most common head and neck malignancy and is related to tobacco and/or alcohol usage. Non-squamous malignancy includes thyroid cancer, salivary gland cancer and sarcomas. These malignancies are not associated with tobacco and/or alcohol usage. According to the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) programmes of the United States, between 1975 and 2001 the incidence for most head and neck cancer sites has globally decreased, except for tongue (up 16 per cent), tonsil (up 12 per cent), nasal cavity and sinuses (up 12 per cent), salivary glands (up 20 per cent) and thyroid (up 52 per cent). Estimated new head and neck cancer cases and deaths for 2007 are shown in Table 2.1.

SQUAMOUS MALIGNANT TUMOURS

Squamous cell carcinoma of the head and neck encompasses cancer of the oral cavity, oropharynx, larynx and hypopharynx, nasopharynx, nasal cavity and paranasal sinuses. The main causative factors are tobacco and alcohol usage. In the UK, head and neck cancer represents 5–10 per cent of all tumours making it the eighth most common cancer in males and sixteenth most frequent in females. However, the incidence of head and neck cancer varies with geography with high rates being reported in France, India, South America and Eastern Europe.¹,²,³ In most regions, the majority of cancers arise in the larynx. In the Indian subcontinent, head and neck cancer accounts for 45 per cent of all malignancies with oral cancer being the most common type accounting for one-third of all cancers.⁴ For nasopharyngeal carcinoma, there are wide geographical differences with very high rates in Southeast Asia. This is due to Epstein–Barr virus and inhalation of carcinogens from cured fish and other aetiological agents.

Men are two to three times more commonly affected than women and the incidence increases with age with 98 per cent of cases occurring in patients over 40 years of age. The two most important factors in the aetiology of head and neck cancer are tobacco and alcohol. There is a synergistic interaction between these two agents which is supermultiplicative for the mouth, additive for the larynx and between additive and multiplicative for the oesophagus.⁵ A large case–control study from the United States shows good evidence of a dose–response relationship for both tobacco and alcohol.⁶,⁷ Other factors are also implicated in the aetiology of head and neck cancer; there is a great deal of statistical evidence supporting agents such as diet, viruses, occupational agents, pollutants, genetic influences, but few case-controlled epidemiological studies have been carried out.

Since the histologic distribution and aetiopathologic considerations for cancers at various sites within the head and neck are distinct, the epidemiology and prevention of these tumours will be discussed in more detail under separate anatomic sites.
Cancer of the oral cavity and oropharynx

EPIDEMIOLOGY

It is estimated that in 2007 there will be 22,560 new cases of oral cavity cancer in the United States, 14,870 male and 7,690 female. In the UK, it is the 20th most common cancer. The incidence and mortality increase with age with over 85 per cent of cases occurring after the fifth decade. Over the last 30 years, there has been a slight increase in oral cancer mainly attributable to the increase in tongue cancer in young men, 8, 9, 10, 11 When patients newly diagnosed with oral and oropharyngeal cancer are carefully examined, about 15 per cent will have another cancer in nearby areas, such as the larynx, oesophagus or lung. Of those who are cured of oral or oropharyngeal cancer, 10–40 per cent will develop a second cancer of the upper aerodigestive tract at a later time. Lung cancer often also occurs in these patients. For this reason, it is important for patients with oral and oropharyngeal cancer to have follow-up examinations for the rest of their lives and to avoid smoking and drinking, which increase the risk for these second cancers.

Cancer of the oropharynx is the third most common head and neck cancer after larynx and oral cavity. In 2007, it is estimated that there were 11,800 new cases of oropharynx cancer in the United States, 9,310 male and 2,490 female. In the UK, it has an incidence of 0.8 per 100,000 population per annum. This accounts for 10.9 per cent of all head and neck cancers. 12 Raised incidence rates are observed in the Netherlands, India, France and Italy. 12 There has been a slight increase in tonsil and base of tongue cancer over the last decade and this is largely due to human papilloma virus (HPV) infection of the palatine and lingual tonsils. 13

AETIOLOGY

Tobacco

Cigarettes

Tobacco is the most important factor and over 90 per cent of patients have a history of smoking. Tobacco contains over 30 known carcinogens, such as polycyclic aromatic hydrocarbons and nitrosamines. 14 There is a synergistic interaction with alcohol due to the increased mucosal absorption of these carcinogens as a result of the increased solubility of the carcinogens in alcohol compared with aqueous saliva. The use of filtered cigarettes reduces this exposure, 15, 16 and stopping smoking reduces the risk of head and neck cancer. The risk of oral cancer is reduced by 30 per cent in those who have discontinued for between one and nine years and by 50 per cent for those over nine years, 17 but it is unlikely that it ever returns to the baseline as compared to the rest of the population.

Pipe and cigar smokers have an increased risk of oral cancer compared to other head and neck subsites. 18 This is thought to be due to the type of tobacco used. There are two major types of tobacco – black or dark (air-cured) tobacco is used in the manufacture of cigars and pipe blends and blond (flue-cured) tobacco is used for cigarettes. Black tobacco cigarette users have a three-fold relative risk of oral cavity and pharyngeal cancer when compared to blond tobacco cigarette users. 19 This is because the extract of black tobacco cigarettes is more carcinogenic than blond tobacco cigarettes. 20

In the oropharynx, the sites most commonly affected are those in prolonged contact with surface carcinogen. The crypts of the tonsils, the glossotonsillar sulcus and the tongue base are bathed in saliva to a greater extent than the soft palate or post-pharyngeal wall and are thus more common sites in cases where smoking and alcohol are aetiological factors.

Smokeless tobacco

Oral cancer is strongly associated with different forms of smokeless tobacco consumed by chewing. These include bidi, chutta, paan, khaini and toombak. This is particularly common in the Indian subcontinent and accounts for the high incidence of oral cancer in these countries. Oral cancer increases in a dose-dependent fashion with these agents. 21, 22 There is also a strong association between the site of oral cancer and the site where the tobacco is placed. In India and parts of Asia, oral tobacco is mixed with betal leaf, slat lime and areca nut to form a quid called ‘paan’. The lime lowers the pH which accelerates the release of alkaloids from both the tobacco and areca nut. Chewing paan correlates with alveolobuccal cancer. 23 Paan is also strongly associated with a premalignant lesion oral submucous fibrosis. 24 Bidi smoking causes cancer of the oral commissure, oral tongue and also the base of the tongue. Reverse smoking (chutta) is associated with cancer of the hard palate and palatine arch in India. 25 Other forms of smokeless tobacco include khaini and toombak. Khaini is a mixture of tobacco and lime that is

### Table 2.1 Estimated new cancer cases and deaths in the United States, 2007.

<table>
<thead>
<tr>
<th></th>
<th>Estimated cases</th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td>Both sexes</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Oral cavity/oropharynx</td>
<td>34,360</td>
<td>24,180</td>
<td>10,180</td>
<td>7,550</td>
<td>51,800</td>
<td>23,700</td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>9,800</td>
<td>6,930</td>
<td>2,870</td>
<td>1,830</td>
<td>1,180</td>
<td>650</td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>10,660</td>
<td>6,480</td>
<td>4,180</td>
<td>1,860</td>
<td>1,110</td>
<td>750</td>
<td></td>
</tr>
<tr>
<td>Other oral cavity</td>
<td>2,100</td>
<td>1,460</td>
<td>640</td>
<td>1,680</td>
<td>1,270</td>
<td>410</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11,800</td>
<td>9,310</td>
<td>2,490</td>
<td>2,180</td>
<td>1,620</td>
<td>560</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>11,300</td>
<td>8,960</td>
<td>2,340</td>
<td>3,660</td>
<td>2,900</td>
<td>760</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>33,550</td>
<td>8,070</td>
<td>25,480</td>
<td>1,530</td>
<td>650</td>
<td>880</td>
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</tr>
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</table>
retained in the inferior gingivobuccal sulcus and leads to cancer in this site.\textsuperscript{26} Toombak, the form used in the Sudan, has been extensively studied. It contains very high levels of nitrosamines.\textsuperscript{27} Toombak-associated carcinogens have high prevalence of p53 protein aberration.

**Marijuana**

When marijuana is smoked, a wide range of potential carcinogens are released and absorbed, including polycyclic aromatic hydrocarbons, benzopyrene, phenols, phytosterols, acids and terpenes.\textsuperscript{28} A study from Memorial Sloan Kettering Cancer Center reported an overall risk of 2.6 compared to non-users.\textsuperscript{29}

**Alcohol**

Alcohol is believed to act in a synergistic fashion with tobacco in the aetiology of oral and oropharyngeal cancer.\textsuperscript{30, 31, 32} However, some case–control and cohort studies have shown an increased risk of cancer even in non-smokers.\textsuperscript{33} Over the past few decades, alcohol consumption has been steadily increasing and this matches the increase in oral cancer mortality.\textsuperscript{34} There is variation in oral cavity sites with higher risk of buccal cancer than floor of the mouth cancer in non-drinkers and a higher risk of lateral tongue cancer than other tongue cancers in non-drinkers. In the oropharynx, tumours arise more commonly in the glossotonsillar sulci and more posteriorly in the pharyngoepiglottic fold.

The precise mechanism by which alcohol causes cancer is not clearly defined as alcohol itself is not a carcinogen. Possible mechanisms include:

1. Alcohol may act as a solvent increasing the cellular permeability of tobacco carcinogens through the mucosa of the upper aerodigestive tract.\textsuperscript{30}
2. The non-alcohol constituents of various alcoholic beverages may have carcinogenic activities.
3. The immediate metabolite of ethanol is acetaldehyde and this may have a locally damaging effect on cells.\textsuperscript{35}
4. Chronic alcohol use may upregulate enzymes of the cytochrome P450 system which may result in the activation of procarcinogens into carcinogens.
5. Alcohol can also decrease the activity of DNA repair enzymes resulting in increased chromosomal damage.
6. Alcohol impairs immunity due to a reduction in T cell number, decreased mitogenic activity and macrophage activity.
7. Alcohol is high in calories, which suppresses appetite in heavy drinkers. Metabolism is further damaged by liver disease resulting in nutritional deficiencies and therefore lowered resistance to cancer.

**Dental factors**

Poor oral hygiene is associated with oral cancer, although no causal relationship has ever been established. This may be due to chronic inflammation of the gingiva.\textsuperscript{36} Painful or loose fitting dentures have also been associated with oral and oropharyngeal cancer.\textsuperscript{37, 38} This may also be due to chronic inflammation. There is some evidence suggesting mouthwashes containing alcohol may also be important,\textsuperscript{39} although it is possible that the cancer risk is due to other factors, for example, patients may use the mouthwash to disguise the smell of tobacco or disguise the smell of alcohol.

**Occupational exposure**

Wood dust exposure is associated with the risk of oral cancer,\textsuperscript{40} as well as pharyngeal and laryngeal cancer.\textsuperscript{41} Occupations involving exposure to organic chemicals and coal products are also at increased risk.\textsuperscript{42}

**Infections**

In head and neck cancer, several viruses have been implicated in carcinogenesis, including human papilloma virus (HPV), human immunodeficiency virus (HIV), herpes simplex virus (HSV) and Epstein–Barr virus (EBV).

**Human papillomavirus**

Human papilloma virus has been extensively studied and there seems to be a definite association between virus and tumour formation.\textsuperscript{43, 44} In particular, between 30 and 100 per cent of verrucous carcinomas have HPV.\textsuperscript{45} The proportion of cancers with HPV varies with site with a strong association with tonsil cancer.\textsuperscript{45, 46} Steinberg\textsuperscript{45} reported HPV infection to be highest in tonsil (74 per cent), followed by larynx (30 per cent), tongue (22 per cent), nasopharynx (21 per cent) and floor of the mouth (5 per cent). HPV exists in many different serotypes and specific serotypes are associated with head and neck cancer. For example, benign lesions such as the common wart are associated with ‘low risk types’ and include HPV 6, 11, 13, 32.\textsuperscript{46} High risk types are associated with premalignant lesions and squamous cell carcinoma and include HPV 16, 18, 31, 33, 35, 39.\textsuperscript{46, 47} HPV 16 and 18 appear to be the most common types associated with squamous cell carcinoma. HPV 31, 33 and 35 are more commonly associated with cervical cancer and are not found in oral cancer.\textsuperscript{48, 49} The E6 and E7 open reading frames (ORFs) of the high risk HPVs are particularly important. They bind to and inactivate tumour suppressor genes p53 and pRb, respectively.\textsuperscript{50} This allows uncontrolled cell proliferation which can result in genomic instability and cellular transformation.\textsuperscript{51} There is no relationship between clinical stage and HPV status in squamous cell carcinoma of the head and neck. This suggests HPV infection is not a late event in the evolution of head and neck cancer. As mentioned above, the highest incidence of HPV is found in tonsil cancer suggesting that there is a predilection of HPV infection for patients with tonsil carcinoma.\textsuperscript{44, 45} Patients with HPV-positive tonsil cancer tend to be young, non-smokers and non-drinkers. The molecular characteristics are completely different to HPV-negative tonsil cancers, where p53 is often mutated due to carcinogens in tobacco smoke and amplification of cyclin D1. Probably due to the different pathogenetic origin, HPV-positive tonsil cancers have a better prognosis.

**Human immunodeficiency virus**

A recent study from New York showed HIV infection in 5 per cent of head and neck cancer patients.\textsuperscript{52} In patients under 45 years, HIV infection was present in over 20 per cent. Due to the depressed immunity in HIV patients, the head and neck cancers observed were larger and more advanced in the HIV group. In addition, HIV infection is more common in inner city populations and certain socioeconomic groups and
this will also contribute to the advanced stage at presentation of these patients.

**Herpes simplex virus**

Several studies have shown that patients with oral cancer have higher antibodies to herpes simplex virus, but this does not prove a causal relationship. Antibody levels are higher in smokers and even higher in smokers with oral cancer. It is possible that the immunosuppression produced by smoking may lead to HSV chronic carrier state, resulting in raised antibody levels. HSV-type protein has been reported in 42 per cent of patients with oral cancer and 0 per cent in control patients. However, there is little evidence that HSV gene sequences are present in oral cancer cells or any evidence of gene integration. Therefore, there is currently little emphasis on HSV in head and neck cancer.

**Epstein–Barr virus**

There is no evidence that EBV is associated with oral cancer. However, this virus is strongly associated with nasopharyngeal carcinoma. The association is strongest for WHO types II and III. Eighty-one per cent of Greenland Eskimos have EBV, a population with a high incidence of undifferentiated nasopharyngeal cancer, suggesting that a chronic carrier state exists in endemic populations.

**Nutritional factors**

Several studies suggest high fruit and vegetable intake is associated with a decreased risk of head and neck cancer. This may be due to increased intake of the antioxidants or free radical scavenging vitamins A, C and E. La Vecchia et al. estimated that up to 15 per cent of oral and pharyngeal cancers in Europe can be attributed to dietary deficiencies. Some studies have shown an increased risk with red meat intake and salted meat.

**Inflammatory**

**Gastro-oesophageal reflux disease**

Reflux has been documented in 36–54 per cent of patients, which could suggest reflux to be a risk factor in laryngeal and pharyngeal cancer. However, no direct causal association has been reported.

**Precancer**

Leukoplakia and erythroplakia are significant factors important in the aetiology of oral cancer. Submucous fibrosis is a well-recognized precancerous condition, resulting in tumours in the orpharynx, particularly on the anterior palatoglossal fold.

**Genetic and immunologic predisposition**

Although smoking is the main risk factor, not all people who smoke develop head and neck cancer. Therefore, genetic and immunologic factors also play a role. There are several genetic conditions which are associated with increased risk. Li–Fraumeni syndrome, an autosomal dominant condition involving mutation of the p53 gene, has been associated with head and neck cancer in patients with minimal tobacco exposure. Fanconi’s anemia, Bloom syndrome and ataxia-telangiectasia are autosomal recessive disorders associated with increased chromosomal fragility and cancer susceptibility. There is an increased incidence of head and neck cancer in each of these conditions. There is a genetic susceptibility in the capacity to metabolize carcinogens and repair consequent DNA damage. This involves polymorphisms in GST genes and the cytochrome P450 system.

Immunologic factors are also important. Patients treated for bone marrow transplants and organ transplants have an increased incidence of skin cancer and oral cavity cancer. This may be due to the long-term use of immunosuppressive drugs.

**PREVENTION OF CANCER OF THE ORAL CAVITY AND OROPHARYNX**

**Screening**

Cancers of the oral cavity are generally easily amenable to early detection during routine screening examinations by a doctor or dentist, or by self-examination. Regular dental check ups that include an examination of the entire mouth are important in helping to find oral and oropharyngeal cancers (and precancers) early. Many doctors and dentists recommend that patients look at their mouth in a mirror every month. The American Cancer Society also recommends that doctors examine the mouth and throat as part of a routine cancer-related check-up. On the other hand, tumours of the oropharynx remain relatively asymptomatic and may not be easily accessible to early detection even by an experienced clinician. A high index of suspicion is necessary in adults who present with an otherwise asymptomatic neck mass, especially if there is a history of tobacco and/or alcohol abuse.

**Reducing risk factors**

Most oral cavity and oropharyngeal cancer can be prevented by avoiding known risk factors. Tobacco and alcohol are the most important risk factors for these cancers. The best approach is never to start smoking and limit the intake of alcoholic beverages. Quitting tobacco and alcohol greatly lowers the risk of developing these cancers, even after many years of use. Exposure to ultraviolet rays is an important and avoidable risk factor for cancer of the lips, as well as for skin cancer. Exposure to ultraviolet rays can be reduced by avoiding the midday sun, wearing a wide-brimmed hat and using sunscreen. Avoiding sources of oral irritation (such as dentures that do not fit properly) may also decrease the risk for oral cancer. A poor diet has been related to oral cavity and oropharyngeal cancer. The American Cancer Society recommends eating a variety of healthful foods, with an emphasis on plant sources. This includes eating at least five servings of fruit and vegetables every day, as well as servings of whole grain foods from plant sources such as breads, cereals, grain products, rice, pasta or beans. Eating fewer red meats, especially those high in fat or processed is also recommended. A diet rich in antioxidants, such as carotene, vitamins C and E, seems to prevent head and neck squamous cell cancer in heavy smokers and drinkers.

**Chemoprevention**

At one time, it was thought that because leukoplakia or erythroplakia often preceded the development of oral cancer,
surgically removing these areas would prevent cancer from developing. However, recent studies have found that even when these areas are completely removed, people with certain types of erythroplakia and leukoplakia are still at increased risk of developing a cancer in some other area of their mouth. This risk is particularly high if the affected tissue appears abnormal under the microscope (dysplastic) and has an abnormal amount of DNA in its cells (aneuploidy). One reason surgery does not help prevent cancer is that the entire lining of the mouth can be considered ‘premalignant’. This is referred to as ‘field cancerization’.

Chemoprevention may be beneficial in patients with leukoplakia or erythroplakia. For example, isotretinoin (13-cis-retinoic acid) is a drug chemically related to vitamin A (a retinoid). When used by patients with oral cavity or oropharyngeal cancer, isotretinoin may reduce the risk of developing a second cancer in the head and neck region. Unfortunately, side effects of this medicine limit its use. Another approach has been to develop oral rinses that contain anticancer compounds. A common class of drugs being tested is the non-steroidal anti-inflammatory drugs.

Clinical trials using gene therapy and vaccine therapy are also underway.

Cancer of the larynx and hypopharynx

EPIDEMIOLOGY

The American Cancer Society estimated that 11,300 new cases of laryngeal cancer (8,960 in men and 2,340 in women) would be diagnosed, and 3,660 people (2,900 men and 760 women) would die from the disease in the United States in 2007. These numbers are falling by around 2 to 3 per cent a year, mainly because fewer people are smoking. About 60 per cent of larynx cancers start in the glottis, 35 per cent develop in the supraglottis region and the remaining 5 per cent occur in the subglottis.

Cancer of the hypopharynx accounts for 10 per cent of all squamous cell cancers of the upper aerodigestive tract.

In the UK, the overall incidence is 1 per 100,000 per annum. There is a high incidence in Northern France of 14.8 per 100,000. Subsites of the hypopharynx include pyriform fossa (70 per cent), postcricoid area (15 per cent) and posterior pharyngeal wall (15 per cent). The pyriform fossa is the most common subsite in North America and France. Postcricoid lesions appear more commonly in Northern Europe. The mean age at presentation is 60 years. Pyriform fossa and post-pharyngeal wall have a male predominance of 5 to 20:1 in North America with 50:1 in France. Postcricoid lesions show a female preponderance 1.5:1.

AETIOLOGY

Tobacco

There is a strong association between laryngeal cancer and cigarette smoking. The relative risk of laryngeal cancer between smokers and non-smokers is 15.5 in men and 12.4 in women. Environmental tobacco smoke also increases the risk of laryngeal cancer.

Alcohol

The combined use of tobacco and alcohol increases the risk of laryngeal cancer by 50 per cent over the estimated risk, if these factors were considered additive. Different alcoholic beverages have different carcinogenic content. Beer contains the carcinogen nitrosodimethylamine, while wines contain the carcinogen tannin. Dark liquors (whisky, rum) have greater organic compounds (esters, acetaldehyde) than light liquors (vodka, gin). The risk of laryngeal and hypopharyngeal cancer is increased with dark alcohol intake. Risk is greater for hypopharyngeal cancer than laryngeal cancer. This variation in the risk of alcohol is shown for different sites in the larynx, i.e. supraglottic cancer patients are more likely than glottic and subglottic patients to be heavy drinkers of alcohol.

Occupational factors

Laryngeal cancer is associated with nickel and mustard gas exposure. There may also be association with asbestos exposure. Machinists and car mechanics are at increased risk. Long-term exposure to sulphuric and hydrochloric acid in battery plant workers have increased risk.

Radiation

Postcricoid carcinoma is associated with previous radiation and sideropenic dysphagia. Between 4 and 6 per cent have a history of Patterson Brown–Kelly or Plummer Vinson syndrome. Radiation is also implicated in posterior pharyngeal wall carcinomas.

Nutritional factors

Several studies associate high fruit and vegetable intake with a decreased risk of head and neck cancer. This may reflect increased intake of the antioxidants or free radical scavenging vitamins A, C and E.

Infection

As in oral cavity and oropharyngeal cancer, human papilloma viruses may also be a factor in some cases of laryngeal and hypopharyngeal cancer.

Immunosuppression

Laryngeal and hypopharyngeal cancers are more common in people who are immunosuppressed due to HIV or due to organ transplantation.

PREVENTION

Reducing risk factors

Most laryngeal and hypopharyngeal cancers can be prevented by avoiding the known risk factors. Tobacco use is the most important cause of cancer in these areas. Because alcohol abuse acts synergistically with tobacco smoke, it is especially important to avoid the combination of drinking and smoking. In the workplace, adequate ventilation and the use of industrial respirators when working with cancer-causing chemicals are important preventive measures. As in all head and neck cancers, malnutrition and vitamin deficiencies are also important and eating a healthy balanced diet is recommended.
Chemoprevention

Chemoprevention is the use of drugs to stop cancer from developing. This may involve preventing precancerous lesions, such as dysplasia from becoming cancerous or preventing cancer from recurring once it has been treated. They may also prevent the development of a second tumour in the head and neck area. Various chemopreventive agents are being tested to see if they can reduce the risk of developing a second primary tumour. Several retinoid analogues (chemicals related to vitamin A) are currently being studied. The drug most commonly studied is isotretinoin (Accutane®).

Cancer of the nasopharynx

EPIDEMIOLOGY

Nasopharyngeal cancer (NPC) is rare with an incidence in the UK of 0.5/100,000. It accounts for 1–2 per cent of all head and neck cancers. In the United States, there are approximately 2000 cases per year. However, in southern China and Hong Kong, the disease is endemic with an incidence rate of 50 per 100,000.108 It is also common among the Inuits of Alaska. It is also found more often in immigrant groups in the United States, such as recent Chinese immigrants and those from Southeast Asia, such as the Hmong. In the last few years, the rate at which Americans, including Chinese immigrants, have been developing this cancer has been slowly dropping.

There are three subtypes:

1. WHO type 1: keratinizing squamous cell carcinoma
2. WHO type 2: non-keratinizing (differentiated) carcinoma
3. WHO type 3: undifferentiated carcinoma.

In North America, type 1 accounts for 68 per cent of cases.109 In the Far East, type 2 and 3 account for 95 per cent of cases.110

NPC affects a younger age group than other head and neck cancers. In endemic areas, the incidence rises from age 20 to peak in the fourth and fifth decades.111 All NPCs show a male preponderance of 3:1. In the United States, it is 50 per cent more common in blacks than in whites.

AETIOLOGY

Nasopharyngeal cancer is the result of interaction of genetic and environmental factors.

Genetic factors

The genetic association is with different types of HLA types: in ethnic Chinese, NPC is associated with HLA types A2, B17 and Bw46.112 HLA B17 carries the same risk as Bw46 and is associated with younger onset disease and poorer prognosis.113 In addition, family members of people with NPC are more likely to get this cancer.

Environmental factors

The most important environmental factor is infection by EBV. Almost all nasopharyngeal cancer cells contain EBV. There is a strong association between undifferentiated nasopharynx cancer and positive serology for EBV antigens. Antibody titres to EBV antigens correlate with stage of disease and a fall reflects tumour response to treatment, whereas a rise in antibody levels means progression of disease.114, 115

Dietary factors are also important. People who live in areas of Asia, northern Africa and the Arctic region, where NPC is common, typically eat diets very high in salt-cured fish and meat. Studies indicate that foods preserved in this way that are cooked at high temperatures may produce chemicals that can damage DNA.116

PREVENTION

Reducing risk factors

Most people in the United Kingdom and United States who develop nasopharyngeal cancer have no known risk factors, so their cancers could not have been prevented. Because certain dietary factors have been associated with NPC risk, eliminating them is one way to reduce the number of cases in parts of the world where NPC is common, such as southern China, northern Africa and the Arctic region. Descendants of Southeast Asians who immigrated to the United States and eat a typical ‘American diet’, for example, have lower risk of developing NPC.

Early detection and screening

In some parts of the world, such as China, where NPC is common, some effort is underway for screening for this cancer. Subjects are first selected if their blood shows evidence of infection with the EBV; these patients are then subsequently given regular examinations. This strategy can also be applied to families where one member has developed NPC. It is not yet known if this intervention will lower the death rate from this cancer. Some cases of NPC can be found early in the course of the disease because they result in symptoms that cause patients to seek medical attention. The symptoms may even seem unrelated to the nasopharynx (e.g. in adults, persistent fullness in one ear). In some other cases, NPC may not cause symptoms until it has reached an advanced stage. Most of the time, however, the cancer spreads to lymph nodes in the neck before any symptoms occur. Over 80 per cent of patients are in an advanced stage when they are diagnosed.

Cancer of the nasal cavity and paranasal sinuses

EPIDEMIOLOGY

Cancers of the nasal cavity and paranasal sinuses are rare. About 2000 people in the United States develop cancer of the nasal cavity and paranasal sinuses each year. Men are about 50 per cent more likely than women to get this cancer. Nearly 80 per cent of the people who get this cancer are between the ages of 45 and 85 years. These cancers also occur much more
often in certain areas of the world, such as Japan and South Africa. About 60–70 per cent of cancers of the nasal cavity and paranasal sinuses occur in the maxillary sinus, 20–30 per cent in the nasal cavity, 10–15 per cent in the ethmoid sinuses, and less than 5 per cent in the frontal and sphenoid sinuses.

AETIOLOGY

As in all head and neck cancer, smoking tobacco is a risk factor for nasal cavity cancer. Occupational factors are also important. These include occupational exposure to dusts from wood, textiles and leather, and even perhaps flour. Other substances linked to this type of cancer are glues, formaldehyde, solvents used in furniture and shoe production, nickel and chromium dust, mustard gas, isopropyl (‘rubbing’) alcohol and radium. HPV infection may also be important; HPV DNA type 16 has been detected in over 50 per cent of non-keratinizing carcinomas.

PREVENTION

Reducing risk factors

The best way to prevent cancer of the nasal cavity and paranasal sinuses is to avoid the known risk factors, such as cigarette smoking. Environmental protective measures include adequate ventilation and the use of respirators can reduce occupational exposure to airborne carcinogens. However, because many people with cancer of the nasal cavity and paranasal sinuses have no known risk factors, there is currently no way to prevent all of these cancers.

Early detection and screening

Small cancers of the nasal cavity and paranasal sinuses usually do not cause any specific symptoms. Many of the symptoms of nasal cavity and paranasal sinus cancers can also be caused by benign conditions, such as infections. For these reasons, many of these cancers are not recognized until they have grown large enough to block the nasal airway or sinuses, or until they have spread to adjacent tissues, regional lymph nodes or even to distant areas of the body. Because cancers of the nasal cavity and paranasal sinuses occur so rarely, routine testing of people without any symptoms is not recommended.

NON–SQUAMOUS MALIGNANT TUMOURS

Carcinoma of the thyroid

EPIDEMIOLOGY

In the year 2007, in the United States, it was estimated that there would be 33,550 new cases of thyroid cancer diagnosed. It is more common in women with a ratio of 3:1 and affects mainly young people with nearly two-thirds of cases in the age group 20–55 years. The most common type is differentiated (80 per cent), which includes papillary (85 per cent) and follicular (15 per cent) cancer. Poorly differentiated cancer accounts for 10 per cent of cases, anaplastic 5 per cent and medullary thyroid cancer 5 per cent. The incidence of thyroid cancer is increasing and this increase is mostly related to papillary carcinoma diagnosis, without any significant difference in the less frequent histologies. The increase is the result of the incidental detection of early thyroid cancer because of increasing use of imaging, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and positron emission tomography (PET). Between 1988 and 2002, the increased number of thyroid cancers is the result of increased numbers of small nodules (<1 cm in 49 per cent of cases and <2 cm in 87 per cent of cases). The increase is therefore due to subclinical diagnosis rather than a true disease incidence. As a result, the mortality rates for well differentiated thyroid cancer have remained relatively static and the prognosis is excellent with a five-year survival of all cases of 97 per cent. Medullary thyroid cancer (MTC), which constitutes approximately 5 per cent of all thyroid malignancies, originates from the parafollicular C cells, secretes calcitonin and occurs in both sporadic and hereditary forms.

AETIOLOGY

Diet low in iodine

Thyroid cancer is more common in areas of the world where diets are low in iodine.

Radiation

A history of radiation treatment in childhood is a known risk factor. In the past, radiation was used to treat children with acne, fungal infections of the scalp, an enlarged thymus and tonsillar and adenoidal hypertrophy. Subsequent studies showed that there was an increased incidence of thyroid cancer in these children. In contrast, exposure to radiation in adults carries little risk of thyroid cancer. Children exposed to radioactive fallout from nuclear power plant accidents or nuclear weapons also have an increased incidence of thyroid cancer. For example, children exposed to nuclear fallout from Chernobyl have an eight times incidence of thyroid cancer.

Hereditary conditions

Inherited medical conditions, such as Gardner syndrome, familial polyposis and Cowden disease, have an increased incidence of thyroid cancer. Certain families also have an increased incidence of papillary thyroid cancer. Seventy-five per cent of MTC occur as a sporadic form and 25 per cent as a hereditary form. The hereditary forms can occur in three different settings: as a single component in a hereditary disease (FMTC), in the hereditary syndrome multiple endocrine neoplasia type A (MEN-2A) associated with parathyroid disease and phaeochromocytoma and finally in the hereditary syndrome MEN-2B associated with phaeochromocytoma and finally in the hereditary syndrome MEN-2B associated with phaeochromocytoma and a specific phenotype characterized by mucosal ganglioneuromas, intestinal ganglioneuromatosis and a marfanoid habitus. Both MEN-2 syndromes are autosomal dominant genetic disorders characterized by mutations in the RET proto-oncogene. Patients can now be stratified into...
high-, intermediate- and low-risk groups according to the type of RET mutation.\textsuperscript{128}

**PREVENTION**

**Reducing risk factors**
Most people with thyroid cancer have no known risk factors. Therefore, it is not possible to reliably prevent most cases of this disease.

**Early detection and screening**
Most cases of thyroid cancer can be found early by the detection of a neck lump either by the patient or by their doctor on routine examination. It is unusual for early thyroid cancer to present with any symptoms. In MTC, 80 per cent are familial and 20 per cent sporadic. In the familial forms, mutation of the RET proto-oncogene is present. It is therefore possible to screen family members of patients with MTC for RET mutations. There are several types of mutations which can be classified into low-, intermediate- and high-risk mutations.\textsuperscript{128} If present, these patients can then be treated by prophylactic thyroidectomy. The age of thyroidectomy is also influenced by the type of RET mutation; patients with high risk mutations can be offered prophylactic thyroidectomy as early as three years of age.\textsuperscript{129}

**Salivary gland carcinomas**

**EPIDEMIOLOGY**
There are two main types of salivary glands, the major salivary glands (parotid, submandibular and sublingual glands) and the minor salivary glands. About 80 per cent of all salivary gland tumours are in the parotid gland, 10–15 per cent in the submandibular gland and the rest in the sublingual and minor salivary glands. Most tumours of the parotid gland are benign, whereas 40 per cent of submandibular gland tumours and 80 per cent of minor salivary gland tumours are malignant. There are several different types of malignant tumours of the salivary glands due to the different types of cells which make up normal salivary glands. These include mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma and rare adenocarcinomas, such as basal cell, clear cell, salivary duct and mucinous adenocarcinoma. Salivary gland carcinomas are not common and occur with an annual rate of 1.2 per 100 000 in the United States. About one-third of patients are under the age of 55 years. The incidence of these cancers is increasing, but the cause for this is unknown. The survival depends on cell type and stage of the cancer. The overall five-year survival rate is 68 per cent for all people with salivary gland cancer.

**AETIOLOGY**
Exposure to radiation to the head and neck area for other medical reasons, e.g. radiotherapy for squamous cell cancer, increases the risk of salivary gland cancer.\textsuperscript{130} Industrial exposure to radioactive substances and also accidental exposure from atomic bomb blasts also increase the risk of salivary gland cancer.\textsuperscript{130} Some studies have also suggested that working with certain metals (nickel alloy dust) and minerals (silica dust) may increase the risk for salivary gland cancer. In men, smoking and heavy alcohol consumption was also associated with higher risk, but these factors were not strongly related to salivary gland cancer in women.\textsuperscript{131} Hormonal dependence may also be important; early menarche and nulliparity are associated with increased risk, whereas older age at full-term pregnancy and long duration of oral contraceptive use are associated with reduced risk.\textsuperscript{132} Female patients with salivary gland tumours are also 0.5 times more likely to develop breast cancer.\textsuperscript{133} Diets low in vegetables and high in animal fat may also be an important factor.\textsuperscript{134}

**PREVENTION**
Avoiding certain risk factors, such as radioactive substances, nickel dust and silica dust, may help reduce the risk of developing salivary gland cancer. These cancers can also be found early when the patient or doctor notices a lump within the gland. Checking the salivary gland for lumps should therefore be a routine part of a general medical or dental check-up.

**Sarcomas of the head and neck**

**EPIDEMIOLOGY**
Sarcomas of the head and neck constitute less than 1 per cent of head and neck malignancies. They are divided into those arising from soft tissue sarcomas (STS)\textsuperscript{135} and those arising from bone (osteosarcoma).\textsuperscript{136} Soft tissue sarcomas comprise a heterogeneous group with varied histology and behaviour, and include chondrosarcoma, dermatofibrosarcoma protuberans, Ewing’s sarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumour, rhabdomyosarcoma and synovial sarcoma.\textsuperscript{135} Rhabdomyosarcoma is rare in adults, but is the most common soft tissue sarcoma in children with over 30 per cent occurring in the head and neck. Dermatofibrosarcoma protuberans is a rare tumour of the dermis that has a high recurrence rate. Malignant fibrous histiocytoma is the most common soft tissue sarcoma in middle and late adulthood. Only 4 per cent of liposarcomas occur in the head and neck with the neck being the most common site. Synovial sarcomas occur in the 20–50 year age group with the majority arising in the parapharyngeal space. The most common site of chondrosarcoma in the head and neck is the larynx, maxilla and skull base. Most occur in the age group of 30–60 years. The most common site in the larynx is the posterior lamina of the cricoid cartilage (75 per cent). Malignant peripheral nerve sheath tumours are extremely rare, but more common in patients with neurofibromatosis type 1 (NF1).

Osteogenic sarcoma is a rare highly malignant tumour with an incidence of one in 100 000 with only 7 per cent occurring in the head and neck region. The majority of these arise in the mandible followed by the maxilla. Head and neck osteosarcoma is most common between the ages of 30 and
40 years in comparison to long bone osteosarcoma which is most common in the teenage years.

AETIOLOGY

Genetic predisposition
Studies have shown that some groups of individuals are at an increased risk of developing soft tissue sarcoma. Among them are genetically predisposed individuals, such as those suffering from neurofibromatosis who are at risk of malignant peripheral nerve sheath tumour (MPNT), people with the Li–Fraumeni syndrome and children with retinoblastoma who are predisposed to osteosarcoma, rhabdomyosarcoma and fibrosarcoma. Other heritable syndromes associated with an increased risk of STS include Gardner’s syndrome and nevoid basal cell carcinoma syndrome.

Radiation
Previous exposure to irradiation is another well-documented risk factor for both soft tissue sarcoma and osteogenic sarcoma. Although radiation-induced sarcoma (RIS) is a well-recognized long-term complication of radiation therapy for other sites, the head and neck are less commonly affected. It is difficult to implicate therapeutic irradiation in the causation of head and neck tumours because of the inherent risk of multiple primary tumours in these patients. In addition, patients with certain types of primary tumours, such as retinoblastomas, have an increased sensitivity to radiation therapy, but are at increased risk for the development of sarcoma irrespective of the type of treatment.

Occupational factors
Environmental carcinogens, and chemicals like urethane, ethylene derivatives and polycyclic hydrocarbons, have also been reported to increase the risk of STS at sites other than the head and neck.

Viruses
The role of viruses in the pathogenesis of STS has been investigated, but apart from the association of HIV with Kaposi’s sarcoma and the observation that viral oncogenes, such as the src in the Rous sarcoma virus, can transform cells in culture, no conclusive proof is available for a viral aetiology. Immunosuppression attributable to either HIV infection or antirejection medication in organ transplant recipients has been reported to have predisposed to leiomyosarcoma of the liver in paediatric patients who had a latent Epstein–Barr virus (EBV) infection.

Trauma
Trauma most often draws attention to a tumour and there is no conclusive evidence to support the association of sarcomas to scar tissue. A possible association between artificial implants and soft tissue sarcomas has been debated for a few years and angiosarcomas have been reported to arise around previously placed vascular grafts.

Other factors
Patients with chronic lymphoedema have an increased incidence of soft tissue sarcoma formation. Patients with Paget’s disease of bone, particularly the skull, are predisposed to osteogenic sarcoma.

PREVENTION

Reducing risk factors
Most people with sarcoma have no known risk factors. Therefore, it is not possible to reliably prevent most cases of this disease.

EARLY DETECTION AND SCREENING
Most cases of sarcoma often present late due to the rarity of the disease. Early detection may be possible in patients with a genetic predisposition, such as neurofibromatosis, Gardner’s syndrome and children with retinoblastoma.

KEY LEARNING POINTS

Squamous cell cancer of the oral cavity and oropharynx
- The incidence of oral cavity SCC is increasing, particularly in young men.
- There is a high incidence (15 per cent) of second primaries in patients with oral cavity cancer.
- The main causative factors are tobacco and alcohol.
- There is synergistic interaction between tobacco and alcohol.
- There is a strong association with human papilloma virus, particularly in tonsil cancer.
- Leukoplakia, erythroplakia and submucus fibrosis are important precancerous conditions.
- Genetic predisposition syndromes include Li–Fraumeni, Fanconi’s, Bloom and ataxia telangiectasia.

Squamous cell cancer of the larynx and hypopharynx
- Cancer of the larynx accounts for 30 per cent of head and neck cancer.
- Sixty per cent of larynx cancers are glottic, 35 per cent supraglottic and 5 per cent subglottic.
- Larynx cancer has male predisposition M:F of 4:1.
- Cancer of the hypopharynx accounts for 10 per cent of head and neck cancer.
- The main subsite is pyriform fossa, then postcricoid, then posterior pharyngeal wall.
- The male predisposition M:F is 20:1 in pyriform fossa and posterior pharyngeal wall cancer.
- There is a female predisposition M:F of 1:1.5 in postcricoid cancer.
- Main causative factors are tobacco and alcohol.
- Synergistic interaction between tobacco and alcohol.
• Heavy alcohol consumption associated with supraglottic larynx cancer and hypopharynx cancer.
• There is an association with human papilloma virus in larynx cancer.
• Radiotherapy and sideropenic anaemia are associated with postcriocid cancer.

Squamous cell cancer of the nasopharynx

• Cancer of the nasopharynx accounts for 1–2 per cent of head and neck cancer.
• There is an increased incidence in Southeast Asia.
• There is a male predisposition M:F of 3:1.
• It is more common in the young with peak age of 40–50 years.
• Eighty per cent of cases present with advanced stage disease.
• There is a genetic predisposition with association with HLA types A2, Bw16, B17.
• There is a strong association with Epstein–Barr virus infection and consumption of salt cured fish.
• Antibody levels to EBV correlate with stage of disease and response to therapy.

Squamous cell cancer of the nasal cavity and paranasal sinuses

• Cancer of the nasal cavity and paranasal sinuses is rare.
• There is a male predisposition with age at presentation of 45–85 years.
• The most common site is maxillary sinus, then nasal cavity, then ethmoid sinus, then sphenoid and frontal sinus.
• The majority of patients present with advanced stage disease.
• Causative factors include tobacco and exposure to wood dust.

Thyroid cancer

• There is a female predisposition of F:M of 3:1.
• It affects mainly young patients with peak age 20–55 years.
• There is increasing incidence due to incidental detection through increased use of imaging.
• It has an association with low iodine diet.
• There is a strong association with previous radiation exposure.
• There is an association with multiple endocrine neoplasia (MEN) syndrome.
• There is an increased incidence in patients with Gardner’s syndrome, familial polyposis and Cowden disease.

Salivary gland cancer

• The majority of parotid gland tumours are benign (80 per cent).
• Forty per cent of submandibular and 80 per cent of minor salivary gland tumours are malignant.

• There is heterogeneous histology due to multiple cell types in salivary gland tissue.
• The most common salivary gland cancers are mucoepidermoid, adenoid cystic and acinic cell carcinoma.
• There is an association with previous radiation exposure.

Head and neck sarcoma

• Head and neck sarcoma is uncommon.
• There is an association with previous radiation exposure.
• There is an association with polycyclic hydrocarbon exposure.
• Human immunodeficiency virus is associated with Kapoši’s sarcoma.
• Genetic predisposition in neurofibromatosis includes Li–Fraumeni syndrome and Gardner’s syndrome.

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Molecular biology as applied to head and neck oncology

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A mighty flame followeth a tiny spark.

Dante Alighieri, The Divine Comedy

INTRODUCTION

In 1960, the discovery of the Philadelphia (Ph) chromosome, a reciprocal translocation between chromosomes 9 and 22 \([t(9:22)(q34;q11.2)]\), in chronic myeloid leukaemia (CML), was the first clear evidence suggesting cancer was a genetic disease.\(^1\) The Ph chromosome represents a fusion of the tyrosine kinase proto-oncogene c-Abl (chromosome 9q34) with the serine/threonine kinase gene BCR (chromosome 22q11.2) and directly promotes the development of CML by increasing tyrosine kinase signalling (Figure 3.1). Moreover, the clinical importance of genomic aberrations was highlighted by the significant response to c-Abl tyrosine kinase inhibitors in patients with CML containing the Ph translocation. These findings ushered in the genomic era of cancer research which focused on the identification of genetic aberrations that could be targeted for therapeutic benefit. The advent of high throughput genetic screen tools has accelerated discovery, allowing the identification of many genetic abnormalities present in individual cancers. Extrapolation of screening data suggests that cancer cells contain as many as 12,000 individual aberrations.\(^2,3\) However, no clinical or biological significance could be attached to the vast majority of newly identified genetic abnormalities. Mathematical models suggest that only between five and ten critical aberrations are essential in cancer pathogenesis.\(^3\) The biological mechanisms underlying the striking accumulation of molecular changes and the identification of cancer-causing

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**Figure 3.1** Creation of the Philadelphia chromosome through reciprocal exchange of genetic material between chromosomes 9 and 22. Fusion of the c-Abl-containing region of distal chromosome 9 to the BCR-containing region of chromosome 22 results in formation of a chimeric oncogene that causes chronic myeloid leukaemia.
primary events among the large pool of secondary ‘passenger mutations’ has been an important focus of contemporary cancer research. Although much is known about the molecular basis for head and neck squamous cell carcinoma (HNSCC) pathogenesis, it has not translated into clinical application due to the high level of genetic complexity present in these cancers. In this chapter, we will discuss the genetic basis for HNSCC pathogenesis while highlighting those events that may have therapeutic implications.

**GENETIC BASIS FOR CANCER DEVELOPMENT**

Normal cells can acquire genetic aberrations due to the inherent infidelity of DNA replication machinery. However, this innate mutagenesis is rarely sufficient to support cancer development on its own, as mutations are random and those that affect cancer-related genes also activate protective measures in cells to block oncogenesis. It is now accepted that cancer pathogenesis requires an environment that promotes the development of genetic aberrations, characterized by increased genetic damage or decreased inherent genetic repair and protective mechanisms. While inherited mutations (germline mutations) in several protective genes have been associated with increased cancer risk, much less is known about normal variations (polymorphisms) in the sequence of individual genes (much like skin colour or blood type) that alter gene function and cancer susceptibility. In addition, mutagenic environmental factors can induce genetic mutations (somatic mutations) in cells, which, once established, can be inheritable and propagated in subsequent cell divisions. Accordingly, cancer results from an imbalance in factors promoting the development and accumulation of genetic events and those that prevent, exclude or repair genetic damage.

**CARCINOGENS THAT PROMOTE HNSCC**

Tobacco, alcohol, betel nut and sexually transmitted viral pathogens (human papilloma virus (HPV)) have all been associated with an increased risk of HNSCC. Each of these carcinogens promotes progression to HNSCC by contributing to the accumulation of genetic aberrations, the rate and accumulation of which is dependent on a balance between carcinogen dosage and host susceptibility. Tobacco smoke is an aerosol containing vapour and particulate components with more than 4000 chemicals, at least 60 of which have been shown to be carcinogenic. Tobacco carcinogens are broadly grouped into polycyclic aromatic hydrocarbons (i.e. benzo[a]pyrenes), heterocyclic aromatic amines, aromatic amines, aldehydes, azo-arenes (dibenzo[a,h]acridine and 7H-dibenzoc[7,g]carbazole), N-nitrosamines (N-nitrosodiethylyamine), as well as other agents. Many of these compounds are tumorigenic in mice. Once absorbed, most tobacco carcinogens require activation by cellular enzymes (i.e. cytochrome P450 group) to promote tumorigenesis and their effects can be offset by detoxifying enzymes (i.e. GSTM1). Dysfunction of these enzymatic pathways has been associated with increased risk for HNSCC.

Chronic alcohol exposure results in increased cancer incidence in animal models, confirming its carcinogenic role. Similar to tobacco, carcinogens in alcohol require its metabolism to an active intermediate (acetaldehyde) by alcohol dehydrogenase (ADH), CYP2E1 (along with reactive oxygen species) or catalase. Acetaldehyde is then inactivated by conversion to acetate by acetaldehyde dehydrogenase (ALDH). Acetaldehyde exerts its carcinogenic effect primarily by direct binding to DNA, but also alters methyl transfer, resulting in genetic hypomethylation, which in turn affects the transcription of multiple genes. In addition, reactive oxygen species are generated during alcohol metabolism, which also have mutagenic effects. Factors promoting accumulation of acetaldehyde, including increased alcohol consumption, increased alcohol metabolism, or decreased conversion to acetate result in increased rates of cancer formation. For example, deficiency of ALDH2, which is common in Asians, increases the risk for esophageal cancer formation up to 16-fold relative to those with normal ALDH2. Alcohol also promoted cytochrome P450 activity which increases activation of procarcinogens (both for tobacco and alcohol). In addition, alcohol can also act as a solvent to facilitate entry of carcinogens into cells, especially in the upper aerodigestive tract.

Recent studies show that the human papilloma virus may be responsible for development of HNSCC. HPV is a retrovirus that primarily infects transitional epithelial tissues. The HPV family contains over 70 different types that can be divided into low- and high-risk categories with respect to their ability to promote cancer development. HPV types 16 and 18 are the most common high-risk types associated with cervical and anogenital cancers, while 6 and 11 are low-risk types that cause non-cancer pathologies (e.g. papillomas and condylomas). Infection with high-risk HPV subtypes has been shown to transform benign human keratinocytes in culture, a phenomenon that is not observed with low-risk HPV types. Early viral proteins, E6 and E7, are essential for transforming effects and are more potent in high-risk HPV types. Their functions are discussed in the following sections. A meta-analysis of published trials, including 5046 HNSCC cancer specimens, shows a 26 per cent prevalence of HPV, with the vast majority being HPV type 16 (HPV-16). The predominant location of HPV-associated tumours is in the oropharynx, with a predilection for non-smokers (up to 50 per cent of cases). Similar to cervical cancers, detection of HPV in HNSCC is associated with sexual history, implicating direct exposure as a cause for infection. In addition, immunosuppression has been suggested to increase the risk for infection and development of HPV-related HNSCC.

**INHERITED SUSCEPTIBILITY TO HNSCC**

Susceptibility to the carcinogenic effects of tobacco, alcohol and HPV varies widely between individuals, and is dependent on hereditary factors. A significant role for hereditary susceptibility factors in the development of HNSCC is suggested by several observations. For example, observational evidence suggests that a two- to 14-fold increased incidence of HNSCC is present in first-degree relatives of patients with HNSCC. Several studies and meta-analyses suggest that
certain inherited genetic polymorphisms can increase HNSCC risk by affecting the function of carcinogen activating enzymes (i.e. cytochrome P450 group or ADH) or detoxifying enzymes (GSTM1 or ALDH). Polymorphisms in prominent cell cycle regulators, such as cyclin D1 (CCND1), p53 and P21 (Waf1/CIP1) have also been associated with susceptibility for HNSCC. A study by Storey and colleagues demonstrates a polymorphism at codon 72 in the p53 gene, which modifies susceptibility of p53 to HPV-mediated degradation, is associated with an increased risk of HNSCC development. However, the exact role of these polymorphisms in HNSCC pathogenesis has yet to be validated.

In contrast, several inherited mutations are clearly associated with increased risk for HNSCC development. These mutations and the resulting heritable syndromes including Li–Fraumeni syndrome (p53 mutation), Fanconi anaemia (FANCA-A to FANCA-M mutations), Bloom’s syndrome (BLM mutation), and dyskeratosis congenita (DKCA mutation) have an increased incidence of squamous cell carcinoma of mucosal membranes. The causative genes involved in these inherited syndromes function in DNA repair and surveillance of genetic stability, which explains a higher rate of cancer development in affected patients. It remains unclear why affected patients feature a predilection for SCC development, but it is of interest that some of the genes (p53, BLM, FANCA-M) can be found inactivated uniquely in the genetic blueprint of HNSCC tumours (but not in their host genomes) occurring in the general population (sporadic HNSCC). The collective data suggest that these genes are likely involved in key pathways, inactivation of which is an early event in the development of HNSCC. However, the infrequent inactivation of these genes in the germline of HNSCC patients suggests they likely represent a minor fraction of hereditary influences in HNSCC development.

### SOMATIC GENETIC MUTATIONS IN CANCER

The interplay between the cumulative exposure to carcinogens and host susceptibility factors drives cancer pathogenesis through induction of somatic genomic mutations. Cancer-causing somatic genetic aberrations can be divided into two broad categories: those that affect proto-oncogenes and those that affect tumour suppressor genes (Figure 3.2).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>HNSCC</th>
<th>Other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi</td>
<td>FANC family</td>
<td>&gt; 500-fold higher rate</td>
<td>Haematological</td>
</tr>
<tr>
<td>FAMMM</td>
<td>p16</td>
<td>Increased</td>
<td>Melanoma, pancreas</td>
</tr>
<tr>
<td>N/A</td>
<td>RNASEL</td>
<td>1.5-fold increased risk</td>
<td>Prostate, cervix, breast</td>
</tr>
<tr>
<td>Bloom</td>
<td>BLM (DNA helicase)</td>
<td>Increased</td>
<td>Multiple leukaemias, lymphomas and carcinomas</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>XP-A to XP-G</td>
<td>Increased</td>
<td>UV-induced skin cancer</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>Increased</td>
<td>Leukaemia, lymphoma</td>
</tr>
<tr>
<td>Li–Fraumeni</td>
<td>p53</td>
<td>Increased</td>
<td>Lymphoma, sarcoma</td>
</tr>
</tbody>
</table>

Table 3.1 Genetic cancer syndromes associated with HNSCC.

![Figure 3.2](image-url) Normal pair of (paternally and maternally derived) chromosomes with centromere represented by black dot and both alleles of target gene sequence represented by orange regions (1), and most common genetic alterations that affect the gene sequence to activate it (in the case of the oncogene, 2–4) or inactivate it (in the case of the tumour suppressor gene, 5–8). Note that complete inactivation of tumour suppressor genes requires a combination of two separate inactivational events, each affecting one of two alleles. Proto-oncogenes are activators of oncogenesis, as they promote cellular growth, neovascularization (angiogenesis), cellular dissociation from the environment and cellular migration. Proto-oncogenes are activated by diverse genetic events including chromosomal gain or amplification that increase gene dosage, activating mutations that result in changes or increases in gene activity, or translocation/rearrangement in chromosomes that produce novel genes (such as the Philadelphia translocation) (Figure 3.1). Tumour suppressor genes typically have no direct functional effects on oncogenesis, but normally function to limit the effects of cancer-causing events to the extent that they may induce programmed cell death to assure that detrimental aberrations are not propagated. Their loss allows a permissive environment for cancer pathogenesis, characterized by genetic instability that fosters accumulation of other genetic abnormalities.
Tumour suppressor genes are commonly inactivated through loss of genetic information, inactivating mutations (i.e., missense/nonsense mutations), decreased protein production (i.e., mutation or hypermethylation gene promoter or increased activity of micro-RNAs) or increase in protein turnover (i.e., ubiquitin-based proteasome degradation). Combined, genetic abnormalities confer cells with growth self-sufficiency, insensitivity to antigrowth and cell death signals, limitless replicative potential and an ability to detach from and invade surrounding structures and spread to distant anatomic sites.26, 27

**GENETIC PROGRESSION MODEL FOR HNSCC**

Global genomic screening tools have revealed that HNSCC are characterized by an array of genomic alterations (Figure 3.3). Accumulating evidence suggests that genetic aberrations develop in an arbitrary manner, with those providing survival advantages selected for in a Darwinian manner in individual cells.4, 28 As critical genetic aberrations accumulate, mucosal keratinocytes progress through distinct histopathological stages from benign squamous hyperplasia to dysplasia, carcinoma in situ and finally invasive carcinoma. Individual genomic aberrations accumulate at different stages of the progression axis,29, 30 but it remains to be determined if they directly contribute to or are required for progression (Figure 3.4). The current model of progression to HNSCC suggests deletion of the chromosomal 9p21 region as an early event, given that it is detectable in a significant proportion of hyperplastic lesions of the upper aerodigestive tract. The candidate gene 9p21 region includes p16 and/or p14arf. Another early event in HNSCC progression is deletion of the chromosomal 3p region that is first detectable in benign squamous hyperplasia. The subsequent transformation from hyperplasia to dysplasia appears to be associated with amplification of the 3q26.3 locus and p53 mutation, identifiable in early dysplastic lesions, carcinoma in situ and HNSCC. The transformation of dysplasia to malignancy is also associated with 11q13 amplification (activation of cyclin D1), gains of the chromosomal regions 7q11.2 (EGFR activation), 8q23-24 and deletions of 13q21, 14q23, 4p and

![Figure 3.3](image-url)

**Figure 3.3** (a) Ideogram showing common chromosomal alterations identified by comparative genomic hybridization (CGH) in HNSCC. Each vertical line on either side of the ideogram represents an aberration detected in a single tumour. Thin vertical lines indicate losses (left) and gains (right) of the chromosomal region. The chromosomal locations of high-level gene amplification are shown by thick lines (right). (b) Ideogram showing the most common chromosomal breakpoints identified by spectral karyotyping of HNSCC chromosomes. The number of breakpoints in each chromosome that were identified by SKY, but could not be precisely assigned to a chromosomal band, are noted in the box on top of the chromosome.
5q13-32. Subsequent gains of 1q21, 17q, 19q, 20q and deletions of 5q33-34, 8p, 10p12, 10q, 18q, 4q, 11p14, 11q14-qter and 21q21 and PTEN inactivation appear to be associated with initiation of the metastatic process. The gene targets and the functional and clinical significance of most of these aberrations remain to be defined.

COMMON MOLECULAR SIGNALLING PATHWAYS AFFECTED IN HNSCC

In addition to uncharacterized genomic alterations, HNSCC are characterized by multiple alterations in well-characterized biochemical signalling pathways that control oncogenic properties, such as the balance between cell survival and cell death (apoptosis), angiogenesis, invasion and metastasis. The most common signalling pathways affected in HNSCC are described below (Figure 3.5).

**The p53 pathway**

The p53 protein is a transcription factor that plays an essential role in the pathogenesis of human cancers, including HNSCC. The p53 pathway is activated by cellular stress resulting in either cell cycle arrest to allow repair or apoptosis in case of severe events. The importance of p53 in oncogenesis is evident from the fact that it is mutated in a large fraction of human malignancies, including more than 60 per cent of HNSCC. Moreover, several lines of evidence suggest that the p53 pathway may be inactivated in cases without detectable genetic mutations in p53. Approximately 10–15 per cent of HNSCC feature overexpression of the human variant of mouse double minute proteins 2 and 4 (MDM2 and MDM4), which promote proteasome-based degradation of p53 by ubiquitination. Similarly, the p14ARF gene that inhibits the association of p53 with MDM2 is inactivated in HNSCC by homozygous deletion, somatic mutation or epigenetic silencing. In addition, in cases with HPV infection, the E6 viral oncoprotein binds and degrades p53. Aberrations may also be present in other proteins in the p53 pathway including BCL2, p21, BCL-XL, caspase, BAX and other p53 family members (p73 and p63). Combined, these abnormalities result in p53 pathway inactivation in more than 95 per cent of HNSCC.

**The retinoblastoma pathway**

The retinoblastoma pathway plays a central part in regulation of cell cycle progression from the G1 phase into the S phase, the commitment step in the cell cycle. Detrimental alterations in components of the Rb pathway are required for cancer development, as shown from their ubiquitous presence in human cancer, including HNSCC. The function of Rb revolves around its inhibition of the E2F protein activity by direct binding. When phosphorylated, Rb dissociates from E2F, allowing it to activate transcription of genes required for progression into S phase. Rb is phosphorylated by cyclin-dependent kinases through complex regulatory networks. Although direct inactivation of pRB is uncommon in HNSCC, several indirect mechanisms of pRB inactivation have been identified. An important mechanism of Rb inactivation is fuelled through p16, a central tumour suppressive protein that activates CDK4 and CDK6 proteins which inhibit phosphorylation of Rb. P16 is the protein product of the CDKN2A gene (chromosomal region 9p21), which is inactivated by somatic mutations (approximately 5–15 per cent), homozygous deletions (approximately 30–60 per cent) and epigenetic silencing by hypermethylation (approximately 10–20 per cent). As a result of these and other events, immunohistochemical analysis demonstrates that p16 absence is present in at least 80 per cent of HNSCC.

Figure 3.4 Tumour progression model for HNSCC, showing that histologic progression from normal mucosa to invasive carcinoma and ultimately metastasis is associated with a stepwise accumulation of specific genetic alterations (genetic alterations associated with metastatic progression are highlighted in bold).
exerts its positive effect on cell cycle progression by promoting phosphorylation of pRB by cdk4, is another important mechanism for inactivation of the Rb pathway in HNSCC. Constitutive activation of cyclin D1 through chromosomal amplification (of locus 11q13) (Figure 3.2) can be identified in approximately 30 per cent of HNSCC. The collective data suggest that inactivation of the retinoblastoma pathway is required for HNSCC development.

Epidermal growth factor receptor pathway

The ErbB/HER family of tyrosine kinase receptors, including epidermal growth factor receptor (EGFR/ERBB1), Her2Neu (ERBB2), ErbB3 and ErbB4, are important activators of mitogenic signalling.34 EGFR tyrosine kinases possess an extracellular N-terminal ligand-binding domain, a transmembrane region and a C-terminal intracellular domain which includes the kinase domain and multiple phosphorylation sites. These receptors are activated by various ligands, including tumour necrosis factor alpha (TNFα) and EGF. Ligand binding induces homodimerization or heterodimerization with other ErbB receptors (receptor crosstalk) and results in receptor activation by autophosphorylation. The activated receptor recruits intracellular signalling complexes which activate mitogenic signalling pathways, such as the RAS/MEK/ERK cascade, the STAT cascade, the PI3K/AKT cascade, and several angiogenic, cell adhesion and cell cycle regulatory pathways.

Overexpression of EGFR and its ligands is well documented in HNSCC and premalignant mucosa and occurs in 40–95 per cent of cases. EGFR overexpression in HNSCC is a result of several factors, including transcriptional induction and genetic amplification. In addition, constitutively active EGFR through point mutation in the kinase domain or deletions in the extracellular domain have been described in HNSCC, but appear to be rare. Overexpression of other ErbB receptors in HNSCC is common, but underlying mechanisms are less well defined.

The PI3-kinase pathway

The PI3-kinase pathway is an important downstream effector of the EGFR and many other membrane-based receptors and is a central player in cancer pathogenesis.35 In normal cells, activation of upstream signalling factors, such as EGFR, results in the recruitment of PI3K isoforms to the plasma membrane that subsequently generate 3’-phosphorylated phosphoinositides (PI3, 4P, PI3, 4, 5). Phosphoinositol triphosphate (PIP3) activates PDK1, resulting in phosphorylation of AKT. AKT is the active component of the pathway, promoting cellular survival by affecting the function of many proteins by phosphorylation to promote cell survival. The tumour gene phosphatase and tensin homologue gene (PTEN) is an important negative regulator of the PI3K-AKT pathway activity by regulating PIP3 dephosphorylation, which decreases the phosphorylated AKT fraction and promotes G1 arrest.
Constitutive activation of components of the PI3K cascade is common in HNSCC, occurring in up to 70–90 per cent of cases. It may be achieved through several mechanisms including chromosomal amplification of the PIK3CA locus (chromosome 3q26.3; 30/40 per cent of cases), activating mutations in PI3K (approximately 5 per cent of HNSCC), amplification of AKT (20–30 per cent), or somatic mutation, homozygous deletion or methylation of the PTEN locus in HNSCC.43

DNA repair pathways and genetic instability

Several lines of evidence suggest genomic instability is a cardinal feature of progression to HNSCC.13,37 This is confirmed by progressive accumulation of genetic aberrations as a keratinocyte evolves into an HNSCC. Factors promoting genomic instability may include deficiencies in DNA repair, chromosome cohesion and condensation, mitotic progression, spindle assembly and regulation of chromosomal telomere length. A key method in which genome integrity is disrupted in HNSCC is through abnormalities in the p53 pathway, an inherited mutation which can lead to many different cancers, as demonstrated in patients with Li–Fraumeni syndrome.19 Similarly, studies on telomerase, the enzyme that controls the length of telomeres (repetitive sequences of DNA, located at chromosomal ends) which linearly correlate with cellular lifespan, demonstrate that this pathway is also aberrant in HNSCC.38,39 Overall, the precise contribution of individual pathways to genomic instability in HNSCC remains to be defined.

Angiogenesis

Tumours cannot grow to sizes beyond 5–10 mm without access to the circulatory system for oxygen and nutrients and release of their metabolic waste products. As a consequence, neoangiogenesis is required for HNSCC progression.26,27,40 Tumours secrete multiple soluble factors, including vascular endothelial growth factor (VEGF), acidic and basic fibroblast growth factor (FGF1/2), and interleukin 8 (IL-8) to promote vascular ingrowth. In addition, adhesion molecules mediating cell–cell and cell–matrix interactions, such as integrins and cadherins, also contribute to proangiogenic signals. Several studies have linked neoangiogenesis to development and progression of HNSCC.41 Consistent with this, histopathological studies show increased microvessel density accompanies tumour progression.42 Upregulation of VEGF family members including VEGF-A, VEGF-B, VEGF-C and VEGF-D, VEGF-E and FGF proteins and downregulation of thrombospondin-1 have been revealed in a high percentage of HNSCC and some of these factors have also been detected in serum of HNSCC patients.43

Cellular adhesion, dissociation, invasion, migration and metastasis

In contrast to normal cells, cancer cells have an acquired capability to survive dissociation from their normal environment, invade their environment and metastasize.26,27,44 Metastasis is the unique end product of this cascade and is the cause of 90 per cent of cancer-related mortality. The induction of the metastatic process is an extremely complicated process that remains incompletely understood. From a molecular point of view, an initiating role in the onset of metastasis has been attributed to aberrant homeostasis of cell adhesion pathways.44 In recent years, important groups of cell adhesion proteins have been identified, including proteins from the cadherin and integrin superfamilies. These membrane-bound receptors are central regulators of cell–cell interactions (cadherins) and cell–matrix interactions (integrins). In normal cells, the interactions of cadherins with the outside environment transmit intracellular antigrowth regulatory signals. Not surprisingly, cancer cells are marked by a significant downregulation of cadherins. In addition, the normal integrin profile present at the cell membrane of normal cells may be altered in cancer cells to switch from recognition of and interaction with the physiologic outside environment to adaptation to novel matrix components and associated alteration of intracellular signalling. In addition to cell adhesion molecules, a second important biochemical mechanism involved in invasion and metastasis includes the increased activity of extracellular protease enzymes aimed at degradation of extracellular material during preparation of escape to and settlement in distant anatomic locations. To fulfil this requirement, protease genes, such as the matrix metalloproteinases (MMPs), are upregulated and inhibitors of protease enzymes, such as the TIMPs, are downregulated in both cancer cells and surrounding stroma cells. Alterations of integrins, cadherins, MMPs and TIMPs are common in HNSCC and correlate with the pathological features and clinical outcome of HNSCC.45

CLINICAL UTILITY OF MOLECULAR CHANGES IN HNSCC

Molecular diagnostics

The identification of tumour-specific (somatic) molecular alterations in HNSCC and their earliest neoplastic precursors, coupled with the development of highly sensitive molecular analytic techniques, such as the polymerase chain reaction (PCR), provides several opportunities for improved molecular diagnostics of HNSCC.46 The improved sensitivity of molecular diagnosis over traditional histopathologic assessment of oral neoplasia is evident from studies showing that premalignant lesions containing 3p14 or 9p21 alterations have a significantly higher likelihood of evolving into HNSCC (37 per cent) compared to premalignant lesions without these changes (6 per cent).47 These data were confirmed and extended by the observation that premalignant lesions that harbour additional deletions of 4q, 8p, 11q and 17p had an even higher risk of developing into HNSCC.48 Several studies have demonstrated a correlation between the presence of genetically abnormal cells in histologically benign mucosa within the surgical margins of HNSCC resection specimens and a higher risk for local recurrence.49 Possibilities for improvement of molecular staging are further suggested by data demonstrating the accuracy of PCR-detected molecular alterations in histologically benign lymph node specimens.
aspirates and associated reduction of survival.\textsuperscript{50} Also, Califano and colleagues\textsuperscript{51} demonstrated that histologically benign tissue taken during primary tumour localization examinations of unknown primary HNSCC contained the identical molecular alterations as the lymphatic metastasis. Several studies have demonstrated the possibility of distinguishing primary lung cancer from lung-metastatic HNSCC based on p53 mutation analysis or global expression profiling.\textsuperscript{52, 53, 54, 55, 56} Recently, studies have included PCR-based analysis of promotor hypermethylation events and mitochondrial DNA mutations instead of traditional LOH analysis, suggesting that it may improve sensitivity and specificity.\textsuperscript{57, 58} Tumour-specific methylation events can be detected in the saliva and serum of patients with HNSCC, foreseeing development of a non-invasive routine screening test for smokers and drinkers.\textsuperscript{57, 58} The complement of data foreshadows the introduction of molecular detection of HNSCC in risk groups and molecular staging in HNSCC patients once the findings are validated and analytic techniques optimized.

### Molecular staging of HNSCC

As clinical behaviour of individual tumours is directly determined by the complement of its genetic aberrations, molecular factors may be better predictors of clinical outcome than currently used clinicopathological factors. Indeed, several studies suggest that molecular analysis of HNSCC is associated with improved outcome prediction compared to traditional staging (Table 3.2).

p53 mutation was identified as an independent predictor of poor outcome after surgery with or without radiation therapy in several trials. In addition, p53 mutation was identified as an independent predictor of chemotherapy alone, and chemoradiation resistance in several HNSCC studies.\textsuperscript{59} These studies confirm \textit{in vitro} work which has shown that cell lines with p53 mutation are more sensitive to cisplatin treatment, which may relate to a decreased capacity for DNA repair in affected cells.\textsuperscript{60} Nonetheless, the evidence for p53 mutation as an independent predictor of outcome in HNSCC remains based on small studies with heterogeneous study populations and needs appropriate confirmation.\textsuperscript{61} Also, the clinical relevance of p53 inactivation by other means than point mutation and prognostic evaluation of alterations in p53 pathway members (BCL2, p21, MDM2, BCL-XL, caspases, BAX, p73 and p63) needs further delineation.

Several studies have suggested that alterations in the Rb pathway may also be of prognostic significance in HNSCC. Several studies show independent prognostic significance associated with the presence of cyclin D1 overrepresentation in HNSCC series treated with surgery with or without radiation therapy even after controlling for clinicopathological variables by multivariate analysis.\textsuperscript{62}

Human papillomavirus is well known to compromise oncogenesis, cellular adhesion, invasion and metastasis, such as the VEGF, MMPs, TIMPs, integrins and cadherins, the expression and activity of which may be influenced by the EGFR pathway results in aggressive tumour behaviour. Multiple studies have reported EGFR overexpression as an independent predictor of poor outcome after surgery \textit{\&} radiation therapy.\textsuperscript{63} Also, EGFR overexpression is associated with chemotheraphy and chemoradiation resistance.\textsuperscript{70} These findings are in line with the observed modulation of chemotherapy and radiation therapy resistance of other human tumours by ErbB receptors.\textsuperscript{69} This may relate to the proficiency of ErbB receptors to activate a pro-survival state in cancer cells through activation of downstream pathways including the RAS/MEK/ERK cascade, the STAT cascade, the PI3K/AKT cascade, and several angiogenic, cell adhesion and cell cycle regulatory pathways.

Constitutive activation of PI3-kinase through 3q26 amplification is strongly associated with survival after surgery with or without radiation therapy of HNSCC.\textsuperscript{72} Also, overexpression of AKT provides an independent survival benefit in patients with HNSCC.\textsuperscript{72, 73} A prognostic role for other EGFR-induced survival factors, such as the STATs, the PLC/\gamma gamma factors and members of the MEK pathway is currently under investigation. Members of pathways involved in angiogenesis, cellular adhesion, invasion and metastasis, such as the VEGF, MMPs, TIMPs, integrins and cadherins, the expression and activity of which may be influenced by the EGFR pathway, have been the subject of many prognostic studies with promising results.\textsuperscript{40} For example, it appears that VEGF expression is an independent predictor of surgical and chemotherapy outcome, suggesting that resistance to these treatments is conferred through the activation of neoangiogenesis.\textsuperscript{40}

### Table 3.2 Clinical relevance of molecular factors in HNSCC.

<table>
<thead>
<tr>
<th>Molecular alteration</th>
<th>Prognostic significance</th>
<th>Therapeutic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53 pathway</td>
<td>P53</td>
<td>ONYX-15, adP53</td>
</tr>
<tr>
<td>Rb pathway</td>
<td>Cyclin D1</td>
<td>In progress</td>
</tr>
<tr>
<td>EGFR pathway</td>
<td>EGFR</td>
<td>Cetuximab, panitumumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gefitinib, erlotinib</td>
</tr>
<tr>
<td>PI3K/AKT pathway</td>
<td>PI3 K, AKT</td>
<td>Everolimus, temsirolimus</td>
</tr>
<tr>
<td>Human papilloma virus</td>
<td>HPV</td>
<td>Vaccination, immunotherapy</td>
</tr>
<tr>
<td>Angiogenesis</td>
<td>VEGF</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>DNA repair</td>
<td>Unclear</td>
<td>PARP inhibitors</td>
</tr>
</tbody>
</table>
In addition to the above-described molecular factors, a significant number of uncharacterized chromosomal aberrations have been associated with poor outcome of HNSCC, including deletions of 3p, 5q11, 6q14, 8p21-23, 9p21, 10q, 11q23, 14q, 17p, 18q, 21q11 and 22q and gains of 3q26 and 11q13, 12q24. Some of these genomic abnormalities (3p, 3q26, 9p21) also represent early events in the HNSCC progression model, suggesting that the clinical course of HNSCC may be determined early in its pathogenesis (Figure 3.3). Overall, the prognostic assessment of individual molecular factors has revealed important support for their mechanistic and vital role in HNSCC pathogenesis and the hypothesis that molecular factors can be used as strong prognostic factors. However, a significant degree of outcome variation remains unexplained by the analysis of individual molecular factors. Given the multifactorial nature and genetic complexity of cancer, it is now clearly accepted that the accuracy of molecular staging may be improved significantly by analysis of multiple factors in concert.\textsuperscript{75}

A convincing example of the improved predictive power of combined molecular assessment is provided by breast cancer analysis. Using microarray-based global gene expression profiling (Figure 3.6), van de Vijver and colleagues identified a 70-gene poor prognosis signature that outperformed clinicopathological factors in the prediction of distant metastasis.\textsuperscript{76, 77} The molecular signature was an independent predictor of disease outcome in 295 patients and has been validated in several independent patient groups.\textsuperscript{76, 77, 78} The poor prognosis signature consisted of genes regulating cell cycle, invasion, metastasis and angiogenesis, which supports its direct relationship with oncogenesis. Several other groups have reported equivalent findings in breast cancer and other tumour types. At the Netherlands Cancer Institute, a chip with the breast cancer signature has been developed and is currently being tested in clinical practice.

Microarray studies of HNSCC confirm the improved prognostic analysis of large-scale molecular profiling. A microarray study by Chung and colleagues, who investigated the gene expression profile of 60 HNSCC, identified a high risk gene expression profile predictive of lymph node metastasis (80 per cent accuracy).\textsuperscript{79, 80} Pramana and colleagues\textsuperscript{81} independently confirmed the association of this profile with poor outcome after chemoradiation treatment of HNSCC. Roepman and colleagues identified (in 92 tumours) and independently validated (in 27 tumours) 102 predictor genes that predicted the presence of lymph node metastasis with 86 per cent accuracy compared to 68 per cent accuracy of clinical diagnosis in their cases.\textsuperscript{82} In addition, Ganly and colleagues identified and externally validated MDM2 and ERBB2 (Her2Neu) as predictors of regional recurrence after chemoradiation therapy of laryngeal carcinoma, further implicating the importance of p53 and receptor tyrosine kinase signalling in HNSCC.\textsuperscript{83} Reproducibility issues associated with RNA-based microarray analysis may be overcome by recently developed improvements in DNA-based microarray analysis, which will further increase the accuracy of molecular prediction. Despite this, the assessment of increasing numbers of predictor variables has unmasked multiple statistical issues. Significant effort has been placed on development of robust analytic approaches that may further solidify the value of molecular prediction in cancers such as HNSCC. In addition, the identification of molecular factors will be critically dependent on assembly of homogeneous study populations as the molecular profile of HNSCC is known to be influenced by multiple clinicopathologic variables that may obscure survival correlations.

In addition to prognostic analysis of individual or combined molecular markers, HNSCC can be stratified in several different subgroups based on divergent global molecular
profiles, some of which are associated with poor clinical outcome. Ginos and colleagues performed microarray analysis of 41 HNSCC and demonstrated categorization into several different expression signatures, one of which was associated with recurrence.84

Despite these promising findings, the key question that remains is whether any of the putative predictors can be used to individualize treatment selection. Unfortunately, unlike the example of kinase mutations in other solid tumours, the predictive value of individual or combined molecular markers remains insufficient for routine clinical use in HNSCC. Even more importantly, the inherent genetic differences that predict response to chemotherapy, which may not only serve as treatment selectors, but also as therapeutic targets, remain unidentified.

Molecular therapeutic targets

The unique presence of somatic molecular alterations in cancer cells holds an opportunity for targeted HNSCC treatment.85 Targeted treatment has a theoretical advantage over the standard treatment, due to the ability to selectively target cancer cells and spare their normal environment. This is exemplified by treatment of chronic leukaemia and gastrointestinal stromal tumours with the respective BCR/Abl and cKIT targeting agent Gleevec.86 The characteristic molecular pathways of HNSCC, such as those governed by p53, Rb, EGFR and VEGF, are currently targeted with novel agents in preclinical and clinical trials to establish their efficacy. Of these, cetuximab, an anti-EGFR antibody, given concomitantly with radiation has been shown to be superior to radiation alone without adding to high-grade toxicity.85, 87 Additional anti-EGFR agents are also showing promising results in combination with chemotherapies and/or radiation therapy, including panitumumab and the tyrosine kinase inhibitors (TKI) gefitinib and erlotinib.85

Other approaches have also been employed in HNSCC with some success. Bevacizumab, a monoclonal antibody to VEGF, has been tested in phase II studies of HNSCC patients alone or in combination with EGFR inhibitors.88 Single agent treatment with angiogenesis blockers, such as bevacizumab, demonstrate response rates in the order of 4 per cent, that may increase to 14 per cent when combined with erlotinib.88 In addition, several general tyrosine kinase inhibitors that inhibit multiple tyrosine kinase pathways simultaneously have been developed (sorafenib, sunitinib and others), and are the subject of clinical trials based on successful preclinical treatment of HNSCC cells. HNSCC with defects in DNA repair pathways are currently targeted by inhibitors of poly(ADP-ribose)polymerase (PARP), a nuclear enzyme that corrects DNA damage in DNA repair-deficient tumour cells recovering from radiation therapy.89 Reactivation of p53 protein function with genetically modified viral vectors has also undergone clinical trials.90, 91, 92, 93 ONX-15 is an E1B-deleted adenovirus that replicates exclusively in p53 mutated cells. The agent, applied through intratumoral injection, yielded a 13 per cent response rate as a single agent and a 63 per cent rate in combination with cisplatin and 5-fluorouracil in patients with HNSCC. A second adenoviral vector, Adp53 which leads to p53 re-expression, showed modest activity in phase II trials, with a 12 per cent response rate in the unresectable patients and 27 per cent of respectable patients surviving beyond 18 months.94 Given the complexity of biochemical signalling pathways in human tumours, it is clear that targeted treatment of HNSCC will be most efficacious when multiple signalling pathways are blocked simultaneously, and in conjunction with standard treatment.95, 96

CONCLUSION

The past few years have brought significant advancements in our understanding of the biology of HNSCC. As genetic screening technologies continue to improve, we expect further improvement in delineation of the HNSCC genome. It is expected that prognostic markers and biological therapies that are derived from increased knowledge will lead to a significant and expanding role in the treatment of HNSCC in the future.

KEY LEARNING POINTS

- Cancer results from an imbalance in factors promoting the development and accumulation of genetic mutations and those that prevent, exclude or repair genetic damage.
- Extrapolation of screening data suggests that cancer cells contain as many as 12 000 individual aberrations, but biological and mathematical models suggest that only between 10 and 60 critical aberrations are essential in cancer pathogenesis.
- Genetic mutations develop in an arbitrary manner, with those providing survival advantages selected for in a Darwinian manner.
- Critical molecular alterations for cancer development typically activate genes that promote oncogenesis (proto-oncogens) or inactive genes that limit oncogenesis.

KEY EVIDENCE

- Cancer is caused by a random accumulation of genetic alterations. Genetic alterations critical for cancer cell survival are selected for in a Darwinian manner, and these critical alterations may be exploited for diagnostic, prognostic and therapeutic benefit.
- Evidence for viability of targeted treatment in HNSCC has been derived from a recent study showing improved survival of conventionally treated HNSCC with addition of cetuximab, a monoclonal antibody to EGFR.95
Combined, the complement of genetic abnormalities confers cells with growth self-sufficiency, insensitivity to antigrowth and cell death signals, limitless replicative potential and an ability to detach from and invade surrounding structures and spread to distant anatomic sites.

HNSCC development is increased in the presence of tobacco exposure, alcohol exposure, oncogenic HPV exposure and (non-)syndromal hereditary susceptibility factors including Fanconi anemia, dyskeratosis congenita, Bloom’s syndrome, Li–Fraumeni syndrome and specific polymorphisms in carcinogen-activating enzymes, detoxifying enzymes and cell cycle regulator genes.

Histological progression of mucosal keratinocytes from benign squamous hyperplasia to dysplasia, carcinoma in situ and finally invasive carcinoma is paralleled by a stepwise increase in genomic complexity with accumulation of specific molecular alterations at specific stages along the histologic progression axis.

Common molecular signalling pathways affected in HNSCC include the p53 pathway, the retinoblastoma pathway, the epidermal growth factor receptor pathway, the PI3-kinase pathway, and several DNA repair and genetic instability pathways, angiogenesis pathways and cellular adhesion, dissociation, invasion, migration and metastasis pathways.

The unique presence of somatic molecular alterations in cancer cells has been shown to provide an opportunity for improved diagnostics, improved staging and cancer-specific treatment of HNSCC, but further development is needed to establish these unequivocally into clinical practice.

REFERENCES


Assessment and staging

NICK ROLAND

INTRODUCTION

There is no more an important aspect of head and neck cancer care than the initial evaluation of the patient and the patient’s tumour. The practice requires specific expertise and judgement. Regrettably, it is a process which is still occasionally carried out incorrectly and by surgeons who do not have proficiency. The surgeon must ‘get it right the first time’. The consequence of not doing so can be disastrous.

In general, the first decision to be made in a patient with a confirmed head and neck cancer is whether or not to treat the patient before deciding what form of management strategy is appropriate. Deciding which patients with head and neck cancer should be treated is often more difficult than in many other fields of surgery, because there are seldom absolute objective signs that demonstrate the patient is beyond treatment.

There are several important points when it comes to making the ultimate decision with regard to treatment planning. These are:

- age of the patient;
- tumour factors (site and extent of the tumour);
- intercurrent disease (comorbidity);
- social circumstances;
- patient’s wishes.

Some patients should not be treated, usually because a combination of advanced stage and poor general condition makes the mutilating effects of surgery not worthwhile. It should be noted, however, that although a head and neck tumour may be incurable, there are very few that are unresectable. Virtually every structure in the head and neck to which a tumour may be fixed can be removed in continuity and repaired in some way, shape or form. It is important to remember, therefore, that although the vast majority of patients with head and neck cancer are potentially treatable that not all are curable.

Treatment should not begin until the surgeon and patient have a clear understanding of the goals of treatment. If a patient is unfit for surgery because of advancing age or poor general health, then consideration should be given to whether or not palliative treatment is appropriate by radiotherapy and/or chemotherapy, or whether purely supportive measures will suffice with no active anticancer treatment at all. A final decision on treatment often hinges on a full assessment of the patient including physiological age and general condition.

The aim of this chapter is primarily to describe why and how we appraise a patient and their tumour. The chapter will address the general principles applicable to the topic of
evaluation, classification and staging. In addition, the limitations and pitfalls of this process are described.

**HISTORY**

The clinical features of malignant disease are manifest by the primary tumour, secondary deposits and the general effects of cancer. Taking the history from a patient with a head and neck tumour is no different from taking the history of a patient with any other medical or surgical condition.

1. **Age.** The age of the patient will prove to be an important determinant in treatment planning. This will be due to specific age-related tumour factors and patient comorbidity factors. It may also be complicated by evocative perceptions on the part of the carers and their individual attitudes to age. When a young person develops a head and neck tumour, it often carries a sinister significance. A genetic predisposition or alteration in immune status may have caused their tumour to develop. Elderly people often have impaired functional organ reserve or significant comorbidity. They are less able to be successfully rehabilitated with regard to speech and swallowing than are younger patients after major surgery.

2. **Social circumstance.** Social circumstance is particularly important to consider in context with the patient’s environmental and cultural background. Most head and neck procedures violate normal anatomy and physiology, and usually the psyche of the patient. Every patient who has a head and neck operation requires not only physical support, but psychosocial support afterwards. The decision on the appropriate modality of primary treatment should take into consideration factors such as the patient living alone, if they are unable to read and write or if they are an alcoholic.

3. **Risk factors.** Enquiry should be made into the presence of risk factors for the development of cancer of the head and neck, such as the use of tobacco products, alcohol abuse, and environmental exposure to wood dust or heavy metals.

4. **Related symptoms.** Symptoms related to the tumour will give a hint as to the anatomical position. The duration of symptoms may give a clue to the tumour behaviour. Patients who have had symptoms for a protracted period of many months, but with a small confined tumour, will probably have indolent disease. Those patients with a short history of weeks, but with a tumour causing multiple symptoms due to local extent, will have a more aggressive disease. A tumour that is growing very quickly may not be amenable to treatment by any modality and can act as a ‘clinical biological indicator’, so that any treatment may indeed be worse than the end point of the disease itself. The situation where the operation was a success and the patient a failure is not a desirable end result.

### Table 4.1 Eastern Co-operative Oncology Group (ECOG) scale.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90–100)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g. for example, light housework, office work (Karnofsky 70–80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50–60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30–40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10–20)</td>
</tr>
</tbody>
</table>

5. **Previous medical history.** The patient’s previous medical history should be properly documented. It is paramount to assess the patient’s risks pertaining to intercurrent diseases and that from their head and neck tumour. Comorbidity will compromise planned operative procedures, chemoradiation and the patient’s overall prognosis. Disorders which will potentiate anaesthetic problems, bleeding (anticoagulants, aspirin) and postoperative recovery should be clearly recorded. Tumours that develop in immunocompromised individuals seldom do well by any modality. The patient’s general condition should always be classified using one of the methods of measuring performance status such as the Eastern Co-operative Oncology Group (ECOG) scheme1 or the Karnofsky status (Table 4.1).2

6. **Patients who have been treated elsewhere.** If one is assessing a patient who has had treatment elsewhere, it is important not to assume anything that has gone on before and to start again, both in the history-taking and in the clinical examination, in order not to get caught out. In patient assessment, a useful aphorism to remember is ‘good judgement is usually the result of experience, but experience has usually resulted from previous bad judgement’.

**EXAMINATION OF THE PRIMARY SITE**

When assessing the primary lesion, its exact position, borders and effect on function should be delineated both by inspection and where possible by palpation.

A good light source and head lamp should be used to inspect the oral cavity and oropharynx. Palpation of the tongue and tongue base by a gloved finger may reveal a tumour which is not obvious on inspection alone. In addition to primary tumour assessment, it is important to assess the patient’s dentition and to seek the advice of a restorative dentist if the oral cavity is to be involved in surgical or radiotherapy treatment.
Fibreoptic endoscopy provides excellent access to the nasal cavity, nasopharynx and larynx for clinical examination. The mucosa of the tongue base can be inspected by asking the patient to protrude the tongue. Vocal cord movement should be assessed on phonation. Vocal fold mucosal wave can be further gauged by stroboscopy. The piriform fossa can be exposed by asking the patient to blow their cheeks out against their closed mouth.

A permanent record of the findings should be made preferably by photographs with written description from the examiner. In the absence of this facility, drawings or a pre-printed set of illustrations should be used. Although one ought to think in terms of T-staging, it is advised that a stage is not conferred until all of the appropriate investigations have been completed.

It is important to have a copy of the current TNM (tumour, node, metastasis) staging system, American Joint Committee on Cancer (AJCC) or Union Internationale Contre le Cancer (UICC) both in clinic and in the operating room to facilitate accurate staging.

EXAMINATION OF THE NECK

Involved lymph nodes rarely produce symptoms until they are quite large. Therefore, the surgeon must depend mainly on physical examination to detect clinically enlarged nodes. Detailed drawings using prepared diagrams complement the written report.

The triangles of the neck and the lymph nodes that they contain are examined in turn (Figures 4.1 and 4.2). Having inspected the neck from the front, the clinician stands behind the patient and flexes his or her head slightly. Palpation then takes place in a systematic manner to include all lymph node groups and cervical anatomy (Table 4.2). The position, size and number of nodes should be established. Fixation of the nodes to adjacent anatomical structures or skin should be defined and clearly documented. As with assessment of the primary tumour, think in terms of N-staging, but a stage should not be conferred until all of the appropriate investigations have been completed.

Clothing should be removed until the points of the shoulders can be seen. The index fingers are placed on both mastoid processes and the clinician works down the trapezius muscle until the fingers meet at the clavicle. There are nodes under the trapezius muscle and, because of this, fingers should be inserted under the anterior border of the muscle with the thumb pressing down on the top with the shoulder blades forward. When the clavicle is reached, the posterior triangle (level V) is palpated. Here, the nodes lie between the skin and muscles of the floor of the triangle and therefore can be rolled between these two surfaces. Tension is taken off the sternomastoid muscle by passive, gentle lateral movement of the head to the examined side. The fingers are placed in front of, and medial to, the sternomastoid with the thumb behind it, thus forming a ‘C’ around the muscle. The examination progresses down the muscle carefully because 80 per cent of the nodes lie under the muscle within the jugular chain (levels II–IV) of the deep cervical lymph nodes. The smallest node which can be easily palpated in the jugular chain is probably 1 cm. The jugulodigastric node is the largest normal node in the neck and can be palpated in many normal people. Most clinically positive nodes occur in the upper jugular chain (levels II and III), but the most superior jugular nodes (level II), including the junctional nodes, are difficult to
palpate, particularly in men, and positive lymph nodes in the lower jugular area (level IV) may be difficult to feel since they are often small, deep and mobile.

Attention should be paid to the suprasternal notch and the space within it (the space of Burns), as clinically positive cricothyroid and pretracheal nodes may be discovered. The trachea is palpated and at this point the size of the thyroid gland is assessed. Then, working upwards, the mobility of the larynx and pharynx on the prevertebral fascia is assessed and, in particular, a note made of any pain on palpation of the trachea which may indicate direct invasion of this structure by direct extension from a postcricoid carcinoma.

The submandibular gland and nodes along with the submental nodes (level I) should now be examined. These are all easier to feel and nodes down to 0.5 cm can usually be palpated. At the posterior border of the submandibular gland, the examination continues upwards over the face to assess the preauricular nodes.

A number of normal structures can be confused with a lymph node in the neck. The lateral tips of the transverse processes of both C1 and C2 can simulate lymph nodes, as can the parotid tail, superior horn of the thyroid cartilage and the carotid bulb. Irradiated and obstructed submandibular glands may also simulate lymph node enlargement.

The reliability of the neck examination depends on the experience and ability of the examiner, the gross anatomy of the individual neck and whether or not there has been previous treatment, such as surgery and/or radiotherapy. A fat, thick or a muscular neck can make evaluation difficult, as can a recent incisional biopsy or tracheostomy.

It is important to remember that there is a well-recognized error in tumour palpation in general, with considerable intraobserver and interobserver variation when estimating tumour size. These pitfalls of tumour measurement are particularly common in head and neck cancer. There is considerable error in palpating the neck, with significant variation between experienced observers. The use of calipers or another measuring tool is therefore advised.5

FINE NEEDLE ASPIRATION CYTOMETRY

Fine needle aspiration cytology (FNAC) is the mainstay initial investigation for patients who present with cervical lymphadenopathy. With the advent of rapid access neck lump clinics, an FNAC result is obtained easily and in many cases a diagnosis procured immediately. In these clinics, a surgeon and cytopathologist are available for the evaluation and aspiration of neck masses. Ideally, the clinic should also have an ultrasound facility as this will improve the adequacy of aspirates.

An early indication as to the tissue or tumour of origin may thus greatly influence the early management of a patient with head and neck swelling, reducing dramatically both patient anxiety and resource consumption. The early detection of, for example, a colloid goitre, lymphoma or adenocarcinoma will lead to a very different clinical approach from
the detection of a pleomorphic adenoma or a squamous cell carcinoma. In the head and neck, FNAC is of particular value because of the multiplicity of accessible organs and the heterogeneous pathology encountered (Figure 4.3).

The necessary equipment should be kept in a small box ready for use and comprises a 20-mL syringe, 21-G needles, microscope slides, slide carriers, fixative spray and skin swabs. Air is expelled from a syringe and a needle attached. The lump is stabilized with the left hand as the needle enters (Figure 4.4). Suction is applied, and while this is maintained, several radial passes are made within the substance of the swelling. The suction is released and the needle withdrawn through the skin. The tissue core should thus be retained within the needle itself, rather than transferred to the syringe. The needle is disconnected and 10 mL of air aspirated into the syringe. This is then reconnected to the needle and the specimen expelled on to a slide. A second slide is used to smear the specimen and this process repeated with further slides until the smear is of the right thickness. This can be judged only with experience and feedback from the cytopathologist. Both fixed and air-dried slides should be sent to the laboratory. The slides should be sprayed at once with alcohol fixative, if Papanicolaou or similar stains are to be used. Blood in the specimen will cause a drying artefact, but may not render it useless. If fluid is aspirated, this should be sent in a clean universal container so that a cyospin preparation can be obtained.

In many cases, a preliminary diagnosis is achieved in the clinic. However, in some situations, the aspirate may be inadequate for purpose or interpretation difficult. The submission of inadequate material for diagnosis is simply remedied by repeating the aspirate. Cystic lesions are particularly difficult as cyst content rather than epithelial cells may be aspirated. Ultrasound-guided fine needle biopsy is particularly useful in these cases and in neck masses which are difficult to define by palpation alone.

The ability to apply immunohistochemistry has increased the validity of cytology in many of the disease diagnoses, particularly lymphoma. However, FNAC is no substitute for histology, especially in the determination of nodal architecture in lymphoma, the malignant potential of a follicular thyroid tumour, of extracapsular spread in squamous carcinoma, or in the distinction of a pleomorphic from a monomorphic adenoma. Incisional biopsy of a lymph node is rarely justified as a squamous carcinoma may be implanted into the tissues. Similarly, open biopsy is contraindicated in pleomorphic adenoma or nodal deposits of squamous carcinoma. Although the former practice of Tru-cut needle core biopsies has now been superseded by FNAC, it may be useful in certain instances. In the diagnosis of anaplastic carcinoma, adequate information may be obtained from an outpatient Tru-cut needle core biopsy, if tissue cannot be obtained under general anaesthesia for various reasons.

FNAC is regarded as safe by most authorities. Some report no cell seeding at all, while others have detected spillage of $10^2$–$10^4$ cells, but have also shown that the number of cells required to cause a seeded growth in humans is about twice

(a)

Figure 4.3 Fine-needle aspiration cytology showing (a) squamous cell carcinoma and (b) papillary carcinoma of the thyroid gland.

(b)

Figure 4.4 Technique for fine-needle aspiration cytology showing (a) aspiration of a solitary thyroid nodule and (b) smearing.
that observed. There are no reports of seeding of head and neck tumours, including parotid tumours. Care should be applied if a lump seems to be pulsatile or obviously vascular to avoid inadvertent aspiration of a carotid body tumour. Suspicion of such a lesion is largely regarded either as a contraindication or an indication for the use of a finer (23 G) needle.

Several studies have confirmed the excellent diagnostic accuracy of FNAC. To achieve this high degree of diagnostic accuracy, the cytopathologist must be well trained in the interpretation of head and neck aspiration cytology. If the findings of FNAC do not correlate with the clinical picture, the surgeon should pursue other diagnostic investigations. Clinical acumen should prevail. It is said that FNAC is as useful as the combined intelligence of the surgeon and cytologist. Regular constructive liaison between the two is pivotal.

GENERAL EXAMINATION

General health

The patient’s general health should be assessed with the usual investigations. All patients undergoing major surgery should have a full blood count, urea and electrolytes, liver function tests along with a chest x-ray, electrocardiogram (ECG) and thyroid function tests. Occult hypothyroidism is not uncommon in the elderly nor in those patients having revision treatment when previous surgery or radiotherapy to the thyroid gland can affect its function. Patients should be assessed for deep vein thrombosis (DVT) prophylaxis. Specialist head and neck imaging is discussed subsequently (Chapter 6, Head and neck pathology), but as patients are at risk of metastases and a second primary within the chest, a computed tomography (CT) scan of the chest should be considered as an alternative to a chest x-ray.

A decision as to whether the patient is fit for surgery and general anaesthetic should be made following discussion with the anaesthetist who shares the final responsibility for the patient’s health during any such procedure. The American Society of Anaesthesiologists (ASA) scoring guide estimates a patient’s anaesthetic risk based on age, medical comorbidities, anatomical abnormalities and prior anaesthetic experience. The ASA score gives an objective assessment of a patient’s ability to tolerate a planned surgical procedure. The anaesthetist may order further investigations deemed appropriate on the basis of the patient’s comorbidity.

Nutritional status

Head and neck cancer can cause difficulty in eating and swallowing. In addition, head and neck cancer patients are often heavy smokers and alcohol drinkers who are prone to poor nutrition. Malnutrition can compromise wound healing, immunological function and increase susceptibility to infection. Nutritional status should be assessed with a dietician and preoperative feeding may be required. This may be done orally, intravenously, via a nasogastric tube, feeding gastrostomy or jejunalostomy or, more commonly a percutaneous gastrostomy (PEG). The type of feed and route of administration should be a joint decision with the dietician. Consideration should be given when postoperative feeding problems may be predicted (i.e. in oral, oropharyngeal, laryngeal surgery and radiotherapy) to request preoperative PEGs.

Dental assessment

Presurgical dental assessment is very important for head and neck cancer patients, as many have high levels of dental neglect and dental anxiety. In these patients, subsequent dental problems are inevitable without effective dental intervention. Assessment by a maxillofacial prosthodontist/dental oncologist should take place ideally prior to any definitive treatment. This is especially important for the dentate patient with oral and oropharyngeal tumours and patients requiring maxillectomy with prosthetic obturation. Definitive decisions regarding a cancer patient’s dental and periodontal disease management are best made prior to definitive surgery, allowing any necessary dental extractions to be undertaken at the same time as the ablative surgery, which in turn gives adequate time for socket healing prior to the commencement of any postoperative radiotherapy. Advice is also useful for patients planned for access mandibulotomy procedures, where the position of the mandibulotomy cut can be discussed, often with agreed sacrifice of a lower incisor tooth. Patients requiring composite reconstruction following segmental mandibulectomy should also be discussed where the choice of composite reconstruction will affect future oral rehabilitation, possibly with the use of dental implants.

Psychological assessment

Head and neck cancer patients not only suffer the burden of suffering a life-threatening disease, but they are often unable to conceal their affliction which frequently affects basic social functions such as eating and swallowing. Furthermore, treatments of the cancer can result in disfigurement and dysfunction. Pretreatment psychosocial evaluation is therefore extremely important in these patients. Factors to consider include smoking habits, alcohol dependence, coping skills, personality disorders, a history of psychiatric illness and substance abuse. The presence of comorbidities and level of social support are also important. Awareness of these factors and the expertise of a psychologist and patient support groups are vital. Pretreatment counselling allows appropriate medical support for alcohol and nicotine withdrawal and to reduce patient anxiety and uncertainty.

RADIOLOGY

Imaging is integral to the assessment of the patient, providing vital information about the primary tumour, neck nodes and distant metastases. The primary role of radiology is not usually one of diagnosis, but is one of accurate staging of the extent and spread of disease. There is an emphasis on those
features which will influence the choice of treatment and where appropriate, in planning the best surgical approach. The areas which radiology should address are illustrated in Box 4.1.

The types of investigation and their appropriate role in the evaluation of different tumour sites are dealt with in Chapter 6, Head and neck pathology, but it is worth commenting on the specific roles of the various modalities.

**Computed tomography**

Computed tomography images reflect tissue density. Intravenous iodinated contrast allows some tumours through their abnormal vascularity to become easier to see, but in general the difference in density between neoplastic tissue and normal head and neck anatomical structures is small. The visualization of tumours is therefore more reliant on changes in morphology and alteration of normal anatomy. CT is good at demonstrating bone detail and this remains a major strength. Modern multislice CT technology provides scanners which are incredibly fast requiring just a few seconds of exposure to acquire a volume of data from which high spatial resolution images in all planes can be reconstructed. Many head and neck cancer patients have difficulty with breathing, swallowing, lying flat and keeping still, and CT may well be the only imaging modality which can be tolerated.

**Magnetic resonance**

Magnetic resonance images reflect tissue biochemistry and are particularly influenced by the presence of protons within the tissues. The images of different weighting provide the means to not only visualize tissues, but also to indicate what the tissue is made of. This is known as tissue characterization. T₁-weighted images carry a great deal of spatial resolution with excellent depiction of detailed anatomy. T₂-weighted images are better at highlighting abnormal tissue. The short tau inversion recovery (STIR) sequence retains this positive attribute of a T₂-weighted image and suppresses all fat signals, leaving all abnormal tissue and tissue with a high water content as high signal. The ability of MR therefore to show abnormal tumour tissue as high signal and normal tissue as low signal in an image creates improved contrast resolution when compared to CT. It is therefore the imaging modality of choice for soft tissue oropharyngeal cancers. Scan times compared to CT are much longer varying from around 2 to 5 minutes during which the patient must keep still. MR will not be suitable for all patients with head and neck cancer.

**Positron emission tomography**

Positron emission tomography (PET)/CT images are maps reflecting levels of glucose metabolism within tissues. A short half-life isotope 16-fluoro-deoxy-glucose is injected intravenously. The PET scanner detects gamma rays caused by interaction of positrons emitted by the isotope with electrons within the tissues. Modern scanners incorporate a CT scanner which coregisters the activity with its exact anatomical location. PET has specific value in evaluating the patient with an unknown primary (Figure 4.5). PET will detect the primary in approximately one-third of cases. It is also valuable in the assessment of suspected recurrence of head and neck cancer. Its value in primary staging and surveillance following treatment is still being assessed.

**Specific uses of imaging**

CT and MRI are the mainstay investigations in the preoperative work up of patients with head and neck cancer. As a general rule, every patient with head and neck cancer will require a preoperative CT or MR scan. Each modality has its own advantages, even within anatomic subsites. For example, a CT scan of a sinus tumour may show erosion of bone throughout the paranasal sinuses and skull base, whereas MRI may clearly delineate extension into the soft tissues of

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**Box 4.1 The role and uses of radiological imaging**

- Site and extent of the primary lesion
- Size of the primary lesion
- Neck node involvement (number of nodes, size, position, fixation)
- Distant metastases
- Detection of synchronous primary tumours
- Confirmation of diagnosis, e.g. glomus tumours
- Baseline and postoperative assessment in tumours that have a high risk of recurrence or recur slowly, i.e. adenoid cystic carcinoma

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**Figure 4.5** Positron emission tomography and computed tomography scan illustrating a large nodal metastasis with a small tonsil primary.
the brain. The decision to use either or both imaging modalities is based on the clinical information required in each particular case.

Imaging of the neck can suggest the presence of nodal metastases even when nodes are not obviously palpable (occult nodes). This occurs in approximately 20 per cent of imaged cases. All imaging modalities rely on nodal size to indicate tumour involvement. Those nodes with a minimum axial diameter of more than 10 mm have a high likelihood of neoplastic involvement with the exception of junctional nodes where a 15 mm measurement is employed. In contrast, some patients present with a node in the neck which is shown to contain carcinoma, but the primary site is not clinically obvious. These patients with a so-called ‘primary of unknown origin’ (also called an ‘occult primary’) should have proper imaging evaluation following a thorough clinical examination. Imaging protocols may differ in institutions depending on availability. Although MRI of the neck is useful, PET CT is particularly invaluable in these cases.

In addition, imaging is principally important when the primary tumour is inaccessible, such as those in the maxillary sinus, the parapharyngeal space and the skull base. The information obtained from CT and MR imaging is for the most part useful in the decision to employ and planning of conservation surgery.

Other imaging modalities have useful specific indications (Chapter 6, Head and neck pathology). Ultrasonography (US) is particularly useful in delineation of thyroid nodules and cervical lymphadenopathy. It is of practical use in the acquisition of cytology specimens in ultrasound-guided fine needle aspiration. Barium swallow is used in the evaluation of some hypopharyngeal and cervical oesophageal tumours. An orthopantomogram can illustrate mandibular invasion, intercurrent dental disease and is useful in planning surgical treatment of oral cavity and oropharyngeal tumours. Isotope bone scan may illustrate local bone invasion in oral cavity and oropharyngeal tumours, and bone metastases in a follicular carcinoma of the thyroid.

Many of the patients with head and neck cancer carry risk factors common to other tumours of the aerodigestive tract and studies have shown that the incidence of synchronous tumours (in particular bronchial carcinoma) is high. Routine chest imaging prior to treatment is therefore mandatory. Patients require at least a reported chest x-ray and many centres now perform CT of the thorax preoperatively. This also allows metastatic disease to be detected.

**ENDOSCOPY**

A patient with a head and neck tumour undergoes endoscopy for the following reasons:

1. To define accurately the position and local extent of the tumour
2. To obtain a biopsy
3. To exclude a second (synchronous) primary tumour
4. To locate an occult primary

Almost all patients require rigid endoscopy under general anaesthesia to allow appropriate assessment and the necessary biopsies to be taken. Radiological investigations to evaluate the primary site should be performed prior to biopsy. This is to avoid the effect of upstaging from oedema caused by biopsy trauma. Very occasionally, an outpatient videolaryngoscopic examination may be all that is possible in certain instances (for example, patients with small tumours biopsied elsewhere and occasionally in elderly patients with significant comorbidity that makes general anaesthetic a risk).

Endoscopy and biopsy should be performed by a senior surgeon and in all cases by the head and neck surgeon responsible for any future procedure. The surgeon should define the limits of the tumour in all directions and relate them to anatomical landmarks. In the oral cavity and oropharynx, it is important to palpate a tumour in addition to inspection. Submucosal spread may be greater than the apparent mucosal disease and invasion by the tumour into local structures may be perceptible. In the larynx and pharynx, it is advisable to have a panoramic macroscopic view before going on to use a microscope with a 400 mm lens. In addition, a 0° fiberoptic and 30° and 70° angled fiberoptic endoscopes help assess mucosal spread at the primary site and to evaluate extension into the ventricle of the larynx and the subglottis.

A biopsy should be taken from the viable part of the tumour, i.e. not from its centre, which may be necrotic, and not from its edge, which may only show dysplasia. An appropriate piece is taken with cutting forceps that do not crush the tissue. This is placed directly into formalin: it should not be poked with needles or put on a swab as these manoeuvres may distort the tissue. A biopsy of a tumour in the mouth is best taken with a knife; if lymphoma is suspected, the conventional method was to send half the specimen fresh and half in formalin. However, new immunological staining techniques now mean that fresh specimens are no longer required, but this will depend on local laboratory facilities.

Routine panendoscopy or triple endoscopy (laryngoscopy combined with oesophagoscopie and bronchoscopy) is contentious. The aim is to exclude a second (synchronous) primary tumour elsewhere in the aerodigestive tract. Proponents are of the view that these procedures require little time, are of low morbidity and are easily performed at the time of endoscopy for the primary site. A large meta-analysis of prospective studies found a small advantage to panendoscopy in the detection of primary tumours. Opponents point out that the appropriate use of symptom-directed investigations in addition to routine chest radiography have a similar detection rate compared with screening endoscopy and avoid unnecessary risk and expense in asymptomatic patients.

Therefore, panendoscopy is only recommended for symptomatic patients, patients with primary tumours known to have a significant risk of a synchronous primary tumour (e.g. oropharynx), and patients in whom the preliminary radiological studies have identified a suspicious abnormality.

Patients who present with an unknown primary tumour may be subsequently diagnosed by MRI or PET CT imaging (Figure 4.4). However, those patients in whom no obvious primary is apparent may require panendoscopy and biopsy of the sites which are known to be high risk (ipsilateral tonsil, nasopharynx, ipsilateral tongue base, piriform fossa).

The operative findings should be clearly written in the case file. It is extremely important to provide an accurate account of the exact anatomical location of the tumour. It is
essential that the invasion of the tumour into local structures is identified. Appreciation of potential treatment options in this context will increase awareness of the significance of getting this right. A drawing is made of the operative findings or on to a preprinted set of illustrations. Multiple photographs should be taken and also placed in the case file. It is important to think in terms of TNM staging, but to avoid consigning a stage at this time.

PATHOLOGY

It is important to have a relationship with the head and neck pathologist, to discuss cases regularly and to record details in an agreed and systematic manner. Specimens should be pinned out and details relating to the primary and nodal disease recorded accordingly.

Pathological tumour size should be recorded along with tumour thickness, which is important in tumours, such as the oral cavity and melanoma. The margins relating to microscopic resection should be commented on. Multiplicity of the tumours should also be recorded, along with the presence or absence of perineural, vascular, lymphatic and bone invasion. Differentiated thyroid tumours should be reported as thyroglobulin positive or negative.

Cervical lymph nodes should be recorded on a diagram relating to the levels involved and the report should include which nodes were sampled, the number of nodes sampled, the number of nodes which contained tumour, their pathological site and whether or not there was extracapsular spread. This report should form part of a minimum data set. The allocation of a pN0 classification to a neck dissection must satisfy the following criteria. Histological examination of a selective neck dissection specimen will ordinarily include six or more lymph nodes, while histological examination of a radical or modified radical neck dissection will ordinarily include ten or more lymph nodes.1, 2

It is important to record the type of growth (histology) along with the pathological TNM stage and overall stage. Histological differentiation of the tumour is a factor included in the UICC and AJC staging systems (Table 4.3).3, 4

The histological grading of squamous cell carcinoma represents estimation by the pathologist of the expected biologic behaviour of the neoplasm. It has been suggested that such information, in conjunction with other characteristics of the primary tumour, would be useful in the rational approach to therapy.14 Others have reserved doubts as to the validity of the method because of its subjective nature.15, 16

In a systematic review of 3294 patients, it was found that 46 per cent of patients with poorly differentiated tumours had a nodal metastasis at presentation compared with only 28 per cent differentiated tumours. Distant metastases at presentation were found in 3.4 per cent of poorly differentiated tumours, compared with 1.8 per cent of well-differentiated tumours. Primary and nodal recurrence rates rose for poorly differentiated tumours and survival fell significantly for poorly differentiated tumours.17 In another retrospective review of over 1000 patients, grade and distant metastases were considered. It was found that patients with well-differentiated tumours are at low risk of metastases and patients with poorly differentiated tumours are at high risk of distant metastases. It was suggested they should be considered for systemic chemotherapy.18

Although grading is a common practice, it has not evolved as an important factor in planning therapeutic strategies. It should be used in conjunction with other pathological and stage parameters in providing an overall picture of the tumour’s aggressiveness and remains an adjunctive part of the TNM system.3, 4

Table 4.3 Grading based on differentiation.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade of differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade of differentiation cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

THE MULTIDISCIPLINARY TEAM MEETING

Assessment is not merely a process of a surgeon examining the patient, arranging scans and taking a biopsy of a tumour. It is advisable to obtain as many opinions as possible and not to rush in with a treatment. A multidisciplinary approach should provide each patient with a thorough and well-organized evaluation and treatment plan (Chapter 47, Multidisciplinary team working).

In the United Kingdom, there is legislation through the Improving Outcomes Guidance document that every patient with a diagnosis of head and neck cancer is discussed at a multidisciplinary team meeting (MDTM).19 The core team should include a head and neck surgeon, oncologist, radiologist, pathologist, clinical nurse specialist, dietitian, speech therapist and psychologist. The meetings should be held on a weekly basis and serve a population of approximately one million patients. There should be facility for discussion of base of skull tumours (neurosurgeons will be present) and thyroid tumours (endocrinology and nuclear medicine physicians present) either within the head and neck multidisciplinary team (MDT) or as a separate meeting.

It is important for each member of the team to have a fundamental knowledge of each other’s role and expertise. Awareness of the combined capability and experience available within the MDT is an essential element of the head and neck surgeon’s role. However, every member of the MDT should harness this easily accessible facility for their patients.

STAGING OF CANCER

Staging is the process of subdivision of cases of cancer into groups in which the behaviour may be similar. Staging of head and neck cancer is a system designed to express the relative severity, or extent, of the disease. It is meant to facilitate an estimation of prognosis and provide useful information for treatment decisions. Classification by anatomical extent of the disease as determined clinically and
histopathologically (when possible) is the one that the TNM system primarily uses.

The concept is that an orderly progression of disease takes place with enlargement of and invasion by the primary tumour (T) followed by spread to the regional lymph nodes (N) and eventually spread beyond these nodes to distant metastatic sites (M). The stage at diagnosis in the life history of an individual cancer is numerically assigned a TNM classification. These individual TNM classifications are then assembled into four stage groups (stages I–IV), each with similar survival outcomes based on the observation that better survival is anticipated for cancers with less extension.

**Aims of the TNM staging system**

Cancer is a heterogeneous disease, or rather group of diseases, and the natural history and response to treatment can be both wide and varied. So there are obvious advantages in a staging system for head and neck squamous cell carcinoma (HNSCC). It is important for both clinical and therapeutic research and as an acceptable and reproducible method of staging all sites within the region. It is mandatory to allow any meaningful comparison to be made between different centres, both nationally and internationally. The goals of any cancer staging system are therefore, by definition, far reaching and multiple in nature. The system should act as a dictionary, allowing individual physicians and surgeons to compare and exchange information using language and vocabulary that they can all understand (Box 4.2).

It is worth looking at a few of these points in more detail. First and foremost, staging acts as a guide to the appropriate treatment. The question, ‘How should a patient with carcinoma of the larynx be treated?’ cannot be answered without reference to staging. A patient with a small tumour confined to the true vocal cord which remains mobile can be successfully treated either by surgery or by irradiation with voice preservation, but a patient with an advanced transglottic carcinoma, causing airway obstruction and invading the thyroid cartilage with nodal metastases, usually requires laryngectomy and neck dissection.

Second, the stage of a tumour acts as a guide to prognosis. Accurate prognosis is important, not only to satisfy a patient who wants to know the likelihood of successful treatment, but also to ensure the equivalence of groups in clinical trials. For example, suppose a new form of treatment is being compared with standard practice in the treatment of oropharyngeal carcinoma. If there arises, by chance, a preponderance of more advanced cases in the experimental arm, the survival rate in the experimental arm may be greater, even if in reality there is no difference between the treatments, stage by stage. Prerandomization stratification by stage will prevent this source of error.

Staging also permits more reliable comparison of results between centres by allowing an estimate of case mix. For example, if hospital A publishes better survival figures for laryngeal cancer, it may be assumed that it is a better hospital offering better treatment than other hospitals. Yet, different hospitals serve different populations and consequently the pattern of cancer cases they see may be different. The observed discrepancy may therefore result from the fact that hospital B serves a large population of socially disadvantaged patients who present late with advanced disease. If survival figures are published separately for each stage, it may be found that there is no difference between hospital A and hospital B or even that truly better results from hospital B have been masked by the large proportion of poor prognostic cases treated there.

Finally, staging allows a more reliable examination of reasons behind time trends. For example, the incidence of both malignant melanoma and testicular cancer is increasing in Scotland, yet the proportion of patients dying from these diseases is diminishing. It might be assumed that the improved survival from melanoma has been caused by the development of effective systemic therapy, as is the case for testicular tumours. In fact, examination of the distribution of stages at presentation shows that more cases of melanoma are now being diagnosed early as a result of a public education campaign, but the prognosis of advanced cases has not changed.

**TNM staging nomenclature**

Over the last decade, the two principal staging classifications for head and neck cancer, those of the AJCC and the UICC, have undergone a convergent evolution and are now, to all intents and purposes, identical.

Details can be found in the current UICC handbook. For each primary site in the head and neck, the factors taken into account in the stage classification are described in the appropriate chapter of the UICC handbook, to which every head and neck surgeon should have access. The following general definitions apply to all sites.

The TNM system for describing the anatomical extent of head and neck cancer is based on the assessment of three components, namely T, the extent of the primary tumour, N, the presence or absence and extent of regional lymph-node metastases and M, the presence or absence of distant metastases. All cases are identified by T, N and M categories, which must be accurately determined and recorded before treatment is commenced. The system is confined to carcinoma for all sites and malignancy must be confirmed by histological examination. Two classifications have been described for each head and neck site:

1. Clinical classification (pretreatment clinical classification, designated cTNM) is evidence acquired before primary treatment. It is based on information available prior to first definitive treatment. The clinical stage is essential to selecting and evaluating primary therapy. The UICC classification suggests that for each site the specific methods of
investigation available for TNM classifications should be listed. These include mandatory methods, such as clinical examination and biopsy, which should always be employed to establish the extent of the tumour, and additional methods, such as conventional radiography, along with other special investigations. For cTNM, traditional staging demands that certain prerequisite patient assessment be performed and its use reflects the level of certainty according to the particular diagnostic method used.

2. Pathological classification (postsurgical cytology). The pTNM classification is based on evidence acquired before treatment, supplemented or modified by additional information acquired either surgically or pathologically. Further information regarding the primary lesion may be recorded under the headings ‘G’ for histopathological grading, ‘L’ for lymphatic invasion and ‘V’ for venous invasion. The presence or absence of residual tumour after treatment may be described by the symbol ‘R’. The pathological stage gives information for estimating prognosis and calculating end results.

Within the TNM classification, the oral cavity, pharynx, larynx, maxillary sinus, salivary and thyroid glands are all listed as primary sites, the pharynx being subdivided by convention into the nasopharynx, oropharynx and hypopharynx. The cervical oesophagus is listed as a subsite. Multiple tumours should be classified independently and in the case of multiple synchronous tumours in one organ, the tumour with the highest T category should be classified and the multiplicity or number of tumours indicated in parentheses.

Each site is described under a TNM heading (mandatory) and a cTNM and pTNM classification (optional). After being assigned various TNM categories, patients are grouped into a number of clinical stages (see Table 4.6). Classification is distinguished from staging, which is the grouping of cancers with similar crude survival rates.

The C-factor, or certainty factor, reflects the validity of classification according to the diagnostic methods employed (C1–C5). C1 would be evidence from standard diagnostic means, whereas C5 is evidence from autopsy. Generally speaking, pretherapeutic clinical staging of head and neck cancers should be based on a C2 factor. That would be evidence obtained by special diagnostic means, e.g. radiographic imaging (e.g. CT, MRI or US), endoscopy, biopsy and cytology.

Method of staging

The aim is to define in each patient all of the factors relevant to the natural history and outcome of the relevant disease, thereby enabling a patient with cancer to be grouped with other similar cases. The sex and age of the patient, the duration and severity of symptoms and signs, and the presence and severity of intercurrent disease should all be documented.

CT and MRI are now established as the mainstay investigations in the preoperative work-up of patients with head and neck cancer. Scans to evaluate the primary site should be performed prior to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma. There is a natural desire to confer a stage on the tumour at presentation in the clinic and certainly after endoscopy. This should be avoided. It is better to rely on descriptive text to avoid changing the stage as more information becomes available. The clinical (pretreatment) classification (cTNM) based on examination, imaging, endoscopy and biopsy should be clearly documented in the case file only when all of the above information is collated. This will improve the chance that at least a certainty factor of 2 is applied. The UICC book should be available in every theatre and clinic to assist in applying the correct stage. Once the clinical stage is assigned, it should not be changed on the basis of subsequent information. Clinical staging ends if a decision is made not to treat the patient.

Most of the reasons for staging do not immediately appear to benefit the individual patient and so it might be tempting for the busy surgeon to make no attempt at the staging process beyond a brief assessment for the purposes of choosing either treatment A or B, or worse still for them to assign hurriedly a wholly inaccurate stage. Yet, if the biology of cancer is to be more fully understood and if treatments are to be improved, it is imperative that staging should be carried out fully and accurately on every patient.

While assessment of the tumour, nodes and metastases is usually sufficient for the staging purposes, other factors which are sometimes taken into account include the histological differentiation or grade of the tumour, along with the patient’s age and sex, for example, in cases of soft-tissue sarcoma and differentiated thyroid carcinoma. For tumours such as lymphoma, which do not follow an orderly progression from primary tumour to nodal involvement and then distant metastases, special staging systems have been devised.

Even for epidermoid cancer, there are a variety of different staging classifications. Although these have similar aims and use similar data, the systems differ in important regards and therefore lead to groupings which may not be directly comparable and may thus preclude a meaningful exchange of data not only between centres but also between countries. The use of ‘alternative systems’ is therefore discouraged, other than for research purposes, and then only when correlation to TNM staging is available.

**PRIMARY TUMOUR (T) STAGING**

The extent of primary tumour is indicated by the suffixes 1, 2, 3 or 4, representing progressively more advanced disease. Increase in size is usually the sole criterion for categories 1, 2 and 3, while 4 often indicates direct extension (spread by continuity and contiguity) from outside the primary site, or invasion of underlying bone or cartilage (Table 4.4). Other criteria are applied in special circumstances, such as fixation of the vocal cord in laryngeal carcinoma and the degree of extrapharyngeal extension in nasopharyngeal carcinoma. A uniform description of advanced tumours as T4a (resectable) and T4b (unresectable) has been introduced to define the concept of inoperable fixation.

T1 is used when there is no evidence of a primary tumour, T1, used when the primary is non-invasive or carcinoma in
situ and T\textsubscript{x} when for some reason the extent of the primary tumour cannot be assessed. A frequent error is in the assignment of stage for a primary of unknown origin. This should be T\textsubscript{0} and not T\textsubscript{x} as is sometimes given.

CERVICAL NODE (N) STAGING

The presence of cervical lymph node metastases remains the most significant prognostic indicator of survival and disease recurrence in squamous cell carcinoma of the head and neck. Lymph nodes are described as ipsilateral, bilateral, contralateral or midline; they may be single or multiple and are measured by size, number and anatomical location (Table 4.5). During clinical examination, the actual size of the nodal mass should be measured and allowance made for the intervening soft tissues.\textsuperscript{5} It is well recognized that most masses over 3 cm in diameter are not single nodes, but represent confluent nodes or tumour in the soft-tissue compartments of the neck. Midline nodes are considered ipsilateral nodes, except in the thyroid. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.\textsuperscript{3, 4}

Imaging for node detection and delineation is advisable if the neck is being scanned as part of the evaluation of the primary tumour, if there is a high chance of occult disease (e.g. supraglottic primary), to assess the extent of nodal disease, to define any deep nodal fixation, or if clinical detection is difficult because of a short fat or previously irradiated neck.

Lymph nodes are subdivided into specific anatomic sites and grouped into seven levels for ease of description (Table 4.2). The pattern of lymphatic drainage varies for different anatomic sites. However, the location of the lymph node metastases has prognostic significance. Survival is significantly worse when metastases involve lymph nodes beyond the first echelon of lymphatic drainage.\textsuperscript{20} It is particularly poor for lymph nodes in the lower regions of the neck, i.e. level IV and level V (supraclavicular area).

The seventh edition of the UICC booklet alludes to the importance of levels in some sites, but does not present any definitions. The AJCC Cancer staging manual gives a much more thorough account. It recommends that each N staging category be recorded to show, in addition to the established parameters, whether the nodes involved are located in the upper (U) or lower (L) regions of the neck, depending on their location above or below the lower border of the thyroid cartilage.\textsuperscript{3, 4}

Under the current joint classification, the clinical findings regarding regional cervical lymphadenopathy are defined for each site independent of the primary tumour. The definitions of the N categories for all head and neck sites, except nasopharynx and thyroid, are the same. The natural history and response to treatment of cervical nodal metastases from nasopharynx are different, in terms of their impact on prognosis, so they justify a different N classification. Regional lymph node metastases from well-differentiated thyroid cancer do not significantly affect the ultimate prognosis and therefore also justify a unique system.

METASTASES (M) STAGING

The presence or absence of distant metastases is indicated by M\textsubscript{1} or M\textsubscript{0}, respectively. M\textsubscript{3} can be subdivided further to include the anatomical area involved, such as pulmonary (PUL), hepatic (HEP) or brain (BRA).

The role of imaging in confirmation of metastatic disease status has already been discussed. While it would be inadvisable to contemplate major surgery before excluding the presence of distant metastases, in practice very few patients with squamous cell carcinoma have disease outside the head
and neck at presentation. The converse situation, of a secondary lesion in the head and neck, should be considered when adenocarcinoma occurs in the cervical lymph nodes or salivary glands. A primary lesion particularly in the breast, bowel or chest should then be excluded.

**Stage grouping**

A tumour with four degrees of T, three degrees of N and two degrees of M will have 24 potential TNM categories. In head and neck cancer, with subdivision of T stage (at least six options) and N stage (six options) there are potentially 48 TNM categories (and more depending on further subdivision of T stage at individual sites). This is clearly too many for easy use. Even in the largest reported patient series, there will be some combinations with too few patients for meaningful comparison. It has therefore been felt necessary to condense these into a convenient number of TNM stage groups (Table 4.6). The grouping adopted is designed to ensure, as far as possible, that each group is more or less homogeneous in respect of survival; in addition, that the survival rates of these groups for each cancer site are distinctive. Carcinoma **in situ** is categorized as stage 0; cases with distant metastasis as stage IV. The exception to this grouping is for thyroid and nasopharyngeal carcinoma (Chapter 23, Surgical management of differentiated thyroid cancer and Chapter 30, Pharynx: nasopharynx, respectively).

Advanced tumours (stage IV) have been divided into three categories: stage IVA, advanced resectable disease; stage IVB, advanced unresectable disease; and stage IVC, advanced distant metastatic disease.

A patient with a primary of unknown origin (T0) will be staged according to the N status, i.e. stage III or IV disease. The importance of carefully excluding a primary site is already discussed and the implications of its position will have an effect on prognosis in this subgroup of patients.

**LIMITATIONS OF T STAGING**

The TNM system provides head and neck surgeons with a common means of communication that is clinically orientated and based on pretreatment diagnostic studies. No one system is perfect and the criticisms that were aimed at the old classifications focused on the numerous subcategories that contained so few cases per category that statistical conclusions could not be drawn. In addition, there was lack of agreement on anatomical boundaries, the staging of cervical lymphadenopathy and the fact that host tumour responses and histopathological findings were not taken into account. The main limitations are as follows:

- crude system;
- tumour size not consistently related to prognosis;
- debatable anatomical boundaries;
- can be difficult to accurately assess clinical extent;
- inconsistencies;
- omissions.

For the majority of sites in the head and neck, emphasis is placed on tumour size. It is however, well recognized that T stage alone is of limited prognostic significance in many head and neck carcinomas. It is a significant factor in the presence of nodes on presentation. Patients with larger tumours are more likely to have nodes than those with smaller tumours.

In carcinoma of the larynx, the poorer prognosis with increased T stage is explained by the increasing propensity to nodal metastases with larger tumours. If nodal metastases are removed as a confounding factor, then T stage per se does not influence prognosis.

Tumours of the larynx are classified according to the number of anatomical surfaces involved, rather than size. This has led to a number of problems. For example, a large 3 cm tumour of the supraglottis may still remain T1, whereas in the glottis this will almost certainly be a T2. This mitigates against supraglottic tumours in terms of outcome. In addition, depth of invasion is not measured, but is of prognostic and therapeutic importance. For example, a superficial tumour of the vocal cord mucosa would be T1a. The same tumour may be deeply infiltrating into the vocalis muscle and yet the stage will still remain T1a. These tumours of the same stage would require different resections if laser was chosen as the modality of treatment. A further classification system has been proposed based on the type of cordectomies in this situation.

Tumours of the hypopharynx are classified in terms of both their size and anatomical extent. In the past, the anatomical boundaries of the hypopharynx have been contentious, and it is occasionally difficult to be certain of the exact origin of some of the larger tumours. The dual listing of the aryepiglottic fold in both the supraglottis and hypopharynx (hypopharyngeal aspect of the aryepiglottic fold) sites particularly invokes a problem trying to classify the site of origin in some situations.

In the oral cavity and particularly the oropharynx, the size of the tumour is not always easily measured. There is little difficulty in defining a T1 or T4 tumour, but problems can occur when the tumour measures between 1.5 and 3 cm. Furthermore, increasing severity with a T4 tumour is reflected in deep invasion into muscle, bone or adjacent structures. Bony invasion of the mandible demonstrated radiographically is classified as T4 disease. However bony erosion is not easily defined. The 2 cm lesion in the anterior floor of the mouth that involves the alveolar ridge and is adherent to the periosteum will not necessarily demonstrate bony erosion on radiographic evaluation. Most surgeons agree that the underlying bone should be included in the surgical resection (either a rim or complete resection) and therefore T2 and T4 disease may require essentially the same treatment.

A similar problem is encountered in determining the depth of invasion of lesions into the soft tissue of the floor of the mouth. Superficial invasion of the sublingual area as opposed to invasion of the mylohyoid muscle can be subtle. There is then a reliance on the predictive power of radiographic modalities including CT and MRI. Depth of invasion of lesions of the floor of mouth has been shown to be of prognostic significance and this is similarly difficult to assess by either clinical or radiographic means.

Further confusion relating to prognostic staging of primary disease surrounds the fact that bony involvement of the medial or inferior walls of the maxillary sinus receive only a T2 classification, but when oral carcinoma involves the antrum (erosion of the inferior wall of the sinus), the classification is T4a. This apparent disparity is explained by the
discrepancy in behaviour of the two separate bone involvements and subsequent specific behaviour of these diseases.

There is no mention of the cervical trachea as a subsite within the current lung staging system which is interesting as it was included in previous UICC and AJCC manuals. The reason for its exclusion is that there is currently too little information on outcome to construct a realistic staging system. In addition, there is no mention in either system of a TNM classification for carcinoma of the external auditory meatus or middle ear, although one has been proposed in the past.

**LIMITATIONS OF N STAGING**

There is approximately a 50 per cent reduction in five-year survival rate with the development of cervical lymph node metastases in patients with squamous cell carcinoma of the head and neck. Although the presence of cervical node metastases is of undoubted importance, there are still some fundamental and basic difficulties in classifying node status.

The main criticisms are as follows:

- observer variability (presence of nodal disease and size measurement);
- no inclusion of immunological status;
- importance of extracapsular spread;
- N2 (bilateral involvement) implies better prognosis than N3 (large nodes greater than 6 cm).

The reliability of clinical examination of nodes is contentious with studies showing that observers disagree on their presence. Furthermore, palpable nodes do not always harbour metastases. During clinical examination, the size of the node should be measured with calipers, and allowance made for the intervening soft tissues. There is considerable observer error in estimating the size of the node by palpation alone without a measuring device. Most masses over the size of 3 cm in diameter are not single nodes, but will represent confluent nodes or tumour in the soft tissue compartments of the neck.

One of the main criticisms over the last decade has been the failure of the TNM system to provide a description of the level of nodal involvement. Various studies have confirmed the importance of this parameter and now it is included in the current classification. Although the AJCC manual gives a detailed description of lymph node levels, the inclusion is merely that a designation of ‘U’ or ‘L’ may be used to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). It is advised that specific lymph node level (as well as U/L category) be documented in the pN classification.

In contrast to clinical staging, when size is a criterion for pN classification, measurement is made of the metastasis, not the entire lymph node. Although there is an instruction to identify extracapsular nodal spread, it is still not a quantitative factor in the pN classification.

There have been many suggestions for other pathological factors to be included in the pathological stage.

Numerous attempts have been made to correlate the microscopic appearance of a tumour with its biological behaviour and patient prognosis. Although studies have found a higher incidence of cervical lymph node metastases in poorly differentiated tumours, the single most important pathological feature correlating with cervical node metastases appears to be the tumour-host interface. Tumours with infiltrating margins have a poorer prognosis than those with pushing edges. Vascular and nerve sheath invasion also increases the probability of lymph-node metastases. These observations prompted multifactorial analysis of the cell population (structure, differentiation, nuclear polymorphism, mitosis) and of the tumour-host relationship (mode of invasion, stage of invasion, vascular invasion, cellular response).

While some studies report a close correlation between histological malignancy scores and the outcome of
They more or less all claim that their system is an improvement on any other. Lydiatt et al. provide a review of these. They observe that one of the main disadvantages is that the systems are not intuitive and would require a chart for most clinicians to stage their patients. Analyses comparing the authors’ system to other systems including the UICC/AJCC are flawed, because each one is not independent of the authors’ system. Therefore, because the system was created from the database, it would naturally perform well. The true test is whether the results from an independent database would yield similar results.

The five major sites of the head and neck (oral cavity, oropharynx, larynx, hypopharynx and paranasal sinuses) share the same system. Arguably they should be independent of each other. One advantage of an independent system is better groupings within each site. Different systems are in use for the nasopharynx and thyroid, which are considered to be sufficiently different with respect to risk factors, behaviour and treatment. In their rebuttal of these views, the AJCC Task Force maintains the opinion that independent systems would create problems for clinicians and investigators not remembering which group was staged by which system. They are of the view that any new system should be comprehensive and easily applicable to all the major sites.

**CONCLUSIONS**

The current TNM system relies on morphology of the tumour (anatomical site and extent of disease) with little or no attention given to patient factors. However, the literature does suggest that symptom severity and comorbidity have a significant impact on outcomes. It is therefore recommended that these data be recorded.

Definitions of TNM categories may be altered or expanded for clinical or research purposes as long as the basic definitions are recorded and not changed. Changes in the TNM classification should and will only occur, based on the appropriate collection, presentation and analysis of data, in the forum of the UICC and AJCC.

All of the above inconsistencies make the head and neck a complicated region in which to apply a single concept of classification. However, the end result embraces the orderly description of disease with increasing size and extent and one which lends itself to incorporation into a staging system, so that comparisons of treatment results might be meaningful. The current system, while fallible, is founded on sound principles and represents the combined work and experience of many physicians and surgeons who have spent years treating head and neck cancer. Any shortcomings or criticism of the system must reflect the complexity of the disease rather than any actual deficiencies within the staging classification.

In recent years, the advent of sophisticated imaging technology has made assessment much more accurate. Cases are often demonstrated to be more extensive than is clinically apparent, and are accordingly put into higher stages. Table 4.7, shows the results of treatment for a form of cancer, as staged by an older, less accurate clinical method and using modern sophisticated imaging techniques. The cure rate for each stage of the disease is higher in those staged with the more modern technique, yet the overall cure rate for the
entire cohort of patients, at 46 per cent, is identical whichever staging system is used. This illustrates the phenomenon of stage migration, where apparently superior results are produced by the upstaging of patients. This is called ‘stage migration’ or creep, and is sometimes referred to as the ‘Will Rogers’ phenomenon.' Will Rogers was an American wit from Oklahoma who stated that every time an Oklahoma man moves to California, the average IQ of both states improves.

**FOLLOW-UP POLICIES**

Follow up of patients treated for cancer is performed for several reasons which are of different importance. Some of these are for the direct benefit of individual patients, whereas others are for the benefit of future cohorts of patients. Possible reasons for follow up are given below:

- To monitor the primary tumour site and nodal areas after completion of initial radical therapy. This has the aim of detecting residual disease or relapse at an early stage when it is still possible to institute potentially curative salvage treatment.
- To ensure that the patient is being successfully rehabilitated with regard, for example, to speech and swallowing after radical treatments which may have interfered with normal head and neck physiology.
- To reassure the patient that the team which treated them still cares about their progress and wants to know if any problems develop. Patients can be educated about which symptoms should lead to clinical review earlier than planned. Advice given about secondary prevention strategies, such as smoking cessation, can be reinforced and monitored.
- To prevent treatable morbidity, such as dental decay and hypothyroidism, before it becomes clinically significant by the monitoring and early detection of problems.
- To obtain accurate data about important outcome measures for the purposes of medical audit and clinical governance; these include local and regional control, treatment-related morbidity, second malignant neoplasms, functional impairment and survival.
- To provide training opportunities for trainees in surgery and oncology and the professions allied to medicine.

In patients with head and neck squamous carcinoma, the appropriate frequency of routine follow up varies, depending on several of the factors mentioned above, but principally on the likelihood of relapse and the possibility of salvage treatment. For example, a patient with T2N0 cancer of the anterior tongue treated with brachytherapy alone, without prophylactic neck irradiation or surgery, has a significant likelihood of nodal relapse which may be subsequently cured by neck dissection if detected early, but which might become inoperable if there is a three-month delay. Similarly, a patient with early laryngeal cancer treated by radiotherapy alone requires frequent follow up, so that salvage surgery can be performed without delay in the event of local failure.

In such patients, follow up should be monthly in the first year after completion of treatment, two-monthly in the second year, three-monthly in the third year, then six-monthly to five years (Table 4.8). Subsequently, annual follow up may be deemed appropriate, but in many cases discharge to the care of the general practitioner is a reasonable alternative.

In contrast, a patient who has undergone composite resection of a T2N0 oropharyngeal cancer with postoperative radiotherapy to the primary site and both sides of the neck requires less frequent follow up to detect relapse, as there is very little chance of effective salvage. Nonetheless, follow up is still necessary to monitor deglutition, nutrition and dentition. In this case, an appropriate follow-up schedule might be six-weekly for the first year, three-monthly for the second year and then six-monthly to five years, with optional annual follow up after that.

Different follow-up plans may be more appropriate for patients with rare tumours, such as lymphoma or sarcoma. In patients who have a thyroid cancer, follow up is usually

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<th>Time after treatment</th>
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Table 4.7  Comparison of results of treatment for cancer using an old and a new staging system.

Table 4.8  Follow-up frequency after treatment for squamous cancer of the head and neck.
lifelong as recurrences can occur many years following initial treatment.

**KEY LEARNING POINTS**

- The sex and age of the patient, the duration and severity of symptoms and signs, and the presence and severity of intercurrent disease should all be documented.
- Assessment by endoscopy and biopsy should be performed by a senior surgeon and in all cases by the head and neck surgeon responsible for any future procedure.
- Radiological investigations to evaluate the primary site should be performed prior to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma.
- Staging of head and neck cancer is a system designed to express the relative severity, or extent, of the disease. It is meant to facilitate an estimation of prognosis and provide useful information for treatment decisions. Classification by anatomical extent of head and neck cancer as determined clinically and histopathologically is the TNM system.
- The UICC and AJCC booklets provide a summary and cornerstone for accurate staging.
- The clinical (pretreatment) classification (cTNM) based on examination, imaging, endoscopy and biopsy should be clearly documented in the case file only when all the information is collated.
- Individual TNM classifications should be assembled into four groups (stages I–IV), each with similar survival outcomes.
- The AJCC or UICC book should be available in every theatre, MDT meeting and clinic to assist in applying the correct stage.

**REFERENCES**


51. Lydiatt WM, Shah JP, Hoffman HT. AJCC stage groupings for head and neck cancer: should we look at alternatives?


INTRODUCTION

Radiology is a continually evolving medical speciality which has witnessed many exciting advances since the discovery of x-rays more than 100 years ago, resulting in the numerous imaging modalities now available. In the last ten years alone, we have witnessed major advances in imaging technology with the introduction of high resolution and 3D ultrasound (US), multidetector computed tomography (MDCT), new contrast agents in magnetic resonance imaging (MRI) and the advent of positron emission tomography (PET) in clinical practice. In addition, the role of the radiologist is evolving, particularly as there is increased awareness now that the management of the patient with cancer is best done within a multidisciplinary team comprising surgeons, oncologists, pathologists, radiologists and all the specialist support services.

Imaging is routinely required at the time of presentation for diagnostic and staging purposes in most oncology patients. It has a major role in ascertaining whether tumours are operable, and in patients with tumours more appropriately treated with radiotherapy and/or chemotherapy, it has a role in evaluating the clinical response. It may also be required to answer a specific clinical question in an individual patient.

The imaging modality of choice usually depends on the clinical scenario. One should bear in mind that all imaging techniques utilizing ionizing radiation, including plain films, fluoroscopy, computed tomography (CT) and nuclear medicine investigations carry with them a potential increased lifetime risk of developing cancer. Data from the years 1991–6 suggest that about 0.6 per cent of the cumulative risk of cancer to age 75 years in the UK could be attributable to diagnostic x-rays. However, the average annual radiation dose to the general public from all sources is 2.5 mSv, of which medical exposure only contributes 15 per cent.

In young patients, and those patients who may potentially undergo multiple examinations or extended follow up, it may be more appropriate to choose magnetic resonance imaging or ultrasound as the imaging modality.

Knowledge of the normal anatomy as displayed by cross-sectional imaging techniques is the key to understanding the imaging of head and neck cancer. Although some aspects of the disease, such as the mucosal extent of primary head and neck cancers, are far better assessed by the clinician, the deep spread can often only be assessed with CT or MRI.
PLAIN FILMS

A chest radiograph (chest x-ray) is used as part of the pre-anaesthetic assessment in head and neck cancer patients, but should also be performed to exclude coexistent pathology, such as a bronchogenic carcinoma, and to assess for the presence of pulmonary metastatic disease. However, the sensitivity of a chest x-ray in detecting synchronous primary or metastatic lung tumours is much less than the sensitivity of computed tomography. Thus, if the primary tumour and nodal status place the patient at high risk for pulmonary metastases, then some authors recommend preoperative chest CT in addition.3

A retrosternal thyroid goitre may be apparent on the chest radiograph as a superior mediastinal mass which displaces or narrows the trachea. The trachea may also become stenotic following percutaneous tracheostomy insertion. Although additional thoracic inlet views can be acquired to further assess the degree of narrowing, evaluation with multiplanar computed tomography and respiratory flow-volume loops have been shown to be more sensitive than plain films.6

An orthopantomogram (OPG) is often performed to assess the dentition. It also evaluates periodontal pathology and focal mandibular lesions (Figure 5.1). In patients with oral cancers, particularly those located in the retromolar trigone, it can be useful to assess the extent of mandibular bone involvement (Figure 5.2). However, thin section CT is superior for confirming subtle bone destruction.7

CONTRAST STUDIES (FLUOROSCOPY)

The barium swallow examines the oesophagus. Double-contrast films are used to demonstrate morphology and mucosal lesions, and the addition of bread to the barium allows assessment of motility. Isotonic iodinated water soluble contrast agent should be used in preference to barium when aspiration is present or suspected, or when anastomoses are being assessed postoperatively, since barium aspiration can be fatal.

The pharynx and upper oesophagus are examined using videofluoroscopy or cinel fluoroscopy. Contrast examinations are able to evaluate the act of swallowing by analysing the following features:

- tongue movement;
- soft palate elevation;
- epiglottic tilt;
- laryngeal closure;
- pharyngo-oesophageal segment (cricopharyngeal opening) and pharyngeal peristalsis.

Malignant pharyngeal and oesophageal tumours can be diagnosed by their irregular narrowing of the lumen associated with mucosal destruction, ulceration and shouldering. The length of the tumour can be measured, which is important for staging hypopharyngeal tumours and planning operative intervention for possible free jejunal transfer, as well as radiotherapy field planning. Previous radiotherapy, caustic ingestion and connective tissue disorders can cause smooth oesophageal narrowing.

ULTRASOUND

Ultrasound is an imaging modality utilizing high frequency sound. The probes (transducers) contain piezoelectric crystals which generate pulsed beams of sound in response to either mechanical or electrical stimuli. The crystals also receive the reflected beam which has been attenuated and refracted by tissue interfaces. Recent development in technology, particularly the evolution of high resolution US, has resulted in a greater role for ultrasound in evaluating the neck.

Ultrasound is ideal for examining superficial structures in the neck, but due to attenuation of the sound beam as it passes through the tissues, examination of large necks and deep structures, such as the deep lobe of the parotid, is more difficult. In addition, the ultrasound beam will not readily penetrate bone, cartilage and gas, making it an inappropriate technique for local staging of many primary head and neck cancers.

Ultrasound is extremely useful in differentiating solid from cystic mass lesions, and can detect calcification. An assessment can be made of the size, margin and consistency of a neck mass. Evaluation of the internal structure and the margins of neck nodes will facilitate differentiation between benign and malignant nodes.
Colour flow and Doppler ultrasound can be used to evaluate the vessels within the neck, the relationship of masses to the major vascular structures, and also vascularity within masses and neck nodes.

The accuracy of core biopsy and fine-needle aspiration cytology of small neck masses and nodes is improved with ultrasound guidance, as the metallic needles are clearly seen passing through the subcutaneous tissues into the lesion or node (Figure 5.3).

**COMPUTED TOMOGRAPHY**

Computed tomography uses ionizing radiation. It has evolved significantly since its inception in 1972. Spiral CT scanners which use a single rotating x-ray tube and a complementary series of rotating x-ray detectors are now being replaced by multislice helical scanners also known as multirow detector computed tomography scanners. MDCT scanners use revolving x-ray tubes and a multiple row detector array that simultaneously acquire a series of 4, 16, 32 and, currently, 64 slices. Images are acquired while the patient passes through the gantry providing a three-dimensional volume block of data. Although images are usually acquired axially, multislice scanning enables the radiologist to manipulate the data to produce both thin section images and multiplanar reformats. As images are more rapidly acquired, there is decreased movement and respiratory artefact.

In addition to potentially inducing a new cancer, exposure to a cumulative high dose of ionizing radiation can induce cataracts within the lens of the eye. Therefore, unless relevant to the examination, the orbits should be excluded from the CT. Axial images are acquired with the patient lying supine. Direct coronal images can be obtained if the patient lies prone with the neck extended. This position can be uncomfortable, and has been replaced in most centres by the use of MDCT with coronal reformats. The larynx is optimally assessed with images reformatted to the plane of the vocal cords. Reformats can also aid assessment when there is artefact from dental amalgam (Figure 5.4).

The administration of an iodinated contrast medium results in vascular opacification, enhancement and increased conspicuity of the primary tumour and rim enhancement in pathological nodes. There is a small risk of reaction to the contrast media, including nausea, urticaria and bronchospasm, but patients rarely develop serious long-term sequelae. Anaphylactoid reactions, and death as a consequence, are also rarely seen.8,9 Iodinated contrast media has been implicated as being nephrotoxic and reported as inducing acute renal failure in 1–6 per cent of unselected patient populations and up to 50 per cent in high-risk patient populations.10 An iso-osmolar or a low osmolar non-ionic contrast medium is preferred in patients with renal impairment and diabetes, and hydration before and after the examination may be required.11

CT scans can be displayed on different settings known as windows. Soft tissue and bone settings are routinely used in the head and neck. The scans of bony and cartilaginous structures, for example the laryngeal cartilages in a patient with suspected laryngeal carcinoma, should also be reconstructed using a bony algorithm which is helpful for...
demonstrating bone and cartilage involvement (Figure 5.5). Coronal and sagittal reformats allow better evaluation of the skull base. The pulmonary parenchyma should be reviewed at lung window settings if the chest is also being examined. Beam hardening artefact from dental amalgam can significantly degrade images of the oral cavity (see Figure 5.4). Similar artefacts can also occur at bone–soft tissue interfaces.

**MAGNETIC RESONANCE IMAGING**

Magnetic resonance imaging utilizes a homogeneous magnetic field, which in most clinical scanners ranges from 0.5 to 3.0 tesla in strength. Radiofrequency pulses are used to excite the protons within the nuclei of the cells and coils detect the changes in the magnetic field.

The strong magnetic field requires stringent safety measures and all patients complete a questionnaire prior to scanning. MRI is contraindicated in patients with cardiac pacemakers, cochlear implants and metallic intraorbital foreign bodies. All patients in whom a metallic intraorbital foreign body is suspected require imaging of the orbits with conventional radiography to exclude a potential foreign body. Those patients who have iatrogenic foreign bodies *in situ*, such as surgical clips, embolization coils, vascular stents, prosthetic heart valves and joint prostheses may not be suitable for MRI. It is important to establish the timing of surgery and whether the foreign body is ferromagnetic. Dental prostheses can also be problematic (Figure 5.6a,b).

The long bore of the conventional magnet has been reported to induce moderate to severe anxiety in up to 25 per cent of patients undergoing examination, occasionally resulting in examination failure. MRI scanning in an interventional magnet may be appropriate in claustrophobic patients who fail examination in a conventional magnet without sedation.

Although CT is superior to MRI in assessment of cortical bone, MRI has superior soft tissue contrast compared to CT, and allows true multiplanar imaging. Scan times are long however and require good patient cooperation as images are prone to movement artefact from coughing, swallowing and dyspnoea. An appropriate coil is placed over the region of interest and scans are performed in at least two orthogonal planes. The most common sequences used in head and neck imaging are T1-weighted spin echo, T2-weighted spin echo and short tau inversion recovery (STIR). The T1-weighted sequence displays anatomy well and is used to assess lymph nodes and medullary bone involvement. T2-weighted sequences demonstrate fluid well and the STIR sequence suppresses the signal from fat allowing easy demonstration of pathology, particularly tumours, inflammation and oedema.

Intravenous gadolinium chelates may be administered to assess for pathological enhancement in patients with suspected recurrent tumour following surgery and radiotherapy, and for abnormal enhancement in involved nodes. It is also useful for assessing perineural spread of the primary tumour. After contrast administration fat-suppressed T1-weighted images are used. Gadolinium is generally well tolerated and is safer than the iodinated CT contrast agents. However, it can also induce acute renal failure in patients with renal impairment. Nephrogenic systemic fibrosis is also now recognized as a serious late complication following administration of gadolinium-based contrast to patients with dialysis-dependent renal failure.
MAGNETIC RESONANCE ANGIOGRAPHY

Magnetic resonance angiography can demonstrate flow within vessels and evaluate arterial stenoses. All patients in whom a fibula free flap graft would be the most appropriate method of facial reconstruction, even if they have no evidence of peripheral vascular disease and no history of intermittent claudication, ideally should have preoperative assessment of the leg vessels with MR angiography. This provides an anatomical road map of the arterial tree and allows confirmation that the remaining vessels will adequately supply the foot once the flap has been harvested (Figure 5.7).

NUCLEAR MEDICINE

Nuclear medicine studies utilize radioactive isotopes that are often bound to physiological molecules (radiopharmaceuticals). These investigations predominantly evaluate function and physiology. Anatomical detail and spatial resolution are poor compared to other imaging modalities.

Radioisotope whole-body bone scanning with the conventional isotope technetium-99m methylene diphosphonate (99mTc) has a high sensitivity, but a poor specificity in demonstrating bony metastatic disease in patients and can be used to assess for local bone invasion. However, 99mTc single photon emission computed tomography (SPECT) has a higher specificity than conventional bone scanning and can be used to improve the accuracy of predicting local bone invasion in patients with oral cavity tumours.

Suspected postoperative pulmonary emboli can be confirmed using a ventilation-perfusion scan (VQ scan). These utilize 99mTc-labelled macroaggregated albumin to demonstrate blood flow within the pulmonary capillary network and either Xenon-127 gas or nebulized 99mTc to evaluate the ventilation of the lungs.

Iodine-based isotopes are used in the assessment and treatment of thyroid disease. Functioning thyroid nodules take up iodine-123 (123I). Iodine-131 (131I) can be used to treat and image iodine avid differentiated thyroid tumours.
**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomography is an imaging technique utilizing radioisotopes that emit positrons. Fluorine-labelled deoxyglucose ($^{18}$F-FDG), a glucose analogue, is the isotope used for 98 per cent of PET imaging. Like other forms of nuclear medicine, PET imaging provides functional information. As the anatomical detail and special resolution of a PET scan alone is relatively poor, anatomical correlation with CT or MRI is necessary.

Combined in-line PET-CT scanners allow accurate co-registration of the functional information from the PET scan and the anatomical information from a non-contrasted relatively low-dose CT scan. PET-CT has a higher accuracy of depicting cancer and evaluating its anatomical localization, than PET alone.\(^1\)

False-positive results in PET-CT can occur due to normal physiological uptake in tissues, such as the tonsils and salivary glands. Tracer also accumulates in metabolically active tissues and in muscles, secondary to contraction, such as phonation, during the uptake phase (Figure 5.8). False-negative results are seen in tumours with low metabolic activity, such as salivary gland tumours, in necrotic tumour, and in patients who have undergone recent treatment, particularly PET-CT performed within four months of radiation therapy.\(^2\,\,3\)

In patients with suspected head and neck cancer $^{18}$F-FDG PET-CT is a valuable tool in the preoperative staging of head and neck tumours, as it can evaluate regional lymph node metastases, detect distant metastases and identify unsuspected synchronous primary lesions. It is also useful in evaluating patients with proven pathological cervical adenopathy but an unknown primary lesion (Figure 5.9).\(^4\) However, $^{18}$F-FDG PET-CT rarely provides additional information regarding the T stage of tumour over initial clinical evaluation and cross-sectional imaging with CT and MR.

$^{18}$F-FDG PET-CT is useful in the postoperative patient to monitor tumour recurrence (Figure 5.10a,b) and, after chemoradiotherapy, it can be used to evaluate the response of lesions to treatment, and aid selection of patients for subsequent neck dissection or salvage surgery.\(^5\)

**NASOPHARYNGEAL CANCER**

Squamous cell carcinoma accounts for 70 per cent of superficial malignant tumours in the nasopharynx. Lymphomas account for a further 20 per cent with tumours, such as adenocarcinoma, rhabdomyosarcoma, adenoid cystic carcinoma, melanoma, plasmacytoma, fibrosarcoma and carcinomas making the remainder. Imaging should aim to provide an assessment of the pattern of spread of the tumour especially into areas not easily examined clinically, i.e. deep extension and extension superiorly to the skull base and beyond.

The fossa of Rosenmüller is a common site of origin of nasopharyngeal cancer (Figure 5.11a,b). Submucosal lesions will not be detected endoscopically and MRI with its superior soft tissue contrast is the best suited imaging modality to detect these lesions. Both CT and MRI will detect skull base invasion (Figure 5.12a,b). CT can detect early cortical involvement better than MRI, but MRI is better than CT for the delineation of marrow involvement. It may be necessary to perform both in some patients to accurately determine the disease extent. The pharyngobasilar fascia provides a barrier to disease, but once this is breached, tumour can invade the skull base directly (Figure 5.13). High resolution T1-weighted MR images are used to examine the pharyngobasilar fascia which appears as a continuous low signal intensity linear structure.

Lateral extension into the deep structures of the nasopharynx can occur via the sinus of Morgagni, a natural fascial defect sited in the superolateral wall of the nasopharynx which allows passage of the Eustachian tube and levator veli
palatini muscle. Tumour can then gain access to the masticator and pre- and post-styloid parapharyngeal spaces. This can result in involvement of the third division of the fifth cranial nerve. Retrograde perineural spread to the skull base can then occur. The most common sites of skull base invasion are the petroclinoid fissure and foramen lacerum. This can result in internal carotid artery encasement and extension into the cavernous sinus. Perineural spread is best imaged with T1-weighted fat suppressed MR scans following intravenous gadolinium. This is seen as expansion and added enhancement of the nerve. Tumour may also directly invade the skull base and involve the foramen ovale. Occult submucosal spread may occur in a caudad direction. The inferior limit of disease is often visualized well on coronal images.

Nodal disease is extremely common (85–90 per cent) at presentation and is likely to be bilateral in half. Retropharyngeal nodes are usually the first affected nodes, but level 2 nodes may be involved without retropharyngeal nodal disease.

MR imaging has been shown to have a higher accuracy (92.1 per cent) than PET-CT for the diagnosis of residual and/or recurrent disease following treatment at the primary site. The combined use of both modalities was more accurate for restaging.23

**Figure 5.10** (a,b) 18F-FDG PET CT showing recurrent oropharyngeal tumour invading the skull base post-radiotherapy and photodynamic therapy (PDT).

**Figure 5.11** Axial T1-weighted (a) and T2-weighted (b) magnetic resonance images demonstrating a right-sided nasopharyngeal tumour filling the fossa of Rosenmüller.

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**PARAPHARYNGEAL SPACE PATHOLOGY**

The parapharyngeal space extends from the skull base to the styloglossus muscle at the level of the angle of the mandible.
The prestyloid and post/retrostyloid spaces are divided by the tensor styloid vascular fascia. The carotid sheath lies within the retrostyloid compartment. The deep portion of parotid gland bulges into the lateral aspect of the prestyloid compartment extending through the stylomandibular tunnel anterior to the styloid process, the styloid muscles and the retrostyloid compartment. The majority of tumours in the parapharyngeal space arise either from the deep lobe of the parotid in the prestyloid compartment (see below) or from neural tumours in the poststyloid compartment. True lesions within the parapharyngeal fat are likely to be salivary tumours from salivary gland rests or much less commonly neural tumours from the sympathetic chain. There may, however, only be a thin isthmus connecting a tumour of the deep lobe of the parotid with the gland itself which may not be apparent on imaging and thus an erroneous diagnosis of a parapharyngeal fat mass may be made which may alter the surgical approach.

MR imaging is thought to be better than CT as the initial imaging investigation. Scans should be obtained with contrast enhancement if a neural tumour is suspected. The origin of a mass related to the parapharyngeal space can be inferred by the pattern of displacement of normal anatomical structures. Parotid and extraparotid salivary gland tumours displace the internal carotid artery (ICA) posteriorly. Paragangliomas and most schwannomas displace the ICA anteriorly.

The most common neurogenic tumour is a schwannoma of the vagus nerve. This will usually displace the ICA anteriorly and medially. Vagal schwannomas also tend to separate the carotid artery from the internal jugular vein, whereas schwannomas arising from the cervical sympathetic chain do not cause this. They are usually well-defined soft tissue masses, but areas of haemorrhage and necrosis can occur. If the tumour arises within the jugular fossa, it may expand the fossa and extend both intracranially as well as into the neck. The bone will however remain well corticated. Although

Figure 5.12  Sagittal T1-weighted (a) and T2-weighted (b) magnetic resonance images demonstrating a bulky nasopharyngeal tumour with direct extension into the clivus (arrows).

Figure 5.13  Large nasopharyngeal tumour invading the nasal cavity with loss of the pharyngobasilar fascia and obstruction of the left Eustachian tube resulting in opacification of the left mastoid air cells (small arrow).
Schwannomas are hypovascular; they may demonstrate delayed enhancement following intravenous contrast. Both glomus vagale and glomus jugulare tumours arise around the vagus nerve and tend to displace the ICA anteriorly. Carotid body tumours will displace the ICA anteriorly, but will generally also splay the carotid bifurcation. Paragangliomas within the parapharyngeal space are usually well-defined oval-shaped lesions with vascular flow voids seen on MRI, particularly in tumours larger than 2 cm in diameter (Figure 5.14) and possibly a salt and pepper appearance on T2-weighted images. These tumours enhance avidly following intravenous contrast and if they involve the skull base will cause the bony margins to appear irregular and eroded, similar to a malignant tumour.

Lymph nodes within the parapharyngeal space are those within level 2. Retropharyngeal nodes are outside this anatomical region, although they push into it if enlarged. Necrotic nodes may mimic an abscess on imaging, but clinical correlation will usually differentiate between the two.

**Figure 5.14** STIR (short tau inversion recovery) magnetic resonance image demonstrating flow voids (open arrows) in a large right high T2 signal parapharyngeal paraganglioma.

**ORAL CAVITY**

The oral cavity is made up of the lip, upper and lower gingiva, buccal mucosa, hard palate, floor of the mouth, and oral (anterior two-thirds) of the tongue.

**Lip**

Imaging has little role to play in early lesions which may not be distinguishable from the normal orbicularis oris muscle. The margins of more advanced infiltrative lesions may be defined more readily with imaging.

Bone erosion which usually occurs along the buccal surface of the mandibular or maxillary alveolar ridge is best detected with CT. Once tumour gains access to the mandible, there is the potential for perineural spread along the inferior alveolar nerve. The presence of bone erosion upstages these lesions to T4 and necessitates bony resection.

The lymphatic drainage is to level 1 nodes (submental and submandibular) and level 2 nodes.

**Floor of mouth**

Imaging is used to assess the presence of bone erosion and tumour size which may clinically be underestimated if there is submucosal extension. It is important to determine the relationship of the tumour to the midline septum and to the contralateral neurovascular bundle, since this will alter treatment. Midline spread may occur directly across the genioglossus muscle and midline septum or occur via the potential space between the genioglossus and geniohyoid muscles. Ill-defined tumour margins, invasion of the sublingual space and proximity of tumour to neurovascular structures are highly suggestive of neurovascular involvement. Tumours with a mean diameter of 2 cm or greater are also more likely to invade the neurovascular bundle. These patients are at greater risk of cervical nodal involvement.

Thin-section CT is again the imaging modality of choice if bone involvement is suspected, e.g. fixed lateral floor of mouth tumours but otherwise, MRI may give more information about the tumour especially if there is artefact from dental amalgam. The primary tumour is often seen well on unenhanced T1-weighted MR scans (Figure 5.15a,b) and tumour involvement of the normal marrow is also well demonstrated by this imaging sequence. The periosteum does provide a barrier to tumour infiltration and tumour may gain access to the marrow via tooth sockets in edentulous patients. The specificity of MR imaging has been shown to be significantly lower than that of CT in the assessment of marrow invasion. A prospective study using the MR detection of tumour signal replacing hypointense cortical rim as the main radiological finding for mandibular invasion had high accuracy (93 per cent), sensitivity (93 per cent) and specificity (93 per cent). Another group, however, found that although MR was sensitive it had a poor positive predictive value for mandibular invasion. In a further study, 99mTc single photon emission computed tomography (SPECT) (a radioisotope technique) correctly predicted mandibular invasion in 11/12 cases with no false-positives, and CT only 3/12.

Posterior spread can occur along the mylohyoid muscle and tumour can thus gain access to the deep fascial spaces of the neck. Tumour can also extend posteriorly to involve the tongue base. Obstruction of the submandibular ducts will result in dilatation of the ducts (Figure 5.16) and probable enlargement of the affected gland which can be mistaken clinically for a nodal mass.

The depth of tumour invasion is related to the probability of nodal spread. The lymphatic drainage is to nodes in levels 1 and 2.
Figure 5.15 Axial T2-weighted (a) and T1-weighted (b) magnetic resonance images of a localized tumour in the anterior left floor of the mouth (solid arrow).

Figure 5.16 Axial STIR magnetic resonance image showing bilateral submandibular salivary gland duct obstruction (white arrows).

Figure 5.17 STIR (a) and T1-weighted (b) axial magnetic resonance images of a small right lateral tongue tumour (white arrow).
Tongue

The majority of tumours arise from the lateral aspect (Figure 5.17a,b) or undersurface of the tongue. Large tumours of the anterior and middle third of the tongue tend to spread to the floor of the mouth and coronal imaging can be useful in the evaluation. Spread to the tongue base may occur from tumours of the posterior third. Imaging should assess the size of the lesion and whether the lesion has crossed the midline (Figure 5.18). Identification of the relationship of the mass to the neurovascular bundle is important and will alter management.

Gingiva and buccal mucosa

Buccal mucosa squamous cell carcinoma (SCC) most commonly arises along the lateral walls and spread may occur along the buccinator muscle and into the pterygomandibular raphe with erosion of underlying bone. Lesions involving the lower gingiva may invade the mandible.

Hard palate

Primary SCC of the hard palate is rare and is usually due to tumour spread from adjacent gingiva. Cross-sectional imaging may understage these lesions which are better assessed by endoscopy. Low volume superficial tumours may not be visible on imaging, but more advanced lesions with suspected bone involvement should be examined using CT. Multidetector CT should be assessed in the coronal plane examining soft tissue and bone windows to stage tumours involving the hard palate.

Adenoid cystic carcinoma commonly shows perineural spread into the pterygopalatine fossa via the greater and lesser palatine nerves. This extension may be better imaged using MRI with gadolinium enhancement.

Retromolar trigone carcinoma

The retromolar trigone is a small triangular area posterior to the last mandibular molar tooth. The pterygomandibular raphe lies deep to the mucosa in this region and attaches superiorly to the hamulus of the medial pterygoid plate. Inferiorly, it attaches to the mylohyoid line of the mandible. Tumour spread inferiorly can therefore involve the floor of the mouth. Tumours arising in this region may grow anteriorly into the buccal region or posteriorly into the tonsil via the superior constrictor muscle. Superior extension may occur deep to the maxillary tuberosity invading the buccal space fat lateral to the maxillary antrum. Tumours can gain access via the mandibular and maxillary nerves, to the cavernous sinus and the skull base. Bone involvement is often not detected clinically and may occur early. This should be assessed with imaging and will alter management.

Oropharyngeal cancer

The majority of lesions are due to squamous cell carcinoma, but minor salivary gland tumours can present as a mass within the oropharynx particularly involving the palate. Treatment of tonsillar and soft-palate lesions depends upon the size of the tumour and involvement of surrounding structures. There should be a detailed evaluation of submucosal extension into the soft tissues of the neck; pre- and poststyloid parapharyngeal space, the nasopharynx and the tongue base should be assessed. Bone erosion and invasion of the prevertebral muscles can occur in advanced lesions. Submucosal extension may not be visible clinically and bulky disease close to or invading the skull base and evidence of encasement of the internal carotid artery may preclude surgery.

Lesions involving the anterior tonsillar pillar may spread superiorly to involve both the hard and soft palate (Figure 5.19a,b). Spread from here can occur to the skull base via the tensor and levator veli palatini muscles. Spread can occur along the superior constrictor muscle to the pterygopalatine raphe and buccinator muscle. Large tumours may extend to involve the tongue base along the palatoglossus muscle. Tumours solely involving the posterior tonsillar pillar are rare. These tumours can extend superiorly to involve the soft palate and inferiorly to involve the posterior aspect of the thyroid cartilage, the middle pharyngeal constrictor and the pharyngoepiglottic fold.

Lesions involving the tonsillar fossa arise either from the mucosal lining or from remnants of the palatine tonsil itself. These lesions may present as a nodal mass within the neck, usually located within level 2 (Figure 5.20). The primary lesion may spread anteriorly to the anterior pillar and from here to the sites described previously. Similarly posterior
spread can occur to the posterior pillar and beyond. Deep extension can occur to the superior constrictor muscle allowing access to the parapharyngeal space and thus to the skull base.

Spread to level 2 nodes is the most common pattern of nodal involvement, but tumours involving the posterior wall can give rise to retropharyngeal and level 5 nodal disease.

**LARYNGEAL CANCER**

Cross-sectional imaging may not demonstrate small lesions confined to the mucosa, but is superior to clinical assessment for the delineation of submucosal spread of disease. The larynx and pharynx are complex anatomical regions, but it is the knowledge of this anatomy as displayed on CT and MRI that is the key to oncological staging. Treatment options for patients with laryngeal cancer include surgery, radiotherapy and chemotherapy and combinations of these. The choice of treatment will depend upon the location, spread and volume of disease. Removal of part or whole of the larynx will have significant impact upon a patient’s ability to communicate and self-image.

Mucosal extension of disease and cord mobility is better assessed with endoscopy, but submucosal spread should be determined with cross-sectional imaging. Tumour volume is one of the critical factors determining tumour-free survival and local control following radiotherapy. Multidetector computed tomography-calculated tumour volume has been shown to have a high level of agreement with histology, with...
a slight tendency of MDCT to overestimation proportional to the size of the tumour. Transglottic spread, pre-epiglottic involvement greater than 25 per cent (Figure 5.21a,b), extensive paralaryngeal spread and cord mobility are other predictors. Clinical T stage and invasion of the thyroid cartilage by tumour are also predictors of failure of local control by radiotherapy. A study of 80 patients pre-radiotherapy demonstrated that MR findings of abnormal signal intensity within the thyroid cartilage and a tumour volume greater than 5 cc conferred an adverse prognosis. Work performed by Murakami and colleagues using dynamic helical CT suggests that lesions separate from the thyroid cartilage have a 95 per cent probability of local control, whereas those adjacent had 42 per cent local control. Other important factors were clinical T stage, tumour detectability, maximum dimension, tumour volume, anterior commissure involvement (Figure 5.22), ventricle involvement and thyroid cartilage involvement. Other authors have, however, questioned the reliability of CT, finding considerable interobserver variation in the assessment of tumour volume, cartilage invasion and cartilage sclerosis on the basis of CT imaging, apparently limiting its clinical significance. More recently, the findings of intermediate T2 MR signal intensity (SI) in cartilage and hypopharyngeal extension of tumour have been shown to be predictors of a greater likelihood of local failure when glottic tumours are treated by radiotherapy alone.

The paraglottic spaces are paired fatty regions lying deep to the true and false cords. They merge superiorly with the C-shaped pre-epiglottic fat space. These spaces are of high signal intensity on T1-weighted MR images and of low SI on fat-suppressed MR images. They are of low attenuation on CT. Tumour spread into these regions may be underestimated clinically, but will present as abnormal intermediate SI soft tissue on unenhanced T1-weighted MR images and intermediate to high SI tissue on STIR and T2-weighted MR images. Enhancing tumour is visible on T1-weighted MR images with fat suppression following intravenous gadolinium (Figure 5.23). Pre-epiglottic space invasion (Figure 5.21a,b) is important in the assessment of extension to the tongue base and the hyoid cartilage. MR imaging has been shown to have a sensitivity of 100 per cent, specificity of 84 per cent and accuracy of 90 per cent in this regard.

The correct prediction of laryngeal cartilage invasion is hampered by the irregular ossification of the thyroid cartilage and the reaction of cartilage to both invasion by and proximity of tumour to the cartilage. The ossified cartilage contains marrow fat and will therefore be of high signal on T1-weighted MR images and low SI on fat-suppressed MR images. Cortical bone will have very low SI on T1- and T2-weighted images. Non-ossified hyaline cartilage has an intermediate to low SI on T1- and on T2-weighted images. It has a density similar to squamous carcinoma. There is no enhancement of cortical bone, fatty marrow or hyaline cartilage after intravenous gadolinium. On unenhanced T1-weighted images invaded hyaline cartilage and fatty marrow demonstrate a low to intermediate SI. On T2-weighted images invaded hyaline cartilage invaded by tumour has a higher SI than normal cartilage. Although MRI has a high negative predictive value with cartilage invasion being excluded if none of these signs are present, reactive inflammation, oedema and fibrosis in the vicinity of the tumour may display similar appearances to cartilage invaded by tumour causing MRI to have a positive predictive value of 68–71 per cent. Peritumoral inflammatory changes are most commonly seen in the thyroid cartilage causing the specificity of MRI to detect tumour invasion to be lower at this site (56 per cent) than in the cricoid cartilage (87 per cent) or arytenoid cartilage (95 per cent).

![Figure 5.22](image1.png) **Figure 5.22** T3 left cord tumour with thickening of the anterior commissure on contrast-enhanced computed tomography.

![Figure 5.23](image2.png) **Figure 5.23** Fat-saturated T1-weighted spin echo axial magnetic resonance post-contrast demonstrating a left cord tumour with paraglottic spread (white arrow).
A study examining 111 laryngeal cartilages comparing CT with histopathology, found that sclerosis of a laryngeal cartilage was the most sensitive criterion for invasion for all laryngeal cartilages, but was not very specific being also due to reactive inflammation. The presence of extralaryngeal tumour and erosion or lysis of the cartilage was the most specific indicator of invasion (sensitivity 71 per cent, specificity 83 per cent and negative predictive value 89 per cent) in the thyroid cartilage (Figure 5.24). Sclerosis of the arytenoids and cricoid cartilage can be used as a predictor of cartilage invasion. The presence of arytenoid cartilage sclerosis can be due to invasion or to the presence of tumour adjacent to the perichondrium. Some authors have found that diagnostic accuracy can be improved if sclerosis of the arytenoid cartilage is not taken as an indicator of cartilage involvement.

The high negative predictive value achieved by MRI and its higher sensitivity than CT for cartilage invasion suggests that it should be better than CT for the evaluation of the laryngeal cartilage. The accuracy of MR imaging is better than CT if a meta-analysis is performed, but the use of MR will result in a significant number of false-positive examinations and the positive diagnosis of neoplastic invasion of the cartilage should be made with extreme caution on MRI. The term ‘abnormal signal intensity in the cartilage’ rather than ‘invasion of cartilage’ has been suggested. More attention is now being paid to the degree of abnormal SI on T2-weighted MR scans within the thyroid cartilage. Very bright SI is taken as inflammatory change, whereas intermediate SI has been taken to indicate tumour invasion. New criteria have been suggested: SI in cartilage greater than that of adjacent tumour on T2-weighted or post-contrast T1-weighted MR scans is taken to indicate inflammatory change, whereas SI similar to tumour is taken to represent malignant invasion. This has resulted in an improved specificity (82 versus 74 per cent) and was greatest for the thyroid cartilage (75 versus 54 per cent) with no alteration of sensitivity.

CT is used to stage laryngeal cancer in many centres. This is probably due to a number of factors: time, availability and the ease of volumetric studies with MDCT. CT has a higher specificity than MR in all reported studies and the use of MR imaging will, however, lead to a number of false-positive cases where the larynx will be removed and there will be no evidence of cartilage involvement. It may be that a combination of the two imaging modalities would be ideal.

The latest American Joint Committee on Cancer (AJCC) criteria for laryngeal cartilage invasion have now differentiated between the presence of cortical invasion of the inner margin of the thyroid cartilage (T3) versus complete infiltration of laryngeal cartilage (T4a). Full thickness involvement remains an indicator for surgical management, whereas T3 tumours may be treatable with radiotherapy with or without chemotherapy.

Recognition of involvement of the anterior commissure (Figure 5.22) is also important. Broyle’s ligament lies between the anterior commissure and the thyroid cartilage and invasion of this structure leads to a higher rate of cartilage infiltration. The anterior commissure should not exceed 1 mm in thickness and there should not be any soft tissue in the interthyroidal notch.

Subglottic extension and/or cricoid cartilage involvement is another indicator of a need for a total laryngectomy as the appropriate form of treatment. The presence of an enlarged Delphian node (the node lying anterior to the trachea) is another indicator of subglottic extension or of a subglottic primary (an unusual occurrence).

PHARYNGEAL CANCER

The majority of pharyngeal tumours are squamous cell cancers. The risk factors include excessive alcohol, smoking and previous radiation. The patients present with symptoms of dysphagia and odontophagia. They may present with otalgia due to referred pain along the course of the internal laryngeal nerve from the pyriform sinus and thus to the auricular nerve.

Nodal disease is common in these patients at presentation (75 per cent). A significant number of patients have a synchronous (25 per cent) or metachronous (40 per cent) second primary cancer. Cross-sectional imaging may not identify lesions confined to the mucosa which are best examined clinically. Submucosal spread is, however, better delineated by contrast-enhanced CT or MRI. It is important to understand the anatomy of the paraglottic and pre-epiglottic fat spaces as described previously. The anterior wall of the pyriform sinus is the posterior wall of the paraglottic space. Extension into this space allows tumour to gain access to the larynx and tongue base which may not be clinically apparent. Involvement of the tongue base will generally make a patient inoperable.

The apex of the pyriform sinus is at the level of the true vocal cords and spread from tumour into the larynx at this

Figure 5.24 Contrast-enhanced axial computed tomography demonstrating extralaryngeal tumour and lysis of the right thyroid lamina.
level should be looked for on cross-sectional imaging. Tumours sited in the lateral wall of the hypopharynx can easily involve the thyroid cartilage. Lesions involving the aryepiglottic fold may spread into the supraglottis and the arytenoid cartilages. The diagnosis of laryngeal cartilage invasion can be made if tumour is seen on the extralaryngeal aspect of the cartilage (Figure 5.24) and the cartilage is seen to be destroyed or lytic. Sclerotic change seen in the cartilage on CT may be due to tumour surrounding the cartilage rather than truly invading it. High signal intensity on T2-weighted MR images may be due to peritumoral inflammatory change, rather than true invasion. Involvement of the laryngeal cartilage framework can lead to radiation necrosis if these patients are treated by radiotherapy rather than surgery.

Posterior wall tumours can spread submucosally cranially to involve the posterior tonsillar pillars. The lymphatic drainage of the posterior pharyngeal wall is to retropharyngeal nodes (Figure 5.25a,b). These are not assessable clinically. Tumours of the posterior wall of the hypopharynx may be rendered inoperable by the presence of nodal disease encasing vessels at the skull base. Spread into the prevertebral muscles or vertebrae themselves may also make the patient inoperable (Figure 5.26). The preservation of a high SI fat stripe on axial or sagittal T1-weighted MR scans has been shown to be a good predictor for excluding prevertebral muscle invasion.\textsuperscript{39} The width of this stripe is, however, variable from patient to patient and from superior, where it is wider, to inferior.\textsuperscript{49} The diagnosis of prevertebral muscle involvement can be difficult to make with certainty on cross-sectional imaging. Although this will obliterate the normal fat plane seen posteriorly, it may not always be readily visible in thin patients. Abnormal enhancing tumour extending into and expanding the muscle is a more reliable sign. Overstaging can occur in the presence of a bulky tumour when the fat plane may be effaced but not invaded, but clinical examination may still demonstrate a mobile tumour in these cases. Abnormal muscle contour, T2 MR hyperintensity and enhancement may be present in patients in whom the tumour is mobile and resectable.\textsuperscript{31}

True post-cricoid tumours are rare and have a poor prognosis. These patients may present with hoarseness from involvement of the posterior larynx (arytenoid cartilages and posterior aspect of the cricoid cartilage) causing vocal cord paralysis. It is important to estimate the inferior extent of tumour which may be difficult to assess endoscopically and could thus result in positive surgical margins. Submucosal spread will be identified by abnormal enhancement and wall thickening. PET-CT can be helpful in determining the lower extent of metabolically active disease, although small volume tumour may not be recognized. Barium swallow can also be useful in this regard.

**Figure 5.25** Contrast-enhanced computed tomography demonstrating a primary posterior pharyngeal wall tumour (a) with a rim enhancing right retropharyngeal node (b).

**Figure 5.26** Axial-enhanced computed tomography scan showing bulky pharyngeal tumour with retropharyngeal fascia invasion.

**NASAL CAVITY AND PARANASAL SINUSES**

Plain films, CT and MRI can be used in assessing the paranasal sinuses. CT is superior to plain films and direct coronal CT imaging, with a low radiation dose technique utilizing a low mAs, has been employed for assessing benign inflammatory pathology. However, as it is difficult to distinguish inflammatory conditions from tumour with unenhanced CT then a higher radiation dose enhanced MDCT is necessary when tumour is suspected, and both axial images and multiplanar reformats should be evaluated. MR is superior in this aspect, particularly T2-weighted imaging which can...
Differentiate tumour which appears low signal due to its high cellular content from inflammatory tissue and secretions which have a high water content and thus high T2 signal (Figure 5.27a,b). Although inspissated secretions may sometimes demonstrate low T2 signal, they are generally of increased signal on T1-weighted imaging. 52

Primary malignancy arising in the sinonasal cavity is relatively rare, accounting for only 3 per cent of all head and neck tumours. 53 The tumours are diverse and most lesions are epithelial tumours, including squamous cell carcinomas and melanoma (Figure 5.28), and other non-squamous cell epithelial tumours such as salivary gland lesions, neuroectodermal and neural tumours. Metastases, osseous lesions, soft tissue sarcomas and lymphoproliferative disease also involve the sinonasal cavity (Figure 5.29). 54

Early symptoms of sinonasal malignancy are non-specific and can be mistaken for benign pathology, such as sinusitis. Thus tumours often present at a relatively advanced stage locally and up to 20 per cent may have adenopathy, including involvement of retropharyngeal nodes.

Squamous cell carcinomas comprise 80 per cent of all malignant sinonasal tumours, with the majority of these (85 per cent) arising in the maxillary antrum. Both CT and MRI have a role in evaluating the disease extent and assessing operability, and often complement one another. Local bone destruction is superiorly demonstrated on multiplanar reformat thin section CT, including erosion of the medial and inferolateral walls of the sinus and destruction of the alveolar ridge of the maxilla. Axial images are best for demonstration of lateral tumour extension into the infratemporal fossa (Figure 5.29) and posterior extension into pterygopalatine
fossa, while coronal images are best for spread of tumour superiorly into the orbit and intracranial extension. Coronal and sagittal MR imaging elegantly demonstrate direct tumour extension into the floor of the anterior and middle cranial fossae, the pterygopalatine fossa and the orbits (Figure 5.30a,b). Gadolinium-enhanced MR is used to evaluate perineural spread of tumour which is most commonly seen with adenoid cystic carcinoma, the majority occurring in the maxillary antrum and nasal cavity. The maxillary division of the trigeminal nerve is most often affected, and the nerve may show abnormal enhancement and enlargement.

Non-squamous cell sinonasal tumours are less common than squamous cell tumours. Melanomas account for only 3.5 per cent of sinonasal tumours and more commonly arise from the nasal cavity (Figure 5.28). On MRI, melanotic tumours are high signal on T1 and low signal on T2, whereas amelanotic tumours are low signal on T1 and high signal on T2. Enthesioneuroblastomas (olfactory neuroblastomas) (Figure 5.27) arise in the nasal vault and can spread into the anterior cranial fossa via the cribiform plate. This is best evaluated with imaging in the coronal and sagittal plane.

Salivary gland tumours account for less than 3 per cent of all head and neck tumours, but despite the low incidence there are a wide variety of benign and malignant lesions. Tumours are most commonly seen in the parotid salivary gland. About 50 per cent of all minor salivary gland tumours are malignant. Most occur in the palate and upper lip region.

Plain films and sialography remain useful for sialadenitis and suspected stone disease, but are no longer used for assessing tumours. High frequency ultrasound (7–14 mHz) is an ideal tool for examining the superficial lobe of the parotid and the submandibular salivary glands. It can be utilized to guide fine needle aspiration and core biopsies, particularly of small masses that are difficult to palpate. Benign salivary gland lesions are usually well defined and homogeneous on US (Figure 5.31). Irregular margins, inhomogeneity and disorganized colour flow are features of malignant tumours.

CT or MRI is required to assess the deep lobe of the parotid gland. Calcification is better demonstrated on CT and tumour extension beyond the ramus of the mandible, the course of the retromandibular vein, extension of deep lobe tumours into the parapharyngeal space and displacement of the vessels are also well demonstrated on CT. The facial nerve is not seen on CT and perineural invasion typically seen in adenoid cystic tumours can only be demonstrated well on MR. Ideally, imaging needs to be in the plane of the nerve, and fat-suppressed T1-weighted images following gadolinium contrast demonstrate this optimally.

**SALIVARY GLAND TUMOURS**

The salivary glands are divided into two groups: the major salivary glands and the minor salivary glands. The three pairs of major salivary glands are the parotids, submandibular and sublingual glands. The numerous small glands distributed throughout the oral cavity mucosa, the sinunasal cavity, the hard and soft palates, the pharynx and the larynx comprise the minor salivary glands.

**Figure 5.30** Axial T1-weighted (a) and sagittal T1-weighted (b) magnetic resonance image demonstrating tumour extension into the orbit and anterior cranial fossa.

**Figure 5.31** Ultrasound of a pleomorphic adenoma demonstrating a well-defined hypoechoic mass with typical through transmission.
Pleomorphic adenoma is the most common salivary gland tumour. They are hypoechoic on ultrasound and often display through transmission of sound (Figure 5.31). On CT, they are usually of higher attenuation (i.e. denser) than the surrounding fatty parenchyma, with variable enhancement. Small tumours have fairly homogeneous low T1-weighted and high T2-weighted signal intensity on MR (Figure 5.32a,b). Larger lesions are heterogeneous on all imaging modalities due to dystrophic calcification, necrosis, cystic change and areas of haemorrhage.

Warthin’s tumours (papillary cystadenoma lymphomatosum) are the second most common benign tumour of the parotid (Figure 5.33) and classically have a multiseptated cystic architecture on US, although cyst formation is common resulting in an anechoic lesion on US. CT, however, usually demonstrates the tumour nodule within the thin-walled cyst. The cystic component can generally be differentiated from the solid component on MR, although the cystic component is more readily appreciated on CT.

Mucoepidermoid carcinoma accounts for a quarter of malignant salivary gland tumours with almost half involving major salivary glands, predominantly the parotid, and the remainder occur throughout the oral cavity in the palate, retromolar region, buccal mucosal and lips. Imaging appearances depend on the grade of the tumour. Low-grade lesions appear similar to pleomorphic adenomas. High-grade lesions can metastasize and are locally infiltrating, destroying salivary gland ducts.

Although acinar cell carcinoma is relatively common, accounting for up to a third of parotid gland malignancies, they have no specific imaging features, often appearing as benign lesions on CT and MR.

Adenoid cystic carcinoma is typically a slow growing, widely infiltrative tumour with a tendency to perineural spread. It accounts for 2–8 per cent of all salivary gland tumours and occurs most commonly in the parotid, submandibular gland and palate. Retrograde tumour extension to the skull base from the parotid gland occurs via the facial and mandibular nerve. If there is extensive infiltration, widening of the bony nerve canal can be seen on CT. Contrast-enhanced MR, however, is more sensitive and reliable at demonstrating nerve enlargement and involvement (Figure 5.34a,b).

The parotids contain lymph nodes within the gland capsule and pathology may arise within these, rather than the glandular or stromal tissue.

Reactive lymphoid hyperplasia within intraparotid nodes occurs secondary to infection in the scalp and ear. Intraparotid nodes can also be involved as part of a generalized systemic lymphadenitis due to infections, such as HIV or tuberculosis, and inflammatory conditions, such as sarcoidosis.

Lymphoma and metastases, usually from malignant melanoma or cutaneous or mucosal squamous cell carcinoma can also involve intraparotid nodes.

LYMPH NODES

Radiological identification of lymphatic tumour spread and characterization of cervical lymph nodes is important in
patients with newly diagnosed cancer, as neck palpation is known to be an inaccurate technique for assessment of nodes. The presence of nodal metastases indicates a worse prognosis in patients, and modifies the available treatment options. Cervical nodes are also a common site of involvement in patients with lymphoma. However, none of the currently available imaging methods reliably depict small tumour deposits in non-enlarged nodes or differentiate reactively enlarged nodes from metastatic adenopathy.

Ultrasound

Normal cervical lymph nodes are elliptical in shape. Sonographically, most normal nodes have an outer hypoechoic cortex and a central echogenic (bright) hilus which is continuous with the surrounding fatty tissue. Normal and reactive cervical lymph nodes may show hilar vascularity or appear avascular. Malignant infiltration results in enlarged, more rounded nodes with disruption of the normal sonographic structure. Loss of the usual sharp outline of an involved node suggests extracapsular spread and correlates with advanced malignancy. Nodal calcification can be seen in metastatic nodes from both papillary and medullary carcinoma of the thyroid. Metastatic and lymphomatous infiltration alters the normal vascularity within a node and both peripheral, and mixed peripheral and hilar flow may be demonstrated on colour flow Doppler sonography (Figure 5.35a,b). Power Doppler evaluation of lymph node vascularity in addition to sonographic measurement of node size gives a high diagnostic accuracy of metastatic lymph nodes with a sensitivity of 92 per cent and specificity of 100 per cent.

Ultrasound-guided fine needle aspiration cytology

The accuracy of lymph node evaluation is also increased when US is combined with cytology following a fine needle aspiration. A recent large meta-analysis comparing US alone, with US-guided fine needle aspiration cytology (FNAC), CT and MRI demonstrated that US-guided FNAC was the most accurate imaging modality to detect cervical lymph node metastases.

Computed tomography and magnetic resonance imaging

Assessment of lymph nodes with CT and MRI should ideally be done when staging the primary tumour. Normal lymph nodes usually measure <1 cm in short axis diameter and have an oval shape with a smooth well-defined border.
Benign nodes are a uniform density or signal intensity and contain a distinctive fatty hilus.

The CT and MR criteria used to assess nodes for metastatic involvement are node size and shape, the presence of central necrosis and localized grouping of nodes within an expected lymph drainage region for a known tumour. Studies on cancer staging using lymph node size alone on CT or MRI to assess for metastatic involvement report low accuracy with sensitivities of 65 and 88 per cent and specificities of 47 and 41 per cent, respectively, for CT and MRI. The most accurate CT criterion is the presence of central necrosis which is demonstrated as peripheral/rim enhancement in the node following administration of iodinated contrast media (Figure 5.36). A similar appearance is seen on fat-suppressed T1-weighted MR images post-gadolinium (Figure 5.37a,b). The sensitivity of both MR and CT in detecting necrosis within nodes is similar (93 and 91 per cent, respectively), and better than that of US (77 per cent). However, there is no significant difference in the specificity of the three modalities (89, 93 and 93 per cent, respectively).

Extracapsular spread of tumour beyond the capsule of the lymph node can be very accurately diagnosed on CT and MR when there are poorly defined margins around the node and enhancement of the node capsule.

It was hoped that MR lymph contrast agents could improve the detection of metastatic nodes. In animals, the administration of an ultrasmall superparamagnetic iron oxide (USPIO) preparation intravenously 24–48 hours prior to MR examination of the lymph nodes is beneficial, as there is a decrease in the signal intensity of normal, but not metastatic nodes, on T2-weighted MR sequences. However, the clinical usefulness of USPIO agents is unfortunately limited by technical problems (motion and susceptibility artefacts and spatial resolution) and, although the detection of metastatic lymph nodes on MR following administration of USPIO has a high sensitivity (88 per cent) and specificity (77 per cent), there are false-positive results due to inflammatory nodes and false-negative results from the presence of undetected micrometastases.

Diffusion-weighted MR imaging, which allows visualization of molecular diffusion and perfusion via microcirculation of blood in the capillary network may improve detection of metastatic nodes in the neck. Cancer metastases to regional lymph nodes may be associated with alteration in both water diffusion and microcirculation within the node and calculation of the apparent diffusion coefficient (ADC) can be used as an adjunct tool to help discriminate metastatic neck nodes. In addition, studies have shown a significant difference in diffusion-weighted MR imaging and ADC values for nodes involved by metastatic squamous cell carcinoma, nodes involved by metastatic nasopharyngeal carcinoma and those infiltrated with lymphoma, the ADC value for lymphoma and nasopharyngeal carcinoma being less than that for squamous cell carcinoma. This technique may
therefore have the potential of differentiating between the causes of malignant lymphadenopathy.\textsuperscript{67}

\textbf{\textsuperscript{18}F-FDG PET-CT}

Combined \textsuperscript{18}F-FDG PET-CT imaging is reported to be more accurate in lymph node evaluation than either PET or contrast-enhanced CT alone in patients with squamous cell carcinoma of the head and neck, with a sensitivity, specificity and accuracy of 92, 99 and 97 per cent, respectively, for predicting metastatic lymph node compared to histopathological findings.\textsuperscript{68}

\textsuperscript{18}F-FDG PET has been shown to be superior to combined CT and MRI in the detection of cervical nodes in patients with squamous cell tumours of the oral cavity. The sensitivity of \textsuperscript{18}F-FDG PET for the detection of cervical nodal metastasis on a level-by-level basis was significantly higher than that of CT/MRI, whereas their specificities appeared to be similar.\textsuperscript{69}

\textbf{POST-TREATMENT CHANGES AND RECURRENCE}

Knowledge of previous treatment is essential to enable correct interpretation of images. If staging is performed following emergency tracheostomy, there will be soft tissue swelling, distortion and commonly surgical emphysema from the surgery. This can potentially lead to tumour overstaging.

Following total laryngectomy, there will be loss of the thyroid and cricoid cartilages and the hyoid bone. The neopharynx is formed by suturing the two open ends of the hypopharynx together and recurrence at this site should be looked for. The stoma should have walls of uniform thickness and focal areas of nodularity, intraluminal soft tissue masses or necrosis should be regarded with suspicion.\textsuperscript{70} There will be variable loss of the thyroid, and asymmetry of tissue here may lead to an erroneous diagnosis of disease recurrence (Figure 5.38). A knowledge of the normal imaging appearances of surgical flaps is essential.\textsuperscript{71} Denervation of the flap can give rise to enhancement following intravenous contrast which can be mistaken for disease recurrence (Figure 5.39a,b).

Asymmetry of the neck on clinical examination and imaging may be due to previous neck dissection. This can be due to previous resection of one submandibular gland (Figure 5.40). There will be loss of the normal fat plane

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{Figure_5.38.png}
\caption{Asymmetric thyroid post laryngectomy.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=0.8\textwidth]{Figure_5.39.png}
\caption{Axial T1-weighted magnetic resonance image of a radial free forearm flap reconstruction of the right floor of mouth (a) with enhancement of the denervated muscle (arrow) on fat-saturated axial T1-weighted post intravenous gadolinium (b).}
\end{figure}
around the vascular compartment (Figure 5.41). The internal jugular vein may be absent and there may be surgical resection of the sternomastoid muscle. Damage to the accessory and hypoglossal nerves can occur as a result of neck dissection giving rise to abnormality within the tongue with fat infiltration of the affected side (hypoglossal palsy) and abnormal high signal within the affected trapezius muscle on T2-weighted sequences (accessory nerve palsy) and evidence of compensatory muscle hypertrophy of the levator scapulae muscle which can be mistaken for a mass.

Recognition of recurrent disease after treatment can be extremely difficult. The laryngopharynx will become oedematous following radiotherapy. Expected changes occur with generalized oedema of skin, soft tissues and fat (Figure 5.42). This leads to high SI changes on T2-weighted MR images. The epiglottis, aryepiglottic folds and arytenoids appear swollen and there is thickening of the anterior commissure. Lack of response on follow-up imaging or a failure of reduction of tumour volume by greater than 50 per cent at four months are likely to be due to treatment failure.

Radionecrosis of the laryngeal cartilages may lead to degeneration and lysis. Superimposed infection may lead to air trapping within the necrotic cartilage. Differentiation from recurrent tumour may be impossible on CT and MRI.

Mandibular radio-osteonecrosis is seen in a small percentage of patients and differentiation between this and recurrent tumour is also difficult. On CT, there are areas of sclerosis, rarefaction and sequestration, and pathological fractures may occur.
Positron emission tomography is increasingly used to identify disease recurrence, although inflammatory change (including radio-osteonecrosis) will give rise to false-positive studies. Endoscopy and biopsy can diagnose mucosal recurrence, but follow-up imaging may be useful for deep disease.

**KEY LEARNING POINTS**

**Advantages of ultrasound**
- High definition images of superficial structures
- Assessment of flow in vascular structures
- Guidance for needle aspiration and biopsy

**Disadvantages of ultrasound**
- Poor penetration

**Advantages of computed tomography**
- High spatial and contrast resolution
- Assessment of deep tumour spread, local nodes and distant metastases
- Detects subtle cortical bone destruction

**Disadvantages of computed tomography**
- Uses potentially hazardous ionizing radiation
- Often requires potentially nephrotoxic iodinated contrast media
- Prone to artefact from dental amalgam and metallic implants

**Advantages of magnetic resonance imaging**
- High spatial and contrast resolution
- Assessment of deep tumour spread and local nodes
- Detects cartilage and bone marrow involvement

**Disadvantages of magnetic resonance imaging**
- Long scan times
- Requires stringent safety measures
- Prone to artefact from respiration and movement

**Role of 18F-FDG PET-CT**
- Evaluating patients with pathological cervical nodes and an unknown primary
- Evaluating regional lymph node metastases
- Excluding distant metastases and synchronous primary tumours
- Monitor tumour recurrence in the post-operative neck
- Excluding residual disease after chemoradiotherapy

**Imaging issues**
- Nasopharynx
  - Normal asymmetry of the lateral pharyngeal recess
  - Variability in normal lymphoid tissue
- Parapharyngeal space
  - Displacement of internal carotid artery and parapharyngeal fat
  - Tumour vascularity and bony margins
- Lip carcinoma
  - Bone erosion
  - Soft tissue invasion
- Floor of mouth carcinoma
  - Extent of bone erosion
  - Deep invasion along the mylohyoid and hyoglossus muscles
  - Relationship to ipsilateral lingual neurovascular bundle
  - Extension across the midline and relationship to contralateral neurovascular bundle
  - Tongue base invasion
  - Extension into the soft tissues of the neck
- Tongue
  - Objective size of tumour
  - Involvement of neurovascular bundle
  - Has tumour crossed midline
- Oropharyngeal tumours
  - Objective size of primary tumour
  - Perineural and deep spread of tumour
  - Soft palate to pterygopalatine fossa (V2) and foramen rotundum
  - Façials to masticator space involving branches of V3 at skull base (foramen ovale)
  - Lingual tonsil to neurovascular bundle of tongue
  - Posterior oropharyngeal wall to retropharyngeal space
- Laryngeal tumours
  - Tumour volume
  - Laryngeal cartilage involvement
  - Spread beyond the larynx
  - Paraglottic disease volume
- Sinonasal cavity
  - Differentiation of tumour from secretions
  - Bone destruction
  - Local tumour spread
  - Perineural tumour spread
- Salivary gland tumours
  - Ultrasound-guided fine needle aspiration and biopsy
  - Deep lobe of parotid involvement
  - Intraparotid nodal disease
  - Perineural tumour spread

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**FURTHER READING**


INTRODUCTION

The head and neck region encompasses skin, soft tissue, upper aerodigestive tract elements including laryngopharynx, nose and paranasal sinuses, plus a number of other organ systems, including the ears, thyroid gland, parathyroid glands and pituitary gland, nodal, thymic and mucosa-associated lymphoid tissue, together with more specialized oral, dental, ocular, bone and joint, peripheral and central nervous system components. Within these fields, diseases of the skin adnexa, major and minor salivary glands, accessory mucus glands, ceruminous glands and lacrimal glands are sometimes encountered. In the presence of such anatomical diversity, it is not surprising that the pathology affecting the region is so varied.

History and examination can, on occasion, provide a diagnosis, but pathological evaluation remains the gold standard, especially in malignant disease as a tissue diagnosis, establishing tumour type, tumour grade and tumour stage, is of paramount prognostic importance and substantially influences further management.

PATHOLOGICAL EVALUATION

There are a number of techniques available to evaluate a lesion in the head and neck, ranging from techniques suitable for outpatients, with or without local anaesthetic, to those undertaken under general anaesthesia. Common techniques are described below.

Fine needle aspiration cytology

Fine needle aspiration cytology (FNAC) was first described in the mid-nineteenth century, but it only gained popularity in the 1950s and now in many specialist units it constitutes the first-line investigation for patients presenting with cervical lymphadenopathy and other head and neck masses, especially major salivary gland and thyroid gland lesions.1

FNAC can be undertaken using palpation alone or with ultrasound or computed tomography (CT) guidance and may be performed with or without suction. FNAC primarily relies upon assessment of cytonuclear morphology, generally yielding little background architectural information, although microbiopsies may occasionally be present.

Fixed smears should be immersed in fixative, usually alcohol or less commonly formalin, without delay and are typically stained with the Papanicolaou (Pap) method or sometimes haematoxylin and eosin (H&E). Air-dried smears are best subjected to assisted air flow and/or gentle heat and are usually stained with a Romanowsky type stain, commonly May–Grünewald-Giemsa (MGG) or Diff-Quik variants. Needles and syringe hubs may be rinsed in transport medium in an attempt to maximize the cell yield. The resultant liquor may be handled by a variety of cell concentration techniques, such as filtration or centrifugation, back at the laboratory, dependent upon local preferences and the reliance upon...
either traditional smear techniques or the availability of newer liquid-based cytology technology. The latter may be semi-automated or fully automated. Any clot material is best processed using conventional histology, because free floating cells tend to be preferentially sequestered in such clots and valuable material may otherwise be discarded (Figure 6.1).

**Core biopsy**

A core biopsy is similar to FNAC, but instead of collecting a few clusters of cells a core biopsy, due to the greater calibre of the biopsy needle, will yield a cylinder of tissue that can undergo histological analysis. The relatively poor visualization of overall tissue architecture inherent in this procedure renders it of limited use in the investigation of primary haematolymphoid disorders, where cautious interpretation is recommended. However, when employed selectively the technique may be more helpful in the investigation of metastatic disease.

This technique can also be undertaken with ultrasound or CT guidance.

**Incision biopsy**

Incisional biopsy involves taking a representative sample or wedge of a lesion for histological scrutiny. This is a suitable technique for obtaining a diagnosis in accessible tumours affecting the oral cavity, or pharynx, larynx or hypopharynx. In lesions affecting the major salivary glands or in cervical lymphadenopathy, however, incisional biopsy can compromise further treatment.

There are a number of techniques available to obtain an incisional biopsy specimen under local or general anaesthetic depending on both the site of the lesion and patient factors (Table 6.1).

A sufficient sample of tissue must be obtained to allow histopathological analysis. Diathermy artefact and mechanical disruption, either crushing (compaction) or stretching (rarefaction), during handling or processing of the specimen can make analysis difficult and occasionally impossible. Certain tissues (e.g. lymphoid tissue) and tumours (e.g. neuroendocrine carcinoma) are more susceptible to this than others. It must be noted that a thick biopsy does not necessarily equate to a deep biopsy – it is often the interface between lesion and native stroma that is critical when seeking evidence of invasion and a thick sample from an exophytic epithelial proliferation may still be too superficial to adequately assess this (Figure 6.2).

**Excision biopsy**

Excision biopsy involves complete removal of the lesion and provides a definitive histological diagnosis. This can range from a small vocal cord nodule or polyp to major en bloc or multipart resection specimens.

Where appropriate, the specimen should preferably be orientated by the surgeon. Placing sutures or marker clips in appropriate positions can do this. Annotated diagrams or digital photographs often aid communication. Specimens can be pinned or clipped on to a cork, foam, polystyrene or even thick cardboard block. Dehydrated cucumber slices are a suitable medium for laryngeal biopsies, which are held in place with tissue adhesive. Resection planes or other structures of particular clinical concern ought to be brought to the pathologist’s attention, especially if these may not be immediately obvious following inevitable distortion induced by fixation. It should always be borne in mind that there will be a reproducible reduction in measured mucosal clearance margins of up to circa 50 per cent or so when a fixed, processed, stained and mounted tissue section is compared to the in vivo preoperative state due to shrinkage inherent in those histochemical processes (Figures 6.3 and 6.4).
When requesting pathological analysis of a specimen, it is vital that the pathologist is provided with all relevant information to enable a full assessment of the specimen. Required information includes:

- Patient identification and demographics.
- Type of biopsy: FNAC, core biopsy, incision biopsy or excision biopsy.
- Site of biopsy: if biopsies are taken from multiple sites, each site should be clearly labelled and sent separately.
- Relevant history of lesion: duration, symptoms, etc.
- Previous treatment to area: surgery, radiotherapy, trauma, etc.
- History of tobacco, alcohol or other drug use.
- Relevant past medical history, drug history and family history.
- Differential diagnoses based on clinical history and examination.

---

### Table 6.1 The advantages and disadvantages of commonly used tissue sampling techniques.

<table>
<thead>
<tr>
<th>Type of sample</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine needle aspiration</td>
<td>(1) Relatively risk free</td>
<td>(1) Primary cytological diagnosis by FNAC must be confirmed by histology prior to radical treatment for head and neck cancer</td>
</tr>
<tr>
<td></td>
<td>(2) Quick</td>
<td>(2) Diagnostic yield is both lesion sensitive and operator dependent and there can be a high non-diagnostic rate, but this may be improved with the use of ultrasound</td>
</tr>
<tr>
<td></td>
<td>(3) Can be undertaken in outpatients</td>
<td>(3) Analysis is limited by cytopathological expertise and has been a rate-limiting step</td>
</tr>
<tr>
<td></td>
<td>(4) Does not usually compromise future management</td>
<td>(4) Clinicians must be aware of inherent limitations including a risk of false-positives and false-negatives</td>
</tr>
<tr>
<td></td>
<td>(5) In assessment of cervical lymphadenopathy FNAC has been shown to have a sensitivity of 76–98% and a sensitivity typically of &gt;90%. The rates can vary with regards salivary gland and thyroid masses.</td>
<td>(5) FNAC is of limited help in the diagnosis of lymphoma. Flow cytometry may be helpful in excluding a diagnosis of lymphoma</td>
</tr>
<tr>
<td>Core biopsy</td>
<td>(1) Core biopsy is a simple technique that can be performed in the outpatient setting. It is inexpensive with minimal equipment requirements. The diagnostic yield is higher than for FNAC and the sample undergoes histopathological analysis and therefore specific cytopathological expertise is not required</td>
<td>(1) Appropriate precautions are required in patients on anticoagulation therapy undergoing core biopsy to prevent bleeding and haematoma formation</td>
</tr>
<tr>
<td></td>
<td>(2) The complications of the procedure are relatively minor; the most common being haematoma formation and it does not compromise further treatment, especially surgery, which can occur with open biopsy</td>
<td>(2) There is a theoretical risk of tumour seeding associated with the larger needles used in obtaining a core biopsy, but published case series have rarely encountered this complication</td>
</tr>
<tr>
<td></td>
<td>(3) In contrast to FNAC, a core biopsy sample does in some cases permit a greater chance of sub-classification of a lymphoma and may sometimes obviate the need for an open biopsy</td>
<td></td>
</tr>
<tr>
<td>Incision biopsy</td>
<td>(1) Can provide definitive histological diagnosis</td>
<td>(1) Can affect definitive management of the tumour</td>
</tr>
<tr>
<td></td>
<td>(2) Can require admission as a day-case</td>
<td>(2) Can require admission as a day-case</td>
</tr>
<tr>
<td></td>
<td>(3) May require a general anaesthetic</td>
<td>(3) May require a general anaesthetic</td>
</tr>
<tr>
<td></td>
<td>(4) Higher complication rate than FNAC or core biopsy</td>
<td>(4) Higher complication rate than FNAC or core biopsy</td>
</tr>
<tr>
<td></td>
<td>(5) Costlier than FNAC or core-biopsy</td>
<td>(5) Costlier than FNAC or core-biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1) Higher risk of complication compared to other biopsy techniques</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Can require admission and the need for general anaesthetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3) Costliest method of obtaining a biopsy</td>
</tr>
</tbody>
</table>

FNAC, fine needle aspiration cytology.
If the specimen has been orientated, then an annotated diagram or digital image should be included with the request.

Any clinical photographs of the lesion can also be helpful.

**Figure 6.2** The potential discrepancy between tumour thickness and tumour depth. (a) Employing the uppermost granular layer, or actual surface discounting non-vitalized slough if ulcerated, as a fiducial point this relatively flat contoured tumour’s thickness is roughly comparable to its depth (H&E stain, ultralow magnification). (b) This fungating exophytic tumour’s thickness, however, comfortably exceeds its depth (H&E stain, ultralow magnification). (c) This ulceroinfiltrative, endophytic tumour’s depth on the other hand exceeds its maximal thickness in the perpendicular plane (H&E stain, ultralow magnification). (T, tumour thickness; D, tumour depth.)

**Figure 6.3** Biopsy orientation using a biomount. (a) Three laryngoscopic biopsies glued to a dehydrated cucumber (*Cucumis sativus*) biomount in order to maintain correct orientation in the laboratory. An accompanying endoscopic digital photograph further assists handling of such small biopsies. These may be further inked and/or sliced prior to processing. (b) A correctly embedded, though heavily thermalized, laryngeal biopsy on the left with anucleate cellulolic cucumber biomount to the right (H&E stain, ultralow magnification).

**TISSUE PREPARATION**

Surgical specimens are ideally fixed immediately in theatre by immersion in formalin, which is the routine fixative of choice. This effectively stops metabolism and arrests autolysis and putrefaction, thereby preserving the tissue structure. The apocryphal maxim is that the minimum ratio by volume of 10 per cent formalin to specimen should be ten to one, although this is somewhat arbitrary and if this was ever evidence based, it is likely to be influenced by intangible factors, such as type of tissue, temperature, agitation and so on – more liberal volumes of fixative are preferable to parsimony in this situation. On rare occasions, alternative fixatives, such as glutaraldehyde or alcohol, may be employed if specialized studies, for example electron microscopy, are contemplated. Fresh unfixed material intended for frozen
infiltrates the tissue. The tissue is subsequently embedded by encapsulation in paraffin wax in a mould to provide a rigid support for microtomy. The additional step of decalcification may be instituted in mineralized tissue, which might otherwise hinder sectioning. Automatic tissue processors enhanced by pressure, vacuum, heat and microwave facilities in a self-contained, microprocessor-controlled, programmable unit are used in many modern laboratories, tailored to local conditions.

The prechilled, hardened paraffin wax-embedded tissue block is then sliced, typically at 3–5-μm thick on a microtome. The thin sections are then floated on a warm water bath prior to transfer on to a glass slide. The sections are then dried on a hotplate.

The sections may now be stained, typically with haematoxylin and eosin (H&E) and mounted under a glass or self-adhesive plastic film coverslip to form a permanent preparation. A wide repertoire of additional histochemical and/or immunohistochemical stains may be similarly employed, on replicate sections, either manually or by machine, dependent upon the issues in hand. Finally, the slides are made available to the pathologist for generation of a surgical report.

**Immunohistochemistry**

The principle underpinning all immunohistochemistry (IHC) is the demonstration of an epitope or antigen via its binding to a specific antibody, which in turn, is conjugated to a label that can be visualized histologically. A variety of reporter and linkage systems to produce a visual signal have been developed based on fluorescent molecules, alkaline phosphatase and avidin-biotin, among others.

In general, monoclonal antibodies are more specific than their polyclonal counterparts. Importantly, no antibody is absolutely sensitive or 100 per cent specific – immunophenotyping is most intelligently performed using a panel of expected positive and negative antibodies together with appropriate positive and negative control sections, mindful of aberrant cross-reactivity, spurious coexpression, false positive and false negatives and vagaries of technical quality. Correlation with conventional morphology is imperative.

Among the broad categories of commercially available diagnostic markers are antibodies directed against intermediate filaments (e.g. cytokeratins, desmin, neurofilament protein, vimentin), other epithelial markers (e.g. epithelial membrane antigen, Ber EP4), structural proteins (e.g. calponin), storage granules/products (e.g. chromogranin, calcitonin, thyroglobulin), hormone receptors (e.g. oestrogen, progesterone), nuclear epitopes (e.g. thyroid transcription factor-1, p16), haematolymphoid epitopes (e.g. the CD system, cyclin D1), proliferation indices (e.g. Ki67, PCNA), oncoproteins/tumour suppressor proteins (e.g. bcl-2, p53, p63) and infectious agents (e.g. EBV LMP-1, CMV protein, HHV 8).

A variety of ancillary molecular techniques (e.g. polymerase chain reaction (PCR), in situ hybridization (ISH), genotyping studies) and electron microscopy may be helpful under selected circumstances.

**Multidisciplinary correlation**

The cytological and histopathological diagnostic procedure is a complex process. It cannot be overemphasized that reaching
Subsites of the head and neck

The head and neck is divided into a number of subsites as explained in Table 6.2.

TUMOURS OF THE HEAD AND NECK

Tumour typing

It follows that there are a multitude of benign and malignant tumours that affect the head and neck region. This section will aim to summarize important pathological features of the more common benign and malignant tumours required by the non-pathologist. For a more in-depth description, especially of less common tumours, a dedicated head and neck pathology or other specialist textbook is recommended.

Benign and malignant tumours can be classified according to the proposed tumour cell origin (histogenesis) and/or its differentiation pathway (Table 6.3).

This section is not intended to be an exhaustive account of the pathology of benign and malignant tumours affecting the head and neck, which can be found in any head and neck pathology atlas. We will aim to cover those tumours, both benign and malignant, that are more commonly encountered in clinical practice. Diagnostic cytopathology and histopathology are substantially visual subjects, therefore, illustrations depicting selected examples, but also introducing broader principles, have been chosen to supplement the text.

BENIGN TUMOURS

There is a multitude of benign tumours that affect the head and neck. In this section, a selection of benign tumours will be described.

Benign salivary gland neoplasms

Benign salivary gland classification and tumour-like lesions are largely classified according to WHO criteria and are listed in Table 6.4.

Table 6.2 Head and neck site and subsites.

<table>
<thead>
<tr>
<th>Head and neck site</th>
<th>Subsite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx: From epiglottis to lower border of cricoid cartilage</td>
<td>Supraglottis: epiglottis to false cords</td>
</tr>
<tr>
<td></td>
<td>Glottis: false cords to 5–10 mm below true cords</td>
</tr>
<tr>
<td></td>
<td>Subglottis: 10 mm below true cord to lower border of cricoid cartilage</td>
</tr>
<tr>
<td>Oral cavity: From lips to anterior tonsil fauces</td>
<td>Lips</td>
</tr>
<tr>
<td></td>
<td>Anterior tongue</td>
</tr>
<tr>
<td></td>
<td>Buccal mucosa</td>
</tr>
<tr>
<td></td>
<td>Retromolar trigone</td>
</tr>
<tr>
<td></td>
<td>Floor of mouth</td>
</tr>
<tr>
<td></td>
<td>Tongue base</td>
</tr>
<tr>
<td></td>
<td>Tonsils</td>
</tr>
<tr>
<td></td>
<td>Lateral and posterior pharyngeal wall</td>
</tr>
<tr>
<td>Oropharynx: From level of hard palate to hyoid bone</td>
<td>Pyriform fossa/sinus</td>
</tr>
<tr>
<td></td>
<td>Postcricoid region</td>
</tr>
<tr>
<td></td>
<td>Posterior pharyngeal wall</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>Nasal cavity and paranasal sinuses</td>
</tr>
<tr>
<td>l</td>
<td>Nasal cavity</td>
</tr>
<tr>
<td></td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td></td>
<td>Ethmoid sinus</td>
</tr>
<tr>
<td></td>
<td>Sphenoid sinus</td>
</tr>
<tr>
<td></td>
<td>Frontal sinus</td>
</tr>
<tr>
<td></td>
<td>Parotid</td>
</tr>
<tr>
<td></td>
<td>Submandibular</td>
</tr>
<tr>
<td></td>
<td>Sublingual</td>
</tr>
<tr>
<td></td>
<td>Minor</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Thyroid</td>
</tr>
<tr>
<td></td>
<td>Level I, submandibular IB and submental IA nodes</td>
</tr>
<tr>
<td></td>
<td>Level II, upper jugular nodes including spinal accessory dividing into IIA and IIB</td>
</tr>
<tr>
<td></td>
<td>Level III, middle jugular nodes</td>
</tr>
<tr>
<td></td>
<td>Level IV, lower jugular nodes</td>
</tr>
<tr>
<td></td>
<td>Level V, posterior triangle nodes divided by spinal accessory nerve in to VA and VB</td>
</tr>
<tr>
<td>Neck</td>
<td>Skin</td>
</tr>
<tr>
<td></td>
<td>Temporal bone</td>
</tr>
</tbody>
</table>

Salivary pleomorphic adenoma

Salivary pleomorphic adenoma (SPA) (benign mixed salivary tumour) is the most common tumour affecting the salivary glands. It comprises approximately 50 per cent of all salivary gland tumours, 65 per cent of parotid tumours and 40 per cent of intraoral minor salivary gland tumours. The annual incidence is reported as 2.4–3.05/100 000 and shows a slight female preponderance, as do most salivary gland tumours (Figure 6.5).
MACROSCOPIC APPEARANCE

SPAs tend to be well demarcated, round or ovoid with broad-based surface bossesations, are firm and freely movable. There may be areas of metaplasia (e.g. lipometaplasia) or retrogression (e.g. cystic change, calcification). They are variably encapsulated and, where present, the capsule may be interrupted, part-circumferential, thick or thin. The cut surface may either be homogeneous or variegated, dependent upon the precise histological pattern. Protuberant pericapsular nodules may be seen, sometimes attached to the main body of the tumour by a slender pedicle, although it may not be apparent in the plane of section examined and with time any such initial connection may regress leading to free lying satellite tumourlets. Simple enucleation of the body of a pleomorphic adenoma risks detaching these nodules, which remain behind forming a nidus for recurrence. Predominantly myxoid examples may be semi-fluid and fluctuant – perioperative capsular rupture and spillage may seed

Table 6.3  Classification of tumours by histogenesis with examples.

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>Squamous cell carcinoma Basal cell carcinoma</td>
</tr>
<tr>
<td>Neural ectodermal</td>
<td>Olfactory neuroblastoma Malignant Melanoma Neuroendocrine carcinoma Merkel cell tumour</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Lymphoma Angiosarcoma Osteosarcoma</td>
</tr>
<tr>
<td>Epithelial and myoepithelial</td>
<td>Chondrosarcoma Nerve sheath tumour</td>
</tr>
<tr>
<td>Non-epithelial</td>
<td>Mucoepidermoid carcinoma Adenocarcinoma Sarcoma</td>
</tr>
</tbody>
</table>

Table 6.4  WHO classification of benign salivary gland tumour and tumour-like lesions.11, 12

<table>
<thead>
<tr>
<th>Benign epithelial tumours</th>
<th>Tumour-like lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma</td>
<td>Sialadenosis</td>
</tr>
<tr>
<td>Myoepithelioma</td>
<td>Oncocytosis</td>
</tr>
<tr>
<td>Basal cell adenoma</td>
<td>Necrotizing sialometaplasia</td>
</tr>
<tr>
<td>Warthin's tumour</td>
<td>Benign lymphoepithelial lesion</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Salivary gland cyst</td>
</tr>
<tr>
<td>Canalicular adenoma</td>
<td>Chronic submandibular sialadenitis (Küttner tumour)</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>Cystic lymphoid hyperplasia in AIDS</td>
</tr>
<tr>
<td>Lymphadenoma – sebaceous/ non-sebaceous</td>
<td></td>
</tr>
<tr>
<td>Ductal papillomas:</td>
<td></td>
</tr>
<tr>
<td>inverted ductal papilloma</td>
<td></td>
</tr>
<tr>
<td>intraductal papilloma</td>
<td></td>
</tr>
<tr>
<td>sialadenoma papilliferum</td>
<td></td>
</tr>
<tr>
<td>Cystadenoma</td>
<td></td>
</tr>
</tbody>
</table>

Figure 6.5  Salivary pleomorphic adenoma. The cut surface of a typical salivary pleomorphic adenoma displaying a solid blue/grey hue characteristic of chondromyxoid matrix. More cellular examples tend to be tan or cream/white. Note the localized sessile capsular herniation.
tumour throughout the operative field, again intensifying the risk of recurrence. Such recurrences are classically multinodular (Figure 6.6).9

**MICROSCOPIC APPEARANCE**

SPA arguably presents the greatest morphological diversity of any mammalian neoplasm. Its basic components are epithelium and modified myoepithelium, intermingled with stroma of chondromyxoid appearance and/or mucomyxoid ground substance.11 The appearances vary widely both between adenomas and within the same tumour. A panoply of other changes may be superimposed or even predominate, e.g. metaplastic differentiation (squamous, lipomatous, osseous, neuroid, angiomatoid), degeneration (cystic change, infarction, mineralization, hyalinization, elastosis), specific growth patterns (e.g. pseudoanenoid cystic, clear cell, epithelial/myoepithelial carcinoma-like, basaloid, giant cell, spindle cell, acinar, plasmacytoid, oncocytoid), crystalloid deposition, dysplasia and malignant transformation.

This heterogeneity can occasionally make diagnosis difficult, especially from limited volume needle core biopsies, incisional biopsies or FNAC.14

Subclassification of pleomorphic salivary adenoma into four subtypes has been proposed based on stromal content (Table 6.5). A modified version differentiates three subtypes (Table 6.6).15, 16

This histological classification has limited clinical relevance:

- Myxoid tumours may be more prone to recurrence,16, 19 but this finding is not consistent.19, 20
- Myxoid tumours have more delicate, easily damaged capsules.
- Minor salivary gland pleomorphic adenomas tend to be cellular and unencapsulated.10

### RISK OF MALIGNANT TRANSFORMATION

Clinical features that are associated with an increased risk of malignant transformation include:13–21

- occurrence in the submandibular gland;
- older patient age;
- tumour size greater than 4.5 cm;
- duration of tumour.

**Warthin’s tumour**

Warthin’s tumour (adenolymphoma, papillary cystadenoma lymphomatosum) is the second most common tumour of the salivary glands. It is virtually exclusive to the parotid gland and periparotid lymph nodes11, 22 and can be multicentric and/or bilateral in 4–10 per cent of cases.10, 22 It comprises between 3.5 and 30 per cent of primary epithelial salivary gland tumours with geographical variation.11 It occurs in Caucasians and Asians with a lower incidence in African-Americans and Black Africans.11

<table>
<thead>
<tr>
<th>Table 6.5 Seifert’s classification of salivary pleomorphic adenoma.15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtype</strong></td>
</tr>
<tr>
<td>1 (classical SPA)</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6.6 Alternative subclassification system for salivary pleomorphic adenoma.17, 18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subtype</strong></td>
</tr>
<tr>
<td>Myxoid (stroma-rich)</td>
</tr>
<tr>
<td>Cellular</td>
</tr>
<tr>
<td>Mixed (classical SPA)</td>
</tr>
</tbody>
</table>

Figure 6.6 Recurrent salivary pleomorphic adenoma. (a) Excision of multinodular recurrence of salivary pleomorphic adenoma encompassing the original surgical field, consequent upon incomplete removal at first operation. (b) Whole mount section of another local recurrence showing secondary seeding of fat, residual salivary gland and fibrous tissue. The nodules are clearly of differing composition despite having arisen from the same parent lesion (H&E stain, ultralow magnification).
It can occur over a wide age range, but is common in the sixth decade for women and seventh decade for men. It is more common in males but the male:female ratio has reduced over the last few decades.

There is a link between Warthin's tumour, cigarette smoking and radiation.

**MACROSCOPIC APPEARANCE**

The tumour is a circumscribed, often thinly encapsulated soft mass that contains multiple cystic and solid/papillary areas, which is white to brown in colour. There may be coagulated tan exudate in the cystic spaces.

**MICROSCOPIC APPEARANCE**

Warthin's tumour is composed of ciliated, bilayered oncocytic (oxyphilic) epithelium supported by reactive lymphoid stroma. The cystic areas contain amorphous debris.

Warthin's tumour can undergo infarction or degeneration and metaplastic change either spontaneously or secondary to manipulation (e.g. FNAC, incisional biopsy). Benign oncocytic epithelial inclusions are commonly seen in intraparotid and periparotid lymph nodes. When papillary and/or cystic, these have been termed 'embryonal Warthin's tumours' and the phenomenon probably accounts for Warthin's tumour's propensity for multicentricity and bilaterality. Papillary Warthin's tumours may closely mimic oncocytic adenoma (oncocytoma) of salivary origin. Malignant transformation, either carcinomatous or lymphomatous is exceptionally rare (Figure 6.7).

**BENIGN EPITHELIAL NEOPLASMS**

**Squamous cell papilloma**

Papillomas are benign epithelial lesions that can affect the oral cavity, larynx, sinonasal tract, and nasopharynx.

They are typically polyoid or verrucoid lesions arising from the epithelial surface and can be solitary or multiple lesions depending on site and subtype.

**ORAL CAVITY AND OROPHARYNX**

The pathological features of oral cavity and oropharynx papillomata are listed in Table 6.7.

**LARYNX**

Squamous cell papilloma (and recurrent respiratory papillomatosis) is the most common benign epithelial neoplasm affecting the larynx. It has a bimodal distribution with a peak before the age of five and a second between 20 and 40 years of age. There is convincing evidence that recurrent respiratory papillomatosis is due to human papillomavirus (HPV) infection, with HPV6 and 11 as the dominant subtypes.

Macroscopically, the lesions are exophytic or sessile with a fine lobular surface that can be prone to bleeding when subjected to even minor trauma.

Microscopically, the lesions have a typical papilloma appearance of hyperplastic squamous epithelium overlying a fibrovascular core. Branching papillae covered by thin squamous epithelium may be seen, associated with a basal and parabasal cell proliferation. Koilocytes are often focally present in the upper and superficial zones and contain perinuclear halos.

Immunohistochemical and other studies can confirm evidence of HPV infection, but are not required for diagnosis, treatment or to predict clinical behaviour.

**SINONASAL TRACT**

Unlike the oral cavity and the larynx, papilloma of the sinonasal tract is relatively uncommon. Sinonasal papillomas arise from the ectodermally derived ciliated epithelium of the nasal cavity, termed the 'Schneiderian membrane'. There are three morphologically distinct types of papillomas.
Exophytic (fungiform) papilloma typically arises on the septum around the nasal vestibule. It closely resembles verruca vulgaris (filiform viral wart) and is associated with HPV6, HPV11, HPV16 and HPV57b. It has no known malignant potential (Figure 6.8).

Inverted sinonasal papilloma (Ringertz tumour) may present anywhere within the nose and paranasal sinuses, occasionally elsewhere within the upper aerodigestive tract (e.g. larynx, lacrimal apparatus). It shows a complex, arborescent exoendophytic growth pattern with primary, secondary and tertiary ramifications into underlying stroma. Numerous intraepithelial microabscesses are characteristic and stain for macrophage markers. The epithelium may be squamous (usually non-keratinizing), respiratory glandular, transitional cell-like or a mixture in any combination or permutation. There is historically a contentious association with HPV infection, yet to be conclusively resolved. The tumours may be synchronously or metachronously multicentric, taken as evidence supporting the field cancerization effect and because it is difficult to achieve adequate surgical clearance, there is a risk of persistence/recurrence. With each recrudescence, the likelihood of dysplasia and ultimately malignant transformation heightens – invasive squamous cell carcinoma, adenosquamous carcinoma and adenocarcinoma in decreasing frequency supervenes (Figure 6.9).

Cylindrical cell papilloma (microcystic papillary adenoma, oncocytic Schneiderian papilloma) is unassociated with HPV infection. It comprises exophytic fronds of bilayered, well polarized, oncocytic (oxyphilic) epithelium supported by fibrovascular subintima. Microabscesses confined to the epithelium are invariable, distinguishing it from Rhinosporidiosis with secondary oncocytic metaplasia where subepithelial microcysts are more usually seen. There is a predilection for persistence/recurrence if incompletely excised, but malignant transformation is exceptional.

### Table 6.7 Pathological features of oral cavity and oropharynx papillomas.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Squamous papilloma or verruca vulgaris</th>
<th>Condyloma acuminatum</th>
<th>Focal epithelial hyperplasia, Heck’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV status</td>
<td>Approximately half are associated with HPV infection, typically for squamous papilloma HPV6 and 11 and HPV2 and 57 for verruca vulgaris. Other HPV subtypes implicated include 4, 13 and 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroscopic appearance</td>
<td>Wart-like exophytic lesion</td>
<td>Dome-shaped exophytic nodules which are usually larger than squamous papilloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple clusters or patches of soft, plaque-like lesions</td>
<td></td>
</tr>
</tbody>
</table>

HPV, human papilloma virus.

**Figure 6.8** Exophytic/fungiform nasal papilloma. Classical exophytic/fungiform nasal papilloma characterized by its radially symmetrical, acrohyperkeratotic outline (H&E stain, ultralow magnification).

**Figure 6.9** Inverted sinonasal papilloma. Inverted sinonasal papilloma illustrating a papilliform surface. This is composed of non-keratinizing squamous and transitional cell-like epithelium with scattered intraepithelial microabscesses. There is no significant cytonuclear atypia in this field (H&E stain, medium magnification).
Benign mesenchymal tumours

SCHWANNOMA

Schwannomas (neurilemmomas) are benign encapsulated tumours that originate from the Schwann cells of the peripheral nerve sheath. Schwannoma in the head and neck may arise from the cranial nerves including Vth and VIIth–XIIth, sympathetic chain, cervical or brachial plexus. It is the most common neoplasm affecting the temporal bone, vestibular schwannoma and a common site of occurrence is the neck, but it is rare in the oral cavity.

NF2 gene is a tumour suppressor gene which is inactivated in 67 per cent of schwannoma, which are in the main sporadic in origin.

Approximately 2 per cent are due to neurofibromatosis 2, which is an uncommon autosomal dominant (mutation on chromosome 22) condition characterized by the presence of bilateral vestibular schwannomas and an increased incidence of extra- and intracranial meningiomas.

Macroscopic appearance

Schwannomas of the upper aerodigestive tract and temporal bone are unencapsulated and those in the soft tissue are encapsulated. The tumour is attached to an identifiable nerve and is firm to rubbery with a tan-white to yellow colour. At operation, it may be mistaken for a lymph node and excised without seeking to preserve or repair the nerve, thereby sustaining unexpected neurological damage.

Microscopic appearance

The tumour consists of alternating fields of:

1. Antoni A areas formed by fasciculated (herringbone-like), closely packed monomorphous spindle cells with fibrillar cytoplasm. The cells sometimes form a palisaded arrangement around acellular, collagenized foci known as Verocay (neuroid) bodies.
2. Antoni B areas where haphazardly orientated, the spindle cells are randomly arranged within a loose myxoid stroma.

Secondary areas of vascular wall hyalinization, microcystic degeneration, haemorrhage, foam cell infiltration and calcification may be seen. Focal bizarre, hyperchromatic and multinucleate giant cell transformation is sometimes encountered. In the absence of increased numbers of mitoses, abnormal mitotic spindles, necrosis or other atypical features, this is designated ancient change, probably a degenerative phenomenon, which is of no known clinical relevance.

Most schwannomas are immunoreactive for S100 protein distinguishing them from neurofibromas, which are less commonly positive, but also show neurofilament protein-positive fibres. Confident distinction may occasionally be impossible invoking the rubric benign peripheral nerve sheath tumour, not further specified (Figure 6.10).

Paraganglioma

Paragangliomas are tumours of neuroendocrine origin arising from the extra-adrenal paraganglia of the autonomic nervous system. The extra-adrenal paraganglia can be divided into sympathetic, which occur along the axial region of the trunk, and parasympathetic, which are localized almost entirely in the head and neck region in close association to branches of cranial nerves IX and X. They can also be described as functioning or non-functioning.

Much of the clinical terminology to describe paragangliomas is descriptive and historical (glomus tumours, e.g. glomus jugulare, glomus vagale, glomus tympanicum) and chemodectoma (carotid body tumour) – paraganglioma is now widely accepted as the unifying diagnostic term for these neoplasms.

Head and neck paragangliomas have a familial tendency, which has traditionally been stated as 10 per cent, but with greater understanding of the mode of inheritance, it is felt that 50 per cent or more of head and neck paragangliomas are familial. Head and neck paragangliomas are inherited as an autosomal dominant trait with genetic imprinting, which explains why it is only paternal transmission of the gene that leads to development of a paraganglioma even if the father is unaffected. The affected genes code for subunits of succinate dehydrogenase protein, a mitochondrial enzyme. The genes are found on chromosome 1 and 11.
Head and neck paragangliomas are classified according to their site of origin and innervation. They usually arise from three specific areas (Table 6.8).

MACROSCOPIC APPEARANCE

All paragangliomas, irrespective of site have very similar appearance. They are firm well-circumscribed lesions that are yellow, tan, brown or reddish in colour. They can have a thin, but locally thickened, fibrous capsule. They may be locally infiltrative and not easily excised without sacrificing neighbouring structures. Occasionally, there are areas of fibrosis, haemorrhage or necrosis, more so if preoperative embolization has been successfully accomplished.

MICROSCOPIC APPEARANCE

The neoplastic chief cells are arranged in distinctive spherical nests (zellballen) and trabecula within a richly vascularized fibrous stroma. A slender sustentacular cell population typically mantles the cell islands. The chief cells possess cytoplasmic storage granules containing a variety of neuropeptides, whereas the sustentacular cells do not. Chief cells may show random nuclear enlargement and hyperchromasia. While mitoses, necrosis, locally infiltrative growth and lymphovascular emboli raise the index of suspicion for overt malignant behaviour and metastatic risk, conventional histomorphological criteria do not reliably predict aggressive potential in any individual case. They are, therefore, generally all considered to be of borderline malignancy potential.

The chief cells stain positively for neuropeptide products (e.g. chromogranin A, synaptophysin) and CD56. The sustentacular cells are S100 protein immunoreactive. A low Ki67 proliferation fraction is reassuring. With the exception of a proportion of paragangliomas of the cauda equina, all other paragangliomas are epithelial marker negative, which is a useful aid in the differential diagnosis between paraganglioma, carcinoid tumours and pituitary neoplasms. Preoperative embolization procedures induce a variety of degenerative changes (e.g. hydropic injury, haemorrhage, infarction, necrosis) causing diagnostic difficulty, exacerbated by consequent spurious immunohistochemical profiling (Figure 6.11).

The malignant potential of paraganglioma is listed by site in Table 6.9.

MALIGNANT DISEASE

Malignant disease of the head and neck is the sixth most common form of cancer with 65,000 new cases and 350,000 cancer deaths worldwide per annum. The group as a whole accounts for over 8000 cases and 2700 deaths per year in England and Wales. The majority of tumours arise from the epithelial-lined upper aerodigestive tract, but can also occur in connective tissue (sarcoma, etc.), lymphoid tissue (lymphoma), skin (melanoma, squamous and basal cell carcinoma) and major and minor salivary glands. The incidence of laryngeal cancer in England during 2007 was 5.7 per 100,000 (1436 cases) in males and 1.1 per 100,000 (278 cases) in females. The incidence rate of cancer of the lip, oral cavity

<table>
<thead>
<tr>
<th>Name of paraganglion</th>
<th>Location</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid body</td>
<td>Carotid bifurcation</td>
<td>Most common site (60%) for paraganglioma in head and neck. They occur primarily in adults typically 40–50 years of age. Hypoxia is a risk factor and explains the gender difference (males:females = 8.3:1) seen in altitudes greater than 2000 m</td>
</tr>
</tbody>
</table>
and pharynx was 12.8 per 100,000 (3,215 cases) in males and 6.6 per 100,000 (1,717 cases) in females (www.statistics.gov.uk/statbase/Product.asp?vlnk=8843). Skin cancer, including cutaneous malignant melanoma (and also primary intracranial tumours) are conventionally excluded from the epidemiological statistics relating to head and neck cancers.

Anatomically, the head and neck is divided into over 30 specific subsites (ICD10 codes) and malignancy at each one individually is relatively uncommon, though many have similar behaviour and progression. Knowledge of the subsite helps determine the likely pattern of spread to cervical lymph nodes and aids in treatment planning for surgery, radiotherapy and/or chemotherapy.

### TUMOUR STAGING

Cancer of the head and neck, due to the diversity of pathology and the variation in progression due to anatomical subsites, cannot be meaningfully staged by a single, generic schema.

An ideal staging system has many attributes: precise, site-specific, reproducible, valid, minimal interobserver variability and stable, but must also be simple, easy to use, flexible to account for new advances and widely used.

The TNM system, which evolved from the work of Pierre Denoix in the 1940s, is the only widely accepted staging system available endorsed by both the International Union Against Cancer (UICC) and the American Joint Committee for Cancer Staging (AJCC). There are international expert committees that keep the system under formal continual review and the seventh edition has recently been published by both the AJCC and UICC with implementation from January 2010. There have been some minor changes in TNM staging of the head and neck compared to the sixth edition (2002) and these have been highlighted below (see also Chapter 4, Assessment and staging).

Four categories within the TNM schema are described:

1. **Clinical.** cTNM or TNM is based on findings and assigned prior to starting first definitive treatment.
2. **Pathological.** pTNM is based on the cTNM modified by further information obtained from surgery, especially pathological examination.
3. **Retreatment.** rTNM is used when further treatment is required or recurrence noted after a disease-free interval.
4. **Autopsy.** aTNM is used when the cancer is only classified from the results of post-mortem examination and no evidence of cancer was evident prior to death.

<table>
<thead>
<tr>
<th>Paraganglioma</th>
<th>Malignant potential</th>
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<tbody>
<tr>
<td>Carotid body</td>
<td>Varies from 6–12%(^\text{11,36,37}) and sporadic tumours more likely than familial to be malignant(^\text{11})</td>
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<td>Jugulotympanic</td>
<td>4%(^\text{36})</td>
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<tr>
<td>Vagal</td>
<td>16%(^\text{36})</td>
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Table 6.9 Malignant potential of paraganglioma by site.

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<td>Vagal</td>
<td>16%(^\text{36})</td>
</tr>
</tbody>
</table>

Table 6.9 Malignant potential of paraganglioma by site.
Other descriptors of TNM may occasionally be used and include:

- ‘m’ suffix, which is used when there is more than one primary at a single site pT(m)NM;
- ‘y’ prefix is used when classification is performed during or after initial multimodality therapy ypTNM or yCTNM.

Tumour differentiation refers to how well developed or mature the malignant cells are. Well-differentiated cells resemble normal cells and tend to grow and spread at a slower rate. There is, however, often morphological heterogeneity both between different tumours of the same type and also within the same tumour. Conventionally, tumours are histologically subtyped according to their best differentiated component. They are graded with reference to their worst differentiated elements on the premise that it is these which will behave most aggressively, and thereby be the major determinant of prognosis.

- Gx, grade cannot be assessed
- G1, well-differentiated
- G2, moderately differentiated
- G3, poorly differentiated.

The presence or absence of residual tumour is classified as:

- Rx, the presence of residual tumour cannot be assessed
- R0, no residual tumour is present
- R1, microscopic residual tumour
- R2, macroscopic residual tumour.

**T classification by anatomical subsite**

For T classification by anatomical subsite, see Table 6.10. 40

**Stage grouping**

See Chapter 4, Assessment and staging.

**CARCINOMAS**

The majority of tumours of the head and neck develop from the epithelial-lined upper aerodigestive tract.

**Squamous cell carcinoma**

Squamous cell carcinoma (SCC) and its variants represent by far the most common malignant tumour affecting the head and neck region, accounting for approximately 95 per cent of all primary tumours of the oral cavity, oropharynx, larynx, hypopharynx and the most common epithelial tumour of the sinonasal tract, but it is uncommon in the major salivary glands and thyroid, although these may be affected by direct contiguous invasion from neighbouring structures or metastatic spread. Head and neck squamous cell carcinoma (HNSCC) arises from skin or other mucosa-lined tissue.

Typically, HNSCC spreads by direct invasion or via regional lymphatics, although haematogenous spread, especially to the lungs, is possible.

**SQUAMOUS EPITHELIAL DYSPLASIA**

HNSCC, especially of the oral cavity and larynx, typically originates from a non-invasive (in situ) neoplastic epithelial precursor lesion, which may be localized or represent wider field change phenomenon. The stages of preinvasive proliferation, ranging from squamous hyperplasia through to carcinoma in situ are cumulatively termed squamous intraepithelial lesion (SIL). Further subclassification denotes proposed ‘epithelial dysplasia’ or generically ‘intraepithelial neoplasia’ qualified either by the epithelial type (e.g. squamous intraepithelial neoplasia (SIN), keratinocyte intraepithelial neoplasia (KIN)) or the anatomical subsite (e.g. laryngeal intraepithelial neoplasia (LIN), oral intraepithelial neoplasia (OIN), etc.).

Progression to invasive malignancy is not inevitable, which implies that such lesions may remain stable over time or possess the capacity to regress – indeed most lesions do not proceed to invasive carcinoma in the observed timescale of the studies published to date. The more severe the dysplasia, pari passu the greater the risk of transformation into malignant disease. For example, the risk of malignant transformation of oral dysplastic lesions is 10.3 per cent for mild to moderate dysplasia and 24.1 per cent for severe dysplasia and carcinoma in situ (CIS, pTis). 41 In the larynx, the risk of progression to invasive carcinoma is 0–11.5 per cent for mild dysplasia, 0–45 per cent for moderate dysplasia, 19–54.5 per cent for severe dysplasia and 15.7–63 per cent for CIS. 42

It follows that the aetiology of squamous epithelial dysplasia is identical to that of HNSCC and is explained in greater detail below.

Macroscopically, these lesions are irregular, circumscribed lesions with a white (leukoplakia), red (erythroplakia) or variegated appearance (leukoerythroplakia) (Figure 6.12). It can be difficult to differentiate macroscopically between dysplasia and invasive carcinoma, ergo microscopical analysis is vital.

Histologically, the diagnosis of squamous epithelial dysplasia is based on both cytonuclear and architectural abnormalities, which are broadly comparable across various sites both within the head and neck and outside (e.g. oral intraepithelial neoplasia (OIN), squamous intraepithelial lesion (SIL), cervical intraepithelial neoplasia (CIN), vulval intraepithelial neoplasia (VIN), anal intraepithelial neoplasia (AIN), penile intraepithelial neoplasia (PIN), etc.), even though the pathogenesis and exact biological implications at each site may differ. This may be further graded according to the degree of epithelial thickness involved (e.g. low/high grade, SIN 1/2/3, mild/moderate/severe/CIS). Full thickness abnormality corresponds to intraepithelial carcinoma (carcinoma in situ, pTis) – note that proponents of the SIN nosology merge the categories of SIN 3 and carcinoma in situ (intraepithelial carcinoma, pTis).

The grading of dysplasia remains challenging with over 20 systems developed for this purpose, though as yet neither generally ratified criteria nor internationally unified terminology. All the current systems are subjective and, due to the
### Table 6.10  T classification by anatomical subsite.\(^{40}\)

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>T classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip and oral cavity</td>
<td>T1: Tumour ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T2: Tumour &gt; 2 cm, but &lt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T3: Tumour &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T4a: Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>T4b: Very advanced disease</td>
</tr>
<tr>
<td></td>
<td>Oral cavity – tumour invades cortical bone, deep/extrinsic muscles of tongue, maxillary sinus or skin of face</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>T1: Tumour ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T2: Tumour &gt; 2 cm, but &lt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T3: Tumour &gt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T4a: Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>T4b: Very advanced disease</td>
</tr>
<tr>
<td></td>
<td>Tumour invades masticator space, pterygoid plates and skull base, or encases internal carotid artery</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>T1: Tumour limited to one subsite of hypopharynx and ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td></td>
<td>T2: Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures &gt; 2 cm, but &lt; 4 cm in greatest dimension, without fixation of the hemilarynx</td>
</tr>
<tr>
<td></td>
<td>T3: Tumour &gt; 4 cm in greatest dimension, or with fixation of the hemilarynx</td>
</tr>
<tr>
<td></td>
<td>T4a: Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>T4b: Very advanced disease</td>
</tr>
<tr>
<td></td>
<td>Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue</td>
</tr>
<tr>
<td>Larynx – supraglottis</td>
<td>T1: Tumour limited to one subsite of the supraglottis with normal vocal cord mobility</td>
</tr>
<tr>
<td></td>
<td>T2: Tumour invades mucosa of more than one adjacent subsite of supraglottis, glottis or region outside supraglottis without fixation of the larynx</td>
</tr>
<tr>
<td></td>
<td>T3: Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space and/or with minor thyroid cartilage erosion</td>
</tr>
<tr>
<td></td>
<td>T4a: Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>T4b: Very advanced disease</td>
</tr>
<tr>
<td></td>
<td>Tumour extends through thyroid cartilage, and/or invades tissue beyond the larynx; soft tissues of the neck, deep/extrinsic muscles of the tongue, strap muscles, thyroid gland or oesophagus</td>
</tr>
<tr>
<td>Larynx – glottis</td>
<td>T1: Tumour limited to the vocal cord(s), including involvement of anterior or posterior commissure with normal mobility</td>
</tr>
<tr>
<td></td>
<td>T1a – Tumour limited to one vocal cord</td>
</tr>
<tr>
<td></td>
<td>T1b – Tumour involves both vocal cords</td>
</tr>
<tr>
<td></td>
<td>T2: Tumour extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility</td>
</tr>
<tr>
<td></td>
<td>T3: Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space and/or with minor thyroid cartilage erosion</td>
</tr>
<tr>
<td></td>
<td>T4a: Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>T4b: Very advanced disease</td>
</tr>
<tr>
<td></td>
<td>Tumour invades prevertebral fascia, mediastinal structures or encases internal carotid artery</td>
</tr>
<tr>
<td>Larynx – subglottis</td>
<td>T1: Tumour limited to subglottis</td>
</tr>
<tr>
<td></td>
<td>T2: Tumour extends to vocal cord(s) with normal or impaired vocal cord mobility</td>
</tr>
<tr>
<td></td>
<td>T3: Tumour limited to larynx with vocal cord fixation</td>
</tr>
<tr>
<td></td>
<td>T4a: Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>[Continued over]</td>
</tr>
</tbody>
</table>
Table 6.10  T classification by anatomical subsite. (continued)

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour extends through cricoid or thyroid cartilage, and/or invades tissue beyond the larynx; soft tissues of the neck, deep/extrinsic muscles of the tongue, strap muscles, thyroid gland or oesophagus</td>
<td>T4b Very advanced disease Tumour invades prevertebral fascia, mediastinal structures or encases internal carotid artery</td>
</tr>
<tr>
<td>Major salivary glands T1</td>
<td>Tumour ≤2 cm in greatest dimension without extraparenchymal extension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 2 cm, but &lt; 4 cm in greatest dimension without extraparenchymal extension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour &gt; 4 cm in greatest dimension and/or tumour with extraparenchymal extension</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced disease Tumour invades skin, ear canal, facial nerve or mandible</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced disease Tumour invades pterygoid plates, skull base or encases internal carotid artery</td>
</tr>
<tr>
<td>Nasal cavity and ethmoid sinus</td>
<td>T1 Tumour restricted to one subsite of nasal cavity or ethmoid sinus with or without bony invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, and palate or cribiform plate</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced disease Tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinus</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced disease Tumour invades any of the following orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2 (maxillary division of trigeminal), nasopharynx and clivus</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>T1 Tumour limited to mucosa with no erosion or destruction of bone</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour causing bone erosion or destruction, including extension into hard palate and/or middle meatus only</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa and ethmoid sinuses</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced disease Tumour invades any of the following orbital contents beyond floor and medial wall including anterior orbital contents, skin of cheek, infratemporal fossa, pterygoid plates, cribiform plate, sphenoid or frontal sinus</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced disease Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2 (maxillary division of trigeminal), nasopharynx and clivus</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>T1 Confined to nasopharynx, oropharynx and/or nasal cavity without parapharyngeal extension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour with parapharyngeal extension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades bony structures and/or paranasal sinuses</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space</td>
</tr>
<tr>
<td>Regional lymphadenopathy</td>
<td>Nx Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>All sites except nasopharynx N0</td>
<td>No regional lymphadenopathy</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node ≤ 3 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node &gt; 3 cm, but ≤ 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>N1 Unilateral cervical or bilateral retropharyngeal lymph node metastasis above the supraclavicular fossa, ≤ 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Bilateral cervical lymph node metastasis above the supraclavicular fossa, ≤ 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3a</td>
<td>Lymph node metastasis &gt; 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3b</td>
<td>Lymph node metastasis in the supraclavicular fossa</td>
</tr>
</tbody>
</table>

Extracapsular spread (ECS+ or ECS−) is an added descriptor that does not change the nodal staging described above.
difficulty in distinguishing between normal and often subtly abnormal epithelium, they are susceptible to discrepant interobserver and intraobserver reproducibility. In reality, dysplasia is a dynamic process manifest as a continuous morphological spectrum, therefore, the rigorous application of discrete categories, whatever their arbitrary histological basis is destined to be problematical. Immunohistochemistry, molecular and other biomarkers are presently of limited assistance in resolving this.

The three most commonly used systems (Table 6.11) are:

1. The WHO dysplasia grading system in its present incarnation since 2005, which is similar to that used for precursor lesions in other parts of the body (e.g. uterine cervix, etc.).
2. The similarly based generic squamous intraepithelial neoplasia (SIN) style terminology, loosely modelled on the Bethesda system as originally devised for the uterine cervix.
3. The Ljubljana classification originally proposed in 1971 and refined by a working group of the European Society of Pathology in 1999, which is structured around points of clinical decision, that is minimal follow up, close follow up or surgery.

Aetiology

The main risk factors for HNSCC are tobacco and alcohol use, which either alone or combined, are implicated in 75 per cent of all HNSCC. Tobacco alone increases the risk of cancer occurrence by two- to three-fold, but acts synergistically with alcohol leading to a multiplicative rather than additive increase. Increased duration of exposure to
tobacco and/or alcohol increases the risk of developing HNSCC. Tobacco contains a number of known carcinogens, e.g. polynuclear aromatic hydrocarbons, which cause DNA damage leading to gene mutations. Alcohol causes DNA damage and gene mutation by a number of mechanisms. These include the effect of acting as a solvent for other carcinogens, nutritional deficiencies, acetaldehyde (a byproduct of alcohol metabolism) and the direct effect of ethanol.

Increasingly, since first described in 1983, it is recognized that the human papilloma virus, especially HPV serotypes 16 and 18, is implicated in oropharyngeal HNSCC independent of tobacco and alcohol. HPV-positive tumours typically affect non-smokers, non-drinkers and younger patients. HPV-related HNSCC behaves in a less aggressive manner than non-HPV HNSCC and has a better long-term prognosis. This HPV effect is less significant in larynx and other subsites.

SCC of the lip is associated with sun exposure and pipe smoking. Sinonasal SCC is linked to nickel and chromate exposure and woodworking. Dietary deficiencies have also been linked to the development of HNSCC, especially vitamins (A, C and E), foods (fruit, vegetables and dairy) and elements (iron especially when associated with iron-deficiency anaemia of Plummer–Vinson–Kelly syndrome, which is associated with postcricoid SCC).

Oral cavity SCC is particularly common in India where a third of all cancers originate in the head and neck. The widespread chewing of betel nut, which causes both oral submucous fibrosis, a recognized premalignant condition, and oral cavity SCC has been implicated, as well as the practice of inverse smoking.

HNSCCs are typically sporadic, but a familial inheritance has been noted in some cases. The risk of HNSCC is also increased in patients with any syndrome associated with an increased risk of cancer. Patients with Fanconi’s anaemia have a 700-fold increased risk and the cancer is usually diagnosed in the third decade.

PATHOPHYSIOLOGY

HNSCC is a heterogeneous disease, but a hypothetical progression model has been proposed. Histological progression from normal epithelium to hyperplasia, dysplasia, carcinoma in situ and finally invasive carcinoma is related to a number of factors, including genetic changes causing genetic instability leading to cellular change. Genetic changes include the sequential inactivation of tumour suppressor genes and activation of proto-oncogenes by deletions, promoter methylation, gene amplification and point mutations, etc. Carcinogens produced by tobacco, which include nitrosamines and benz-(a)-pyrene, produce mutations in p53 associated with HNSCC.

The molecular changes are due to a number of genetic alterations, which include loss of heterozygosity (LOH) of 9p21, seen in 70–80 per cent of HNSCC. Other abnormalities include LOH 3p, 17p, 11q and 13q.

The E6 and E7 viral oncoproteins on HPV16 and 18 cause inactivation of tumour suppressor genes and activation of proto-oncogenes by deletions, promotor methylation, gene amplification and point mutations, etc. Carcinogens produced by tobacco, which include nitrosamines and benz-(a)-pyrene, produce mutations in p53 associated with HNSCC.

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MACROSCOPIC APPEARANCE

HNSCC appearance varies depending on subsite, but can be an exophytic or ulcerative lesion with an irregular friable, pale surface. On skin, it typically looks like a non-healing scab or ulcer, which can intermittently bleed. On mucosal surfaces, lesions typically start as whitish or reddish plaque-like lesions.
leukoplakia or erthyroplakia), which then progress to ulcerated, or fungating masses with irregular indurated borders (Figure 6.13). Invasive SCC will typically arise within a premalignant lesion and can be difficult to distinguish with the naked eye and hence the opportunity to biopsy areas of concern even within a previously diagnosed lesion must not be missed.

**MICROSCOPIC APPEARANCE**

Histologically, mature squamous epithelial cells possess dense haematoxyphilic (purple/blue on H&E) nuclei with a low nucleus–cytoplasmic ratio. The more superficial cells contain smaller, pyknotic nuclei. The cytoplasm is densely eosinophilic (pink on H&E), sometimes orange and finely reticulated owing to keratin intermediate filaments. Mitoses are normally only a feature of the basal/parabasal (reserve/germinative cell or progenitor compartment) layers.

The histological appearance of HNSCC is very similar across all sites in the head and neck (larynx, skin, etc.) and further afield. Well-differentiated SCC characteristically shows cytoplasmic and/or extracellular keratinization plus intercellular prickles (spinous processes corresponding to desmosomes highlighted by cell shrinkage allowing separation between adjacent cell membranes). The term ‘epidermoid’ is employed for tumours displaying a subjectively squamoid morphology, albeit without this objective evidence of squamous differentiation proper.

Malignant squamous cells display some or all of the following features:

- irregular shape and orientation;
- increased and abnormal mitoses;
- nuclear hyperchromatism;
- coarse and clumped chromatin;
- nuclear pleomorphism;
- elevated nucleus–cytoplasmic ratio;
- prominent nucleoli and macronucleoli;
- premature keratinization (dyskeratosis) or loss of keratin production;
- disordered cell polarity;
- disorganized growth.

The defining feature of invasive HNSCC is breach of the subepithelial basement membrane allowing malignant cells to infiltrate into normal tissue, thereby gaining access to lymphatics, blood vessels and nerves (Figure 6.14). Typically, carcinoma in situ or areas of dysplasia will surround invasive HNSCC, although this is by no means invariable. This phenomenon of field cancerization reflects the long-term exposure of head and neck mucosa to carcinogens causing genetic alterations, which enable multifocal tumours to arise due to independent genetic events.54, 55

Microscopical description includes:

- histological subtype or variant, if applicable;
- histological grade;
- presence or absence of keratinization;
- histological growth pattern;
- quality of advancing margin (cohesive or non-cohesive margin: the latter is associated with a worse prognosis);
- presence of necrosis;
- intensity of host lymphocytic or other inflammatory cell response;
- stromal desmoplasia.

Figure 6.13  Laryngeal squamous cell carcinoma. (a) Total laryngectomy specimen opened in the posterior sagittal plane to disclose advanced, fungating carcinoma effacing much of the epilarynx and supraglottis with local extension on to the left true vocal cord. (b) Transverse section through this confirms bilateral midline tumour herniating through the anterior commissural ligament (Broyles’ ligament) into anterior strap musculature without naked eye evidence of laryngeal framework destruction. Other tissue planes (weak spots) allowing tumour to gain access outside the larynx include the paraglottic space and the cricothyroid interspace.

(leukoplakia or erthyroplakia), which then progress to ulcerated, or fungating masses with irregular indurated borders (Figure 6.13). Invasive SCC will typically arise within a premalignant lesion and can be difficult to distinguish with
The terms 'early stromal invasion', 'minimally invasive carcinoma' and 'microinvasive carcinoma' are sometimes casually used to denote early invasive squamous cell carcinoma of limited infiltration. However, these presently have no agreed, validated definition in the head and neck and are, therefore, potentially confusing. 'Superficial extending carcinoma' implying lack of involvement of deep structures and 'deeply invasive carcinoma' denoting infiltration into muscle and beyond, while biologically valid concepts, are also of limited clinical utility. It is more helpful to measure tumour depth and/or thickness and overall dimensions, and place this within the recognized TNM schema with any relevant subjective descriptive comments, until such time as there is a clinically relevant evidential basis for these other definitions.

It is also important to assess for the presence of malignant cells within lymphovascular channels and also neurotropism, signifying vascular or perineural invasion, which are associated with an unfavourable prognosis.

Cytologically, SCC may be so well differentiated that it is impossible to reliably discriminate it from non-neoplastic (hyperplastic, regenerative/reparative, metaplastic, post-irradiation) squamous epithelium, for example in FNAC from inflamed branchiogenic or other benign cysts. Furthermore, the presence of invasion per se cannot be directly evaluated on FNAC – dissociated dysplastic squamous cells may be cytomorphologically indistinguishable from detached invasive carcinomatous squamous cells proper. Paradoxically, extreme reactive atypia may exceed by some degree the limited pleomorphism of a well-differentiated invasive SCC. The presence of inflammation and necrosis (tumour diathesis), marked atypia and abnormal mitoses favour infiltration, but are by no means infallible. Obviously, the context is all important and, in experienced hands, FNAC from a cervical lymph node containing abnormal squamae against a background of...
proven SCC may be reasonably taken as presumptive evidence of a secondary deposit until otherwise proven.

For these reasons, only under exceptional circumstances should radical cancer treatment be undertaken on the basis of a primary diagnosis reached by FNAC without more definitive tissue diagnosis and even then rigorous clinico-radiological correlation must be exercised.

**IMMUNOHISTOCHEMISTRY**

The association of HPV and HNSCC (Figure 6.15) has become more recognized in the last few years, but testing for evidence of HPV remains difficult and controversial. PCR and/or ISH studies remain the gold standard to identify the presence of high-risk HPV DNA (HPV16 and 18). Semi-quantitative immunohistochemistry for p16 protein is used as a surrogate marker for HPV oncoprotein activity with the caveat that immunostaining is a less sensitive technique, which ought to be validated against PCR/ISH with known positive and negative controls and subject to rigorous quality control.

**HNSCC VARIANTS**

A number of morphological variants of SCC are recognized, which include among others:

**Verrucous carcinoma** (VC, Ackerman’s tumour) is a controversial manifestation of well-differentiated SCC, typically occurring in the oral cavity but rarely said to occur in the larynx (1–3 per cent of all laryngeal malignancies), hypopharynx, sinonasal tract and nasopharynx plus other sites outside the head and neck.

Verrucous carcinoma, to the naked eye is a warty, exophytic lesion that arises from a broad (sessile) base. It has a superficial spreading growth, but can be deeply destructive extending into muscle, cartilage or bone. Histologically, VC lacks significant atypia and is characterized by blunt incursions and an expansile advancing margin sometimes eliciting brisk lymphocytic response. If adequately sampled, approximately 20 per cent of VCs contain areas of conventional pattern SCC, although often very localized and it is these elements, which determine overall prognosis ab initio independent of irradiation – some regard these as hybrid or composite tumours.

Incisional biopsy diagnosis of VC is problematical as its predominant bland morphology may be indistinguishable from benign squamoproliferative lesions on superficial or limited volume material. Typically, three or four biopsies are required, or even excision biopsy, before the overall architecture is appreciated and the diagnosis is seriously entertained. A high index of pathological suspicion and clinical persistence are thus prerequisites.

**Spindle cell carcinoma** (carcinosarcoma, sarcomatoid carcinoma, carcinoma with sarcomatoid stroma, Lane tumour) (Figure 6.16) occurs in the upper respiratory tract or less commonly the oral cavity. Patients are typically elderly males and a significant number will have had previous irradiation.

Spindle cell carcinoma usually has a polypoidal, exophytic configuration with either a broad base or narrow pedicle, which can occasionally autoamputate and be expectorated by the patient. The surface tends to be ulcerated. It is usually a bimorphic lesion with areas of SCC, either in situ or invasive, associated with bizarre spindle cell and/or giant cell proliferation of sarcomatoid appearance. The squamous component can be difficult to identify due to the ulceration and the sarcoma-like component predominates. Immunohistochemistry may be helpful, although the spindle cells are often negative for epithelial markers, sometimes even immunoinert.

**Papillary squamous cell carcinoma** (confusingly also known as ‘ verrucous squamous cell carcinoma’, apt to be confused with Ackerman’s tumour) is an uncommon variant. It may affect most anatomical subsites of the head and neck, including the larynx and hypopharynx.

Macroscopically, the tumour is similar to verrucous carcinoma, but lacks the typical surface keratinization. Microscopically, the lesion is composed of obviously atypical squamous cells overlying fibrovascular papilliform stromal cores. The tumour behaves in a similar manner to conventional HNSCC and management is therefore similar.

**Figure 6.16** Sarcomatoid carcinoma of epilarynx. (a) Cross-section of epiglottic resection specimen, for biopsy-proven sarcomatoid carcinoma. This is ulcerated and polypoidal, but also infiltrates deeper, penetrating into and through epiglottic cartilage. (b) Representative field beneath the tumour surface exhibiting highly pleomorphic spindle and bizarre giant cells with abnormal mitoses reminiscent of undifferentiated pleomorphic sarcoma (H&E stain, high magnification).
Adenosquamous carcinoma is an uncommon variant of HNSCC, which is considered aggressive and associated with a poor prognosis. It predominantly affects males in the sixth or seventh decade. The larynx, and occasionally the hypopharynx, is the most commonly affected site. Macroscopically, the tumour resembles a typical HNSCC. Microscopically, the tumour is characterized by the presence of conventional squamous cell carcinoma admixed with a variable proportion of true glanduloductal elements indicative of divergent differentiation. Mucin histochemistry and keratin immunoprofiling may aid distinction from acantholytic squamous cell carcinoma with pseudoglandular growth and also from mucoepidermoid carcinoma.

Basaloid/basaloid-cystic squamous cell carcinoma is a high-grade aggressive variant of squamous cell carcinoma typically found in middle-aged male patients affecting the oropharynx, larynx and hypopharynx (Figure 6.17). Macroscopically, these are firm to hard tumours with central necrosis and superficial ulceration. Microscopically, the tumour is infiltrating and deeply invasive and presents a typical basaloid appearance consisting of pleomorphic cells arranged in a lobular configuration with palisading. Cystic degeneration with central comedonecrosis is often a feature. There may be minimal objective evidence of squamous cell differentiation.

Other unconventional variants include acantholytic (pseudoadenoidal/pseudoangiosarcomatoid,) small cell, clear cell, giant cell and lymphoepithelial carcinoma. In practice, many SCCs are heterogeneous in pattern at least focally (Figure 6.18).

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a distinct subtype of squamous cell carcinoma that classically originates from nasopharyngeal mucosa, occasionally from other head and neck sites, rarely further afield. Worldwide, it is an uncommon disease with an incidence of less that 1 per 100 000, but has a very distinct geographical distribution. In China, 18 per cent of all adult cancers are NPC and it is especially common in northern provinces, Kwantung and Taiwan, but is uncommon in children (2 per cent). In contrast, 10–20 per cent of all paediatric cancers in northern and central Africa are NPC. Ethnic groups with intermediate risk include Greenland Eskimos and Maghrebin Arabs, but Caucasian populations have the lowest risk. Other factors implicated in the development of NPC include Epstein–Barr virus (EBV) and dietary factors, especially a high intake of salted fish and preserved vegetable products.

Macroscopically, the tumour can be a bulging, exophytic and lobulated, or ulcerative mass. Occasionally, there may be
no visible tumour, necessitating blind biopsy of the nasopharynx.

Microscopically, NPC is classified according to the WHO system, which is dependent on the presence or absence of keratinization. Twenty-six per cent of tumours contain more than one type and are then classified according to the dominant type:

- **I. Keratinizing squamous cell carcinoma** represents approximately 25 per cent of NPC in North America, but only 2 per cent of Chinese patients. This type is rarely found in patients less than 40 years of age. Like HNSCC in other sites, this type of NPC can be classified as well, moderately or poorly differentiated. The cells grow in well-defined nests with easily demonstrable intercellular bridges and keratin pearl formation. The stroma undergoes a desmoplastic response to invasive growth.

- **II. Non-keratinizing NPC**, which is associated with EBV, can be divided into differentiated or undifferentiated, but is of no clinical or prognostic significance:
  - **Differentiated non-keratinizing NPC** which is the least common subtype accounting for 12 per cent worldwide (2 per cent in China). As the name suggests, there is little or no evidence of keratinization, vague intercellular bridges and it may undergo cyst formation. The growth pattern is analogous to transitional cell carcinoma. There is no desmoplastic response to invasive growth.
  - **Undifferentiated non-keratinizing NPC** (undifferentiated carcinoma of nasopharyngeal type, UCNT, lymphoepithelial carcinoma) is the most common subtype accounting for approximately 63 per cent of cases, rising to 95 per cent in China, and is the most common type to affect children. The cells possess round nuclei, prominent eosinophilic nucleoli, and/or dispersed or microvacuolated chromatin with scant cytoplasm. There is generally a prominent non-neoplastic intratumoral and peritumoral lymphoid cell infiltrate, though this may on occasion be sparse. When there is a diffuse, non-cohesive growth pattern, such malignant cells are easily overlooked on cursory inspection. Other recognized growth patterns include cohesive or nested cells. There is no desmoplastic response to invasive growth.

Immunohistochemistry can be helpful in UCNT. Epithelial cell markers highlight the malignant cells and lymphoid cell markers confirm the reactive lymphocytosis and its characteristic distribution. Antibodies against EBV LMP-1 (latent membrane protein 1) are less sensitive than in-situ EBER (EBV encoded early RNA) studies. These are more usually positive in Asian than European and North American patients, reflecting the strong association between NPC and EBV (Figure 6.19).

**Basal cell carcinoma**

Basal cell carcinoma (BCC) is the most common skin malignancy, especially in geographical areas with a predominantly Caucasian population. Australia accounts for 80 per cent of non-melanoma skin malignancies. The tumour can involve skin in any region, but most commonly affects the head and neck region (85–93 per cent) and very rarely metastasizes (0.1 per cent). There is a high risk (35–50 per cent) of developing further lesions at other sites in the head and neck or distant region.

According to the UICC/AJCC TNM classification, carcinoma of the vermilion border of the lip and commissures qualifies as a head and neck cancer, though in practice there may be some degree of collaboration with the dermatology multidisciplinary team (MDT) in the management of such patients, dependent upon local circumstances.

There are myriads of histological patterns of BCC, although these can be more broadly categorized as low-risk variants (e.g. nodular, nodulocystic, adenoidal, keratotic, pigmented) and high-risk variants (e.g. superficial/multifocal, infiltrative, morphoeic/fibrosing, micronodular,
basi-squamous) according to their propensity to locally aggressive behaviour and/or risk of local recurrence. In practice, many BCCs display more than one growth pattern.

**EPIDEMIOLOGY**

The incidence of BCC has been increasing over the last few decades. There are a number of risk factors associated with the development of BCC, which are listed below.

**Risk factors**

- Cumulative ultraviolet (UV) exposure including the potentiating effect of some chemicals and severe sunburn during childhood and adolescence.
- Patients with fair skin (Fitzpatrick types I and II), which can be associated with red hair, are at a higher risk than patients with dark skin (Fitzpatrick type VI).
- Exposure to ionizing radiation.
- Patients who are immunosuppressed, e.g. AIDS or transplantation.
- Arsenic and other chemical exposure due to their toxic effect.
- A number of syndromes are associated with the development of BCC, including Gorlin’s syndrome, xeroderma pigmentosum, and epidermolysis verruciformis.

**MACROSCOPIC APPEARANCE**

Growth patterns of basal cell carcinomas are outlined in Table 6.12.

**MICROSCOPIC APPEARANCE**

BCC are composed of hyperchromatic basaloid cells within a fibromucinous stroma. The cells are typically small and uniform. Rarely, they can contain giant tumour cells, clear cells, granular cells and signet ring cells. Mitoses are conspicuous.

Most BCCs are clearly invasive and can infiltrate deeply when located in regions of embryonic fusion planes (e.g. around the nose and ears). Whether superficial BCC represents in-situ or early invasive disease remains enigmatic (Figure 6.20).

In most cases, BCC is distinctive on routine examination, but occasionally immunohistochemistry is employed to aid discrimination from SCC or other neoplasms – both SCC and BCC characteristically express intense and diffuse high molecular weight cytokeratins, cytokeratin 5 (or cytokeratin 5/6) and nuclear p63 staining, thus absence of staining with these markers merits consideration of some other diagnosis. Most SCCs show substantial epithelial membrane antigen (EMA) positivity, whereas BCC is usually negative. BCC is typically immunoreactive for Ber-EP4, unlike cutaneous SCC, which is usually negative though non-cutaneous SCCs may sometimes express this marker. Smooth muscle actin (SMA) positivity is seen in a significant proportion of BCCs, but rarely in cutaneous SCC. BCCs are generally diffusely bcl-2 positive with skin SCCs being negative or only focally staining. bcl-6 is positive in a minority of SCCs, but rarely positive in BCC. p16 immunoreactivity is expressed at a higher frequency in SCC compared to BCC and broadly correlates with the histological grade of SCC.

The status of squamous differentiation in BCC is historically controversial. There is no consensus definition for usage of the term ‘basi-squamous carcinoma’. The descriptor ‘metatypical’ is sometimes used to designate rare tumours with intermediary features between BCC and SCC. Nonetheless, BCCs showing moderate/severe squamous cell atypia portend a higher risk of recurrence and/or metastasis. A minor degree of squamous cell atypia is not unusual in BCCs showing trichogenic differentiation and this is of no known biological significance.

**Adenocarcinoma**

This is a glandular malignancy that typically affects the sinonasal tract and specifically has no features diagnostic of the various salivary gland adenocarcinomas.

There are two main subtypes of adenocarcinoma:

1. Intestinal type adenocarcinoma
2. Non-intestinal type adenocarcinoma.
EPIDEMIOLOGY

Adenocarcinoma, along with the salivary gland type malignancies, account for 10–20 per cent of sinonasal tumours.\footnote{11} Intestinal-type adenocarcinoma is associated with cumulative exposure to hard wood dust and leather dust and the tumour typically occurs in the ethmoid sinus.\footnote{63} The tumour can arise from any sites in the sinonasal tract, usually the upper part of the nasal cavity or maxillary sinus, but in these cases there is usually no association with wood dust exposure.\footnote{64}

There does appear to be a male preponderance and this is likely due to occupational exposure.\footnote{11}

Sinonasal intestinal-type adenocarcinoma may be morphologically and immunohistochemically indistinguishable from metastatic colorectal adenocarcinoma.

MALIGNANT SALIVARY GLAND DISEASE

Malignant salivary gland tumours are very uncommon and represent approximately 0.5 per cent of all malignancies, 5 per cent of all head and neck cancers and an incidence in the Western world of 2.5–3/100 000/year.\footnote{13}

Despite the low incidence, over 40 named malignant salivary gland neoplasms are recognized (Table 6.13). This section will describe the pathological characteristics of the more common malignant neoplasms and the authors recommend reference to a specific head and neck pathology atlas for information regarding less common tumours.\footnote{11, 18, 31}

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is the most common malignant salivary gland neoplasm (12–29 per cent of all salivary gland malignancies).\footnote{18} It typically affects the parotid gland, but may also occur in the minor salivary glands. The tumour is triphasic comprising goblet cell mucocytes, epidermoid cells (usually with little keratinization) and nondescript cells of intermediate size and shape.

MACROSCOPIC APPEARANCE

There is a low frequency of mucoepidermoid tumour in the UK (2 per cent), compared with the rest of Europe (15–20 per cent). It is found more frequently in female patients and can present at any time between the first and ninth decade, but peaks in the fifth decade.\footnote{31, 65} The major risk factor for development is previous therapeutic radiation exposure with a latent period of 7–32 years.\footnote{31} The growth and outcome is influenced by the histological grade of the tumour.

MACROSCOPIC APPEARANCE

The tumour has a variety of appearances. It can be unencapsulated or incompletely encapsulated, circumscribed or infiltrative. Tumours are predominantly solid, tan-white to pink masses, often cystic filled with a viscous brown fluid. Areas of scarring can also be present and may occasionally prevail.

MICROSCOPIC APPEARANCE

The tumour consists of varying proportions of admixed mucinous, epidermoid and intermediate type cells. Low-grade tumours are macrocystic and microcystic with plentiful mucocytes, fewer epidermoid cells and infrequent intermediate type cells. Extravasated, dissecting mucin pools may be seen. There may be a sclerosing/fibrosing component. Reactive tumour-associated lymphoproliferation is characteristic.\footnote{18} High-grade tumours are more solid and contain fewer mucinous elements with a preponderance of atypical epidermoid cells and epidermoid cells. High-grade tumours are easily mistaken for SCC and recourse to exhaustive sampling augmented by a panel of mucin histochemistry may be diagnostic.

This diversity makes FNAC interpretation challenging.\footnote{14} The behaviour of mucoepidermoid carcinoma is very varied and various systems have been proposed to attempt to grade tumours and hence predict outcome. A commonly used system is described in Table 6.14.\footnote{16, 65}

High-grade tumours tend to be aggressive compared to low-grade tumours, although immaterial of grade

<table>
<thead>
<tr>
<th>Table 6.13</th>
<th>WHO classification of salivary gland malignancy.\footnote{11, 12}</th>
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<tbody>
<tr>
<td><strong>Malignant epithelial tumours</strong></td>
<td><strong>Haematolymphoid tumours</strong></td>
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<tr>
<td>Acinic cell carcinoma</td>
<td>Hodgkin’s lymphoma</td>
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<tr>
<td>Mucoepidermoid carcinoma</td>
<td>Diffuse large B-cell lymphoma</td>
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<tr>
<td>Adenoid cystic carcinoma</td>
<td>Extranodal marginal zone B-cell lymphoma (MALToma)</td>
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<td>Polymorphous low-grade adenocarcinoma</td>
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<tr>
<td>Clear cell carcinoma NOS</td>
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<tr>
<td>Epithelial/myoepithelial carcinoma</td>
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<tr>
<td>Basal cell adenocarcinoma</td>
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<tr>
<td>Sebaceous carcinoma</td>
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<tr>
<td>Sebaceous lymphadenocarcinoma</td>
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<tr>
<td>Cystadenocarcinoma</td>
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<tr>
<td>Low-grade cribriform cystadenocarcinoma</td>
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<tr>
<td>Mucinous adenocarcinoma</td>
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<tr>
<td>Oncocytic carcinoma</td>
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<tr>
<td>Salivary duct carcinoma</td>
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<tr>
<td>Adenocarcinoma NOS</td>
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<tr>
<td>Myoepithelial carcinoma</td>
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<tr>
<td>Carcinoma ex-pleomorphic adenocarcinoma</td>
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<tr>
<td>Carcinosarcoma</td>
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<tr>
<td>Metastasizing pleomorphic adenoma</td>
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<tr>
<td>Squamous cell carcinoma</td>
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<td>Small cell carcinoma</td>
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<td>Large cell carcinoma</td>
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<td>Lymphoepithelial carcinoma</td>
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<tr>
<td>Sialoblastoma</td>
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<td>Secondary tumours</td>
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</table>
mucoepidermoid tumours have a tendency to metastasize, which is not reliably predictable from conventional histomorphological criteria in any individual case.

Central mucoepidermoid carcinoma (Figure 6.21) is defined as tumour developing in an area, which normally lacks any salivary gland tissue, typically the mandible near the third molar region and associated with an unerupted tooth or cyst. The tumours are usually low-grade and definitive diagnosis can be difficult until tumour excision. 66

Acinic cell carcinoma

EPIDEMIOLOGY

Acinic cell carcinoma accounts for 7–17.5 per cent of all malignant salivary gland neoplasms. Approximately 80 per cent arise from the parotid gland and the remaining 20 per cent arising mainly from the minor salivary glands or submandibular glands, and only 1 per cent from the sublingual gland. 18 There is a male preponderance and they usually present in the third decade of life. 67

MACROSCOPIC APPEARANCE

Macroscopically, the tumours are of a firm to rubbery consistency and range in colour from a tan-grey to yellow or pink mass. They are usually rounded, well circumscribed and can be encapsulated. They can contain areas of haemorrhage or cystic change. Recurrent tumours tend to be less well-demarcated and can appear multinodular. 18, 32

MICROSCOPIC APPEARANCE

Acinic cell carcinomas recapitulate the serous acinar cell of normal salivary gland tissue, containing zymogen granules in the cytoplasm. Reactive lymphoid stroma is characteristic and may mimic lymph node involvement. 67

There are a number of recognized growth patterns, which can coexist in a single tumour (Table 6.15). Histochemical stains for zymogen granules may be positive. Immunohistochemically, the most useful stain is alpha-amylase. Reactivity, however, is variable and unpredictable – of note, the papillary-cystic variant is postulated to show intercalated ductal rather than acinar differentiation and attempts to demonstrate cytoplasmic granules are generally non-contributory (Figure 6.22).

Table 6.14 Grading system for mucoepidermoid carcinoma. 65

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Point value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracystic component</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Neural invasion</td>
<td>+2</td>
</tr>
<tr>
<td>Necrosis</td>
<td>+2</td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>&lt;4/10 HPF</td>
</tr>
<tr>
<td>Anaplasia</td>
<td>+4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total score</th>
<th>% Death from disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0–4</td>
<td>3.3%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>5–6</td>
<td>9.7%</td>
</tr>
<tr>
<td>High</td>
<td>7–14</td>
<td>46.3%</td>
</tr>
</tbody>
</table>

Figure 6.21 Mucoepidermoid carcinoma. (a) Whole mount slide of a low-grade mucoepidermoid carcinoma illustrating an expansile multilobulated architecture, substantial macrocystic and microcystic growth plus peripheral lymphoid tissue response (H&E stain, ultralow magnification). (b) Intermediate-grade tumour depicting epidermoid cells surrounding a rudimentary tubuloductal lumen lined by goblet cell mucocytes, characterized by abundant microvacuolated cytoplasm. It may require a determined search to find these cells in higher grade tumours (H&E stain, high magnification). (c) The same tumour stained for neutral mucousubstances corroborates intracytoplasmic mucin and aids identification of such cells (dPAS stain, high magnification).
Adenocarcinoma not otherwise specified

Adenocarcinoma not otherwise specified (NOS) refers to malignant tumours with glandular or ductal differentiation that do not have specific histologically defining features to enable further subclassification as a recognized subtype.

### EPIDEMIOLOGY

Adenocarcinoma NOS is the second or third most common malignant salivary gland neoplasm. It is more common in women and frequently seen in the fifth to eighth decade with a mean age of diagnosis of 58 years and rarely seen in adolescents or children. Sixty per cent occur in the major salivary glands, usually the parotid and 40 per cent occur in the minor salivary glands.

### MACROSCOPIC APPEARANCE

Macroscopically, tumours appear as a firm tan-white mass, which can be circumscribed to poorly demarcated with an irregular periphery and potentially infiltrative appearance. There may be areas of haemorrhage, cystic change or necrosis.

### MICROSCOPIC APPEARANCE

Adenocarcinoma NOS is a diagnosis of exclusion and therefore tumours that fall within this category can display a variety of features. Common to all tumours in this group is the presence of glandular or ductal features, an invasive growth pattern and the lack of histological characteristics of other salivary adenocarcinomas.

The malignant epithelium can display various architectural features including glandular, ductal, papillary, solid, nest-like, etc. There may be clear cell change and/or mucinous differentiation. The tumours can also be graded into low, intermediate and high based on the degree of gland formation, cellular pleomorphism and mitotic count.

- Low-grade tumours have easily identifiable gland and duct-like structures. There is usually a single cell type with small nucleoli, abundant cytoplasm, distinct cell borders and little nuclear pleomorphism with few mitoses. This can occasionally lead to a benign diagnosis if the invasive growth is not identified.
- Intermediate-grade tumours also have easily identified gland and duct-like structures. Unlike low-grade tumours, there is greater nuclear pleomorphism with more mitoses.
- High-grade tumours tend to be solid, with areas of haemorrhage and necrosis. Unlike low- and intermediate-grade tumours, the gland and duct-like structures are much harder to identify. The cells are much more abnormal and varied. Cellular features include frequent atypical mitoses and enlarged, hyperchromatic, pleomorphic nuclei.

### Adenoid cystic carcinoma

**EPIDEMIOLOGY**

Adenoid cystic carcinoma (ACC) accounts for approximately 10–12 per cent of all malignant salivary gland tumours and is the most common malignant tumour of the submandibular gland. It represents approximately 5 per cent of parotid
neoplasms and 30–50 per cent of minor salivary gland neoplasms. There is no sex predilection and it is usually seen in patients in their forties to sixties, rarely in patients less than 20 years old.

Lower-grade ACC pursues a pernicious course typified by relentless, troublesome local recurrence, ultimately presaging wider dissemination after a prolonged interval of years or even decades. Many malignant salivary gland tumours show a proclivity for perineural growth, though this is paradigmatic for ACC with perineural sheath and intraneural growth, the latter commonly visualized microscopically some considerable distance beyond what would be regarded as adequate clearance adjudged by the unaided eye. This neurotropism may radiate in a tentacular fashion well beyond the main body of the tumour. Positive surgical resection planes are, therefore, sometimes an unexpected and unwelcome feature of pathology reports, as this signifies a heightened risk of local recurrence. Obversely, the histological suggestion of clearance from the planes of section usually available examined by routine sampling is not particularly reassuring. High-grade (solid) ACC is an aggressive, destructive malignancy.

MACROSCOPIC APPEARANCE

The tumour is usually a poorly circumscribed solid white tumour. ACC is usually unencapsulated and infiltrates into surrounding soft tissue, muscle and bone sometimes directly through lymph node capsules.

MICROSCOPIC EXAMINATION

Bilroth originally described adenoid cystic carcinoma in 1856 and called it a cylindroma, reflecting the jigsaw arrangement of the cells on microscopic examination.

There are often two recognizable malignant cell subpopulations representing epithelial and myoepithelial components. Three pure growth patterns have been described but many tumours are mixed.

- **Tubular pattern** represents the most differentiated form of adenoid cystic carcinoma. Small nests of cells form few true glandular or tubuloductal spaces and occasional cords.
- **Cribriform pattern** is the most common pattern and most tumours will contain areas displaying this pattern even if not the predominant type. In addition to true gland lumina containing secretions, cells group to form multiple pseudocysts (pseudolumina) containing mucoid basement membrane material. The overall pattern resembles ‘Swiss cheese’. This architecture represents an intermediate level of cellular proliferation and biological aggressiveness.
- **Solid pattern** is the least common type and unlike the other two types there are few if any glandular spaces. Cells in the solid type tend to be larger and more pleomorphic with mitoses, interspersed with areas of necrosis. A biphasic cell population may not be apparent and without at least some better-differentiated fields, it may be impossible to arrive at the diagnosis.

ACC may be graded according to the predominant growth pattern:

- I, mostly tubular with some cribriform elements;
- II, either entirely cribriform or cribriform/tubular with less than 30 per cent solid component;
- III, any tumour with more than 30 per cent solid growth.

Histochemistry for mucosubstances may demonstrate both true secretions and basement membrane deposits. Immunohistochemical staining for laminin and type IV collagen duplicates the latter. Staining for epithelial markers typically highlights the luminal secretory cells and myoepithelial cell markers decorate the basally located abluminal cells, which mantle the basement membrane material (Figure 6.23).

Carcinoma ex-pleomorphic adenoma

Carcinoma ex-pleomorphic adenoma arises from within a pre-existing salivary pleomorphic adenoma or at the site of a previous pleomorphic adenoma.

EPIDEMIOLOGY

Carcinoma ex-pleomorphic adenoma is not uncommon and accounts for approximately 12 per cent of all salivary gland malignancies and 6.2 per cent of all pleomorphic adenomas. Risk factors for malignant transformation of a pleomorphic adenoma include a submandibular gland site, prolonged duration of tumour, older age of patient (mean, 61 years) and tumour greater than 4 cm. It commonly affects the parotid gland and rarely the sublingual gland.

There is no gender predilection and patients typically present in the sixth to seventh decade.

MACROSCOPIC APPEARANCE

Carcinoma ex-pleomorphic adenoma tends to be larger than its benign counterpart. Tumours tend to be poorly circumscribed, firm, tan-white and extensively infiltrative masses. They can occasionally be well circumscribed and appear encapsulated. The residuum of a pre-existing adenoma is often identified, sometimes alluded to by an effete fibroelastotic, occasionally mineralized vestigial scar. The malignant component tends to radiate centrifugally from this nidus, if present (Figure 6.24).

MICROSCOPIC APPEARANCE

The malignant element of a carcinoma ex-pleomorphic adenoma typically comprises high-grade adenocarcinoma or salivary duct carcinoma often with squamoid differentiation, but other specific subtypes of salivary carcinoma are seen and these may on occasion be monotypic rather than mixed. The benign pleomorphic adenoma component can be difficult to identify, may require extensive sampling and in some cases it may never be identified.
The association of pleomorphic adenoma, carcinoma and sarcoma (carcinosarcoma, true malignant mixed tumour) is very rare, as is the phenomenon of benign metastasizing pleomorphic adenoma, which may be completely indistinguishable histologically from the usual non-metastasizing examples.

Invasion of tumour through the original lesion’s capsule carries prognostic significance and has been classified as:11

1. **Non-invasive.** Also called dysplasia, intracapsular carcinoma or in-situ carcinoma ex-pleomorphic adenoma.
2. **Minimally/microinvasive carcinoma.** <1.5, 5 or 8 mm invasion.
3. **Frankly invasive carcinoma.** >1.5, 5 or 8 mm invasion.

In principle, (1) and (2) have a favourable prognosis compared to (3), although the precise cut-off point to define a category of invasion with minimal metastatic potential is presently unascertained.25

Ordinary benign pleomorphic adenomas may show peripheral permeative growth, lymphatic tumour embolus, necrosis and focal internal cytological atypia without signifying malignant transformation. Caution should be exercised in the interpretation of such features if prior FNAC has been attempted. Such tumours are sometimes termed ‘atypical pleomorphic adenoma’ and generally behave no differently from their more typical counterparts. The wide morphological heterogeneity of pleomorphic adenoma potentially includes localized areas of pseudoadoenoid cystic and epithelial/myoepithelial carcinoma-like growth, which may result in over-diagnosis of malignancy on FNAC by the unwary.
NEUROECTODERMAL TUMOURS

Neuroectodermal tumours can be divided into two groups. The first group shows evidence of epithelial differentiation, e.g. carcinoid tumour of the larynx. The second group is a diverse group of tumours that shows non-epithelial differentiation.

**Olfactory neuroblastoma**

These are uncommon malignant tumours of the upper nasal cavity affecting specialized olfactory mucosa and arising from the superior turbinate, cribriform plate and superior one third of the nasal septum ([Figure 6.25](#)). The reported incidence is four cases per million with a bimodal distribution in the second and sixth decade, and no sex or racial predilection.11

**MACROSCOPIC APPEARANCE**

Macroscopically, olfactory neuroblastoma appears as a soft, polypoidal, highly vascular mucosa-covered mass.

**MICROSCOPIC APPEARANCE**

The malignant cells are uniform, with small round nuclei, scant cytoplasm and possess finely stippled (salt and pepper) chromatin.11

Hyam’s classification system divides olfactory neuroblastoma into four types ([Table 6.16](#)).

![Figure 6.23](#) Continued.

![Figure 6.24](#) Carcinoma ex-salivary pleomorphic adenoma. Cut surface of a longstanding adenoma seen centrally forming a discrete, cream, elastotic scar with focal calcification. This is part-circumferentially surrounded by peripheral lobules of tan carcinoma ex-adenoma, in this example pure acinic cell carcinoma.
The better-differentiated (grade I and II) examples are sometimes termed ‘aesthesioneuroblastoma’. Homer–Wright pseudorosettes are formed by cells mantling solid, fibrillary neuropil stroma. Flexner–Wintersteiner rosettes consist of cells surrounding an empty pseudolumen. Other tumours may form perivascular rosettes encircling blood vessel lumina. Immunohistochemistry may aid discrimination between this and other primitive neoplasms (so-called round blue cell tumours), such as lymphoma, Ewing’s tumour, melanoma, Merkel cell tumour, rhabdomyosarcoma, nephroblastoma, retinoblastoma and PNET. There is, however, no single specific positive marker.

Mucosal malignant melanoma

Mucosal malignant melanoma (MMM) is a rare tumour that originates from melanocytes. These are of neuroectodermal derivation and migrate to ectodermally derived mucosa during embryogenesis.

Between 15 and 20 per cent of malignant melanomas arise in the head and neck but the vast majority, over 80 per cent, are of cutaneous or upper aerodigestive tract origin. Mucosal malignant melanoma represents merely 0.5–3 per cent of malignant melanomas from all sites.

Common sites for mucosal malignant melanoma include the sinonasal tract and the oral cavity. Uncommon sites include the nasopharynx, larynx and other sites with non-ectodermally derived mucosa.

It is more common in men, but this finding is not consistent, and the tumour affects a wide age range (20–80 years).

MACROSCOPIC APPEARANCE

Mucosal melanomas are usually pigmented and colour ranges from a light tan to black depending on the amount of melanin production, though amelanotic examples do occur. There is a confounding propensity for primary lesions to spontaneously regress.

MICROSCOPIC APPEARANCE

They typically comprise epithelioid and/or spindle cells. Plasmacytoid, rhabdoid, small cell, giant cell, balloon cell, neurotropic and desmoplastic variants are recognized. The cells are markedly pleomorphic and may contain pigment. Nucleoli are conspicuous and intranuclear inclusions are typical. An adjacent inflammatory infiltrate and necrosis can also be present. Surrounding melanocytic atypia or melanoma in situ may mantle vertical growth phase disease.

Histochemical confirmation of brown pigment as melanin may be helpful. With few exceptions, the cells show nuclear and cytoplasmic immunoreactivity for S100 protein. Vimentin, HMB-45, melan A and CD56 are usually positive. Epithelial markers are reciprocally negative, although up to 10 per cent of melanomas may show focal cytokeratin reactivity. Coexpression of CD10 is associated with tumour progression. The desmoplastic variant may be substantially immunoinert.

Table 6.16 Hyam’s grading classification of olfactory neuroblastoma.

<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Lobular</td>
<td>Lobular</td>
<td>May be lobular</td>
<td>May be lobular</td>
</tr>
<tr>
<td>Pleomorphism</td>
<td>Absent or slight</td>
<td>Present</td>
<td>Prominent</td>
<td>Marked</td>
</tr>
<tr>
<td>Neurofibrillary matrix</td>
<td>Prominent</td>
<td>Present</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Rosettes</td>
<td>Homer–Wright rosettes (pseudo-rosette)</td>
<td>Homer–Wright rosettes (pseudo-rosette)</td>
<td>Flexner–Wintersteiner (true rosettes) may be present</td>
<td>Flexner–Wintersteiner (true rosettes) may be present</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Absent</td>
<td>Present</td>
<td>Prominent</td>
<td>Marked</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>Prominent</td>
</tr>
<tr>
<td>Glands</td>
<td>May be present</td>
<td>May be present</td>
<td>May be present</td>
<td>May be present</td>
</tr>
<tr>
<td>Calcification</td>
<td>Variable</td>
<td>Variable</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Other neuroectodermal tumours

Other neuroectodermal tumours include Ewing sarcoma, primitive neuroectodermal tumour and melanotic neuroectodermal tumour of infancy.
Lymphoma is the second most common primary malignancy occurring in the head and neck region. In white populations, lymphoma is a more common cause of cervical lymphadenopathy than metastatic disease. Approximately 25 per cent of all extranodal lymphomas occur in the head and neck. Thus, although in the UK the overwhelming majority of haematolymphoid tumours, predominantly lymphomas and leukaemias, are managed by specialist haemat-oncology multidisciplinary teams, head and neck surgeons are frequently involved in the initial diagnosis of lymphoma. It, therefore, behoves the head and neck pathologist to possess a sound working knowledge of lymphoproliferative conditions and their differential diagnosis. Access to expert second opinion is inevitable at some point.

It is beyond the ambit of this chapter to delve into the complexities of lymphoma diagnosis and the interested reader is referred to the comprehensive World Health Organization (WHO) classification of tumours of haematopoietic and lymphoid tissues (fourth edition, 2008), which is internationally recognized, periodically reviewed and updated. This takes a multiparameter approach to classification incorporating clinical, morphological and immunophenotypical features plus genetic studies into account with the expectation that the schema will continually evolve and be refined over time.

Lymphomas are broadly divided into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). HL is characterized by Reed–Sternberg cells and is subdivided into classical HL (incorporating nodular sclerosing, mixed cellularity, lymphocyte-rich and lymphocyte-depleted subtypes) and...
nodular lymphocyte predominant HL, according to site of involvement, clinical features, growth pattern, presence of fibrosis, composition of cellular background, number and/or degree of atypia of the tumour cells and frequency of Epstein–Barr virus (EBV) infection. The immunophenotype of the neoplastic cells in these classical HL subtypes is identical.

Roughly 85 per cent of NHLs are B-cell lymphomas, which include follicular lymphoma, marginal zone lymphoma and MALT lymphomas, the latter often extranodal involving the mucosa-associated lymphoid tissue of Waldeyer’s ring including the ocular adnexa and thyroid gland (NHL of the thyroid gland is more common than undifferentiated (anaplastic) carcinoma of the thyroid gland). Diffuse large B-cell lymphoma is the most common aggressive NHL. Mantle cell lymphoma and Burkitt’s lymphoma are aggressive NHLs sometimes seen in the head and neck. Cutaneous T-cell NHLs (e.g. mycosis fungoides) may be indolent. Peripheral T-cell NHLs, however, may behave more aggressively. Extranodal NK/T-cell lymphoma is strongly associated with EBV and shows a predilection for the upper aerodigestive tract, prototypically the nasal cavity. Its angiocentric and angiodestructive nature may simulate Wegener’s granulomatosis and other midline facial necrotizing conditions (so-called ‘idiopathic midline destructive disease’ in the older literature). Plasma cell neoplasms, most commonly plasma cell myeloma and extramedullary plasmacytoma, are occasionally encountered in the head and neck region.

| Table 6.17 Secondary tumours of head and neck |
|---|---|
| Site | Primary tumour |
| Paranasal sinuses | Kidney<br> Lung<br> Breast<br> Thyroid<br> Prostate |
| Nasopharynx. Very rare. Case reports or small case series | Malignant melanoma<br> Kidney<br> Lung<br> Thyroid<br> Colon<br> Breast<br> Cervix |
| Hypopharynx and larynx | Melanoma<br> Kidney<br> Breast<br> Lung<br> Prostate<br> Colon<br> Stomach |
| Oral cavity and oropharynx | Breast<br> Kidney<br> Lung<br> Prostate<br> Thyroid<br> Colon |
| Salivary glands. More common accounting for 5% of salivary gland malignancies. Predominantly occur in the parotid glands | 80% of parotid gland secondary tumours are from other primary head and neck neoplasms. 85% of submandibular gland secondary tumours are from distant sites including lung, kidney and breast |
| Ear and temporal bone. Very uncommon, but post-mortem study suggests may be more common especially in patients with disseminated malignant disease | Breast<br> Lung<br> Head and neck<br> Prostate<br> Melanoma<br> Thyroid<br> Kidney |

Mesenchymal tumours

Apart from the lymphomas, mesenchymal tumours are uncommon malignancies of the head and neck. Malignant mesenchymal tumours (sarcomas) include:

- Fibrosarcoma
- Malignant fibrous histiocytoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Liposarcoma
- Angiosarcoma
- Kaposi sarcoma
- Malignant peripheral nerve sheath tumour
- Synovial sarcoma
- Chondrosarcoma (Figure 6.26)
- Mesenchymal chondrosarcoma
- Osteosarcoma
- Chordoma.

Secondary tumours

Uncommonly, a number of primary tumours can metastasize to the head and neck region (Figure 6.27) and include those listed in Table 6.17.

**KEY EVIDENCE**

- Meticulous and judicious pathological evaluation of head and neck neoplasms is foundational to subsequent effective clinical management and resource utilization.
- Morphological assessment by light microscopy constitutes the cornerstone of cytological and histological diagnosis, supplemented by ancillary ultrastructural, immunohistochemical, molecular and genetic studies, where relevant.
- Fine needle aspiration cytology is a comparatively low-risk, cost-effective preliminary investigation in the management of head and neck tumours, subserving both triage and diagnostic roles in experienced hands.
The histiocytopathological diagnostic process is historically heuristic in nature, correlating clinical, pathological, radiological and treatment outcome observations using population and individual case study evidence.

KEY LEARNING POINTS

- The head and neck pathologist must be an accomplished practitioner familiar with perhaps the widest range of organ/tissue-specific malignancies out of all the anatomically defined site-specific specialities.
- In relative terms, head and neck cancer is uncommon, accounting for approximately 8000 new cancer cases (approximately 3 per cent of all cancers) and responsible for approximately 2700 deaths (roughly 5 per cent of all cancer-related deaths) per annum in the UK.
- Tumour site, type, grade and stage are major determinants of survival in head and neck cancer, which is influenced to a lesser degree by a variety of other patient-specific and tumour-specific factors. These are accommodated in the current UICC/AJCC TNM classification.
- Squamous cell carcinoma in its numerous manifestations accounts for upwards of 90 per cent of all malignant head and neck tumours with lymphoma as the second most common malignancy.
- Fine needle aspiration cytology is an established first-line investigation for suspected head and neck cancer. It is rapid, comparatively atraumatic, requires minimal specialized equipment and in experienced hands offers good clinical efficiency, as long as awareness of its inherent limitations and pitfalls is maintained by all concerned.
- The application of immunohistochemistry and molecular markers with deeper understanding of their genetic basis continues to yield insight into the pathogenesis of many head and neck tumours. Their routine use in diagnosis, treatment and prognostication is likely to become more widespread.

REFERENCES


INTRODUCTION

Early attempts to control malignant disease of the upper aerodigestive tract by surgical means were hampered by the limitations of anaesthesia, lack of antibiotics and ignorance of the biology of the disease process. Both surgeons and patients showed remarkable heroism in an often futile cause, and the discovery of ionizing radiation at the turn of the twentieth century led to a rapid loss of enthusiasm for surgical excesses. Ever since, the pendulum has swung from one modality to the other as long-term patient survival has increased and concerns, such as functional outcomes and quality of life, have become more prominent.

However, nearly two-thirds of head and neck squamous cell carcinomas (HNSCC) present at an advanced stage and despite many recent advances in medical and surgical oncology, there has been little evidence of an improvement in long-term survival. Novel reconstruction techniques have made radical surgical approaches more feasible, but there has been a significant trend towards organ preservation therapy. However, we must not compromise elimination of the disease in our quest to retain 'function', as an organ containing residual tumour will soon become more of a burden to the patient than the primary radical resection.

This chapter addresses the current treatment options available to the patient with HNSCC and some of the factors involved in the decision-making process. Non-squamous disease and malignancies of the thyroid and salivary glands will not be dealt with in any depth. The reader is directed to the chapters on site-specific disease for a more thorough account of these topics.

THE MULTIDISCIPLINARY TEAM

The sheer complexity and diversity of the anatomy, physiology and pathology of the multiple potential tumour subsites of the head and neck necessitates a team approach to HNSCC. No single clinician can be expected to have the requisite expertise; multiple healthcare specialties have a subspeciality dedicated to HNSCC, and multidisciplinary cooperation across these fields is essential to concentrate expertise at the bedside and clinic. There is no substitute for expert radiological, cytological and histologic opinion and the consequent inclusion of diagnostic and nursing specialists has significantly widened the scope of the multidisciplinary team (MDT).

The benefits of working in a team environment are manifold, with improved consistency and continuity of care. There may be increased opportunities for education, audit and clinical trials and support for patients and colleagues. Inevitably, cancer treatment has become more concentrated
TREATMENT CHOICE

Unfortunately, the heterogeneic nature of HNSCC, as well as the diversity of patient characteristics and consequent paucity of level 1 evidence precludes the use of simple algorithms, and each case must be discussed on its own merits. Evidence-based decisions depend more on retrospective outcome studies than randomized controlled trials in most areas, and there are very few trials with a surgical arm.

A large number of factors influence decision-making (Table 7.1), and these will be briefly dealt with in turn.

Tumour–related factors

The observation that tumours spread in a predictable manner from the primary to regional nodes to distant systemic metastases was first proposed by Halsted, and forms the cornerstone of our ability to predict outcomes and choose appropriate therapies for cancers. The TNM system was developed as an extension of this concept by Denoix in the 1940s for the Union Internationale Contre le Cancer (UICC), The American Joint Committee on Cancer (AJCC) first met in 1959 with the intention of classifying tumours to aid determine and select appropriate treatment and investigation of tumour subgroups in clinical trials. The two

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Age, general medical condition/performance status, especially pulmonary reserve. Occupation, tolerance and compliance with therapy. Socioeconomic background and mobility</td>
</tr>
<tr>
<td>Tumour</td>
<td>Site and stage of primary, invasion of adjacent structures. Histology-grade and depth of infiltration. Extent of previous treatment. Presence of nodal or distant metastases</td>
</tr>
<tr>
<td>Healthcare</td>
<td>Local expertise in resectional and reconstructive surgery, radiotherapy and medical oncology. Support services for rehabilitation, dentistry and prosthetics. Appropriate nursing support. Cost, convenience, compliance, complications and competence</td>
</tr>
</tbody>
</table>
- **diagnostic**, used to diagnose cancer and recurrence accurately, as well as screen asymptomatic patients
- **prognostic**, accurately risk-stratifying patients and predicting response to therapies
- **therapeutic**, the marker itself being a target for treatment
- **cost effective**, being easily detectable by a standard, reliable and simple assay on a small sample.

Unsurprisingly, no such marker exists, and no marker is currently contributing significantly to the decision-making process. The increasing use of gene microarray technology is currently producing large amounts of data of questionable clinical relevance. However, there are a couple of interesting markers with significant clinical potential, as follows.

### HUMAN PAPILLOMAVIRUS

Epidemiological data have shown a dramatic increase in cancers of the oropharynx, particularly tongue base and tonsil in the younger population. Over the same time, there has been a marked concomitant improvement in survival rates for this subgroup of tumours, around 60 per cent of which test positive for HPV-16 infection. These cancers tend to be poorly differentiated with basaloid features, but have an excellent response to therapy. It has been hypothesized that this may be partly explained by the presence of functional wild-type p53 activity in this subset of tumours. Diagnostic testing may involve polymerase chain reaction (PCR) of tumour samples or detection of human papillomavirus (HPV) DNA in plasma, but is likely to be highly sensitive. The recent introduction of widespread vaccination for high-risk HPV subtypes in schoolgirls in the UK will hopefully lead to a rapid decrease in incidence in the near future. It is a sobering thought that much of the improvement in survival data for oropharyngeal carcinomas may be accounted for by this subset of the disease, and not improvements in our treatment regimes.

### EPIDERMAL GROWTH FACTOR RECEPTOR

Activation of epidermal growth factor receptor (EGFR) leads to a phosphorylation cascade via a tyrosine kinase pathway.

---

**Table 7.2** Historical survival data following standard therapy for head and neck cancer.

<table>
<thead>
<tr>
<th>Survival (%) by stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip</td>
<td>95</td>
<td>95</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>69</td>
<td>49</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Bucosal mucosa</td>
<td>75</td>
<td>65</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Alveolar ridge</td>
<td>78</td>
<td>64</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Oral tongue</td>
<td>72</td>
<td>52</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Tonsil</td>
<td>100</td>
<td>90</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>90</td>
<td>90</td>
<td>45</td>
<td>10–40</td>
</tr>
<tr>
<td>Piriform sinus</td>
<td>58</td>
<td>50</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>Supraglottic larynx</td>
<td>86</td>
<td>100</td>
<td>57</td>
<td>12</td>
</tr>
<tr>
<td>Glottic larynx</td>
<td>96</td>
<td>88</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Paranasal sinus</td>
<td>80</td>
<td>54</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>T1, 52</td>
<td>T2, 45</td>
<td>T3, 39</td>
<td>T4, 10</td>
</tr>
</tbody>
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with wide effects on cell proliferation, apoptosis, invasion, angiogenesis and metastasis. These EGFR-related molecular pathways are found to be altered in 90 per cent of HNSCC, and elevated EGFR expression is known to be related to poor prognosis. One study has demonstrated overexpression as a biomarker for good response to accelerated fraction radiotherapy. Cetuximab, a monoclonal antibody to EGFR has shown efficacy in treatment of locally advanced HNSCC and other agents are currently in development.

**Patient-related factors**

The only non-tumour-related factor explicitly mentioned by TNM is age in differentiated thyroid cancer. HNSCC patients typically are of advanced age and have multiple comorbidities as they share risk factor exposure with a number of systemic diseases, such as hypertension, myocardial infarction, cerebrovascular events and chronic pulmonary obstructive disease. Aged patients are more likely to receive substandard treatment of their primary tumour, 38 per cent of those > 60 years and 64 per cent > 80 years receiving suboptimal treatment in one series, with predictable adverse outcomes.

Immunosuppression by factors such as HIV can have severe adverse effects on prognosis. Fanconi anaemia gives a 500–700-fold increase in the risk of HNSCC, the majority of which are HPV-associated. Patients with head and neck cancer are frequently malnourished, which may have adverse prognostic implications. Although survival benefits of preoperative nutritional supplementation have been demonstrated only in severely malnourished patients, supplementation may correct nutrient deficiencies, minimize malnutrition-related morbidity and mortality, reduce the length and cost of hospitalization, and may prevent alcohol withdrawal syndrome. Nutritional support given pre-operatively for 7–10 days decreases postoperative complications by approximately 10 per cent in malnourished patients with weight loss of 10 per cent or more.

Inadequate pulmonary function will preclude many types of partial laryngeal surgery where aspiration is a significant risk. Patients of low socioeconomic status, black patients and those without private medical insurance were shown to have a poorer prognosis in a recent National Cancer Database (NCDB) survey of advanced laryngeal cancer in the United States, which may simply reflect inequalities in access to care in that society.

There are a number of measurement tools of functional status, of which the Karnofsky index (Table 7.3) is the best known. The patient’s physical condition may play a major role in determining which treatment pathway is most appropriate. One study has shown the considerable impact of the patient’s performance status on prognosis in a wide variety of tumours. As comorbidities increase, the proportion of patients receiving no treatment increases in parallel.

The prognostic impact of comorbidities could thus be due to the physiological burden of chronic disease itself or the selection by patient and doctor of suboptimal treatment regimes. For HNSCC at least, it seems that the former is more likely.

The patient’s occupation may have a bearing on how much facial disfigurement or alteration in speech and swallowing they are prepared to endure. Occasionally, logistical factors, such as willingness to travel significant distances on a daily basis for 6–7 weeks for treatment, may be crucial.

The patient’s wishes are of course the final determining factor in choice of treatment, as they will bear the burden of the disease and treatment-related complications and endure the long-term dysfunctions thereof. The trade-offs between increased chances of survival on the one hand and increased acute toxicity and long-term disability must be adequately explained, and the patient’s own priorities respected. One must remember that patient priorities may not be the same as those of healthcare professionals; 46 per cent of medical staff believed their patients would sacrifice survival prospects for better voice and quality of life, whereas only 20 per cent of patients agreed.

Family members and friends also frequently play a part in the decision-making process, and their agendas may conflict with those of the patients. Patients with advanced HNSCC consistently prioritize cure and long-term survival over quality of life issues far more than their peers and health-care professionals. They may be more willing to undergo radical aggressive treatment than we give them credit for, and this serves to underscore the importance of determining their

<table>
<thead>
<tr>
<th>General category</th>
<th>%</th>
<th>Specific criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to carry on normal activity. No special care needed</td>
<td>100</td>
<td>Normal general status, no complaint, no evidence of disease</td>
</tr>
<tr>
<td>Unable to work. Able to live at home and care for most personal needs. Various amount of assistance needed</td>
<td>70</td>
<td>Able to care for self, unable to carry on normal activity or do work</td>
</tr>
<tr>
<td>Unable to care for self. Requires institutional or hospital care or equivalent. Disease may be rapidly progressing</td>
<td>40</td>
<td>Disabled, requires special care and assistance</td>
</tr>
<tr>
<td>Terminal states</td>
<td>10</td>
<td>Moribund</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Dead</td>
</tr>
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</table>
priorities in the initial discussion of treatment options. What may seem an irrational decision to an objective clinician may be anything but when one is confronted by one's own mortality.

Social support networks are critical in the endurance of difficult treatments, and married patients seem to be willing to undergo more aggressive treatment than single patients. It may be that married patients have a perceived sense of responsibility to their loved ones or simply perceive they will have greater support during the recovery phase. There is certainly a positive prognostic effect of marriage, which may be associated with better health habits and social support.

Health-care factors

In the ideal situation, the full range of therapies in terms of surgical modalities, reconstruction, radiotherapy and chemotherapy, should be made available to the patient. In practise, local expertise tends to be stronger in some areas than others, and support services may be inadequate for some of the more demanding options. The recent trend towards centralization of services in the UK and central importance of the MDT approach may mitigate against this. However, the 5 Cs of Cost, Convenience, Compliance, Complications and Competence may in practice play more of a role than we would like to think in the treatment decision.

TREATMENT GOALS

The primary goal of oncologic treatment is either curative or palliative. There are a number of secondary goals, such as preservation of form and function, and, where this is not possible, to restore form and function to a degree that a reasonable quality of life is restored also. Every effort should be made to minimize sequelae of treatment and in the prevention of development of second primary tumours. Cessation of smoking and excessive alcohol intake are cornerstones of the latter.

Resectability

One key issue which may determine the treatment pathway is the feasibility of surgical resection. As anaesthetic, reconstructive and rehabilitive techniques have progressed, the boundaries of what was once thought to be irresectable have been gradually pushed back. In 2002, the TNM staging classification was modified to reflect this by dividing the T4 stage into T4a and T4b (Table 7.4) with the latter being generally categorized as unresectable, or at the borders thereof, and thus more suitable for non-surgical therapy. There is obviously a middle ground where resection is still technically feasible, but the likely morbidity or mortality would preclude such an option in all but the most extreme cases. A tumour is only deemed truly unresectable when the surgeon doubts the ability to remove all gross tumour on anatomical grounds or believes local control will not be achieved by surgery followed by adjuvant radiotherapy.

It must be emphasized that the T4b stage does not imply incurability, and in some instances (for example, nasopharyngeal cancer (NPC) extending into the intracranial compartment) concomitant chemoradiotherapy (CCRT) may give excellent results.

There are three criteria repeated across most tumour sites, and these will be examined in turn:

1. Vascular encasement/invasion. The presence of disease in intimate relationship with the great arterial

<table>
<thead>
<tr>
<th>Table 7.4 T4 versus T4b tumour classification for various sites of head and neck cancers.</th>
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<tbody>
<tr>
<td><strong>Site</strong></td>
</tr>
<tr>
<td>Oral cavity</td>
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<tr>
<td>Oropharynx</td>
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<tr>
<td>Hypopharynx</td>
</tr>
<tr>
<td>Supraglottis, glottis, subglottis</td>
</tr>
<tr>
<td>Maxillary sinus, nasal cavity, ethmoid sinus</td>
</tr>
<tr>
<td>Salivary glands</td>
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<tr>
<td>Thyroid</td>
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</table>

vessels of the neck is a not uncommon problem in the N3 neck, and the critical question is whether the carotid can be preserved surgically. Preoperative imaging is usually the key to accurate assessment; the computed tomography (CT) criterion of 180° circumferential attachment has been shown to have lower predictive value than 270° encirclement of the vessel on magnetic resonance imaging (MRI). Actual demonstration of tumour within the vessel lumen is highly specific for vascular involvement, but rarely seen and poorly sensitive. In the case of a non-salvageable artery, temporary transfemoral balloon occlusion of the affected vessel may be attempted, and transcranial Doppler sonography may be used to objectively assess the flow in the ipsilateral middle cerebral artery if resection is still contemplated.

2. Prevertebral fascia involvement. Fixation of tumour to the prevertebral musculature may be suspected clinically in extensive pharyngeal or laryngeal tumours which have reduced mobility on the vertebral column. Attempts to strip tumour off the longus colli/capitis muscle complex is rarely a fruitful endeavour, with a high incidence of residual disease and lymphatic spread to inaccessible nodes in the retropharynx and posterior neck. The retropharyngeal space usually contains fat, lymph nodes and connective tissue, and generally provides a stripe of high signal on T1 MRI which is an excellent indicator of resectibility. Effacement of this signal by tumour is a very poor prognostic sign.

3. Mediastinal invasion. This rare eventuality is sometimes seen in extensive hypopharyngeal, transglottic and thyroid cancers which may infiltrate mediastinal fat and invade the great vessels at the root of the neck. On occasion, these may be amenable to surgical approach with the aid of a thoracic surgeon, particularly in the case of differentiated thyroid carcinoma. However, obliteration of the periaortic fat and >45° contact with the aorta on CT suggests a dismal prognosis. Transoesophageal ultrasound is gaining popularity in staging of oesophageal cancer and may occasionally be useful in these rarer situations.

INDICATORS OF EXTENSIVE SURGICAL REQUIREMENTS

Selection of the appropriate surgical approach and degree of resection requires adequate preoperative planning including examination under anaesthesia and imaging techniques. Before undertaking potentially mutilational surgery, the patient must be fully informed of the likely consequences; changing the surgical plan mid-operation without adequate consent is to be avoided at all costs.

1. Laryngeal cartilage invasion. Recently, the TNM staging for advanced laryngeal cancer has altered, with minor degrees of cortical invasion of the thyroid cartilage restaged as T3 and T4a being reserved for gross invasion through the full width of cartilage. The latter stage is associated with reduced efficacy of medical modalities, and is generally seen as an indication for laryngectomy. In some patients, distortion of the cartilages may be clinically obvious, but radiological findings are often critical. The thyroid cartilage often contains areas of ossification and chondrification in continuity and the latter may be isointensified to an adjacent neoplasm. MRI has a high sensitivity, but low specificity and may lead to false positives and inadvertent laryngectomy, whereas the low sensitivity of CT may lead to inappropriate organ-sparing protocols.

2. Pre-epiglottic fat invasion. Invasion of pre-epiglottic fat by supraglottic tumours increases the risk of spread of disease to the neck and requires a cuff of tongue base to be resected with consequences for function and attendant reconstructive options. Conservation laryngeal surgery is not possible if the hyoid bone is involved. MRI is an excellent modality for determining the extent of pre-epiglottic involvement.

3. Mandibular invasion. Unexpected bony invasion discovered intraoperatively can have major adverse consequences if adequate reconstructive options have not been planned. The periosteum generally forms an effective barrier, but once breached invasion is inevitable. Imaging studies by CT and MRI are complicated by the often dismal state of the patient’s dentition, with false positives common from cortical erosion by recent dental extractions, inflammatory odontogenic disease or the sequelae of radiotherapy. CT specificity seems higher than MRI for detection of cortical invasion, marrow involvement and inferior alveolar canal invasion. Specialist dental CT software (DentaScan®) technology may be used to reformat thin axial slices into panoramic and cross-sectional views, and PET/CT fusion studies show great promise in this area. Occasionally, invasion will not become obvious until intraoperative periosteal stripping, and flexibility in surgical planning is essential.

4. Skull base invasion. Similar parameters are used as for mandibular invasion – bone thinning, erosion and displacement on CT, and replacement of marrow on T1-weighted MRI. Involvement of cranial nerves may cause foraminal enlargement on CT or direct enhancement of the nerves on MRI. Muscle denervation may result in secondary fatty replacement and atrophy. Nodular dural enhancement or thickening >5 mm with pial enhancement is highly suggestive of dural invasion, often a preliminary step before parenchymal invasion. Extension of disease into the cavernous sinus makes surgical resection unfeasible.

5. Orbital invasion. Infiltration of the orbit is somewhat limited by the tough periorbita, but this is not readily identifiable on imaging. Peritumoral oedema can result in false positives on MRI with abnormal signal within the extraocular muscles. This is less of an issue with CT, and both modalities are best used in combination with clinical assessment.
INFORMED CONSENT

Obtaining informed consent to a procedure is fundamental to good medical practice, ensuring that the provision of treatment is not only legal but ethical. There are three essential requirements in the consent process (Box 7.1). The doctor must give sufficient information to the competent patient to enable them to understand the risks and benefits of treatment and a realistic idea of other options that may exist. The competent patient may then use this information to make a voluntary reasoned decision without coercion. If this process is not followed and the surgeon carries out a procedure without adequate consent, the surgeon has committed assault even if the patient comes to no significant harm as a result of the surgery. The competent patient also has the right to refuse treatment in their best interest, no matter how irrational this may appear to others.

The amount of information offered to the patient is critical to the consent process. A reasonable standard of disclosure is the amount of information that a ‘reasonable person’ would want before agreeing to treatment. It is reasonable to explicitly ask the patient what they would like to know and what questions need to be answered during the consent process. Express consent may be written or verbal, although for obvious medicolegal reasons, the former is preferred. Consent is implied if the patient accepts an investigation or treatment without question or behaviour to suggest non-consent.

The issue of mental capacity is covered by the Mental Capacity Act 2005. A competent patient is capable of understanding, retaining and weighing information relevant to a specific decision. They must also be able to communicate their choice by any means. A patient cannot be deemed to lack capacity simply because the treating clinicians disagree with their decision.

PRINCIPLES OF ONCOLOGIC SURGERY

The importance of preoperative planning cannot be overemphasized, enabling the surgeon to make an explicit surgical plan based on the tumour’s biological behaviour, location and extent. Result of biopsies and staging investigations and the outcome of the MDT discussion should be documented in the case notes, and any preoperative imaging studies available in theatre. A thorough medical and anaesthetic assessment of the patient should take place before any major procedures are undertaken and any intercurrent illnesses or nutritional problems addressed adequately to optimize the patient’s condition. Informed consent should be documented and the entire theatre and anaesthetic teams should be made aware of the nature of the procedure and any likely changes to the operative plan that may become necessary. The anaesthetist should ideally be familiar with the management of potentially difficult airways and have experience of fibreoptic intubation techniques. The type (for example, laser or microlaryngoscopy) and location (trans-nasal, transoral) of endotracheal tube should be discussed with anaesthetic staff, and if major surgery to the upper airway is planned, an elective covering tracheostomy may be fashioned. The patient should be positioned and attention paid to likely pressure areas. A thorough endoscopic examination of the tumour should also be carried out to confirm the stage of the tumour and the appropriate nature of the surgical plan. If reconstruction is being planned, a template of the likely defect may be fashioned to enable the reconstructive team to plan their procedure. Following this, the neck may be gently extended by means of a sandbag under the shoulders and the head turned away from the side of the operation. Local deep vein thrombosis (DVT) prophylaxis measures should be followed, such as compression stockings and Flowtron® boots.

Wound infection can have potentially dire consequences, and if the aerodigestive tract is to be entered and mucosa breached, the procedure is regarded as clean-contaminated, and appropriate prophylactic antibiotics given on induction of anaesthesia. Due to the frail nature of many patients with cancers of the upper aerodigestive tract and major possible consequences of infection, most surgeons would also give prophylactic antibiotics for clean procedures which may last for more than 90 minutes, such as a neck dissection. The antibiotic regime should be broad-spectrum, and local microbiological protocols should be followed. Typical agents would include co-amoxiclav, ceftriaxone, or clindamycin in combination with metronidazole. There is some evidence to suggest that courses lasting more than 24 hours are potentially counterproductive in altering the general flora of the patient and encouraging the emergence of resistant strains. However, it is common clinical practice to continue the antibiotic course until either the drains are removed or there is good evidence of no anastomotic leak following a contrast swallow. Patients should be screened for MRSA (methicillin-resistant Staphylococcus aureus) before major surgery and, if positive, appropriate decontamination and isolation precautions followed after liaison with the infection control team. The prophylactic agent should be selected for its efficacy on MRSA, with teicoplanin or vancomycin generally favoured.

The planned incision should be carefully marked, bearing in mind likely extensions that may be required and relaxed skin tension lines. A long-acting local anaesthetic solution, such as bupivacaine 0.5 per cent with 1:200,000 adrenaline may be infiltrated along the incision line for analgesic and haemostatic purposes, and allowed to have its effect on the tissues while patient preparation continues. In the case of parotid surgery, a nerve monitor may be inserted into the facial muscles at this juncture. The operative site is washed with sterile povidone-iodine solution and draped appropriately, giving good exposure of the surgical site and any likely extensions. Once the entire team is in position and

<table>
<thead>
<tr>
<th>Box 7.1 Essential requirements of the consent process</th>
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<tbody>
<tr>
<td>• You must have the capacity (or ability) to make the decision.</td>
</tr>
<tr>
<td>• The medical provider must disclose information on the treatment, test or procedure in question, including the expected benefits and risks, and the likelihood (or probability) that the benefits and risks will occur.</td>
</tr>
<tr>
<td>• You must comprehend the relevant information.</td>
</tr>
<tr>
<td>• You must voluntarily grant consent, without coercion or duress.</td>
</tr>
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mandibulotomy.

permission sought from the anaesthetist to commence, the surgeon should murmur to themselves the aphorism of Sir Harold Gillies’ seven times seven turn your knife in your hand err you cut the skin of a fellow man’ before taking the plunge.

The ideal of a bloodless field is highly dependent on a combination of hypotensive anaesthesia and meticulous surgical technique. Tissues should be handled with precision and care, the assistant providing countertraction as dissection proceeds to better visualize and deal with vessels before they are violated. To gain adequate access to the oropharynx, a mandibulotomy is generally required. The lip incision may be stepped at the vermilion border and should sweep downwards lateral to the symphysis menti to improve cosmesis (Figure 7.2). Paramedian mandibulotomy should be carried out just anterior to the mental nerve to preserve sensation to the lower lip. Titanium reconstruction plates should be aligned and their screw holes drilled while temporarily placed. The incision is marked in pencil on the mandible before a reciprocating saw is used to complete the mandibulotomy. At the end of the procedure the mandible is repositioned and aligned by fixing the plates using the predrilled screw holes.

Once adequate access is achieved, the tumour excision should be planned. In the oral cavity and oropharynx, a margin of 10 mm from gross visible or palpable tumour is acceptable, and smaller margins are reasonable in the glottic area. Seventy-five per cent of patients with a positive margin will go on to develop a local recurrence, whereas only 25 per cent with negative pathological margins will do so. In the United States, the reported incidence of positive pathological margins is 16 per cent. The margin should be marked with ink or diathermy spots on the mucosa before excision, as inevitable distortion will occur as resection proceeds. Handling of the tumour should be avoided whenever possible; care and gentle minimal manipulation is advised. Any questions about the complete nature of the resection should result in samples from the resection edges being sent for frozen section pathological assessment. Once the specimen has been examined for completeness, it is orientated for the pathologist. This may be achieved by sewing it to an acetate sheet with the anatomical landmarks and orientation drawn in to aid the pathologist.

The wounds should be thoroughly washed with saline, water or 10 per cent hydrogen peroxide solution, and the contaminated instruments discarded for a fresh set. The surgical team should remove their gowns and gloves and rescrub for the reconstruction or closure of the wound. A nasogatric feeding tube may be placed or percutaneous gastrostomy fashioned according to the likelihood of returning to oral intake. Adequate closed suction drainage should be applied to the wound and maintained on suction during closure to prevent any haematoma formation. Blake drains are ideally suited to the wide skin flaps of neck surgery. There are many ways to close the skin, but good apposition of the superficial cervical fascia over platysma is essential for success, and the use of buried absorbable sutures is ideal for this. The skin itself may be closed by interrupted sutures evert ing the skin edges or stainless steel clips. Topical chloramphenicol ointment may be applied in place of a dressing for the immediate postoperative period.

The drains are generally removed when producing serous fluid at a rate of <30 mL/day, and sutures removed at day 7 unless the incision area has been irradiated when 10 days should suffice. Antireflux medication, hyoscine patches and regular mouthwashes may be prescribed. If the pharynx has been repaired, the patient should be kept nil by mouth for 7–10 days, when a contrast swallow may be performed to assess any possible anastomotic leaks. Should the area be watertight, oral feeding may be recommenced at this stage.

Early mobilization is the key to rapid successful rehabilitation of the postoperative head and neck patient, and intensive physiotherapy and proactive nursing care may aid this.

**THE ROLE OF SURGERY**

Curative surgery should be directed primarily towards the extirpation of disease, maximizing the chances of oncologic control and cure before concerning oneself with functional preservation. The latter is of little moment to the patient with an inadequate resection and persistent mutilating disease. Resectability should not be confused with operability, and frequently the patient’s overall health or expectations of recovery will preclude surgical intervention. Similarly, demonstrating the extent of one’s surgical repertoire by means of a heroic resection as a technical exercise with little prospect of cure or functional recovery does the patient few favours.

**Anatomical subsites**

Early stage tumours (T1 or 2) with no nodal involvement may be treated by a single modality depending on the level of local expertise and the anatomical location of the disease. There is not a single level I study comparing radiotherapy with surgical resection for the evaluation of local control or survival.31

**ORAL CAVITY AND OROPHARYNX**

Management is highly dependent on the degree of involvement of the oral tongue, tongue base, hard and soft palates.
The majority of T1–3 tumours of oral tongue, floor of mouth and hard palate should be comfortably resectable without significant functional impairment, especially with microvascular tissue transfer reconstruction. Excellent oncological results can be achieved in this way, with disease-specific survival of 65–95 per cent. Bony involvement of the hard palate or mandible is again amenable to composite flap reconstruction, with obturation reserved for major hard palate defects in those with a poor performance status. The functional morbidity of total glossectomy has historically been regarded as too great to warrant primary surgery, and CCRT undoubtedly has a role to play in high-volume T4 tumours of the oral tongue and tongue base. However, if preservation of a lingual artery and hypoglossal nerve are feasible, free flap reconstruction may give acceptable functional results (Galm, unpublished observations).

Tumours requiring resection of more than one-third of the soft palate or more than half of the tongue base are usually considered candidates for chemoradiation, but aggressive surgical approaches via mandibulotomy with free flap reconstruction are oncologically sound and can have surprisingly good functional outcomes.

**LARYNX**

The earliest attempts to resect the larynx were met with unsurmountable complications and poor surgical outcomes. Of the first 103 total laryngectomies performed, 39 per cent died from the operative procedure and only nine survived for a year, the longest survivor lasting five years.

In 1961, Pressman et al. noted the highly compartmentalized nature of the larynx, underpinning the rationale of the subtotal and partial laryngectomy, with the hope of maintaining speech and swallowing without the need for a permanent stoma. In 1972, the CO₂ laser was introduced for transoral resection of early laryngeal tumours with good effect, and more recently this technique has been extended to more advanced tumours.

For early stage glottic cancer (T1–T2 N0), options include transoral laser excision, radiotherapy and open partial laryngectomy. Rates of local control, laryngeal voice preservation and survival seem equivalent between these options, unless there is anterior commissure involvement, when laser treatment appears to provide inferior local control and voice quality. Open partial laryngectomy appears to be best suited to a subset of bulky T2b lesions and to salvage local recurrences from other modalities, as it has greater complication rates and involves greater overall cost. Laser surgery seems best suited to smaller T1a lesions, with radiotherapy effective for all early cancers.

By definition, a T4 laryngeal cancer has already produced an organ that is not functioning adequately with cord fixation, cartilage invasion and loss of structural integrity. Functionally, speech and swallowing will be impaired and frequently the airway will be compromised. Under these circumstances, preservation of the ‘organ’ is of dubious benefit as return to useful function is highly unlikely and careful surveillance for persistent disease is necessary, with the added morbidities of salvage laryngectomy casting a long shadow over the patient. Survival data suggest a clear benefit to laryngectomy under these circumstances, and quality of life data seem to suggest this is the correct approach.

Most of the debate therefore focuses on the T3 tumour, where the total laryngectomy long represented the gold standard. Conservative laryngeal surgery, designed to retain some degree of laryngeal function, may take the form of transoral laser surgery, supracricoid and near-total laryngectomy. These modalities achieve local control rates similar to primary chemoradiation, with survival rates of 50–65 per cent. The French surgeon Lacouraeyer pioneered the supracricoid laryngectomy, realizing that impaction of the hyoid bone on the cricoid cartilage could permit restoration of physiologic speech and swallowing via the cricohyoepiglottopexy or cricohyoidodemiglottopexy (Figure 7.3). At the Laennec Hospital in Paris, the five-year actuarial local control rates for T3 laryngeal tumours was 91.4 per cent, with

![Figure 7.3](image-url) The partial laryngeal resections comprising the cricohyoepiglottopexy (CHEP) and cricohyoepiglottopexy (CHP).
89.8 per cent laryngeal preservation and 98.3 per cent local control.\textsuperscript{38} It remains to be seen whether this technique retains such a success rate outside this major centre.

**HYPOPHARYNX**

T3–4 tumours will typically require a laryngopharyngectomy with either primary closure or flap reconstruction. Involvement of the cricopharyngeus or cervical oesophagus will necessitate the addition of an oesophagectomy. Patients with good performance status and limited T3 disease may be candidates for supracricoid laryngopharyngectomy in centres specializing in this technique. Transoral laser surgery has proven surprisingly effective, with five-year local control rates of 57 per cent for T4 disease.\textsuperscript{39} The majority of patients will have nodal disease, and this must be addressed at the time of surgery.

**Transoral laser surgery**

The CO\textsubscript{2} laser was first introduced in the 1970s for laryngeal microsurgery,\textsuperscript{40} and was increasingly used for benign conditions, such as papillomatosis. In the 1980s, Steiner\textsuperscript{41} popularized its use for malignant disease, and expanded its indications throughout the upper aerodigestive tract. Initially popular for debulking obstructive disease and removing limited early glottic cancers, laser surgery is now used in organ preservation in a wide variety of HNSCCs. A number of specialized gags and instruments have been designed to aid exposure in difficult areas and the precision and haemostatic properties of the laser enable tumour resection with accuracy and speed. The small focal diameter of the CO\textsubscript{2} laser enables minimal carbonization with low rates of infection, swelling and scarring.

There are technical differences compared to traditional open oncological surgery. For instance in larger tumours, incisions may be made through the tumour to better delineate its depth. Judicious use of the operating microscope aids the distinguishing of normal tissues from tumour, which may be resected piecemeal from particularly inaccessible areas, such as the pyriform fossae or areas where major blood vessels may be encountered, such as the tongue base and tonsil. Steiner claims that the laser acts to seal lymphatics, preventing dissemination of micrometastases during this process. It is obviously important to maintain topographic accuracy for pathological assessment of surgical margins using this technique, and an experienced pathologist is invaluable.

Blindly following deeply infiltrating tumours into the tissues of the neck is highly technically demanding and should only be carried out by surgeons with extensive exposure to this technique. Open surgical treatment of the neck, if indicated, is generally carried out by Steiner after an interval of 1 week.

Defects following resection are typically allowed to granulate or covered in collagen mesh and fibrin glue. Larger oral cavity defects may be covered by a split skin graft to prevent excessive scarring and reduction in tongue mobility.

Whereas transoral surgery to early laryngeal tumours has rapidly become widely accepted and its results and indications well understood, the more extensive laser resections are still subject to debate. Excellent results have been reported by the specialist centre, but we await widespread replication by other units.\textsuperscript{42} Certainly, the prospect for organ-sparing without the morbidities of CCRT or long post-operative recovery from open resections remains of great interest.

**Neck dissection**

Crile first described en bloc dissection of the cervical lymphatics in 1906\textsuperscript{43} and improvements in anaesthesia, blood transfusion and the development of antibiotics led to its further popularization by Hayes Martin, who reported a series of 1450 radical neck dissections (RND) in a landmark 1951 paper.\textsuperscript{45} He included the sternocleidomastoid and internal jugular vein in the resection and condemned Crile’s preservation of the accessory nerve as oncologically unsound. Such an extensive resection was regarded as excessive for the N0 neck, but by the early 1960s regional failure rates of >50 per cent were reported in early tongue cancers treated surgically. The technique of modified radical neck dissection with preservation of the non-lymphatic structures was popularized by Bocca and colleagues as a less morbid procedure more suitable for the N0 neck,\textsuperscript{44} and became the treatment of choice for patients whose occult metastasis rate would be expected to exceed 20 per cent.

The discovery of predictable patterns of cervical metastatic spread by Lindberg in Texas then Shah at Memorial-Sloan Kettering\textsuperscript{46} has led to the concept of selective dissection of the high risk areas of the N0 neck as an alternative to MRND, and these procedures are now being increasingly used in selected situations in the N+ neck.\textsuperscript{48} Elective dissection of the N0 neck is also valuable in staging the neck for occult metastases, aiding the decision-making process for adjuvant therapy provision.

In the future, sentinel lymph node biopsy, long a standard of care in melanoma and breast cancer, may lead to even more conservative and selective surgical approach, and endoscopic approaches to the neck are being developed in animal models.\textsuperscript{47}

**Reconstruction**

Heroic surgery to the head and neck was in its early days characterized by major functional and cosmetic defects, with multiple procedures involving local tissue flaps and skin grafts frequently being inadequate. Reconstruction of the pharynx and upper oesophagus was blighted by high rates of stricture, fistula and wound breakdown and palliative efforts were attempted to form skin-lined local flaps to divert saliva from the great vessels. It is not surprising that surgery was not for the faint-hearted, and frequently led to abysmal quality of life for the brief period before locoregional residual disease asserted its presence.

The modern era of reconstructive head and neck surgery began with Bakamjian’s introduction of the deltopectoral flap for reconstruction of the pharynx and cervical oesophagus in 1965.\textsuperscript{48} McCraw \textit{et al.}\textsuperscript{49} recognized axial patterns of the blood flow in regional flaps in 1977, mapping out 13 potential
myocutaneous flaps, and soon after Ariyan introduced the pectoralis major ‘workhorse’ flap. In the 1980s, microvascular free flaps were popularized, in particular the radial forearm fasciocutaneous flap of Yang, which revolutionized reconstruction of the oral cavity and oropharynx. Composite flaps, such as the free fibular flap, permitted reliable mandibular reconstruction for the first time, ending the era of the ‘Andy Gump’ deformity.

Head and neck surgery often has dramatic functional effects on speech, respiration and alimentation and the surgical site is often highly visible, leading to unique challenges for the reconstructive surgeon. Some surgeons are willing to partake both in resection and reconstruction, which requires a heroic stamina and degree of technical versatility. Others prefer to work as part of two surgical teams, with the oncological resection not being compromised by thoughts of potential reconstructive challenges. Advanced tumours leaving sizeable defects will usually undergo further adjuvant treatment, and this must be borne in mind when the mode of reconstruction is selected. The ability of the patient to withstand the prolonged operative and postoperative course of a free flap reconstruction may also be a limiting factor.

The first choice for repair of a sizeable defect will usually be a free microvascular tissue transfer due to the wide range of options available, as long as there are reasonable donor and recipient vessels available. In contrast, pedicled flaps have a limited mobility and often excessive bulk. Cutaneous defects of the face are ideally suited to primary closure by local tissue flaps, with undermining of adjacent wound edges to allow for tension-free closure. Larger local flaps, such as the nasolabial or glabellar, can allow for closure of larger defects.

Defects created in the neck are more amenable to reconstruction by pedicled flaps, such as the pectoralis major or latissimus dorsi. These flaps are limited by their vascular pedicle, and the temptation to overstretch or manipulate them to cover higher defects must be resisted. They are also extremely bulky and will only offer limited contouring over the facial skeleton. They are, however, ideal in covering the great vessels of the neck following fistula formation or postradiotherapy necrosis.

Small oral and pharyngeal defects may be closed directly by primary closure, for instance following wedge resection of the tongue. Excessive tension and scarring may lead to tethering of the tongue, with impaired speech and swallow. Following partial glossectomy, skin or mucosal grafts may be applied to the exposed muscle, but the best functional result probably comes from use of the free radial forearm flap which restores bulk and mobility.

For larger defects, pedicled flaps have the advantage of relatively short operative time and there is no requirement for microsurgical operative skills or equipment. However, there is a higher rate of flap necrosis, dehiscence and fistula formation compared to the use of free flaps in the pharynx. Indeed, studies have suggested the overall costs of pedicled flaps to be greater than free flap transfer in this situation. The radial forearm and anterolateral thigh flaps are now the workhorses of this area. The latter is somewhat bulkier than the former, and its donor site may be closed primarily, but its elevation is somewhat more technically demanding. Both provide thin pliable tissue that can be easily contoured or even tubed or folded to reconstruct the hypopharynx or soft palate.

Circumferential defects in the cervical oesophagus may be reconstructed via the jejunal free flap (which requires a laparotomy), pedicled pectoralis flaps or a gastric pull up. Total glossectomy results in significant and much feared functional deficits. The dynamic features of the tongue have been lost and this must be made up for by increased bulk to allow the reconstructed tongue to contact the palate during the propulsive phase of deglutition. Therefore for tongue defects greater than two-thirds, the rectus abdominis or anterolateral thigh are preferred to the radial forearm free flap.

Appropriate reconstruction of the mandible depends on the location of the defect. The anterior region, comprising the symphysis and parasympysis is subjected to the greatest forces during mastication, and thus gives the greatest functional deficit when resected and has the highest propensity for mechanical failure when reconstructed. The fibular free flap is the cornerstone of anterior mandibular repair, providing a long segment of robust bone capable of tolerating multiple osteotomies. Donor-site morbidity is relatively low, and the graft is potentially long enough to reach from condyle to condyle. However, the skin paddle is relatively small and unreliable, and the blood supply may be tenuous in those patients with peripheral vascular disease. In this eventuality, the scapular flap, with its potential for two independent skin paddles may be more appropriate. The iliac crest free flap provides a large amount of bone stock shaped in the contour of a hemimandible, but its use has been limited by its bulk, the unreliable immobile skin paddle and the risk of donor site pain and hernia formation. The radial forearm osteocutaneous flap is limited by its poor bone stock which will not withstand multiple osteotomies, but may have some use in small segmental defects with larger overlying mucosal deficits.

Massive soft tissue defects in association with extensive mandibular resections may necessitate multiple free flaps, for example a fibular osteocutaneous in combination with an anterolateral thigh fasciocutaneous flap. Smaller defects of the anterior mandible alone without major soft tissue loss may be repaired by neovascularized bone grafts if less than 5 cm in length.

Lateral mandibular defects are functionally less disabling and segmental defects may be repaired by a reconstruction plate if adequate soft tissue cover is possible. Reconstruction of the posterior mandible can be technically demanding, and the overall function provided by soft-tissue repair alone with a rectus abdominis flap is often surprisingly well tolerated despite some inevitable malocclusion.

Radiotherapy

Ionizing radiation may cause DNA damage at a cellular level by direct interactions from secondary electrons generated within the tissues, or by an indirect effect of free radical formation. This damage may be affected by factors in the tumour microenvironment, such as temperature and degree of hypoxia. The biological consequences of this DNA damage are a loss of reproductive ability and cellular function; it is thought to be the former which is more important in HNSCC.
If a cell is unable to repair its DNA damage before mitosis, cell death will occur. In general, malignant cells have a lower capacity for repair and a shorter cell cycle than normal tissues. This is the basis of the therapeutic ratio in terms of radiosensitivity of tumours compared to neighbouring healthy tissues.

Tissues may be broadly divided into early-responding (including mucosae and tumour) and late-responding (such as muscle, nerve, bone and fat), where the complications of treatment only become apparent weeks to months after cessation of therapy. The size of dose fraction is thought to be critical in determining this late response.

The basic principle of radiotherapy is to achieve as high a dose to the tumour and any occult extensions as possible, while minimizing the dose to surrounding normal tissues. Unfortunately, HNSCC is biologically rather radioresistant and usually in close juxtaposition to critically radiosensitive organs such as the eye, brain, salivary glands and spinal cord.

Ionizing radiation is either particulate (usually electrons) or high-energy electromagnetic radiation (short wavelength x-rays or gamma-rays). X-rays may be classified by their energy level, measured in volts.

The early enthusiasm which greeted radium implants and orthovoltage generators (producing about 100 kV) in the first half of the twentieth century as a ‘magic bullet’ was soon tempered by the long-term side effects experienced by survivors. External beam therapy was characterized by poor tissue penetration, with severe skin damage and poor cure rates for deep tumours. In the 1950s with the advent of linear accelerator and telecobalt units generating supervoltage (2–6 MV) radiation and deeper tissue penetration, with skin sparing, the popularity of radiotherapy began to recover.

Linear accelerator beams also produce a better edge definition, with less of a penumbra, or shadow edge, allowing for narrower treatment margins of normal tissue. Cobalt sources emit megavoltages of gamma rays and were extremely popular for many years due to their relative simplicity of use, but the physical properties and safety issues are inferior to those of a linear accelerator.

Radiation dose is prescribed using the SI units of absorbed dose, the gray (Gy), named after the pioneering radiobiologist LH Gray. The previous unit was the rad, equivalent to 1 centigray (0.01 Gy).

Planning of treatment involves careful delineation of the primary tumour and any neck fields to be included along with the exclusion of local critical tissues, such as the orbit and central nervous system (CNS) from the fields. Close liaison with a radiation physicist is often useful at the time of planning in determination of the treatment pattern. To ensure patient immobility during treatment, a thermoplastic mesh shell (Orfit) is moulded to the contours of the patient’s head and neck as they lie on the treatment simulator. Holes may be cut for the eyes and nose, and the mesh fixed to a base-board to ensure replication of positioning for each treatment session.

Radiotherapy is less effective in hypoxic tumours, particularly those with bony or cartilaginous involvement. It is also unsuitable for patients with fistula, exposed bone or inadequate wound healing. Various patient factors may also play a part in the treatment decision. Claustrophobia, an inability to lie flat or neck problems may prevent adequate positioning. Good patient compliance and motivation must be assured as missing just a single fraction can have severe adverse consequences in terms of the overall outcome. The patient’s nutritional and immune status also need to be optimized prior to treatment and support staff need to monitor nutritional input and local skin/mucosal care during and immediately following the treatment. A full dental assessment is also mandatory if the mandible is within the radiotherapy field, as post-radiotherapy there is a high incidence of osteoradionecrosis following infections or extraction of diseased teeth.

During the course of treatment, the patient should be monitored by a multidisciplinary team on a weekly basis.

**PRIMARY RADIOThERAPY**

For early stage HNSCC, no level I evidence exists comparing primary radiotherapy with other modalities, in particular conservative surgery. For early stage mucosal disease, cure rates of 70–90 per cent would be expected from this modality alone from prospective and retrospective cohort studies.31 Involvement of bone or muscle will drop the cure rate to 50–70 per cent32 and hence combined modality therapy is recommended in these circumstances.

Primary radiotherapy has been commonly used to treat early tumours of the base of tongue, hypopharynx and larynx due to the surgical morbidity of accessing these areas adequately for resection. Advances in surgical techniques and reconstructive options have resulted in a great variation in local practices in these areas. Oral cavity lesions are more surgically accessible and only brachytherapy is useful in this region in avoiding the morbidity of mucositis, trismus and xerostomia associated with external beam irradiation.

Similarly in treatment of the neck, radiotherapy may be curative for N1 disease, but total response rates in the N2 neck are only around 50–70 per cent with poor long-term outcomes.33 Thus, if external beam irradiation is being used to treat the primary tumour, it is generally also used to treat the high risk N0 and N1 neck. On occasion, radiotherapy may be used to treat the primary site (if early stage) following a neck dissection, for example in early hypopharyngeal cancer with extensive neck disease.

Conventional external beam radiotherapy would typically involve a dose of 60–67 Gy to the primary tumour and gross adenopathy delivered in single fractions of 1.8–2 Gy per day, 5 days per week for 6–7 weeks.

**PREOPERATIVE RADIOThERAPY**

The uninterrupted preoperative blood supply to a tumour was thought to make the cells potentially more radiosensitive, and it was hoped that larger tumours may be shrunk to an easily resectable size and the possibility of intraoperative embolization of tumour would be reduced.

In the 1960s, a number of clinical trials examined the combined effects of radiotherapy and surgery in an effort to improve locoregional control of advanced HNSCC, and promising results were found with a view to reduction of regional recurrence, but the surgical morbidity was increased. Vandenbrouk’s 1977 study compared preoperative and postoperative radiotherapy (PORT) in hypopharyngeal
cancer, with reported five-year survivals of 20 and 56 per cent, respectively. Such unfavourable results led to the discontinuation of preoperative irradiation in favour of PORT.

POSTOPERATIVE (ADJUVANT) RADIOTHERAPY

The purpose of PORT is to address clinical and pathological findings that are known to lead to increased failure rates at the primary and regional sites. Following surgery, only microscopic well-vascularized normoxic islands of tumour should remain, which should theoretically be relatively radiosensitive.

Numerous studies have demonstrated improvements in locoregional control of HNSCC when PORT is used appropriately.\textsuperscript{54} Indications include positive (or close) margins, perineural spread, lymphovascular invasion, bone invasion, extension into soft tissues, multiple involved nodes, extracapsular spread and involved nodes \textgreater{} 3 cm in diameter. The interval between surgery and irradiation is critical, and most retrospective studies indicate that a delay of no greater than 4–6 weeks is preferable.\textsuperscript{55} The increasing use of microvascular tissue transfer has improved the attainment of this goal.

There is no significant dose–response relationship for total doses from 57.6 to 68.4 Gy unless there is evidence of extracapsular spread (ECS) within the neck, when 63 Gy was found to be more beneficial than 57.6 Gy.\textsuperscript{56} There is thus a consensus that a dose of 60–66 Gy should be delivered to the surgical bed and all anatomical sites at risk of recurrence.

A recent review of 8795 patients in the Surveillance, Epidemiology and End-Results (SEER) US database has shown a 10 per cent absolute increase in five-year cancer-specific survival and overall survival in patients with N+ disease treated with PORT.\textsuperscript{57} There is no level I evidence for the use of PORT, but there is a broad consensus to its efficacy and a prospective trial would now be considered unethical.

SALVAGE RADIOTHERAPY

Traditionally, surgery has been the major modality in the context of recurrent disease, but radiotherapy has a role in those who have not previously been irradiated. Many patients in this situation are simply not surgical candidates due to tumour extent or comorbidities.

Reirradiation is gaining in popularity with modalities such as intensity-modulated radiotherapy (IMRT) allowing for improved sparing of local tissues. The likelihood of success is heavily dependent on the location and extent of disease. Inadequate previous treatment, whether surgical or by radiotherapy, also may have a favourable prognosis.\textsuperscript{31} Patients with multifocal locoregional recurrences have a very poor prognosis and are unlikely to benefit from retreatment. Survival rates remain very poor, and distant metastatic disease is not infrequent.

Radiotherapy may be beneficial in the palliative setting for control of local symptoms, such as pain, bleeding and fungation.

INTERSTITIAL RADIOTHERAPY (BRACHYTHERAPY)

Interstitial radiotherapy refers to the implantation of a radioactive source directly into the treatment field providing specific intense local irradiation with a very rapid fall off in dose from the surface of the source. It is highly operator-dependent and relies on local expertise to produce optimum results. Most published series originate in highly specialist centres and their applicability to less expert units is questionable.

This technique thus allows an increased concentration of radiation at the implant site while minimizing the dose to surrounding tissues. In some units, it is the treatment of choice for small tumours of the oral cavity (<30 mm) without bony involvement. Significantly less serious side effects, in terms of mucositis, trismus and xerostomia, are achievable with this technique. Brachytherapy is also occasionally used postoperatively in the oral cavity or oropharynx for positive or close resection margins in unfavourable tumours. It may provide particular benefit in the context of previously irradiated unresectable recurrent disease of the oral cavity, nasopharynx and oropharynx. Recent studies have suggested a potential role in the postoperative neck in high risk or recurrent disease.\textsuperscript{51}

LOW-DOSE RATE IMPLANTS

Low-dose rate (LDR) implants have a relatively long half-life and thus longer overall treatment times. Radiation exposure to medical staff may be minimized by the use of remote afterloader techniques. Under a general anaesthetic, fine needles are placed through the tumour site and hollow plastic tubes threaded over these to remain in place. These hollow applicators are then afterloaded remotely by machine without direct clinician exposure to the radioactive source. The patient must be nursed in isolation in a shielded room until the course is completed, generally after a week. The treatment time is thus much shorter than conventional external beam radiotherapy, countering the risk of tumour repopulation.

HIGH-DOSE RATE IMPLANTS

With high-dose rate (HDR) implants, temporary implantation of iridium-192 sources can give an adequate local dose in minutes, so there is little opportunity for migration of the source and the treatment is relatively cheap. The actual radiation dose tends to be higher than with LDR, giving some concern as to the risk of late effects. The novel technique of pulsed-dose brachytherapy (PDR) combines the two techniques to give a pulse of high dose for 10–30 minutes each hour amounting to approximately the same dose as in LDR.

ALTERED FRACTIONATION

Radiotherapy schedules have conventionally been given as daily fractions 5 days per week for 5–7 weeks for historical reasons of convenience. The rationale for departing from this scheme is to increase the biological dose without increasing the risk of late normal tissue damage.

HYPERFRACTIONATION

Hyperfractionation is defined as dividing the treatment into smaller than conventional doses per fraction without altering
the overall treatment duration to increase the therapeutic differentiation between late-responding normal tissue and tumour; for example, a regime of 1.2 Gy given twice daily over 7 weeks for a total of 81.6 Gy, increasing the dose while keeping the treatment time constant. Locoregional control rates have been improved by about 15 per cent over historical controls in HNSCC by this method, without any overall increase in late complications.

**ACCELERATED FRACTIONATION**

This involves shortening the overall treatment duration using conventional doses to minimize tumour growth during treatment fractions, for example 1.6 Gy twice daily for 6 weeks. A range of different regimens have been devised and once again locoregional control rates have been improved at the expense of increased acute toxicity, but it has proven difficult to demonstrate an improvement in overall survival.

The Meta-analysis of Radiotherapy in Carcinomas of the Head and Neck collaborative group (MARCH) have demonstrated an 8 per cent survival benefit at five years for hyperfractionated therapy, and an overall five-year survival benefit of 3.4 per cent for all altered fractionation schedules in the 15 randomized trials assessed. There was a more significant benefit in locoregional control, again most pronounced in the hyperfractionated group and in younger patients with good performance status. It is possible that the latter are better able to tolerate the increased early side effects.

**HIGHLY CONFORMAL RADIOTHERAPY**

In an effort to further minimize damage to normal tissue, efforts have been made to increase the conformity of the radiation dose to the tumour morphology. With standard radiotherapy techniques, a large safety margin of normal tissue is irradiated along with tumour. In IMRT, CT images are used to provide a 3D reconstruction of the tumour and specific target doses to the tumour and maximum tolerable doses to surrounding tissues planned on a slice-by-slice basis. A computer-derived algorithm then determines the beam parameters to provide the desired dose distribution to what is often a highly irregular target. A large number of radiation portals with dynamic multileaf collimators (MLC) are required to achieve this highly tailored dose distribution. The MLC are Tungsten plates only a few millimetres thick whose position is controlled by small electric motors controlled by the planning computer.

Tomotherapy is a new variant of IMRT which combines a highly sophisticated computer-controlled radiation beam collimation with an on-board CT scanner to create an image of the treatment site. It therefore combines planning, patient positioning and treatment delivery into one system. Helical tomography integrates a linear accelerator into a spiral CT scanner which continuously rotates around the patient on a gantry.

The use of PET/CT fusion images for IMRT planning may better delineate tumour from normal contiguous tissues. This may be particularly useful in reirradiation of recurrent disease.

Excellent local control rates have been reported in naso- and oropharyngeal primary sites with this technique, with potential for preservation of salivary tissue and reduced xerostomia. However, long-term outcome data are understandably sparse.

**STEREOTACTIC RADIOSURGERY**

This highly conformal technique allows for the delivery of relatively large doses in a single or a few fractions, and is being increasingly used in the treatment of recurrent HNSCC, particularly in inaccessible areas such as the skull base. Multiple low-dose radiation beams are delivered in a pattern that allows them to overlap at the target lesion. The dose provided results in significant cell damage regardless of cell cycle phase, and to a degree does away with the classical concept of radiosensitivity. Fractionation of the dose may be useful in treating larger targets in close proximity to vital structures.

**PARTICLE RADIOTHERAPY**

High energy protons may be focused with magnetic fields to produce a very narrow beam with little scatter, and thus highly conformal therapy is possible. Most energy deposition comes towards the end of the particle’s track, thus sparing superficial tissues, and the range of the protons may be adjusted by varying the energy of the beam. Current clinical uses are mostly restricted to NPC.

Carbon ions are relatively heavy charged particles used in tumours otherwise thought to be poorly radiosensitive, such as chordomas and chondrosarcomas of the skull base.

Neutron beams are less dependent on tumour oxygenation for efficacy and have been extensively investigated in salivary gland malignancies with mixed results.

**Chemotherapy**

HNSCC has proven much more resistant to cure by chemotherapy than many other solid tumours, such as the lymphomas and sarcomas. However, although indications for single modality treatments are very limited, much attention has recently been paid to combination regimes with both radiotherapy and surgery. Medical oncology is a highly technical specialty requiring a significant amount of supportive care for the patients in terms of clinical nurse specialists experienced in recognizing and treating the complications of these often highly toxic regimens.

Since the advent of platinum-based agents in the 1970s, the role of chemotherapy has gradually evolved from producing short-lived local responses in the palliative setting to the widely used curative multimodality regimes for advanced HNSCCs. Its use has been spurred on by the observation that even when locoregional control has been achieved in advanced HNSCC, the long-term prognosis is still disappointing, with second primaries and metastatic disease accounting for a large proportion of treatment failures.

Chemotherapeutic agents (Table 7.5) typically act by interfering with basic cellular processes, usually associated with mitosis, thus selectively affecting those tissues with high turnover. There is thus a degree of synergy with radiotherapy,
Table 7.5 Classes of agents.

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>Cyclophosphamide, chlorambucil, melphelan: bind covalently to DNA, forming crosslinks and inhibiting replication</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Methotrexate: antifolate agent which inhibits dihydrofolate reductase</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil-pyrimidine antagonist: inhibits DNA synthesis</td>
</tr>
<tr>
<td>Plant derivatives</td>
<td>Vincristine: derived from rosy periwinkle, prevents tubulin spindle formation during mitosis</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel/docetaxel: yew tree derivatives, prevent microtubule disassembly</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Actinomycin D, doxorubicin, bleomycin: intercalate between DNA base-pairs, prevent mitosis</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Carboplatin: cisplatin-platinum derivatives, crosslink DNA</td>
</tr>
</tbody>
</table>

and scope for combinations of agents with differing mechanisms to work synergistically.

**INDUCTION (NEOADJUVANT) CHEMOTHERAPY**

Neoadjuvant therapy is used prior to definitive therapy with the intention of improving the success rate of the primary therapy. It was hoped that initial debulking of tumour by this means might improve the efficacy of local therapy, and drug delivery to tumour would be optimal before the blood supply was reduced by local therapies. The potential to eradicate micrometastatic disease before clinical presentation was also a hope. Response to induction therapy may also be used to assess prognosis and select the definitive course of treatment. Many pilot studies in the 1980s appeared to suggest high response rates of HNSCC to cisplatin with acceptable toxicity, but it has proved difficult to translate this into an overall survival benefit.

However, several studies demonstrated that tumour response to induction chemotherapy predicted a beneficial response to further treatment, and a better overall prognosis. This finding led the Veterans Affairs (VA) Laryngeal Cancer Study Group to investigate non-surgical laryngeal preservation. In their landmark study, patients with advanced laryngeal cancer were randomized to receive either standard therapy or the use of targeted therapy, such as cetuximab. In any case, the marginal benefits of treatment must be carefully weighed against the potential impact on quality of life.

Patients with bulky locoregional disease or high tumour volume and prior treatment of recurrence are likely to respond poorly to chemotherapy and may be more suited to supportive care.

**ADJUVANT CHEMOTHERAPY**

A randomized controlled trial of PORT followed by chemotherapy versus PORT alone in high-risk HNSCC patients failed to demonstrate a survival advantage in the face of high toxicity and poor patient compliance of this prolonged treatment plan. In view of the perceived success of concurrent chemoradiotherapy, this approach has been sidelined.

**SALVAGE/PALLIATIVE CHEMOTHERAPY**

Chemotherapy has long been the standard of care for patients presenting with recurrent or advanced disease not suitable for radical treatment. Cisplatin and 5FU are the standard agents in combination, but although they have a high initial response rate with tolerable toxicity, this has not translated into a significant prolongation of survival. Patients with a poor performance status may be more suited to a single agent therapy or the use of targeted therapy, such as cetuximab. In any case, the marginal benefits of treatment must be carefully weighed against the potential impact on quality of life.

**CONCURRENT CHEMORADIOThERAPY**

The rationale behind combining the two non-surgical modalities lies in their potential synergies. Chemotherapy has both a potential radiosensitizing effect for locoregional disease and also
has a systemic antimitostatic effect. Concurrent regimens are rapidly increasing in scope and popularity and in many units represent the primary treatment of locally advanced disease and the adjuvant of choice for high-risk surgical pathology.

**DEFINITIVE CONCURRENT CHEMORADIATION**

The first randomized controlled trial demonstrating improved survival of CCRT over radiotherapy alone in advanced resectable HNSCC was published in 1997. The CCRT arm also showed a reduction in distant metastases in the face of increased local and systemic toxicity.

The MACH-NC meta-analysis of 63 trials, including almost 11,000 patients showed the addition of chemotherapy to locoregional treatment conferred an overall survival benefit of 4 per cent at five years, but the benefit of CCRT was 8 per cent at five years. Adjuvant and neoadjuvant regimens showed no survival benefit. A similar meta-analysis of nasopharyngeal carcinoma showed a significant survival advantage for CCRT.

The RTOG91-11 study strongly indicated the superiority of CCRT to other methods of combined therapy administration, leading to a marked increase in popularity of this organ-preserving strategy. It is now routinely used as the standard of care in many centres for all locally advanced subsites within the head and neck.

The Groupe d’Oncologie Radiotherapie Tete et Cou (GORTEC) randomly assigned 226 patients with advanced oropharyngeal disease to either CCRT or radiotherapy alone, with observed improvement in overall survival at three years for the CCRT arm at the cost of increased toxicity.

The management of locally advanced nasopharyngeal carcinoma (NPC) has altered radically in recent years following publication of the US Intergroup Nasopharynx study. Patients with stage III or IV disease showed a significant five-year survival benefit from CCRT compared to radiotherapy alone, a finding confirmed by the Meta-analysis of Chemotherapy in NPC study.

However, the MACH-NC demonstrated a non-significant increase in death for laryngeal preservation protocols combined with classical laryngectomy followed by PORT (6 per cent at five years). Also, the US National Cancer Database analysis of cancer deaths has shown survival from laryngeal cancer decreasing over the 1990s compared to the 1980s, the only common cancer to show such a finding. Further analysis of the data from 1995–8 has shown a definite survival advantage for CCRT at five years. Also, the US National Cancer Database study of Chemotherapy in NPC showed the addition of chemotherapy to CCRT with observed improvement in overall survival at three years for the CCRT arm at the cost of increased toxicity.

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**ADJUVANT CCRT**

Locoregional recurrence and distant metastases are not infrequent after surgical resection of advanced HNSCC, especially in tumours with adverse pathological features.

Two major phase 3 trials have examined the efficacy of CCRT in the postoperative setting in the context of high-risk pathological findings, such as multiple lymph node involvement, ECS and positive resection margins. Both studies showed improved local control by CCRT and disease-free survival compared to conventional PORT with no effect on distant metastases and an observed increase in toxicity. Comparative analysis of the trials revealed that ECS and positive resection margins were the most powerful predictors of additional benefit from adjuvant CCRT. However, a five-year updated analysis of the RTOG trial no longer showed statistical significance for any end point. The performance status of the patient and availability of appropriate supportive care are critical to adequate compliance to this approach. Compounds that reduce treatment toxicity, such as amifostine to protect salivary output or palifermin to alleviate mucositis, need further evaluation in this setting.

**Targeted therapies**

The epidermal growth factor receptor is a member of the ErbB growth factor receptor tyrosine kinase family and is overexpressed in around 95 per cent of all HNSCC. Overexpression of EGFR has been associated with disease recurrence and worse patient survival, and several strategies have been developed to target this molecule. Cetuximab is a chimerical monoclonal antibody directed to the EGFR. In combination with radiotherapy, it has shown increased survival in advanced HNSCC patients compared to radiotherapy alone. It does not cause significant myelosuppression or mucositis, and may represent an alternative to CCRT for those who cannot withstand the toxicity of platinum-based chemotherapy regimens. Cetuximab has yet to be directly compared with CCRT in a randomized clinical trial.

Other targeted agents include panitumumab, a fully human monoclonal antibody to the EGFR, and erlotinib, which inhibits the tyrosine kinase downstream from the EGFR. Bevacizumab is a monoclonal antibody to the vascular endothelial growth factor (VEGF), thought to be essential for angiogenesis in rapidly growing tumour tissues. Tirapazamine is a hypoxic sensitizer currently being evaluated in phase II studies.

**Salvage surgery**

As CCRT has played an increasing role in the primary management of advanced HNSCC, surgeons are increasingly being called upon in the context of locoregionally recurrent or persistent disease. NCDB data in the United States show a doubling in rates of primary CCRT use for advanced oropharyngeal and laryngeal primaries between 1985 and 2001. This effect was most pronounced in teaching hospitals, strongly suggesting that the trend will continue when current trainees become independent practitioners.

The surgeon is thus increasingly confronted with diagnostic dilemmas, the clinical picture being confused by the inevitable tissue oedema, necrosis and chondritis secondary to CCRT. The post-treatment patient also commonly complains of hoarseness, dysphagia, respiratory distress and pain; these are often the symptoms which brought them to medical care. The surgeon is thus increasingly confronted with diagnostic dilemmas, the clinical picture being confused by the inevitable tissue oedema, necrosis and chondritis secondary to CCRT. The post-treatment patient also commonly complains of hoarseness, dysphagia, respiratory distress and pain; these are often the symptoms which brought them to medical care.
attention in the first instance. Patients with suspected recurrent disease are generally subjected to examination under anaesthesia and biopsies. There is a relatively high rate of false negatives due to difficulties in interpreting histological changes and the growth pattern of recurrent tumours. Recurrence is often multifocal, dispersed throughout the treated region and often beneath an intact mucosa.

Imaging studies are notoriously difficult to interpret without an adequate post-treatment baseline study. However, the baseline study itself may be confused by the presence of residual disease, which may be difficult to tell apart from progression of CCRT-related tissue changes. CT79 and MRI findings have been compared with salvage laryngectomy specimens with disappointing results. PET scans appear to show significant benefits in this regard as non-tumour FDG uptake appears unaffected by treatment,80 whereas recurrent disease shows significantly higher uptake rates. Differentiation between inflammatory changes and recurrent tumour remains a significant problem. Diffusion-weighted MRI gives an indication of the cellularity of tissues by measuring the apparent diffusion coefficient (ADC) of water molecules. Recurrent tumour tends to have a low ADC in comparison to necrosis, which exhibits a high ADC secondary to the loss of membrane integrity. Thus, a combination of imaging modalities may be useful in guiding further biopsies.

In the case of the N+ neck treated with CCRT, there is ongoing debate as to the wisdom of a planned neck dissection. Those patients with an N1 neck and good clinical response to CCRT81 generally may be closely observed. Those with N2/3 necks and residual palpable disease or suspicious radiological findings on completion of treatment will generally undergo a neck dissection of some description. However, the specimen obtained is not uncommonly free of obvious tumour and there is a high chance of overtreating these patients.82 In this situation, PET once again would appear to be of value, with a surveillance scan three to four months following treatment completion to direct biopsies.83 Earlier scans have a high false-negative rate as FDG uptake is suppressed by the treatment and the number of viable tumour cells drops. Later scans may compromise the success of salvage surgery.

If salvage resections are deemed possible by the MDT and desirable by the patient, a number of issues need to be examined before proceeding. Complication rates are significantly increased in this patient population;84 a meta-analysis of historical series (1980–98) found a weighted mortality rate of 5.2 per cent, and a major complication rate of 27 per cent. The vast majority of these patients had undergone irradiation alone with no CCRT and had not undergone free flap reconstruction. The RTOG91-11 trial found a pharyngocutaneous fistula rate of 30 per cent post-CCRT versus 15 per cent for radiation alone, and a later smaller study had similar figures of 31.6 and 15.6 per cent, respectively.85 Thus, the poor quality of tissue in the local surgical site may preclude optimal wound healing, and it is probably advisable to utilize free tissue transfer to optimize recovery in these conditions. However, prolonged operative time and increased rate of systemic postoperative complications may limit this option.

Tumours that survive the challenge of CCRT may be expected to be more aggressive and resilient in the face of other treatment modalities. The overall five-year survival in the historical meta-analysis was 39 per cent, with the stage at recurrence having a major impact on prognosis. T3 and T4 recurrences in a further series had a two-year survival of 31 per cent and a five-year survival of 15 per cent, a fairly gloomy prospect.86 The authors found that a disproportionate number of survivors had undergone inadequate primary treatment, and there were very few successful salvages in patients who had undergone radical initial therapy. It would appear that the best chance of a cure is at the first attempt.

In contrast, the two-year survival post-salvage laryngectomy in the RTOG91-11 trial was 76 per cent, but one must remember that high volume and T4 tumours were excluded from this study, as were patients with a Karnofsky score <60. A more recent (and realistic) series of 38 patients with biopsy-proven recurrence post-CCRT showed a two-year survival of 27 per cent.87

A further challenge to the surgeon is the extent of resection. CCRT does not appear to kill tumour cells concentrically, leaving a smaller, less aggressive tumour, but cells appear to die in diffuse patterns throughout the tumour, and thus the resection should probably be based on the initial pretreatment tumour volume rather than the palpable residual volume.88

PALLIATIVE CARE

Palliative care is interdisciplinary care that provides support for the physical, emotional and psychological suffering of patients with any advanced illness regardless of age, diagnosis or life expectancy. The goal is to prevent or alleviate suffering and to improve the quality of life for people facing severe, complex illness. The complex nature and often uncertain prognosis of HNSCC may lead to situations where radical treatments are given with palliative intent, and there is a spectrum of palliation from the primary treatment through salvage treatment to end-of-life terminal care. Patients with HNSCC often have a relapsing course with periods of freedom from disease and symptoms interspersed with bouts of serious illness, debility and physical or psychological symptoms. Whereas treatment modalities have increased the disease-free interval for patients with advanced HNSCC, cure rates have not significantly changed and patients are often living longer with quiescent subclinical disease.

During the period when treatment aims are altering from eradication of disease to symptom control, it is important to involve the specialist palliative care staff at an early stage. However, the patient must not feel they are being abandoned by their clinical team and it must be emphasized that active medical care will continue albeit with different aims.

Ideally, the patient should be cared for in a home situation by the family and community health service. Macmillan, Ian Rennie or Marie Curie cancer nurses can be invaluable in providing support under these circumstances and direct contact with palliative care physicians through attendance at a day hospice may be useful.

Admission to hospice care is not necessarily permanent and discharge is common after admission for respite, convalescence or short periods to optimize symptom control. Of course, if home social support networks are lacking then
institutional care may be the only sensible option. On occasion, a strong relationship has been built up between the patient and the surgical or oncology staff where they have been treated, and it may be suitable for continued care to be provided in the hospital environment with input from the palliative care team.

**Symptom control**

**PAIN**

Intractable pain is unacceptable in the palliative care setting and utmost effort should be made to determine the underlying cause. A full pain history and examination should be sought rather than simply reaching for the drug chart to increase the opiates. In HNSCC, pain may have aetiologies and pathophysiological mechanisms different from other malignancies. Nociceptive pain from destruction of local tissues is common, but also neuropathic pain from the tumour damaging or travelling along nerves should be recognized. Nociceptive pain may be treated according to the WHO pain relief ladder (Figure 7.4).

For mild pain, non-opioid agents, such as paracetamol, aspirin or ibuprofen, may be appropriate. Failure to control pain should result in prescription of a mild opiate in conjunction with a simple analgesic, such as paracetamol and codeine. If this proves inadequate then, by definition, the pain is severe and strong opiates, such as morphine or diamorphine, are indicated. Many patients, relatives and even some health-care professionals are unduly concerned about making this final step to a strong opiate due to fears of addiction or severe side effects, but the patient should not be denied the undoubted benefits these drugs offer.

Long-acting agents should be used on a regular basis to avoid breakthrough pain, and there is no place for PRN (pro re nata, or as needed) prescribing. The initial dose can be titrated with a shorter acting agent, such as oramorph 4-hourly, before switching to a slow-release preparation, such as MST. Gentle laxatives and antiemetics should be prescribed to prevent constipation and excessive nausea, respectively. If the oral route is unavailable then transdermal patches containing fentanyl are available. Alternatively, subcutaneous opiates may be administered, and towards the end of life these may be given by syringe driver.

Neuropathic pain from raised intracranial pressure or direct nerve damage may be more responsive to anticonvulsants, steroids, local anaesthetics and tricyclic antidepressants.

**SKIN**

Following radiotherapy, dermatitis and soft tissue damage is not uncommon in the face and neck. A progression from erythema to blistering to ulcerations and slough is commonly seen. The acute changes will generally settle around 2 weeks after treatment. The scalp should be washed very gently with mild shampoo if involved. Topical low-potency steroid creams and aloe vera have been used prophylactically and as treatment for skin damage, but a systematic review has shown no benefits. A plain lanolin-free nonscented hydrophilic cream may be helpful as long as the skin remains intact. Itching may be treated with low-potency steroid cream with close clinical observation for further skin damage.

**XEROSTOMIA**

On occasion, surgery to the oral cavity and mandible can cause difficulty with oral continence of secretions and salivary drainage. Speech therapy input and the judicious use of hyoscine patches may alleviate this. A much more common problem in those who have undergone radiotherapy is xerostomia, particularly if CCRT has been used. This can lead to difficulties with eating and swallowing, dental caries and decreased quality of life. Frequent sips of water, ice cubes, sugar-free chewing gum and artificial saliva may all prove useful. Pilocarpine is a parasympathomimetic sialogogue, but its side effects (including sweating, rhinorrhoea and urinary frequency) may prevent its wider use in this patient population.

**DYSPHAGIA AND ODYNOPHAGIA**

Artificial hydration and nutrition via the nasogastric or gastrostomy route is commonly used as a temporary measure during the recovery phase from treatment. However, the requirement may become lifelong if swallowing difficulties do not settle with time. Alterations in smell and taste also often have an adverse effect on the appetite, and nutritional supplements may be necessary.

**PSYCHOLOGICAL SYMPTOMS**

Patients are often understandably frustrated by the many setbacks experienced during their clinical pathway, and...
Changes in outward appearance and essential functions may be difficult to bear. Even small cosmetic alterations can have a huge adverse impact on patient body-image and self-esteem. Between 20 and 50 per cent of patients with HNSCC experience moderate to severe depression at some point after diagnosis, and the use of antidepressants is often helpful under these circumstances.

The high rate of locoregional recurrence in HNSCC is also a source of considerable anxiety which may be particularly pervasive. Benzodiazepines and selective serotonin reuptake inhibitors (SSRI) may be helpful in the short term, and many centres have a psychologist with an interest in the psychosocial impact of HNSCC. Patients may experience guilt and self-blame about the toll the illness is taking on their loved ones, and alterations in their ability to leave the house and interact socially with others can lead to difficult changes in the dynamics of long-term relationships. The Macmillan clinical nurse specialist is invaluable in this situation, and can provide the patient with access to patient-support groups and facilities, such as Maggie’s Centres, which may provide supportive information and counselling.

END-OF-LIFE ISSUES

Predicting the terminal phase of a patient’s illness may be difficult. Late signs include the patient becoming bed-bound and comatose, only able to take sips of fluid and unable to take oral medications or tolerate artificial hydration or nutrition. Clear communication with patient and family is essential to ensure they understand that the terminal phase has arrived. Issues such as the emergency management of the airway or the potential for major vessel erosion must be considered by the medical staff and discussed with patient and family if they are likely to arise imminently. A supply of opiates or benzodiazepines should be rapidly available at the bedside and all carers informed if asphyxiation or a carotid blowout seem likely.

Artificial hydration and nutrition may become burdensome and inappropriate towards the end of life and may prolong the dying process unnecessarily.

THE FUTURE

Caution must be exercised in the extrapolation of clinical findings in highly expert tertiary centre-structured trials to general clinical practice in units where local expertise and clinical support networks may fall short of our highest aspirations.

Advances in robotic surgery and fibreoptic carbon dioxide lasers may soon allow for surgical laryngeal functional preservation in more extensive tumours without the local and systemic morbidity of CCRT.

Whereas preservation of function is crucial to the success of many interventions in HNNSC, we must not lose sight of the fact that in a curative context successful extirpation of disease must not be sacrificed for short-lasting secondary benefits. Also preservation of a functionless organ which may be harbouring residual disease is of no benefit to the patient. The top priorities of the patient with HNSCC are almost universally cure and prolongation of life, with functional and cosmetic considerations much lower down the list of priorities than clinicians might be tempted to suppose.

KEY EVIDENCE

- Head and neck cancer is the most complex ‘organ site’ for treatment decision-making and thus a specialist multidisciplinary team is required for optimal patient management.
- Adequate initial assessment of the primary, nodal sites and potential distant metastases is essential for the decision-making process.
- New standards of patient care for locally advanced disease employ cisplatin-based chemotherapy with radiation with the intent of preserving speech and swallowing.

KEY LEARNING POINTS

- Head and neck cancer is the most complex ‘organ site’ for treatment decision-making and thus a specialist multidisciplinary team is required for optimal patient management.
- Adequate initial assessment of the primary, nodal sites and potential distant metastases is essential for the decision-making process.
- New standards of patient care for locally advanced disease employ cisplatin-based chemotherapy with radiation with the intent of preserving speech and swallowing.

REFERENCES


• 65. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation...


Principles of conservation surgery

IAN GANLY AND JATIN P SHAH

INTRODUCTION

Surgery for head and neck cancer can have significant effects on function such as speech and swallowing, as well as major effects on aesthetic appearance. There is therefore much interest in developing alternative strategies in the treatment of head and neck cancer. Organ-preserving radiation and chemoradiation is an example of this. Improvements in radiation delivery techniques, such as hypo- and hyperfractionation regimes and conformal 3D radiation, intensity-modulated radiation therapy (IMRT), dose painting and image-guided radiotherapy have led to radiation doses being concentrated to the tumour with limitation in damage to surrounding normal tissue. New chemotherapeutic agents and regimes have also led to chemoradiation being introduced as an alternative to radical surgery, especially for cancers of the larynx, hypopharynx and oropharynx. In addition, our greater understanding of tumour biology related to local progression and its behaviour and spread has led to the development of modified surgical approaches to head and neck cancers, which previously would have been removed with radical surgery. The introduction of the CO₂ laser has led to the development of transoral resection of cancers of the larynx, hypopharynx and oropharynx, whereas the introduction of endoscopes, image guidance systems and powered instrumentation now allows nasal cavity and paranasal sinus tumours to be removed by an endoscopic approach in selected cases, where previously open surgery, such as craniofacial resection, was used. This chapter will focus only on the conservation surgical approaches in head and neck cancer. Chemoradiation will be discussed in Chapter 45, Chemoradiation in head and neck cancer. Conservation surgery of the skin is discussed in Chapter 38, Non-melanoma and melanoma skin cancer, and conservation surgery of the thyroid in Chapter 23, Surgical management of differentiated thyroid cancer.

DEFINITION

The aim of conservation or functional head and neck surgery is to preserve form or function without compromising oncological resection. Therefore, conservation surgery is any operation which gives the same oncological result as radical surgery – long thought to be the most effective treatment – but allows preservation of function or aesthetic appearance.

Sites of conservation

Conservation surgery applies most commonly to the neck and larynx. However, conservation surgical procedures for the oral cavity, oropharynx, hypopharynx, paranasal sinuses and parotid gland have now been reported.
CONSERVATION SURGERY FOR THE NECK

Introduction

The single most important factor affecting prognosis for squamous cell carcinoma of the head and neck is the status of the cervical lymph nodes. Metastasis to the regional lymph nodes reduces the five-year survival rate by 50 per cent compared to that of patients with early stage disease. The American Cancer Society has reported that 40 per cent of patients with squamous carcinoma of the oral cavity and pharynx present with regional metastases. Therefore, management of the cervical lymph nodes is an important component in the overall treatment plan for patients with squamous cell carcinoma of the head and neck.

Regional cervical lymph nodes are grouped into several levels. Lymph node levels of the neck were first described by Memorial Sloan-Kettering Cancer Center and were classified into levels I–VII (Figure 8.1, Table 8.1). The gold standard operation for removal of cervical lymph nodes in both patients with clinically negative and clinically positive necks was the classical radical neck dissection. This involves removal of all five levels (I–V) of the neck, including the sternocleidomastoid muscle, internal jugular vein and accessory nerve, and submandibular salivary gland. However, with our greater understanding of the patterns of lymph node spread, it is now possible to carry out more modified neck dissections to preserve form and function. This is through our understanding that the location of metastases is mainly determined by the location of the primary site. Cancers of the oral cavity typically spread first to the nodes in levels I, II and III, whereas cancers of the oropharynx, hypopharynx and larynx spread first to the nodes in levels II, III and IV (Figure 8.2). This observation is based on the philosophy that nodal spread of cancer proceeds in an orderly and predictable fashion as determined by the lymphatic drainage pattern in the neck.1, 2 To determine lymph node levels at risk from a particular primary site, Shah3 analysed pathology specimens from 1119 classical radical neck dissections (RND) for squamous cell carcinoma of the upper aerodigestive tract.

Table 8.1 Clinical and surgical landmarks for neck node levels.

<table>
<thead>
<tr>
<th>Node level</th>
<th>Clinical landmarks</th>
<th>Surgical landmarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Submental and submandibular triangles</td>
<td>Superior-lower border of the body of the mandible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior–posterior belly of digastric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior–hyoid bone</td>
</tr>
<tr>
<td>Level II</td>
<td>Upper jugular lymph nodes</td>
<td>Superior–base of skull</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior–posterior border of sternocleidomastoid muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior–lateral limit of sternohyoid</td>
</tr>
<tr>
<td>Level III</td>
<td>Middle jugular lymph nodes</td>
<td>Inferior–hyoid bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior–hyoid bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior–posterior border of sternocleidomastoid muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior–lateral limit of sternohyoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior–cricothyroid membrane</td>
</tr>
<tr>
<td>Level IV</td>
<td>Lower jugular lymph nodes</td>
<td>Superior–cricothyroid membrane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posterior–posterior border of sternocleidomastoid muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior–lateral limit of sternohyoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior–clavicle</td>
</tr>
<tr>
<td>Level V</td>
<td>Posterior triangle lymph nodes</td>
<td>Posterior–anterior border of trapezius muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anterior–posterior border of sternocleidomastoid muscle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior–clavicle</td>
</tr>
<tr>
<td>Level VI</td>
<td>Anterior compartment of the neck</td>
<td>Superior–hyoid bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior–suprasternal notch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral–medial border of carotid sheath on either side</td>
</tr>
<tr>
<td>Level VII</td>
<td>Superior mediastinal lymph nodes</td>
<td>Superior–suprasternal notch</td>
</tr>
</tbody>
</table>

Figure 8.1 (a) Memorial Sloan-Kettering Cancer Center levelling system of cervical lymph nodes; (b) current modification of levelling system; (c) levels VI and VII. Redrawn with permission from Shah JP, Patel SG. Head and neck surgery and oncology, 3rd edn. New York: Mosby CV, 2003.
This consisted of 343 RNDs for the clinically negative neck (N0) and 776 RNDs for the clinically positive neck. From this study, the incidence of pathological positive neck specimens was 82 per cent for the clinically positive neck and 33 per cent for the clinically negative neck.

Tables 8.2 and 8.3 show the percentage of patients with pathological positive nodes at each level for \( cN_1 \) and \( cN_0 \) disease. In the \( cN_1 \) setting (Table 8.2), patients with primary oral cavity tumours had the majority of positive nodes in levels I–III, levels IV and V were involved in 20 and 4 per cent of specimens, respectively. In patients with primary oropharyngeal tumours, the majority of positive nodes were in levels II–IV, levels I and V were involved in 17 and 11 per cent of specimens, respectively. In patients with hypopharyngeal tumours, most positive nodes were in levels II–IV, levels I and V were involved in 10 and 11 per cent of specimens, respectively. In patients with primary tumours of the larynx, most positive nodes were in levels II–IV, levels I and V were involved in 8 and 5 per cent, respectively.

In the \( cN_0 \) setting (Table 8.3), patients with primary oral cavity tumours had the majority of positive nodes in levels I–III, levels IV and V were involved in 9 and 2 per cent of specimens, respectively. In patients with primary oropharyngeal tumours, the majority of positive nodes were in levels II–IV; levels I and V were involved in 7 per cent. In patients with hypopharyngeal tumours, most positive nodes were in levels II–IV, levels I and V were not involved. In patients with primary tumours of the larynx, most positive nodes were in levels II–IV, levels I and V were involved in 14 and 7 per cent, respectively.

The question of level V metastases was addressed in a separate study on 1277 RNDs by Davidson et al. Metastases were found in 40 (3 per cent) patients. Level V metastases were highest in patients with hypopharyngeal and oropharyngeal primary sites (7 and 6 per cent, respectively). Only three of 40 patients with a \( cN_0 \) neck had a positive level V lymph node. The incidence of level V metastases is small and extremely unlikely in the \( cN_0 \) setting.

Therefore, in the N0 setting, selective neck dissection removing lymph nodes selectively draining the lymph node basin most at risk can now be done. In the \( N^+ \) setting, however, comprehensive neck dissection of all five levels is necessary.
The highest functional morbidity of a comprehensive radical neck dissection removing all five levels of lymph nodes results from compromise of shoulder function due to loss of the spinal accessory nerve. Andersen et al.\textsuperscript{5} studied the oncological safety of a comprehensive modified neck dissection preserving the spinal accessory nerve in the N+ setting. The regional failure rates and disease-specific survival rates in patients with N+ disease were comparable for classical radical neck dissection and modified comprehensive neck dissection type I, preserving the accessory nerve as long as the nerve was not directly infiltrated by tumour.

Conservation neck dissection for N0 disease (selective neck dissection)

Selective neck dissection spares all non-lymphatic tissue, including the sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve. However, it removes only selected levels of lymph nodes on the involved side of the neck, unlike a comprehensive neck dissection. The extent of selective node dissection is determined by the predictive pattern of metastases based on the location of the primary tumour. It is based on the clinical observation that squamous cell carcinomas of the upper aerodigestive tract metastasize in a predictable and sequential pattern. Selective neck dissections are therefore generally carried out for the clinically negative neck (N0) where there is at least a 15–20 per cent risk of occult metastatic disease. Common selective neck dissections, and their indications are shown in Figures 8.3 and 8.4 and Table 8.4. These include the supraomohyoid neck dissection (SOHND) in which lymph nodes in levels I–III and the submandibular salivary gland are removed (Figure 8.3a); the extended supraomohyoid neck dissection in which lymph nodes in levels I–IV and the submandibular gland are removed (Figure 8.3b); the anterolateral neck dissection (LND) in which lymph nodes in levels II–IV are removed (Figure 8.3c); posterolateral neck dissection (PLND) in which lymph nodes in levels II–V and also the suboccipital and retroauricular lymph nodes are removed (Figure 8.3d); central or anterior compartment neck dissection in which lymph nodes at level VI in the prelaryngeal, pretracheal and paratracheal regions are removed (Figure 8.3e).

- Supraomohyoid neck dissection. Supraomohyoid neck dissection is recommended for squamous cell carcinoma of the oral cavity with a high risk of micrometastases in a clinically negative neck. Byers\textsuperscript{6} reported a recurrence rate of 5.8 per cent in 154 N0 patients treated with supraomohyoid neck dissection. Similar recurrence rates were reported by Spiro et al.\textsuperscript{7} and O’Brien.\textsuperscript{8}

- Extended supraomohyoid neck dissection. Extended supraomohyoid neck dissection is recommended for squamous cell carcinoma of the lateral tongue. This is based on the observation that patients with primary carcinoma of the lateral border of the oral tongue have a small, but increased risk of skip metastases to level IV compared to other sites in the oral cavity. Therefore, selective treatment of the N0 neck in lateral tongue cancer should include level IV.

- Anterolateral neck dissection. Anterolateral neck dissection (LND) is recommended for squamous cell carcinoma of the larynx or pharynx with a high risk of micrometastases in a clinically negative neck. If the primary tumour crosses the midline, this procedure is carried out bilaterally. LND is indicated for cancer of the oropharynx when the primary tumour is treated with surgery for a clinically negative neck. If postoperative radiation therapy is indicated, it is not necessary to perform bilateral LND because radiation alone is effective in treating the node negative contralateral neck. Cancers of the hypopharynx frequently metastasize to both sides of the neck. Therefore, bilateral LND is recommended in the cN0 setting. In supraglottic and advanced glottic cancer bilateral neck dissection is generally recommended. LND is not indicated for early glottic lesions.

- Posterolateral neck dissection. Posterolateral neck dissection is recommended for primary cutaneous malignancies of the posterior scalp, e.g. melanoma and squamous cell carcinoma.

- Central compartment neck dissection. Central compartment neck dissection is recommended for differentiated thyroid carcinoma in which the disease is limited to the pretracheal and paratracheal nodes (level VI).

Conservation neck dissection for N+ disease

MODIFIED RADICAL NECK DISSECTION FOR N+ DISEASE

Comprehensive neck dissections involve the removal of all lymphatic tissue in the lateral neck (levels I–V) and are generally carried out for the clinically positive neck (N+). They can be classified into radical and modified radical neck dissection (Figure 8.5), depending on what other structures are excised. The gold standard operation is the radical neck dissection which involves the removal of lymph nodes in levels I–V, as well as the sternocleidomastoid muscle, internal jugular vein, spinal accessory nerve and submandibular salivary gland. Modified radical neck dissection is divided into types I, II or III, depending on the structures which are conserved. Type I MRND involves preservation of one structure: the spinal accessory nerve. Type II involves preservation of two structures: the spinal accessory nerve and the sternocleidomastoid muscle. Type III involves preservation of the spinal accessory nerve, internal jugular vein and the sternocleidomastoid muscle. Type I MRND is the most commonly employed neck dissection for squamous cell carcinoma of the upper aerodigestive tract with clinically positive neck disease. Type III MRND is most commonly employed for metastastic differentiated carcinoma of the thyroid. Bocca coined the term ‘functional neck dissection’ and employed this type of operation for squamous cell carcinoma, mostly in patients with larynx cancer. The operation was safe and successful in patients with cN0 neck, but in patients with cN+ neck, regional failure with recurrence occurred in 29 per cent.\textsuperscript{9} Based on what we know today regarding the patterns of neck metastases, dissection of all five levels of lymph nodes in the cN0 neck is unnecessary. Furthermore, in the cN+ setting, the operation is unsafe due
to high failure rates. Thus, the ‘functional neck dissection’ has fallen out of the repertoire of contemporary head and neck surgery. A modification of the type III mRND is that described by Ballantyne, where level V is removed using an anterior approach. With this technique, the medial aspect of level V is removed, preserving the accessory nerve and cervical plexus. This offers better functional results and quality of life. However, the operation is not recommended if there is evidence of level V disease clinically or radiologically, for the N3 neck, fixed nodal disease or when multiple levels are involved. It is also not recommended after radiotherapy.

**SELECTIVE NECK DISSECTION FOR N+ DISEASE**

The use of selective neck dissection in patients with clinically positive neck disease is controversial. Some studies have recommended that it may be used for nodal metastases.
confined to the first echelon nodes (usually N1) when the primary is being treated by surgery. However, it is important to point out that postoperative radiation therapy to the neck is required in this setting. For node-positive disease, the results of selective supraomohyoid neck dissection are more variable. In 1985, Byers reported a regional recurrence rate of 15 per cent. In 1997, Pellitteri et al. reported a regional recurrence rate of 11 per cent. In 1999, Byers reported that the regional recurrence rate was 36 per cent in patients with pN1 neck disease who had not received radiation therapy, but was 5.6 per cent among those who had received postoperative radiation. For pN2b disease, the failure rate was 8.8 per cent with radiation and 14 per cent without. In 1996, Spiro et al. reported a recurrence rate of 6 per cent in patients who had received postoperative radiation following supraomohyoid neck dissection. Andersen et al. reported a ten-year retrospective of 106 previously untreated clinically and pathologically node-positive patients undergoing 129 selective neck dissections; regional metastasis was clinically staged as N1 in 58 patients.

Table 8.4 Classification of different types of neck dissection with clinical indications.

<table>
<thead>
<tr>
<th>Comprehensive</th>
<th>Nodal levels removed</th>
<th>Structures preserved</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical neck dissection</td>
<td>Levels I–V</td>
<td>None</td>
<td>N+ neck for SCC where SAN involved</td>
</tr>
<tr>
<td>Modified radical neck dissection type I</td>
<td>Levels I–V</td>
<td>SAN</td>
<td>N+ neck for SCC where SAN free of disease</td>
</tr>
<tr>
<td>Modified radical neck dissection type II</td>
<td>Levels I–V</td>
<td>SAN, SCM</td>
<td>N+ neck for SCC where IJV involved but SAN free of disease</td>
</tr>
<tr>
<td>Modified radical neck dissection type III</td>
<td>Levels I–V</td>
<td>SAN, SCM, IJV</td>
<td>Metastatic differentiated thyroid carcinoma</td>
</tr>
<tr>
<td>Selective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraomohyoid neck dissection</td>
<td>Levels I–III</td>
<td>SAN, SCM, IJV</td>
<td>N0 neck for SCC of oral cavity and oropharynx (include level 4);</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N0 neck malignant melanoma where primary site is anterior to ear (include parotidectomy for face and scalp)</td>
</tr>
<tr>
<td>Lateral neck dissection</td>
<td>Levels II–IV</td>
<td>SAN, SCM, IJV</td>
<td>N0 neck for SCC of larynx and hypopharynx</td>
</tr>
<tr>
<td>Posterolateral neck dissection</td>
<td>Levels II–V, suboccipital, retroauricular nodes</td>
<td>SAN, SCM, IJV</td>
<td>N0 neck malignant melanoma where primary site is posterior to ear</td>
</tr>
</tbody>
</table>

Figure 8.4 Skin incisions for various types of neck dissection. (a) Comprehensive; (b) supraomohyoid; (c) jugular; (d) comprehensive (thyroid); (e) modified (parotid); (f) posterolateral. Redrawn with permission from Shah JP, Patel SG. Head and neck Surgery and Oncology, 3rd edn. New York: Mosby CV, 2003.
(54.7 per cent), N2a in five (4.7 per cent), N2b in 28 (26.4 per cent), N2c in 14 (13.2 per cent) and N3 in one (0.9 per cent). Extracapsular extension of tumour was present in 36 patients (34.0 per cent) and postoperative radiation therapy was administered to 76 patients (71.7 per cent). Overall, nine patients experienced disease recurrence in the neck for a regional control rate of 94.3 per cent illustrating that in highly selective patients selective neck dissection for node-positive disease is possible.

NECK DISSECTION FOR N+ DISEASE POST-CHEMORADIATION

Organ-preserving chemoradiotherapy is an emerging alternative in the treatment of laryngopharyngeal carcinoma. Management of the clinically positive neck in such patients remains controversial. It is generally accepted that patients with N0 and N1 disease can be treated by chemoradiation (CMTT) alone. However, for N2/3 disease, there is insufficient data to determine when to perform a neck dissection. Many investigators recommend neck dissection for all patients with N2a or N3 disease, regardless of response or if persistent disease is present as determined clinically or by computed tomography (CT) or magnetic resonance imaging (MRI). Brizel et al.\textsuperscript{16} reported a four-year disease-free survival of 75 per cent for N2/N3 for those with a CR in the neck who had neck dissection, compared to 53 per cent in those with CMTT who did not have a neck dissection ($p = 0.08$). They therefore recommended a mRND for N2/3 disease irrespective of neck response. This suggests that clinical/radiographic response in the neck is a crude predictor of the pathologic response and supports the idea that mRND eradicates residual disease that would otherwise recur regionally and/or seed distant sites. Evidence for residual disease was reported by Grabenbauer et al.,\textsuperscript{17} who found, in patients who had a neck dissection following a complete response in the neck, an incidence of 23 per cent residual disease – the rate of positive histology being 20 per cent for N1, 20 per cent for N2a/b and 54 per cent for N2c/N3 disease. However, other investigators have reported no detectable disease following a complete response to CMTT.\textsuperscript{18} The reason for this variation in pathological positive nodes in neck dissection specimens is related to the pathologic processing; meticulous step
sectioning is more likely to identify residual disease than a sampling of one or two sections from the neck. Another argument put forward for neck dissection post-CTRT is that if patients develop recurrence, very few can be salvaged. For example, in the University of Florida experience in 138 patients with positive neck disease treated by radiotherapy (RT) alone, 35 developed neck recurrence, salvage was attempted in nine patients and only successful in two. However, one must also balance the benefits of neck dissection against possible sequelae since wound complications are increased post-CTRT. Acute events such as chyle leak, wound breakdown, and flap necrosis occur in 17 per cent of patients and late complications, such as soft tissue fibrosis, can be severe, causing reduced neck movement, tightness and pain. Therefore, to improve the utility of neck dissection in patients with a complete response post-CTRT, we need to identify those patients who have residual disease. One possible approach is to use quantitative positron emission tomography (PET), an area of current research.

Alternatively, one could adopt a policy of performing a neck dissection in all patients, but reducing morbidity by carrying out a selective neck dissection rather than a comprehensive neck dissection. Several authors have now reported such an approach with no significant negative impact on regional recurrence rates.

**CONSERVATION SURGERY FOR CANCER OF THE LARYNX**

The choice of therapy for early stage squamous cell cancer of the larynx is determined by patient- and tumour-related factors, as well as physician preference. Opinions on therapy vary across disciplines and between countries because both surgery and radiotherapy are equally effective. Conservation laryngeal operations are historically the original organ preservation techniques; the first hemilaryngectomy was carried out by Billroth in 1874. With the availability of the laser, operating microscope and sophisticated endoscopes, transoral laser resections of laryngeal and pharyngeal lesions have gained popularity. The main aim of all conservation procedures is to maintain speech and swallowing and avoid a tracheostomy. Conservation laryngeal surgery options thus may be classified into open partial laryngeal surgical procedures and transoral endoscopic laser surgical procedures. In both types of surgery, the principles of resection are the same, and securing negative margins is crucial to the success of the procedure.

**Principles of organ preservation laryngeal surgery**

**LOCAL CONTROL**

Local control is the most important principle, since survival will be compromised if local failure occurs. This is because early detection of the recurrence is difficult due to alteration in the anatomy following index treatment. Therefore, organ preservation surgery should only be used when resection of the tumour can be confidently achieved.

**ACCURATE ASSESSMENT OF TUMOUR EXTENT**

The surgeon must be able to confidently predict the degree of tumour extension. This requires a comprehensive knowledge of laryngeal anatomy. Clinical examination using flexible laryngoscopy allows for assessment of vocal cord and arytenoid mobility, which helps to determine what deeper structures are invaded. Cancers involving the glottis and supraglottis have different effects on vocal cord mobility and arytenoid mobility. In glottic cancer, impaired cord mobility may be due to the bulk of the tumour on the cord surface or superficial thyroarytenoid muscle invasion. If the cord is fixed, studies have shown that this is due to invasion of the thyroarytenoid muscle. For cord fixation, the thyroarytenoid muscle is less likely and the most common cause of cord fixation is deep arytenoid cartilage invasion superiorly. For arytenoid mobility, there are two types of arytenoid impairment: pseudofixation due to the weight of the tumour and actual fixation due to cancer invasion of the intrinsic laryngeal muscles, the cricoarytenoid joint or both. All patients should also have an examination under anaesthesia so that the tumour can be assessed by direct laryngoscopy using angled telescopes to visualize the ventricle, anterior commissure and subglottis. Palpation of the vallecula is also important in the case of supraglottic cancers to assess the extent of submucosal invasion.

Clinical examination may be aided by imaging, such as CT and MRI. Coronal T1-weighted MRI is useful to assess subglottic extension. The cricoarytenoid area is best assessed by axial CT scans which will show sclerosis if perichondrial or direct arytenoid cartilage invasion has occurred. Sagittal MRI is good for the assessment of pre-epiglottic space invasion. MRI is also highly sensitive for assessment of thyroid cartilage invasion; enhancement into cartilage on postgadolinium fat-suppressed scans are highly sensitive to invasion. PET has also gained popularity. The most promising role for this is in the assessment of post-treatment effects and the detection of early recurrence.

**Cricoarytenoid unit**

The cricoarytenoid unit is the basic functional unit of the larynx. The cricoarytenoid unit consists of an arytenoid cartilage, the cricoid cartilage, the associated musculature and the nerve supply from the superior and recurrent laryngeal nerves for that unit. It is the cricoarytenoid unit, not the vocal folds, that allows for physiologic speech and swallowing without the need for a tracheostome. Therefore, preservation of at least one functional unit allows organ preservation laryngeal surgery.

**Open partial laryngeal surgery**

**CLINICAL ASSESSMENT**

When considering a patient for conservation laryngeal surgery, the following general principles should be considered:

- The patient must be able to tolerate a general anaesthetic.
The patient should not have any medical problems that may impair wound healing, e.g. transplantation patients or those with diabetes mellitus.

The patient should have good pulmonary function to tolerate the postoperative course, which often involves a period of aspiration. This is the main problem of conservation laryngeal surgery. The amount of postoperative aspiration varies with the type of surgery. Vertical hemilaryngectomy typically causes little impact on swallowing function, whereas supraglottic laryngectomy results in dysphagia and aspiration. A percutaneous gastrostomy tube may be required for patients with a significant prolonged period of aspiration.

The patient should play an active role in speech and swallowing rehabilitation. All patients should have a speech and swallowing assessment preoperatively and both the patient and family should participate in the work required for rehabilitation.

Any patient undergoing partial laryngectomy should be informed of the complexities of salvage conservation procedures, and must give consent for total laryngectomy. Any patient who cannot do this is not a good candidate for conservation laryngeal surgery. Careful preoperative planning will reduce the incidence of conversion to total laryngectomy.

CONSERVATION SURGERY FOR GLOTTIC LARYNGEAL CANCER

The possible surgical options include vertical partial laryngectomy and supracricoid partial laryngectomy with cricohyoidoepiglottopexy.

Vertical partial laryngectomy

**Technique**

This procedure may be a lateral or an anterolateral vertical partial laryngectomy. The technique involves vertical cuts through the laryngeal cartilage (Figure 8.6). The majority of the ipsilateral thyroid cartilage, true vocal cord, portions of the subglottic mucosa and false cord are removed. The extent of resection depends on the preoperative and intraoperative assessment of tumour extent. The strap muscles are closed over the residual perichondrium to form a pseudocord. A tracheostomy is generally required for 3–7 days.

If the anterior commissure is involved, a frontolateral partial laryngectomy can be performed.

**Criteria for the selection of a lesion suitable for vertical partial laryngectomy**

There are certain criteria which must be met before a patient is considered suitable for a vertical partial laryngectomy. These are shown in Box 8.1, and are general guidelines. However, these criteria are not absolute and may be extended.

**Oncological results**

For T1 glottic cancers, local recurrence rates are reported to be less than 10 per cent. If the anterior commissure is not involved, local control of 93 per cent has been reported, whereas if the anterior commissure is involved, the local control rate is reduced to 75 per cent due to subglottic recurrence. Therefore, when the anterior commissure is involved, a wide surgical margin in the subglottis is indicated.

For T2 glottic cancers, higher local failure rates of 4–26 per cent are reported. This is due to subglottic and supraglottic invasion. Subglottic extension is associated with cricoid cartilage invasion, which is not resected in the standard vertical partial laryngectomy. Extension into the supraglottis through the ventricle may result in thyroid cartilage invasion.

For T3 glottic cancers, local recurrence rates are higher, ranging from 11 to 46 per cent.

**Box 8.1 Criteria for selection of a lesion suitable for vertical partial laryngectomy**

- Lesion of mobile cord extending to anterior commissure
- Lesion of mobile cord involving vocal process and anterosuperior portion of arytenoid
- Subglottic extension should not be more than 5 mm
- Select patients with fixed vocal cord lesion not extending across the midline
- A unilateral transglottic lesion not violating the above criteria
- True cord/anterior commissure lesion not involving more than anterior third of the opposite cord

**Figure 8.6** Vertical partial laryngectomy.
Excellent oncologic results can therefore be expected for T1 glottic carcinomas, although once the anterior commissure is involved or if there is extension beyond the glottis, vertical partial laryngectomy should be used with caution. It is not recommended for advanced T2 or T3 lesions.

Functional results and complications

Following partial laryngectomy, there is some degree of hoarseness. More impairment to the voice occurs if there is no reconstruction, whereas the best voice is associated with replacement of the glottis with an adjacent false cord flap. Complications are uncommon and include delay in decannulation, stenosis and dysphagia. Laryngocutaneous fistula is uncommon.

Supracricoid partial laryngectomy with cricothyroidoplasty

Technique

Supracricoid partial laryngectomy with cricothyroidoplasty (CHEP) operation involves resection of both true cords, both false cords, the entire thyroid cartilage, paraglottic spaces bilaterally and a maximum of one arytenoid (Figure 8.7). Reconstruction is performed using the epiglottis, hyoid bone, cricoid cartilage and tongue. A temporary tracheostomy and feeding tube is required. This procedure is mainly used for T1b glottic carcinomas with anterior commissure involvement, selected T2 and T3 glottic carcinomas.

Oncologic results

The local recurrence rate for T2 glottic cancers is 4.5 per cent (three of 67), whereas the local recurrence rate for T3 glottic cancers is 10 per cent (two of 20). The consistently low recurrence rates are mainly due to the complete resection of the entire thyroid cartilage and bilateral paraglottic spaces.

Transglottic lesions (i.e. lesions which extend across the laryngeal ventricle involving both the true cord and false cord) have a failure rate of 23 per cent for conservative procedures which involve either extended vertical partial laryngectomy or extended supraglottic partial laryngectomy.

CONSERVATION SURGERY FOR SUPRAGLOTTIC LARYNGEAL CANCER

Surgical treatment of tumours of the supraglottic larynx creates a significant physiologic disturbance in the act of deglutition. Almost every patient aspirates to a varying degree following surgery. Most patients handle this with little difficulty and can handle most types of foods without significant pulmonary complications. However, patients with a poor pulmonary reserve, advanced stage of emphysema, and those of advanced age are poor candidates for conservation surgery. The conservative open surgical options available for supraglottic cancers include the supraglottic horizontal partial laryngectomy and the supracricoid laryngectomy with cricothyroidoplasty.

Horizontal supraglottic partial laryngectomy

Technique

In this procedure, the epiglottis, hyoid bone, pre-epiglottic space, thyrohyoid membrane, upper half of the thyroid cartilage and the supraglottic mucosa are removed (Figure 8.8). The vallecula is transected superiorly, the ventricles inferiorly and the aryepiglottic folds laterally. Closure is by approximating the base of tongue to the lower half of the thyroid cartilage and closing the posterior false cord mucosa to the medial pyriform sinus mucosa. A temporary tracheostomy is required. Bilateral selective neck dissection is carried out at the same time. In this procedure, it is important to identify and preserve the internal and external branches of the superior laryngeal nerve. The tongue base sutures are placed in the midline and 1 cm off to avoid damage to the hypoglossal nerves and lingual arteries.

Criteria for the selection of a lesion suitable for supraglottic partial laryngectomy

Several criteria related to tumour factors must be met in patients considered suitable for supraglottic partial laryngectomy. These are shown in Box 8.2. These criteria give good general guidelines, but the indications for the operation expand as the experience of the surgeon increases. A supraglottic partial laryngectomy may also be necessary for the surgical treatment of highly selected patients with primary tumours of the base of the tongue and secondary extension to the supraglottic larynx, tumours of the pyriform sinus involving its medial wall, and bulky tumours of the
pharyngeal wall and secondary extension to the supraglottic larynx.

**Oncologic results**

When local recurrence is analysed by T stage, high local control is obtained for selected T1 and T2 tumours, but extremely variable results are obtained for T3 and T4 lesions with local recurrence of 75 per cent for T3 and 67 per cent for T4. Therefore, supraglottic laryngectomy should be considered with extreme caution in T3 and T4 lesions.\(^4\)\(^9\)\(^,\)\(^5\)\(^0\)\(^,\)\(^5\)\(^1\)\(^,\)\(^5\)\(^2\)\(^,\)\(^5\)\(^3\)\(^,\)\(^5\)\(^4\)\(^,\)\(^5\)\(^5\)\(^,\)\(^5\)\(^6\) Lee *et al.*\(^5\)\(^2\) reported that improved local control is obtained if postoperative radiotherapy is given, although poorer functional results may occur as a consequence. Extension of supraglottic lesions below the false cord and impaired cord mobility are contraindications for supraglottic laryngectomy.

**Functional results and complications**

Normal to mild breathiness in voice occurred in 87 per cent of patients, and 67 per cent had mild to no evidence of hoarseness.\(^5\)\(^5\) Aspiration is common and complete swallowing rehabilitation may take up to three months.\(^5\)\(^6\) Hirano *et al.*\(^5\)\(^7\) noted that 84 per cent of patients had removal of the nasogastric tube within 30 days, whereas the rest required feeding for up to three months. Factors which were significant for duration of nasogastric tube removal were the extent of removal of the arytenoid cartilage\(^5\)\(^7\)\(^,\)\(^5\)\(^8\) and the preservation of the superior laryngeal nerves.\(^5\)\(^6\) Resection of the hyoid and tongue base was not related to swallowing outcome. Laryngocutaneous fistula rates are more common than vertical hemilaryngectomy and range from 0 to 12 per cent. Other complications include aspiration pneumonia (0–10.8 per cent) and inability to decannulate the tracheostomy (0–5.5 per cent).\(^5\)\(^9\)

**Supracricoid partial laryngectomy with cricothyroidopexy**

**Technique**

Supracricoid partial laryngectomy with cricothyroidopexy (CHP) is suitable for supraglottic carcinomas not amenable to supraglottic laryngectomy due to one of the following:

- glottic level involvement through the anterior commissure or ventricle;
- pre-epiglottic space invasion;
- decreased cord mobility;
- limited thyroid invasion.

These lesions are not rare; the incidence of spread to the glottis may be between 20 and 54 per cent. This is due to spread within the paraglottic space.\(^6\)\(^0\) This operation involves resection of both true cords, both false cords, the entire thyroid cartilage, both paraglottic spaces bilaterally, and a maximum of one arytenoid, thyrohyoid membrane and epiglottis (Figure 8.9). Reconstruction is performed using the hyoid bone, cricoid cartilage and tongue. A temporary tracheostomy and feeding tube is required.
Criteria for the selection of a lesion suitable for supracricoid partial laryngectomy

Indications and contraindications for supracricoid partial laryngectomy with CHP and CHEP are shown in Box 8.3.

Oncologic results

Laccourreye et al. have reported no local recurrences of supraglottic carcinomas treated this way in 68 patients (T1-1, T2-40, T3-26, T4-1) over a follow-up period of 18 months. Chevalier and Piquet reported a local recurrence rate of 3.3 per cent. In tumours with pre-epiglottic space invasion, Laccourreye et al. reported a local control of 94 per cent in 19 patients with a five-year follow-up period. The reason for such good results is due to the en bloc resection of bilateral paraglottic spaces, pre-epiglottic space and thyroid cartilage. Contraindications to this procedure are the following:

- subglottic extension > 10 mm anteriorly and 5 mm posteriorly because of cricoid cartilage involvement;
- arytenoid fixation;
- massive pre-epiglottic space involvement with extension of the vallecula;
- extension to the pharyngeal wall, vallecula, base of tongue, postcricoid region, interarytenoid region;
- cricoid cartilage invasion.

Functional results and complications

Swallowing and speech problems are to be expected in this procedure. Success in this operation is dependent on careful patient selection, intraoperative technique and postoperative rehabilitation. Nasogastric feeding is required from 30 to 365 days and total laryngectomy may be required in up to 10 per cent of patients. Dysphagia is more common if one arytenoid is resected. Voice studies have shown these patients have poorer voice due to instability of the neoglottis resulting from a wide surgical resection.

Box 8.3 Criteria for selection of a lesion suitable for supracricoid partial laryngectomy

**Indications for supracricoid laryngectomy**

- T1 and supraglottic lesions with ventricle extension
- T2 infrahyoid epiglottis or posterior one-third of the false cord
- Supraglottic lesions extending to glottis or anterior commissure, with or without vocal cord mobility
- T3 transglottic carcinoma with limitation of the vocal cord
- Selective T4 lesions invading the thyroid cartilage

**Contraindications for supracricoid laryngectomy**

- Bulky pre-epiglottic space involvement
- Gross thyroid cartilage destruction
- Interarytenoid or bilateral arytenoids involvement
- Fixed arytenoids
- Subglottic extension > 10 mm anteriorly or > 5 mm posteriorly
- Inadequate pulmonary reserve

CONSERVATION LARYNGEAL SURGERY FOR RADIATION FAILURE

Patients who fail radiotherapy for glottic cancer who were originally suitable for vertical partial laryngectomy may still be eligible for this surgery provided the tumour has not progressed. Local control in such patients may be from 80 to 90 per cent. Of those with supraglottic carcinoma treated with radiotherapy who fail, only 30 per cent may still be suitable for conservation surgery. Sorenson et al. reported poor oncologic and functional results in such patients and advocated total laryngectomy in these patients.

Contraindications to hemilaryngectomy after RT failure include:

- tumour involving the arytenoid;
- subglottic extension > 10 mm anteriorly and 5 mm posteriorly because of cricoid cartilage involvement;
- cartilage invasion of the thyroid or cricoid.

One alternative for larger lesions is to use either supracricoid laryngectomy with cricohyoidopexy or cricohyoidoepiglottopexy as the salvage procedure. This can give local control rates of 83.3 per cent.

Transoral endoscopic laser resection

INTRODUCTION

In recent years, transoral endoscopic laser resection has become accepted as an alternative to open partial laryngeal surgery and radiotherapy. Oncologic results are comparable between all techniques, but transoral laser microsurgery has potential advantages over both open surgery and radiotherapy which are summarized in Box 8.4. In this technique, the cancer is removed via a transoral route using specialized rigid laryngoscopes to expose the tumour and then using the CO₂ laser and microlaryngeal instruments to remove the tumour under microscopic visualization. The technique relies on removal of cancer in a blockwise method, resulting in several resection specimens. This requires cutting through cancerous tissue, which of course is against the principles of conventional oncologic surgery. However, with microscopic laser surgery, it is possible to see the structure of the cut surface of the tumour, allowing exposure of the superficial and deep extension of the tumour more precisely and allowing one to differentiate between malignant and non-malignant structure. This way the surgeon can individually adjust the safety margin. The microscope can also facilitate the detection of any further dysplastic or neoplastic changes of the mucosa surrounding the tumour (field cancerization). The technique also has several other advantages over traditional surgery. Dissection through healthy tissue to reach the tumour is not required and contributes to limited surgical trauma and limited blood loss. This means that the need for reconstruction is usually not necessary as the resulting defect is smaller and heals spontaneously. This also has a major impact on function of speech and swallowing. By preserving functionally important structures, such as cartilage, muscle and nerves, a more rapid and effective rehabilitation of the patient is achieved.
Tracheostomy is rarely indicated, patients are able to swallow sooner and often experience very little or even no pain postoperatively. As a result, the length of operation, hospital stay and duration of illness are markedly shortened and therefore costs are reduced accordingly. Lastly, during and after laser surgery, all surgical options still remain open. For example, during the operation, the procedure can be changed to an open approach at any time. Postoperatively, further laser resections can be done or an open conventional surgery performed. Laser surgery can be repeated many times for local recurrences, as well as second primary tumours. The learning curve for transoral laser surgery of tumours of the larynx and pharynx, however, is quite steep. Significant experience with a large number of patients is required to gain the expertise, technical dexterity and judgment for a successful outcome. Large experience, therefore, is reported only from a few centres.

**TRANSORAL ENDOSCOPIC LASER RESECTION FOR GLOTTIC CARCINOMA**

**T1, T2 tumours**

Transoral laser resection of early T1 and T2 glottic cancers has been reported with excellent oncologic results. Steiner et al.\textsuperscript{79} reported on 158 patients with T1a and 30 patients with T1b cancers, with five-year local control rates of 96 and 85 per cent, respectively, and a larynx preservation rate of 97.6 and 99 per cent, respectively. For T2a glottic cancers (n = 129) and T2b cancers (n = 115), five-year local control rates were 84 and 70 per cent, respectively, with larynx preservation rates of 96 and 86 per cent. Excellent results have been reported by Ledda et al.\textsuperscript{80} (five-year local control of 98 per cent for 103 patients with T1 or T2 cancers).

**T3, T4 tumours**

For large volume T2, T3 and T4 tumours, organ-preserving chemoradiation is now the standard treatment. The surgical treatment is total laryngectomy. However, conservation surgery by endoscopic laser resection is possible for T3 tumours. Steiner et al.\textsuperscript{79} have reported on 95 patients with T3 glottic cancers with a five-year local control rate of 69 per cent, larynx preservation rate of 84 per cent, overall survival of 58 per cent and recurrence-free survival of 60 per cent.

**TRANSORAL ENDOSCOPIC LASER RESECTION FOR SUPRAGLOTTIC CARCINOMA**

**T1, T2 tumours**

Endoscopic laser resection of supraglottic laryngeal cancer can be carried out for all T-stage tumours. For tumours
located in the supraglottis, exposure for laser microsurgery is dependent upon the use of a distending laryngoscope (Figure 8.12). Steiner (personal communication) has reported five-year local control rates for T1 \((n = 23)\) and T2 \((n = 72)\) cancers of 95 and 85 per cent with larynx preservation rates of 96 and 99 per cent, respectively. Overall survival rates were 87 and 73 per cent, respectively. These results are comparable to open supraglottic laryngectomy, but functional results are superior since clinically relevant aspiration did not occur in the laser-treated patients.

**T3, T4 tumours**

For large volume T2, T3 and T4 tumours, organ-preserving chemoradiation is now the standard treatment. This is because open surgery is radical and involves either a total laryngectomy, total laryngopharyngectomy and flap, or total laryngectomy and glossectomy. However, many institutions have now advocated conservation surgery in this setting by transoral endoscopic laser resection, allowing larynx and pharynx preservation. No tracheostomy is required, but patients require percutaneous endoscopic gastroscopy (PEG) feeding in the postoperative period. Adjuvant PORT (postoperative radiotherapy) is required. In supraglottic cancer, it is important to treat both sides of the neck. For the clinically negative neck, either separate or synchronous selective neck dissection can be performed or both necks can be treated with PORT bilaterally. For the clinically positive neck, either separate or synchronous comprehensive neck dissections should be performed with transoral laser resection. Steiner (personal communication) has reported the five-year local control rates for T3 \((n = 76)\) and T4 \((n = 45)\) cancers of 79 and 69 per cent with larynx preservation rates of 95 and 84 per cent, respectively. Overall survival rates were 67 and 54 per cent, respectively. Again, patient selection is important, as good pulmonary function and patient motivation is required for the entire time it takes to rehabilitate the patient. This surgery may not be possible if there is extensive field change.

**CONSERVATION SURGERY FOR RECURRENT EARLY STAGE LARYNGEAL CANCER**

Between 10 and 40 per cent of patients with early stage laryngeal cancer treated with radiotherapy recur after treatment. Many of these patients recur with higher T-stage disease and require salvage total laryngectomy. However, some patients still have T1 or T2 tumours which are amenable to salvage partial laryngectomy (PL). In many institutions, salvage surgery is often by total laryngectomy due to lack of experience in conservation surgery of the larynx, as well as the belief that increased complications are associated with partial laryngectomy of irradiated cartilage and that negative tumour margins are difficult to achieve in a fibrotic oedematous larynx. However, salvage partial laryngectomy is possible in select patients who do not progress on therapy or who recur with early stage disease. Such patients require careful endoscopic and radiologic assessment. Salvage partial laryngectomy may be by frontolateral vertical PL, supracricoid PL or by transoral laser resection. For frontolateral vertical PL, Shah *et al.*\(^81\) emphasized the importance of excluding patients in whom the recurrent tumour has extended beyond its original site, thereby making it unsuitable for a conservation operation, and of checking resection margins by intraoperative frozen sections. McLaughlin *et al.*\(^82\) also highlighted the importance of CT scanning to determine if salvage was possible, recommending total laryngectomy if cartilage invasion, vocal cord fixation, extensive subglottic disease or recurrence beyond the original is seen on CT scan. Local control rates of 66–96 per cent have been reported for PL in early stage glottic laryngeal tumours.\(^81\),\(^82\),\(^83\),\(^84\),\(^85\),\(^86\),\(^87\),\(^88\),\(^89\)

Salvage supracricoid partial laryngectomy with cricothyoidopiglottotopexy for radio-recurrent glottic cancer involves removal of the thyroid cartilage and both paraglottic spaces with preservation of the cricoid cartilage, hyoid bone, epiglottis and one or both arytenoids cartilage and recurrent laryngeal nerves. It has been advocated as a better operation than the frontolateral vertical partial laryngectomy, where patients often end up with a small glottis and poor voice. In the supracricoid partial laryngectomy (SCPL) with CHEP, rehabilitation takes time and patients require a temporary tracheostomy and PEG due to aspiration. Therefore, patient motivation and support are essential, as well as good pulmonary function in patients treated this way. Salvage by endoscopic laser resection has also been advocated. Local control rates are reported to be 60–70 per cent.\(^75\) Patients have to be selected and monitored carefully afterwards.

For supraglottic cancers, salvage partial laryngectomy by horizontal supraglottic partial laryngectomy\(^90\) or supracricoid partial laryngectomy and cricothyoidopexy (CHP)\(^70\),\(^91\) is possible if the tumour has not extended beyond the original site as assessed endoscopically and by CT imaging. However, in general, salvage surgery for supraglottic cancer often requires a total laryngectomy.

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**Figure 8.12** Distending laryngoscope for endoscopic resection of supraglottic tumours and tumours of the pyriform sinus. Reproduced with permission from Wolfgang S, Ambrosch P. *Endoscopic laser surgery of the upper aerodigestive tract*. Stuttgart: Thieme.
CONSERVATION SURGERY FOR CANCER OF THE HYPOPHARYNX

Carcinoma of the hypopharynx includes cancer of the pyriform sinus (70 per cent), postcricoid region (15 per cent) and posterior pharyngeal wall (15 per cent). Of all head and neck sites, hypopharyngeal cancer has the poorest prognosis with an overall five-year survival of less than 20 per cent. This is because patients usually present with advanced stage disease (stage III/IV) either due to advanced T stage or neck metastases. Approximately 66 per cent of patients have nodal disease at first presentation, and of the remaining, 34 per cent present with N0 disease and 41 per cent present with occult neck metastases. Therefore, management of hypopharyngeal cancer involves not only treatment of the primary, but also the neck.

T1 and small volume T2 tumours without neck metastases

Patients are usually treated with radiation to the primary and the neck bilaterally. However, partial pharyngectomy and bilateral selective neck dissection can also be performed.

T1 and small volume T2 tumours with neck metastases

Patients may be treated with comprehensive neck dissection for the neck and radiation to the primary. Alternatively, partial pharyngectomy and comprehensive neck dissection with PORT can be carried out.

Large volume T2, T3 and T4 tumours with/without neck metastases

RADICAL SURGERY

Patients may require radical surgery. If the larynx is not involved, surgery involves resection of the primary tumour (preserving larynx) with reconstruction, neck dissection and postoperative radiation therapy. If the larynx is involved, surgery entails excision of the primary tumour with laryngectomy and reconstruction, and neck dissection followed by postoperative radiation therapy. Reconstruction of the pharynx may be by free jejunum or tubed free radial forearm flaps for circumferential defects and by free radial forearm flaps, anterolateral thigh flaps or pedicled pectoralis myocutaneous flaps for partial pharyngeal defects. This type of surgery is radical and associated with significant effects both on speech and swallowing. For this reason, organ-preserving chemoradiation has now been advocated and has largely superseded radical surgery for this disease. For cancer of the pyriform sinus, five-year survival figures of 25 per cent are comparable to surgery with larynx preservation rates of 35 per cent. However, many of these patients suffer the long-term sequelae of chemoradiation which include swallowing difficulty from stenosis of the hypopharynx and aspiration from a nonfunctioning larynx. For this reason, alternative surgical conservation approaches have been advocated by some investigators using transoral endoscopic laser resection.

CONSERVATIVE TREATMENT BY TRANSORAL ENDOSCOPIC LASER RESECTION OF PYRIFORM SINUS TUMOURS

Endoscopic laser resection of patients with pyriform sinus tumours can now be carried out with synchronous or separate neck dissection. For tumours located in the pyriform sinus, exposure for laser microsurgery is dependent upon the use of the distending laryngoscope (Figure 8.12). Steiner et al. have reported their results for 129 patients which comprised 24 patients with T1, 74 with T2, 17 with T3 and 14 with T4 tumours. Seventy-five per cent of patients had stage III/IV disease and 25 per cent stage I/II disease. Forty-two per cent of patients had surgery alone and 58 per cent surgery and postoperative radiotherapy. With a median follow up of 44 months, 87 per cent of patients were controlled locally. Local and locoregional recurrence rates for each T stage are shown in Table 8.5.

Of the 17 patients with either local or locoregional recurrence, ten were able to be salvaged; eight had further laser microsurgery ± radiotherapy, one had partial pharyngectomy with laryngeal preservation and one had partial pharyngectomy with total laryngectomy. Six patients had palliative treatment and one patient was unknown. The five-year overall survival was 71 per cent for stage I/II and 47 per cent for stage III/IV disease. The five-year recurrence-free survival was 95 and 69 per cent, respectively. These are extremely high cure rates reported for hypopharynx cancer, and are not duplicated by other authors in the literature.

The EORTC organ preservation chemoradiation study reported on 100 patients with stage III/IV disease; a 25 per cent disease-free survival and 35 per cent organ preservation rate was reported. In contrast, Steiner et al. have reported a five-year overall survival of 47 per cent, recurrence-free survival of 69 per cent and an organ preservation rate of 99 per cent for patients with pyriform sinus tumours treated by laser resection. In addition, functional results were excellent compared with radical surgery and chemoradiation with 27 per cent of patients requiring no feeding tube and 73 per cent requiring a feeding tube for a median duration of 7 days (range 1–25 days). Excellent oncologic results have also been published by Vilaseca et al. who reported on 28 patients with hypopharyngeal carcinomas with a four-year overall and disease-specific survival of 43 and 59 per cent, respectively, and a larynx preservation rate of 78 per cent. These data suggest that function-preserving laser surgery for pyriform sinus cancer has a definite role to play in the management of these patients.

Table 8.5 Local and locoregional recurrence rates.

<table>
<thead>
<tr>
<th>No. patients (n = 129)</th>
<th>Local recurrence</th>
<th>Locoregional recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (24)</td>
<td>2 (8.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>T2 (74)</td>
<td>5 (6.7%)</td>
<td>3 (4.1%)</td>
</tr>
<tr>
<td>T3 (17)</td>
<td>2 (11.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>T4 (14)</td>
<td>3 (21.4%)</td>
<td>2 (14.3%)</td>
</tr>
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</table>
CONSERVATION SURGERY FOR CANCER OF THE ORAL CAVITY

Limited resection of oral cavity cancers is to be condemned. However, it is possible to carry out conservation surgery to the mandible during resection of oral cavity and oropharynx cancers. To determine if the mandible is invaded by cancer, careful assessment of the mandible is best carried out by bimanual palpation under anaesthetic. Radiographic imaging should be used to supplement the clinical evaluation; CT is effective at assessing cortical erosion, whereas MRI is particularly useful for determining marrow involvement and involvement of the inferior alveolar nerve.

Tumour invasion of the mandible

In order to assess the extent and need for mandible resection it is necessary to understand the process of invasion of the mandible. Tumours do not invade directly through intact periosteum and cortical bone towards the cancellous part of the mandible because the periosteum acts as a protective barrier. Instead, the tumour advances along the attached gingiva towards the alveolus. In patients with teeth, the tumour extends up to the alveolar process and then invades the mandible via the dental sockets to extend into the cancellous part of the mandible. In edentulous patients, the tumour extends up to the alveolar process and then infiltrates the dental pores to extend into the cancellous part of the mandible. In the irradiated mandible, the periosteal barrier is weak and therefore direct invasion through the lingual plate may occur.

Mandibulotomy approach for access for oral cavity and oropharynx cancers

Previously, resection of oral cavity lesions in regions with limited access, such as the retromolar trigone and posterior tongue, were resected with a segment of mandible. However, there are no lymphatic channels passing through the mandible and therefore there is no need for an in continuity composite resection. Segmental mandibulectomy should be carried out if there is:
- gross invasion by oral cancer;
- tumour close to mandible in a previously irradiated patient;
- invasion of the inferior alveolar nerve or canal by tumour;
- massive soft tissue disease adjacent to the mandible.

If none of these criteria is present, then access to the primary tumour can be with a mandibulectomy approach. Mandibulectomy can be performed in one of three locations: lateral (through the body or angle of the mandible), midline or paramedian. Access is best by a paramedian approach due to the disadvantages of the lateral and midline approach (Box 8.5).

The paramedian mandibulectomy avoids all of the disadvantages outlined in Box 8.5. The preferred site is between the lateral incisor and canine teeth since the roots of these two teeth diverge. Therefore, bone cuts can be performed without damaging the teeth. Only the myohyoid muscle is divided, the genioglossus and geniohyoid muscles are preserved. This results in minimal problems with swallowing.

Marginal mandibulectomy

If the periosteum or superficial aspect of the cortical mandible bone is involved, it is possible to carry out a marginal mandibulectomy rather than segmental mandibulectomy. In the dentate patient, marginal mandibulectomy is possible since the cortical part of the mandible inferior to the roots of the teeth remains uninvolved by tumour. However, in edentulous patients, the feasibility of mandibulectomy depends on the vertical height of the body of the mandible. With ageing, the alveolar process recedes and the mandibular canal comes closer and closer to the surface of the alveolar process. This eventually leads to a pipestem mandible and in these circumstances it may be impossible to carry out a marginal mandibulectomy with iatrogenic fracture. Marginal mandibulectomy is contraindicated when there is gross invasion into the cancellous part of the mandible or when there is massive soft tissue disease. It is also contraindicated in the irradiated mandible or in the edentulous patient with a pipestem mandible.

CONSERVATION SURGERY FOR CANCER OF THE OROPHARYNX

Cancer of the oropharynx includes the soft palate, tonsil, base of tongue and posterior pharyngeal wall.
T1 and T2 tumours with/without neck metastases

The primary is usually treated with radiotherapy. If the neck is clinically negative, radiation therapy is usually used as well. If clinically positive, the neck is treated with comprehensive neck dissection and PORT. Surgery can also be used to treat the primary tumour either by open resection or transoral laser resection.

T3 and T4 tumours with/without neck metastases

RADICAL SURGERY

Radical surgery of cancer of the tonsil or base of tongue involves a paramedian mandibulotomy for access, resection of the primary, comprehensive neck dissection and reconstruction with free tissue (usually free radial forearm flap, anterolateral thigh, free rectus muscle or occasionally pedicled myocutaneous pectoralis major flap). Such surgery has significant effects on speech and swallowing and because of this organ-preserving chemoradiation is now often advocated. However, even chemoradiation has both acute and chronic toxicity associated with it, also affecting speech and swallowing. Recently, conservation surgery using transoral laser resection has been used by some investigators.104

CONSERVATIVE SURGERY BY TRANSORAL LASER RESECTION

An alternative to chemoradiation or radical surgery is transoral laser resection followed by PORT. This technique requires appropriate usage of retractors and distending pharyngoscopes to give adequate access and the CO2 laser to resect the tumour. A temporary tracheostomy may be required, as well as a temporary PEG tube for feeding. Such a technique has a learning curve. As in laryngeal cancer, this technique relies on resection in blocks of tissue and this poses problems with margin assessment by the pathologist. Because of this, postoperative radiotherapy is generally recommended in all such patients. As in all conservation surgery, selection of patients is paramount in the success of the technique. In particular, the patient must play an active role both in speech and swallowing rehabilitation. The technique does have limitations and these are listed below:

- extension to the retromolar trigone;
- lateral spread to the internal carotid artery and masticator space;
- field change;
- inferolateral spread to the soft tissue of the neck;
- contralateral lingual artery involvement.

The largest series to date is by Steiner et al.104 who reported on 48 patients with base of tongue cancer (T1, 2 per cent; T2, 25 per cent; T3, 15 per cent; T4, 58 per cent; 94 per cent had stage III/IV disease). Selective neck dissection was carried out in 43 patients and 23 patients had postoperative radiotherapy. The five-year local control rate was 85 per cent, recurrence-free survival 73 per cent and overall survival 52 per cent. Swallowing was normal in 92 per cent of patients and 88 per cent had understandability of speech. These results suggest that organ-preserving laser microsurgery has a role to play in the management of selected patients with base of tongue cancer both in terms of oncologic control and functional results.

Recently, transoral robotic surgery (TORS) has been employed by some with the claims of improved visualization, better assessment and manoeuvrability, and more accurate resection with satisfactory margins.105 However, the role of robotic surgery in conservation procedures in the head and neck is evolving and requires further experience.

CONSERVATION SURGERY FOR CANCER OF THE NASAL CAVITY AND PARANASAL SINUSES

Malignant and benign tumours of the paranasal sinuses and skull base are resected by open procedures which allow for complete en bloc resection. Several facial incisions have been described to approach these types of tumours (Figure 8.13). Lateral rhinotomy alone can be used for anteriorly located nasal lesions. A Weber–Ferguson incision is used for tumours involving the medial wall of the maxillary sinus requiring maxillectomy. The Weber–Ferguson incision with a Lynch extension is used for tumours of the ethmoid sinus. For more advanced tumours of the maxillary sinus requiring subtotal or total maxillectomy, a Weber–Ferguson incision with subciliary extension is used. For tumours with anterior skull base involvement, an anterior craniofacial approach is required (Figure 8.14). This involves both a transfacial and transcranial incision for complete en bloc removal of tumour. All of these approaches result in a facial incision which may be cosmetically unacceptable to some patients, but also may result in disfigurement of the facial skeleton when large bony resections are required. Craniofacial surgery is also associated with significant morbidity and mortality, with an overall complication rate of 33 per cent and mortality of 4–6 per cent.106

The advent of rigid endoscopes has revolutionized the management of paranasal sinus inflammatory disease by functional endoscopic sinus surgery (FESS). More complex intranasal pathology can now be managed; for example, dacrocystorhinotomy can be carried out for nasolacrimal duct obstruction, orbital decompression for exophthalmos of hyperthyroidism and endoscopic repair of cerebrospinal fluid leaks. Recently, endoscopic techniques have been successfully used to manage benign tumours, such as inverted papilloma,107, 108, 109, 110, 111 angiofibromas,112, 113, 114, 115 and hypophyseal tumours.116, 117 Certainly, the endoscopic approach for benign disease has advantages over open surgical resection. As there is no facial incision, resection of normal tissue is avoided, resulting in better function as well as cosmesis, and improved visualization of the tumour can be obtained using angled endoscopes, as well as increasing microscopic visualization of the tumour by magnification of images obtained. The availability of real-time image guidance, neuro-navigation and intraoperative MRI has further improved the safety and accuracy of endoscopic resections.
However, whether or not endoscopic resection can be safely and successfully carried out for malignant sinonasal disease still remains questionable. A recent report by the international collaborative group encompassing 17 international sites reported on the prognostic factors important in sinonasal tumours with skull base invasion. This study reported that intracranial involvement, comorbidity, surgical resection margins and pathology were the main factors predicting survival. Endoscopic approaches do not allow for complete en bloc removal of tumour, and therefore resection margins remain a controversial area. Random biopsies of the resection bed following excision may be used to check for completeness of endoscopic removal. Another area of controversy is whether or not the endoscopic technique can be used for tumours with intracranial extension; for tumours invading periosteum or bone, endoscopic removal of tumour may be possible with resection of bone provided the tumour is mainly in the midline with no lateral extension. However, reconstruction of the resultant bony defect is then required. For open surgery, the galealpericranial flap is used, but this is not possible with the endoscopic approach. Reconstruction with non-vascularized tissue, such as fascia lata and tissue glue, has been reported, but this remains an open question.

**Figure 8.13** Different incisions used for resection of paranasal sinus tumours. (1) Lateral rhinotomy; (2) Weber–Ferguson; (3) Weber–Ferguson with Lynch extension; (4) Weber–Ferguson with subciliary extension; (5) Weber–Ferguson with subciliary and supraciliary extension.

**Box 8.6** Criteria for selection of a lesion suitable for endoscopic resection of paranasal sinus tumours

**Possible indications**
- Midline lesions with limited lateral extension
- Benign tumours, such as inverted papilloma and angiofibroma
- Low-grade malignant tumours
- Resection for palliative intent
- Medical comorbidity limiting open surgical approach

**Possible contraindications**
- Lateral extension of tumour
- Intracranial invasion involving brain ± dura
- Intraorbital invasion
- High-grade malignant tumours
area of uncertainty. For tumours requiring dura excision this is also possible, but again reconstruction is the main area of concern.121 When intracranial extension into brain occurs, endoscopic resection is contraindicated. Histology of the malignant tumour is also a significant predictor of survival; therefore more aggressive types of tumours, such as sinonasal undifferentiated carcinoma, melanoma, high-grade sarcomas, high-grade squamous and adenocarcinomas are best treated with open surgery. However, for benign tumours or low-grade malignant tumours, such as low-grade sarcomas, small central esthesioneuroblastomas or salivary gland tumours, endoscopic approaches may be possible. Lastly, endoscopic resection may be the treatment of choice when the objective of surgery is palliation or when the patient has significant comorbidity which precludes an open surgical approach. A summary of possible indications and contraindications for endoscopic surgery for paranasal sinus tumours is shown in Box 8.6.

CONSERVATION SURGERY FOR TUMOURS OF THE PAROTID GLAND

Warthin’s tumour excision without parotidectomy

Surgery is the mainstay for treatment for both benign and malignant parotid tumours. The most common benign tumours are pleomorphic adenoma and Warthin’s tumours (adenolymphoma). Conservation surgery, i.e. enucleation for pleomorphic adenoma, is not recommended due to the high incidence of local recurrence. This is due to the presence of pseudopodia.122, 123 Treatment of recurrent pleomorphic adenoma results in a higher incidence of facial nerve paresis and Frey’s syndrome.124 However, enucleation is possible in Warthin’s tumours where there are no pseudopodia. Heller and Attie125 reported on 162 patients with Warthin’s tumours, of whom 112 were amenable to a simple enucleation. In only two patients did an additional tumour develop. No permanent facial nerve injuries occurred.

Preservation of facial nerve for malignant tumours

For early stage parotid cancers, superficial parotidectomy with facial nerve preservation is advocated. However, for late stage cancer or cancers, the resection may need to involve removal of the mandible, zygoma and temporal bone, as well as part or all of the facial nerve. In the last decade, there has been a trend to a more conservative approach to the facial nerve. Most surgeons now advocate preservation of the facial nerve branches unless they are adherent to or directly invaded by tumour. This approach, however, relies on the use of postoperative radiation to control for microscopic residual disease.126 If major branches or the main trunk are involved, then immediate cable grafts should be done using branches of the cervical plexus or sural nerve.

KEY LEARNING POINTS

Conservation surgery for the neck
• For the N0 neck, selective neck dissection can be done. The type of neck dissection is determined by the location of the primary tumour.
• For the N+ neck, radical neck dissection is the old standard. Modified radical neck dissection type I can be done preserving function to the shoulder. Type II–III modified neck dissection can be done for metastatic thyroid cancer.
• For the N+ neck, selective neck dissection is controversial. Recurrence rates up to 36 per cent have been reported. This can be reduced to 5–8 per cent if postoperative radiotherapy is given.
• Neck dissection for residual neck disease following chemoradiation is associated with significant morbidity. Selective neck dissection can be done provided the residual disease is localized to one level of the neck.

Conservation surgery for cancer of the larynx
• The aim of conservation laryngeal surgery is to maintain speech and swallowing and avoid tracheostomy.
• It may be by open surgery or transoral endoscopic laser surgery.
• Preservation of at least one functional cricoarytenoid unit is required.
• The success of open partial laryngectomy is dependent on good preoperative pulmonary function and good postoperative speech and swallowing rehabilitation.
• Open partial laryngectomy for glottic cancer:
  – It can be carried out by vertical partial laryngectomy (VPL) or by supracricoid partial laryngectomy with cricohyoidepiglottopexy (SCPL-CHEP).
  – VPL is suitable for T1,T2 and select T3 lesions with local failure occurring in 7 per cent T1, 4–26 per cent T2 and 11–46 per cent T3 tumours.
  – SCPL-CHEP is suitable for T1b and select T2,T3 tumours. Local failure of 5 per cent for T2 and 10 per cent T3 tumours is reported. Patients in general have poor quality voice and require nasogastric tube feeding for several weeks due to aspiration.
• Open partial laryngectomy for supraglottic cancer:
  – It can be carried out by horizontal supraglottic partial laryngectomy (HSGPL) or by supracricoid partial laryngectomy with cricohyoidepexy (SCPL-CHP).
  – HSGPL is suitable for T1,T2 supraglottic cancers. It is contraindicated if there is extension below the false cord or there is impaired vocal cord mobility. Aspiration is
common. Preservation of the superior laryngeal nerve is important. Nasogastric feeding and delayed tracheostomy decannulation is not uncommon.

- SCPL-CHP is suitable for T1, T2 and select T3 tumours. It is suitable if the vocal cord is invaded or there is pre-epiglottic space invasion.

- Transoral endoscopic laser surgery:
  - Transoral endoscopic laser surgery involve blockwise removal of cancer allowing an individualized approach to surgery.
  - It has comparable oncological results to open surgery and radiotherapy.
  - Compared to open surgery, it is a short operation, can be done as an outpatient procedure, with better voice, and avoids tracheostomy and nasogastric feeding.
  - Compared to radiotherapy, it is of lower cost, can be repeated and radiotherapy still remains an option should laser treatment fail.

Conservation surgery for recurrent early stage laryngeal cancer

- Provided there is no progression of disease, conservation surgery for early glottic cancer can be done by VPL, SCPL-CHEP or transoral laser surgery.
- Local control rates of 66–96 per cent for VPL and 60–70 per cent for transoral laser surgery have been reported.
- In general, salvage surgery for recurrent supraglottal laryngeal surgery is not amenable to partial laryngectomy and requires total laryngectomy.

Conservation surgery for cancer of the hypopharynx

- Conservation surgery with open partial pharyngectomy is possible for T1, T2 pyriform sinus cancer.
- Transoral endoscopic laser resection for T1–T3 pyriform sinus cancer is possible, but over 50 per cent require postoperative radiotherapy. Oncological results are comparable to chemoradiation. Functional results are superior to chemoradiation.

Conservation surgery for cancer of the oral cavity

- Limited resection of oral cancers is to be condemned.
- However, conservation surgery of the mandible is possible.
- Marginal mandibulectomy can be done rather than segmental mandibulectomy if invasion is limited to the peristome or superficial bone cortex.
- Marginal mandibulectomy is contraindicated in the edentulous patient, irradiated mandible or if there is extensive soft tissue cancer.

Conservation surgery for cancer of the oropharynx

- Conservation surgery for T1–T3 tumours of the tonsil and base of tongue can be carried out by transoral endoscopic laser resection or transoral robotic surgery. Postoperative radiation is required.
- Surgery is dependent on careful patient selection, adequate exposure and visualization via specialized retractors and the use of endoscopic laser or robotic instrumentation.

Conservation surgery for cancer of the nasal cavity and paranasal sinuses

- Conservation surgery by endoscopic surgery is possible for benign tumour and centrally located low-grade malignancies.
- Surgery is assisted by real-time image guidance, intraoperative magnetic resonance imaging (MRI) and neuronavigation.
- Surgery is not en bloc and therefore is dependent on intraoperative frozen section margins to ensure completeness of resection.

Conservation surgery for tumours of the parotid gland

- Conservation surgery by enucleation for pleomorphic adenoma is to be condemned. Enucleation is acceptable for Warthin’s tumour.

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Measures of treatment outcomes

JANET A WILSON AND HELEN COCKS

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There are two ways to live your life, one is as though nothing is a miracle, the other is as though everything is a miracle.

Albert Einstein

INTRODUCTION

Health-care resources are rationed throughout the world. All clinicians therefore share a responsibility to ensure that their treatment is effective and efficient. Efficacy implies that a treatment actually achieves what it sets out to do, for example, cure a given proportion of patients of their disease. Efficiency incorporates concepts of cost efficiency, that is to say could the resources be obtained more cheaply? The costs include not only the health-care resources required to provide the treatment, but also the costs to the patient in terms of treatment-related morbidity – and the resultant cost of not treating another condition because of the expenditure. Modern health-care systems demand robust outcome measures. These should be disease specific and reflect the concerns of the patient. Their measurement is compounded by the fact that patients and carers, as well as patients and healthy ‘observers’, have different opinions as to what constitutes the most favourable outcome.

The traditional end point for assessing outcomes of treatment of patients with head and neck cancer (HNC) – survival, local and regional disease control have been expanded in recent years to include measurements of functional status and quality of life (QOL). This chapter will address functional outcome as opposed to QOL per se, to which Chapter 10, Quality of life, is devoted.

MORTALITY

For most cancers, the reporting of mortality remains the cornerstone of outcomes assessment (Box 9.1). Nonetheless, despite the many advances in the method of cancer treatments, it must be accepted that there are many cancers, including most head and neck cancers, where these treatment developments have not been mirrored by changes in mortality rates which have remained static over the last three or four decades. It is important, however, not to let a lack of improvement in mortality obscure the value of a genuine therapeutic advance. For example, modern techniques of head and neck resection with skillful reconstruction often result in a far superior cosmetic and functional outcome and quality of life, even if the cure rate is no greater than with older, more morbid procedures. It is also important to monitor mortality rates of those patients receiving the relatively recently introduced organ preservation treatments.

SURVIVAL ANALYSIS

Survival analysis is a technique for analysing ‘time to event’ and can be used for many outcomes not simply death (Box 9.2). Problems with survival analysis are the
non-parametric distribution of the data and the fact that the time to event is not always observed, it is not appropriate to wait for all patients in the study to die. Also, a number of patients may be lost to follow up, termed ‘censored events’. The Kaplan–Meier survival curve is the most common means of expressing survival in a study group. It is used to estimate survival rates and hazards from such incomplete data assuming that those censored subjects have the same prospect of survival as uncensored subjects. The median survival time is the survival time at which the cumulative survival is equal to 0.5.

The log rank test provides methods for comparing two or more survival curves, but is only appropriate where relative mortality does not change over time (proportional hazards assumption).

**COMORBIDITY**

Comorbidity refers to disease that coexists with and is unrelated to the index disease and has been shown to play a major role in the treatment, outcome and prognosis of a number of malignancies. There is significant comorbidity in head and neck cancer patients due to the long-term effects of smoking and alcohol lying second only to lung or colorectal cancer. Several studies have shown the importance of comorbidity on outcome and the prognosis of head and neck cancer. It is an independent prognostic indicator even when age and TNM stage have been controlled for, hence its inclusion here. In 1948, the first attempt to quantify the performance status of patients with advanced cancer was made by Karnofsky. Since then, there has followed the evolution of a variety of instruments to measure comorbidity (Box 9.3). Information can be obtained from patient questionnaires, patient-based interviews and from reviewing the medical notes. The most widely used are discussed below.

**Kaplan–Feinstein index**

The Kaplan–Feinstein index (KFI) was developed for assessment of comorbidity on outcome in diabetes mellitus and has been used to study the impact of comorbidity in several cancers. Specific diseases are classified and a score given of mild, moderate or severe according to severity of organ decompensation. Where multiple comorbidities are present, an overall score is assigned according to the highest ranked illness, and where there are two or more moderate outcomes the overall score is defined as severe.

**Adult comorbidity evaluation**

Adult comorbidity evaluation (ACE-27) is a modification of the KFI, validated and especially designed for comorbidity evaluation in patients with cancer. It includes conditions such as diabetes, dementia and AIDS, which were not included in the original KFI. An overall score of 1, 2 or 3 is assigned according to the highest ranked single condition, except where two or more grade 2 illnesses occur in different organ systems where a score of 3 is given.

**Charlson comorbidity index**

The Charlson comorbidity index (CCI) is a weighted sum of the presence or absence of each of 19 conditions. Each condition is assigned a weight from 1 to 6, where a higher value indicates more severe disease. The index is the sum of all the weights.

Most data on comorbidity in head and neck cancer relate to use of one of these three indices. The KFI has been found to be most successful in stratification of survival analysis in patients with squamous cell cancer of the head and neck.
Table 9.1  Advantages and disadvantages of patient-based and case-review approaches.

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Patient-based</td>
<td>Functional impact of disease more accurate</td>
<td>Patients may have limited insight into illnesses</td>
</tr>
<tr>
<td>approach</td>
<td>Allows for both prospective and retrospective</td>
<td>Can only be obtained prospectively</td>
</tr>
<tr>
<td>Case-review</td>
<td>evaluation</td>
<td>Severity of comorbidity may be difficult to</td>
</tr>
<tr>
<td>approach</td>
<td>More accurate</td>
<td>determine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only positive comorbidities may be documented</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time required to review notes</td>
</tr>
</tbody>
</table>

when compared with the Charlson index, and two other scales not discussed here, the cumulative rating scale and the index of co-existent disease. The CCI is simple to use and has been used to evaluate comorbidity in laryngeal cancer and thyroid cancer, and has been validated against the ACE-27 for use in head and neck cancer. However, because answers evaluate the presence or absence of disease rather than severity, it has been found to be less sensitive than the ACE-27 in assessing comorbidity.

The ACE-27 has been widely used in the head and neck cancer population and is applicable in the UK setting. It can be used to grade comorbidity retrospectively from case notes showing reliability and good interrater agreement. Some comorbidity items on the ACE-27, such as adrenal disease and pancreatitis, are not routinely asked about and may be missed from case note review. In addition, severity of symptoms may also be lacking from the patient record. The ACE-27 has been used in the head and neck cancer population and is applicable in the UK setting. It can be used to grade comorbidity retrospectively from case notes showing reliability and good interrater agreement. Some comorbidity items on the ACE-27, such as adrenal disease and pancreatitis, are not routinely asked about and may be missed from case note review. In addition, severity of symptoms may also be lacking from the patient record.

The importance of different categories of symptom between patients and carers. In 1992, Mohide et al. demonstrated that carers ranked impaired communication and self-image/self-esteem as the two most important QOL outcome domains following laryngectomy. The patients themselves ranked the physical symptoms of tracheal mucus production and interference with social activities as the two most important items. It is important to bear this lack of correlation between patient and carer priorities in mind when counselling patients about treatment options.

**IMPACT OF HEAD AND NECK CANCER ON OUTCOME**

Treatment for head and neck cancer is likely to affect some of the most basic human functions – verbal communication, social interaction, eating and breathing. Traditional treatment for many advanced head and neck cancers has been surgical excision with or without adjuvant radiotherapy. It is easy to see how speech and swallowing can be affected in patients undergoing resection for large oral cavity or oropharyngeal lesions and in the most extreme case of the laryngectomy. Recently, much emphasis has been placed on organ preservation by the use of combined modality chemoradiotherapy showing approximately the same long-term survival as surgery and adjuvant radiotherapy. Therefore, the clinical trade off is no longer the length of life, but functional outcome and quality of life. Anatomic preservation does not guarantee that function will remain intact; patients experience a number of significant debilitating side effects. Vocal quality is reduced and swallowing problems are common due to the stiffening...
of tissues in the pharynx and upper oesophagus. A disease-specific quality of life survey covering five domains (speech, eating, aesthetics, pain/discomfort and social/role functioning) demonstrated that speech and eating had the most impact on well-being. It is essential that these outcomes are measured in addition to survival to validate the use of these regimes and so that clinicians can provide patients with evidence and information regarding the potential effects of their treatments.

Impairment, disability and handicap

The World Health Organization has proposed an International Classification of Impairment Disabilities and Handicaps (ICIDH). This was most recently modified in 1997. Most self-assessment questionnaires have been developed with the purpose of measuring psychosocial handicapping effects of voice disorders as referred to by the WHO in their definition of disability and handicap: ‘the social, economic or environmental disadvantage resulting from an impairment or disability’.

VOICE AND SPEECH

Outcome measures: the tools available

Choosing the most appropriate outcome measure is essential for the efficacy of any study. Many tools exist for the measurement of outcomes of voice and speech. Most have been developed from a diverse population of dysphonic and dysarthric patients, but are applicable to the study of the head and neck cancer patient (see Table 9.2). Some of the most commonly used will be discussed here in more detail.

ASSESSING OUTCOME OF VOICE

In 1989, Hirano identified over 50 techniques being used for the evaluation of voice throughout the world. Still today, there exists no established voice outcome package. Measurements of voice available that are useful for measuring vocal change over time can broadly be divided into subjective or perceptual measurements and ‘objective’ or instrumental measurements (although not truly objective because interpretation is required). In addition, recent years have seen the development of tools to measure the functional effects of voice disorders from a patient’s perception (self-assessment).

Self-assessment

VOICE HANDICAP INDEX

Voice Handicap Index (VHI) is a standardized, self-assessment scale that measures patient perception of the impact of dysphonia on various aspects of routine living. It was derived retrospectively from symptoms identified from review of written case histories from a seven-year period. Initially, 85 items were identified. These were refined by responses from a group of 65 subjects who presented varied voice pathology, but of whom 84 per cent had either a mass lesion or neurogenic disorder, including 26 per cent laryngectomee patients.

The authors report good internal consistency with good test–retest reliability. They also found that VHI scales correlated well with patients’ perceptions of voice disorder severity; however, there is little information on validity of the VHI. The VHI is the most widely used of the self-assessment questionnaires. It consists of 30 statements on voice-related aspects in daily life each with a score of 0 to 4, where 0 stands for never, 1 for almost never, 2 for sometimes, 3 for almost always and 4 for always. The maximum score is therefore 120, values above 60 indicate a severe disability, those between 40 and 60 moderate disability and less than 40 mild or no disability. The questions are divided into three subscales or domains: physical, functional and emotional, with ten questions in each.

The VHI has been used as an outcome assessment tool in laryngeal cancer in both patients with a laryngeal and

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<th>Perceptual measures</th>
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<td><strong>Voice</strong></td>
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Adapted from Ref. 28
alaryngeal voice, but overall there is a paucity of outcome data of this nature. Several studies have explored post-treatment outcomes for early glottic cancer. A meta-analysis identified six studies between 1966 and 2005 with 208 patients (202 T1a) treated with laser excision and 91 (85 T1a) with external beam radiotherapy, showing VHI scores of the two groups to be similar. In the assessment of laser excision of the T1a larynx, Brondbo et al. reported favourable results showing no impact of voice on daily life.

In the assessment of voice following partial laryngectomy, the VHI has also been used to compare endoscopic laser excision with open resection and in outcome assessment of supracricoid partial laryngectomy. One study used a modification of the VHI in the assessment of voice in the laryngectomee; they showed that voice handicap severity is moderate in this group of patients and in the range of ‘common’ dysphonia. Another showed the VHI to be significantly higher in the laryngectomee than in patients with functional voice disorders, but differing only slightly from patients with organic laryngeal dysphonia.

A study from the Veterans Affairs Group compared the surgically voice-restored laryngectomee and patients undergoing radiotherapy for laryngeal cancer. Physical voice handicap scores did not differ significantly, but emotional and functional handicap scores were higher in the laryngectomee. However, there was considerable diversity of scores for the laryngectomy group, with some scoring less than the radiotherapy group. It is difficult to draw too many conclusions here since laryngectomy patients had more advanced stage disease.

There does not appear to be any data looking at voice outcome in patients treated with chemoradiotherapy as a primary modality, but a recent paper from London’s Royal Marsden Hospital showed that in the laryngectomee there was a wide variation in the handicap reported on the VHI with functional aspects of the voice significantly affected by age, radiotherapy and chemotherapy. Physical aspects were significantly affected by age and chemotherapy and only age significantly affected the emotional aspects of the voice.

One study has looked at partner perception of voice handicap using a modification of the VHI. This showed good agreement among all three of the VHI subscales. However, whether these proxy ratings can be extrapolated to the head and neck cancer population is not known.

**VOICE SYMPTOM SCALE**

The Voice Symptom Scale (VoSS) is the most rigorously evaluated and psychometrically robust measure currently available for self-assessment of voice quality. Unlike the other voice rating tools available, it is patient derived. It originated in an open-ended questionnaire, resulting in 467 problems reported by 133 consecutive patients with voice disorders from a British non-cancer population. A prototype summary list of all these problems was administered to 168 voice patients and these underwent principal component analysis. Third, a modified 44-item scale was administered to 180 new subjects and with further analysis the final VoSS 30-item questionnaire was born which was further tested on 319 subjects including a few with malignancy. It has good reliability. The VoSS consists of 15 items, eight relating to impairment to emotional response and seven to physical symptoms and is unique in that it addresses other symptoms, which may arise from the laryngopharynx, such as sore throat and phlegm.

The VoSS has not yet been widely used in the head and neck cancer population, but a study looking at a population of patients treated by endoscopic resection or radiotherapy for early glottic cancer produced similar results for three self-report vocal performance questionnaires – VHI, VoSS or Voice Performance Questionnaire (VPQ). The exception was the emotional subscale of the VoSS, which gave better results for those treated with radiotherapy and in addition reflected the concurrent pharyngeal symptoms.

**VOICE ACTIVITY AND PARTICIPATION PROFILE**

Voice Activity and Participation Profile (VAPP) was developed in Hong Kong and was developed as a means to investigate perception of voice problem, activity limitation and participation restriction. Initial items were selected by consultation with 45 dysphonic patients and ten speech and language pathologists, resulting in a 28-item questionnaire consisting of five sections: self-perception of voice (one item), effect on job (four items), effect on daily communication (12 items), effect on social communication (four items) and effect on emotion (seven items). Each item uses a visual analogue scale 10 cm long ranging from not affected at the left end to always affected at the right. This was then tested on 40 further dysphonic patients with benign disease and 40 controls. This study showed good internal consistency and test–retest reliability and good correlation with the VHI. The authors also compute an activity limitation score and a participation restriction score, which seems to have been fairly arbitrarily assigned.

**Short-form self-assessment questionnaires**

Both the VHI and the VoSS are 30-point questionnaires and can be time consuming to complete and score and may provide a degree of redundant information. Although these are extremely useful as research tools, in the clinical setting concise, clinically useful self-report questionnaires are of more use. Two short-form, voice-related scales have been reported, the Vocal Handicap Index-10 item questionnaire (VHI-10) and the Vocal Performance Questionnaire (VPQ).

**VOCAL HANDICAP INDEX–10 ITEM QUESTIONNAIRE**

Item analysis carried out on the VHI by patients with voice disorders and controls identified the ten most robust VHI items resulting in the creation of the Vocal Handicap Index-10 item questionnaire (VHI-10). Statistical analysis comparing validity with the VHI on a large number of patients with a wide spectrum of voice disorders showed good correlation. As for the VHI, a five-point item scale is used, resulting in a total score of between 0 and 40.
VOCAL PERFORMANCE QUESTIONNAIRE

The VPQ\(^47\) was designed for evaluation of voice therapy in non-organic dysphonia. It is a 12-item questionnaire which examines the physical symptoms and socioeconomic impact of the voice disorder. The patient selects a statement that best answers each question. The statements are graded in terms of severity of vocal performance. A numerical score of 1–5 is assigned to each answer and these are summed to provide an overall score of vocal severity – maximum score 60 and minimum score 12.

These two short-form voice-related scales (VPQ and VHI-10) use a single total score. This has been found to be valid and there is high internal consistency. In addition, the two questionnaires correlate highly with one another.\(^48\)

PERCEPTUAL ASSESSMENT: CLINICIAN RATED

GRBAS

The GRBAS rating scheme\(^49\) is considered as a practical minimum standard for the perceptual rating of voice.\(^50, 51\) It has established inter- and intrarater reliability with trained expert raters.\(^52\) It consists of five domains: grade (representing overall voice quality), roughness (which looks at fluctuations in fundamental frequency, indicative of vocal edge abnormalities), breathiness (which assesses air escape), asthenia (a general decrease in power of or weakness of the voice) and strain (which assesses hyperfunctionality). All are assessments of laryngeal function.

Assessment is made on a recording of a voice reading an established phonetically balanced passage, such as the ‘rainbow passage’ or on current conversational speech. Each aspect of the GRBAS scale is given a score of 0–3, where 0 is normal, 1 shows slight deviance, 2 moderate deviance and 3 severe deviance. This scale has been shown to be reliable across all parameters except strain.\(^53\)

Patients’ self-assessment using the GRBAS scale has been evaluated and patients appear to have good validity and consistency using the scale as a self-assessment tool, however, correlation with clinician assessment is poor.\(^54\)

Correlation between self-assessment using the VHI and clinician-rated perceptual data using the GRBAS has also shown little correlation, with patients indicating only mild functional and emotional consequences, but GRBAS scores showed severely dysphonic voice with supracricoid laryngectomy VHI mean values of 29.9.\(^54\)

The GRBAS scale has been used in the assessment of voice in the head and neck cancer population, in partial laryngeal surgery and in the comparison of radiotherapy and laser excision in the treatment of early glottic lesions. Interestingly, it has also been used as a tool to assess alaryngeal speech.\(^55, 56\) It has not been developed for or validated in this group of highly specialized patients and whether it really is of clinical use is questionable.

PERCEPTUAL ASSESSMENT OF ALARYNGEAL SPEECH

Although attempts have been made to develop a scale for perceptual evaluation of alaryngeal speech, a reliable, reproducible perceptual rating system developed for assessment of voice in the laryngectomee does not seem to exist.

Van As \(\text{et al.}^{37}\) report the use of a semantic bipolar seven-point scale (e.g. ugly–beautiful, deviant–normal, low–high), for both untrained and trained raters, initially consisting of 19 or 20 items. They describe wide ranging inter- and intrarater reliability, (e.g. better for deviant–normal than creaky–not creaky) and overall better for trained listeners. Finally, they attempt to reduce the number of items into subsets representing underlying perceptual dimensions – quality and pitch for untrained listeners and quality, pitch and tempo for trained listeners. However, this scale has not been used subsequently.

Eadie and Doyle\(^58, 59, 60\) report the use of direct magnitude estimation (continuous) and equally appearing interval (interval) scales for the auditory perceptual rating of naturalness, severity, acceptability and pleasantness of tracheoesophageal voice. When rated by naive listeners, they have found that female voice is considered less acceptable and natural when gender is known and not correctly identified when gender is not known.

Instrumental measures

A large number of instrumental voice measurements can be used to diagnose and determine the extent of disease and evaluate nature and severity of dysphonia. Only a few are useful in measuring changes in voice quality with time, and most have little use in the assessment of outcome in the head and neck cancer patient, although measurements may help with targeting rehabilitation. Discussed here are a few of the more common and potentially more useful measures.

MAXIMAL PHONATION TIME

Maximal phonation time (MPT) is the time for the production of a prolonged /a/, for as long as possible after maximal inspiration at a spontaneous comfortable pitch and loudness measured in seconds. Generally, three measurements are made and the longest taken.

FLOW VOLUME LOOPS

These are sensitive tests of upper airway flow and are useful where problems are associated with laryngeal or tracheal obstruction. They are obtained with forced inspiration and expiration.

ACOUSTIC MEASURES OF SPEECH SIGNAL

Acoustic analysis is widely used in testing vocal function because it is objective and reproducible, as long as the same equipment is used on each occasion. A prerequisite is a voice sample recorded on to digital audiotape (DAT). Standard protocols exist from the National Centre for Voice and Speech for the recording of speech samples.

From these recordings, acoustic measurements of the speech signal can be made, including frequency, amplitude,
The main use of acoustic measurements in the literature of head and neck cancer patients has been to compare outcomes for treatments for early glottic tumours, in the assessment of voice after supracricoid laryngectomy and in the assessment of speech therapy following treatment for such lesions. These measurements have also been assessed in the laryngectomy group of patients. Measurements of jitter and shimmer require a speech signal near to periodicity to allow the software to produce any measure of cycle-to-cycle variation. In the laryngectomy voice is often aperiodic, making assessment of these acoustic measures problematic; Van As-Brooks et al. describe the use of visual inspection of narrow-band spectrogram to enhance acoustic measures in the laryngectomee.

SPEECH

Speech sounds are produced by regulating air flow from the lungs. The role of the oral cavity is in articulation, oronasal separation and resonance. The utterance of most consonants requires the closing off of the nose and articulation relies on movements of the tongue, pharynx, palate, lip and jaw. Consequently, many speech disorders result from treatment for oral cavity, oropharynx and maxilofacial tumours. These can be divided into those due to inadequate oronasal separation and articulation disorders. Speech and language therapists are highly trained in listening and identifying abnormalities in speech and are best placed to assess hypernasality.

Articulation is usually evaluated by intelligibility tests, the most significant measure of speech being how well it is understood. Analysis of articulation can determine the source of speech disorder, regardless of the language in which the test is carried out. Because of this, most scales for assessment of speech are clinician-rated, rather than self-assessment tools.

Self-assessment tools

THE FUNCTIONAL INTRAORAL GLASGOW SCALE

This is a self-assessment tool described by one group used to study 196 patients undergoing surgery for oral cavity cancer. It consists of an ordinal five-grade scale: always understandable (5), needing repetition sometimes (4), needing repetition many times (3), understandable only by relatives (2), incomprehensible (1). This very simple scale showed good correlation with a conversational understandability test performed by speech and language therapists and with an objective computer-based method of speech analysis.

Clinician-rated tools

A vast array of clinician-rated intelligibility tests exist and are naturally language specific; in practice, they are the domain of the expert speech and language therapist.

SPEECH INTELLIGIBILITY TEST

The simplest measure seems to be the Speech Intelligibility Test. Patients are required to read a phonetically selected passage, the rainbow passage, which is recorded. These recordings are graded by experienced listeners according to the number of words written correctly by the listeners.

ASSESSMENT OF INTELLIGIBILITY OF DYSARTHRIC SPEECH

The Assessment of Intelligibility of Dysarthric Speech (ASSIDS) is used by the speech and language therapist and contains assessment of single word and sentence intelligibility. It requires a recording of either 50 single words or sentences of 5–15 words selected at random. Each sample is judged by a pool of scorers (one scorer can be used if improvement is being sought in an individual patient). The recording is listened to and transcribed by the scorer and an intelligibility score given as a percentage of responses that were correct. In addition to percentage intelligibility, scores can be calculated for speaking rate, rate of (un)intelligible speech and a communication efficiency ratio. These calculations are based on a healthy person speaking a 220-word paragraph at a rate of 190 words per minute.

Scales designed specifically for the head and neck patient population

There are a couple of tools that have been specifically designed for the assessment of the head and neck cancer patient.

PERFORMANCE STATUS SCALE FOR HEAD AND NECK CANCER PATIENTS

The Performance Status Scale for Head and Neck (PSSH) is designed to assess unique areas of dysfunction experienced by this group of patients. It has three domains: (1) understanding of speech, (2) normalcy of diet and (3) eating in public. There is a score from 0 to 100 for each domain. The higher the score, the better the ability of the patient to function.

VOICE PROSTHESIS QUESTIONNAIRE

The Voice Prosthesis Questionnaire looks specifically at the surgically voice-restored laryngectomy. It has recently been published and shows good reliability and validity and is the first designed specifically for the valved laryngectomy patient. It is a self-administered 45-point questionnaire and has sections relating to speech, leakage, valve changing, maintenance, QOL, humidification and hand free issues.

DYSPHAGIA

Introduction

Dysphagia has always been an important functional outcome of the treatment of larger head and neck cancer tumours.
Over the past few years, it has become increasingly apparent that non-surgical therapy while organ sparing, may not be so sparing of function, particularly swallow competency. There seems reasonably convincing evidence of a direct relationship between total radiation dose and severity of dysphagia. In one early study, a substantial majority of patients receiving more than 74 Gy were still gastrostomy dependent at 12 months compared with fewer than the one in five who had received only 60 Gy. Conversely, larger doses of ionizing radiation and/or chemotherapy are equally likely to improve overall survival rates. Thus, there is increasing hope that more precisely distributed radiation might prove ‘dysphagia sparing’. Intensity modulated radiotherapy (IMRT) remains under assessment in this respect. IMRT has been shown to preserve salivary function and hence reduce the distressing xerostomia which remains a substantial factor contributing to dysphagia in many patients treated non-surgically. The ability of IMRT schedules to reduce aspiration remains more controversial. One study suggests that sparing of the pharyngeal constrictors significantly improves swallow competency. 

The impact of swallow dysfunction in head and neck cancer patients may be considered under three principal headings:

1. Aspiration and recurring pulmonary infection
2. Poor nutritional status with secondary impact on healing and probably prognosis
3. Quality of life issues around resumption of what is one of the most fundamental of human and human social activities – the ability to eat a meal.

Nonetheless, we lack sufficient high quality research. Dysphagia assessments fall broadly into two categories: those that assess the severity of the swallowing disorder and those which try to establish its cause. In head and neck cancer patients, issues of causation generally relate to the biomechanics of the altered swallow mechanism, whether sensory or motor. A management challenge experienced by most head and neck cancer centres is that dysphagia tends to be a long-lasting problem, persisting for many months after treatment and therefore for considerable periods of time following patient discharge from hospital. Given the relative rarity and heterogeneous nature of head and neck cancers, it is likely that many patients do not find community services adequate for their assessment and therapy needs. Radiological evidence suggests that the biomechanics of persistent post-chemoradiotherapy dysphagia are centred on reduced laryngeal elevation and criopharyngeal opening. At a median follow up of 26 months following treatment, one disease-free cohort were found to have established normal swallowing in fewer than 10 per cent of patients. Twenty per cent suffered from increasing dysphagia, although others responded to dilatation of pharyngeal stenosis.

In the longer term, surrogate measures of swallow performance, such as nutritional status and method of intake, whether oral, partial oral or total reliance on tube feeding are valuable, albeit relatively insensitive, indicators. Recently, more interest has been focused on the longer-term dysphagia impact on patient and carer psychological well-being.

Swallowing remains one of the most complex, partially reflex phenomena in the human body and its vulnerability in the face of anatomical and physiological changes is perhaps therefore not surprising. The many requirements for a competent swallow are shown in Box 9.4.

Equally, there are numerous specific causes for head and neck cancer dysphagia, but these can be grouped as follows.

### Major causes of dysphagia in head and neck cancer patients

Xerostomia is recognized as one of the most unpleasant side effects of radiotherapy and has been the subject of considerable research over the years. More recently, attempts have been made to assess the functional impact of tongue dysfunction. Impairment of tongue base movement disables the tongue base thrust, which forms the key to bolus propulsion during the normal swallow. Food accumulates in the hypopharynx, resulting in overspill and aspiration. Tongue strengthening exercises have therefore been developed to reduce this side effect. Silicone strain gauge tongue pressure measuring devices have been developed to pursue tongue power over time. The research requires further development, but at present it has been shown that a fixed position array of sensors is a more reliable assessment method of tongue function.

Because of the life-threatening potential of aspiration, it remains the focus of much assessment, intervention and research. One chemoradiotherapy study demonstrated a 59 per cent incidence of aspiration, with a 9 per cent fatality rate. Swallowing therapy does improve certain grades of aspiration, but the most severe categories of aspiration show a disappointing response. More conspicuous is the development of a pharyngo-oesophageal sticture following non-surgical therapy due to a combination of severe mucositis and scarring of the fibromuscular wall of the pharynx. Dilatation does improve swallow performance in the presence of such a stricture, but a majority of stricture patients require permanent gastrostomy feeding.

The most simple assessments are direct bedside clinical assessments. The dysphagia parameters were originally established by John and Enderby. The therapy outcome measure categories are fairly broad, and acceptably reliable after a short period of training.

Attempts have been made to define swallow performance (Table 9.3) in terms of the volume and speed of the swallow mechanism, although conventionally such quantitative swallow performance measures at the bedside have tended to

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**Box 9.4 Requirements for efficient swallowing**

- Facial tone
- Rotatory and lateral movement of mandible
- Fine motor control tongue
- Adequate saliva
- Sensate oral mucosa
- Pharyngo-oesophageal wave
- Competent, mobile larynx
be applied more in neurological rather than head and neck cancer patients. One advantage of bedside assessment is that it provides personal contact with the patient. As with other direct assessments, it has the added benefit of being able to address severity, causation and to some extent possible therapeutic manoeuvres.

Traditionally, patients aspirating more than around 10 per cent of any bolus should be restricted from taking the relevant consistency orally. More recent advice, however, suggests a more pragmatic approach may be appropriate, allowing clinicians to incorporate other parameters, such as age, oral health, reflux and cough reflex. Up to 30 per cent of chemotherapy patients being tube fed rather than being fed by gastrostomy may aspirate.

Evans blue dye test can be added to the bedside assessment in patients with suspected fistula or with a tracheostomy. The test has undergone recent studies to evaluate its sensitivity and specificity in predicting aspiration. Comparison of the modified Evans blue dye test with check endoscopy via a tracheostomy site in an acute rehabilitation hospital demonstrated an overall false-negative rate of 50 per cent. However, a superior sensitivity – 82 per cent – was demonstrated in a subsequent survey of long-term tracheotomized patients. A further extension of clinical assessment is to perform a direct instrumental observation, i.e. functional endoscopic evaluation of swallowing. This can be used in isolation or in conjunction with the blue dye test to detect more subtle levels of aspiration that may not otherwise be detectable.

**VIDEOFLUOROSCOPY**

Videofluoroscopy remains the most frequently applied assessment of complex swallow problems as it allows assessment of anatomy (although to a lesser extent than direct endoscopic observation, see below under Functional endoscopic evaluation of swallowing), coordination in movements of the oropharyngeal and oesophageal stages of swallowing and it is therefore a very helpful tool in assessing dysphagia of unknown origin. However, videofluoroscopy is a relatively expensive and time-consuming investigation involving transportation of the patient to the radiology department, usually the involvement of a multiprofessional team and with limited opportunities for repeat assessments. Many units provide such a service no more than weekly, some with lesser frequency. In the head and neck cancer patient, a definite distinction cannot be made between cancer, oedema and irradiation fibrosis. Post-surgical reconstruction is more easily assessed by, for example, flexible endoscopy.

As with any swallow assessment, the procedure is not entirely natural. With videofluoroscopy, the substances ingested are not entirely normal foodstuffs. The timing of the swallow has to be directed by the examining clinicians, i.e. the patient is usually required to await the command to swallow. Typically, the volumes involved are considerably smaller than the normal bolus volume. Assessments of the reliability of videofluoroscopy show superior accuracy for aspiration than for determination of pathophysiology. The situation is improved with group discussion. The application of protocols and use of frame-by-frame analysis seems inconsistent.

In the most expert of hands, videofluoroscopy can be applied using timing parameters and also other semi-quantitative estimates of swallow performance. The most usual of these is the oropharyngeal swallow efficiency (OPSE). This is calculated as:

\[
\frac{\text{Bolus transfer to upper oesophagus}}{\text{Oropharyngeal transit time}} \times 100\%
\]

Table 9.3  Swallowing assessments.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>References</th>
</tr>
</thead>
</table>
| Direct | Nathadwarawala et al<sup>87</sup>  
Evans’s blue dye test  
Videofluoroscopy, including OPSE  
Functional Endoscopic Evaluation of Swallowing  
Electromyography | |
| Observer-rated questionnaires | Winklmairer et al<sup>88</sup>  
Logemann et al<sup>89</sup>  
Bastian<sup>90</sup> and Aviv et al<sup>91</sup>  
Crary et al<sup>92</sup> and Carnaby-Mann and Crary<sup>93</sup>  
List et al<sup>69</sup>  
John and Enderby<sup>86</sup> | |
| Self-report questionnaires | Kulbersh et al<sup>84</sup>  
Lovell et al<sup>95</sup>  
McHorney et al<sup>96</sup> | |
Clinical value in assessing rehabilitation of head and neck cancer patients.

In contrast, the penetration–aspiration scale (Table 9.4) assesses the presence and depth of invasion of material entering the airway, and the patient response to the aspiration and the ability to eject any misdirected material.\(^\text{108, 109}\)

However, the reliability of this assessment is disappointing.\(^\text{109}\) In the United States, the costs of videofluoroscopy for a head and neck cancer patient are over $450. It may well have a larger part to play, therefore, in the clinical research setting to evaluate the impact of still novel treatment approaches, such as chemoradiation: in one study, 54 per cent of chemoradiation patients aspirated compared with only 33 per cent undergoing radiation alone. The significance of this relatively small study is not clear since it was the larger tumours that had undergone chemoradiotherapy.\(^\text{111}\) Nonetheless, the findings underline the ongoing importance of videofluoroscopy in assessing silent aspiration, particularly in a group of patients undergoing immunosuppressive systemic therapy. Indeed, a longer-term follow up of non-laryngectomy survivors of head and neck cancer at five years, showed an ongoing 44 per cent aspiration. Aspirators had lost a mean of 10 kg from their pretreatment status, while non-aspirators had a small weight gain. Aspiration was also found to be associated with lower scores on a number of quality-of-life scales.\(^\text{82}\)

### Table 9.4 Penetration–Aspiration Scale.\(^\text{108}\)

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Material does not enter the airway</td>
</tr>
<tr>
<td>2</td>
<td>Material enters the airway, remains above the vocal folds, and is ejected from the airway</td>
</tr>
<tr>
<td>3</td>
<td>Material enters the airway, remains above the vocal folds and is not ejected from the airway</td>
</tr>
<tr>
<td>4</td>
<td>Material enters the airway, contacts the vocal folds and is ejected from the airway</td>
</tr>
<tr>
<td>5</td>
<td>Material enters the airway, passes below the vocal folds and is not ejected from the airway</td>
</tr>
<tr>
<td>6</td>
<td>Material enters the airway, passes below the vocal folds and is ejected into the larynx or out of the airway</td>
</tr>
<tr>
<td>7</td>
<td>Material enters the airway, passes below the vocal folds and is not ejected from the trachea despite effort</td>
</tr>
<tr>
<td>8</td>
<td>Material enters the airway, passes below the vocal folds and no effort is made to eject</td>
</tr>
</tbody>
</table>

### Functional endoscopic evaluation of swallowing

Fibreoptic endoscopic evaluation of swallowing has emerged over the past two decades as not only a complement to videofluoroscopy, but as a useful investigation in its own right. Endoscopic evaluation can assess in some detail anatomical arrangements following surgery, plus ancillary features such as vocal cord movement. It is readily repeated at the patient’s bedside as often as should be required and is therefore a more flexible option than videofluoroscopy. There is no doubt, however, that there are certain parameters which videofluoroscopy alone can address, such as oral transit time or indeed oropharyngeal swallowing efficiency. However, whether these translate to important clinical sequelae in the head and neck cancer population remains in doubt. Aviv\(^\text{112}\) found no statistical difference in pneumonia in a group of diverse dysphagia patients assessed either by videofluoroscopy or endoscopic evaluation of swallowing. Patients with absent pharyngeal motor function combined with poor pulmonary reserve and diminished or absent laryngeal sensation are expected to aspirate.\(^\text{113}\)

Flexible endoscopic evaluation of swallowing with sensory testing (FEESST) allows more specific assessment of sensory and motor components than in a standard endoscopic evaluation. A review of over 1300 patients undergoing FEESST including 207 with head and neck cancer found it to be a safe examination with epistaxis incidence of less than 0.1 per cent.\(^\text{113}\) Any patient with completely insensitive laryngopharynx is at extremely high risk of aspiration. Moderate sensory deficits will also result in aspiration if there is a coexisting motor dysfunction.\(^\text{113}\)

Aspiration occurring during a swallow cannot be detected on FEESST as there is a ‘white out’ during contact between the tongue base and the posterior pharyngeal wall as the bolus is propelled out of the oropharynx. Fortunately, aspiration during the swallow reflex itself is not a common occurrence, as most aspiration occurs before or after the swallow has taken place. Endoscopic evaluation of swallowing has variable reliability in different series. However, one study found that combining the technique with the penetration aspiration scale developed for videofluoroscopy could achieve concurrence by different raters on events of penetration and aspiration in 97 per cent of instances.\(^\text{114}\) Sharing the video image with the patient being examined offers additional therapeutic opportunities through visual biofeedback as the patient observes the impact of swallowing manoeuvres or head positions on their swallow performance. Endoscopic swallow evaluation is relatively cheap yet only a small minority of speech and language therapists in North America have access to the procedure.\(^\text{105}\) In the head and neck cancer population, endoscopic evaluation of the response of the upper aerodigestive tract to therapy is carried out routinely and regularly following therapy.

In a multidisciplinary team setting, therefore, it is a straightforward matter to combine such a structural assessment with a functional swallowing assessment, for example by the speech and language therapist team members. This is not only a pragmatic approach to swallow evaluation, but clinically sensible, as it allows the twin objectives of eradication of disease and maximal preservation of function to be monitored in parallel.

In addition, the introduction of endoscopic swallow evaluation on a much more regular basis has opened up new areas of relevant research to trace their response to non-surgical therapy, such as the quantification of laryngopharyngeal oedema.\(^\text{115}\)

### Electromyography

Surface electromyography (sEMG) signals have been used to identify swallow events.\(^\text{92}\) The full application of sEMG has
yet to be established as the interrater reliability of a method has only recently been established. There is, not surprisingly, higher agreement among more experienced assessors, but even novices achieve a 0.51 kappa coefficient.

At least in the short term, the principal value of the technique in head and neck patients probably is as an adjunct to biofeedback and rehabilitation manoeuvres.

Observer-rated questionnaires

Two brief observer ratings are in fairly regular use to assess both speech and swallowing. The Performance Status Scale for Head and Neck has been referred to above in the context of speech outcome. Understandability of speech is scaled 1 to 5. Swallow performance is assessed by (1) eating in public (scale 1–5) and (2) normalcy of diet (scale 1–10). These two scales have been shown to show a strong correlation with the head and neck subscale of the FACT (Functional Assessment of Cancer Therapy, head and neck scale) health status questionnaire, while also providing additional information not reflected by FACT. The Therapy Outcome Measure (TOM) is a practical tool to measure care outcomes simply and quickly in a wide variety of clinical settings. There is only one TOM scale specific to head and neck patients (laryngectomy); three other scales cover voice, dysarthria and phrenology and one addresses dysphagia.

Self-report questionnaires

MD ANDERSON DYSPHAGIA INVENTORY

The MD Anderson Dysphagia Inventory (MDADI) presents 20 items self-scored on a scale of 1 to 5. A global assessment examines overall daily routine, the emotional subscale has six items on the distress caused by dysphagia; the functional subscale has five items addressing ease of food preparation and eating in public. An eight-item physical subscale assesses dietary consistency, aspiration, weight maintenance and fatigue. The higher the MDADI score, the better the day-to-day functioning for quality of life. Pretreatment swallowing exercises may improve swallowing in patients treated non-surgically.

UNIVERSITY OF WASHINGTON QOL

The University of Washington Quality of Life (UW-QoL) questionnaire version 4 has 12 domains including pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. The patient scores each from 0 (poorest function) to 100 (highest or near normal function). Additionally, the questionnaire asks patients to nominate up to three domains as being particularly important to them in the previous 7 days. Patients also rate global health-related quality of life. The UW-QoL was the most popular questionnaire in a UK survey.

The ability for patients to be able to prioritize their most personally important quality of life domains is important, not only because it promotes a patient-focused analysis of treatment outcome, but also because it enables clinicians to attempt to weigh up the differential impact of different therapies. For example, in nasopharyngeal carcinoma patients, the UW-QoL demonstrated the three most important issues in a Singapore population were swallowing (59 per cent), hearing (45 per cent) and xerostomia (41 per cent).

Patients frequently rate problems, such as interference with social activities, as more troublesome than speech disturbance. Survival and being cured of cancer are most important for more than three-quarters of patients at all time points (except in the oldest cohort). Next important was being pain free followed by having energy and being able to return to normal activities.

The SWAL-QoL outcomes tool for oropharyngeal dysphagia in adults was developed in 2000 by McHorney et al. McHorney’s team eventually reduced a 93-item instrument into two separate tools, the SWAL-QoL, which has 44 items encompassing ten quality-of-life domains, and the SWAL-CARE, a 15-item tool relating to quality of care and patient satisfaction. The SWAL-QoL aims to provide quality-of-life and quality-of-care outcomes for dysphagia researchers and clinicians. It remains the most comprehensive assessment of swallow performance to date.

There is no single ‘best fit’ self-report outcome tool. From the patient’s point of view, there is merit in having a single questionnaire, which addresses both functional outcome and general quality of life. Separate tools, one to assess the number of key functional outcomes and one for generic quality of life are likely to be more sensitive to change. Very specialist, extensive, single function instruments (even those that do encompass general quality of life items) might best be reserved for a research setting.

Indirect functional outcomes of swallowing

The most conspicuous impact of swallow dysfunction, after aspiration pneumonia, is that of nutritional status. Over half of head and neck cancer patients are likely to be malnourished at diagnosis of their head and neck cancers and nutritional assessment is important not only at base line, but also prior to replacement or removal of feeding tubes and at the time of recommendation for recommencing oral feeding. Nutritional status is affected by general quality of life issues, such as fatigue, loss of appetite and problems with social eating in addition to more specific swallowing problems, dental disease, trismus, xerostomia and cough. Physician-scored rating correlates poorly with quality-of-life scores further emphasizing the importance of including quality of life as part of the overall functional assessment.

A number of techniques can be used to assess nutritional status. All methods have limitations and consequently measuring a combination of variables is usually carried out in most cases. Nutritional screening must be reliable, practical and easy to perform, simple to interpret and low in cost. Screening tools must correlate well with more sophisticated techniques for assessing body composition. Effective nutritional screening will also anticipate nutritional depletion and allow action to be taken to prevent its onset or correct it before it becomes clinically significant.

This is particularly true in head and neck cancer patients where weight loss, low body weight, loss of appetite and a reduction in oral intake (due to, for example, nausea or dysphagia) are common markers of nutritional deficiency.
Different nutritional parameters yield differences in the number of head and neck surgical subjects classed as malnourished: the most powerful predictor of major postoperative complications is a weight loss of > 10 per cent in the six months before surgery. Patients with severe nutritional deficit appear to have a reduced two-year survival, perhaps linked to abnormal cell-mediated immunity. There is some evidence that so-called ‘immune enhancing’ nutritional formulas (e.g. arginine, nucleic acids and fish-oil derivatives) can reduce the incidence of postoperative infectious complications compared with standard supplements.120

The relevance and inseparable nature of general quality of life to head and neck cancer functional outcomes has already been alluded to. Consideration should also be given to the distress caused to spouses, carers and significant friends and family members. The impact of head and neck cancer and its treatment on those around the patient is a very new area of research, but one recent paper found that the frequency of distress (20 per cent) in partners was so high as to suggest the need for a routine psychological screening for those caring for patients.78

**KEY EVIDENCE**

- Comorbidity is an independent prognostic indicator for outcome and prognosis for head and neck cancer, even when TNM stage is controlled for.1, 5, 6, 7, 8
- Disease-specific quality of life surveys show speech and eating have the most impact on well-being. Measurement of these outcomes is essential to validate use of new treatment regimes.
- Voice outcome for early glottic cancer as measured by the VHI is similar for laser excision and external beam radiotherapy.31
- The total radiation dose received is directly related to severity of dysphagia. Significantly more patients receiving more than 74 Gy are gastrostomy dependent than those receiving only 60 Gy.72

**KEY LEARNING POINTS**

**Impact of head and neck cancer**
- Voice, speech intelligibility, social communication
- Swallowing, diet, social eating
- Disrupted body image, depression, anxiety
- Work impairment, social isolation
- Airway: aspiration, swimming, bathing

**Acoustic measurements of voice**
- Frequency

**REFERENCES**


References


Quality of life

Simon Rogers

Health is a large word. It embraces not the body only, but the mind and spirit as well ... and not today's pain or pleasure alone, but the whole being and outlook of a man.

James H West

Introduction

For patient and their carers, quality of life (QOL) following head and neck cancer (HNC) is a crucially important issue. The treatment of HNC is more than cure and survival. The cancer and its treatment affect functions that are integral to human existence – for example, communication, eating, socialization and interpersonal contacts. Over the last decade, there has been a tremendous increase in the number of publications on this subject, which reflects the importance of the patient perspective as an outcome parameter in addition to survival, recurrence and complication rates.

This chapter is written in two sections. The first section explores the general topic of QOL assessment and covers definitions, why, when and how to measure, and perceived barriers. The second section looks at the QOL in patients with HNC and covers outcomes, predictors and carers.

Quality of Life Assessment

Definition of quality of life and health-related quality of life

Quality of life is a concept that has become increasingly important in relation to patient outcomes following treatment for cancer. Nevertheless, it is a concept that is difficult to define and measure because it is broad and individual to each person (Box 10.1).

There are many definitions, but the following are particularly useful:

- ‘An individual’s perceptions of their position in life taken in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns.’ Quality of life as defined by the World Health Organization.¹
- A person’s sense of well-being that stems from satisfaction or dissatisfaction with the areas of life that are important.²
- The measure between age expectations or present experience, and the perceived and actual goals (Calman-gap theory).³⁻⁴

Box 10.1 Quality of life

Quality of life is not:
- a single entity which can be simply measured
- the same as toxicity
- absolute or static, but relative and variable

Quality of life questionnaires are:
- subjective
- always an approximation
- a pale reflection of what we all think of as quality of life
It is the third definition that has become more widely used in clinical practice as it addresses how a patient perceives problems as a consequence of the illness and its treatment and how much this differs from what they expected. This difference can be measured.

Because QOL is such a broad, multidimensional concept, efforts have been made to focus on certain issues and the term ‘health-related quality of life (HRQOL)’ has evolved. This is a more restricted concept and does not, for example, include satisfaction or well-being. It is restricted to those factors that are part of an individual’s health. Aaronson et al. have defined HRQOL as ‘the assessment of the impact of the disease and its treatment on the physical, psychological and social aspects of quality of life’. It is essential that the assessment includes the perceived effects of cancer and treatment (disease specific) and where possible is patient-derived and assessed in a cultural setting.

The enormous breadth of QOL makes it impossible to summarize all the issues in one chapter and, unfortunately, it is likely that certain aspects have regrettably been omitted. Only some of the key aspects have been covered and further reading around the subject is recommended.

### Why measure HRQOL

In the management of HNC, outcome is more than just cure and survival. Clinicians are very familiar with the traditional outcomes, such as laboratory test (e.g. infection rates), imaging (e.g. videofluoroscopy), clinical measurement (e.g. fistula rates), process indicators (e.g. length of stay), recurrence and mortality. However, clinicians are less aware of outcomes based on patient experience, symptoms, function/dysfunction, satisfaction, importance and quality of life. A combination of both the objective and subjective can give additional insight into the issue, as shown in the assessment of speech and swallowing following soft palate reconstruction using a radial forearm free flap in conjunction with a superiorly based pharyngeal flap and radial forearm free tissue transfer. In this study, both questionnaire data and speech intelligibility and videofluoroscopy were used to demonstrate the benefit of using a superiorly based flap in patients having more than half their soft palate resected. In addition to being used in combination if the relationship between the objective and subjective scoring is strong, it is possible to use only one as a surrogate for the other. An example of this is when reporting HRQOL using a permanent gastrostomy feeding tube as an indicator of HRQOL, as the presence of a long-term gastrostomy strongly indicates a poor HRQOL outcome.

The value of patient-derived outcome following treatment was recognized in the policy framework for the commissioning of cancer services. It recognized the need for information on the quality and outcome of care and it emphasized that, in the critical appraisal of outcome, it is imperative to include the patient’s perspective of function/dysfunction and well-being/distress. The measurement of QOL has been suggested as a national outcome parameter by the British Association of Head and Neck Oncologists in the national dataset and also is often a mandatory secondary outcome to any randomized control trials.

Another reason to include HRQOL as an outcome is when two methods of treatment produce equivalent cure rates. In this situation, one of the major factors determining which treatment should be chosen is the post-treatment quality of life.

It can be assumed that clinicians appreciate the patient’s perspective and with experience it is possible to recognize patients’ concerns and to address these. However, differences in perspectives between doctors and patients can easily occur with doctors overestimating the objective symptoms and underestimating more subjective problems. This was highlighted in a survey of 278 patients regarding appearance issues after surgery. Worst appearance scores were reported in those with advanced disease, free flaps, segmental jaw resection and neck dissection. One hundred and fourteen patients (41 per cent) were identified as having a potential appearance problem based on their University of Washington Head and Neck Cancer Questionnaire domain score. However, only seven (6 per cent) had the issue mentioned in the case notes or letters. Of these, five had intervention. Given the important problem of appearance following HNC, it raises the potential for unrecognized patient and care needs that are not identified in a busy clinical setting.

Other advantages in measuring HRQOL include providing a baseline against which effectiveness of an intervention can be measured. Measurement may enable priority to be given to those particular patients who appear to be making poor progress, and providing valuable information for subsequent patients and give a good idea of the likely impairment they can expect following surgery. This can then help the patient and clinician in the decision-making process before and after treatment. Higginson et al. suggest the following additional value of HRQOL measurement, which may facilitate communication, screen for hidden problems (e.g. psychological distress), identify preference, train new staff, be useful in clinical audit and clinical governance. There is evidence that routine HRQOL assessment has a positive impact on patient–doctor communication and could actually improve HRQOL and emotional functioning. Its measurement and analysis encourage multidisciplinary team working, can help to identify poor outcome groups, give better insight as to the expectations of patients and carers, and can give information about cancer journey.

Given sufficient information, patients can make a choice between treatments and can engage in discussion of trade-offs between the burden and the HRQOL outcome. This was demonstrated in a retrospective chart analysis of 140 patients with stage I and II glottic cancer in the study period 1990–8. The premise was that both options were offered based on equivalent control rates. Their choice was between (1) transoral microendoscopic laser surgery as a single stage, short duration of definitive treatment with histological assessment of margins and radiotherapy for recurrence or second primaries or (2) percutaneous radiotherapy which they were advised had a superior expected voice quality. In this cohort, 75 patients chose radiotherapy and 65 surgery.

### When to measure HRQOL

There is relatively little benefit in measuring HRQOL on every patient without a very clear purpose. Usually, the
HRQOL hypothesis being tested is part of a clinical trial or an explicit objective in a clinical study. HRQOL can have a major role in treatment decisions in certain situations, such as (1) when two treatments both have a very good chance of cure; (2) when two treatments have equivalent survival outcome, but different HRQOL outcomes; (3) when either treatment is very unlikely to give cure; (4) if the HRQOL outcome is very poor; or (5) the intention is non-curative and the sole consideration is the quality of time the patient and carer have remaining. HRQOL is an important additional factor in treatment decisions in some cases, for example, when there is a ‘meaningful’ difference in HRQOL between two treatments but the HRQOL benefit is counter to the expected survival advantage. In this situation, the patient has to trade off survival benefit against additional HRQOL burden. HRQOL is of little value when there is no meaningful difference between HRQOL between different treatments or when survival is ‘significantly’ better with one treatment than another.

When measuring HRQOL, there are two study designs, cross-sectional or longitudinal. Cross-sectional assessment allows the recruitment of many patients as they are at different time points in their cancer journey. This design has been frequently used in the past, particularly for questionnaire validation and predictors of HRQOL outcome and patient-derived function. Cross-sectional surveys are limited by dropout and response shift. Over time, there is a survivorship effect. Also, patients cope and adapt and this makes differences between patient groups less noticeable. The term used for data collected over a period of time on a group of patients is ‘longitudinal’. This might be pretreatment and at intervals following this, such as six months and one year, or it might be related to an intervention where the timing of the assessment is of critical importance if a change is to be adequately detected. Longitudinal data have distinct advantages as they capture the change in the patient’s HRQOL during the cancer journey and also reflect greater changes in domain scores.

**How to measure HRQOL**

Health-related quality of life is usually measured by questionnaire. Depending on the scope of enquiry, and the number and complexity of the items contained, questionnaires can be delivered in a variety of ways. If the questionnaire is relatively simple, patients can be sent postal questionnaires or asked to fill out questionnaires in the clinic. If a battery of questionnaires is needed to test a hypothesis, they can form the basis of a semistructured interview. In this situation, patients can be given time and encouragement to complete all the items. Also, semistructured interviews are a useful approach for patient-generated index or utility assessment as these approaches need to be carefully explained to patients and tend to be more time consuming. On some occasions, open interview is better, for example, in item generation, where little is known about an issue or where the quality of life construct is much wider and rapidly changing, such as in palliative care.

**THE PROPERTIES OF AN IDEAL QUESTIONNAIRE**

There are many different questionnaires available (Box 10.2). As an introduction to this area, the ideal features of questionnaires will first be discussed, and then focus will move to commonly used HRQOL questionnaires.

There are certain ideal properties of a questionnaire and these include reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility. The following criteria are helpful in identifying an appropriate questionnaire:

- disease specific;
- functional status included;
- represents global construct of quality of life;
- patient self-administered;
- short, easily understood questions;
- sensitive to change over short time periods;
- sensitive to changes in dysfunction due to illness and treatment;
- clinical relevance;
- adequate validity and reliability.

Sadura et al. suggested that the high compliance rate found in a study they carried out to demonstrate the implementation of HRQOL data collection on cancer clinics was due to the fact that patients filled in the questionnaires in clinic, rather than taking them home with them. A second factor in achieving high patient compliance was that patients could complete the questionnaire within 10 minutes. Additionally, they suggested that patients appreciated the interest being shown in aspects of their disease; this appreciation seems to create a positive feedback loop within the patient–health-care worker team.

**TYPES OF QUESTIONNAIRE AVAILABLE**

Questionnaires can be broadly classified into six different groups:

1. The performance measures such as Karnofsky or ECOG. These have been used for a long time and essentially report level of physical function. They were used to help validate the newer questionnaires when no other measures were available, but essentially their enquiry is very limited and does not address the facets of HRQOL.
2. The global or generic questionnaire, such as SF36, HAD, CESD, EQ-5D. These questionnaires can be used in other disease states and in the normative population. Comparison to the non-cancer group is of value when assessing the impact of HNC.
3. The general cancer questionnaires, such as EORTC C30 and FACT G. These can be used in any cancer...
as the items contained are germane to cancer and its treatment. These items include broad concepts that are affected by cancer, such as cognitive level or pain.

4. The HNC cancer-specific questionnaires, such as EORTC H&N and UW-QOL. These focus on the problems encountered specifically in patients with cancer of the head and neck and its treatment. This enquiry is highly relevant as key issues are addressed, such as speech, swallowing and shoulder function.

5. The H&N function-specific questionnaires, such as PSSHN. These are limited in their enquiry and focus on certain elements of function only. However, because the questionnaire is focused on only one domain, the enquiry can have more depth. Newer questionnaires have emerged aimed at being more sensitive and responsive; examples include dysphagia,24 pace of oral rehabilitation,25 PEG feeding tube,26 shoulder27 and xerostomia.28

6. Finally, there is a whole raft of other ‘quality of life’ issues that can be tested using questionnaires. Examples include emotion, coping/distress, pain, family/social support, appearance/body image, fatigue, self-esteem, satisfaction, sexual function, personality and spirituality. If enquiry extends into these fields, it is better to take advice from colleagues with wider experience in the use of these measures, such as a clinical psychologist.29, 30

**CHOICE OF QUESTIONNAIRE**

It must be recognized that although there is a wide choice of questionnaires (Box 10.3), they all have their unique features, strengths and limitations. There is no perfect questionnaire. Careful consideration must be given before embarking on developing a new questionnaire. It might be better to use several questionnaires so that the area of interest has been captured. The process of validation is time consuming and lengthy, and there is agreement that no new general cancer or head and neck-specific questionnaires are needed for general use. However, there is scope for additional specific questionnaires to better assess in detail certain issues, such as dysphagia in laryngectomy patients. However, it must be recognized that validation takes a long time.

In choosing a questionnaire, it is important to identify the domains of interest relevant to the purpose of the HRQOL data collection. It is essential to identify why the data are being collected as this shapes the study design and the use of one or several questionnaires. It is possible to use a modular questionnaire, where one group has developed several questionnaires for both general cancer and HNC (e.g. FACT, EORTC, or alternatively to use a single questionnaire that covers the HRQOL construct, e.g. UW-QOL).

Patients tend to answer similar domains in the different questionnaires in the same way (e.g. swallowing questions), thus it is possible to draw inferences from domain scores in different questionnaires. There can be strong correlation between questionnaires, e.g. the UW-QOL cluster paper, also items in UW-QOL shoulder, CES D, etc.43

HRQOL should be included as an outcome when there is a need to test a specific hypothesis. The collection of HRQOL is time consuming and hence routine collection for the sake of it has limited value.

**Barriers to measuring HRQOL in clinical practice**

Although there are many perceived benefits to measuring HRQOL, there are several difficulties (Table 10.1).

Patients are happy to complete questionnaires in clinic, as it would help them describe their health problems to their doctor. Although questionnaire length is not a major issue, most prefer a short questionnaire of less than 20 items.44 It seems that patients assume that this information from the

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**Box 10.3 Examples of head and neck questionnaire commonly used in the literature**

- Functional Assessment of Cancer Therapy-Head and Neck Subscale31
- EORTC Quality of Life Head and Neck 35-32
- University of Washington Head and Neck Cancer Questionnaire v 43
- Performance Status Scale for H&N Cancer34
- Less often reported
- Quality of life Questionnaire35
- McMaster Univ H&N Radiotherapy Q46
- Functional Status in H&N Cancer37
- H&N Cancer-Specific Quality of Life8
- H&N Oncology health status assessment38
- Head and Neck Survey39
- Self-Evaluation of Communication Experiences after Laryngeal cancer40
- Liverpool University Questionnaire41
- Structured QOL 34 item42

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**Table 10.1 Difficulties and benefits to measuring HRQOL.**

<table>
<thead>
<tr>
<th>Perceived difficulties</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of resources</td>
<td>57</td>
</tr>
<tr>
<td>Not convinced of value</td>
<td>16</td>
</tr>
<tr>
<td>Not part of departmental practice</td>
<td>11</td>
</tr>
<tr>
<td>Lack of information about questionnaires</td>
<td>7</td>
</tr>
<tr>
<td>Unable to process the data collected</td>
<td>6</td>
</tr>
<tr>
<td>Forgot to distribute</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefits</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>More information about the patient</td>
<td>28</td>
</tr>
<tr>
<td>Identification of problems</td>
<td>22</td>
</tr>
<tr>
<td>Research</td>
<td>10</td>
</tr>
<tr>
<td>Quality of life as an outcome</td>
<td>10</td>
</tr>
<tr>
<td>Terminate aggressive surgery</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>20</td>
</tr>
</tbody>
</table>

There was little change in domains between three and six months. By 12 months postoperatively, patients approached pretreatment scores. Patients with posterior sites tended to have a bigger deterioration in scores to one year than patients with anterior sites, most notably in social function. Using the EQ-5D compared to national reference data, patients under 60 years of age fared significantly worse than expected for their age, but this was not so for older patients. Older patients had a QOL similar to what would have been expected for their non-cancer peers and the fall in QOL over time in the cancer group seems to mirror the expected age-related changes. Also, comparison has been made using head and neck cancer-specific questionnaires in a general population. Compared to a group of patients attending for a check up at their dentist, the key differences at baseline were anxiety, pain, swallowing, chewing and mood. At one year, there were big differences in all domains with deterioration in the oral cancer group. The difference was least notable in pain, shoulder, mood and anxiety. Eighty-three per cent of the people attending their dentist, compared to 78 per cent of the cancer group at one year, either reported good, very good or outstanding QOL.

It is possible to compare HNC with other disease states by using general questionnaires. For example, comparison using the EQ-5D mean VAS score suggests that HNC patients fit in the middle of a range from no illness, psoriasis, liver transplant, cystic fibrosis, HNC, irritable bowel syndrome, HIV, chronic liver disease, dementia and chronic fatigue syndrome.

### QUALITY OF LIFE IN HEAD AND NECK CANCER

#### The issue of survival

Survival and cure are of primary importance. This supports aggressive treatment; however, there is high individual variability and the primacy of survival is influenced by treatment.

#### Comparison with normative data and other disease states

There are several articles in the literature that give a review of QOL in HNC. Of those published more recently, several address general issues, three have focused on psychosocial aspects, one on neck dissection, and three on the issue of questionnaires. The HRQOL of patients with HNC can be compared to normative reference data and other disease states. There are reference data for many general questionnaires, such as the Medical Outcomes Short Form 36 (SF 36). Patients with HNC scored lower than norms, particularly for physical role limitation, mental role limitation and social functioning. There was a strong association found between tumour stage and severity of pain. At three months following surgery, there was a considerable deterioration in physical functioning, limitation of physical role, energy and general health perception. There was little change in domains between three and six months. By 12 months postoperatively, patients approached pretreatment scores. Patients with posterior sites tended to have a bigger deterioration in scores to one year than patients with anterior sites, most notably in social function. Using the EQ-5D compared to national reference data, patients under 60 years of age fared significantly worse than expected for their age, but this was not so for older patients. Older patients had a QOL similar to what would have been expected for their non-cancer peers and the fall in QOL over time in the cancer group seems to mirror the expected age-related changes. Also, comparison has been made using head and neck cancer-specific questionnaires in a general population. Compared to a group of patients attending for a check up at their dentist, the key differences at baseline were anxiety, pain, swallowing, chewing and mood. At one year, there were big differences in all domains with deterioration in the oral cancer group. The difference was least notable in pain, shoulder, mood and anxiety. Eighty-three per cent of the people attending their dentist, compared to 78 per cent of the cancer group at one year, either reported good, very good or outstanding QOL.

It is possible to compare HNC with other disease states by using general questionnaires. For example, comparison using the EQ-5D mean VAS score suggests that HNC patients fit in the middle of a range from no illness, psoriasis, liver transplant, cystic fibrosis, HNC, irritable bowel syndrome, HIV, chronic liver disease, dementia and chronic fatigue syndrome.

### HRQOL outcome in general in different HNC sites

There is a great deal of published data from which an indication can be gleaned as to the difference in HRQOL between different sites.

Papers have either reported HRQOL in a mixture of head and neck patients or specific to a subsite, such as oral cavity, oropharynx and larynx. There were a few sites excluded, as they are not usually considered in the main group. Specific examples include parotid, oesophageal, thyroid, skull base and non-melanoma cervicofacial skin cancer.

It is often easier to use a graph to depict the data contained in tables (Figure 10.1). This shows that the HRQOL is similar across the different subsites at presentation, that there is a dip in the first three to six months following treatment, and a plateau over the longer term. It has been suggested that outcome at one year reflects the long-term situation. The graph also demonstrates that the HRQOL outcome is potentially better for laryngeal and oral cavity subsites compared to oropharynx and hypopharynx. In clinical practice, the poor HRQOL in oropharynx and pharynolarynx has influenced the treatment protocols aimed at organ preservation. However, it must be considered that HRQOL outcome and individual domains are significantly affected by the stage of the cancer and the use of combined treatment modalities. Also, domains can move in different directions (get better or worse). For example, from pretreatment to follow up, anxiety, mood and pain can improve following primary surgery for oral and oropharyngeal cancer, while the other function domains deteriorate. What the patients would benefit from is a questionnaire will be used to improve care for other patients, hence value the enquiry. Computer network support and the use of touch screen technology perhaps offers the key to allowing HRQOL data to be available in routine clinics to help inform the decision process and also identify problems that could then be amenable to intervention.

Health-related quality of life outcomes have become a standard component of secondary outcomes in randomized control trials. By including the patient perspective, there is supplementary information on clinical benefit that gives the study added relevance. When using HRQOL data in clinical trials, various points need to be considered (Box 10.4).

#### Box 10.4 Factors to take into account when reporting quality of life in clinical trials

- Recruitment bias
- Dropout – survivorship effect
- Non responders
- Sufficient power – rare diverse cancer
- Allow for other variables e.g martial status, comorbidity, personality
- Lack of blindness – informal intervention
- Cross-cultural validity
- Agreed standard of analysis and reporting
- Establishing clinical meaning and a clinically relevant difference
consider as important domains can differ and hence the impact on their HRQOL as a result of changes in different domains can influence outcome if those domains considered most important are most severely affected.33

Patients most at risk of a poor HRQOL outcome

There are a number of different patient and treatment factors that are associated with HRQOL. These include age, gender, site, stage, emotional status, smoking and alcohol, marital status and income, performance status, method of reconstruction, access, mandibular resection, neck dissection, percutaneous endoscopic gastrostomy and postoperative radiotherapy.8, 51 It is possible to postulate some of the patient characteristics which are associated with poor outcome (Box 10.5). In recognizing this, it might be appropriate to discuss different treatment strategies that should be the standard protocol or it might be possible to arrange additional support for the patient and their carer. The rationale for identifying this group as having potential problems with HRQOL is explained further in the next section.

Key HRQOL issues

In this section, the most common HRQOL issues in patients with HNC will be explored (Box 10.6). Focus will be on the more recent literature.

COPING

The patient might find it difficult to cope and, if cured, may become less satisfied with the residual level of dysfunction. The appreciation and promotion of coping strategies is an important facet of optimizing HRQOL, as at times there is very little to be done to improve a handicap following such surgery. Family and carer support is vital. As much as possible should be done to assist the patient’s carers in the cancer journey. It has been said that ‘learning to live with cancer is no easy task … learning to live with someone else’s cancer

may be even more difficult’. Denial, alcohol and fatalism are examples of poor coping styles.25 An avoidance-focused coping style was generally associated with lowered HRQOL. There seems to be a stronger association between HRQOL and coping style, which in part relates to cognitive and emotional function.73 Interventions aimed at improving coping can be effective in improving quality of life and reduce depressive symptoms in HNC patients. A short-term psychoeducational coping strategies intervention showed that compared with their baseline scores, the intervention group had improved physical and social functioning, global quality of life, fatigue, sleep disturbance than the matched control subjects.74

Dental status

Although there is a limited research base, some studies in the non-HNC population show significant associations between oral health status and HRQOL.75 Teeth are important for the appearance of a smile, as well as chewing, and optimal dental care is essential for both dentate and edentulous patients. It is recognized that there is a deterioration in masticatory efficiencies following treatment of oral cancer.76 In oral cancer in particular, dental status is important, as patients tend to be limited to semisolid diets postoperatively and have difficulty wearing dentures.77 Dental status is important in HRQOL. Partially dentate individuals without dentures fair worse and tend to report a poorer HRQOL and also more ‘problems with their teeth’, ‘trouble eating’, and ‘trouble enjoying meals.’78 It is helpful before treatment starts to have an understanding of the patient’s dental expectations and motivation so that appropriate dental care can be planned on an individual basis.

Box 10.5 Possible problem pool

- Alcohol abuse
- Deprivation
- Personality
- Pre-existing distress
- Single with poor family support structure
- Site: Oropharynx and hypopharynx
- Stage IV disease
- Younger patient
- Unknown factors

Box 10.6 Key issues

- Coping
- Dental status
- Disfigurement
- Emotion
- Fear of recurrence
- Function
- Oral rehabilitation
- Pain
- Personality
- Sociodemographic
- Speech
- Swallowing
- Shoulder
- Xerostomia

Figure 10.1 Health-related quality of life (HRQOL) over time from diagnosis comparing laryngeal, oral, oropharyngeal and hypopharyngeal sites.
DISFIGUREMENT

In HNC, disfigurement has been identified as a key HRQOL domain for many years. The domain is common to the head and neck-specific HRQOL questionnaires. Following HNC, there can be overt alteration in body structure, loss of function and its implications for social interaction have been associated with depression. Any additional burden of communication difficulties and social rejection greatly confounds the problems experienced. Appearance concerns can be missed in a busy clinical setting and efforts should be made to identify problems as simple advice, counselling therapy, camouflage and possible revision surgery might help alleviate distress.

EMOTION

Several studies over the years have reported a high incidence of psychological distress in this patient population. Anxiety is at its highest before treatment, and both anxiety and depression tend to improve from this baseline. Some patients have pre-existing psychological distress and this group find the cancer diagnosis much harder to deal with. Depression is also common along with worry, anxiety, mood disorders and fatigue. Psychological interventions have a role in reducing this distress. Early detection and appropriate specialist referral are integral components of patient care. It is possible to screen for psychological morbidity relatively easily using the HAD. In addition, single item domain measures would appear to be effective.

FEAR OF RECURRENCE

Recurrence following HNC tends to occur within the first two years following treatment. This is a particularly stressful time for patient and carers. One study reported that at three months post-treatment, over 80 per cent of patients expressed concern over the possibility of recurrence and that this level reduced to 72 per cent at seven months. Fears of recurrent disease remain for some time following initial treatment and are not necessarily related to the stage of disease or radicality of treatment. There is an association with psychological morbidity, especially anxiety. Therefore, an attempt should be made to identify patients who have a notable fear of recurrence and they should be offered appropriate support.

FUNCTION

The importance of function in HNC is reflected in the number of domains that tap into these issues in the HNC questionnaires. In most situations, the better the functional outcome following treatment the better the HRQOL as function and HRQOL are inextricably linked. With better function, the patient perceives fewer consequences as a result of cancer and this leads to better acceptance of the situation and QOL. There are many ways of limiting the functional deficits following surgery and ways of preserving function in laryngeal malignancy. Good function has many components and its precise HRQOL 'value' in clinical practice remains elusive, as function is strongly influenced by the extent of disease at presentation where the patient’s primary concern is for cure.

ORAL REHABILITATION

Oral rehabilitation is a key aspect of HRQOL by virtue of the importance to human existence of social interaction, eating and drinking. A patient’s HRQOL is improved if they are successfully rehabilitated. There are many aspects to oral rehabilitation which by necessity are beyond the scope of this chapter; however, there are notable positive effects on eating, effective restoration of the mandible, appropriate use of osseointegrated implants in allowing rehabilitation to be achieved and minimizing trismus.

PAIN

Pain has been considered a critical aspect of HRQOL and indeed uncontrolled pain is of major significance in the patient’s well-being. Head and neck pain is heterogeneous in nature and influenced by other factors such as distress or dysfunction. It would appear that patients having both surgery and radiotherapy were significantly more likely to have troublesome pain. However, better analgesia regimes tend to mean that pain is well controlled following successful treatment and hence functional disorders play the more dominant role.

PERSONALITY

Personality is a predictor of HRQOL in HNC patients. It has been suggested that before treatment, optimists report better role, cognitive and emotional function, less pain and fatigue and a better global rating of HRQOL than did pessimists. Following treatment, optimists report better role and cognitive functioning, less pain and better global HRQOL than did pessimists. Pessimists reported a greater deterioration in the role domain following treatment than did optimists. High neuroticism, but not extraversion, has been associated with a lowered QOL. A sense of humour is beneficial to HRQOL. Interestingly, neuroticism has been associated with a risk of HNC as a result of increased alcohol consumption implicating a link between personality trait and the prognosis. Personality has also been associated with one-year survival independent of other sociodemographic and clinical variables.

SOCIODEMOGRAPHIC

Deprivation influences the incidence and outcome of patients with cancer. At presentation, HRQOL was not linked to deprivation, however, following surgery patients from more deprived areas reported poorer HRQOL especially in the pain domain. Living alone, and heavy alcohol and smoking consumption were associated with lower HRQOL scores and, as these are linked with deprivation, they could be used to heighten awareness among the head and neck team of a patient at risk. In patients with oral cancer treated with microvascular free-flap reconstruction, sociodemographic
factors have been shown to predict quality of life. In addition, heavy drinking and unemployment have been associated with an increase in risk of death and can influence cognitive functioning. Marital status may influence prognosis through mechanisms of health behaviour and/or social support mechanisms.

**SPEECH**

Speech is a key HRQOL domain in HNC. As a functional issue, it is repeatedly cited as one of the most important aspects by patients. In the oral cavity and oropharynx, primary closure when feasible is a better option than free flap reconstruction, in relation to postoperative swallowing and speech function. There are several recent papers that address the issue of HRQOL and speech and specialist assessment and intervention is essential in order to help address the needs of HNC patients.

**SWALLOWING**

In the oropharynx, surgical resection seems to affect swallowing more than speech. Chemoradiation rather than surgery, followed by radiation, for oropharyngeal primaries has been associated with significantly better emotional and functional scores. The difference is much less noticeable for laryngeal and hypopharyngeal primaries. Nutritional support is paramount and, when comparing patients with dysphagia from a variety of medical conditions, long-term nutrition via the feeding tube maintained the patients’ quality of life. However, for HNC patients, the presence of a feeding tube was found to be the strongest negative predictor of QOL. In patients with long-term feeding tubes following surgery for oral and oropharyngeal cancer, those with PEGs reported significant deficits in all UW-QOL domains compared to non-PEG or PEG-removed patients, and also reported a much poorer quality of life. The major PEG-related problems were not those of discomfort, leakage or blockage, but interference with family life, intimate relationships, social activities, and hobbies. More can be done to counsel and support patients with long-term PEG placement.

**SHOULDER**

There is an appreciation of the significant detrimental impact on shoulder function following a modified radical and radical neck dissection. This has led to a change in practice toward more selective approaches. The problems are much less following function preserving neck dissections, but radiotherapy might cause additional problems. However, even after a unilateral selective level 1 to 3 clearance, there was significant loss of shoulder flexion and abduction in the operated side compared to the non-operated side, but not in regard to the other cervical spine and shoulder measurements. The benefit of performing sentinel node biopsy on HRQOL is yet to be fully evaluated. Physiotherapists have a role in screening patients with shoulder dysfunction postoperatively, thus allowing early intervention.

**XEROSTOMIA**

Xerostomia can have a significant impact on the quality of life of patients treated by radiation therapy. Treatment can result in a profoundly dry mouth which causes additional problems with eating, swallowing, dental health and speech. In a study by Wijers et al., 64 per cent of the long-term survivors still experienced a moderate to severe degree of permanent xerostomia after treatment by conventional twodimensional radiation therapy. Adjuvant radiotherapy after primary surgery is identified as one of the biggest detrimental factors to HRQOL, but is used on the premise that cure rates are improved. Recently, there has been a great deal of interest in ways of reducing xerostomia and its potential beneficial impact on HRQOL.

In conclusion, the evaluation of HRQOL in patients with head and neck cancer is integral to optimal patient care. Survival is usually the initial primary concern of patients, however after treatment there is a shift towards HRQOL and living with the consequences of head and neck cancer treatment (survivorship). It is feasible for HRQOL evaluation to be part of routine clinical practice and this supports holistic care for individual patients and their carers.
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**FURTHER READING**


Complications and their management

KIM AH-SEE AND MRINAL SUPRIYA

You are a true surgeon from the moment you are able to deal with your complications.

Owen H Wangensteen

INTRODUCTION AND DEFINITION

A complication following head and neck surgery can be defined as an adverse event that impacts on the patient's recovery, alternatively described as a possible 'side effect' of surgery.

An awareness of the possible complications enables the surgeon to provide informed consent when discussing surgery with the patient. While not all conceivable complications can be covered, particular emphasis may be placed on certain outcomes depending on the individual and their comorbidities. As a general rule, minor but frequently occurring problems, such as auricular paraesthesia after parotidectomy, should be discussed in addition to rarer but more significant complications, such as facial nerve damage. Remember that clear documentation of such preoperative discussions will mitigate possible future medicolegal issues.

The incidence of complications will vary from surgeon to surgeon. Some of this variation may be due to differing definitions. For example, what do we mean by a wound infection? However, underpinning the ability to quote our own complication rates is personal audit of our work. All surgeons, including trainees, must be active in this regard.

This chapter cannot be all inclusive, but basic principles will be highlighted. A careful preoperative assessment, meticulous surgical technique, high quality postoperative care and appropriate rehabilitation are the cornerstones of preventing and managing complications.

General and specific complications will be discussed in some detail with emphasis, where appropriate, on elements of prevention, identification and management.

CLASSIFICATION

These can be initially classified as general or specific. General relates to the risks of undergoing any surgical procedure while specific relates to the particular operation in question. These will be discussed below.

In addition, complications may be classified as: early, occurring during or within 24 hours of surgery; intermediate complications arise during the early days or weeks postoperatively; and finally, late complications generally occur months or years after surgery (Table 11.1).

PREVENTION AND EVALUATION

Patients undergoing head and neck surgery usually have a history of tobacco and alcohol consumption. As such they are

<table>
<thead>
<tr>
<th>Classification of complications</th>
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<tbody>
<tr>
<td>General and specific</td>
</tr>
<tr>
<td>Early, intermediate and late</td>
</tr>
<tr>
<td>Local and systemic</td>
</tr>
<tr>
<td>Major and minor</td>
</tr>
</tbody>
</table>

Table 11.1 Classification of complications.
likely to suffer from both cardiovascular and respiratory disease. These have a significant impact on recovery from surgery and are therefore an important part of the pre-operative evaluation. Advice should be sought from the anaesthetist involved who may recommend further medical assessment. Smoking cessation has a positive effect on post-operative wound healing. Several tools exist for the global assessment of a patient’s fitness. The ASA and CEPOD scores are outlined in Tables 11.2 and 11.3, respectively. Two commonly used measures of performance status are described in Tables 11.4 and 11.5.

Control of coexisting medical conditions is required for optimal outcome (Table 11.6).

A successful operation will only remain so with optimal postoperative care, whether this is on the ward, in high dependency or in intensive care. General guidelines exist for postoperative care and all surgeons should be familiar with these as part of good medical care. Optimal postoperative care requires:

- clinical assessment and monitoring;
- respiratory management;
- cardiovascular management;
- fluid, electrolyte and renal management;
- control of sepsis;
- nutrition.

### MANAGEMENT: GENERAL

Mortality rates in head and neck surgery are fortunately low. However, the development of medical complications is associated with a longer hospital stay and increased mortality rates. Likewise the presence of pre-existing comorbidities requires prompt management to reduce the incidence of subsequent major surgical complications.

#### Cardiovascular

The risk factors for deep vein thrombosis (DVT) in hospitalized patients are described in Box 11.1. Identification of these risk factors will require consideration of DVT prophylaxis, such as TED stockings, pneumatic compression and low molecular weight heparin preoperatively. Recent NICE guidelines recommend the screening of all patients admitted to hospital according to the list

### Table 11.2 ASA score.

<table>
<thead>
<tr>
<th>Class</th>
<th>Physical status</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A completely healthy patient</td>
<td>A fit patient for tonsillectomy</td>
</tr>
<tr>
<td>II</td>
<td>A patient with mild systemic disease</td>
<td>Essential hypertension, mild diabetes without end organ damage</td>
</tr>
<tr>
<td>III</td>
<td>A patient with severe systemic disease that is not incapacitating</td>
<td>Angina, moderate to severe COPD</td>
</tr>
<tr>
<td>IV</td>
<td>A patient with incapacitating disease that is a constant threat to life</td>
<td>Advanced COPD, cardiac failure</td>
</tr>
<tr>
<td>V</td>
<td>A moribund patient who is not expected to live 24 hours with or without surgery</td>
<td>Ruptured aortic aneurysm, massive pulmonary embolism</td>
</tr>
<tr>
<td>E</td>
<td>Emergency case</td>
<td></td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disorder.

### Table 11.3 CEPOD scores.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Elective – Operation at time to suit both surgeon and patient</td>
</tr>
<tr>
<td>2</td>
<td>Scheduled – Operation within 24 hours. Delayed operation after resuscitation</td>
</tr>
<tr>
<td>3</td>
<td>Urgent – Operation between 1 and 3 weeks. Early surgery preferred, but not life saving</td>
</tr>
<tr>
<td>4</td>
<td>Emergency – Operation within 1 hour. Immediate operation or resuscitation simultaneous with surgical treatment</td>
</tr>
</tbody>
</table>

### Table 11.4 WHO performance scale.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity, but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care, but unable to carry out work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable only of limited self-care; confined to bed more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry out any self-care; totally confined to bed or chair</td>
</tr>
</tbody>
</table>
of recognized risk factors for venous thromboembolic
events.8

Patients can be further categorized into low, medium or
high risk depending on the number of risk factors present.9
Fortunately, the rate of DVT and subsequent pulmonary
embolism (PE) in head and neck surgery is low (o1 per
cent).9 Symptoms of DVT and PE are as mentioned in
Box 11.2. Definitive diagnosis may require V/Q scanning or D-
dimer test.

Ischaemic heart disease is common in patients with head
and neck cancer. Preoperative optimization is required as
described above to minimize risk, however postoperative car-
diac failure or myocardial infarction (MI) may occur and
require treatment. Commonly, in surgical patients, MI occurs
due to an imbalance between myocardial oxygen supply and
demand in the presence of pre-existing coronary artery disease.
Myocardial oxygen supply may be diminished by anaemia or
hypotension, whereas oxygen demand may be increased by
tachycardia and hypertension resulting from postoperative
pain, withdrawal of anaesthesia or shifts in intravascular
volume. Perioperative myocardial infarction usually occurs 1–4
days after surgery when the effects of anaesthesia have dis-
sipated and perioperative pain and fluid shifts are occurring.10

Respiratory

PNEUMONIA

Preoperative respiratory status in head and neck cancer
patients may be poor with a history of chronic obstructive
pulmonary disease (COPD) being common.11 Additional risk
factors for respiratory complications are previous myocardial
infarction and American Society of Anesthesiologists (ASA)
grade.12 Optimizing pulmonary function preoperatively is
important and may require input from physiotherapy and
respiratory physician colleagues.

The creation of a tracheostomy or tracheotomy sig-
nificantly increases the patient’s vulnerability to postoperative
pneumonia11 and demands meticulous postoperative stoma
care with humidification and regular suctioning of secretions.
Impaired postoperative swallowing with aspiration will
eventually lead to bronchopneumonia. Strict adherence to a
‘nil by mouth’ policy with an alternative nutritional route is
necessary. Careful monitoring during rehabilitation of swal-
lowing will require input from speech and language therapy
with videofluoroscopic and endoscopic evaluation.13 The
presence of thoracic and abdominal wounds, as may be
required for total laryngopharyngo-oesophagectomy, further
restricts patient mobilization and respiratory function.

The diagnosis of bronchopneumonia is made clinically
and supported by further investigations, including full blood

<table>
<thead>
<tr>
<th>Karnofsky performance scale</th>
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<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
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<td>70</td>
</tr>
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<td>60</td>
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<tr>
<td>50</td>
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<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
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<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical comorbidities.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidity</strong></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Respiratory disease</td>
</tr>
<tr>
<td>Endocrine disease</td>
</tr>
<tr>
<td>Renal disease</td>
</tr>
<tr>
<td>Haematological disease</td>
</tr>
</tbody>
</table>

BP, blood pressure; CXR, chest x-ray; ECG, electrocardiogram; GFR, glomerular filtration rate; PFT, pulmonary function test.

Common risk factors include:
- Age over 60
- Obesity (BMI > 30)
- Varicose veins
- Dehydration
- Previous VTE
- Thrombophilia
- Cancer
- Heart failure
- Recent MI or stroke
- Oestrogen therapy (including HRT)
- High dose progestogen
- Pregnancy
- Puerperium
- Immobility
- Inflammatory bowel disease
- Nephrotic syndrome

Assessment of individual risk factors should include:
Symptoms and signs of pneumonia are shown in Box 11.3. Management of bronchopneumonia requires rigorous physiotherapy and appropriate antibiotic therapy; microbiology advice for the latter is advisable.

**PNEUMOTHORAX/HAEMOTHORAX**

Damage to the pleura during surgery, for example when dissecting low in the neck or when mobilizing the oesophagus, will result in pneumothorax.

Clinical features are shown in Table 11.7.

Treatment choice is dictated by the degree of collapse. An iatrogenic pneumothorax $\geq 3$ cm (from chest apex to lung) or $>15$ per cent in size by chest x-ray should be considered for drainage using a smaller bore chest tube.  

Small iatrogenic pneumothoraces in clinically stable patients may be carefully observed. Clinical instability, significant symptoms, or a larger pneumothorax should prompt placement of a small bore chest drain. Haemothorax or pleural effusion can be difficult to diagnose even with radiology in a supine patient. Chest x-ray should, if possible, be in an upright position to demonstrate the fluid. Aspiration and/or drainage may be required, especially if the patient is symptomatic.

**Nutrition**

The nutritional state of a head and neck cancer patient should be addressed preoperatively to facilitate wound healing in the postoperative period and to reduce complication rates. Simple measures of nutritional status are weight, body-mass index (BMI), skin fold measurements (e.g. triceps) and serum albumin and lymphocyte count. Patients undergoing major head and neck surgery are at risk of malnutrition and close collaboration with the dietician is important.

**REFEEDING SYNDROME**

Rapid refeeding in a patient with malnutrition can result in the potentially fatal 'refeeding syndrome'. This condition is seen in an undernourished patient, who is fed (enterally or parenterally) over a short period of time and results from metabolic and hormonal changes. Typically this condition is manifest by hypophosphataemia as well as low potassium, magnesium and thiamine deficiency. Slow and measured feeding over the first week, accompanied by close electrolyte monitoring and vitamin supplementation, prevent development of this condition.

Technical problems related to the provision of nutrition can occur. These include problems with nasogastric (NG) tube placement, percutaneous endoscopic gastromy (PEG) tube procedures and long-line and total parenteral nutrition (TPN) related problems. The position of a NG tube should be confirmed both clinically and radiologically prior to initiating feeding. Aspiration of feed from a misplaced or displaced NG tube is a serious complication requiring immediate cessation of tube feeding and urgent physiotherapy. If long-term tube feeding is anticipated, then PEG tube
feeding should be considered. This is aesthetically more convenient for the patient and, although complications such as cellulites, ileus, tube extrusion, tube blockage and peristomal leakage can occur, is more acceptable to patients than long-term NG tube placement.\textsuperscript{15,19}

**MANAGEMENT: SPECIFIC METABOLIC COMPLICATIONS**

**Shock**

Shock in a postoperative patient can have a significantly adverse outcome, therefore every effort should be made to prevent it, while the surgeon should actively aim for early diagnosis if it does happen. Shock is defined as a state where the circulation is unable to meet the metabolic requirements of the body. For clinical purpose this can be either due to lack of circulatory fluid (hypovolaemic shock), or due to failing heart (cardiogenic shock), or because of increased metabolic needs of the body (septic shock). Initial management involves the administration of oxygen and volume infusion with isotonic crystalloids. Intubation and mechanical ventilation, with appropriate sedation and paralysis, decreases the basal metabolic rate by about 30 per cent and should be considered early. A urinary catheter is vital to measure urinary output, an excellent measure of tissue perfusion (normal in adult is about 0.5 mL/kg per hour or about 30–50 mL/h for most adults). Patients refractory to a crystalloid fluid bolus of 1–2 L should be considered for central venous (CV) catheter.

**HYPOVOLEAMIC SHOCK**

Hypovolaemic shock can occur after extensive head and neck surgery, especially if involving free tissue transfer. Early compensatory circulatory response includes increased heart rate and progressive vasoconstriction. Tachycardia is the earliest measurable circulatory sign of shock.\textsuperscript{20} Vasoconstriction leads to increased diastolic pressure, reduced pulse pressure and cool peripheries. Assessing severity of shock as proposed by ATLS can help institute appropriate therapy. It is important to note that a consistent drop in systolic pressure occurs late, after loss of more than 30 per cent of circulating blood volume. As mentioned before, establishing a patent airway, obtaining adequate intravenous access, controlling obvious haemorrhage and assessing tissue perfusion should be initiated. Ringer’s lactate or normal saline is the initial fluid of choice, 1–2 L given as an initial fast bolus. The total amount of fluid needed is roughly 3 mL for each millilitre of estimated blood loss.\textsuperscript{20} Indicators of end-organ perfusion, i.e. urinary output, mental state and peripheral perfusion, should be monitored. Patients showing transient response should be considered for blood transfusion. Patients not responding should be considered for early surgical intervention as ongoing blood loss is likely to be the underlying problem. The possibility of non-haemorrhagic shock should also be considered in these cases. Central venous pressure (CVP) monitoring or cardiac ultrasonography can help differentiate shock in these selected patients (see Table 11.8).

**SEPTIC SHOCK**

Postoperative infection can result in a spectrum of disease ranging from strictly localized lesion to massive systemic inflammatory response syndrome (SIRS). High risk patients should be closely monitored for evidence of SIRS. Elderly persons, those with comorbid conditions and those who are immunocompromised are especially at high risk, including those with cancer on chemotherapeutic agents, those with end-stage renal or liver disease, those with advanced HIV or those on steroids for chronic conditions. Indwelling catheters (vascular, urinary) also place patients at high risk. Sepsis is the presence of SIRS in the setting of infection. Severe sepsis is defined as sepsis with evidence of end-organ dysfunction as a result of hypoperfusion. Septic shock is defined as sepsis along with persistent hypotension despite fluid resuscitation and resulting in tissue hypoperfusion.\textsuperscript{21} Bacteraemia is defined as the presence of viable bacteria within the liquid component of blood and is seen in fewer than 50 per cent of cases of sepsis.\textsuperscript{22}

SIRS is defined by the presence of at least two of the following four criteria:\textsuperscript{21}

1. Temperature higher than 38 °C or lower than 36 °C.
2. Heart rate greater than 90 beats per minute.
3. Respiratory rate greater than 20 breaths per minute.
4. WBC count higher than 12 000/mm\textsuperscript{3} or lower than 4000/mm\textsuperscript{3} or with more than 10 per cent immature forms (bands).

<table>
<thead>
<tr>
<th>Blood loss (mL)</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
<td>&gt; 120</td>
<td>&gt; 140</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>Normal or increased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>14–20</td>
<td>20–30</td>
<td>30–40</td>
<td>&gt; 35</td>
</tr>
<tr>
<td>Urine output (mL/h)</td>
<td>&gt; 30</td>
<td>20–30</td>
<td>5–15</td>
<td>Negligible</td>
</tr>
<tr>
<td>CNS/Mental state</td>
<td>Slightly anxious</td>
<td>Mildly anxious</td>
<td>Anxious, confused</td>
<td>Confused, lethargic</td>
</tr>
<tr>
<td>Fluid replacement</td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crystalloid and blood</td>
<td>Crystalloid and blood</td>
</tr>
</tbody>
</table>
Complications from sepsis include central nervous system dysfunction, adult respiratory distress syndrome (ARDS), liver failure, acute renal failure (ARF) and disseminated intravascular coagulation (DIC). In septic shock, ARDS has been observed in about 18 per cent of cases, DIC in about 38 per cent and renal failure in about 50 per cent.22

The reported mortality rate in sepsis and septic shock varies according to the underlying host condition, infecting organism, aggressiveness of treatment and the subsequent development of complications. The mortality rate for severe sepsis is quoted as anywhere between 30 and 50 per cent.22 Therefore, every effort should be made to diagnose these early.

Altered mental status is perhaps the most consistent clinical feature in sepsis. Narrow pulse pressure and tachycardia are the earliest signs of shock. Early sepsis is characterized by warm shock, i.e. tachycardia, warm extremities and adequate capillary refill. Laboratory investigations should include white blood cell (WBC) count, haemoglobin, comprehensive chemistry panel, coagulation studies, blood culture and other cultures and sensitivities dictated by clinical examination.

Patients with severe sepsis and septic shock require admission to an intensive care unit for careful monitoring and goal-directed therapy. Antibiotics are given parenterally in adequate doses to achieve bactericidal serum levels and must have a broad spectrum covering Gram-positive, Gram-negative and anaerobic bacteria because all classes of these organisms produce identical clinical pictures.

**CARDIOGENIC SHOCK**

Cardiogenic shock in the postoperative set up is usually due to myocardial ischaemia or infarction. This results in decreased pumping ability of the heart that causes global hypoperfusion. This is defined as sustained hypotension (systolic blood pressure less than 90 mmHg lasting more than 30 minutes) with evidence of tissue hypoperfusion (oliguria/oligaemia). The usual symptoms of acute cardiac ischaemia (e.g. chest pain, shortness of breath, diaphoresis, nausea, vomiting) may be absent in these patients due to ongoing medications. However, as in any shock, circulation is markedly impaired leading to tachycardia, delayed capillary refill, hypotension, diaphoresis and poor peripheral pulses. Breathing may be laboured and presence of audible coarse crackles with or without wheezing points towards left ventricular failure while right ventricular failure is marked by jugular venous distention. An ECG is helpful if it reveals an acute injury pattern consistent with an MI. A normal ECG, however, does not rule out the possibility. The usual work up also includes tests for cardiac enzymes (e.g. creatine kinase, troponin, myoglobin), complete blood count (CBC), electrolytes, coagulation profile and arterial blood gas (ABG). All patients require intravenous access, high-flow oxygen and cardiac monitoring. The key is involving a cardiologist at the earliest opportunity because their expertise is invaluable for facilitating transfer to more definitive care (e.g. cardiac catheterization suite, intensive care unit, operating room).

**Acid–base imbalance**

The extracellular pH is tightly controlled within 7.35–7.45 as cellular enzymes need a strictly controlled biochemical environment to function normally. Any change in the pH triggers a compensatory mechanism through buffers which include bicarbonate, protein, haemoglobin and phosphate. Of these the bicarbonate system is the most important and is represented by the Henderson–Hasselbalch equation:

\[
\text{pH} = 6.1 + \log[HCO_3^-]/\text{PaCO}_2 \times 0.03.
\]

The respiratory system is able to regulate pH by modulating alveolar ventilation in the presence of constant metabolic production of CO₂. An increase in alveolar ventilation (e.g. tachypnoea) will decrease the PaCO₂ and vice versa. Brainstem respiratory centres which are sensitive to H+ concentration respond rapidly. In contrast, the renal control is slow and maximum effect takes place only after several days. This principally involves controlling the secretion of H+ relative to the amount of filtered HCO₃⁻. A modern portable gas analyser can easily measure pH, PaCO₂ and PaO₂, which are usually carried out on arterial blood taken from the radial, brachial or femoral artery. Acidosis means an increase in arterial hydrogen ion concentration and can be due to respiratory failure leading to CO₂ retention (respiratory acidosis) or relative lack of bicarbonate due to GI loss (metabolic acidosis). Conditions leading to hyperventilation wash off alveolar CO₂ and lead to a rise in pH (respiratory alkalosis) while loss of body acids is the usual cause for raised plasma bicarbonate and hence the pH (metabolic alkalosis).

Lactic acidosis is usually implicated in postoperative acid–base imbalance. Inadequate tissue perfusion due to any form of shock results in anaerobic metabolism leading to lactic acid production and subsequent metabolic acidosis. Patients with an arterial lactate level of more than 5 mmol/L and a pH of less than 7.35 are critically ill and have a very poor prognosis. Multicentre trials have shown a mortality rate of 75 per cent in these patients.24 Therefore, it is important to consider intensive unit care early on. Lactate acidosis should always be suspected in the presence of elevated anion gap metabolic acidosis (anion gap = sodium – (chloride + bicarbonate); the gap is usually between 6 and 12 mEq/L). The normal value for anion gap must be adjusted in patients with hypoalbuminaemia. Reduction in serum albumin by 10 g/L reduces the normal value for anion gap by 2.5 mmol/L. The normal value for anion gap must be adjusted in patients with hypoalbuminaemia. Mechanical ventilation should be initiated early on as initial tachypnoea results in ventilatory muscle fatigue. Normal saline should be used for fluid replacement, avoiding solutions containing lactate. Antibiotics, surgical drainage and debridement of a septic focus are of obvious importance in appropriate cases. Controversy continues to surround the use of alkali in treating lactic acidosis.25 Sodium bicarbonate (NaHCO₃) breaks down into carbon dioxide and water in the tissues. Therefore, if its use is being considered, it is important to ensure that patients have effective ventilation to eliminate carbon dioxide and are able to handle additional sodium and volume load. In addition, dialysis may be needed in patients with coexisting renal failure or congestive heart failure.26
Calcium balance

Hypoparathyroidism is predictable after total thyroidectomy, less so after laryngectomy or hemi/subtotal thyroidectomy. Intraoperative mobilization and postoperative fibrosis can impact the blood supply to a preserved parathyroid leading to their insufficiency. The incidence rises if radiotherapy to the neck is given, before or after surgery. It can also happen due to tumour invasion or combined therapy. Having said that, most patients in whom all parathyroid tissue has been removed do not develop permanent hypoparathyroidism, presumably due to ectopic parathyroid.

Patients undergoing total thyroidectomy performed for benign pathology should commence thyroxine prior to discharge from hospital. Likewise, monitoring diabetic control and glucose homeostasis, although there is little evidence that the presence of diabetes contributes to higher wound infection rates.

Postoperative monitoring of serum calcium and thyroid function tests is required and will need correction if abnormal. Circumoral tingling, peripheral tingling and numbness, carpopedal spasm, hyperreflexia, positive Chvostek’s sign (tapping the facial nerve just anterior to the ear results in contraction of the facial muscles, seen in 10 per cent of normals) and Trousseau’s sign (elicited by inflating a blood pressure cuff for 3–5 minutes 10–20 mmHg above the level of systolic blood pressure leading to mild ischaemia that unmasks latent neuromuscular hyperexcitability, and carpal spasm is observed) are all classic pointers to this diagnosis. The early symptom of paraesthesia can be subtle and, if untreated, can result in severe hypocalcaemia leading to tetany (may include laryngospasm), focal or generalized seizures and cardiac arrhythmia. Therefore, all patients undergoing the above-mentioned procedures must have baseline calcium level estimated (corrected to albumin level) followed by a repeat test for calcium and albumin in the first postoperative day. Some authorities recommend more frequent assessment, starting in the recovery room, followed by a test every 8 hours following total thyroidectomy. The critical period for determining the need for supplemental calcium has been demonstrated to be in the first 24–72 postoperative hours.

Patients having hypocalcaemic tetany should be managed with an initial slow intravenous injection of 10–20 mL of 10 per cent calcium gluconate (providing approximately 2.25–4.5 mmol of calcium), with plasma-calcium and ECG monitoring (risk of arrhythmias if given too rapidly). This can be repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence. If magnesium deficiency is present, add 20 mL (~40 mmol) of 50 per cent magnesium sulphate solution to 230 mL N saline (10 g/250 mL). Infuse 50 mL of this (equivalent to 2 g MgSO4, 8 mmol) over 10 minutes, and at 25 mL/h thereafter. Chronic hypocalcaemia is best managed with oral calcium together with either vitamin D, or activated (hydroxylated) vitamin D. Lack of parathyroid hormone (PTH) dampens vitamin D activation (1,25 hydroxylation). Activated vitamin D is responsible for calcium absorption from the small intestine and therefore enteral calcium supplements alone are less effective in elevating serum calcium. Ergocalciferol (vitamin D2) is the most frequently administered preparation because of its safety margin and low cost. The usual dose is 50 000–150 000 U per day. However, to be active it must be 25-hydroxylated in the liver and 1-hydroxylated in the kidney. Therefore, significant liver or renal disease limits its use. Vitamin D preparations that act more rapidly are also available. Alfacalcidol (1α-hydroxycholecalciferol) at a dose of 0.1 µg daily is useful in patients with existing renal impairment. Calcitriol (1,25-dihydroxycholecalciferol) given at a dose of 0.25–1.0 µg per day is also available. These preparations have shorter half-lives than vitamin D but are more potent and more expensive. If the patient is unable to receive oral medication, these vitamin D preparations can be administered parenterally. All patients on supplemental vitamin D must have their serum calcium level checked at intervals (initially weekly). Loss of PTH impairs calcium absorption in the nephrons and therefore high serum calcium level can lead to nephrolithiasis.

Bleeding

Vascular injury giving rise to bleeding is one of the commonly encountered problems in head and neck surgery. The presence of major neurovascular bundles in the neck makes thorough anatomical knowledge indispensable, along with experience in using vascular instruments. Traditionally, postoperative haemorrhage has been classified as immediate, reactionary (within 24 hours of the operation) or secondary. Using this classification, immediate haemorrhage is said to occur when there has been inadequate control of bleeding by the end of the surgical procedure, whereas in reactionary bleeding the haemorrhage is typically attributed to the opening up of a vessel in spasm or an inadequately applied tie or clip to a vessel as the blood pressure rises after anaesthesia or patient coughing. In practice, the difference between the immediate and reactionary classifications is of little relevance. It is much more important to appreciate the possibility of haemorrhage after head and neck surgery, diagnose the complication at an early stage, commence appropriate resuscitation and stop the bleeding together with addressing any underlying causes. Such causes may include anti-coagulant therapy, unrecognized bleeding disorder, a recent large transfusion or sepsis and disseminated intravascular coagulation. General considerations include monitoring full blood count, coagulation screen and electrolytes. One should also assess the need for blood transfusion, vitamin K (if elevated PT), protamine sulphate (if heparin or low molecular weight heparin (LMWH) overdose) and clotting factors/fresh frozen plasma (Figure 11.1).

Management of bleeding

- Diagnose the problem.
- Resuscitate the patient.
- Stop the bleeding.
- Treat the cause.

The haemorrhage may present with bleeding via the sutured incisional wounds, either in the skin or from a mucosal surface in the mouth, pharynx or larynx. It is important to appreciate that bleeding into the oral cavity and pharynx may compromise the airway, either by obstruction or as a result of
aspiration of blood into the lower respiratory tract. In patients who have had a temporary tracheotomy performed at the time of their major resection of a head and neck carcinoma, this complication is avoided provided the tracheotomy tube cuff is inflated. For those without such airway protection there is even more urgency to return to the operating room swiftly, with the added problems of securing the compromised airway for the surgical team and anaesthetist. Haemorrhage into the neck wound space may also compromise the airway. This complication is noted particularly with thyroid surgery but can arise with neck dissections.

The source of the bleeding may be the wound edges themselves, from tissue transferred into the wound either on a pedicle or by free transfer, or from vessels in the wound. The most notable major vessels with potential for bleeding during and after neck dissection are the carotid artery and the branches of the external carotid, the thyrocervical trunk, the transverse cervical artery and the internal jugular vein. A bleed following a major neck operation, for example neck dissection or parotid surgery, usually manifests by swelling of the wound site. This may be preceded by ongoing filling of a surgical drain that becomes unable to remove the collecting blood. Drainage may also fail if the drain is of insufficient calibre, it becomes blocked by a clot or the vacuum seal fails and suction is lost. Thus, an empty or non-filling drain cannot be interpreted as ruling out the presence of bleeding.

Postoperative haematoma can be avoided by meticulous haemostasis and closed suction drains. An expanding haematoma needs a return to theatre with re-exploration and control of the site of bleeding. Stable haematomas can be aspirated with application of a pressure dressing, while organized non-fluctuant haematoma can be managed conservatively.

Patients with evidence of bleeding following major head and neck surgery are acutely ill. Immediate management is required. Intravenous access of appropriate calibre is needed. A significant active haemorrhage requires two large bore (e.g. 14G) cannulas situated in non-peripheral sites (e.g. the antecubital fossa). At the time of placing the cannulas, blood must be taken for cross-matching to allow for possible transfusion unless this has been arranged preoperatively. Management is as discussed above under Shock. A neck pressure dressing is very unlikely to stop a haemorrhage and simply delays definitive management of the situation while further compromising the haemodynamic status of the patient. Ongoing bleeding requires prompt return to theatre. The wound is reopened and irrigated with saline. Points of haemorrhage are identified and controlled.

Secondary haemorrhage is less predictable in terms of onset and severity. It commonly occurs 5–10 days after surgery and the cause is attributed to infection, producing breakdown of clot leading to bleeding. It may be unheralded and unexpected resulting in late presentation. In these situations the wound is explored and proximal vascular control is required to control the haemorrhage.

**Internal jugular vein injury**

To avoid troublesome bleeding from the internal jugular vein (IJV), it should be mobilized circumferentially using a spreading motion perpendicular to the vessel wall. In the event of a large accidental IJV rent, this can be repaired using a running 6-0 vascular suture. It is good practice to tie off tributaries away from the IJV wall to avoid eddy currents and subsequent thrombosis formation. Injury to vagus, hypoglossal and accessory nerves should be avoided while ligating the vessel.

Troublesome bleeding can ensue if either end of the IJV retracts. Packing with haemostatic sponge may control bleeding if the superior pole retracts into the temporal bone, failing which one may need to skeletonize the jugular vein or sigmoid sinus to control the bleed. Similarly, a sternal split may rarely be needed if the lower stump retracts into the mediastinum.

In cases of a slipped ligature or venous tear, one must consider the possibility of air embolism. This serious problem can be identified by a ‘sucking’ noise and can cause acute cardiovascular collapse. Placing the patient in the Trendelenburg position can reduce this risk. Direct pressure, aspiration from the tip of a CVP catheter if in situ, stopping nitrous oxide from the anaesthetic circuit, increasing venous pressure and turning the patient into the left lateral Trendelenburg position are all accepted management steps for this potentially lethal complication. Blind clamping may extend the rent and should not be attempted.

**Carotid artery rupture**

Cases with prior radiation, significant atheromatous disease, tumour adherence and extensive deep scarring, are all prone to carotid artery rupture intraoperatively. The incidence ranges from 3 to 4 per cent in patients undergoing neck dissection. This risk is raised seven-fold in irradiated patients. The mortality and neurological sequelae more than double in cases with non-elective carotid resection compared to elective ligation. Intraoperative repair of tears in stable patients can be performed using vascular nylon sutures with or without shunting. Similarly, if tumour invasion necessitates carotid resection, the saphenous vein or synthetic patches can be used as a graft. The assistance of a vascular colleague will be required.

Irradiation, flap necrosis, mucocutaneous cervical salivary fistula and deep neck space infection all place patients at
higher risk of postoperative carotid blow out due to arterial wall necrosis. In all cases stabilizing the patient with control of airway (consider cuffed tube), fluid resuscitation (crystalloids and blood) and direct pressure application always comes first. Any other intervention can be considered only after the patient is stabilized from a respiratory and cardiac standpoint. Debridement and wound toilet along with vascular tissue cover of a threatened carotid blowout can prevent this condition from developing into an impending or acute carotid blowout. In the presence of impending or acute carotid blowout, after stabilization, all such patients should be referred for angiography which is both diagnostic as well as therapeutic. Adequacy of contralateral carotid to the circle of Willis can be assessed by temporary balloon occlusion, while monitoring neurological status and measuring back flow pressure. If judged adequate, ligation or embolization is associated with a lower risk of cerebrovascular accident. If collateral supply is insufficient, the options include stenting or arterial bypass surgery. In circumstances where no acute intervention radiology support is available, surgical re-exploration and ligation of the thoracic duct is needed if neck exploration fails in its identification or the patient develops chylous fistula. Alternatively, a reduction in the volume of feed all can help locate the duct. Sclerosants such as tetracycline have also been advocated though they make subsequent exploration extremely difficult. Thoracoscopic ligation of the thoracic duct is needed if neck exploration fails in its identification or the patient develops chylothorax.

**Chyle leak**

Neck dissection, mostly of the left side, carries a risk of chylous fistulae, occurring in 1–3 per cent of cases with some papers reporting incidence as high as 5.8 per cent. The thoracic duct is located to the right of and behind the left common carotid artery and the vagus nerve. From here, it arches upward, forward and laterally, passing behind the IJV and in front of the anterior scalene muscle and the phrenic nerve. It then opens into the IJV, the subclavian vein or the artery. Precise knowledge of these anatomic relationships is important to avoid injuring the duct during a neck dissection. One must also remember that the thoracic duct may be multiple in its upper end and that at the base of the neck it usually receives a jugular, a subclavian and usually other minor lymphatic trunks, which must be ligated or clipped individually.

Chyle leak is apparent as clear fluid intraoperatively and is confirmed by increased flow on Valsalva manoeuvre by the anaesthetist. This involves changing the ventilation circuit to manual (in an intubated patient), closing the expiratory valve and increasing the circuit pressure to about 30 mmHg. Persistent chyle leak can cause serious nutritional, immunological and electrolyte imbalance. It is generally not advisable to try and identify this vessel specifically during surgery as this may increase the probability of damaging it. The vessel is quite fragile and surrounded by fatty tissue, which makes it prone to tearing. Therefore, direct clamping and ligating may be counterproductive. If a leak is identified during surgery the duct is ligated, without going through the vessel wall, along with surrounding tissue with a non-absorbable suture or vascular clips. If this fails, fibrin sealant and collagen felt or vicryl mesh may be used; muscle flaps can be used in severe cases. Diathermy does not seal the fragile lymphatic vessels.

Postoperative presence of milky appearance in the neck drain after starting feed points towards chylous fistula. This can be confirmed either by identifying triglycerides greater than 100 mg/dL or chylomicrons more than 4 per cent in the drained fluid. Alternatively, a reduction in the volume of drain fluid on stopping enteral feed supports a diagnosis of chyle leak. The management is controversial, however most authors favour medical management as the initial step. A low output leak will usually close spontaneously and can be managed with aspiration, pressure dressing and low fat elemental diet supplemented with medium chain triglyceride (MCT) delivered enterally. MCTs are thought to be absorbed directly into blood rather than the thoracic duct. Unresponsive cases may benefit from TPN and decrease the need for surgical intervention. Close monitoring of volume, electrolytes and nutritional status is of vital importance in managing these cases.

Surgical re-exploration and ligation of the duct is advised in the presence of complications (e.g. flap necrosis), deteriorating general condition or a ‘high output leak’ (>300 mL/day suggested by Scott-Brown, >500 mL/day by Kassel et al., and >1000 mL by Nussenbaum et al.). Identifying the duct in these circumstances is usually very difficult due to oedematous and friable tissue. The Trendelenburg position, continuous positive pressure ventilation and a high fat preoperative feed all can help locate the duct. Sclerosants such as tetracycline have also been advocated though they make subsequent exploration extremely difficult. Thoracoscopic ligation of the thoracic duct is needed if neck exploration fails in its identification or the patient develops chylothorax.

**Infected**

Infection following head and neck surgery can be either local or systemic. Systemic infection is fortunately rare but may arise if local infection is inadequately treated.

Localized infections can occur around intravenous access sites, while prolonged urethral catheterization will predispose to urinary tract infection. Early mobilization will prevent skin breakdown and development of cutaneous infection.

Local wound infection is uncommon after clean procedures when no mucosal surface is open (e.g. neck dissection). In these circumstances prophylactic antibiotics are not required and careful wound care will suffice. However, in clean-contaminated operations, such as laryngectomy, prophylactic antibiotic use is indicated. Standard practice usually involves a single intraoperative dose of a broad-spectrum antibiotic followed by 24–48 hours of antibiotic. There is little evidence in the literature to support the use of longer courses of antibiotics.

Preoperative risk factors are related to patient factors, such as diabetes mellitus, nutritional deficiency, excessive tobacco and alcohol intake and poor oral hygiene. Tumour factors include stage and site, while previous treatments (prior radiotherapy, chemotherapy) can have a detrimental effect on wound healing. In addition, the presence of a tracheostomy increases the risk of wound infection rates.
Intraoperative risk factors are related to the type of surgical procedure (composite resection, partial or total pharyngolaryngectomy, reconstruction with regional or distant flaps) and surgical technique (inadequate haemostasis and drainage, poor pharyngeal closure, duration of the procedure or inadequate sterile surgical technique).

Postoperative risk factors are related to wound care, the nutritional and metabolic state of the patient, and the healing of the mucosal repair (Figure 11.2).

Increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is an important source of wound infection complicating the postoperative recovery. This is a particularly difficult infection to eradicate and can lead to devastating, potentially fatal, infection. Early advice from microbiology is paramount in helping control this infection. Monitoring the patient’s MRSA status requires regular swabs from wound sites, along with strict barrier nursing to avoid transmission to other patients.

*Clostridium difficile* infection is also an increasing problem that surgeons must be aware of. Widespread use of broad-spectrum antibiotics in an increasingly elderly group of patients is a risk factor. Most of the steep rise in *C. difficile* infection is in patients aged over 65 years. Age is an independent risk factor as natural immunity to the organism reduces with advancing years. Likewise, patients with malignancy, sepsis, multi-organ failure, or those who stay in intensive care or high dependency units for prolonged periods (where there can be surrounding environmental contamination), are particularly vulnerable. Diagnosis is made on the presence of gastrointestinal symptoms and stool culture. Again, advice from microbiology is recommended for appropriate treatment, while strict patient isolation and meticulous hygiene standards are paramount to prevent further spread.

Neurological

### NERVE INJURY

The nerves at risk of injury during head and neck surgery are listed in Box 11.4.

Three degrees of nerve injury are recognized.

1. **Neuropraxia** consists of damage to the myelin sheath without damage to the axon fibres. Microsurgical intervention is not indicated, as function spontaneously returns.

2. **Axonotmesis** is characterized by combined damage to the axon and the nerve sheath. Subsequent proliferation of the Schwann cells and nerve fibre regeneration takes place and surgical intervention is not necessary.

3. **Neurotmesis** is complete interruption of all structures of the nerve. Because of the elasticity of the nerve, a gap between the nerve ends develops; spontaneous regeneration therefore is rarely observed. The regenerative capacity of the axons leads to the development of neuromas at the proximal nerve stump. Microsurgical intervention is indicated.

Prevention of nerve injury demands excellent anatomical knowledge and awareness of variations thereof. Meticulous surgical technique when handling and working in the vicinity of nerves is required.

Intraoperative nerve monitoring is increasingly popular with surgeons in an attempt to avoid nerve injury. Intraoperative nerve injury will require direct end-to-end repair, if possible, or the use of cable grafts if a significant gap exists between cut ends.

Development of postoperative palsy may indicate external pressure on nerves from oedema or bleeding. Late recognition of nerve deficit may require future exploration with a view to reconstruction with or without cable grafting.

### INCREASED INTRACRANIAL PRESSURE

The intracranial pressure (ICP) rises three-fold when one internal jugular vein is divided and five-fold when both are tied. Symptoms are likely to arise if both veins are tied simultaneously, but may also occur even if staged procedures result in both veins being sacrificed or if a dominant jugular is divided.

Measures to help reduce the risk of raised ICP include:

- no constricting dressings around the neck;
- avoid hyperextension of neck (especially after bilateral dissection);
- nurse upright.

Signs and symptoms of increased ICP include:

- restlessness and headache;

[Box 11.4 Nerves at risk]

<table>
<thead>
<tr>
<th>Nerves at risk</th>
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</thead>
<tbody>
<tr>
<td>Cranial nerves VII–XII</td>
</tr>
<tr>
<td>Brachial plexus</td>
</tr>
<tr>
<td>Phrenic nerve</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve</td>
</tr>
<tr>
<td>Superior laryngeal nerve</td>
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<tr>
<td>Sympathetic chain</td>
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</tbody>
</table>

Figure 11.2 Local wound infection around stoma following laryngectomy.
Adherence to good basic surgical principle help decrease this risk, for example maintaining a sterile operative field, gentle tissue handling, precise use of cautery, keeping the flaps moist and careful drain placement. Gentle curved skin crease incisions and including platysma in the skin flap helps achieve good cosmesis and flap viability. Antibiotic prophylaxis confined to the perioperative period is recommended for contaminated/clean-contaminated head and neck surgery and usually consists of cephalosporin with or without metronidazole. Postoperative erythema and induration are common, especially in cases with previous irradiation, and in most cases resolve over a few days. Cases with wound dehiscence need good nursing care in the form of wound culture, appropriate antibiotic therapy, regular saline dressing and optimizing nutritional status. We now have a wide variety of dressings which can be tailored for individual wounds to encourage healing. The principle in dealing with these wounds is to have a stepwise approach of initially clearing the infection, then encouraging granulation and finally inducing epithelialization. Chronic wound environment is characterized by disequilibrium between matrix-degrading enzymes and their inhibitors. Studies of basic fibroblast growth factor (bFGF) on irradiated endothelial cell cultures suggest that bFGF can be a potent inducer of repair. This has sparked interest in utilizing various growth factors for chronic wounds though clinical trials have shown mixed results.

**Pharyngocutaneous fistula**

The risk of pharyngocutaneous fistula remains high in cases undergoing laryngeal/hypopharyngeal/floor of mouth tumour resection, especially if they have had irradiation to these areas. Its incidence in the past ranged from 5 to 65 per cent while recent series have rates from 9 to 23 per cent. It remains the most common complication after major hypopharyngeal or laryngeal ablation (Figure 11.4). Early (<48 hours) postoperative fever has been shown to be a good predictor of future fistula and wound infection. This is clinically apparent 7–11 days after surgery as a tender erythematosus lower skin incision/flap with or without pyrexia and leukocytosis. Nasogastric/PEG feed, antibiotic and minimal debridement (if needed) leads to spontaneous healing of the majority (50–80 per cent).

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**Box 11.5 Signs of upper airway obstruction**

- Stridor/stertor
- Increased respiratory rate
- Use of accessory muscles of respiration
- Agitation/confusion
- Peripheral cyanosis
- Bradycardia;
- Increasing blood pressure;
- Facial cyanosis and swelling.

Treatment includes inducing an osmotic diuresis using intravenous mannitol, 200 mL of 25 per cent initially. A prompt diuresis will occur within 10–15 minutes and the ICP will start to reduce and the symptoms will improve. It is rare for mannitol to be needed again.

**Airway**

Upper airway obstruction should always be anticipated in head and neck surgery. The old aphorism ‘when you think about a tracheostomy, that’s the time to perform it’ still stands. Therefore, an elective tracheostomy should be considered prior to surgery in which there is a risk of significant tissue edema or bleeding. This controlled procedure is a more attractive scenario than an emergency tracheostomy under difficult circumstances, with progressive airway obstruction.

A system of staging upper airway obstruction can be used and may help determine best treatment. The staging system is clinically based and ranges from stage I: in which there are no subjective signs of shortness of breath, respiratory rate is normal and no stridor is present, to stage IV: in which the patient is cyanotic, has severe stridor and may eventually have cardiac arrest. In the presence of acute upper airway obstruction following head and neck surgery, initial medical treatment include humidified oxygen, systemic corticosteroids and nebulized adrenaline. Failure to improve or progression requires urgent airway intervention including either intubation, if considered safe and feasible, emergency cricothyroidotomy or tracheostomy. Signs of upper airway obstruction are shown in Box 11.5.

A critical part of tracheostomy is meticulous aftercare either on the ward, high-dependency unit or intensive care unit. Clearly document the type and fixation of the tube and the placement of tracheal stay-sutures (in case of tube displacement), as well as postoperative instructions including, suctioning and oxygen therapy (Figure 11.3).

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**Wound Healing**

Many patients with a head and neck lesion have high risk factors, i.e. malnutrition, preoperative radiation, poor oral hygiene, chronic infection, advanced age, necrotic tumour mass, anaemia and exposure to non-sterile cavities intraoperatively. This makes careful preoperative planning necessary to optimize these risk factors and minimize the problems associated with wound healing. Adherence to good basic surgical principle help decrease this risk, for example maintaining a sterile operative field, gentle tissue handling, precise use of cautery, keeping the flaps moist and careful drain placement. Gentle curved skin crease incisions and including platysma in the skin flap helps achieve good cosmesis and flap viability. Antibiotic prophylaxis confined to the perioperative period is recommended for contaminated/clean-contaminated head and neck surgery and usually consists of cephalosporin with or without metronidazole.

Postoperative erythema and induration are common, especially in cases with previous irradiation, and in most cases resolve over a few days. Cases with wound dehiscence need good nursing care in the form of wound culture, appropriate antibiotic therapy, regular saline dressing and optimizing nutritional status. We now have a wide variety of dressings which can be tailored for individual wounds to encourage healing. The principle in dealing with these wounds is to have a stepwise approach of initially clearing the infection, then encouraging granulation and finally inducing epithelialization. Chronic wound environment is characterized by disequilibrium between matrix-degrading enzymes and their inhibitors. Studies of basic fibroblast growth factor (bFGF) on irradiated endothelial cell cultures suggest that bFGF can be a potent inducer of repair. This has sparked interest in utilizing various growth factors for chronic wounds though clinical trials have shown mixed results.
of small fistulas by secondary intention. A cuffed tracheostomy tube may be needed if the fistula tract is close to the tracheostome. Contrast swallow or methylene blue dye swallow is performed to assess the leak (Figure 11.5). Conservative management may fail due to residual/recurrent tumour, massive fistula with extensive mucosal dehiscence, poor general status or concomitant metabolic problems of the patient. After addressing the general health of the patient, one can consider delayed closure in the presence of healthy granulation tissue. Pectoralis major or latissimus dorsi myocutaneous flaps remain the preferred option for this though free flaps can also be used (Figure 11.6). Patients with exposed major vessels are an exception as they need urgent cover with vascularized local, pedicled or free flap to prevent vascular blow out.

**FLAPS: GENERAL CONSIDERATIONS**

Economic and functional analysis of patients undergoing head and neck surgery suggests that the best outcome results from primary closure wherever possible. However, in situations where this is impractical, the modern surgeon has an option of wide ranging flaps. Reconstruction of head and neck defect with pedicled flap or microvascular free tissue transfer has become commonplace in the last two decades, but unfortunately has also led to an increase in complications particular to them. Not surprisingly, patients with poor cardiopulmonary or vascular health undergoing tissue transfer can translate into longer intensive care, total hospital stay, increased medical complications and higher rates of mortality. Given these issues the optimum management of flap complications remains their prevention.

**Local skin flaps**

Most local (except nasolabial) and free skin flaps are based on a random-pattern blood supply referring to anastomoses found within the dermis and subdermal plexus. These have AV shunts (precapillary communications between the arterial and venous circulations) that allow blood to bypass the capillary bed. However, complete opening of these AV shunts can direct blood away from the nutrient capillary bed and compromise the viability of the distal flap despite normal or even increased total blood flow. The previously taught length–width ratio is only a rough guideline, and it cannot be relied on as an absolute determinant of flap success. A variety of factors may cause a skin flap to fail, with necrosis of all or part. The most common cause of flap failure is vascular insufficiency due to excessive length (with a random blood supply) or excessive tension. Vasoconstrictors such as nicotine (hence consider delaying surgery in smokers),
epinephrine and dopamine may also affect viability.\textsuperscript{54} Underlying haematoma or seroma can cause flap necrosis due to increased wound tension, pressure on feeding vessels and vasoconstriction resulting from breakdown products. Therefore, ensuring adequate haemostasis and securing a dressing (e.g. acroflavin soaked cotton wool) with overlying ties can help prevent this complication. It is also important to control factors such as diabetes, hypertension and infection, and avoid compression of the flap pedicle as these are known to affect viability.

**Locoregional myocutaneous flap**

Historically, locoregional flaps (LRF) such as pectoralis, trapezius and latissimus dorsi were commonly used and often described as the ‘workhorse’ of reconstruction. Pectoralis major myocutaneous flap remains the most commonly used LRF and a large series reported a complication rate of 35 per cent including dehiscence, haematoma and infection in relation to a number of comorbidities, smoking and oral cavity reconstruction.\textsuperscript{55} Partial muscle or cutaneous necrosis can result as the distal portion of an LRF is one angiosome distal to its vascular territory and is seen in 14–29 per cent of cases\textsuperscript{53} (Figure 11.7). However, complete flap loss is rare, occurring in less than 10 per cent of cases.\textsuperscript{33} Partial or total

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**Figure 11.6** (a) Pharyngocutaneous fistula; (b) mobilized pectoralis major flap; (c) healed pectoralis major flap in place post-operatively.

**Figure 11.7** Failing distal end of pectoralis major myocutaneous flap. Notice the bluish mottled appearance.
loss can result in dehiscence, frequently leading to fistula.\textsuperscript{53} Irrespective of the choice of any flap, pedicled or free, a comprehensive understanding of vascular anatomy is essential to ensure flap survival and achieving the best possible functional and aesthetic results. Minimizing skin and subcutaneous tissue avulsion, avoiding inwardly bevelled skin incisions, and identifying and preserving vascular pedicle are all essential towards this end. It is critical to avoid undue compression, tension or kinking of vascular pedicle when insetting the flap.\textsuperscript{53}

**Free tissue transfer**

The development of microvascular techniques has led to the frequent use of free tissue transfer (FTT) in reconstructing head and neck defects. Compared to LRF, any advantage in terms of functional and aesthetic outcome still remains a topic of debate. Overall complication rates between LRF and FTT have recently been shown to be equivalent. LRFs tend to have late wound breakdown while FTTs are associated with early complications.\textsuperscript{56} Recent series have shown failure rates for FTT ranging from 1 to 8 per cent.\textsuperscript{57} Prior radiation, atherosclerosis, smoking, sepsis, advanced age and poor surgical technique are associated with failure of FTT.\textsuperscript{33} Use of the operating microscope or surgical loupes helps achieve good microvascular anastomosis and some authors have reported comparable results while utilizing anastomotic coupling devices.\textsuperscript{58} Ensuring adequate donor and recipient vessels is important. LRFs are typically associated with minimal donor site morbidity while this varies considerably for FTT, skin graft failures and sensory loss being the most commonly encountered problems.\textsuperscript{53} Preoperative clinical (e.g. objective Allen’s test) and/or noninvasive vascular assessment (colour flow Doppler evaluation) can dramatically improve donor site morbidity during FTT. Monitoring free flaps is critical as timely intervention is directly related to successful salvage.\textsuperscript{58} The gold standard for non-buried flap monitoring is clinical observation. Cold, white and non-blanching flaps are indicators of arterial insufficiency while the more common venous insufficiency is marked by a swollen, bluish flap with dark blood on pin-prick testing. Objective tests for monitoring flaps include hand-held Doppler, surface temperature probe, impedance plethysmography, photoplethysmography, micro-lightguide spectrophotometer and more recently implantable Cook–Swartz Doppler probes. Early recognition of a failing flap with return to theatre within 24 hours postoperatively has superior salvage rates than cases delayed beyond 24 hours.\textsuperscript{59} Timely re-exploration and revascularizing of a failing flap is critical for its salvage. One series reported the median time of return to theatre is 60 minutes in successful salvage, while this was 105 minutes for failed ones.\textsuperscript{59} Venous congestion has also been managed with leeches.\textsuperscript{60}

### Complications and their management

**LASERS**

Meticulous safety precautions during use of the CO\textsubscript{2} laser in head and neck surgery will minimize the risk of laser complications. The use of laser-safe anaesthetic tubes, clear communication with your anaesthetist and protection of the patient with moist towels and swabs is imperative.\textsuperscript{61} The complications from CO\textsubscript{2} laser arise either directly from the laser beam itself or from the reflected beam. In addition, late effects of laser surgery can occur.

A laser fire occurs if the three components of fire exist together: a source of ignition (laser); flammable material (tubes, swabs); and oxygen (air and anaesthetic gases).

Strict precautions as above should be taken prior to laser use. In the event of an airway fire consider the steps in **Box 11.6**.\textsuperscript{62} Direct laser damage to other tissues, such as skin or eyes, requires appropriate topical treatment such as antibiotic cream or ointment.

Early postoperative complications of laser use include the development of oedema with possible airway compromise. Close monitoring of the airway is required and administration of intravenous steroids (e.g. dexamethasone 8 mg twice a day) for the first 24 hours postoperatively. Progressive airway obstruction may require reintubation or indeed tracheostomy.

Late complications from the laser include web formation and airway stenosis.\textsuperscript{63} Management of webs and stenoses can be very challenging and may require resection and reconstructive procedures. Some success has been reported with the use of topical mitomycin C following division of webs and stenotic segments in the upper airway.\textsuperscript{64}

### COMPLICATIONS OF RADIOThERAPY AND CHEMOTHERAPY

The use of radical radiotherapy with or without additional chemotherapeutic agents is commonly associated with significant morbidity and occasionally mortality. The basic principle of treatment with radiotherapy is to maximize the chance of cure by delivering a high dose of ionizing radiation to the tumour and any occult extension. Allowance is made for microscopic extension not seen on planning imaging by incorporating a margin of presumed extension together with a further margin of expected normal tissue. It is inevitable that normal cells will be unavoidably affected by the treatment, producing unwanted toxicities. Generally, these complications can be considered as acute (early complications arising during or shortly after treatment has ended) or late (generally permanent) (see **Box 11.7**). The normal tissues affected most by chemotherapy and radiotherapy are those with the highest rate of cellular
Radiation of the head and neck can cause irreversible damage to skin, mucosal surfaces, salivary gland tissue, vasculature, muscle and bone.

### Skin effects

With conventional fractionated radiation therapy, cutaneous erythema develops in the irradiated area about 2–3 weeks into the treatment regime. This may progress to skin peeling or dry desquamation. Pruritus is common and the induced scratching may result in skin breakdown with infection. With higher doses to the skin, blistering can occur with moist desquamation. This usually settles within one month of completion of the treatment. Secondary infection may occur in areas of moist desquamation. It is important to keep these areas clean and avoid abrasion. Hair loss occurs in the treated area after about 3 weeks. This is usually transient unless the radiation dose to the skin is above 50 Gy with regrowth expected to start in the region of three months after the end of the treatment. Increased suntan-like pigmentation may occur in the treated area. It is important to warn patients what to expect and thus to avoid rubbing, scratching or scratching. Soaps and cosmetics should not be applied to the treated areas and washing should be with lukewarm water only. Wet shaving is not recommended but use of an electric razor is permitted. Skin should be protected from sun exposure both during the treatment and lifelong afterwards.

The late effects of radiotherapy on the skin include atrophy, telangiectasia, hypopigmentation and fibrosis. The risk of a skin cancer developing in a radiotherapy field is increased permanently.

### Mucosal effects

The upper aerodigestive tract mucosa is highly susceptible to toxicity from radiotherapy and chemotherapy because of the high cellular turnover, the diverse and complex microflora and trauma associated with normal mastication and swallowing. The early reaction of mucosa to treatment is similar to skin. Mucositis is the term devised for the inflammatory response which has been graded by the Radiation Therapy Oncology Group (see Box 11.8).

Virtually all patients undergoing radiotherapy (with or without additional chemotherapy) will develop a grade 1 or 2 mucositis. High grade toxic effects are greater with concurrent chemotherapy regimes and, in particular, mucosal toxicity of concurrent radiotherapy and cisplatin is almost twice as much compared with radiotherapy given as a single modality or with induction chemotherapy. The first signs of mucosal damage with chemotherapy arise within the first few days of therapy but with radiation alone the changes are seen after 1–2 weeks. The mucosa becomes reddened and oedematous. Pain is initially mild, becoming more severe and requiring analgesia with the inflammatory serosanguinous discharge associated with grade 2 mucositis. Grade 3 mucositis may require opioid analgesia. The onset of significant pain results in compromised chewing and swallowing and adequate analgesia is very important. Otherwise, the pain effects on oral intake may lead to significant dehydration and weight loss. Taste disturbance and altered, unpleasant oral sensation is common and may enhance the anorexic effects of the pain. Swallowing is also compromised by the xerostomia due to salivary gland dysfunction arising from the direct effects of radiotherapy on these tissues. Input from the dietetic service is essential. Initially, the patient may have to change from a solid to soft diet and oral nutritional supplements may be required. It is common practice in those receiving chemo-radiotherapy to have a PEG inserted prior to treatment in anticipation of significant compromise in oral feeding with the need for an alternative route for enteral nutrition. Severe mucosal toxicity can compromise treatment protocols. At times the reactions are so severe as to require a temporary unplanned break in the therapy or even complete cessation. Any reduction in treatment or alteration in the schedule because of severe mucosal morbidity adversely affects patient survival rates.

Acute mucosal reaction with oedema in the larynx may lead to hoarseness of the voice where it is not already compromised by disease. The mucositis may also result in a compromised airway in a patient where there is already narrowing produced by a tumour. This should be anticipated by the surgeon with possible intervention by laser debulking in advance of definitive treatment and awareness that a tracheostomy may become necessary.

Management of these early complications requires appropriate patient education, the optimization of the oral region by pretreatment intervention and prompt treatment of acute lesions resulting from the treatment. Pretreatment interventions include dental assessment and intervention to ensure optimal dental status and oral hygiene (that may include extraction of carious teeth if repair is not possible), input from dieticians and possible placement of a PEG tube.

### Dental effects

The risk of dental caries increases following radiotherapy and chemotherapy. This is due to altered saliva production, a change in the oral flora and loss of mineralizing components.
When radiotherapy doses exceed 54 Gy the resulting xerostomia is often irreversible. The saliva that is produced is more viscous and some of the lubricating effects of saliva are lost. The buffering capacity of saliva is reduced and the oral flora becomes more pathogenic. Patients must maintain excellent oral hygiene to avoid plaque accumulation and avoid periodontal disease. Plaque removal by brushing and flossing is essential. The use of high concentration fluorides is advocated and topical antimicrobial rinses are available. Saliva substitutes are available to help the symptom of xerostomia. The patient should attend a dental practitioner to ensure elimination of oral disease before cancer therapy.

### Vascular effects and tissue necrosis

Initial effects of vascular inflammation and fibrosis associated with therapy may lead to long-term problems with tissue hypovascularity and hypoxia. Trauma and injury, including surgical and dental procedures, may result in non-healing areas with necrosis and there is a risk of secondary infection. The mandible is susceptible to osteoradionecrosis because of the unilateral nature of its blood supply compared with the maxilla.67 The need for pre-therapy and subsequent dental care has been highlighted above. When bone exposure occurs, coverage with mucosal or vascularized tissue is required. Presenting features of osteoradionecrosis include pain, reduced sensation, fistula, infection and pathologic fracture. Hyperbaric oxygen therapy has been used to treat bone necrosis and is thought to help by increasing tissue oxygenation and increase angiogenesis.68 Availability of this treatment is often limited and patients may have to travel considerable distances to have their therapy. In non-responsive or severe cases a partial mandibular resection of sequestered bone may be required with free tissue reconstruction to maintain function and help cosmesis. Radionecrosis may also affect the skull base. Fortunately this is a rare, but potentially very serious, complication. Presentations include cacosmia, epistaxis, ear discharge and headache. This can progress to meningitis, blindness, lower cranial nerve dysfunction and carotid artery haemorrhage.

Where soft tissue fibrosis occurs in the region of the mandible the functional result may be significant trismus. These changes should be anticipated or identified as early as possible to limit progression of the trismus. Patient interventions include mandibular stretching exercises and the use of prosthetic aids.

The cartilages of the larynx may also develop chondro-radionecrosis as a delayed complication (Figure 11.8). The incidence of this complication has reduced over time to reflect the improved management of the oral cavity.69 Radiotherapy to the larynx may result in oedema, perichondritis and frank cartilage necrosis. Symptoms mimic those of cancer recurrence and this may present a diagnostic dilemma. Conservative treatments include use of antibiotics and steroids with humidification. There appears to be a role for hyperbaric oxygen therapy which may avoid the need for total laryngectomy.70

### Hypothyroidism

Hypothyroidism can develop years after radiotherapy to the neck in up to 25 per cent of patients treated. This possibility is increased if there has also been some surgical intervention that included partial removal of the thyroid gland. It is wise to check thyroid function routinely in those at risk. Thyroid replacement therapy should be started if the TSH level is elevated, even if the free thyroxine level is normal, as compensated hypothyroidism may lead to overt myxoedema.

### Visual effects

The lens of the eye is one of the most radiosensitive structures in the body and doses of radiation as low as 6 Gy may result in cataract formation. Radiation planning takes account of this fact, however it may not be possible to avoid this dosage and if this is the case then the patient should be warned beforehand and made aware that this can be corrected surgically. The retina is relatively radioresistant but the optic nerve and chiasm are sensitive to radiation. Ultimately there is a trade off between maximizing cure and avoiding blindness. Fortunately irreversible visual loss is unusual in head and neck malignancies but can arise, for example, when treating sinonasal tumours invading the orbit.

**Figure 11.8** Non-cuffed Shiley tracheostomy tube *in situ*.

### KEY EVIDENCE

- Smoking cessation has a positive effect on postoperative wound healing.3
- The creation of a tracheostomy or tracheotomy significantly increases the patients’ vulnerability to postoperative pneumonia.11
- Patients undergoing total thyroidectomy should commence thyroxine prior to discharge from hospital.27
- Increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infection are important sources of infection complicating the postoperative recovery.40, 41, 52, 43
- The intracranial pressure (ICP) can rise three-fold when one internal jugular vein is divided and five-fold when both are tied.
The ability to recognize the complications at an early stage in order to initiate prompt and effective management is critical for favourable outcome. This, in turn, depends on awareness and careful postoperative assessment.

Rigorous audit of complications is imperative for identifying areas in patient care that could improve outcome.

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PART TWO

BENIGN DISEASE

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Benign neck disease

RICARD SIMO AND JEAN-PIERRE JEANNON

To study the phenomenon of disease without books is to sail an unchartered sea, while to study books without patients is not to go to sea at all.

Sir William Osler

INTRODUCTION

Neck masses present commonly to clinicians. In the adult population, approximately 80 per cent of non-thyroid neck masses are neoplastic, and of these 80 per cent are metastatic, and in 75 per cent of these metastatic masses, the primary index tumours is located above the clavicle. In children under 15 years, 90 per cent of neck masses are benign and of these up to 55 per cent may be congenital.

Benign neck masses can be classified as congenital and acquired. The latter group are often enlarged lymphadenopathies, but there may be a wide range of different pathologies involved causing their swelling. The introduction of the fine needle aspiration biopsy/cytology (FNAB/FNAC) with or without the use of ultrasound scanning (USS) guidance has revolutionized the management of neck lumps and has now become the gold standard investigation.

The evaluation and management of patients who present with a neck lump, should have a systematic and uncompromising clinical approach. This must include a thorough history, examination of the external and internal head and neck, followed by relevant investigations, which may include bloods tests and radiological imaging.

History

The history should include the age, sex, past medical history, travel abroad, the mode of onset and duration of the mass, associated symptoms including dysphonia, dysphagia, odynophagia, sore throat, referred otalgia, nasal obstruction, cranial nerve neuropathies, weight loss, anorexia, malaise and night sweats.

Examination

The examination should include an inspection of the skin over the skull, face and neck, and of the ears, nose, oral cavity and oropharynx. The fiberoptic endoscope should be used to inspect the nasal cavity, nasopharynx, oropharynx, larynx and hypopharynx. The neck should be examined in a systematic fashion and the number, size, site, shape, texture and involvement of the skin and the deep cervical structures noted. Additionally, while concentrating on the head and neck as a source to explain the presence of a neck mass, it is frequently worth extending the general physical examination to include the chest and breasts in women, including the axillae.

Investigations

The investigations of patient with neck lumps should be tailored to each individual case and it would not be appropriate for all patients to have all possible available investigations. All patients with neck lumps should have as a minimum a full blood count (FBC), chest x-ray and FNAB/FNAC.
If an inflammatory mass is suspected, especially in a young patient, the above investigations together with an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Epstein–Barr virus and cytomegalovirus titres, liver function tests, lactic dehydrogenase (LDH) test, brucella and toxoplasma serology may be advisable.

Once a clinical or tissue diagnosis has been made, it is possible to determine what if any further tests or imaging is required. If the diagnosis is infective or inflammatory a plain chest x-ray or no further imaging may be required. If a neoplastic lesion is diagnosed, computed tomography (CT) scanning, magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning alone or a combination may be performed to determine the exact anatomical location, extent and radiological staging of the lesion.

A basic understanding of the different pathologies in patients presenting with a neck lump is essential to direct adequate investigations and conclude an accurate working diagnosis without compromising the patient’s clinical outcome. Occasionally, one needs to be very conscious that a working diagnosis may be incorrect, so it is paramount that patients are reviewed frequently during the early stages, to come. Occasionally, one needs to be very conscious that a diagnosis without compromising the patient’s clinical outcome may be incorrect, so it is paramount that patients are reviewed frequently during the early stages, to ensure resolution of the mass, if that is what is anticipated, or refer onwards to a specialist or second opinion if the anticipated diagnosis has not been confirmed, or doubt of diagnostic accuracy persists.

Aetiology

The lymphatic system arises from five primitive sacs (two jugular sacs, two posterior sciatic sacs and a single retroperitoneal sac) developed from the venous system. From these, endothelial buds extend centrifugally to form the peripheral lymphatic system. Two principal theories have been postulated to explain the origin of the lymphangiomas:

1. **Sequestration of lymphatic tissue** derived from segments of the primitive sacs which retain the proliferative growth potential and bear no connection with the normal lymphatic system.

2. **Endothelial fibrillar membrane proliferation** from the walls of the cyst, penetrate the surrounding tissue along the lines of least resistance between muscles and vessels, canalize and produce more cysts.

Clinical features

Although congenital and in the majority of cases present at birth, sometimes they can manifest for the first time in young adults. They can appear anywhere in the head and neck. To palpation, they feel cystic and transilluminate. They may remain static or involute, but in some cases they may gradually increase in size and occasionally, especially after internal haemorrhage or infection, can grow rapidly potentially risking pressure on the respiratory system possibly leading to a life-threatening airway compromise or obstruction.

Diagnosis and investigations

The diagnosis is usually made on clinical grounds, but CT and MRI scanning will more accurately determine the size, the exact anatomical location, its relationship with important structures and aid the surgical planning.

Treatment

The treatment of these lesions is difficult and challenging and many methods of treatment have been described over the years. The treatment strategy varies depending on the anatomical location, size and involvement of the surrounding structures. Observation has been proposed by Broomhead (1964) as up to 15 per cent of patients may have spontaneous regression. Repeated aspirations may be helpful in the event of rapid increase in size causing pressure symptoms, while awaiting definitive treatment. Injection of sclerosants, such as bleomycin, tetracyclines and alcohol, has been suggested, but internal scarring is reported to be unpredictable resulting in difficulty with any subsequent surgery and it is not currently recommended. The intralesional injection of OK-432 (Picibanil®) has shown promising results. It causes an inflammatory reaction thrombosis with subsequent necrosis. Surgical excision remains the treatment of choice, but it is challenging and it should be therefore, best undertaken by experienced surgeons in specialist centres. Surgery can be helped by the injection of tissue blue into the lymphatic spaces (Figure 12.1).

Dermoid cysts

Dermoid cysts are classified as epidermoid, true dermoid and teratoid cysts depending on the types of tissues identified pathologically within them. Twenty per cent of all dermoid cysts are found in the neck and 30 per cent of these in the face. They make up 28 per cent of all midline cysts, with no sex predominance.

- **Epidermoid cysts** contain only skin, but no other adnexal structures. They are lined with squamous epithelium with or without keratinous material. These are the most commonly encountered variety.
True dermoids cysts are lined with squamous epithelium and contain skin with appendages such as hair, hair follicles, sebaceous glands and sweat glands. Teratoid cysts are lined either with squamous or respiratory epithelium. They contain all three embryological elements: ectodermal, endodermal and mesodermal elements, such as nails, teeth, brain and glandular tissue.

Aetiology

These lesions develop as a consequence of ectodermal differentiation of multipotential cells trapped at the time of closure of the anterior neuropore, especially along the lines of fusion, hence their being located along the midline of the neck. In the head and neck, other areas of tissue fusion may present with dermoid cysts, outer angular dermoids and the nasal dorsum.

Clinical features

The peak age of incidence is usually the second and third decade. They can present as cystic or solid painless mass, usually in the submental region, above or below the mylohyoid muscle. More infrequently, they can manifest as an inflammatory swelling (Figure 12.2).

Diagnosis and investigations

The diagnosis is usually based on the patient’s age, the clinical location and presentation. Ultrasound-guided fine needle aspiration cytology (FNAC) may be useful in the diagnosis of these lesions. Cross-sectional imaging, such as CT and MRI may be useful when there is a large lesion, to aid surgical planning.

Thyroglossal duct cysts

Thyroglossal cysts are the most common upper neck midline lesions. They can present as a mass or a lump, at any level between the foramen caecum and the upper mediastinum, with the majority presenting about the level of the hyoid bone. They are usually sporadic, but a rare familial variant has been documented, identified as an autosomal dominant in prepubertal girls. Thyroglossal duct carcinoma, although rare, may present and be identified by the pathologist in a thyroglossal duct cyst (see Chapter 23, Surgical treatment of differentiated thyroid cancer).

Aetiology

Embryologically, the thyroid gland originates from the floor of the primitive pharynx between the first and second pharyngeal pouches. In addition to the major median enlage, there are smaller paired lateral enlarges, which contribute to the parafollicular or calcitonin-secreting C cells. The median enlage loses its lumen at about the 5th week of gestation and breaks into fragments, the lower end dividing into two portions that become the lobes of the thyroid gland. Thyroglossal duct cysts arise from epithelial cells when they cease to remain inactive. The stalk should atrophy during the 6th week, but should it persist as a patent tract, then it becomes a thyroglossal duct along which cysts can develop. It may run from the thyroid gland inferiorly, upwards and in the region of the hyoid bone, the tract may be located behind, through or in front of the bone, ending deeply in the junction of the anterior two-thirds and posterior third of the tongue, at the foramen caecum area of the tongue. The methods involved for the development of cystic changes is not fully understood. A fistula is usually caused by spontaneous drainage of an abscess or more commonly resulting following an attempted drainage of a misdiagnosed midline neck abscess or resulting from an inadequate attempt at excision usually associated with leaving an intact hyoid bone.

Figure 12.1 Operative picture of a lymphangioma of the supraclavicular region.

Figure 12.2 Dermoid cyst.
Clinical features

Ninety-five per cent of thyroglossal cysts present as an asymptomatic cystic mass at or about the level of the hyoid bone. The mass moves on swallowing or on protrusion of the tongue. Up to 5 per cent of these cysts present as an acute inflammatory episode with or without an infection, and 15 per cent may have an associated discharging fistula. There is no sex preponderance. The mean age of presentation is five years with a range between four months to old age. Ninety per cent are in the midline, but 10 per cent may be to one or other side, with 95 per cent of these being in the left side. Seventy-five per cent are prehyoid, with the remaining 25 per cent being located above or below the hyoid, and can sometimes be found within the mediastinum (Figure 12.3).

Diagnosis and investigations

Patients with suspected thyroglossal duct cysts should be investigated with thyroid-stimulating hormone (TSH) estimation and ultrasound-guided FNAC. TSH and T4 will determine the thyroid status of the patient. Ultrasound scanning may help with the location and diagnosis of the cyst, and will also confirm the presence of a normal thyroid gland in its anatomical position. FNAC will demonstrate cystic contents containing colloid. Isotope scan either 99mTc or 123I may be useful if the cyst is located above the hyoid or in the posterior tongue or to identify and exclude the possibility of a lingual thyroid. CT scanning or MRI should be considered in the presence of large cysts, when malignancy is suspected and when the possibility of a lingual thyroid has been considered.

Treatment

Surgical excision is the treatment of choice, as there is always a risk that these cysts could become infected, resulting in scarring of the neck skin and development of recurrent episodes of the cyst enlarging, causing patient discomfort. The Sistrunk procedure was described in 1920, which resulted in cure in the majority of cases. Previously, the hyoid bone was not excised which resulted in a large percentage of recurrences associated with infections. A modification of Sistrunk’s technique is currently being employed as the standard surgical procedure without the need to excise the tongue base epithelium. The excision is performed through a transverse midline neck incision just below the cyst. In the common thyroglossal duct cyst, the lesion is dissected from the infrahyoid strap neck muscles and the laryngeal cartilages. Then, the dissection proceeds upwards to the region of the hyoid bone. At this point, the suprahyoid muscles, mylohyoid, geniohyoid and genioglossus muscles, are detached from the hyoid bone and the middle third of the hyoid bone between the lesser cornu is cut and mobilized in continuity with the soft tissue specimen, which includes the thyroglossal duct cyst. The completion of the surgery involves further dissection upwards, into the tongue base to include an excision of a core of tissue which should include a tissue tract or raphe between the mylohyoid muscles, a portion of each genioglossus muscle and up to the area of the foramen caecum. This technique has resulted in a significant reduction of the recurrence rates when compared with a simple excision or removal of the cyst alone (Shalang procedure).25, 26, 27, 28, 29, 30, 31, 32, 33, 34

Treatment of recurrent cysts and fistulae

Up to 8 per cent of thyroglossal cysts may recur following adequate surgical excision. If a substandard excision, with no excision of the hyoid bone, has been carried out, a full Sistrunk’s procedure should be undertaken. However, if a full Sistrunk’s procedure has been carried out, further surgery may be difficult. In these cases, the previous incision scar should be excised, with a full central compartment neck dissection and excision of the scar tissue up to the foramen caecum.25, 26, 27, 28, 29, 30, 31, 32, 33, 34

Branchial cysts

The word ‘branchial’ is derived from the Greek bragchia meaning gills. Branchial cysts appear as a developmental failure of the branchial apparatus. Branchial anomalies account for up to 17 per cent of all paediatric cervical masses. They often manifest in young adults with an incidence peak in the third decade. Cysts are usually lined by stratified squamous epithelium, except in 10 per cent of cases where they may have respiratory epithelium. Eighty per cent have lymphoid tissue in their outer wall and they contain straw-coloured fluid in which cholesterol crystals are found.

Aetiology

Four theories have been suggested to explain the origin of branchial cysts.
1. **Branchial apparatus theory.** This theory suggests that branchial cysts represent the remains of pharyngeal pouches or branchial clefts, or a fusion of these two elements. The development of the branchial apparatus extends from the 3rd to the 8th week of gestation. This theory should suggest that cysts should be present at birth, whereas the peak of incidence is usually the second to third decade.

2. **Cervical sinus theory.** This theory advocates that branchial cysts represent the remains of the cervical sinus of His, which is formed by the second arch growing down to meet the fifth arch. The second arch mesoderm almost covers the neck entirely and forms the platysma muscle.

3. **Thymopharyngeal duct theory.** This theory suggests that the cysts are remnants of the original connection between the thymus and the third branchial pouch from which it originates. However, a persistent thymic duct has never been described and there has never been a branchial cyst found deep to the thyroid gland.

4. **Inclusion theory.** This theory postulates that branchial cysts are epithelial inclusions within a lymph node. This theory is supported by the fact that most branchial cysts have lymphoid tissue in their wall and have been reported in the parotid and the pharynx. This theory also explains why most branchial cysts have no internal opening, that the peak of age incidence is later than for a congenital lesion and that it is almost unknown in neonates.

### Clinical features

Sixty per cent of branchial cysts are located in the upper third of the neck, at the anterior margin of the sternocleidomastoid muscle, although they have been reported in any site of the neck or parotid gland. Eighty per cent are said to present as persistent and 20 per cent are intermittent swelling. Seventy per cent are clinically cystic, although up to 30 per cent may feel solid. In up to 40 per cent of cases, patients may have had an upper respiratory tract infection prior to noticing the mass. Inflamed cysts may complicate with abscess formation with the possibility of rupture (Figure 12.4).

### Diagnosis and investigations

All patients with a suspected branchial cyst should be investigated with at least an FBC and ultrasound-guided FNAC. Ultrasound-guided FNAC yields acellular fluid with cholesterol crystals on microscopy examination. However, cytological findings should be taken with caution as squamous debris may suggest the possibility of malignancy. If lymph nodes are necrotic, as is seen in squamous cell carcinoma and tuberculosis, they may be difficult to distinguish sonographically from a second branchial cleft cyst, but FNAB is usually helpful. CT scanning and MRI are useful investigations in large cysts (Figure 12.5) to allow surgical planning.

### Treatment

Surgical excision is the treatment of choice. This is indicated as cysts have a tendency to become infected, can enlarge to a large size causing local discomfort, pressure symptoms and obvious cosmetic deformity. The procedure is initiated by a transverse cervical incision made on the neck skin crest overlying the cyst. The platysma is incised and subplatysmal flaps are elevated. The cervical fascia is incised over the anterior border of the sternocleidomastoid muscle, which is retracted laterally. The cyst is then identified and dissected from its fascial attachments and capsule, ensuring that the cyst wall is not ruptured. During the dissection, the carotid sheath and its contents should be identified and mobilized out of the surgical area. Also, the marginal branch of the facial nerve, vagus, accessory and hypoglossal nerves should be identified and preserved. The cyst is excised completely and there is usually no need to look for a tract, although the tail of the cyst may need to be dissected from the tail of the parotid gland or parapharyngeal space.

### Branchial fistulae and sinuses

Branchial fistulae are congenital defects consisting of a skin-lined tract, opening internally as a slit on the anterior aspect of the tonsillar fossa if it is of second arch origin. The external
opening is at the anterior border of the sternocleidomastoid muscle, at the junction of its middle and lower thirds. Branchial sinuses or branchial pits open along a line between the tragus and the sternoclavicular joint at the anterior border of the sternocleidomastoid muscle, but with no internal opening.

**Aetiology**

They arise as a failure of completion of development of the branchial apparatus including the first, second, third and fourth arches. During the 4th week of intrauterine life, six branchial arches develop as neural crest cells migrate cranially. During the 5th week, the second branchial arch grows over the third and fourth branchial clefts, which form a cervical sinus. Failure of the cervical sinus to close may therefore potentially communicate with the second branchial pouch in the area of the tonsil fossa, the third pouch in the area of the larynx and the fourth pouch opening in the piriform fossa.

**Clinical features**

They present almost always in young infants as a discharging sinus which may or may not have an internal fistulous opening. Clinically, second branchial cleft fistulae are the most common. They have a cutaneous opening along the anterior border of the sternocleidomastoid, usually at the junction of the middle and lower thirds, tracking up between the internal and external carotid arteries ending in the tonsillar fossa. Third and fourth branchial fistulae are more rare, opening low in the neck and ending in the piriform sinus.

**Diagnosis and investigations**

The diagnosis is made on clinical grounds. A CT fistulogram may be helpful to determine the pathway of the tract, differentiate a sinus from a fistula and aid surgical planning (Figure 12.6).

**Treatment**

Surgical excision is the treatment of choice. The excision is performed in a stepladder fashion, removing the mouth of the sinus with an ellipse of neck skin. The tract is followed upwards as high as possible and then another transverse cervical or cervicofacial incision is made. The dissection is then continued to the tonsillar area where the tract usually disappears and should be ligated before it avulses to minimize a recurrence of symptoms (Figure 12.7).43, 44, 45

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**ACQUIRED BENIGN NECK DISEASES AND MASSES**

**Non-inflammatory neck masses**

**SEBACEOUS CYSTS**

Sebaceous cysts are skin appendages or lesions occurring mainly where there are sebaceous glands and are most common in hairy skins, particularly in the beard region and scalp.

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*Figure 12.6* Fistulogram of a left branchial fistula.

*Figure 12.7* Left branchial fistula tract emerging between the constrictor muscles.
accumulate in the centre to form a sebaceous horn and they also have a tendency to become infected.

**Diagnosis and investigations**

Sebaceous cysts often display very distinct clinical features and rarely require investigations. They have a non-specific sonographic appearance and FNAB/FNAC is best avoided.

**Treatment**

Surgical excision is the treatment of choice as they are unsightly, have a tendency to grow, burst, become infected and reoccur. The excision should be performed very carefully ensuring that the punctum – and the scar if they have been previously incised and drained due to infection – is excised with a small ellipse of healthy skin to avoid leaving part of the capsule of the cyst which will lead to the recurrence of the lesion.46

**ACQUIRED DERMOID CYSTS (IMPLANTATION DERMOMS)**

Dermoid cysts are usually solitary, with solid and cystic areas containing skin appendages.

**Aetiology**

Acquired dermoids occur due to a penetrating injury or following surgery resulting in the implantation of dermal or skin structures deep into the subcutaneous tissue.

**Clinical features**

These cysts present at the site of a penetrating injury and often display solid and cystic areas containing sebaceous material.

**Diagnosis and investigations**

The diagnosis is often made on clinical grounds; however, ultrasound-guided FNAC may be helpful in some cases where the history of injury is not clear.

**Treatment**

Surgical excision is the treatment of choice. The incision should include the injury tract which should be completely excised in continuity with the cyst to avoid recurrence.47

**PILOMATRIXOMA OR CALCIFIYING EPITHELIOMA OF MALHERBE**

Pilomatrixoma is a benign tumour of the prickle cell layer of the skin, first described by Malherbe and Chenantais in 1880 as a calcified epithelioma. It is most frequently seen in the first two decades of life with two-thirds of these occurring in patients under ten years of age and it is more common in females with a female to male ratio of 3:2. The majority of these tumours (68 per cent) occur in the head and neck region. Malignant transformation has been described, but is very rare.

**Aetiology**

The aetiology is unknown, although an episode of local inflammation or trauma may precede their development.

**Clinical features**

Pilomatrixomas are usually solitary and present as a firm, nodular superficial lesion measuring up to 3 cm in size. There is usually no discoloration, but if situated very superficially a blue-red colour may be seen (Figure 12.8).

**Diagnosis and investigations**

Pilomatrixomas have very distinct clinical features. If the diagnosis is suspected, FNAC can be performed. Cytopathological features include the identification of basaloid and squamous cells, calcium deposits and foreign body giant cells.

**Treatment**

Surgical excision is the treatment of choice if the lesion is bothersome or there is doubt about diagnosis. The excision must be carefully performed in the same manner as for an epidermoid cyst, as leaving part of the capsule will result in the recurrence of the lesion.48, 49

**LIPOMAS**

Lipomas are benign lesions of the adipose layer. The adipose cells are organized into large lobules divided by loose fibrous septa. Lipomas can be multiple and occasionally can be painful (Dercum disease). Although the majority of lipomas are sporadic, a minority can be familial. The most common familial lipomatosis affecting the head and neck is Madelung’s lipomatosis. In the neck region, lipomas may be subfascial or arising from the muscles. They grow very slowly and have a very low risk of malignant transformation.

**Aetiology**

The aetiology is unknown; however, history of preceding trauma which leads to the breakdown of the adipose layer and abnormal growth has been suggested.

**Clinical features**

Lipomas usually occur in adults and have a variable size. The tumour has a smooth, lobulated surface with a well-defined edge. They tend to be soft and as they lie in the dermis the skin over the lesion can be moved over it.

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**Figure 12.8** Pilomatrixoma left post-auricular region.
Diagnosis and investigations
Lipoma has a very characteristic appearance on USS and does not require FNAC. In large lipomas, CT scanning and MRI may be useful in assessing the anatomy of the lesions and aid surgical planning.

Treatment
Surgical excision is the treatment of choice when the lesion is of large size causing an obvious cosmetic deformity, when there is suspicion of malignancy or by patient's choice. \(^{50, 51, 52}\)

Inflammatory neck masses

ACUTE CERVICAL LYMPHADENITIS

Acute cervical lymphadenitis is common especially in the paediatric population. It results as a consequence of a viral or bacterial infective process in the upper aerodigestive tract, the ears or the skin of the head and neck.

Clinical features
The mass is usually painful and can result in an abscess, which will become fluctuant. The patient is usually toxic and the primary infective process is usually evident, although in small children it may not be clear.

Diagnosis and investigations
The diagnosis is made on clinical grounds. If the episode is severe and the child requires admission, then basic haematological investigation may aid diagnosis. Usually, no other investigations are required unless there is clinical suspicion that the patient is developing an abscess or it may be a neoplastic underlying process. In these cases, ultrasound-guided FNAC may aid the diagnosis.

Treatment
If a bacterial infection is suspected or diagnosed, treatment is initially empiric with supportive therapy and broad-spectrum antibiotic therapy. \(^{53, 54}\)

INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis or glandular fever is a viral infection caused by Epstein–Barr virus (EBV) that usually affects adolescents and younger adults. EBV infection is also associated with the development of EBV-associated lymphoid or epithelial cell malignancies, such as Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma and multiple sclerosis.

Aetiology
Epstein–Barr virus is a gamma-herpes virus that infects over 90 per cent of the human population worldwide. It is usually transmitted between individuals in saliva, and establishes replicative infection within the oropharynx, as well as lifelong latent infection of B cells. Primary EBV infection generally occurs during early childhood.

Clinical features
Primary EBV infection generally occurs during early childhood and is asymptomatic or results in a mild self-limiting illness characterized by fever, tonsillitis and lymphadenopathy. If delayed until adolescence or later, it can be associated with the clinical syndrome of infectious mononucleosis, which is characterized by fever, pharyngitis, lymphadenopathy especially cervical and malaise. Five per cent of patients develop a maculopapular rash and up to 50 per cent of patients may develop palatal petechiae, acute bacterial tonsillitis usually with a grey fibrinous medial exudate, splenomegaly and hepatomegaly. In severe cases or in immunocompromised patients, autoimmune haemolytic anaemia, thrombocytopenia, splenic rupture, encephalitis, cranial nerve paralysis and acute upper airway obstruction as a result of significant tonsillar hypertrophy can develop.

Diagnosis and investigations
The diagnosis is made on clinical grounds. The full blood count will show more than 50 per cent of monocuclear cells and more than 10 per cent atypical lymphocytes. The ESR and CRP will be elevated. Monospot and Paul Bunnell tests will be positive, although may be negative especially in the first 2 weeks of the disease. Hepatic enzymes may also be elevated. \(^{55, 56, 57, 58, 59, 60}\)

Treatment
The treatment is largely supportive with conservative measures, including rest and hydration. Avoidance of contact sports and heavy lifting is advised for at least 6 weeks and alcohol should also be avoided while the liver function tests remain abnormal.

Broad-spectrum antibiotic therapy may be useful in cases of secondary bacterial infective tonsillitis but ampicillin and its derivates should be avoided, as patients may develop a maculopapular rash. Corticosteroid therapy is advisable in cases of impending airway obstruction, thrombocytopenia and haemolytic anaemia, as well as other complications such as cranial nerve paralysis. Antiviral chemotherapy with acyclovir or famcyclovir has been reported to help in some cases. \(^{55, 56, 57, 58, 59, 60}\)

CAT SCRATCH DISEASE

Cat scratch disease mainly affects children and young adults with a peak of incidence between two and 14 years. The disease appears to be very common in the United States where over 24 000 people may be affected every year, but also affects Europe, Africa, Australia and Japan.

Aetiology
Cat scratch disease is caused by the Rickettsia Bartonella sp. Bartonella henselae is the most common species to cause the widest spectrum of diseases in humans, and cats, especially kittens, are the main reservoir.

Clinical features
Cervical lymphadenopathy is preceded by an erythematous papula at the site of inoculation. Systemic symptoms, such as
fever, malaise, anorexia, headache and splenomegaly, can occur but tend to be more common in immunocompromised patients.

**Diagnosis and investigations**
Serological testing for *Bartonella henselae* is both sensitive and specific of cat scratch disease. More recently polymerase chain reaction RNA of this bacteria has been used in its diagnosis.

**Treatment**
Several antibiotics, such as gentamicin, rifampicin, ciprofloxacin and especially azithromycin, which is associated with rapid resolution, have been advocated. However, the use of antibiotics in cat scratch disease with no systemic symptoms remains controversial as many infections may resolve without treatment.61, 62

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**CERVICAL NECROTIZING FASCIITIS**
This is a rare, but life-threatening, infection that causes progressive necrosis of the skin and subcutaneous tissue, such as the fat and fasciae.

**Aetiology**
It results from an odontogenic or tonsillar bacterial infection or complicates a deep space neck infection or surgery. *Streptococcus milleri* or *S. viridans* and mixed anaerobes are the most common aetiological agents.

**Clinical features**
The diagnosis is made on clinical grounds and the picture is very characteristic with initial cellulitis of the skin with disproportionate pain which progresses to necrosis of the subcutaneous tissues and skin.

**Diagnosis and investigations**
The white cell count and inflammatory parameters are raised. The ultrasound scan and CT scan may show oedema and air pockets of the skin, which are diagnostic features.

**Treatment**
If untreated, cervical necrotizing fascitis can be fatal, so early diagnosis and treatment are essential. Intravenous high-dose antibiotic therapy, against aerobic and anaerobic bacteria, with debridement of all necrotic areas, are mandatory.63, 64, 65

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**CHRONIC CERVICAL LYMPHADENITIS**
There are a wide range of chronic inflammatory conditions that may present with enlarged lymph nodes or lymphadenopathy. They are often associated with systemic symptoms, such as malaise, weight loss, anorexia and night sweats, and therefore history taking is very important. These include HIV and AIDS, sarcoidosis, toxoplasmosis, actinomycosis and tuberculosis. In all of them, except tuberculosis, the enlargement of the lymph nodes may be very non-specific and therefore a clinical diagnosis may be difficult.

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**HIV-AIDS**
Acquired immunodeficiency syndrome (AIDS) is a viral disease caused by human immunodeficiency virus (HIV). The infection is classified as:
- acute infection or seroconversion illness
- asymptomatic infection
- persistent generalized lymphadenopathy (PGL)
- full blown AIDS.

**Aetiology**
HIV-AIDS results from the HIV virus being transmitted via contaminated blood or human secretions. It is prevalent in homosexuals, promiscuous heterosexuals and intravenous drug abusers.

**Clinical features**
Up to 30 per cent of seroconverted patients develop PGL and it may be the first manifestation of the disease. As with acute seroconversion illness, it tends to be non-specific. It is characterized by multiple diffuse lymphadenopathy involving two or more extrainguinal sites for greater that three months. It may be an early sign of HIV infection with 70 per cent of patients developing diffuse lymphadenopathy within the first few months after seroconversion. PGL can also present associated with other manifestations of the disease (Box 12.1).

**Investigations**
When suspected, HIV serology is indicated and diagnostic. FNAC will help the diagnosis of PGL and will also assist to identify other causes of infection, such as tuberculosis (TB), Kaposi’s sarcoma (KS) or non-Hodgkin’s lymphoma (NHL).

**Treatment**
The CD4 lymphocyte count is the most important reference factor for initiating antiretroviral therapy (ART) in asymptomatic patients. The large number of available drugs, the increased sensitivity of tests to monitor viral load, and the possibility of determining viral resistance is leading to a more individualized approach to therapy.66, 67, 68, 70, 71

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**Box 12.1 Otorhinolaryngological manifestations of HIV infection**
- Candidiasis
- Hairy leukoplakia
- HIV-gingivitis
- Necrotizing ulcerative gingivitis
- Kaposi’s sarcoma
- Non-Hodgkin’s lymphoma
- Benign lymphoepithelial cyst parotid gland
- Benign hyperplasia of the lymphoid tissue
- Pneumocystis carinii pneumonia
- Tuberculosis
- Opportunistic infections
TUBERCULOUS ADENITIS

Tuberculosis is the oldest documented infectious disease. It is the leading cause of death from a single infective agent and is on the increase. Among the factors associated with reversal of a previous decline are increased world travel and a rising incidence of immunodeficiency through HIV infections or intravenous drug abuse. Pulmonary tuberculosis is the most common manifestation, but extrapulmonary disease is likewise on the increase with tuberculous adenitis or historically named ‘scrofula’ being the most common. The word ‘scrofula’ comes from the Latin scrofulae meaning brood sow. In the Middle Ages, it was believed that the ‘royal touch’ of the sovereign of England or France could cure the disease. It was therefore known as the King’s Evil. The kings were thought to have received this power by descent from Edward the Confessor who some legends said had received the power from St Remigius. Tuberculous adenitis can affect any lymph node group of the head and neck, including the salivary glands and thyroid. It is therefore imperative to have a high index of suspicion especially in certain ethnic groups.

Aetiology

Mycobacterium tuberculosis is an obligate aerobe, non-spore forming slender rod. Humans are the only reservoir and it is usually acquired from contact from a TB-infected patient via air-borne transmission. After a short period of replication in the lungs, silent dissemination occurs through the lympho-hematogenous system to extrapulmonary sites, including the cervical lymph nodes. This pathophysiological process differs from non-tuberculous atypical mycobacterial adenitis (NTM) which is addressed later in this chapter.

Clinical features

Ninety per cent of patients have unilateral involvement mainly of the jugular chain, followed by the submandibular triangle and the posterior triangle. The lymph nodes are usually firm, painless and they present with a characteristic erythematous skin discoloration. If the disease has progressed without being diagnosed, they tend to fistulae, present an obvious discharging sinus or form a ‘cold’ abscess, which suggests the clinical diagnosis. TB can also affect the ear, nose, pharynx, larynx, salivary and the thyroid gland and this may be particularly difficult to diagnose as patients often present with a discrete mass resembling a neoplastic lesion (Figure 12.9).

Diagnosis and investigations

Head and neck tuberculosis can be very difficult to diagnose as the clinical features may resemble neoplastic disease especially when presenting as a single-organ involvement. Full blood count is non-specific and may be normal. ESR is often elevated. Chest x-ray is mandatory, but only up to 20 per cent of patients will have positive changes. Soft tissue x-rays of the neck may be helpful as they will show dystrophic calcification characteristic of TB infection. Mantoux and Heaf test may not be diagnostic if the patient has been vaccinated against TB, but a grade IV skin reaction on this test may suggest active infection. Ultrasound scanning of the nodes will often show multiple matted nodes, but may be unspecific. FNAC can reveal mycobacteria, but may be positive in only 40 per cent of patients; however, the use of FNAC and polymerase chain reaction allows a quick and accurate diagnosis with high specificity (84 per cent) and sensitivity (100 per cent). If possible, excision biopsy (although this may be very difficult as matted and neurologic damage and bleeding may be excessive) or incision biopsy (if there is already skin involvement of the affected nodes) should be undertaken. Samples should be sent for microbiology as well as histological analysis and this should provide the definitive diagnosis. The microbiology cultures may take up to 6 weeks to grow mycobacteria and may delay treatment. HIV testing is advised in all patients.

Treatment

The treatment of active tuberculous adenitis, once suspected or proven, is by the use of antituberculous therapy. Increasing resistance is currently a significant problem and therefore chemotherapy should be adjusted according to sensitivity. Surgery has a limited role and should only be used as a diagnostic tool or in cases of residual disease.

NON-TUBERCULOUS ATYPICAL MYCOBACTERIAL ADENITIS

Non-tuberculous atypical mycobacteria is increasing in the Western world and, contrary to tuberculous infection, affects otherwise healthy immunocompetent children of middle-class families.

Aetiology

Mycobacterium avium and Mycobacterium avium intracellulare are the main two pathogens. The route of entry is usually through the oropharynx or the eye from injection of contaminated soil leading to superficial lymphadenopathy in the neck.

Clinical features

Patients affected by NTM are usually young healthy children without symptoms or signs of systemic illness and with multiple cervical lymphadenopathy. The lymphadenopathy often adheres to the skin causing a characteristic red-purple
discoloration and occasionally causing abscess with sinus formation and scarring (Figure 12.10).

**Diagnosis and investigations**
The diagnosis is made on clinical suspicion and the definitive diagnosis relies on isolating the organisms in culture either from microbiological swabs, FNAC or incisional biopsy.

**Treatment**
Most children may eventually develop their own immunity, so a period of observation may be advisable, especially if the lesion is in the parotid gland. Antibiotic therapy with macrolides, such as clarithromycin or azithromycin, with or without antituberculous therapy has been suggested. In some studies, up to 67 per cent of resolution has been experienced without surgical excision. Surgical curettage with or without antibiotic therapy may be an option and has been advised with some success in selected cases especially if a full surgical excision may lead to significant morbidity. Surgical excision is the ultimate treatment of choice and it appears to be more effective than antibiotic therapy alone.76, 77, 78, 79, 80, 81

**BRUCELLOSIS**

Brucellosis is primarily a disease of the domestic animals and causes contagious abortion or other reproductive problems in cattle (Brucella abortus), pigs (B. suis), goats (B. melitensis), dogs (B. canis) and sheep (B. ovis). Current pasteurization, other hygienic preventive measures and adequate animal vaccinations have greatly reduced the incidence of the disease in Western countries.

**Aetiology**
Human spread by Brucella sp. occurs by direct contact of infected tissue with conjunctiva or broken skin, by ingestion of contaminated meat or dairy products and by inhalation of contagious aerosols.

**Clinical features**
The clinical features are often non-specific and some infections are subclinical. When the infection is clinically evident, most patients complain of night sweats, chills, undulating pyrexia and malaise. Up to 20 per cent of patients will develop cervical lymphadenopathies and a similar percentage will have splenomegaly.

**Diagnosis and investigations**
When the diagnosis is suspected, blood cultures will often isolate the bacteria and provide definitive diagnosis. Serology will also provide the diagnosis in those cases in which the clinical picture is less obvious.

**Treatment**
The treatment is done by multiple antibiotic therapy, as treatment with single agents is associated with a 30 per cent chance of relapse. The current recommendation by the World Health Organization (WHO) is the use of doxycycline 200 mg with rifampicin 900 mg daily for 6 weeks.82

**TOXOPLASMOSIS**

**Aetiology**
Toxoplasmosis is a worldwide infection cause by Toxoplasma gondii, a protozoon transmitted by the ingestion of cysts excreted in the faeces of infected cats, or from eating undercooked beef or lamb.

**Clinical features**
Congenital infection usually causes hydrocephalus or microphaly. Acquired infections present with generalized malaise, myalgia, fever, cough and maculopapular rash. If not treated, a chronic phase will develop, which may be asymptomatic or present with isolated cervical lymphadenopathy. In immunocompromised patients especially with HIV-AIDS, it may cause encephalitis.

**Diagnosis**
The diagnosis is made on clinical history and complemented by serology which will confirm diagnosis. The white cell count will show lymphocytosis with atypical mononuclear cells. FNAC may suggest the diagnosis, although may be non-specific. Lymph node biopsy will reveal features supporting the diagnosis of toxoplasmosis. Cerebrospinal fluid (CSF) analysis may demonstrate the parasite and confirm the diagnosis if there is central nervous system involvement.

**Treatment**
Where treatment is indicated, a combination of sulphadimidine, pyrimethamine and folic acid is used and the blood count should be monitored regularly until it becomes normal.83, 84, 85

**ACTINOMYCOSIS**

**Aetiology**
Actinomycosis is a bacterial infection caused by Actinomyces israelii, an anaerobic organism which is a commensal in the healthy oral cavity. The organism may become pathogenic.
when the mucous membrane is injured. Infection is usually associated with severe dental caries and periodontitis.

**Clinical features**

Patients present with a firm indurated mass with ill-defined edges usually lateral to the mandible. If left untreated, the infection may spread to the adjacent tissues and may become bony hard. Once the infection is established, multiple sinus may develop which discharge pus and watery fluid characteristically containing sulphur granules.

**Diagnosis and investigations**

The diagnosis may be suspected on clinical grounds which is usually very characteristic. The FNAC may show sulphur granules which are diagnostic. The biopsy will again show the characteristic colonies of sulphur granules, but the organism may be difficult to culture.

**Treatment**

The treatment is with intravenous benzylpenicillin or cephalosporins in high doses that may require to be continued for at least 6 weeks. However, longer courses of antibiotic therapy up to a year may be necessary in resistant cases or immunocompromised patients. Removal of carious teeth is imperative to excise the site of origin of the infection.

**Neck abscesses**

**SUPERFICIAL SOFT TISSUE NECK ABSCESES**

Cervical abscesses are relatively uncommon in comparison with the number of acute and chronic lymphadenitis cases in the paediatric and adult population. However, small children under the age of four years and immunocompromised patients appear to be more susceptible.

**Aetiology**

Failure of patients to localize the organism at the site of attachment to nasal or pharyngeal epithelium will result in the spread of infection via lymphatics causing suppuration. The most common pathogens are *Staphylococcus aureus*, *Streptococcus pyogenes* and, in the paediatric population, atypical mycobacteria.

**Clinical features**

The development of the abscess is often preceded by an upper respiratory tract infection, although sometimes this may not be obvious from the history especially in the young paediatric population.

**Diagnosis and investigations**

The diagnosis is based on the clinical suspicion. FBC, ESR and CRP are useful to ascertain the inflammatory origin and to monitor progress. Ultrasound and CT scanning will be useful to determine whether the mass has a central area of necrosis that may require incision and drainage.

**Treatment**

The treatment involves a combination of supportive therapy, broad-spectrum antibiotic therapy until culture and sensitivity results are available, and surgical incision and drainage. Repeated needle aspiration is not usually helpful unless the abscess arises from a thyroglossal duct cyst, in which case incision and drainage is reserved as last resort and only antibiotic therapy and repeated aspiration has failed.

**RETOPHARYNGEAL SPACE ABSCESS**

Retropharyngeal space abscess is less common than in the past, but still represents a life-threatening infection that can result in airway obstruction and death if not recognized.

**Aetiology**

In infants, aetiology is usually due to an upper respiratory tract infection and in adults is usually due to tuberculous lymphadenitis.

**Clinical features**

Children with retropharyngeal abscesses have or recently had an upper respiratory tract infection or dental sepsis. They appear ill, unwell, toxic and with pyrexia of 38–39°C. The abscess swelling may obstruct the posterior nares and push on the soft palate, potentially with a risk of respiratory obstruction. In adults, the clinical features are those of an insidious onset with low-grade fever, mild oropharyngeal discomfort and low risk of obstruction.

**Diagnosis and investigations**

The diagnosis is made on clinical grounds and investigations should not be advised if airway obstruction is present or an imminent risk. The white cell count and inflammatory markers, such as ESR and CRP, are usually raised. A plain lateral soft tissue neck x-ray will often show the abscess, but must be interpreted with caution. CT scanning will delineate the abscess (Figure 12.11).

**Figure 12.11** Computed tomography scan demonstrating a retropharyngeal abscess.
Treatment
In children, retropharyngeal abscesses represent a real emergency. In this situation, the children should be taken to the operating theatre and, once the airway is secured, the pus should be incised and drained. It may be necessary to keep the child intubated and ventilated until the drainage has subsided and the infection resolved. The insertion of a tracheostomy is currently rarely needed. In adults, once the pus is drained and the diagnosis confirmed, antituberculous chemotherapy should be commenced.88, 89, 90, 91, 92, 93, 94, 95, 96, 97

PARAPHARYNGEAL SPACE ABSCESS
Parapharyngeal space abscesses tend to be more common in adults than in children. They often result from an infective process of the upper aerodigestive tract, especially tonsillitis or tonsillectomy in 60 per cent of cases or a dental infection in 30 per cent of patients. This, however, may be trivial or it might have occurred and resolved a few days prior to the onset. In the remaining 10 per cent, the cause is otogenic.

Aetiology
Streptococcus viridans was the most common pathogen (39 per cent of positive cultures), followed by Staphylococcus epidermidis (22 per cent) and Staphylococcus aureus (22 per cent).

Clinical features
Patients are usually unwell, pyrexial and toxic. They present with trismus due to the affection of the pterygoid muscles and the tonsil may be displaced medially. It usually displaces the upper third of the sternocleidomastoid muscle, especially posteriorly.

Diagnosis and investigations
The diagnosis is based on the history and examination and made on clinical grounds. The white cell count and the inflammatory markers, such as ESR and CRP, are usually raised. The ultrasound or CT scan will delineate the abscess and confirm diagnosis. Needle aspiration under ultrasound or CT guidance should be considered.

Treatment
Small loculated abscesses or cellulites can be managed conservatively with intravenous broad-spectrum antibiotics covering aerobic, as well as anaerobic bacteria for 12–24 hours. Needle aspiration under ultrasound or CT guidance should be considered and may be helpful in small collections. However, large collections will require formal incision and drainage via an external approach. The collection is accessed medial to the carotid sheath and the insertion of a drain is mandatory to prevent recollection.88, 89, 90, 91, 92, 93, 94, 95, 96, 97

SUBMANDIBULAR SPACE ABSCESS OR LUDWIG’S ANGINA
The word ‘angina’ comes from the Greek ankhon meaning ‘strangling’. Ludwig’s angina is the cellulitis of the submandibular space that can lead to a compromise of the airway due to easy spread of the infection through the sublingual soft tissue. It is named after the German physician Wilhem Frederick von Ludwig, who first described the condition in 1836. Over 80 per cent of patients have a dental infection and the rest usually have an upper respiratory tract infection.

Aetiology
Streptococcus viridans was the most common pathogen (39 per cent of positive cultures), followed by Staphylococcus epidermidis (22 per cent), Staphylococcus aureus (22 per cent) and Escherichia coli.

Clinical features
Patients are often elderly or young children, and they are unwell and toxic. There is trismus and excessive salivation. The swelling is diffuse, and there is erythema and cellulitis of the skin. The floor of the mouth appears oedematous, brown in colour with the tongue pushed upwards and back which can cause a potential airway obstruction (Figure 12.12).

Diagnosis and investigations
The diagnosis is based on the history and examination, and made on clinical grounds. The white cell count and the inflammatory markers, such as ESR and CRP, are usually raised. The ultrasound or CT scan will delineate the abscess and confirm diagnosis. Needle aspiration under ultrasound or CT guidance should be considered.
raised. The ultrasound or CT scan will delineate the abscess and confirm diagnosis, although abscess formation is rare.

Treatment
Ludwig’s angina is a cellulitis rather than abscess. Airway management is paramount and high-dose intravenous antibiotic therapy targeted to the causing bacteria should be commenced. Needle aspiration under ultrasound or CT guidance should be considered and may be helpful in some circumstances. However, established collections will require formal incision and drainage via an external approach. The collection is best accessed through a lateral transverse cervical incision at the level of the hyoid bone, and a drain should be inserted. Tracheostomy may be required for airway management in a significant proportion of patients with well-established Ludwig’s angina.88, 89, 90, 91, 92, 93, 94, 95, 96, 97

MISCELLANEOUS RARE CAUSES OF NECK MASSES

Organized haematomas

Aetiology
Aetiology involves blunt or penetrating trauma of the neck.

Clinical features
Patients present with a neck mass that usually causes local discomfort and occasionally constant pain.

Diagnosis and investigations
A history of trauma is usually present, although not always obvious. Ultrasound-guided FNAC will suggest diagnosis, but the sonographic appearances depend on the age of the haematoma. If in the liquid state, the blood can be aspirated. CT scan and MRI will display distinct radiological features and determine the anatomy. The sonographic appearance depends on the age of the haematoma. If in the liquid state, the blood can be aspirated. Follow-up ultrasound may be helpful to ensure that there is no underlying lesion.

Treatment
Surgical excision is the treatment of choice, although it may be difficult due to the surrounding fibrosis of the lesions.98, 99

Castleman disease

Castleman disease is a rare entity, which is characterized by hyperplasia of lymph nodes and capillary proliferation that usually affects adolescents and young adults. Three histological patterns has been described: hyaline vascular type, plasma cell type and mixed type. Two clinical types have been identified: a localized type (ECL) usually of benign clinical course and a multicentric type (ECM), which has a worse prognosis and may lead to the development of non-Hodgkin’s lymphoma.

Aetiology
It is unknown, although up to 50 per cent of multicentric variants are caused by Kaposi sarcoma-associated virus (KSHV), a gammaherpes virus that causes Kaposi sarcoma and primary effusion lymphoma.

Clinical features
Patients usually present with a progressive enlarging lateral cervical lymphadenopathy often associated with autoimmune iron-deficiency anaemia. ECM may present with B symptoms, such as fever, anorexia and weight loss.

Diagnosis and investigations
Full blood count shows iron-deficiency anaemia and the ESR is elevated. FNAC often shows a lymphocytic aspirate and it is not normally diagnostic, therefore surgical excision is advised for histological diagnosis. Imaging studies are often not useful.

Treatment
The anaemia is difficult to treat as it often does not respond to iron supplement. Surgical excision is usually therapeutic in ECL, although it may be difficult in ECM. Treatment with ganciclovir or the anti-CD20 B cell monoclonal antibody, may improve the outcome in some patients with ECM. In ECM, long-term follow up is advised in association with haemato-oncology teams.100, 101, 102

Kikuchi disease

Kikuchi disease (KD) is a self-limiting disease of the lymph nodes that usually affects young women. It is also known as Kikuchi–Fujimoto disease and was first described by Kikuchi in Japan in 1972. Histologically, it is characterized by a histiocytic necrotizing lymphadenitis.

Aetiology
It is unknown, however an autoimmune aetiology has been proposed as some human leukocyte antigen (HLA) class II genes are more frequent in patients with KD. An association with systemic lupus erythematosus (SLE) has also been reported.

Clinical features
The disease often presents with persistently intermittent fever and tender enlarged cervical lymph nodes. It is self-limiting, but it may take up to three months to resolve.

Diagnosis and investigations
The diagnosis can be confirmed by histopathological findings of the lymph node in open biopsy.

Treatment
The disease is usually self-limiting and does not respond to antibiotic therapy. Supportive therapy with non-steroidal anti-inflammatory drugs may help to alleviate the lymphadenopathy tenderness and pyrexia.103, 104
**Kawasaki disease**

Kawasaki disease (KWD) is an acute, self-limiting vasculitis of childhood, although it may also occur in adults. It was first described by Tomisaku Kawasaki in Japan in 1967. In some countries, Kawasaki disease has now surpassed acute rheumatic fever as the leading cause of acquired heart disease in children.

**Aetiology**

The aetiology is unknown; however, the acute presentation and the clustering of cases may indicate an infectious aetiology.

**Clinical findings**

The illness is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash and cervical lymphadenopathy. Coronary artery aneurysms or ectasia develop in approximately 15–25 per cent of untreated children and may lead to myocardial infarction and sudden death.

**Diagnosis and investigations**

The diagnosis is based on the recognition of this characteristic sequence of clinical events, none of which are pathognomonic. Establishing the diagnosis may be further complicated by the occurrence of other, seemingly unrelated, clinical features, such as irritability, neck stiffness, sterile pyuria, pneumonitis and hepatitis. There is no laboratory test that can help in confirming a diagnosis.

**Treatment**

Treatment is with intravenous gammaglobulin therapy and high doses of aspirin.\(^{105, 106}\)

**Other rare causes of cervical neck masses**

Other rare causes of cervical neck masses include sarcoidosis, fibromatosis colli, Rosai–Dorfman disease, Kimura disease, dermatofibroma and prominent transverse process of atlas.\(^{107, 108}\)

**Aetiology**

The aetiology of pharyngeal pouch has not been fully established. The two factors which appear to be the most important in the aetiology of pharyngeal pouch are:

1. **Cricopharyngeal hypertonicity**: failure of relaxation of the cricopharyngeous muscle is thought to raise intraluminal pressure within the pharynx promoting pouch formation.\(^2\)

2. **Pharyngeal/oesophageal incoordination**: dysmotility of the reflex bolus has been identified as an important factor in production of the pouch.\(^3, 4\) This may or may not be associated with gastro-oesophageal reflux.

Pharyngeal pouches usually enlarge in a posterolateral direction displacing the oesophagus, although it appears that right-handed individuals have left-sided pouches and left-handed ones have right-sided pouches.

**Clinical features**

Pharyngeal pouches may be found as an incidental finding in the asymptomatic patient being investigated for other symptoms. If there are no adverse effects relating to this incidental finding and the patient is asymptomatic, then the pouch can be ignored.

 Symptoms usually present in the elderly. Dysphagia is the most common presenting symptom of a pharyngeal pouch. The dysphagia may be progressive as the pouch enlarges. Weight loss may result from prolonged dysphagia. Regurgitation of food after meals may occur as the pouch empties itself. Chronic cough may be a symptom of aspiration which can be a feature of this condition. Silent aspiration may result from the pharyngeal pouch, and respiratory assessment is important if surgical intervention is to be contemplated. Very rarely, a pharyngeal pouch may present as a lateral neck mass.

**Diagnosis and investigations**

The diagnosis is often suspected from the history. Initial physical examination is indicated including fibreoptic naso-laryngoscopy. This is essential to exclude any other laryngeal or hypopharyngeal pathology. Occasionally, the pouch can be seen when asking the patient to perform a valsalva manoeuvre during the laryngoscopic examination. If a pharyngeal pouch is suspected, then a water-soluble contrast swallow study is indicated and is usually diagnostic (Figure 12.13). Direct laryngoscopy and pharyngoscopy under general anaesthetic may be appropriate if the contrast swallow studies are negative.

**Treatment**

If the pharyngeal pouch is asymptomatic and there are no respiratory complications, then it can be managed conservatively. In patients with obvious gastro-oesophageal reflux, treatment with proton-pump inhibitors may help their symptoms. Management of pharyngeal pouches has changed considerably over the last decade.\(^5\) Endoscopic approaches are now favoured, as they are quick, safe and well established. However, the traditional open approaches are still practised as they have specific indications, and there will be a proportion of patients in whom the endoscopic approach is not possible due to unfavourable anatomy or in cases of recurrence. The two approaches have been compared
in terms of results and morbidity. The endoscopic diverticulotomy has been shown to be superior due to shorter inpatient stay and faster return to oral diet. However, there is little evidence using objective measurements comparing the two procedures and little evidence to show which has a higher recurrence rate. The open procedure is almost always followed up by a contrast study prior to commencement of oral diet, to ensure that pharyngeal healing has occurred. The endoscopic procedure usually does not have a follow-up contrast study. In those cases where one is performed postoperatively, there is usually a small residual pouch visible. The open approach is the only one to perform a cricopharyngeal myotomy which, is thought to be the most important factor in pouch formation. The advantages of the endoscopic approach are that it results in a short anaesthetic time, short inpatient stay and quick return to oral diet. It is, therefore, suitable for the elderly patient with comorbidity.

Endoscopic approaches

In the past, the endoscopic diathermy diverticulectomy or Dohlman’s procedure was popular and indicated in patients who had a poor anaesthetic risk. Currently, however, endoscopic stapling and transoral CO₂ laser diverticulotomy have substituted this approach. Endoscopic stapling is possibly the most popular procedure and it is now established as the recommended treatment of choice in the majority of patients with symptomatic pharyngeal pouches.

Endoscopic stapling diverticulotomy

The procedure is performed as follows: a distraction distending diverticuloscope is introduced into the pharynx. This instrument has two limbs, one is introduced into the lumen of the oesophagus and the other in the pouch. The diverticuloscope is opened up in order to visualize the pouch. The pouch contents are aspirated in order to empty the pouch. A rigid endoscope is introduced to inspect the mucosal lining of the pouch. Any necessary biopsies should be taken. A stapling gun is introduced under direct vision with the aid of a rigid endoscope. The staple gun is then activated and divides and seals the bar which separates the pouch and the oesophagus. The advantages of the endoscopic approach are that it results in a short anaesthetic time, short inpatient stay and quick return to oral diet. It is, therefore, suitable for the elderly patient with comorbidity.

Open approaches

Open techniques are currently less rarely performed and reserved for recurrent cases and those unsuitable for endoscopic approach. They include surgical inversion, diverticulopexy with or without cricopharyngeal myotomy and in cases in which the pouch is small, cricopharyngeal myotomy alone.

Open surgical excision or one-stage diverticulectomy

Initially, it is necessary to perform an endoscopic assessment of the pouch so it can be identified and inspected. This will also allow the pouch to be packed with gauze, such as BIPP, so it facilitates the identification of the pouch in the neck. At the time, a rigid dilator is also inserted in the oesophagus to facilitate the cricopharyngeal myotomy performed at the time of the procedure. Pharyngeal pouches are accessed via a lateral pharyngotomy approach. This involves a horizontal skin crease incision at the level of the cricoid cartilage. The sternocleidomastoid muscle is mobilized and retracted laterally. The neurovascular bundle of the carotid sheath is also mobilized and retracted posterolaterally. The middle thyroid vein often needs to be divided in order to access the pouch. The pouch is excised and pharyngeal defect repaired by suturing in layers. A cricopharyngeal myotomy is also performed to facilitate swallowing and to prevent the recurrence of the pouch.

PHARYNGEAL POUCH CARCINOMA

It is a recognized sequela of this condition. It is thought to result due to chronic inflammation of the pouch due to the effect of its contents. Dysplasia and metaplasia is thought to result as a consequence. This condition is usually associated with a poor prognosis due to late presentation and coexistence of comorbidity.
Laryngoceles

A laryngocele is an abnormal cystic dilatation of the saccule of the larynx. The saccule is a small mucosal pouch which lies between the vestibular fold of the larynx and the inner surface of the thyroid cartilage. It is thought to be an anatomical vestigial remnant within the ventricle of the larynx and contains numerous mucinous glands. Laryngoceles can be internal (within the larynx), external (outside the larynx) or mixed (both). They are usually unilateral and can rarely be bilateral. Laryngoceles can contain either air or mucous and, if they become infected, they are called ‘laryngopyoceles’.

Aetiology

The aetiology of laryngoceles is unknown. They may be congenital or acquired. Intraluminal laryngeal pressure has been postulated as the causative factor in producing laryngoceles. The association with activities, such as glass blowing and playing wind instruments, has only been made in case reports. There is, therefore, little evidence to suggest causation. A small proportion of laryngoceles has been identified to coexist with laryngeal carcinomas. External laryngoceles have been found in up to 16 per cent of laryngectomy specimens for laryngeal carcinomas, as opposed to 2 per cent in laryngectomy specimens for pyriform sinus carcinoma. It has been suggested that the neoplastic growth results in increased luminal pressure in the larynx precipitating laryngocele formation. Other laryngeal pathologies, such as amyloidosis, scleroderma and SLE, have also been associated with the formation of laryngoceles. The above associations, however, are subject to significant reporting bias and therefore should be considered with caution.

Clinical features

Laryngoceles may often be asymptomatic and have been identified to be a prevalent incidental autopsy finding. Dysphonia is the most common presenting symptom. A lateral neck mass may result due to pathological enlargement through the thyrohyoid ligament. Acute airway obstruction may result in stridor if the laryngocele enlarges and obstructs the larynx. Securing the airway and resection of the laryngocele is indicated. Laryngoceles can also become infected and produce laryngopyoceles. These behave as abscesses and require incision and drainage if external, or endoscopic decompression and drainage if internal.

Diagnosis and investigations

Full physical examination including fibreoptic nasolaryngoscopy is essential to rule out any coexisting laryngeal pathology, especially in those high-risk patients with carcinoma of the larynx. Cross-section imaging with a contrasted CT scan is the investigation of choice for laryngoceles (Figure 12.14). If patients are found with any mucosal lesions, endoscopic assessment under general anaesthesia with biopsies should be undertaken.

Treatment

As the majority of laryngoceles are asymptomatic and are not associated with any pathology, treatment may not be necessary. However, as there is a potential risk of infection and pyocele formation, advice should be given to patients to make an informed decision with regards to surgical intervention. Internal laryngoceles can be treated with transoral laser resection. The CO₂ laser can be used to marsupialize or excise the pouch. External laryngoceles can be approached via a lateral pharyngotomy/thyrotomy approach. The lateral surface of the larynx is exposed, the external component of the laryngocele is mobilized and resected and the mucosal defect repaired. A covering tracheostomy may be necessary for large lesions.

Figure 12.14  Computed tomography scan demonstrating a large laryngocele arising from the right laryngeal ventricle.

KEY EVIDENCE

- This is a diverse chapter addressing multiple benign disorders.
- There is a lack of substantive high level of evidence due to the intrinsic nature of the disorders addressed in most areas with most evidence being level 2 or below.
- Congenital abnormalities of the head and neck are best treated with surgical excision whenever possible. 45
- Head and neck tuberculosis should be treated with systemic antituberculous therapy and surgery has a limited role in its management. 72, 73, 74, 75

KEY LEARNING POINTS

- Benign neck masses and visceral benign neck diseases are common and represent a diverse group of disorders.
The evaluation and management of patients who present with a neck lump should have a systematic and uncompromising clinical approach.

The examination of these patients should be comprehensive and always include a fibre-optic endoscopic examination of the upper aerodigestive tract.

All patients with neck lumps should be investigated with ultrasound-guided fine needle aspiration as an initial investigation whenever possible.

The great majority of congenital neck masses can be treated with surgical excision if indicated, however surgery requires meticulous technique to avoid recurrence.

Acquired non-inflammatory neck masses are mainly treated with surgical excision.

Acquired inflammatory neck masses should be treated medically and surgery is reserved for diagnostic purposes and if the mass develops into an abscess.

Head and neck acquired neck abscess requires incision and drainage in most instances.

Pharyngeal pouch surgery has evolved and the majority of these can be dealt with endoscopic rather than open surgery.

Laryngoceles are rare but when developed, primary laryngeal cancer should always be excluded.

REFERENCES


INTRODUCTION

This chapter deals with benign tumours of the oral cavity and jaws. The first section covers the common soft tissue hyperplasias and benign neoplasms. The second section deals with bony lesions – odontogenic neoplasms, a group of lesions unique to the jaws; reactive and neoplastic fibro-osseous lesions and true benign neoplasms of bone and cartilage. Clinical presentation, radiological findings and salient histological features are outlined. The chapter is an introduction to these diverse lesions and a source of reference for more detailed study. In most cases, simple conservative excision is sufficient management, but for some lesions, such as the ameloblastoma, treatment is controversial. Some benign lesions may be the presenting feature of a more serious systemic condition and although rare, they merit discussion.

COMMON SOFT TISSUE SWELLINGS: HYPERPLASIAS AND BENIGN NEOPLASMS

The vast majority of soft tissue masses occurring in the oral cavity are hyperplastic inflammatory responses to local, often chronic, trauma or infection. They may be predominantly of epithelial or connective tissue origin or a combination. These hyperplastic lesions are found in 3 per cent of adults and account for more than 80 per cent of diagnostic oral pathology specimens. In other lesions, such as some squamous papillomas, the aetiopathology is less certain and the distinction between reactive hyperplasia and benign neoplasia is somewhat arbitrary. True benign neoplasms of diverse histogenesis may occur within the mouth, but most are rare. The following account considers lesions mainly according to their cell of origin rather than the pathological process.

Benign: (adj.) harmless, non-malignant, non-cancerous, innocent.
in situ hybridization. Papillomas respond to simple excision or ablation by laser or cryosurgery. Verruca vulgaris may regress spontaneously.

CONDYLOMA ACUMINATUM

The oral counterpart of anogenital condyloma acuminatum (HPV types 6, 11, 16 and 18) tends to be larger than the papilloma, with a broad base and pink nodular surface. Histologically, the fronds are short and blunt with prominent clusters of koilocytes. Lesions tend to recur, but unlike the anogenital lesions, there is no documented malignant transformation.

FOCAL EPITHELIAL HYPERPLASIA (HECK’S DISEASE)

Multiple soft, rounded, pink swellings on the lips, cheek and tongue, induced by HPV 13 and 32, are found mainly in children and young adults. The condition is rare in the United Kingdom, but up to 40 per cent of children are reported to be affected in some regions of the world. Histologically, sharply defined areas of acanthosis with ‘mitosoid bodies’ are seen. Lesions resolve spontaneously.

PAPILLOMAS IN IMMUNODEFICIENCY

Florid HPV-induced lesions are common, especially in HIV infection and may coalesce as widespread papillomatosis. Multiple, and unusual, HPV subtypes are typical. White hairy leukoplakia seen on the lateral tongue in 20–25 per cent of HIV-infected patients contains the Epstein–Barr virus.

KERATOACANTHOMA

This benign tumour of hair follicle epithelium is seen on the lips. Aetiology is unknown. It is characterized by rapid growth followed by slow, spontaneous involution. The mature lesion, a nodule with a central crater, mimics squamous carcinoma clinically and histologically. Simple excision, often necessary for diagnosis, is curative.

VERRUCIFORM XANTHOMA

This wart-like lesion is seen mainly on the gingiva of female adults and may be a response to local trauma. The histological characteristic is epithelial papillomatosis with foamy histiocytes filling the connective tissue papillae. Recurrence is rare after simple excision.

Fibroepithelial hyperplasias

These common lesions result from an overgrowth of both surface epithelium and one or more element of the supporting connective tissues. There are several clinical subtypes, affecting both the lining mucosa, gingivae and mucoperiosteum (Box 13.1).

<table>
<thead>
<tr>
<th>Box 13.1 Fibroepithelial hyperplasia</th>
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<tr>
<td><strong>Localized gingival hyperplasia</strong></td>
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<tr>
<td>• Fibrous epulis</td>
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<td>• Ossifying fibrous epulis</td>
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<td>• Vascular epulis</td>
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<td>• Giant cell epulis (peripheral giant cell granuloma)</td>
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<tr>
<th><strong>Generalized gingival hyperplasia</strong></th>
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<tr>
<td>• Idiopathic plaque-induced</td>
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<td>• Hereditary autosomal-dominant (gingival fibromatosis)</td>
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<td>• Fibrous enlargement of the maxillary tuberosity</td>
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<td>• Drug-induced</td>
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<td>- nifedipine and verapamil</td>
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<th><strong>Mucosal fibroepithelial hyperplasias</strong></th>
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<tr>
<td>• Fibroepithelial polyp</td>
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<td>• Denture-irritation fibroepithelial hyperplasia (denture granuloma)</td>
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<tr>
<td>• Leaf fibroma</td>
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<tr>
<td>• Papillary hyperplasia of the palate</td>
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<td>• Giant cell fibroma</td>
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<td>• Cowden syndrome</td>
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LOCALIZED GINGIVAL HYPERPLASIA

Minor localized swellings of the gingivae (epulides) are commonplace and many resolve following a ‘scale and polish’ and improvement of oral hygiene measures. Persistent or symptomatic lesions may appear as painless, triangular swellings of the interdental papilla which gradually increase in size. Histologically, four main types are recognized on the basis of the predominant component of the core. The composition influences the clinical appearance and may also reflect differences in aetiology and pathogenesis.

Fibrous epulis

This is the most common type, accounting for more than 50 per cent. Typically, it presents as a firm, smooth-surfaced, broadly pedunculated or sessile mass. The colour is often similar to the adjacent gingiva, but depends on the vascularity of the core and the thickness and integrity of the surface epithelium. Typically, lesions occur on the labial or buccal aspect of the tooth, most commonly an incisor or canine. Males and females are equally affected, with no strong age predilection.

Histologically, the proportion of fibroblasts to collagen fibres varies and may reflect the maturity of the lesion, age of the patient and nature of the irritation. Highly cellular lesions are more common in adolescents.

Simple surgical removal is curative and the lesion is unlikely to recur if initiating factors are removed and a good standard of oral hygiene is maintained.
Ossifying fibrous epulis

Mineral deposits or bone are seen in 30 per cent of fibrous epulides. Some show droplets of dystrophic mineral, while others develop well-formed trabeculae of metaplastic woven, or even lamellar, bone. Cementum-like material is also seen occasionally. Ossifying fibrous epulides tend to occur in adolescents and young adults and show a greater tendency to recur than their non-ossifying counterparts.

Vascular epulis

Highly vascularized epulides are more common in females and are linked to pregnancy. Lesions may grow rapidly during pregnancy and may regress postpartum or become more fibrous. Vascular epulides present as red, soft lesions with a glazed or ulcerated surface and may bleed spontaneously or on minimal trauma. Histologically, the core consists of solid sheets of non-canalized endothelial cells and/or masses of thin-walled blood vessels in an oedematous stroma. Ulceration and associated inflammation are common. A minority display a lobular architecture similar to the pyogenic granuloma.

Giant cell epulis (peripheral giant cell granuloma)

This accounts for around 10 per cent of epulides, and predominantly affects females. Occurrence is usually anterior to molars, and mainly mandibular, but lesions may occur in edentulous areas. Typically, it presents as a purplish, hourglass swelling extending from the buccal to lingual aspect and may cause pressure erosion of the underlying interdental bone. The histological appearances are distinct with abundant multinucleated osteoclast-like giant cells lying in highly vascular stroma of oval to spindle-shaped mononuclear cells. Dilated blood vessels and haemosiderin-laden macrophages are seen at the periphery, particularly in the zone of dense fibrous tissue that separates the lesion from the surface epithelium. The aetiology is uncertain and the lesion appears distinct from the central giant cell granuloma and brown tumour of hyperparathyroidism which arise within the jaw bone. If the origin – peripheral or central – is in doubt, then x-rays and serum biochemistry are necessary.

GENERALIZED GINGIVAL HYPERPLASIA

Four categories of generalized gingival fibrous hyperplasia are recognized (Box 13.1). It arises as an exaggerated response to dental plaque, resulting in fibroblastic proliferation and increased collagen production. Idiopathic cases are generally seen at puberty suggesting a hormonal influence. Between 10 and 60 per cent of patients on epanutin are affected. Fibrous enlargement of the maxillary tuberosity usually presents in adults, but appears to have a genetic basis. In all categories, surgical removal tends to be followed by recurrence, unless excellent plaque control is maintained.

MUCOSAL FIBROEPITHELIAL HYPERPLASIAS

These may be seen as a distinct polyp, either broad-based or on a peduncle, or as a more diffuse overgrowth (Box 13.1). The lip and buccal mucosa are the usual sites. The surface is usually the same colour as the surrounding mucosa, unless trauma has resulted in ulceration or frictional keratosis. The hyperplasias associated with ill-fitting dentures typically affect the mandibular labial and buccal sulci and have an elongated shape indented by the denture flange. ‘Leaf fibroma’ is the term given to pedunculated palatal lesions. More generalized papillary hyperplasia of the palate presents as an erythematous, pebbled area often beneath an ill-fitting denture associated with chronic candidal infection. All forms share similar histological features of hyperplastic surface epithelium covering a core of collagenous connective tissue with variable inflammation and vascularity. Conservative excision is curative provided the irritating factors are removed. The giant cell fibroma is a histological variant of the fibroepithelial polyp characterized by the presence of stellate, multinucleated fibroblasts of no clinical significance.

Cowden syndrome, a rare autosomal disorder, is characterized by multiple hamartomas and benign and malignant neoplasms at almost any body site. Oral manifestations include multiple papules consisting of a fibrovascular core covered by acanthotic epithelium. Facial lesions include cysts and adnexal tumours.

Tumours of fibrous tissue

Nodular fasciitis, often referred to as a pseudotumour, presents as a subcutaneous/submucosal soft tissue mass that often grows rapidly over a period of 1–2 weeks causing suspicion of a malignancy. Preceding minor trauma is probably an important aetiological factor. Mainly labial and buccal, although any mucosal site may be affected, lesions are typically 2–5 cm. Affected individuals are usually young adults (<30 years) with no gender predilection.

The histological features can be worrisome, with richly cellular areas of plump myofibroblasts, readily detected mitotic activity and sometimes apparent infiltration of adjacent tissues. The loose myxoid stroma, extravasated erythrocytes and scattering of chronic inflammatory cells aid the diagnosis. Recurrence following even incomplete surgical removal is rare and should prompt re-evaluation of the diagnosis.

There are no true benign purely fibrous soft tissue tumours of the oral cavity. Benign fibrous histiocytoma and myofibroma are rarely reported. Benign fibrous histiocytoma is analogous to its counterpart in the skin and presents as a subepithelial, firm, circumscribed nodule. Myofibroma occurs both as a soft tissue lesion and less commonly as an intraosseous lesion. Occurrence over a wide age range including infants as young as nine months is reported. Diagnosis in infants should prompt examination for multiple lesions (myofibromatosis) which has a poor prognosis when multiple vital organs are involved. In solitary cases, conservative excision is curative.

FIBROMATOSIS

Fibromatosis shows locally aggressive behaviour and frequent recurrence, but does not metastasize. Presentation is usually in the first decade with a painless slowly growing mass. The cheeks, tongue and submandibular region are favoured oral sites. Lesions may cause erosion of bone. Intraosseous lesions
of both maxilla and mandible are also described. Histologically, differentiation from a low-grade fibrosarcoma may be difficult. Lower mitotic count and nuclear staining with beta-catenin immunohistochemical stain may help. Recurrence rate in one oral series was 24 per cent, significantly lower than that for other body sites (50–70 per cent). Treatment is surgical with the aim of establishing disease-free margins. Given the poorly defined periphery of the lesion and large size, this is often difficult. Chemotherapy and radiotherapy have been used, but the latter is not desirable in a young patient.

**Vascular lesions**

**PYOGENIC GRANULOMA**

Pyogenic granuloma, an exuberant mass of granulation tissue, arises following acute or chronic trauma or infection. All ages and both genders are susceptible. Lesions present as small red soft lesions that may ulcerate or bleed spontaneously. Histologically, they consist of lobular proliferations of endothelial cells and young capillaries in an oedematous, inflamed stroma. Conservative surgical excision is usually curative, but around 15 per cent of cases recur.

**CALIBRE-PERSISTENT ARTERY**

This is a developmental anomaly affecting the lower lip in 80 per cent of cases with the remaining lesions affecting the upper lip and hard palate. In the lower lip, it arises when the inferior alveolar artery retains its large size and muscular wall, even in its terminal portion within the orbicularis oris muscle. Symptoms of persistent ulceration, non-healing lip fissure or a pulsatile nodule usually occur after the age of 40 years. Removal of the abnormal vessel during diagnostic biopsy is curative, although excessive haemorrhage may be a surgical problem.

**HAEMANGIOMAS**

These common tumours are generally accepted as hamartomas rather than true neoplasms. They occur more commonly in the head and neck than any other body site. Oral lesions account for 14 per cent and reportedly are found in 0.5 per cent of adults. Most are present at birth or arise in early childhood, but some present in old age. The lips, tongue, cheek or palate are the most common intraoral sites and lesions vary in size, shape and surface appearance. Most are dark reddish-purple, soft and either smooth and flat or raised and globular. Typically, they blanch on pressure. Larger lesions often contain phleboliths which may be detected radiologically. Trauma may cause haemorrhage or lead to a sudden increase in size due to thrombosis and inflammation. The facial muscles, jaw bones and major salivary glands may also be affected and the juvenile haemangioma is the most common tumour affecting salivary glands in children.

Haemangiomas are classified according to the ratio of endothelial cells to vessels and the calibre and thickness of the vessel walls into capillary, cavernous, arteriovenous and mixed. Capillary haemangiomas include sheets of non-vascularized endothelial cells sometimes arranged in lobules similar to the pyogenic granuloma. Other histological variants, such as epithelioid and sclerosing, are unusual in the mouth. Haemangiomas may be treated by conservative surgical excision or debulking, intralesional injection of sclerosing chemicals, cryosurgery, laser ablation and ligation of the feeder vessel. Congenital capillary haemangiomas usually spontaneously regress by six years of age.

**VARICOSITIES AND VENOUS LAKES**

Sublingual varicosities affecting the ranine veins and venous anomalies of the lips increase in frequency with age and rarely require treatment.

**STURGE–WEBER SYNDROME**

This congenital disorder is characterized by haemangiomas of the face with a distribution over one or more branches of the trigeminal nerve, oral mucosa and ipsilateral leptomeninges over the cerebral cortex.

**HEREDITARY HAEMORRHAGIC TELANGIECTASIA**

Transmitted as an autosomal dominant trait, this is characterized by multiple knots of dilated malformed capillaries (telangiectases) in skin, oral and nasal mucous membranes and internal organs.

**LYMPHANGIOMA**

Lymphangiomas, hamartomatous malformations of lymph vessels, are less common than haemangiomas and generally present in infancy and early childhood. The tongue is the most common intraoral site and a frequent cause of macroGLOSSIA. Typically, lesions have a pebbled or verrucous surface due to the superficially located lymphatic vessels abutting on to the surface epithelium and often, hyperkeratosis. Histologically, lesions are poorly circumscribed and composed of capillary and cavernous lymph sinususes lined by cytologically bland endothelium.

**CYSTIC HYGROMA**

This lymphangiomatous malformation typically affects the submandibular region and neck, and presents at birth with a large, fluctuant swelling often ramifying into the base of tongue and floor of mouth. The extensive cystic dilatation of the vessels accounts for the progressive growth. The cystic fluid is straw-coloured with low protein content. Lack of a discrete margin and growth along tissue planes and neurovascular bundles hamper removal, and early intervention when the lesion is smaller offers the best chance of cure.

**Tumours of adipose tissue**

‘FIBROLIPOMA’

Some fibroepithelial polyps – reactive fibroepithelial hyperplasias – include mature adipose cells within their fibrous
core and are sometimes referred to as ‘fibrolipomas’. It is uncertain whether the adipose tissue represents entrapped fat cells or degenerative metaplasia.

**HERNIATED BUCCAL FAT PAD**

Acute trauma from cheek biting may rupture the buccal fat pad allowing a portion to herniate as a yellowish-coloured sessile or pedunculated submucosal mass, 3–4 cm in diameter. Once formed, the mass does not increase further in size, but surgical removal is necessary to prevent fresh trauma. Histologically, the herniated mass is composed of normal mature adipose tissue supported by fibrovascular septae.

**LIPOMA**

The lipoma, a benign neoplasm of adipocytes, presents mainly in adults as a soft, smooth submucosal mass, often with a yellowish surface discoloration. The cheek, tongue and floor of mouth are the usual sites, but cases have been reported within maxillary bones and paranasal sinuses. Magnetic resonance imaging is more useful than computed tomography and ultrasonography in preoperative diagnosis. Histologically, mature adipocytes are supported by fibrovascular septae with variable circumscription and encapsulation. As in lipomas at other body sites, several histological variants are recognized including intramuscular (infiltrating), fibrolipoma, angiolipoma, myxolipoma, spindle cell, pleomorphic, myolipoma and angiomylipoma. In addition, hibernomas and lipoblastomas have been reported. Recurrence after conservative surgical removal is rare. Intramuscular lipomas are typically more diffuse and are generally managed by debulking. ‘Lipomatosis’ is applied to extensive involvement of a wide area of stromal connective tissue.

**MULTIPLE HEAD AND NECK LIPOMAS**

Multiple lipomas are seen in several syndromes including neurofibromatosis, Gardner syndrome, Proteus syndrome and hemifacial hypertrophy.

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**Tumours of peripheral nerves**

Reactive and benign neoplasms of peripheral nerves are listed in Box 13.2.

**TRAUMATIC (AMPUTATION) NEUROMA**

The traumatic neuroma is a disorganized overgrowth of nerve fibres, Schwann cells and scar tissue associated with the proximal end of a severed nerve. Small lesions may affect the oral mucosa following minor trauma, but rarely develop in tooth extraction sockets. Lesions arising following parotid gland surgery and within skin flaps may be misdiagnosed clinically as recurrent neoplasm.

**LINGUAL SUBGEMMAL NEUROGENIC PLAQUE**

This is a hyperplastic neural lesion arising adjacent to taste buds of foliate papillae which has distinctive histological features that may be misinterpreted as neurofibroma or neuroma of multiple endocrine neoplasia syndrome.

**MUCOSAL NEUROMA**

These usually present as sessile, painless nodules and may be mistaken clinically for simple fibroepithelial polyps. Lesions tend to be multiple (between two and eight) and may also involve perioral and perinasal skin. Their correct diagnosis is important since they are pathognomonic of the multiple endocrine neoplasia syndromes (MEN) and are most frequently associated with MEN IIb (Box 13.3). Initial presentation with oral lesions is usual. Prompt referral to an endocrinologist is indicated if the diagnosis is suspected in an otherwise asymptomatic youngster. Prophylactic total thyroidectomy is performed early since medullary carcinoma is inevitable and particularly aggressive in MEN IIb.

The histological differentiation between mucosal neuroma and benign neural lesions, such as palisaded encapsulated neuroma and neurofibroma is subtle. In the mucosal neuroma, connective tissues are expanded by a proliferation of hyperplastic nerves, intertwined with each other and embedded in a loose fibrous stroma. Inflammatory cells are lacking and the perineural sheath is characteristically thickened.

**PALISADED ENCAPSULATED NEUROMA**

This presents as a solitary mucosal polyp rarely affecting facial skin. Trauma is a likely aetiological factor. The diagnosis is usually made in elderly adults and hence, clinical features are helpful in differentiation from mucosal neuroma. Histologically, the lesion is circumscribed but without a well-defined capsule. Interlacing bundles of Schwann cells form the bulk and axonal processes can be identified on careful examination. Simple conservative excision is curative.

**SCHWANNOMA**

This relatively common benign nerve sheath tumour has a distinct predilection for head and neck. Lesions are usually solitary unless associated with neurofibromatosis. The slow-growing discrete lump is usually asymptomatic. Because of their origin from nerve sheath cells, schwannomas...
are encased by a true capsule. The nerve of origin can often be identified macro- or microscopically. Histologically, the distinctive short fascicles of palisaded Schwann cells with wavy nuclei make up the cellular areas and diagnostic Verocay bodies, and the intervening paucicellular zones are myxoid. The behaviour is benign and recurrence and malignant transformation are exceptionally rare.

**NEUROFIBROMA**

The neurofibroma shows a variety of growth patterns. The localized neurofibroma (90 per cent of all cases) occurs as a sporadic solitary benign tumour presenting as a slow-growing circumscribed mass. At surgery, a well-circumscribed glistening white tumour is usual. The neurofibroma is a benign proliferation of several components of peripheral nerve: Schwann cells, neurites and perineurial fibroblasts are embedded in a myxoid stroma. A true capsule is lacking and mast cells are characteristically scattered throughout. The component cells are present in varying proportion resulting in a variable histological appearance.

The diffuse and plexiform neurofibromas are typical of neurofibromatosis 1 (NF1), an autosomal dominant inherited disorder with an incidence of 1 in 2500 to 3000 live births. Signs and symptoms are detailed in Box 13.4. The phenotypic expressivity is highly variable. Plexiform neurofibromas develop in childhood and usually involve limbs, although oral lesions are evident in 4–7 per cent of patients. The macroscopic ‘bag of worms’ consists of multiple, hyperplastic tortuous nerves with expansion of all cellular components which spill out into the surrounding soft tissues. Conservative excision is curative in the sporadic cases, but further tumour growth following attempts at removal will occur in NF1 cases. Malignant change in neurofibromas is exclusively in the setting of the NF1 syndrome and at a rate of 2–29 per cent.

**GRANULAR CELL TUMOUR**

This rare benign tumour of Schwann cell origin affects mainly the head and neck with over 50 per cent arising on the tongue. All age groups are affected with a male:female ratio of 1:2. Between 10 and 20 per cent of patients have multiple lesions. Typically, the mucosal swelling is 1–2 cm, smooth, sessile and firm. Lesions may appear pale or white, particularly when infested with candidal organisms. Histologically, polygonal or elongated cells with granular cytoplasm merge with skeletal muscle cells. The granules are periodic acid Schiff (PAS)-positive and may represent an accumulation of lysosomes. The cells are uniformly, strongly positive for S-100 protein. Pseudoepitheliomatous hyperplasia of overlying surface epithelium, seen in 30 per cent of cases, may be misdiagnosed as carcinoma, especially if the biopsy specimen is superficial. Granular cell tumours rarely recur following conservative removal, but aggressive or frankly malignant forms, although rare, have been described.

**CONGENITAL (GRANULAR CELL) EPULIS**

This is a rare congenital tumour, presenting as a 1–2 cm soft, pedunculated mass of the anterior maxillary alveolar mucosa with 90 per cent of lesions occurring in females. The exact histogenesis is uncertain. The mass is composed of large, rounded and polyhedral, histiocytic-like cells with abundant granular cytoplasm. In contrast to the adult granular cell tumour, immunohistochemistry shows the lesional cells are negative for S-100 protein. Congenital epulides tend to regress spontaneously and disappear by eight months of age.

**Tumours of muscle**

**LEIOMYOMA**

This rare tumour arises from vascular smooth muscle, typically presenting as a slowly enlarging, firm submucosal nodule which may be painful. The tumour is well-encapsulated. Solid forms are composed of interlacing bundles of smooth-muscle cells. The vascular form (angiomymoma, angioleiomyoma) includes multiple tortuous blood vessels with hyperplastic walls. Conservative excision is curative.

**RHABOMYOMA**

This benign neoplasm of striated muscle is more common in the head and neck region than any other site, but is still rare.
within the mouth. The adult form typically affects middle aged or older males, while the fetal form affects newborn and young children. Both forms present as a submucosal nodule. Histologically, the lesion is encapsulated. The adult form consists of large uniform polygonal cells with cross-striations within a fibrous stroma. The fetal form is more cellular and has a myxoid stroma. Mitotic figures are exceeding rare, an important distinction from rhabdomyosarcoma.

Lesions of lymphoid tissue

Lymphoid tissue is native in many oral sites and may undergo expansion following antigenic stimulation, resulting in clinical swelling. Two common clinical presentations are localized swelling of the posterolateral tongue (enlarged lingual tonsil) and palatal lesions. Palatal lymphoid hyperplasia has a clinical presentation similar to a minor salivary gland neoplasm. The histological distinction from a follicular lymphoma requires immunohistochemistry.

Melanocytic lesions

Oral mucosal pigmented naevi are rare, but examples equivalent to the skin forms – junctional, compound, dermal and blue – are seen mainly on the lips and palate. Idiopathic oral melanotic naevi due to hyperpigmentation of basal keratinocytes rather than the presence of increased melanocytes or naevus cells are more common, and affect mainly the lower lip, gingivae and buccal mucosa. Clinical features important in distinguishing naevi and macules from malignant melanoma include small size, regular outline, even colour and lack of surface ulceration.

Peutz–Jeghers syndrome, transmitted through an autosomal dominant gene, is characterized by mucocutaneous freckling and gastrointestinal polyposis. The café-au-lait spots of polyostotic fibrous dysplasia and neurofibromatosis rarely affect the oral mucosa.

Choristomas and related developmental lesions

Choristomas are hamartoma-like malformations of well-differentiated tissues foreign to the site of the lesion. Complex hamartomas are more common in females and may occur in the soft palate, oropharynx and tonsil. The pedunculated polyp histologically consists of varying proportions of fully differentiated cartilage, bone, smooth muscle, fibrous, adipose tissue and skin. Oral glial choristomas (heterotopic neuroglial tissue) are less common than their nasal counterparts. Typically, they present in female infants as a polyoid or sessile mass on the tongue, oropharynx or soft palate. They are amenable to conservative excision.

ORAL NEUROECTODERMAL TUMOUR OF INFANCY (PIGMENTED EPULIS OF INFANCY)

This is a rare congenital neoplasm. More than 90 per cent of cases present during the first year of life and 80 per cent occur on the anterior maxillary alveolus. Typically, it presents as a sessile, non-ulcerated, lobulated firm mass, 2–4 cm in diameter, with a deep blue or black colour. Radiographs usually show a poorly demarcated radiolucency of the underlying bone. Histologically, the lesion is biphasic with epithelioid melanocytic-like cells and small round neuroblast-like cells. Developing tooth buds may be incorporated within the lesion. The lesion is thought to develop from neural crest cells38 and at presentation, urinary vanillylmandelic acid levels are often high. The tumour is locally aggressive and wide surgical excision is the treatment of choice.

Lesions of the jaws

Odontogenic tumours

Odontogenic tumours, derived from elements of the tooth-forming apparatus, range from hamartomatous tissue proliferations to benign neoplasms to malignant neoplasms with metastatic potential. An abbreviated form of the WHO classification is shown in Box 13.5. Odontomas, developmental anomalies rather than true neoplasms, account for 29 per cent.1 Of the true odontogenic neoplasms, the ameloblastoma has a prevalence equalling or even exceeding that of other odontogenic neoplasms combined. The diagnosis of odontogenic tumours depends on clinical and radiological features, as well as the precise histology and accurate information including position, relationship to teeth, tooth vitality and circumscription should be submitted to the reporting pathologist. The histological distinction between some odontogenic tumours relies on subtle features. The rarity of many lesions adds to the diagnostic challenge.

Box 13.5 Benign odontogenic tumours

<table>
<thead>
<tr>
<th>Arising from odontogenic epithelium only</th>
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<tr>
<td>Ameloblastoma</td>
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<tr>
<td>Squamous odontogenic tumour</td>
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<tr>
<td>Calcifying epithelial odontogenic tumour</td>
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<tr>
<td>Adenomatoid odontogenic tumour</td>
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<tr>
<td>Keratocystic odontogenic tumour (odontogenic keratocyst)</td>
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<table>
<thead>
<tr>
<th>Including odontogenic epithelium, as well as ectomesenchyme with or without hard tissue formation</th>
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<tr>
<td>Ameloblastic fibroma</td>
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<tr>
<td>Ameloblastic fibroodontoma or fibro-odontoma</td>
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<tr>
<td>Complex and compound odontoma</td>
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<tr>
<td>Calcifying cystic odontogenic tumour</td>
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<tr>
<td>Dentinogenic ghost cell tumour</td>
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<table>
<thead>
<tr>
<th>Odontogenic ectomesenchyme only</th>
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<tbody>
<tr>
<td>Odontogenic fibroma</td>
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<tr>
<td>Odontogenic myxoma</td>
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<tr>
<td>Cementoblastoma</td>
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</table>
AMELOBLASTOMA

Ameloblastoma, although the most common odontogenic neoplasm, is still rare comprising 0.04 per cent of all oral biopsies in Caucasian Americans and 5.28 per cent in Nigerians. There are several distinct subtypes (see Box 13.6) with important differences in current recommendations for management.

Conventional solid multicystic ameloblastoma

This is the most common type. All age groups are affected with a mean age of 36 years and around 8 per cent occurring in children and adolescents. Males and females are almost equally affected. Presenting symptoms include swelling (generally painless), delayed eruption or mobility of teeth. Mandibular tumours outnumber maxillary by a ratio of 5:1. Racial differences exist with regards to site – the molar and ramus region is mainly affected in Caucasians, while the anterior mandible is the favoured site in Blacks.

Radiologically, a uni- or multilocular radiolucency is typical. Larger lesions may be associated with root resorption, a useful radiological indicator of the neoplastic nature. Honeycombed and soap bubble appearances are even stronger indicators.

The microscopic appearances are characteristic with two cell types forming islands (follicular subtype) or interlacing strands (plexiform subtype) within a fibrous stroma. The outermost tall columnar cells display reversed polarity and resemble the ameloblast or enamel-forming cell of the normal developing tooth. The central, angular epithelial cells resemble the stellate reticulum of the tooth germ. Neither enamel nor dentine are formed, since in normal development, enamel deposition follows dentine formation and the initiating dentine is not possible. Cystic change, within the larger epithelial islands and the fibrous stroma, is common.

Published recurrence rates, ranging from 20 to 90 per cent, are difficult to interpret and the length of follow up and treatment modality both need to be considered. In a large review of the world literature, recurrence rates of 34.7 and 22.6 per cent were reported following conservative and radical treatment, respectively. There was no significant difference in recurrence of mandibular tumours when the treatment modalities were compared, but maxillary tumours were more likely to recur following conservative treatment.

The average time to recurrence was 7.2 years and was shorter following conservative therapy (4.8 years) compared with radical therapy (11.1 years).

Treatment options


Given the benign nature of the tumour, there is reluctance to perform extensive surgery in the first instance. Conservative management includes enucleation and curettage, and marsupialization followed by planned enucleation. If the remaining bony structure is compromised, the patient must be instructed to adhere to a soft diet and avoid contact sports to prevent pathological fracture. Prolonged radiological follow up is mandatory, initially at close intervals to monitor bony in-fill.

2. Surgical excision with peripheral ostectomy.

This procedure involves surgical exposure of a large area of bone. The tumour is then enucleated, preferably en masse and the bony cavity is ground away 2–3 mm beyond the visible margin using a round craniotomy (acrylic) bur. Teeth in contact with tumour and those preventing adequate access should be removed. Again, prolonged clinical and radiological follow up are essential. The technique is most suitable for tumours of the mandibular symphys and body, and is not recommended for tumours extending into the condyle, sigmoid notch or posterior maxilla.

3. Radical treatment: resection and reconstruction.

The well-known ability of ameloblastoma to infiltrate cancellous bone for 4–5 mm beyond the radiological limits and the occasional death due to direct intracranial extension led to the recommendation of radical surgery, such as segmental mandibulectomy. The resection margin should be 1–1.5 cm beyond the radiological extent of tumour. Wide resection may be the only option in large mandibular tumours involving the condyle/sigmoid notch or lower border. Radical resection is almost always recommended for maxillary tumours. The bone is less dense and local spread may be more than anticipated radiologically, and the consequences of a maxillary recurrence are severe with a mortality of up to 60 per cent.

In children, treatment is complicated by active growth, less dense bone and the presence of unerupted teeth which can hamper attempts at curettage. Fortunately, tumours in children tend to be unicystic and generally more amenable to conservative treatment.

Malignant transformation of ameloblastoma appears to be very rare. Metastasizing ameloblastoma refers to the dissemination of cytologically benign tumour most commonly to the lungs, pleura and regional nodes, and is seen occasionally in tumours of long duration or multiple recurrences.

Unicystic ameloblastoma

These account for 5–15 per cent of all ameloblastomas. Diagnosis depends on clinical findings at operation along with radiological and pathological features. The minimum

<table>
<thead>
<tr>
<th>Box 13.6 Subclassification of ameloblastoma</th>
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<tr>
<td>• Conventional solid multicystic</td>
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<tr>
<td>– plexiform</td>
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<tr>
<td>– follicular</td>
</tr>
<tr>
<td>– acanthomatous</td>
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<tr>
<td>– granular cell</td>
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<tr>
<td>• Unicystic</td>
</tr>
<tr>
<td>– type I luminal</td>
</tr>
<tr>
<td>– type II intraluminal</td>
</tr>
<tr>
<td>– type III intramural</td>
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<tr>
<td>• Peripheral</td>
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<td>• Desmoplastic</td>
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criterion is the demonstration of a single cystic sac lined by odontogenic epithelium with ameloblastomatous features. Some lesions are associated with the crown of an unerupted tooth mimicking a dentigerous cyst radiologically. The posterior mandible related to an impacted third molar is the most frequent site.

The three distinct histological subtypes are depicted in Figure 13.1. Types I and II are most likely to be 'dentigerous', whereas mural invasive tumours (type III) are usually not tooth-associated. Recurrence rates following conservative treatment are 11 per cent for intraluminal tumours and up to 25 per cent for those with a mural component. Currently, conservative treatment is advocated in types I and II. It is suggested that type III lesions have the same tendency to local recurrence as conventional ameloblastomas and hence, should be managed similarly. Nevertheless, until further studies are available, the treatment of unicystic ameloblastomas is somewhat controversial.

Peripheral ameloblastoma

Generally, this presents as a discrete painless, firm, smooth gingival swelling indistinguishable from the common epithelides (see above under Localized gingival hyperplasia, p. 240). The lesion occurs only within the soft tissues overlying tooth-bearing areas of the jaws. The histological features are identical to central intraosseous tumours yet the behavioural differences are marked. The diagnosis cannot be made on biopsy alone as extraosseous extension of a central tumour must be excluded radiologically. In peripheral ameloblastomas, erosive, cup-like defects are acceptable. Age at presentation (mean age, 52 years) is older than that of the conventional type and there is a male preponderance (2:1). The majority are sited in the mandibular canine to molar region. Adolescents and young adults are mainly affected (mean age, 15 years). The histological appearances may be indistinguishable from a dentigerous cyst radiologically. The presence and amount of radiopaque material is variable and when lacking, the radiological appearances may be indistinguishable from a simple dentoalveolar lesion. At operation, the encapsulated solid

Figure 13.1 Histological classification of unicystic ameloblastoma: 1 indicates flattened ameloblastomatous epithelium lining the luminal surface (type I); 2 shows papillomatous fronds of ameloblastomatous epithelium projecting into and often filling the lumen (type II); 3 indicates areas of actual tumour invasion of the fibrous wall by discrete islands or tongues of epithelium, some of which may maintain a connection with the luminal lining (type III).

AMELOBLASTIC FIBROMA, AMELOBLASTIC FIBRODENTINOMA AND FIBRO-ODONTOOMA

Ameloblastic fibroma is a benign tumour in which both the epithelial and mesenchymal components are neoplastic. Differentiation from ameloblastoma is important since ameloblastic fibroma does not have the capacity for destructive, infiltrative growth and requires only simple, conservative excision. Radiologically, a uni- or multilocular radio-locuity with smooth, sclerotic margins is typical. Adolescents and young adults are mainly affected (mean age, 15 years). The histopathological findings are characteristic with neoplastic epithelium arranged in delicate cords and islands within a cellular stroma which resembles immature dental pulp. When the epithelial component is scant, the appearances can resemble hyperplastic dental follicle, the soft tissue cap that surrounds the crown of unerupted teeth. Misdiagnosis can usually be avoided if the pathologist is aware of the clinical and radiological details. Ameloblastic fibrodentinoma and ameloblastic fibro-odontoma are neoplasms similar to ameloblastic fibroma in terms of cell types and architecture, with the additional formation of dental hard tissues, either dentine only or both dentine and enamel.

ODONTOOMA

Odontoma, regarded as hamartomatous lesions rather than neoplasms, are characterized by variable amounts of enamel, dentine and cementum along with soft tissues resembling dental papilla or follicle and remnants of reduced enamel epithelium. Two architectural patterns are recognized. In complex odontoma, the hard and soft tissue components are haphazardly arranged without a recognizable tooth-like structure. In the compound type, multiple 'denticles' (minature teeth) are present within a fibrous sac. The distinction is not clear cut and may be complicated by immature forms containing epithelial elements similar to those in the ameloblastic fibroma. The existence of the hybrid lesions has led to uncertainty about the true nature of the ameloblastic fibroma and its variants and some workers consider the latter represent immature complex odontoma.

ADENOMATOID ODONTOGENIC TUMOUR

The adenomatoid odontogenic tumour accounts for around 3 per cent of all odontogenic tumours. Females in the second decade of life are mainly affected. A well-defined unilocular radiolucency with speckled radiopaque flecks, overlying the unerupted upper canine is typical. Presentation can be with swelling, but is more often radiological on investigation of delayed tooth eruption. The presence and amount of radiopaque material is variable and when lacking, the radiological appearances may be indistinguishable from a simple dentoalveolar lesion. At operation, the encapsulated solid
or cystic tumour shells out from the surrounding bone. Microscopically, the solid nests of whorled epithelial cells admixed with duct-like structures and globules of dentine-like material are characteristic. Recurrence after simple enucleation is rare.

**KERATOCYSTIC ODONTOGENIC TUMOUR (FORMERLY ODONTOGENIC KERATOCYST)**

This entity was formerly categorized as a developmental odontogenic cyst. The recent designation as a benign tumour is based on the tendency for local recurrence following curettage and molecular evidence of a bi-allelic loss of tumour suppressor genes which supports a neoplastic aetopathogenesis. The lesion occurs in two clinical settings. Most are sporadic solitary cases, presenting at a mean age of 40 years. The lesions that occur as part of the naevoid basal cell (Gorlin) syndrome are frequently multiple, present at a younger age (mean age, 26 years) and show a greater tendency to recur. The syndrome (see Box 13.7) is an autosomal dominant transmitted disorder. The mutation affects a component of the hedgehog signalling pathway.

Small keratocystic odontogenic tumours may be incidental radiological findings. A multilocular radiolucency with a well-defined sclerotic margin is typical, but a small unilocular lesion associated with the crown of a unerupted tooth or apex of a carious tooth can mimic a dentigerous (follicular) or inflammatory radicular cyst. Larger lesions may present with swelling or tooth mobility. A well-defined unilocular radiolucent lesion between the roots of adjacent teeth is typical. The largest series contains only 36 cases, hence, age, site and gender predilections are uncertain. Histologically, the tumour consists of rounded islands of squamoid epithelial cells embedded in a dense fibrocollagenous stroma. The differential diagnosis includes ameloblastoma and intraosseous squamous cell carcinoma. The biological potential of this tumour has not been fully elucidated and conservative, but complete excision is generally recommended.

**CALCIFYING ODONTOGENIC CYST (FORMERLY CALCIFYING ODONTOGENIC CYST)**

This exceptionally rare benign, locally infiltrative tumour may present with swelling or tooth mobility. A well-defined unilocular radiolucent lesion between the roots of adjacent teeth is typical. The largest series contains only 36 cases, hence, age, site and gender predilections are uncertain. Histologically, the tumour consists of rounded islands of squamoid epithelial cells embedded in a dense fibrocollagenous stroma. The differential diagnosis includes ameloblastoma and intraosseous squamous cell carcinoma. The biological potential of this tumour has not been fully elucidated and conservative, but complete excision is generally recommended.

**SQUAMOUS ODONTOGENIC TUMOUR**

This exceptionally rare benign, locally infiltrative tumour may present with swelling or tooth mobility. A well-defined unilocular radiolucent lesion between the roots of adjacent teeth is typical. The largest series contains only 36 cases, hence, age, site and gender predilections are uncertain. Histologically, the tumour consists of rounded islands of squamoid epithelial cells embedded in a dense fibrocollagenous stroma. The differential diagnosis includes ameloblastoma and intraosseous squamous cell carcinoma. The biological potential of this tumour has not been fully elucidated and conservative, but complete excision is generally recommended.

**CALCIFYING EPITHELIAL ODONTOGENIC TUMOUR (PINDborg TUMOUR)**

Originally described in 1955, this benign but locally aggressive tumour accounts for less than 3 per cent of odontogenic tumours. An irregular uni- or multilocular radiolucent area containing radiopaque spicules of varying size is typical. Association with the roots or crown of a tooth may lead to a non-neoplastic initial diagnosis. The tumour presents across a wide age range (mean age, 37 years). Mandibular tumours outnumber maxillary ones by 2:1.

The pathological features are diagnostic: sheets of pleomorphic squamoid epithelial cells with amyloid and concentric calcified bodies within the supporting stroma. The epithelial cytological atypia may be striking and could lead to a misdiagnosis of malignancy. The growth potential appears similar to or less than the conventional ameloblastoma and recurrence after conservative treatment is < 20 per cent.

**DENTINOGENIC GHOST CELL TUMOUR**

The dentinogenic ghost cell tumour is a solid variant of calcifying cystic odontogenic tumour consisting of epithelial islands resembling conventional follicular ameloblastoma, together with central masses of ghost cells and abundant dentinoid material. Currently, the behaviour of this solid tumour is considered analogous to the conventional ameloblastoma and the same controversies regarding optimal treatment apply.

**ODONTOGENIC MYXOMA**

The odontogenic myxoma accounts for 3 per cent of odontogenic neoplasms and typically presents with progressive swelling that occasionally ulcerates through the covering alveolar mucosa. Rapid growth may occur and displacement...
of teeth is usual. A multilocular radiolucency, described as soap bubble or honeycombed, is typical and the radiological differential diagnosis includes ameloblastoma and haemangioma. Occurrence across a wide age range is reported (mean age, 30 years). There is no gender predilection. The biopsy findings are of sheets of stellate fibroblastic cells separated by abundant mucoid ground substance. Lack of capsule, infiltrative growth with permeation of narrow spaces around delicate trabeculae of residual lamellar bone are important features. Islands of odontogenic epithelium are sometimes seen, but are not a diagnostic prerequisite. Small lesions may be difficult to distinguish from a hyperplastic dental follicle. Treatment of large odontogenic myxomas usually necessitates radical resection. Smaller tumours should be assessed individually, but there is a high rate of recurrence following inadequate conservative treatment.

**ODONTOGENIC FIBROMA**

There are only around 70 reported cases with equal numbers in both jaws and a male to female ratio of 1:3. Presentation occurs across a wide age range (mean age, 35 years). A unilocular radiolucency with well-defined sclerotic borders is typical, although multicellular lesions are sometimes seen. Occasional cases show root resorption.

Two distinct histological patterns are recognized. The 'simple type' consists of cellular fibroblastic tissue with variable amounts of myxoid ground substance separating the collagen bundles. The 'WHO type' is more cellular and less collagenous and includes aggregates of inactive odontogenic epithelium. In contrast to odontogenic myxoma, odontogenic fibroma lacks infiltrative growth, shells out easily and never requires radical treatment.

**BENIGN CEMENTOBLASTOMA**

The cementoblastoma shares many similarities with osteoblastoma (see below under Osteoid osteoma and osteoblastoma, p. 252), but confinement to tooth-bearing areas of the jaws and root attachment confers its odontogenic status. Peak incidence is in adolescents and young adults (mean age, 20 years). Pain and swelling are presenting features. Most cementoblastomas occur in the mandible, associated with the first molar tooth. Radiologically, a well-defined radiopaque mass that fuses with, and may cause resorption of, the tooth root is typical. A thin radiolucent rim (representing the fibrous capsule) separates the lesion from adjacent bone. At surgery, the lesion separates easily from the bone. Microscopically, the features are indistinguishable from those of an osteoblastoma. In more mature lesions, prominent Pagetoid reversal and resting lines may be seen at the periphery. Recurrence is likely if initial removal is incomplete.

**PERIPHERAL ODONTOGENIC TUMOURS**

The peripheral ameloblastoma is discussed in detail above under Peripheral ameloblastoma, p. 247. Peripheral variants of odontogenic fibroma, calcifying cystic odontogenic tumour, calcifying epithelial odontogenic (Pindborg) tumour and adenomatoid odontogenic tumour are described. The histological appearances resemble the central counterpart. The peripheral odontogenic fibroma is much more likely to be the WHO type and the presence of the inactive odontogenic epithelial islands helps to distinguish it from a cellular fibrous epulis. All peripheral odontogenic tumours show indolent growth and complete conservative excision is curative.

**MALIGNANT ODONTOGENIC TUMOURS**

These are rare. Some appear to be malignant counterparts of benign odontogenic tumours. Others may arise by malignant transformation of epithelial residues or the lining of odontogenic cysts (Box 13.8). The aetiology is unknown. Odontogenic carcinomas seem to occur more frequently in the elderly. Clinical symptoms include swelling, pain, bleeding, mucosal ulceration, tooth mobility and paraesthesia or anaesthesia. Involvement of local lymph nodes and distant metastases may occur early. Radiologically, extensive jaw destruction with ill-defined borders, sometimes including patchy radiopacities, is typical. Due to their rarity, specific treatment protocols are not available. The prognosis is poor even after surgical resection with tumour-free margins.

**FIBRO-OSSEOUS LESIONS**

This is a group of lesions, some developmental with a genetic aetiology, some neoplastic, characterized by replacement of bone by cellular fibrous tissue in which variable amounts of metaplastic mineralized tissue is deposited. The histological features can be similar and precise clinical and radiological information is essential for the pathologist making the final diagnosis.

The WHO classification of fibro-osseous lesions is shown in Box 13.9.
Box 13.9 Classification of fibro-osseous lesions of the maxillofacial region

- Ossifying fibroma (OF)
  - conventional OF
  - juvenile aggressive OF: psammomatoid OF, trabecular OF
- Fibrous dysplasia (FD)
  - monostotic FD
  - polyostotic FD
  - craniofacial FD
- Osseous dysplasias (OD)
  - periapical OD (POD)
  - focal OD (FOD)
  - florid OD (FIOD)
  - familial gigantiform cementoma
- Central giant cell lesion (granuloma)
- Cherubism

Ossifying fibroma

CONVENTIONAL OSSIFYING FIBROMA

Conventional ossifying fibroma (COF) is a benign neoplasm which originates from periodontal ligament cells and is distinguished by a fibrous capsule separating it from adjacent normal bone. The clinical, radiological and histological features are summarized in Table 13.1. As this is a true benign neoplasm, growth will continue and surgical removal is indicated. The capsule allows the tumour to be shelled out intact and complete removal is curative.

JUVENILE (AGGRESSIVE) OSSIFYING FIBROMA

Two distinct types with differing clinical and histological features are recognized and summarized in Table 13.1. Like the conventional ossifying fibroma, these are true neoplasms with the potential for continued, often rapid growth leading to significant morbidity if they extend to erode the base of skull or involve structures such as the orbit, when blindness may ensue.

JUVENILE TRABECULAR OSSIFYING FIBROMA

The trabecular type is restricted to children and adolescents with a mean age of ten years and involves the jaw bones in over 90 per cent of cases with only 6 per cent affecting the bones of the sinonasal cavity.

JUVENILE PSAMMOMATOID OSSIFYING FIBROMA

The psammomatoid type is not restricted to children or adolescents. It has been reported in adults as old as 72 years, although the mean age is 20 years. The bones of the sinonasal cavity are twice more commonly affected than those of the jaws, suggesting that this neoplasm is distinct from the COF with a different cell of origin.

Fibrous dysplasia

Fibrous dysplasia (FD), a developmental condition, with a genetic basis may be monostotic or polyostotic. Lesions restricted to the craniofacial region may involve several bones, but are designated ‘craniofacial FD’, rather than polyostotic. Polyostotic FD may be associated with endocrinopathies. For example, the McCune-Albright syndrome affects females and is characterized by precocious puberty, functional disorders of the pituitary, thyroid and adrenal glands, and café-au-lait skin pigmentation. The genetic change responsible for FD is an activating point mutation of the GNAS1 gene that encodes for a component of G protein complex which is involved in cell signalling. The resulting constitutive activation of the complex and overproduction of the signalling molecule cAMP results in impaired maturation of stem cells into functioning osteoblasts. Clinical severity and extent of disease depends on the timing of the mutation during embryogenesis with earlier timing leading to widespread and systemic manifestations.

Diagnosis is usually made in childhood or adolescence following painless diffuse enlargement of the jaw(s). The maxilla is more commonly affected than the mandible. Radiologically, early lesions may be radiolucent, but in later stages, a diffuse ‘ground-glass’ radiopacity is characteristic. Lesions are poorly defined and merge with normal adjacent bone. Histologically, biopsy material shows replacement of bone by richly cellular fibrous tissue in which delicate trabeculae of immature woven bone (‘Chinese characters’) are deposited. The lack of osteoblastic rimming and imperceptible merging of lesional and normal tissue are important diagnostic features and the biopsy should include the apparent interface of lesional and normal bone. Following diagnostic biopsy, further surgical intervention is discouraged since it may act as a stimulus. Once skeletal maturity is reached, trimming of excessive bone may be indicated for cosmesis.

Osseous dysplasias (formerly cemento-osseous dysplasias)

The osseous dysplasias (OD) are specific to the tooth-bearing areas of the jaws and an origin from the periodontal ligament is favoured. They are almost certainly reactive in nature and four subtypes with different clinical presentations are recognized (see Table 13.2). All types are more common in black female adults and the prevalence in this population may be as high as 6 per cent. Periapical and focal lesions are usually incidental radiological findings. Florid OD may expand the jaws and occasionally erupt through the covering alveolar mucosa presenting with poorly fitting dentures and ulceration. The poor cellularity of mature, sclerotic lesions leads to increased susceptibility to infection and chronic osteomyelitis.

Radiologically, the appearance depends on the age of the lesion. Periapical OD in its initial stages may be misinterpreted as periapical infection of non-vital teeth. Histologically, the four subtypes are indistinguishable. In early stages, cellular fibrous tissue predominates with increasing deposition of trabeculae of woven bone and
rounded cementum-like globules of mineralized tissue. In advanced lesions, mineralized tissue predominates with masses of woven and lamellar bone fusing with basophilic acellular masses of globular cementum. Surgical intervention is only indicated when secondary osteomyelitis is present with the intention of removal of all necrotic infected tissue and adjacent sclerotic mineralized tissue of reduced vitality.

### Table 13.1 Clinical, radiological and histological features of ossifying fibroma.

<table>
<thead>
<tr>
<th></th>
<th>Ossifying fibroma</th>
<th>Juvenile psammomatoid ossifying fibroma</th>
<th>Juvenile trabecular ossifying fibroma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Posterior mandible</td>
<td>Sinonasal 62%</td>
<td>Maxilla 50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maxilla 20%</td>
<td>Mandible 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mandibular 10%</td>
<td>Sinonasal 6%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Young to middle-aged adults</td>
<td>Mean 20 years, range 3 months to 72 years</td>
<td>Mean 10 years, range 2 to 30 years</td>
</tr>
<tr>
<td><strong>Sex and race</strong></td>
<td>Female: male 2:1</td>
<td>Female: male 1.3:1</td>
<td>Female: male 1.2:1</td>
</tr>
<tr>
<td><strong>Radiological features</strong></td>
<td>Unilocular mixed radiolucency/radiopacity, sclerotic rim</td>
<td>Well defined, tends to be radiopaque</td>
<td>Well-defined radiolucency with variable speckled radiopacity</td>
</tr>
<tr>
<td><strong>Histological features</strong></td>
<td>Encapsulated cellular fibrous stroma, trabeculae of woven bone and spherical cementoid material, osteoblastic rimming</td>
<td>Densely cellular stroma, spherical psammomatoid calcifications. May be surrounded by osteoid halo</td>
<td>Densely cellular stroma, delicate poorly mineralized interfacing bony trabeculae</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Enucleation</td>
<td>Complete surgical excision</td>
<td>Complete surgical excision</td>
</tr>
</tbody>
</table>

### Table 13.2 Clinical features of osseous dysplasias.

<table>
<thead>
<tr>
<th></th>
<th>Periapical osseous dysplasia</th>
<th>Focal osseous dysplasia</th>
<th>Florid osseous dysplasia</th>
<th>Familial gigantiform cementoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Apices of mandibular incisor teeth</td>
<td>Body of mandible, sometimes at an extraction site</td>
<td>Bilateral mandible ± maxilla</td>
<td>Bilateral mandible ± maxilla</td>
</tr>
<tr>
<td><strong>Sex and race</strong></td>
<td>F &gt; M, 8–9:1, 60–70% Black</td>
<td>F &gt; M, 8–9:1, 60–70% Black</td>
<td>F &gt; M, 26:1, 78% Black</td>
<td>F &gt; M, Black</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Middle aged, mean 45 years</td>
<td>Middle aged, mean 45 years</td>
<td>6th and 7th decades</td>
<td>Young age. Autosomal dominant inheritance with variable expression</td>
</tr>
<tr>
<td><strong>Radiological features</strong></td>
<td>Radiolucent initially, well-defined</td>
<td>Radiolucent initially, well-defined</td>
<td>As in focal lesions, but greater tendency for expansile sclerotic lesions to develop with maturity</td>
<td>Considerable jaw expansion by densely opaque masses</td>
</tr>
<tr>
<td></td>
<td>Progressively opacifies with maturity</td>
<td>Progressively opacifies with maturity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histological features</strong></td>
<td>Cellular stroma with variable deposition of metaplastic bone and cementoid-like material merging with normal bone</td>
<td>Cellular stroma with variable deposition of metaplastic bone and cementoid-like material merging with normal bone</td>
<td>As in focal lesion, but tendency for fused globular masses of hypocellular masses of cementoid material to dominate</td>
<td>As in florid osseous dysplasia</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Nil required and active treatment contraindicated</td>
<td>Nil required unless secondary infection ensues</td>
<td>High rate of secondary infection, managed by curettage of necrotic tissue + antimicrobial therapy</td>
<td>As in florid osseous dysplasia. Surgery may be needed for cosmesis of facial deformity</td>
</tr>
</tbody>
</table>
Central giant cell lesion

Central giant cell lesion (CGCL), a reactive, reparative lesion, mainly affects the posterior mandible of young adult females. Most cases are sporadic, but some are related to systemic conditions, including Noonan syndrome. Lesions may be incidental findings or present with pain, paraesthesia, swelling and loose teeth. Radiography shows an expansile, multilocular radiolucency with well-defined, scalloped borders and intralesional wavy septae. Tooth displacement, loss of lamina dura and root resorption are typical. Histology shows osteoclast-like, multinucleated giant cells supported by a highly vascular stroma containing spindle-shaped fibroblasts and trabeculae of metaplastic bone. Enucleation may be followed by recurrence, and calcitonin, glucocorticoids and interferon alpha have been advocated for persistent lesions.

The brown tumour of hyperparathyroidism is morphologically similar to CGCL and parathormone levels should be determined especially in elderly patients and when lesions are multifocal.

CGCL must be distinguished from the giant cell tumour (GCT) of bone. GCT mainly affects long bones with occasional cases in the sphenoid, ethmoid and temporal bones. Subtle histological differences are described. GCT is locally aggressive and malignant forms, capable of lung metastases, may occur sporadically or in Paget’s disease.

Cherubism

This autosomal dominant inherited condition (mapped to chromosome 4p16.3) presents in early childhood with symmetrical swelling of the maxilla, mandibular angle and ramus, delayed eruption and tooth displacement, visual impairment and cervical lymphadenopathy. Affected bones are expanded by well-demarcated ‘soap bubble’ radiolucencies followed by progressive sclerosis. Microscopy resembles central giant cell lesion with the addition of characteristic perivascular collagenous cuffs. Lesions regress after puberty, and surgery should only be carried out to improve function in severe cases.

Benign Tumours of Bone

Osteoma and other bony overgrowths

Exostoses (localized overgrowths) are more common than neoplasms. Most exostoses consist of lamellae of compact bone, although larger ones may have a cancellous core. Torus palatinus develops in the midline of the palate. Torus mandibularis forms bilaterally on the lingual aspect of the mandible in the premolar region. Tori and other exostoses present as hard, rounded swellings covered by mucosa of normal appearance unless traumatized.

Osteomas are more common in the paranasal sinuses than the jaw bones. Lesions may arise on the surface of the bone presenting clinically as slow-growing, hard swellings, or be confined within the substance of the cancellous bone. Radiologically, a sharply defined, densely radiopaque mass is typical. Osteomas resemble mature bone. Compact (ivory) osteomas consist of dense lamellae arranged in layers. cancellous osteomas consist of slender trabeculae supported by fatty marrow surrounded by a cortical shell. Generally, exostoses and osteomas are only removed if they interfere with dentures or for cosmesis.

Multiple jaw osteomas raise the possibility of Gardner’s syndrome (familial adenomatous polyposis). The osteomas may be present for a decade or more before intestinal malignancy develops and their correct diagnosis can lead to early recognition of the syndrome and the opportunity for prophylactic colectomy.

Osteochondroma (cartilage-capped osteoma) grow by ossification beneath a cartilaginous cap. Most maxillofacial lesions affect the condyle and coronoid process and may interfere with joint function. Their status – developmental versus neoplastic – is uncertain and some may be difficult to distinguish from condylar hyperplasia.

Osteoid osteoma and osteoblastoma

These two benign tumours show identical histological features, but subtle clinicoradiological differences. In the jaws, osteoblastoma is more common than osteoid osteoma. Both tumours typically affect patients <30 years and present with localized pain that is particularly severe at night and relieved by aspirin. The osteoid osteoma is always <2 cm in maximum dimension. Osteoblastoma has a greater tendency for growth and thus may present with swelling.

Radiologically, both present as well-defined lucent lesions with a sclerotic rim and sometimes speckled intralesional calcification. At operation, a nidus of soft tissue with gritty areas that easily shells out from the surrounding bone is typical.

The histological features (a cellular and vascular stroma with active formation of osteoid and woven bone) can be worrying and reminiscent of malignant osteosarcoma. Peripheral maturation into lamellar bone, as well as precise clinical and radiological information, is important in determining the correct diagnosis. Recurrence following conservative treatments, such as curettage, is reported in the range of 10–20 per cent.

Cartilaginous tumours

Benign cartilage tumours of the jaws are rare, and many ultimately prove to be malignant. Typically, chondromas present as firm nodules, <3 cm in diameter, in the anterior maxilla and posterior mandible. They consist of hyaline cartilage often with focal calcification/ossification accounting for the variable radiographic appearances. The histological distinction from a low-grade chondrosarcoma is notoriously difficult. Chondroblastomas and chondromyxoid fibromas are also encountered. Cartilaginous tumours can grow in the soft tissues as a result of seeding of tumour cells at operation and the treatment of choice is wide excision and prolonged follow up.

Synovial chondromatosis is rare in the temporomandibular joint and is usually diagnosed by the characteristic
radiological images produced by the multiple metaplastic nodules of cartilage within the synovial connective tissue.

**KEY LEARNING POINTS**

- Most oral swellings are a hyperplastic response to chronic irritation.
- Biopsy diagnosis is necessary since hyperplastic and benign neoplasms may have similar clinical manifestations.
- The range of epithelial and connective tissue benign lesions is wide.
- Lesions may herald or represent part of a systemic, sometimes serious, condition.
- Odontogenic tumours are unique to the jaws and include the ameloblastoma.
- Treatment of ameloblastoma is controversial in view of its variable invasive potential.

**REFERENCES**


INTRODUCTION

While paragangliomas of the head and neck will usually present to otolaryngologists, they demand a multidisciplinary approach, and are best managed by teams with an up-to-date knowledge of these complex lesions. The genetics of paragangliomas is an intriguing and emerging field, and in some cases, genetic investigation and appropriate referral to a clinical geneticist may be indicated. In virtually all cases, accurate diagnosis can be achieved preoperatively by appropriate imaging and skilled radiological interpretation. Treatments are becoming more conservative with an increasing acceptance of ‘watch and wait’ and radiotherapy as viable therapeutic options. Where surgery is being advocated, the emphasis is on function preservation, modifying traditional approaches in order to achieve this. Postoperatively, cranial nerve rehabilitation with the assistance of a dedicated team of therapists will often be a vital part of management.

NOMENCLATURE

Historically, paragangliomas have been described according to their histological appearance (glomus tumours), their staining characteristics (non-chromaffin paraganglioma) or their physiological function (receptoma or chemodectoma). Currently, the accepted nomenclature supported by the World Health Organization describes paragangliomas according to their anatomical location (carotid paraganglioma, vagal paraganglioma, etc.).
located at the adventitia of the bifurcation of the common carotid artery, and associated with the nerve of Hering, a branch of the glossopharyngeal nerve. Paraganglia in the jugulotympanic region are much smaller than carotid paraganglia (0.5 mm versus 2.5 mm) but well described: in 1953, Guild’s examination of 88 temporal bones revealed a total of 248 paraganglia, of which 135 were associated with Jacobson’s nerve (the tympanic branch of the glossopharyngeal nerve), and 113 were associated with Arnold’s nerve (the auricular branch of the vagus nerve) and the adventitia of the dome of the jugular bulb. Vagal paraganglia are described at all three ganglia along the suprahyoid course of the Xth nerve, namely the superior jugular ganglion, the middle ganglion, and the inferior nodose ganglion. There are two recognized pairs of laryngeal paraganglia: a superior paraganglion situated in the false cord and associated with the superior laryngeal vessels, and an inferior paraganglion closely associated with the cricoid cartilage in the subglottis. The fact that paragangliomas have been identified in the orbit, pterygopalatine fossa, thyroid, nasopharynx and sphenoid and maxillary sinuses, suggests that these locations also harbour paranganglia, although normal paranganglial tissue has not been found at these sites.

Microstructure of paraganglia

All paraganglia are characteristically composed of two distinct cell types: type I and type II cells. Type I cells have the capacity for the synthesis and storage of catecholamines and are characterized by a rich concentration of cytoplasmic organelles, and by hormone-containing granules. Type II cells are sustentacular cells and are similar to Schwann cells morphologically. A feature of paraganglial cells that is relevant to their investigation and management is their rich density of somatostatin receptors (SSR2 in particular): this can be exploited by the use of somatostatin analogues in the radiological investigation and treatment of paragangliomas (see below under Radionuclide techniques and 18F-DOPA-PET). In common with other endocrine tissue, paraganglionic tissue is richly vascularized.

Physiology

In terms of function, the paraganglion system forms part of the physiologically important, but generally poorly understood, diffuse neuroendocrine system (DNES). This term describes a wide variety of cells throughout the body that are anatomically associated with neural structures and are functionally active, secreting hormones, neurotransmitters and other regulatory proteins to exert either endocrine, paracrine (i.e locally active) or autocrine (i.e autoregulatory) effects. Examples of cells within the DNES include thyroid ‘C’ cells, gastroenteropancreatic hormone-producing cells, and pituitary endocrine cells. Cells within this family share a common embryological origin (the neural crest), a common biochemistry (the amine precursor and uptake decarboxylase (APUD) system), common histological features, and are primarily homeostatic in function.
The most active biochemical pathway in cells of the DNES is the synthetic pathway that governs the synthesis of catecholamines from tyrosine. Interestingly, while abdominal paraganglia are able to complete this pathway with the conversion of norepinephrine to epinephrine, head and neck paraganglia lack the enzyme (phenylethanolamine-N-methyltransferase) necessary for this step, and produce only norepinephrine.\textsuperscript{16}

The anatomical distinction between head and neck (i.e. branchiopericardic and intravagral) and thoracoabdominal (i.e. aorticosympathetic) paraganglia seems to be maintained in their physiological function. The adrenal medulla could be loosely described as ‘the largest paraganglion in the body’ in that it is microscopically identical to other ‘extra-adrenal paraganglia’. The function of aorticosympathetic paraganglia seems to be to secrete catecholamines in infancy and early childhood during the maturation of the adrenal medulla, a theory supported by the fact that these paraganglia degenerate in early childhood.\textsuperscript{17}

The fundamental role of the carotid paraganglion is well understood and was the subject of the Nobel Prize for Physiology and Medicine awarded to Heymans et al. in 1938.\textsuperscript{18} The carotid paraganglion acts as a chemoreceptor stimulated by hypoxic blood chemistry (low PaO\textsubscript{2}, an increase in \(\text{PCO}_2\) and a low pH). Stimulation results in discharging of Hering’s nerve, with reflex communication to the respiratory centre in the medulla oblongata and a consequent increase in respiratory rate and depth. The exact mechanisms of chemoreception are only poorly understood, but it has been postulated that the mitochondrial respiratory chain in type I cells is sensitive to hypoxia, and triggers a release of catecholamine to Hering’s nerve.\textsuperscript{19}

The physiological role of other head and neck paragangliomas is less clear, but it may be reasonable to suggest that they also play a part in respiratory regulation. This contention, proposed by Lack,\textsuperscript{20} is supported by the fact that the anatomy of head and neck paraganglia suggests an atavistic relation to gill arches of aquatic species. Further evidence is provided by the close proximity of paraganglia to structures that might allow detection of hypoxia (the jugular bulb), or its correction (the vagus nerve and the larynx).

**PATHOLOGY OF PARAGANGLIOMAS**

**Epidemiology**

Paragangliomas are rare tumours and most general otolaryngologists will not expect to see more than one tumour each year. The true incidence is difficult to calculate with estimates ranging from 1:300,000\textsuperscript{21} to 1:500,000\textsuperscript{22} but it is important to recognize that calculations are hampered by confusion over nomenclature as discussed above.\textsuperscript{23} In terms of frequency, carotid paragangliomas are the most common, followed by jugulotympanic, vagal and laryngeal in descending order of frequency, the latter two being exceedingly rare, with only 190 and 81 cases identified in the English language literature, respectively.\textsuperscript{24, 25}

A large series of 236 patients with paragangliomas reported a mean age of presentation of 47 years with a range of ± 16 years (1 s.d.).\textsuperscript{26} A younger age of presentation occurs in those patients with a familial tendency towards paragangliomas (see below under Genetics). There is a tendency towards a higher rate of incidence among women in this series (60 per cent), and this trend seems to be more marked in the less common tumours, with ratios of 6:1 F:M described in jugulotympanic paragangliomas.\textsuperscript{27}

**ASSOCIATION WITH HYPOXIA**

No carcinogens are particularly associated with paragangliomas, but there is a well-recognized association between hypoxia and carotid paraganglion hypertrophy. This is manifested by increased rates of carotid paraganglion hypertrophy at altitude, and in patients affected by conditions that induce hypoxia (chronic obstructive pulmonary disease, cystic fibrosis and cyanotic heart disease).\textsuperscript{28, 29} In these cases, however, caution should be exercised in management, with great care taken to recognize a distinction between neoplasia and hypertrophy – the latter is likely to be self-limiting and harbours no risk of malignancy. Rodriguez-Cuevas et al.\textsuperscript{30} describe a series of 40 natives of Mexico City, in which surgical treatment was carried out in 27 patients with enlarged carotid paraganglia with some surgical morbidity (seven permanent cranial nerve palsies): none of the patients had presented with any functional impairment, none of the ‘tumours’ showed any malignant behaviour, and histological findings were consistent with type I cell hyperplasia, rather than neoplasia. In such populations and locations, it would seem sensible to pursue a conservative, rather than aggressive management strategy.

**BIOLOGICAL ACTIVITY, MALIGNANCY AND FUNCTIONALITY**

The majority of paragangliomas are slow-growing, benign, but locally invasive and destructive lesions. Spread is centrifugal, following paths of least resistance, and can lead to extensive bony destruction at the skull base. Growth is slow, with a median increase in dimension of 0.83 mm/year and a median tumour doubling time of ten years.\textsuperscript{31} Malignancy is defined by regional spread (WHO classification)\textsuperscript{2} and is rare in head and neck paragangliomas. A recent National Cancer Database report from the United States identified only 59 cases of malignant tumours, representing the largest published series in the literature.\textsuperscript{32} In the majority of cases (69 per cent), metastatic spread was limited to regional lymph nodes, although distant metastasis to liver, lung, bone and skin are also reported.\textsuperscript{33, 34} Five-year survival was 77 per cent for regional disease and 11 per cent for distant metastasis. In this series, only one case of malignancy with distant spread arose from a carotid paraganglioma, suggesting that lesions from other sites may be more aggressive.\textsuperscript{32} The National Cancer Database report concludes that the rate of malignancy in paragangliomas is approximately 10 per cent, other large series suggest slightly lower figures of 4–6 per cent.\textsuperscript{35, 36} There is no formal staging system.

Production of catecholamines is unusual in head and neck paragangliomas, in contrast to phaeochromocytomas and, to a lesser extent, extra-adrenal abdominal paragangliomas. Paraganglion cells have the capacity to produce norepinephrine (see above under Physiology), and in some this physiological
activity can lead to classical symptoms of catecholamine excess (palpitations, diaphoresis and headaches) associated with hypertension in patients with paragangliomas. One study reporting on a series of 297 patients with paragangliomas (204/297 were located in the head and neck), found rates of catecholamine excess as measured by urinary catecholamines in 9.7 per cent of patients with levels measured \( n = 93 \).{36} This level falls to 4.5 per cent if the whole group is included, and a true figure is likely to be closer to this level, given that the study is from a tertiary referral centre (the Mayo Clinic), and that those patients who did not have levels measured were likely to have been asymptomatic.

### HISTOPATHOLOGY

Paragangliomas of the head and neck demonstrate the same cell types as normal paraganglia: type I and II cells, and a profuse capillary network; they are also indistinguishable from paragangliomas in the thorax and abdomen. Tumours are encapsulated by a dense fibrous pseudocapsule. The characteristic histopathological feature they demonstrate are ‘zellballen’ (literally, cell balls), a nesting arrangement of type I cells that is demonstrated to a lesser degree in normal paraganglion tissue. These zellballen are surrounded by fibrovascular stromal tissue, and as they grow, may develop central degeneration or necrosis.

Malignancy is not reliably detected on histopathological grounds. The type I cells may be heterogenous in shape and size, and demonstrate nuclear atypia and pleomorphism, but these features are not clear indicators of malignancy. Similarly, the fibrous pseudocapsule may often be breached at points within the specimen, but equally, this feature should not be seen as evidence of capsular invasion and aggressive tumour behaviour.\[37\]

Immunohistochemistry may offer potential for more reliable differentiation between benign and malignant variants of paragangliomas than histopathology. Edstro¨m Elder et al.{38} analysed 32 phaeochromocytomas and abdominal paragangliomas, using a number of immunohistochemical markers and gene expression techniques. The combined use of the monoclonal antibody MIB-1 (a marker for the nuclear protein Ki-67), with the measurement of telomerase activity (hTERT), were highly sensitive markers for malignancy. While these techniques have not been employed with head and neck parangangliomas, the biological similarities between disease at the two sites would certainly suggest that these techniques warrant further investigation.

### GENETICS

Approximately 10 per cent of paragangliomas of the head and neck are thought to be familial in aetiology, and the study of the genetics of these lesions has been a very fertile area of research during the past decade. Patients with familial paragangliomas tend to present earlier than those with sporadic tumours (mean age of presentation, 30 years), and they are prone to the development of multiple paragangliomas at different sites. For an example of aggressive bilateral familial paragangliomas, see Figure 14.2. Significantly, patients with some variants of familial paragangliomas are also more likely to develop malignant tumours, and to develop phaeochromocytomas.\[39, 40, 41\]

#### Historical background

An awareness of the familial nature of some paragangliomas dates back as far as 1933, when carotid body tumours were described in two sisters.\[42\] By the 1960s, it was well understood that head and neck paragangliomas were found in clusters in some families, and that within these families, tumours were often multiple.\[43\] In the early 1990s, Dutch researchers investigated a five-generation pedigree with evidence of familial paragangliomas (16/95 individuals affected), and mapped a locus of homozygosity (PGL1) in affected family members to chromosome 11q23\[44\]. Subsequent studies identified the loci PGL2, 3 and 4.\[45, 46, 47\] Interestingly, while the latter families demonstrate an autosomal dominant pattern of inheritance, the PGL1 families are characterized by maternal imprinting, whereby the phenotype is only expressed if inherited from the paternal side.

#### Identification of SDHD, B and C

Subsequent research identified the gene defined by PGL1 as SDHD, a gene encoding a subunit of succinate-ubiquinone oxidoreductase (mitochondrial complex II), a component of the mitochondrial electron transport chain involved in the Krebs cycle.\[48\] Further studies have revealed that the genes implicated by the loci PGL3 and 4 (SDHC and SDHB) also encode for subunits of the same protein complex. The relative frequency of different gene mutations varies with geographical location: in the Netherlands, where two founder mutations are implicated, there is a strong tendency towards SDHD-associated disease, representing 97 per cent of 32 Dutch families investigated. In central Europe (Germany and Poland),\[49\] and the United States, SDHD and SDHB are found in almost equal proportions, with SDHC a rare occurrence. As yet, no gene has been identified associated with the PGL2 locus.
Possible pathogenetic mechanisms suggested by molecular genetics

The close association between familial paragangliomas and the SDHX family of genes has led to speculation about the pathogenesis of the lesions. As noted above, it has long been recognized that chronic hypoxia due to disease (i.e. chronic obstructive pulmonary disease (COPD)), or the physiological strain of living at high altitude lead to an increased rate of carotid paraganglion hypertrophy. The link between SDHX and hypoxia lies in the role played by mitochondria in oxidative respiration and their role as oxygen sensors. Normal cells generate vascular endothelial growth factor (VEGF), and other growth factors (i.e. erythropoietin) in response to hypoxia – a process mediated by production of reactive oxygen species by the mitochondrial respiratory chain and promoted by the stabilization of hypoxia-induced factors (HIF-1 and -2). It has been demonstrated in vitro that SDH inactivation leads to a stabilization of HIF-1 and -2, with subsequent downstream activation of VEGF and erythropoietin. This theory is supported by functional studies using immunohistochemistry and measurements of enzyme activity to analyse MCII function and vascular growth factor expression in paragangliomas.

Although these studies offer interesting insights into the tumorigenesis of familial paragangliomas, it is not clear how significant the mechanism of inappropriate hypoxic drive is in the more common sporadic form of paraganglioma. Studies that have sought genetic defects in SDHX genes in sporadic paragangliomas have not found mutations in these genes, but it may be that in these tumours there is epigenetic modification of gene function, leading to MCII dysfunction.

Differing clinical characteristics of SDHX varieties of familial paraganglioma syndromes

In counselling patients and determining management, it is important to recognize differences between the various SDHX types of familial paragangliomas. These are summarized in Table 14.1, with information drawn from a study based upon a central European (Germany and Poland) registry of head and neck paragangliomas (HNPG) (n = 121) and pheochromocytomas (n = 371). This study identified and investigated a total of 66 carriers of SDHD (n = 34) and SDHB (n = 32) mutations and assessed clinical characteristics related to the two genes. A later study from the same group used the same registries and expanded their search to other centres in Europe to identify 22 patients with the SDHC mutation to provide similar clinical information.

Table 14.1 demonstrates that SDHX genetic defects are far from homogenous. While both SDHD and SDHB tend to present at the age of 30 and have a similar penetrance, in other respects they differ quite markedly. The SDHB mutation is associated with a high rate of malignancy, and is more likely to be associated with other malignancies presenting at a young age. SDHD presents a more benign phenotype, although these patients are more likely to develop multiple tumours. SDHC is particularly characterized by a phenotype that is restricted to the head and neck. The association of SDHD and SDHB with pheochromocytoma and extra-adrenal paraganglioma deserves special attention. It should be noted that in the case of SDHB, patients with the genetic defect are more likely to present with a pheochromocytoma than with a paraganglioma.

SCREENING FOR FAMILIAL PARAGANGLIOMAS

The identification of patients and their relatives carrying SDHX genes is of importance for genetic counselling and further management. In the case of patients with subclinical pheochromocytoma, this could be a life-saving intervention. In considering whether to submit a patient presenting with a paraganglioma for genetic testing, it is important to recall that even a thorough family history may not reveal hidden disease. This is particularly true in families with an SDHD mutation, where maternal imprinting can cause a mutation to apparently skip generations (while the phenotype is only expressed if inherited from the paternal side, genotype...
transmission is unaffected by imprinting). Figure 14.3 illustrates this phenomenon with a sample pedigree.

All patients with a family history of paragangliomas or phaeochromocytoma should be offered genetic testing, and referred to a clinical geneticist. Apparently isolated patients with multiple paragangliomas or paragangliomas and phaeochromocytoma should also be referred for genetic testing. The case for investigating patients with unifocal disease and no positive family history is less clear cut. Those studies that have reported screening for SDHX mutations in such patients40, 55, 56 have found various positive rates (8, 9 and 19 per cent, respectively). Given that the mean age of presentation in mutation-positive cases is 30 years compared to 47 years in paraganglioma patients as a whole,26, 40 it would seem reasonable to prioritize younger patients for screening. In Neumann's study,40 the only one to specify age at presentation, nine of ten mutation-positive patients from a total of 77 individuals screened were under 50 years old. Screening all those patients with unifocal disease and no clear family history who were under 50 years old would lead to genetic testing of a little over half the presenting population, with an estimated detection rate of approximately 20 per cent.

Patients who are identified as carriers of SDHX genes should be thoroughly investigated, including screening of potentially susceptible relatives. The radiological investigation of paragangliomas will be discussed below under Radiological investigations, but clearly, these patients should be followed up in the long term, preferably with the involvement of a clinician with a special interest in this rare condition and the involvement of a clinical geneticist. The management of familial paragangliomas is an evolving subject, but a distinction must be made between SDHD and SDHC variants, where a relatively conservative approach might be adopted to prevent excessive iatrogenic morbidity, and SDHB variant, where a more aggressive approach would be warranted by the inherent increased risk of malignancy.

ANATOMICAL CLASSIFICATION SYSTEMS EMPLOYED

Carotid paragangliomas

Carotid paragangliomas are most commonly classified according to size (see Figure 14.4), in a system initially proposed by Shamblin et al.57 This system categorizes tumours by the degree to which they encase the carotid arteries, and also reflects the degree to which the tumour adheres to the vascular adventitia. Group I tumours are relatively easy to excise surgically, but larger lesions can prove particularly difficult to remove without vascular grafting.

Jugular and tympanic paragangliomas

Uncertainty about the anatomical origins of paranganglial tissue in the middle ear and the proximity of ‘tympanic’ and ‘jugular’ paranglia have led to these two lesions being conflated into ‘jugulotympanic’ paragangliomas by the WHO classification, and in classification systems such as the one advocated by Oldring and Fisch.58 The Glasscock–Jackson system59 expands the tympanic subclassification. The salient distinction between jugulare and tympanicum lies in the bony integrity of the jugular bulb: if the lesion is in the middle ear and the jugular bulb is intact, then it is a tympanic paraganglioma – if the bulb is eroded, then the origin of the tumour is most likely to be jugular, and will need neurological expertise if surgery is undertaken. For examples of tympanic and jugulotympanic tumours, see Figures 14.5 and 14.6.

Vagal paragangliomas

Arising from paranganglia associated with the vagal ganglion, these lesions arise below the skull base. As they enlarge, they may extend into the jugular foramen and are then subject to the same classification system as jugulare tumours.

CLINICAL FEATURES OF PARAGANGLIOMAS

The clinical features associated with paragangliomas differ according to their location.

Carotid paragangliomas

Carotid paragangliomas typically present with a slowly enlarging, pulsatile, painless, soft mass at the angle of the mandible. Classically, the mass is expansile, mobile only laterally, and can be emptied of blood by gentle pressure;
releasing the tumour will allow it to refill slowly. A bruit may be heard over the mass and this can be silenced with pressure. Occasionally, the mass will project into the lateral oropharynx, displacing the tonsil, soft palate and uvula. Some 10 per cent of patients present with neurological symptoms associated with the mass, most frequently affecting the Xth nerve.
but symptoms related to the VIIth, IXth and XIIth nerves have also been reported. There may also be an associated Horner’s syndrome due to the involvement of the cervical sympathetic chain, or carotid sinus syndrome, characterized by bradycardia and syncopal episodes. In functional paragangliomas, patients may present with symptoms of headache, palpitations or diaphoresis.

**Tympanic paragangliomas**

Tympanic paragangliomas present typically with pulsatile tinnitus, which is present in approximately 80 per cent of patients, and is the primary symptom in over half of patients. Hearing loss is the primary presenting symptom in some 30 per cent, and a symptom in a total of 60 per cent. Hearing loss is predominantly conductive in character, but can be sensorineural if the labyrinth is involved by tumour. The tympanic membrane can be eroded, leading to a patient presenting with bleeding from the ear, but this is a late sign. Typically, the clinician will find a bluish-red mass on otoscopy (Figure 14.7): if the inferior border of the lesion can be seen, this is a Glasscock–Jackson type I tumour; if not, then involvement of the jugular bulb cannot be ruled out. Important differential diagnoses are a high jugular bulb (this will usually be darker in colour), and an aberrant internal carotid artery (this will normally be placed in the anterior mesotympanum). For these reasons, and because of the vascularity of paraganglioma tissue, myringotomy and biopsy should not be undertaken due to the risk of haemorrhage.

**Jugular paragangliomas**

These lesions, while they may extend to the middle ear and cause similar symptoms to tympanic paragangliomas, are likely to produce neurological signs and symptoms in addition to those described above. In Sanna’s series of 55 patients with jugular paragangliomas, 45 per cent presented with pulsatile tinnitus as a primary presenting complaint, while tinnitus and hearing loss were symptoms in 72 and 77 per cent of cases, respectively. Significantly, 43 per cent of the patients had at least one cranial nerve deficit at presentation. The most commonly affected nerves were the IXth and Xth, with 38 per cent of cases affected in each case; 13 per cent of patients had paralysis of all four lower cranial nerves. As might be expected, the degree of cranial nerve impairment increased as the size of the tumour increased, with intracranial extension being strongly associated with cranial nerve deficits. A similar incidence of preoperative cranial nerve deficit (46 per cent) is found in Jackson’s series of 152 patients. Intracranial extension (to the posterior cranial fossa via the medial wall of the jugular bulb) is common in jugular paragangliomas, affecting 62 per cent of 55 patients in Sanna’s series, and 36 per cent in Jackson’s series. It is important to recognize that these two authors define ‘intracranial’ slightly differently. Sanna et al. include both intradural and extradural extension, whereas Jackson considers only intradural extension as significant.

**Vagal paragangliomas**

Vagal paragangliomas present most commonly as a mass in the neck, usually a little more cranial than a carotid paraganglioma. In common with carotid paragangliomas, vagal tumours can project into the lateral oropharynx. As noted above, the three suprathyroid ganglia can all contain paraganglion tissue, and paragangliomas can arise from any of these sites. The most common site is the inferior, nodose ganglion, located some 2 cm caudal to the jugular foramen. Tumours at the jugular foramen can develop into dumb-bell lesions with both intracranial and cervical components. If cranial nerve impairment is present, the pattern of impairment is likely to reflect the anatomy described: lesions at the jugular foramen risk involvement of all four lowest cranial nerves, while lesions originating at the nodose ganglion may only impair vagal function. Netterville et al. described the largest series of vagal paragangliomas in the literature (46 cases), and found a neck mass to be the most common presenting symptom, with tinnitus, hoarseness and a pharyngeal mass also common; 36 per cent of patients presented with at least one cranial nerve impaired.

**Laryngeal paragangliomas**

Laryngeal paragangliomas are exceedingly rare. Lesions in the supraglottis (the more common type) present with hoarseness, shortness of breath and dysphagia. Hoarseness usually recovers after treatment, and for this reason is generally considered to be due to a mass effect rather than a neurological impairment. Infraglottic paragangliomas represent only 15 per cent of laryngeal paragangliomas and present with hoarseness, haemoptysis and dyspnoea due to tracheal obstruction.

**INVESTIGATIONS**

The issue of genetic investigation of patients with paragangliomas has been discussed. Further specialized investigations are endocrine and radiological, with the aim of establishing any functionality and determining the extent of disease.
Endocrine investigations

The purpose of endocrine investigations is two-fold: to identify those patients with a functioning paraganglioma, and to screen for subclinical phaeochromocytoma. While the majority of patients with functioning tumours will be hypertensive and have at least one symptom of catecholamine excess, it is reasonable to screen all patients with a paraganglioma. It is important to recognize that prior to investigation, β-blockade should be ceased for at least 7 days.

Combined 24-hour urinary collection of metanephrine, norepinephrine, epinephrine and dopamine is highly sensitive and specific for tumoral catecholamine excess, with measurement of norepinephrine alone sensitive in 89 per cent of cases. In a study of nine functioning head and neck paragangliomas from a pool of 205, the range of abnormal results for norepinephrine was from 2019 to 2331 nmol, with a normal range of <1005 nmol (<170 μg), emphasizing the specificity of this test. Patients in whom abnormally elevated levels of catecholamines are detected should be investigated radiologically for evidence of synchronous paragangliomas (in particular extra-adrenal abdominal paragangliomas) and phaeochromocytomas. Synchronous tumours should provoke genetic investigation.

Radiological investigations

A wide array of radiological tools play an important role in both the investigation and management of paragangliomas, and close collaboration with radiological colleagues is advised to ensure the maximal use of available local facilities.

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Paragangliomas are detectable with both contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), but these two modalities have different strengths in different anatomical sites. The particular strength of CT scanning is in the evaluation of paragangliomas of the temporal bone, allowing accurate estimation of tumour size, bony destruction and detailed assessment of surgical landmarks. MRI is particularly valuable in assessing intracranial extension and in the assessment of soft tissues (for example, in detecting encroachment and encasement of the internal carotid artery and internal jugular veins). A further benefit of MRI lies in the ability to distinguish tumour from surrounding inflammatory tissue or fluid (for example, in the mastoid cavity). Classical radiological appearances are well established: Olsen originally described the ‘salt-and-pepper’ pattern seen on T₂-weighted magnetic resonance images in paragangliomas that are more than 2 cm in diameter (the pattern arises because of tumour vascularity); the ‘lyre’ sign, is produced by the splaying of the branches of common carotid artery by a carotid paraganglioma. In addition to standard imaging techniques, both CT and MRI venography and arteriography can be employed to determine the involvement of the vascular structures related to the lesion under investigation.

Figure 14.8 Preoperative angiogram demonstrating the ‘tumour blush’ of a glomus vagale tumour.

Screening protocols for pulsatile tinnitus

Tympanic and jugular paragangliomas typically present with pulsatile tinnitus, and this presentation should encourage radiological screening. The presence of objective tinnitus (in which the pulsation is audible to a second party in addition to the patient) is of importance, and should be sought: these patients are more likely to yield positive results. Differential diagnoses include vascular malformations, other rare neoplastic lesions (facial nerve haemangioma and cavernous haemangioma) and acoustic neuromas (although these only rarely present with pulsatile tinnitus). For the purposes of screening, both CT and MRI will detect the presence of paragangliomas in the temporal bone, as described above, but as a first-line screening tool, MRI would be a preferable choice in terms of radiation exposure, the ability to image the internal acoustic meatus, and a reduced likelihood of contrast reaction.

Angiography

Once an important tool in the diagnosis of paragangliomas, angiography has been largely superseded by non-invasive imaging modalities. Nevertheless, angiography plays an important role in evaluating the important feeder vessels preoperatively prior to tumour embolization. Figure 14.8 represents a vagal paraganglioma imaged in this manner. Temporary balloon occlusion testing, to assess cerebral perfusion, may be indicated in certain large carotid paragangliomas or in order to determine whether the patient will tolerate common carotid clamping to enable tumour removal. This test can also evaluate whether or not a patient will tolerate internal carotid artery sacrifice, which is rarely indicated when removing extensive jugulare tumours.
**Ultrasonography**

Ultrasonography has a role in the diagnosis and assessment of neck masses and in the cost-effective follow up of carotid and low vagal paragangliomas that are being managed conservatively. Grey-scale ultrasound can be employed to demonstrate the size of carotid lesions, and can also assess encasement of carotid vessels; colour Doppler flow imaging will demonstrate the hypervascularity of paragangliomas. Ultrasound is ineffective at imaging bony structures and neck lesions that extend to the skull base will require further imaging with CT or MRI.

**Radionuclide techniques and 18F-DOPA-PET**

While imaging modalities, such as MRI and CT, allow very accurate assessment of the anatomical relations of tumours, radionuclide techniques have a place in confirming diagnoses when other radiological findings are equivocal, in whole-body screening for occult disease and in postoperative assessment to ensure tumour control when postsurgical tissue changes can make other imaging difficult. Paraganglial tissue is richly supplied with somatostatin, and this is the basis for 111In-pentetreotide scanning, which employs the radiolabelled somatostatin analogue octreotide to target paraganglioma tissue. 123I-metaiodobenzylguanidine (MIBG) scanning is another technique that depends upon the uptake of radiolabelled material by the APUD system. 18F-DOPA-PET (18fluorine-dihydroxyphenylalanine positron emission tomography) is a relatively new whole-body technique that identifies neuroendocrine cells due to their uptake of dopamine, a technique that also exploits an understanding of the APUD system. Of these three techniques, MIBG is recognized to be the least sensitive, with rates of detection low (in a study of eight paragangliomas, only four were detected by this method, while all eight were detected with 111In-pentetreotide scanning). 18F-DOPA-PET appears to be the most sensitive technique, and in one study of patients with familial paragangliomas, a number of lesions were identified that were not detectable on magnetic resonance scanning, even (in a small number of cases) after retrospective review, rendering this technique ideal for the screening of subclinical disease. Radionuclide techniques also have a role to play in the management of metastatic disease.

**Radiotherapy**

Prior to the development of microsurgical techniques in the 1970s, radiotherapy was the mainstay of treatment of temporal bone neoplasms. As techniques pioneered by Fisch increasingly permitted access to the infratemporal fossa, surgeons enthusiastically adopted surgical management of these challenging tumours. Radiotherapy does not usually lead to a reduction in tumour volume, but can halt tumour progression resulting in tumour control. Radiotherapy can be either fractionated external beam, with a typical dose of 45 Gy in 25 fractions given once daily; stereotactic radiosurgery, in which one high dose of radiation is administered in a highly focused region concentrated on the tumour mass; or stereotactic radiotherapy, a fractionated adaption of stereotactic radiosurgery.

Studies that have addressed questions of local control in radiotherapy predominantly describe treatment with external beam (stereotactic radiosurgery is a relatively recent phenomenon with limited follow up at present). Krych et al. described 33 patients with a median follow up of 13 years and a ten-year control rate of 92 per cent. Complications included xerostomia, loss of smell and taste, hearing loss (two patients), and dysphagia. A rate of local control with radiotherapy in 90–95 per cent of patients is found in other large series, with similar complications quoted. Major complications of radiotherapy are rare, but include osteonecrosis (1.7 per cent) and brain necrosis (0.84 per cent). In many historical cases of radiation-induced complications, doses administered were much higher than those currently given. The risk of radiation-induced malignancy is a more serious complication: Krych et al. identified three reported cases of radiation-induced malignancy reported in the world literature between 1966 and 2005. Two of these tumours were fibrosarcomas, while one was an anaplastic astrocytoma: the time of onset of disease post-radiotherapy ranged from eight to 25 years. Taking these three reported malignancies into account, the rate of radiation-induced malignancy is likely to stand at between 0.5 and 1 per cent.

**Surgery**

Lesions at different locations require different surgical approaches, and each site will be considered individually. In all cases, with the exception of tympanic paragangliomas, surgical management is often multidisciplinary, involving vascular and interventional radiological colleagues. A further observation is that due to the complications involved in surgery at the skull base, the low rate of malignancy and the slow growth of these lesions, a policy of tumour removal at all costs is often inappropriate. Subtotal resection with cranial nerve preservation is being increasingly adopted as an acceptable treatment plan. Functioning tumours should have been identified preoperatively and appropriately controlled prior to and during surgery.

**PREOPERATIVE EMBOLIZATION AND ASSESSING CROSSFLOW**

Preoperative embolization on the day prior to surgery has become a standard procedure in larger paraganglioma
surgery. Studies that have compared embolized with non-embolized procedures have observed highly significant reductions in intraoperative haemorrhage and operation time. Embolization must be superselective, in that only the artery feeding the tumour is embolized, and in the temporal bone, multiple cannulations may be required to ensure that all compartments of the tumour are devascularized. While uncommon (approximately 1 per cent), complications of embolization include intracranial stroke and cranial nerve neuropathy (often temporary, due to tissue oedema or due to partial occlusion of the vasa nervorum) and for this reason, it is reserved for larger tumours. Even when preoperative embolization is employed, patients often lose in excess of 2 units of blood during the resection of a large jugular paraganglioma.

In rare instances, it may be necessary to determine the feasibility of carotid sacrifice, which can be assessed by preoperative balloon occlusion testing.

**CAROTID PARAGANGLIOMAS**

Traditionally, in the United Kingdom, resection of carotid paragangliomas is performed by vascular surgeons, and given the importance of vascular control – and the potential for vascular trauma – it would be recommended to undertake this surgery in partnership with a vascular surgeon. In large tumours, temporary occlusion of the common carotid artery with heparinization may be necessary to facilitate removal. The structures most at risk in the procedure are the hypoglossal nerve and the superior laryngeal nerve. Preoperative cranial nerve lesions suggest tumour involvement and do not bode well for postoperative preservation. The vagus nerve, and the external carotid artery, which may need to be ligated to facilitate resection, may be at risk in larger tumours.

The patient is positioned with neck extended and rotated to allow maximum exposure to the upper neck. Subcutaneous injection with 40 mL of 1:100 000 adrenaline will aid haemostasis. The incision should follow a skin crease 2 cm below the mandible to prevent injury to the marginal mandibular branch of the facial nerve and should be continued through platysma. Superior and inferior flaps should be raised in order to maximize exposure, and this can be achieved in the upper neck without damage to the marginal mandibular nerve by incising the fascia overlying the submandibular gland and reflecting this over the nerve in a cuff. With the flaps raised, the anterior border of the sternocleidomastoid is incised and retracted to allow exposure of the carotid sheath.

Vascular control is vital to the success of this operation, and early control with sloops of the common carotid artery is achieved after exposure and dissection of the contents of the carotid sheath. The hypoglossal nerve will be seen running lateral to the paraganglioma, and this should be mobilized from the tumour and reflected superiorly. The tumour should also be freed from the vagus nerve laterally, and, as much as possible, the superior laryngeal nerve posteriorly. If possible, ligation of the ascending pharyngeal artery, the principal feeding vessel for the tumour, can aid controlled dissection, which should follow the tumour’s mobilization.

The tumour is dissected in an adventitial plane from the caudal pole cranially, using careful bipolar dissection to limit bleeding as much as possible. The extreme vascularity of paragangliomas can make this dissection difficult, particularly in larger (type 2 and 3) tumours. Van der Mey et al. recommend temporary occlusion of the common carotid artery with heparinization if preoperative balloon occlusion testing suggests the patient will tolerate this. If not, the use of a Javed shunt can be helpful. On rare occasions, the tumour can extend to the skull base, and the surgeon must be prepared to undertake an infratemporal approach to the jugular foramen. With the excision of the tumour complete, meticulous attention should be paid to haemostasis, and a drain sited under two-layer closure.

Results for carotid paraganglioma surgery are generally good. In a series of 45 tumours, Plukker et al. reported only three permanent cranial nerve palsies and three vascular complications – all occurring in type 3 tumours.

**TYMPANIC PARAGANGLIOMAS**

The excision of tympanic paragangliomas is determined by their size. Small tumours (i.e. Glasscock–Jackson type 1), in which all borders of the tumour can be visualized through the tympanic membrane, can be removed via a tympanotomy approach. The vascularity of the tumour can make dissection difficult, but gentle mobilization and the identification of the feeding vessel (the tympanic branch of the ascending pharyngeal artery) should facilitate excision. Larger tumours that fill the middle ear cleft or extend to the mastoid cavity will need more extensive exposure and, to this end, an extended facial recess approach is recommended. Some authors have recommended the use of laser instruments (Nd-YAG and KTP) in excising tympanic paragangliomas, arguing that relatively large lesions can be safely removed via a simple tympanotomy approach using this technique, although our preference is for an extended facial recess approach for larger tumours even when the laser is being used. Surgical complications are unusual, but include tympanic membrane perforation and conductive hearing loss following disruption of the ossicular chain.

**JUGULAR PARAGANGLIOMAS**

The resection of jugular paragangliomas is a considerable surgical challenge: the lesions are difficult to access, highly vascular, and are closely related to, if not adherent to, vital neurological and vascular structures. A tailored, multidisciplinary approach is vital, involving vascular and neurosurgical colleagues as appropriate. In all cases, preoperative embolization is recommended. Multiple cranial nerve monitoring is also recommended with facial and vagal recording as a minimum standard with additional monitoring of IX, XI and XII as indicated. A lumbar drain to enable intraoperative reduction in intracranial pressure can be used in tumours with a large intracranial extension.

The challenge of surgery is to remove the lesion, while preserving preoperative neurological function (Figure 14.9a,b). The extent of the surgery is tailored to the individual case, the basis of which is an infratemporal fossa approach to the jugular foramen. Where possible, middle ear function is preserved by performing an extended facial recess.
approach. In situations where there is a significant preoperative sensorineural loss or access to the petrous apex is required, then sacrifice of the inner ear should be considered. Functioning bulbar nerves are preferably left undisturbed even if this requires some tumour to be left behind. Carotid sacrifice is rarely indicated, but if this is being considered then preoperative occlusion testing should have been carried out.

The surgery commences with a postauricular incision that extends in a skin crease into the neck. A wide mastoidectomy is performed, with decompression of the sigmoid sinus and removal of the mastoid tip. The inferior tympanic bone should be removed to skeletonize the external auditory canal and improve access to the distal internal carotid artery. Access to the jugular foramen is hampered laterally by the facial nerve and, traditionally, the nerve has been anteriorly rerouted from the fallopian canal and implanted into the anterior epitympanum, but in most cases, this can be avoided by skeletonizing the fallopian canal (the ‘fallopian bridge’ technique) (for an illustration, see Figure 14.10a,b). An intermediate solution is to perform a ‘short mobilization’. The vertical portion of the facial nerve below the posterior semicircular canal is in the authors’ experience the site most commonly involved by tumour. If the nerve is functioning normally prior to surgery, the nerve is probably best left in situ with the tumour attached, whereas if the nerve is paralysed prior to surgery resection and interposition nerve grafting is indicated. Exposure in the neck is facilitated by retraction or division of the sternomastoid muscle. Vascular control is achieved with slooping of the proximal internal carotid artery, and exposure distally; the internal jugular vein is ligated distally, and the sigmoid sinus packed extra-luminally. The tumour within the jugular bulb is then carefully dissected from the internal carotid artery and lower cranial nerves, remembering that the inferior petrosal sinus drains into the anteromedial jugular bulb, and has not yet been controlled: this is packed intraluminally once the tumour has been removed.

Extensive anterior exposure of the tumour may require transection of the external auditory canal, and the ear to be reflected forwards. The mandible is dislocated from the tympanic bone, and may be retracted or partially excised; further exposure anteriorly can be achieved with resection of the zygoma. Access to and mobilization of the entire intrapetrous carotid can be achieved by this approach.

Intracranial extension can be either intra- or extradural. The tumour may be resected in one stage with the extracranial component, or removed at a later date. Sanna et al. advocate a staged resection for tumours with >2 cm intracranial extension, employing the upper portion of the original incision. They argue that the tumour excision is less problematic because the remnant has devascularized, and that closure of the dural defect is less prone to failure when
the surgical wound is less extensive. Jackson\textsuperscript{65} advocates a
one stage procedure with extensive local and, if necessary,
free tissue flap closure and the protection of a lumbar drain.
Both authors achieve similar results in terms of cerebrospinal
fluid leak rates (3.7 and 4.5 per cent, respectively).

The results of surgery for jugular paragangliomas vary
considerably according to the size and location of the
tumour, but it should be recognized that complications,
particularly in terms of cranial nerve injuries, are common.
Death is a rare but recognized complication: in Jackson’s
series of 182 patients, five patients died following surgery due
to internal carotid artery resection (three) or pulmonary
embolus (two, this occurred in functioning tumours).
Tumour control rates, defined as complete removal of
tumour without recurrence, are 85 per cent (Jackson) and 83
per cent (Sanna). Cranial nerve defects are often present
preoperatively, but further deficits postoperatively are also
common: in Sanna’s series, new cranial nerve deficits occur-
red in 33, 30, 25 and 12 per cent of cranial nerves IX, X, XI
and XII, respectively. Jackson’s rates of new cranial nerve
deficit are slightly higher, with the same nerves affected in 57,
40, 62 and 56 per cent of cases, respectively.

VAGAL PARAGANGLIOMAS

Many of the issues and surgical approaches previously
described with reference to carotid and jugular paragangliomas
apply to vagal paragangliomas. As previously described, vagal
paragangliomas can arise at different points along the vagus
nerve as it leaves the jugular foramen. Those lower lesions may
be approached through the neck, in an approach similar to
that described for carotid surgery, while higher lesions that
extend to the skull base will require an infratemporal approach
that described for carotid surgery, while higher lesions that
be approached through the neck, in an approach similar to
nerve as it leaves the jugular foramen. Those lower lesions may
paragangliomas can arise at different points along the vagus
nerve or one of its branches, alternative treatment strategies
such as ‘watch and wait’ or radiotherapy should be very
carefully considered.

LARYNGEAL PARAGANGLIOMAS

The surgical treatment of laryngeal paragangliomas is con-
servative, but due to the high degree of local recurrence,
open, rather than endoscopic techniques are generally
advocated.\textsuperscript{93} In most cases, the tumour, which is generally
located in the false cord, can be excised by a lateral phar-
yngotomy approach, in cases of larger tumours, supraglottic
laryngectomy may be necessary. Subglottic paragangliomas
should be excised by a laryngofissure approach.

CRANIAL NERVE REHABILITATION

Postsurgical cranial nerve injury is common in para-
ganglioma management, and the rehabilitation of cranial
nerve deficits are slightly higher, with the same nerves affected in 57,
40, 62 and 56 per cent of cases, respectively.

Management of malignant disease

Malignancy is rare in paragangliomas, with spread to local
lymphatics most commonly found. If lymph node involve-
ment is suspected clinically and confirmed with imaging,
surgical excision should be accompanied with neck dissec-
tion. Radiotherapy has been demonstrated to lead to residual
viable tissue in lesions that are effectively ‘controlled’ in
terms of local spread,\textsuperscript{65} and for this reason is not recom-
manded as a sole modality for treatment of malignant
lesions. Lee et al.\textsuperscript{52} note a trend in recent years towards
the use of adjuvant radiotherapy in these patients and
draw a tentative conclusion that this combination therapy is
likely to offer an increased survival next to single modality
treatment with surgery, an assertion tempered by the small
numbers of patients involved. Traditional chemotherapy
has little role in the treatment of malignant paragangliomas
as might be suggested by the slow rate of growth in these
tumours.

KEY EVIDENCE

- Studies of a five-generation pedigree in the
  Netherlands identified a locus of homozygosity
to chromosome 11.\textsuperscript{144} Subsequent \textit{in vitro}
  studies have demonstrated an association between
  hypoxia-induced growth factors and the proteins
  (SDHD, B and C) associated with this and other
  affected loci.\textsuperscript{19}
- \textsuperscript{18}F-DOPA-PET appears to be the most sensitive
  imaging modality available for paragangliomas,
  and may provide useful for the identification of
  subclinical lesions, particularly in familial
cases.\textsuperscript{76}
KEY LEARNING POINTS

- Paragangliomas are rare, usually benign vascular lesions that can be found at many locations in the head and neck, but primarily affect the carotid body, tympanum and jugular bulb.
- The lesions predominantly affect patients in their fifth and sixth decades with a female sex bias.
- A small but significant proportion of tumours are familial. In this group, there is an important association with pheochromocytoma. Patients with germline abnormalities of the SDH family of genes will often suffer multiple tumours during their lifetime, and are at greater risk of malignancy (SDHB). Any patients with multiple tumours, a positive family history or an early presentation should be referred for genetic investigations.
- Management of paragangliomas is focused upon disease removal or control, with an emphasis upon preservation of neurological function. Treatment can be conservative (‘watch and wait’), surgical or radiotherapeutic, depending upon patient and tumour factors.

REFERENCES


INTRODUCTION

Tracheostomy is one of the oldest surgical procedures. There are references to the creation of a surgical airway in many ancient texts. Until the end of the nineteenth century and the introduction of asepsis, together with the development of safe anaesthetic techniques, the procedure was extremely hazardous. Tracheostomy was seen as a last resort in hopeless cases and was the cause of great anxiety for the patient and surgeon alike. Chevalier Jackson established the principles of the operation at the beginning of the twentieth century and these remain in place today. The development of percutaneous tracheostomy over the past 15 years has taken surgical airway management out of the exclusive province of the otolaryngologist. There are now a wide variety of clinicians confronted by the challenges of tracheostomy care and decannulation strategies.

A tracheotomy is a surgical opening in the trachea, while a tracheostomy is the creation of a stoma at the skin surface which leads into the tracheal lumen.

TEMPORARY TRACHEOSTOMY

A temporary tracheostomy may be either an elective or an emergency procedure. The most common use of an elective temporary tracheostomy is for prolonged ventilatory support in a ventilated patient. A temporary tracheostomy may also be planned as part of a major surgical procedure in which there are concerns about postoperative swelling or bleeding, which may precipitate upper airway obstruction. A temporary tracheostomy may be short term, long term or permanent.

An emergency tracheostomy is a rare procedure, perhaps only indicated in cases of severe trauma. In all other cases, it could be argued that the performance of an emergency tracheostomy is indicative of an underestimation of the severity of the breathing problem. The majority of cases can be dealt with by carrying out an urgent procedure under local anaesthesia with the patient awake. In extremis, it should be possible to perform a cricothyroidotomy and maintain ventilation via a wide bore cannula until conversion to a formal tracheostomy can be undertaken.

A permanent or ‘end’ tracheostomy is an elective procedure carried out as part of a surgical procedure involving the removal of the larynx, such as a laryngectomy or pharyngolaryngectomy. A permanent tracheostomy is also created in laryngeal diversion procedures used to prevent aspiration. The continuity between the laryngopharynx and the trachea is permanently disrupted and the cut end of the trachea is sutured to the skin.
The effects of a tracheostomy include:

- laryngeal bypass – loss of cough and phonation;
- reduction in respiratory dead space;
- loss of nasal mucosa filtration and humidification;
- increased risk of infection;
- tube acts as foreign body leading to local inflammation;
- sump above tracheostome and below larynx, when mucus collects.

**INDICATIONS**

Indications for tracheostomy are the following:

- upper airway obstruction;
- removal of secretions;
- prolonged ventilation;
- part of another procedure.

**Upper airway obstruction**

When confronted by a patient with an upper airway obstruction, it is essential to carry out a rapid but complete assessment of the patient’s overall condition. There may be coexisting medical problems which are contributory to their breathing problems and the management of such problems may need to be incorporated into the solution of the airway problem. It is important to ascertain the precise level of obstruction so that any intervention provides relief at the lowest level of obstruction. With the advent of improved intubating laryngoscopes and advanced techniques, such as fibreoptic intubation or the use of oesophageal airways, upper airway obstruction is no longer the most common indication for tracheostomy.

**Prolonged ventilation**

Tracheostomy is the safest means of assisting ventilation where prolonged positive pressure is needed. It is easier to secure a tracheostomy tube than either an orotracheal or nasotracheal tube and the reduced dead space assists weaning of respiratory support. It has been demonstrated that the introduction of percutaneous tracheostomy has led to a doubling in the number of tracheostomies being carried out. It may be that the ease of access to tracheostomy has resulted in reduced duration of intubation. With the introduction of low pressure cuffs for endotracheal tubes, a longer period of intubation has become acceptable. There are studies showing an increased rate of subglottic stenosis if intubation continues for more than 10 days, although there are those who would argue that intubation can be prolonged for up to 3 weeks. There is evidence that early tracheostomy in trauma patients reduces the length of ventilation and hospital stay and it may be that the same applies for general intensive treatment unit (ITU) patients.

**Removal of secretions**

The accumulation of secretions in the lower respiratory tract is responsible for a reduction in gas diffusion within the alveoli. This results in respiratory failure. A tracheostomy reduces the dead space, so reducing the work of breathing and also makes it easier to aspirate secretions with less upset to the patient.

**Part of another procedure**

A permanent tracheostomy is an unavoidable consequence of a major head and neck procedure in which it is necessary to remove the whole of the larynx. A temporary tracheostomy should be regarded as mandatory for all major resections involving the oral cavity or pharynx. In these cases, the tracheostomy allows protection of the lower airway from aspiration of blood, in the event of a haemorrhage, as well as guarding against upper airway obstruction from postoperative swelling. Percutaneous tracheostomy is probably not appropriate in these cases, as the pretracheal tissues fit tightly around the tube. In the event of tube displacement, the tissues can collapse inwards, closing the airway with a potentially fatal outcome.

**ANATOMY**

As with any surgical procedure, when performing a tracheostomy, it is essential to have a sound knowledge of the relevant applied anatomy of the upper trachea. Problems are likely to happen if the surgeon strays from the midline. The recurrent laryngeal nerve runs in the tracheo-oesophageal groove and the great vessels are lateral to this within the carotid sheath. It is rare in a straightforward tracheostomy to lose sense of where the midline is, but in obese patients and small children, it is possible to lose the anatomical landmarks and stray laterally. The thyroid isthmus crosses in front of the trachea covering a variable number of the tracheal cartilaginous rings. It is a highly vascular structure and inadvertent damage during dissection or friction from the tube may result in postoperative haemorrhage. The innominate artery crosses the front of the trachea, from left to right, at a variable height. In cases of a high innominate artery, it may be encountered during dissection or may suffer erosion from the tracheostomy tube with potentially fatal postoperative haemorrhage.

**CONTRAINDICATIONS**

There are no absolute contraindications to tracheostomy. However, in the case of terminal patients, very careful consideration must be given to the psychological effects on the patient and the quality of life aspects. There is no right or wrong answer and each patient must be approached on an individual basis.

**PREOPERATIVE CONSIDERATIONS**

In the elective setting, it is imperative that adequate consent is received from the patient or their relatives. As part of this process, it is necessary to cover the risks and benefits of the
procedure in some detail. This must be a frank and open discussion and the potential complications and sequelae of tracheostomy must be pointed out. This is particularly true of paediatric tracheostomy.

**OPERATIVE PROCEDURE**

**Cricothyroidotomy/minitracheostomy**

In an emergency, rapid control of the upper airway can be achieved by use of an airway inserted through the cricothyroid membrane. Once an incision has been made through the membrane, a minitracheostomy tube or a wide bore cannula attached to a syringe half filled with saline can be used to keep the tract open and provide an alternative airway.

The patient is positioned with the neck extended over a pillow. The cricothyroid membrane can be palpated and the area is infiltrated with local anaesthetic and epinephrine. The cricothyroid membrane can be incised either with a scalpel or a wide bore cannula attached to a syringe half filled with saline. In the former case, once the airway has been opened, the blunt handle of the scalpel can be inserted and rotated to create space for a tube to be passed into the trachea. In the latter case, the needle of the cannula is used to breach the membrane and as the needle and cannula are inserted, the plunger of the syringe is withdrawn. Once air bubbles into the syringe, the trachea has been entered, the cannula can then be introduced over the needle. The cannula can be connected via a universal connector to an ambubag and the patient can be ventilated for a short period of time. Using this system, CO₂ is not cleared and so conversion to a formal tracheostomy should be undertaken as soon as possible.

A minitracheostomy tube should not be left in situ for more than a short time as there will inevitably be some friction between it and the cricoid cartilage which will predispose the patient to subglottic stenosis.

**Percutaneous tracheostomy**

First described over 50 years ago, this technique has grown in popularity and is now the most common procedure for the provision of an alternative airway for ITU patients. The growth of the procedure followed the introduction over the last 10–15 years of commercial kits based on well-defined techniques. In the United Kingdom, the most commonly employed kit depends on the dilatation technique originally described by Ciaglia et al.

The patient should be positioned as for a formal surgical tracheostomy (see below under Open surgical tracheostomy). The trachea is punctured, using a needle and cannula, just below the first tracheal cartilage ring. A syringe half filled with saline is attached to the cannula. Gentle aspiration allows correct positioning of the cannula, because air is aspirated through the saline as the needle passes into the trachea. The needle is withdrawn and a guide wire is inserted through the cannula, which is itself withdrawn to allow for either a single or graded serial dilators to be passed over the guide wire. The dilators create a passage which is wide enough for the insertion of a standard tracheostomy tube, which is passed over the largest of the dilators and secured in position within the trachea. It is advisable to view the internal lumen of the trachea during this procedure by using a flexible bronchoscope, as this is likely to reduce complications.

**Open surgical tracheostomy**

Although there are many variations in the technique of open surgical tracheostomy, they are all based on the same fundamentals. The technique described is that preferred by the author. The procedure should, when possible, be carried out in an operating theatre, under sterile conditions. It is usual for the patient to have a general anaesthetic but, where this is deemed hazardous, the procedure can be carried out under local anaesthetic.

The patient should be positioned supine, with the neck extended by placing a sandbag under the shoulders. It is important that the patient is positioned square on the table with the shoulders at the same level. This will ensure that the midline structures of the neck are truly in the midline throughout the operation. When operating under local anaesthesia, it may be necessary to compromise on the degree of neck extension as overextension may further restrict the airway.

A horizontal incision is sited halfway between the sternal notch and the lower border of the cricoid cartilage. Once the skin has been incised, dissection continues through the subcutaneous tissues to the strap muscles, which are retracted laterally, following blunt dissection in the midline to separate them. Following this manoeuvre, the thyroid isthmus should be visible. The isthmus should be clamped, divided and transfixed. At this point, the anterior tracheal wall is encountered. It is useful to identify the cricoid cartilage so as to plan the point of entry into the trachea. Ideally, the tracheostomy should be made between the second and fourth tracheal rings. Before entering the trachea, it is important to select an appropriately sized tracheostomy tube and check that the cuff and all the connecting equipment works properly, so that ventilation can continue uninterrupted following the tracheostomy. There needs to be good communication between the surgeon and the anaesthetist.

Having informed the anaesthetist that the trachea is about to be opened, the tracheostomy can be performed. The guiding principle should be to cause as little disruption to the trachea as possible, maintain cartilage and prevent damage to the cricoid cartilage. These aims are best achieved by the use of a vertical slit between silk stay sutures. Once the trachea has been opened, the anaesthetist should withdraw the endotracheal tube under the direction of the surgeon who can visualize the tube being withdrawn. When the tip of the endotracheal tube is immediately above the tracheostomy, withdrawal can stop and the tracheostomy tube should be inserted. The cuff should be inflated and the tube connected to the ventilator.

The incision should be closed loosely and the tracheostomy tube secured in position with tapes, sutures or both.

**CHOICE OF TUBE**

There is a wide variety of tracheostomy tubes available, made from different materials and with different features.
The choice of tube depends on the indication for the tracheostomy, the postoperative needs of the patient, as well as the anatomy of the patient, while also taking into account patient comfort and management of the tracheostomy.

Where possible the tracheostomy tube chosen should feature an inner tube, as described below, as this promotes a safe airway, reducing the risk of obstruction. Consequently, the tracheostomy tube can stay in place for up to 29 days without disrupting the airway. The first tube inserted at the time of the procedure should be a cuffed tube. The most commonly used tubes are polyvinylchloride (PVC) tubes available with or without cuffs and fenestrations.

**Cuff**

Cuffed tracheostomy tubes are used to provide a seal to allow positive pressure ventilation or to prevent aspiration. The pressure of air within the cuff must be high enough to provide an adequate seal, but not so high as to damage the tracheal mucosa resulting in subglottic stenosis. It is therefore imperative that cuffs are not overinflated where the pilot balloon feels solid. The use of modern low-pressure cuffs has for the most part reduced this problem where the recommended cuff pressure of 15–25 cmH₂O can be easily monitored.

**Inner tube**

Several tubes are now supplied with an inner tube, which fits snugly inside the main tube. The tip of the inner tube projects a few millimetres beyond the distal end of the main tube. This means that secretions will collect in the inner tube, which can be removed, cleaned and replaced without disruption to the patient or their airway. The process for cleaning the inner tubes is determined through local guidelines.

With a strong focus on hospital decontamination processes, manufacturers are now developing inner tube systems, which are disposable.

**Fenestration**

The fenestration is sited at the point of maximum curvature in the tube and may be in the form of a single hole or a number of small holes. The fenestration allows air to pass from the tube through the larynx, so increasing the air available for phonation and increasing the volume of the voice. Fenestrated tubes feature an inner tube which is fenestrated, as well as one that is non-fenestrated, so that the clinical needs of the patient can be met without disrupting the airway. The differences between the inner tubes are usually identified by the colour of the 15 mm connector or the inner tube itself.

**Flexibility**

In some cases, a rigid tracheostomy tube will not conform to the anatomy of the patient and will lie at an awkward angle or in a position which results in tracheal trauma from the tip of the tube rubbing against the tracheal wall. In these circumstances, it may be better to use a softer more flexible tube usually made from silicone. If the use of a softer tube results in obstruction of the tube due to kinking, it may be necessary to use an armoured flexible tube. Armoured tubes are reinforced with metal wire along the shaft of the tube, which needs to be considered in terms of imaging and radiotherapy.

**Adjustable flange**

An adjustable flange allows the intratracheal length of the tube to be altered to take account of the depth of the stoma, which may be increased by alterations in anatomy, such as a huge thyroid mass, or to bypass intratracheal obstruction. These tubes can be fixed or predetermined in that they are suitable for depth of stoma only.

In most cases, hyperflexible tracheostomy tubes and adjustable flange tubes do not feature an inner tube and so meticulous postoperative care in terms of airway assessment, suction and humidification is required. These tubes can block easily and may require changing after 7–10 days if there are any difficulties with secretions. The Uniperc™ adjustable flange tracheostomy tube (Portex) has been developed for the larger neck and may be inserted surgically or percutaneously. It features an inner tube which may be removed, cleaned and replaced, hence it may stay in place for 29 days.

Extra length tubes with disposable inner tubes are also available which are predetermined with a choice of either distal or proximal extensions, however, these are not adjustable. Although inner tubes are featured with some adjustable and extra length tubes, secretions may still build up at the distal end of the tube, so continuous nursing care and monitoring is required to prevent obstruction.

It is not recommended that patients are discharged home with single lumen tubes. The Moores tube (Kapitex®) is flexible, features an inner tube system and is very useful when a long, soft, flexible tube is needed and the cuff is no longer necessary.

Flexible and adjustable flange tubes can be customized where patients have specific needs.

**POSTOPERATIVE CONSIDERATIONS**

On their return to the ward, it is important that the patient is looked after by a nurse who is experienced in the care of tracheostomy patients and knowledgeable about the potential complications, as well as the different types of tubes. Local guidelines, procedures or protocols should be in place for the management of patients with a tracheostomy. Communication materials must be available for the patient.

The original tracheostomy tube must be secured in position for at least 3 days to allow a good tract to form. The tube may be changed after 7 days, if this is clinically indicated, and any sutures can then be removed. Tubes should be secured with tapes fastened by a secure knot on both sides of the neck, with the neck in a neutral position. If the neck is extended when the tapes are fastened, then the tapes will be
too long and will not hold the tube in the appropriate position so that it may be coughed out. Alternatively, Velcro tracheostomy tubes holders can be used and can be adjusted quite easily around the neck.

The cuff should be deflated once the risk of aspiration has passed, in most cases there is no need for cuff inflation after the first 12 hours.

Following tracheostomy, the inspired air passes directly into the trachea without being warmed and humidified by the upper airway. As a result, the air is irritant to the trachea and there is an increase in the quantity and viscosity of the tracheal secretions. The patient may require frequent suctioning in the early postoperative period and the use of humidified oxygen, nebulizers or heat and moisture exchangers is essential to reduce the risk of tube obstruction due to crust formation. As the trachea becomes accustomed to the presence of the tube and the patient learns to clear the secretions by coughing through the tube, so the need for suctioning decreases.

Swallowing problems are common following tracheostomy. These are usually due to the sensation of pressure in the upper oesophagus because of an inflated cuff and because the movement of the larynx during swallowing is reduced because of a tethering effect of the tube.

If at any stage there are doubts regarding the position of the tube, or whether the lumen of the tube is obstructed, a flexible nasendoscope can usually be passed through the tube to inspect the lumen of the tube and the trachea.

## Complications

Complications of tracheostomy are listed in Table 15.1.

### Immediate

Haemorrhage is the most common fatal complication of tracheostomy, as well as the most common complication. Bleeding is usually due to damage to the thyroid veins or the thyroid isthmus. If there is significant bleeding at the end of the procedure, the wound should be explored and any bleeding vessel ligated. Packing the tracheostomy wound to tamponade the bleeding is widely practised, but should pressure applied to any bleeding vessel via the tracheostome. Persistent bleeding may cause displacement or obstruction of the tube due to crust formation. As the trachea becomes accustomed to the presence of the tube and the patient learns to clear the secretions by coughing through the tube, so the need for suctioning decreases.

Swallowing problems are common following tracheostomy. These are usually due to the sensation of pressure in the upper oesophagus because of an inflated cuff and because the movement of the larynx during swallowing is reduced because of a tethering effect of the tube.

If at any stage there are doubts regarding the position of the tube, or whether the lumen of the tube is obstructed, a flexible nasendoscope can usually be passed through the tube to inspect the lumen of the tube and the trachea.

Table 15.1 Complications of tracheostomy.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Immediate</th>
<th>Intermediate</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td>Extubation</td>
<td></td>
<td>Tracheocutaneous fistula</td>
</tr>
<tr>
<td>Air embolism</td>
<td>Obstruction</td>
<td>Subcutaneous emphysema</td>
<td>Tracheal stenosis</td>
</tr>
<tr>
<td>Local damage</td>
<td>Subcutaneous emphysema</td>
<td>Infection</td>
<td>Fistula</td>
</tr>
</tbody>
</table>

### Intermediate

Accidental extubation is easily avoided provided that the tube is adequately secured at the time of the procedure, by suturing the flanges of the tube to the skin. If the tube is displaced and comes to lie in the pretracheal space, the complication may not become immediately apparent. The patient can continue to breathe and the soft tissues gradually prolapse around the tracheal opening which slowly begins to seal. Dyspnoea slowly increases and, by the time the displacement is apparent, the tube may be impossible to replace as the tracheotomy has virtually closed. An experienced nurse will pick up on the early warning signs. Any difficulty breathing through the tube must be fully investigated. The use of a flexible scope passed through the lumen of the tube may identify displacement or obstruction of the tube due to crust formation, granulation tissue or poor placement of the tube tip with respect to the tracheal wall.

If the tracheostomy tube or the trachea is obstructed and the skin incision has been closed tightly, then air may be forced out into the soft tissues of the neck during expiration resulting in subcutaneous emphysema. Surgical emphysema, under these circumstances, can track up to the lower eyelids and down into the upper chest. In severe cases, the swelling may cause displacement of the tube.

Tracheo-oesophageal fistulae may be the result of intraoperative damage to the posterior wall of the trachea or persistent rubbing of the tip of the tube on the posterior wall in the early postoperative period. The fistula usually presents when the patient starts to show signs of aspiration, in spite of the cuff being inflated. Tracheoarterial fistulae present most commonly in previously irradiated patients, particularly if a low tracheostomy has been carried out. There is rarely any premonitory sign and the usual presentation is with sudden massive haemorrhage. The tracheostomy tube must be changed immediately for a cuffed tube, the cuff should be inflated to prevent further aspiration of blood and compression applied to any bleeding vessel via the tracheostome. The wound should be explored immediately as there is a very high mortality associated with this complication. The most common artery affected is the innominate, although there are reports of tracheocarotid fistulae.
Late

Epithelialization of the tract is a normal event in the evolution of a tracheostomy. The longer the tracheostomy has been present, the more established the process is and the more likely the tract is to persist following decannulation. The incidence can be reduced if great attention is paid to ensuring an airtight seal is maintained once the stoma has been occluded. If there is evidence of granulation tissue in the fistula, simple cautery with silver nitrate may effect a closure. A small number of cases will require formal surgical closure. This involves excision of the tract all the way down to the anterior tracheal wall and closure in several layers.

Tracheal stenosis is almost always the result of damage to the cricoid or first tracheal ring at the time of surgery or damage to the trachea from the rubbing of a poorly positioned tube, resulting in mucosal inflammation.

Decannulation

If the patient is able to breathe around the tube when it is occluded, then there is no need to downsize the tube. This is usually the case, if the initial cuffed tube has been replaced with an uncuffed fenestrated tube. Decannulation should take place in an ordered sequence and local protocol should be followed. The tube should be blocked during the day and unblocked at night for the first 24 hours. If the patient tolerates this, then the tube can be occluded for a full 24-hour period and if this is tolerated then the tube can then be removed. If the patient is unable to tolerate this occlusion of the tube, then it may be necessary to downsize the tube to give more room around the tube. Patients who have been dependent on the tracheostomy for a long time may require a more prolonged decannulation process as it may take some time for them to overcome their anxiety about being unable to breathe without the tube in place.

Once the tube has been removed, an airtight dressing must be applied to occlude the stoma. In most cases, several gauze squares covered with an occlusive dressing will be sufficient. The dressing should be changed whenever an air leak appears to improve the chance of full closure of the fistula. Where possible, the patients should be encouraged to support the tracheostomy site while talking and coughing to promote healing.

LONG-TERM TRACHEOSTOMY

Certain clinical situations are such that the patients will require a tracheostomy long term or permanently. Discharge plans and continuing care issues need to be addressed at the earliest opportunity and action plans put in place. For patients with an end tracheostomy (following total laryngectomy), physical, psychological and social assessments and preparation should be made in the preoperative phase to ensure the best outcomes for the patients and their families. This is best achieved through a combination of multidisciplinary pretreatment assessment clinics, home visits and patient visits.

Careful consideration of the discharge destination, immediate support and communication needs is required to ensure patient safety. Where possible, patients are encouraged to maintain independence and need focused education to acquire skills in self-care in terms of their tracheostomy. Patients, their partners and families need to be included in the education programme at the earliest opportunity in order to gain proficiency and confidence in what is required.

Community care teams need to be included and good communication across the care boundaries is required to provide support to patients where care issues can be complex and challenging. Community-based teams require specific education in terms of tracheostomy care and the ongoing supply of specialist equipment.

After discharge, it is essential that strategies are put in place for trouble shooting and the management of complications arising. This can be achieved through clinical nurse specialists, Macmillan nurses or key workers who have expertise in altered airways, who can assess patients and advise on treatments as soon as problems arise reducing the need for emergency admission to hospital.

Patients with end tracheostomy will undergo continuing voice rehabilitation programmes and so become very familiar with maintenance of their voice prosthesis and problem-solving strategies.

RESUSCITATION

The aim of tracheostomy care is to prevent complications arising from the tracheostomy itself. This can be achieved through constant vigilance and attention to detail, taking into account the needs for suction, humidification, stoma care and specific tube care.

Airflow through the tube should be checked regularly to identify problems early and prevent emergency situations.

Patients with a tracheostomy can experience breathing difficulties at any time which may be very distressing. Nurses and the medical team should be alert to this and investigate any changes immediately.

It is essential that specific equipment is kept at the patient’s bedside (Box 15.1), so that emergency events can be dealt with much more effectively and efficiently, ensuring the patient’s safety.

Box 15.1 Bedside equipment

- Oxygen apparatus
- Suction apparatus (in working order)
- Tracheal dilators
- Two spare tracheostomy tubes
  - one the same size and type as worn by the patient
  - one a size smaller
- Stitch cutter
- Endotracheal tube tapes/tracheostomy tube holders
- Lubricating gel
- 10 mL syringe
Figure 15.1 Guidelines for emergency care of tracheostomy patients.

Figure 15.2 Guidelines for emergency care of laryngectomy patients.
In the event of respiratory or cardiopulmonary arrest, the procedure as stated in the local resuscitation policy should be followed. The presence of a tracheostomy tube or an endotracheal tube may sometimes cause anxiety for members of the resuscitation team not familiar with the anatomy of the altered airway. In the first instance, it is essential to ensure that there is no obstruction of the airway or within the trachea. This can be assessed by feeling for airflow through the tracheostomy by placing a hand in front of it, inspecting the inner tube and performing tracheal suction to ensure the easy passage of the catheter.

For patients with a tracheostomy, it is essential that resuscitation is given using the tracheostomy and not the mouth, and the guidelines outlined in Figure 15.1 may be followed. Patients with laryngectomy will require mouth-to-stoma resuscitation, rather than mouth-to-mouth resuscitation, as the stoma is the only point of entry to the lower airway. The stoma should be examined for any obstruction and as the stoma is the only point of entry to the lower airway, resuscitation is given using the tracheostomy and not the passage of the catheter.

KEY EVIDENCE

- The evidence in support of this chapter is from retrospective observational and cohort studies. There have been few publications in the past 30 years related to open surgical procedures and the majority of publications in the past 15 years have been concerned with the impact of the introduction of percutaneous techniques, primarily in the intensive care setting.

KEY LEARNING POINTS

- Effects of tracheostomy: laryngeal bypass, reduced respiratory dead space, loss of nasal functions, increased risk of infection.
- Indications for tracheostomy: upper airway obstruction, removal of secretions, prolonged ventilation, part of another procedure.
- Complications of tracheostomy: immediate (haemorrhage, air embolism), intermediate (accidental extubation, tube obstruction, tracheo-oesophageal fistula), late (persistent tract, stenosis).
- Resuscitation: for patients with a tracheostomy, the stoma is likely to be the easiest means of access to the airway and may be the only route of access to the airway. Local guidelines should be followed.

REFERENCES

INTRODUCTION

The structures within the laryngotracheal region provide vital function in terms of ventilation, swallowing and voice. Because of the complex anatomy within this region, traumatic injuries can produce significant acute dysfunction, create a life-threatening condition and/or result in long-term upper aerodigestive tract morbidity. Comprehensive assessment and prompt management are essential to minimize the likelihood of perioperative complications and long-term morbidity and thus optimize patient outcome.

Key evidence

Key learning points

Acknowledgements

References
that penetrating wound injuries were more likely to result in death. This mortality rate may be related to the higher likelihood of concomitant injury involving critical organs or tissues including the chest, skull base and/or critical neurovascular structures from gun or knife injuries. This is in contrast to the review by Bhojani et al. who reported a higher mortality rate in patients with blunt trauma. These patients were also older and more likely to require emergency airway management compared to those with penetrating wounds. The variability in reported injury outcome may relate to the referral pattern and geographical diversity.

Inhalation-type injuries involving the laryngotracheal complex occur following exposure to fires and/or noxious gases or ingestion. Airway oedema commonly occurs following these exposures and in the majority of cases, it resolves without sequelae. However, inhalational injuries or ingestion of corrosive agents, such as bleaches or acids, may cause full thickness burns that result in scar formation with potentially devastating morbidity to the upper aerodigestive tract.

Laryngotracheal complex injuries may occur following a cricothyroidotomy, a transaryngeal tracheostomy, a high tracheostomy or other therapeutic procedures including upper aerodigestive tract endoscopy, endolaryngeal surgery (cold steel, laser), routine tracheostomy (percutaneous or open) or as a result of prolonged placement of a nasogastric tube. Most commonly, these lesions occur after orotracheal intubation resulting in chronic inflammation, granulation tissue, fibrosis and resultant stenosis. In the past three decades, modifications in the tracheostomy cuff and avoidance of a high tracheostomy have reduced the incidence of tracheal stenosis, but have not significantly reduced the rate of subglottic stenosis. Stenosis in this region may be related to the intubation (multiple insertions, prolonged duration or traumatic intubation), the tube utilized and patient factors. Comorbidities, such as diabetes and vascular disease, may increase the risk of developing laryngotracheal stenosis. To minimize the injury to the local tissue associated with intubation, it is recommended that a low cuff pressure and the smallest diameter polyvinyl chloride tube be used.

In recent years, a greater awareness and recognition of this problem, in addition to improved technique, better instrumentation, development of modern materials and timely intervention, have significantly decreased the development of adverse laryngotracheal complex sequelae after routine airway management.

**PATHOPHYSIOLOGY**

The degree of pathology following injury to the laryngotracheal complex will vary and is largely dependent upon the mechanism of injury (Figure 16.1).

External trauma to the laryngotracheal complex in both the adult and paediatric population can lead to rapid asphyxiation due to aspiration of blood, intrapulmonary haemorrhage, cricotracheal separation and/or recurrent laryngeal nerve palsy. In cases of external trauma, concomitant cervical spine injury (8–14 per cent), closed head injury (13–28 per cent), chest trauma (13 per cent), fractured ribs or sternum, pneumothorax, haemorrhax, or disruption of the oesophagus (3–14 per cent) may occur and should be included in the evaluation.

The compression force of blunt trauma may result in a fracture of the thyroid and/or cricoid cartilage and/or laceration of associated endolaryngeal soft tissue structures (Figure 16.2a–e). The majority of fractures in this region involve the thyroid lamina (median or paramedian location) and are usually longitudinal in nature. These injuries occur in patients of all ages, despite the common belief that ossified cartilages are at an increased risk of fracture from external trauma. With penetrating injuries, compound wounds may develop and lead to significant disruption of the laryngotracheal complex. These injuries may result in varying degrees of oedema, haematoma, inflammation, displacement of laryngeal structures and scar tissue formation. Perichondritis may occur with the long-term possibility of chondronecrosis and major laryngeal dysfunction. Cricotracheal separation caused by a ‘clothesline-type injury’ is a rare injury that emergency personnel should consider when treating these patients (Figure 16.3). These injuries are associated with significant disruption of the laryngotracheal complex and unilateral or bilateral recurrent laryngeal nerve avulsion. Cricoarytenoid joint dislocation or subluxation may occur with all mechanisms of accidental trauma.

In the paediatric population, laryngotracheal injuries have a somewhat different pathophysiology due to the decreased prevalence of violent trauma compared to the adult population. However, seemingly minimal trauma can lead to a devastating injury with the associated consequences of airway obstruction and loss of normal phonatory function. Minor anterior neck trauma can result in airway oedema, haematoma formation and even rupture of the membranous trachea. Due to the loose attachment of submucosal tissue to the underlying perichondrium and a relative paucity of fibrous tissue, the elasticity of the trachea prevents fracture, but minor traumatic forces are often translated to the laryngotracheal complex leading to vocal cord avulsion, arytenoid dislocation or subluxation and/or significant soft tissue injury.

Simple airway manipulation, as seen in endotracheal intubation, may cause laceration of endolaryngeal soft tissue, haematoma formation, dislocation/subluxation of the
Figure 16.2 This case involved external trauma from a motor vehicle accident. (a) Soft tissue hallmark of blunt trauma. (b) CT scan demonstrates a paramedian thyroid cartilage fracture. (c) Intraoperative exposure demonstrates the laryngeal fracture. (d) Fracture reduction and repair using 28-gauge wire. (e) Patient at one-year follow up with a normal voice and well-healed incision. (Reproduced with permission from Patrick J Gullane).
cricoarytenoid joint or laryngeal nerve palsy. 26, 27 Similarly, endolaryngeal surgery using either cold steel instruments or carbon dioxide (CO₂) laser, is associated with a variety of injuries which may cause significant laryngotracheal dysfunction (synechia, cricoarytenoid joint ankylosis, subglottic stenosis). Prolonged intubation is associated with significant inflammation, formation of granulation tissue, the development of secondary infection and scar formation and the development of ‘laryngeal bed sores’ as described by Benjamín 28 particularly in the posterior glottic and subglottic region. The long-term sequelae include glottic and/or subglottic stenosis with airway compromise and/or vocal cord dysfunction. In addition to the duration of intubation, factors such as patient age, concomitant medical illness (diabetes, vascular disease, immunosuppression, gastro-oesophageal reflux disease), endotracheal tube material and the level of care are associated with the development of complications after endotracheal intubation.

CLASSIFICATION OF STENOTIC LESIONS

Stenotic lesions in this region are delineated by the anatomic location (i.e. supraglottic, subglottic and posterior glottic) and associated structures. To assist in the management of posterior glottic stenosis, Bogdasarian and Olsen 29 developed a four-tier classification system based on the structures involved (Figure 16.4a–d): type I includes an isolated interarytenoid band; type II stenosis is more extensive and includes a posterior glottic mucosal tunnel, but no arytenoid cartilage ankylosis; type III has ankylosis of one arytenoid joint; and in type IV both arytenoid joints are fixated.

CLASSIFICATION OF TRAUMATIC LARYNGOTRACHEAL INJURY

A number of classification systems have been developed to assist in the evaluation and management of patients with traumatic laryngotracheal complex injuries. 4, 30, 31 Trone et al. 31 developed one of the first classification systems to describe injury involving the upper airway in order to facilitate the development of an appropriate treatment plan. This classification system (Table 16.1) utilizes physical examination, fibreoptic laryngoscopy and computed tomography (CT) scanning. Patients are divided into four groups according to the extent of the injury: group 1, minor endolaryngeal haematoma and no detectable cartilage fracture; group 2, oedema, haematoma, minor mucosal disruption, non-exposed cartilage and/or non-displaced fractures on CT scan; group 3, massive oedema, mucosal tears, exposed cartilage and/or vocal cord immobility; group 4, as with group 3 with the addition of more than two fracture lines or massive mucosal trauma. Fuhrman et al. 4 modified this classification to include complete cricotracheal separation as a fifth group. Trone et al’s classification system 31 does not stress the independent prognostic importance of injury involving the anterior commissure, cricoarytenoid joint dislocation/subluxation, cricoid fracture and unilateral or bilateral recurrent laryngeal nerve palsy. 1 However, this classification has provided criteria for tracheostomy and/or surgical exploration, demonstrated prognostic merit and its simplicity has permitted wide application to the management of laryngotracheal injuries. 1, 4, 32, 33 Other classification systems that describe disruption of the laryngotracheal complex have been presented by Ogura et al. 30 and Richardson, 34 but do not help to differentiate between a non-operative or operative approach. The classification system therefore should be based on the underlying cause, the type and degree of injury and its sequelae.

ASSESSMENT

Successful management of the patient following cervical trauma requires a multidisciplinary team approach that includes an emergency physician, a trauma surgeon, an anaesthesiologist, radiology and appropriate ancillary staff (Figure 16.5).

Signs and symptoms

The signs and symptoms associated with laryngotracheal injury will vary depending on the mechanism and severity of the injury. Symptoms may present acutely or develop slowly over time and rapidly escalate to a medical emergency. This is
in sharp contrast to the presentation following intubation, which produces inflammatory changes that occur over a prolonged period of time with a slow onset of airway symptoms.

The clinical manifestations of injury following intubation commonly present weeks after extubation with symptoms and signs of chronic airway dysfunction and/or loss of normal phonation. Patients may present with stridor and dyspnoea. Depending on the degree of stenosis, the dyspnoea may be minimal at rest and significantly worsen with exertion. Patients may also complain of a dry cough and have difficulty handling their secretions.

Following acute trauma to the cervical region and laryngotracheal complex, patients may be asymptomatic for the first 24–48 hours after the injury and therefore these cases must be managed with a high degree of suspicion and expert level of care. Dysphonia and shortness of breath are the two most common symptoms encountered followed by dysphagia, odynophonia and an inability to lie supine. The clinical signs include those associated with acute airway obstruction (stridor, tachypnoea, sweating, tachycardia and the use of the accessory muscles of respiration), neck ecchymosis, loss of the normal laryngeal prominence, tenderness, subcutaneous emphysema, grossly displaced cartilage fractures, tracheal deviation and/or haemoptysis. Cricotracheal separation should be suspected when the mechanism of injury is a ‘clothesline-type’ of trauma and with the presence of aphonia, cervical ecchymosis, extensive subcutaneous emphysema and elevation of the hyoid (Figure 16.6).
Airway management

The primary management of accidental laryngeal trauma begins with the assessment of the airway. Providing that it is stable, evaluation of the patient can safely begin with a thorough and comprehensive history to provide information regarding the mechanism of injury (accidental versus iatrogenic, blunt versus penetrating, high versus low velocity) and the extent of laryngotracheal complex disruption. Past or present medical illnesses (cardiac, respiratory, diabetes) and medications are also noted.

Management of laryngotracheal trauma requires the ability to recognize impending airway obstruction and the ability to expedite safe and prompt care. The establishment of a safe and stable airway is the primary goal in patients presenting with any degree of airway obstruction. This should

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**Table 16.1  Laryngotracheal injury classification according to Trone et al.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minor endolaryngeal haematoma without detectable fracture</td>
</tr>
<tr>
<td>2</td>
<td>Oedema, haematoma, minor mucosal disruption without exposed cartilage, non-displaced fractures noted on computed tomography scan</td>
</tr>
<tr>
<td>3</td>
<td>Massive oedema, mucosal tears, exposed cartilage, cord immobility</td>
</tr>
<tr>
<td>4</td>
<td>As group 3, with more than two fracture lines or massive trauma to laryngeal mucosa</td>
</tr>
<tr>
<td>5</td>
<td>Complete laryngotracheal separation</td>
</tr>
</tbody>
</table>

*Group 5 added by Fuhrman et al.*

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**Figure 16.5  Management algorithm for patients following laryngotracheal injury.** *Minor mucosal disruption and minimally/non-displaced cartilage fracture can be managed conservatively.*
Once the patient is stabilized, the cervical spine and any concomitant neurovascular injury can be assessed and a complete systems review performed. X-rays may be limited to a routine trauma series within the Accident and Emergency Department. Precise and comprehensive assessment of any potential laryngotracheal injury requires knowledge of the anatomy and the ability to complete the examination without causing any additional discomfort or disruption to the airway. Careful palpation for any evidence of subcutaneous emphysema, haematoma or possible cartilage fractures should be performed. Evaluation of the endolarynx using fiberoptic nasoendoscopy is a key component of the examination in order to assess airway patency, mucosal lacerations, haematoma, arytenoid position, cartilage exposure or vocal cord mobility.37

Treatment for primary airway control includes simple endotracheal intubation, fiberoptic awake intubation and/or tracheostomy under local anaesthesia. Occasionally, an emergency cricothyroidotomy may be required and/or an open cricothyroidotomy to secure the airway and to exclude any significant injury, such as laryngotracheal separation.3 Gussack et al. recommend that endotracheal intubation is performed by the most experienced anaesthesiologist using a small-sized tube under direct visualization for minor laryngotracheal disruption and/or a supraglottic haematoma.38 This study reported successful intubation in eight of 11 patients with acute laryngeal trauma. Because endotracheal intubation is extremely challenging and difficult in these patients, Schafer39 recommends a tracheostomy under local anaesthesia in patients with signs or symptoms of potential airway obstruction. A failure rate as high as 76 per cent of cases of laryngotracheal injury has been reported with intubation.40 There is also a significant risk of iatrogenic injury to the already compromised airway and/or other neurovascular structures (cervical spine), which may lead to potentially devastating sequelae.39 In cases of laryngotracheal separation, ‘blind’ placement of an endotracheal tube across the area of separation can convert a stable situation to one that is life threatening. Those that advocate endotracheal intubation for primary airway management, generally do so with significant expertise within the setting of a tertiary referral centre.38 We recommend tracheostomy under local anaesthesia as the gold standard for primary airway management in adults with acute laryngeal trauma.1, 3, 4, 39, 40, 41, 42

In paediatric patients, primary airway management requires a different approach and includes a gaseous induction with spontaneous ventilation and securing the airway with rigid bronchoscopy followed by tracheostomy. Cricothyroidotomy is rarely used in paediatric patients as it may compound any injury present and may not provide an adequate airway.12

The indications for tracheostomy under local anaesthesia include any evidence of airway obstruction, inability to lie supine, significant upper aerodigestive tract oedema or when open surgical exploration is indicated. The tracheostomy is optimally performed in the operating theatre with the availability of airway instrumentation, suction and lighting, an experienced surgical assistant and with the support of anaesthesia and nursing. Placement of the tracheostomy incision should be slightly lower than usual to avoid the area of laryngotracheal injury. A horizontal incision, midway between the cricoid cartilage and the sternal notch is most frequently used and if necessary, lateral extension of the incision will allow adequate exposure of all structures within the neck region to assess and repair any other injury that is present.

Once the airway has been established, further evaluation of the laryngotracheal injury can be performed. A variety of laryngoscopes, microlaryngeal instruments and rigid telescopes facilitate the precise examination of the endolarynx, which should include the mucosal surfaces, the cartilaginous framework, including the integrity and mobility of the cricoarytenoid joint. Video equipment can provide precise and careful documentation for future comparison. A thorough evaluation of the oesophagus and tracheobronchial tree is also necessary for complete assessment.

**IMAGING**

With the advancement in imaging technology and instrumentation, CT scans and magnetic resonance imaging (MRI) are now the gold standard for examination of the laryngotracheal region.

In patients with stenotic upper airway obstruction, CT scans and MRI provide details regarding the location and dimensions of the stenotic segment. Endoscopy with a flexible bronchoscope will assist in visualizing the lesion, to identify the precise size, extent and location of the stenotic area relative to the true vocal cords. Rigid bronchoscopy may be used to assess the stiffness of the lesion and will help to determine the usefulness of non-operative interventions, such as laser vaporization or dilatation.

In the assessment of laryngotracheal complex trauma, CT scanning and MRI has replaced traditional imaging methods including laryngeal tomography and laryngograms.3 CT scans and MRI provide comprehensive assessment of the cartilaginous laryngeal framework and associated soft tissue structures and can assist in identifying cartilage fractures (single, multiple, angulated, displaced, undisplaced), haematoma, cricoarytenoid joint dislocation/subluxation and stenosis. It can provide excellent assessment of the nature and extent Figure 16.6 Intraoperative view of posterior cricoid plate fracture with associated tracheal disruption. (Reproduced with permission from Patrick J Gullane.)
of laryngotracheal disruption to assist in treatment planning and operative intervention if necessary.

Some surgeons have recommended CT scanning for all patients with trauma involving the laryngotracheal complex to adequately assess and to assist in the surgical planning for reconstruction. However, Schaefer contends that a more selective approach is warranted and that CT scanning does not provide additional information when clear indications for surgical exploration exist and may potentially delay treatment. A CT scan should never be performed in a patient with an unsecured airway and since a CT scan requires the patient to lie supine for an extended period of time, the patient’s airway status should be monitored. It is therefore essential that experienced staff and resources are available to respond to any deterioration of the airway during imaging. In patients with cervical neck trauma, we prefer to obtain a CT scan with contrast, but this should not be performed at the expense of safe airway management.

Because of the high prevalence of associated occult vascular or oesophageal injury, angiography and swallowing studies (with or without contrast) may also be indicated in patients presenting with penetrating cervical trauma.

MANAGEMENT

Non-operative and operative interventions are available for the treatment of patients with pathology involving the laryngotracheal complex and a comprehensive patient evaluation will provide the necessary information regarding the best management. The challenge is to select the most efficacious treatment, which will maximize functional outcome and minimize additional morbidity from unnecessary surgery or delayed treatment.

Non-operative approach

The mechanism of injury, the severity of symptoms and other patient factors, such as comorbidities, will determine the available options for non-operative treatment ranging from medical management to dilatation and/or stents.

In patients with subglottic stenosis, non-operative treatment including corticosteroid injections, airway dilatation, laser vaporization and stents usually precedes consideration of surgical intervention. Dilatation may provide temporary relief of symptoms, but it is rarely a definitive therapy. In some cases, aggressive dilatation may cause trauma to the region thus worsening the stenosis and increasing airway dysfunction. Mitomycin-C has been used following dilatation to prevent recurrence of the stenosis; however, others have reported no improvement. When non-operative treatment has failed to improve airway function or with continued decline in patient symptoms, surgical intervention is usually recommended.

In patients with acute traumatic injuries, the goal of treatment is to stabilize the fracture and to promote normal soft tissue healing. Schaefer and Close reported good functional outcome following a non-operative approach in patients with minor mucosal lacerations (excluding the anterior commissure region or free edge of the vocal fold) and undisplaced, single fractures of the laryngeal cartilaginous framework. Bent et al. reported normal airway and phonatory function in patients with non-displaced thyroid cartilage fractures and minimal intralaryngeal injury who were treated without surgery. This approach included at least 24 hours of close observation in an intensive care or high dependency unit, constant humidification, voice rest and elevation of the head of the bed. A subset of patients may require establishment of a safe airway (intubation or tracheostomy) and a panendoscopy to rule out concomitant injury to structures within the upper aerodigestive tract. If this examination is negative and no other indication for surgical exploration is found, these patients can be effectively managed non-operatively. Close observation and frequent reassessment by those experienced in managing these patients are required to ensure satisfactory healing and successful extubation or decannulation.

Specific treatment with medication for these injuries is limited, but there is some evidence for antireflux therapy to prevent irritation of mucosal injuries and subsequent development of laryngeal stenosis, especially in patients with gastroesophageal reflux disease. Occasionally, nasogastric tube feeding is required, however this may potentiate gastroesophageal reflux and may cause added insult to the injured larynx. The use of corticosteroids remains controversial and there are no definitive studies regarding its efficacy in the treatment of patients with trauma to the upper airway. Potentially, corticosteroids may reduce soft tissue oedema, but must be administered within hours of the injury. Similarly, the role of antibiotics in preventing sequelae of uncontrolled infection leading to perichondritis, impaired wound healing, cartilage destruction and loss of airway function, is controversial. The use of broad-spectrum antibiotics (penicillin, cephalosporin) is recommended for comminuted injuries and those requiring surgical exploration and repair.

Operative approach

The goal of surgical intervention involving the laryngotracheal complex is to restore primary function, including ventilation, airway protection and phonation. Significant debate and controversy exists in the literature regarding the indications for surgery, its timing, method of repair and the use of intraluminal stenting.

CRICOTRACHEAL STENOSIS

Because of the unique function and complex anatomy in this region, many surgical techniques have been described for treatment of subglottic stenosis. We have found that circumferential tracheal or combined cricotracheal resection with primary anastomosis provides optimal outcome in the appropriately selected patients, based upon preoperative evaluation of the stenotic region and patient comorbidities. Several principles should be followed to ensure a successful result and to minimize the risk of postoperative complications with simple resection and primary anastomosis. The segment of excised trachea should not exceed 5 cm to ensure that there is no tension on the anastomosis. The proximal margin of the resected segment must be at least 5 mm distal to the true vocal cords because more proximal lesions will require a complex reconstruction to restore function. Similarly, patients...
who present with cricoarytenoid ankylosis and fixed vocal cords should be selected carefully and may require an associated laryngofissure with laryngeal repair. This surgery should be approached with caution in patients with diabetes, severe vascular dysfunction, poor pulmonary function, prior radiation treatment to the trachea or larynx and in patients who are being treated with immunosuppressive drugs, including corticosteroids. The risks associated with poor wound healing may be minimized with preoperative treatment of comorbidities, complete excision of the stenotic tissue, an adequate thyrotracheal repair and support of the airway postoperatively.

To optimize patient outcome following cricotracheal resection with thyrotracheal anastomosis, a few key surgical details are outlined. A low collar incision is used and the airway is exposed from the hyoid bone to the manubrium. The region of stenosis is identified, the margins delineated and an en bloc resection of the stenotic region is performed. To avoid injury to the recurrent laryngeal nerves, the dissection is limited to the inner aspect of the cricoid cartilage and to minimize the risk of tracheal ischaemia, minimum lateral dissection is used. If the stenosis extends close to the vocal cords, a laryngofissure may be necessary to improve the exposure for the resection and anastomosis (Figure 16.7a,b).

If a laryngofissure is performed, the posterior aspect of the cricoid plate is thinned and at least 50 per cent of the plate is maintained to retain the vertical height. The trachea is mobilized to the level of the carina and lateral stay sutures are used to elevate the proximal margin of the trachea. The anastomosis between the trachea and the subglottis is completed using a running No. 4-0 PDS suture posteriorly and No. 4-0 vicryl laterally and anteriorly. To prevent irritation of the oesophagus, the posterior knots are placed inside the airway and to minimize granulation tissue within the airway, the vicryl sutures are tied exterior to the airway. A T-tube is used to support the airway and is positioned approximately 6–7 mm cephalad to the vocal cords. At the proximal end of the T-tube, a bronchial blocker (Figure 16.8a,b) is placed transorally to permit ventilation through the horizontal arm of the T-tube and is required to complete the anastomosis. A T-tube is used to protect the anastomosis and to stent the airway. A distal tracheostomy is rarely necessary.

TRAUMA

In cases of major disruption of the cartilaginous and/or soft tissue framework of the larynx, suture repair, rigid internal fixation and/or intraluminal stenting may be required. Stanley et al. reported that spontaneous healing with normal phonatory function will not occur with non-operative treatment alone and the result will be a permanent dysfunction of the larynx. However, the optimal approach to minimally or non-displaced fractures is controversial and there are no definitive studies detailing the absolute indications for internal fixation versus non-operative management. Other factors that must be considered in the selection of the most beneficial approach include the presence of concomitant major injuries (i.e. neurovascular, chest, abdomen), associated medical morbidity, time from injury and individual patient factors.

The ideal timing for surgical intervention is associated with significant controversy and debate in the literature. Some recommend that a period of observation is required prior to surgery to allow any significant oedema in the upper aerodigestive tract to subside. However, others recommend exploration within 24 to 48 hours, to avoid the establishment of active infection and early scar formation. The potential long-term result of significant delay are airway and voice dysfunction. A recent multi-institutional review of 392 patients with external laryngeal trauma reported that 80 per cent of surgical interventions were performed within 48 hours of the injury, supporting early surgical exploration as the preferred standard of care.
anterior midline tracheal incision. Once the endolarynx is exposed, repair of a significant mucosal tear, a subluxed or dislocated arytenoid or fractured cartilaginous structures can be performed. Because of the delicate surrounding tissue, any excessive and unnecessary handling should be avoided to prevent additional injury. Mucosal tears can be primarily repaired with fine monofilament sutures (5/0 monocryl). For large defects, local rotation flaps or free tissue transfer using either buccal mucosa or skin may be employed. These reconstructions must be secured with sutures and supported by intraluminal stenting.

Successful functional outcome after trauma requires that the cartilaginous fractures are anatomically reduced and stabilized. Adequate exposure to the fracture line is essential to achieve a good outcome and, in general, we prefer to elevate the outer perichondrial layer 1–2 cm lateral to any median or paramedian thyroid cartilage fracture. However, if the fracture is located more laterally along the lamina, the outer perichondrial layer is incised in the midline and then elevated in continuity with the overlying strap muscles. A similar approach can be used for the management of fractures involving the cricoid cartilage. Historically, a number of techniques including simple suturing of perichondrium or wiring of cartilage segments (24- or 26-gauge wire) have been described with varying success. Mini-reconstruction adaptation plates are now frequently utilized for the management of laryngotracheal complex injuries and permit immediate fixation and stabilization of these cartilage fractures. The main disadvantages with using this technique are the increased cost, ease of stripping the screw, additional skill required by the surgeon and potential for infection. However, the advantages in allowing primary tissue healing and being able to recreate normal laryngeal framework dimensions, make this technique an excellent alternative to traditionally described methods in the management of laryngotracheal complex fractures.

Reconstruction of the anterior commissure region either after fracture or laryngofissure requires precise suturing of the anterior aspect of each vocal fold to the corresponding outer perichondrial layer. Cartilage loss can be easily managed using local tissue including strap muscle flaps sutured into the defect. More extensive loss can be repaired using free cartilage grafts from a variety of sites, including the septum or more commonly the rib. All repairs should have a temporary tracheostomy sufficient for ventilation, placed two to three rings distal to the area of repair to avoid contamination and potential delay in wound healing.

Indications for the use of airway stenting include disruption of the anterior commissure, massive mucosal trauma and/or significant destruction or loss of the cartilaginous laryngotracheal complex. The ideal stent should consist of a material which is inert, of sufficient strength and length to stabilize the cartilaginous structures from the supraglottic to the subglottic region, has a shape that mirrors the internal structure of the larynx and does not cause any added injury due to excess movement and pressure. Contemporary advances in the development of alloplastic materials have seen the emergence of a variety of softer and more inert intraluminal stents. In patients with significant traumatic laryngeal disruption, we prefer to use a Montgomery laryngeal stent secured with prolene sutures. In general, the adolescent size is sufficient for the adult larynx and can be removed endoscopically approximately 2–4 weeks following surgery (Figure 16.9). Other alternative stents include the Aboulker stent, a T-tube or silastic sheeting individually fashioned to promote mucosalization and prevent the formation of endolaryngeal synechia. The anterior commissure, the interarytenoid area and the subglottis are at significant risk of excessive scarring. Regardless of the material that is used, stenting the upper airway represents a risk–benefit analysis with the need for stabilizing the airway being balanced with the possible negative effects of added endolaryngeal injury and/or infection.
CRICOARYTENOID JOINT DYSFUNCTION

Injury to the cricoarytenoid joint is a rare phenomenon and it is most commonly caused by routine endotracheal intubation, but can be due to blunt or penetrating cervical trauma. The true incidence of this condition is unknown, however, it is estimated to occur in less than 1 in 1000 cases of routine intubation. The gender distribution is approximately equal and it can occur at any age. There is some controversy about the mechanism of injury that leads to either anterior or posterior displacement. Historically, anterior dislocation was thought to be due to inappropriate placement of the laryngoscope blade or the arytenoid cartilage being caught up within the lumen of the endotracheal tube. Quick and Mervin postulated that posterior dislocation was caused most commonly on the left-hand side by a right-handed physician potentially directing the endotracheal tube against the arytenoids. However, Dudley et al. reported that posterior dislocation was more likely to occur due to premature extubation with an incompletely deflated cuff. Paulsen et al. demonstrated in a human laryngeal model that it was not possible to dislocate or sublux the arytenoid cartilage in this method and more likely it was the development of hemorrhhoes (secondary to a variety of external and internal traumatic mechanisms) involving the joint space which leads to ankylosis and subsequent dysfunction of the cricoarytenoid joint. Underlying systemic conditions, including chronic renal disease, acromegaly and chronic steroid use, may lead to degeneration of the ligaments or joint spaces and can place these patients at an increased risk to traumatic cricoarytenoid joint dysfunction. The majority of these patients present with a clear history of endolaryngeal manipulation (intubation, micro-laryngeal surgery) or external trauma. The most common symptoms include dysphonia (hoarseness, breathiness) or airway obstruction and on physical examination and/or stroboscleolaryngoscopy, there is poor mobility of the vocal cords and/or a displaced arytenoid (anterior, posterior, lateral or combination). Evaluation with CT imaging is helpful to assess the relationship of the arytenoids and the underlying cricoid cartilage. However, the diagnosis is confirmed with electromyography (EMG) of the laryngeal muscles which demonstrates normal neural function of the recurrent laryngeal nerve despite poor vocal cord mobility. The differential diagnosis should include ankylosis of the cricoarytenoid joint and posterior synechia caused by prolonged intubation, inflammatory disease, local infection or longstanding unrecognized recurrent laryngeal nerve palsy.

Standard treatment combines reduction of the cricoarytenoid joint and ideally it should be performed within one month after symptom onset. The role of speech pathology remains to be established with some advocating its routine use, while others feel it has no place in the acute management of patients with traumatic cricoarytenoid joint dysfunction. Failed reduction is approached in a manner similar to vocal cord paralysis to return the vocal fold to a more functional position. Techniques include vocal fold injection (silicone, fat), medialization thyroplasty and/or arytenoid adduction procedures. Arytenoidectomy has been advocated if symptoms of significant airway obstruction predominate, however, this should be preceded by a sufficient trial of non-operative interventions. The outcome after therapy for traumatic cricoarytenoid joint dysfunction is generally excellent in terms of airway patency, however, return to normal phonation is relatively uncommon.

CONCLUSION

Advancements in the assessment and management of patients with trauma to the laryngotraacheal region have lead to enhanced patient outcome and health-related quality of life. Improvements in imaging and fibreoptic endoscopy have facilitated the evaluation of patients with acute trauma and more chronic stenotic lesions. Successful outcome following traumatic laryngotracheal injuries depends upon patient, injury and treatment-specific factors. However, in our experience, early repair of mucosal and cartilaginous injury has led to improved functional outcome with a normal airway, no dysphagia and acceptable voice in the majority of patients, and the extent and severity of injury remain strong predictors of patient outcome. Good function following surgical management of stenotic lesions requires appropriate patient selection, complete resection of the pathologic tissue, an acceptable thyrotracheal anastomosis and support of the airway postoperatively. Patient comorbidities may increase the risk of complications in the perioperative period and should be assessed and if possible treated preoperatively to minimize this risk. Patient and family counselling is essential to provide patients with realistic expectations after complex surgery, which may require prolonged periods of rehabilitation and recovery.

**KEY EVIDENCE**

- Traumatic laryngeal and tracheal injuries are complex, potentially devasting and uncommon.
- Following these types of traumatic injuries, chronic upper aerodigestive tract dysfunction is common and requires prolonged rehabilitation.
The best outcome is achieved with a multidisciplinary team approach in centres with significant expertise in managing complex head and neck disease.

KEY LEARNING POINTS

- Understand the functional anatomy of the larynx and trachea.
- Be aware of the pathophysiology of laryngeal and subglottic stenosis.
- Be familiar with the classification systems of laryngotracheal complex injuries.
- Comprehensive assessment and prompt management are essential to minimize the likelihood of perioperative complications and long-term morbidity.
- Understand the presentation and management both closed and open of acute and chronic laryngeal and tracheal trauma and stenosis.

ACKNOWLEDGEMENTS

Thank you to Christine B Novak, PhD (Research Associate Wharton Head and Neck Centre, and Scientist, Toronto Rehabilitation Institute, University Health Network, Toronto, Canada) for her assistance and contributions to this manuscript.

REFERENCES

Penetrating neck injuries

ANDREW J NICOL AND JOHANNES J FAGAN

INTRODUCTION

The patient presenting to the Accident and Emergency Department with massive bleeding from a penetrating neck injury requires haemostatic surgery. The question, however, is how to manage the stable patient with penetrating neck trauma. The past two decades have seen a major shift in management of such patients from mandatory surgical exploration towards a more selective, conservative approach, based on clinical findings and special investigations. The advent of diagnostic tools, such as oesophagography, flexible endoscopy, angiography, colour flow Doppler imaging and multislice helical computed tomography (CT) has resulted in an increasing confidence in our ability to better evaluate injuries to the neck. The fact that certain of these injuries can safely be managed conservatively or more effectively by endovascular intervention has further swung the pendulum towards a selective, conservative approach. Groote Schuur Hospital Trauma Centre currently treats 220 patients with penetrating neck trauma per annum. In such a busy centre, it is essential that patients be assessed expeditiously, but safely.

RESUSCITATION

Resuscitation is performed according to the guidelines of the Advanced Trauma Life Support (ATLS) course. The main priority on admission of a patient to the Accident and Emergency Department is to exclude conditions that can cause death within the ensuing few minutes.

AIRWAY CONTROL AND CERVICAL SPINE PROTECTION

A definitive airway is required in patients presenting with massively bleeding wounds, rapidly expanding haematomas, stridor, acute respiratory distress, airway obstruction from blood and secretions, and unconscious patients who are...
unable to protect the airway. This might require placement of a cuffed endotracheal tube in the adult patient. With a large, open wound communicating directly with the trachea, the endotracheal tube may be inserted directly through the wound. Airway control in the majority of patients with penetrating neck injuries can be safely achieved with rapid sequence induction and direct laryngoscopy. A tracheostomy performed in the Accident and Emergency Department is not advisable due to the bleeding that can be encountered, making visualization difficult. Fibreoptic laryngoscopy is not usually appropriate in the emergency setting, but can be considered in more stable patients where there is not an immediate threat to the airway. Blind, awake intubations are also inappropriate in penetrating neck wounds, as patients are often intoxicated and combative, and deaths have been attributed to this method of intubation.\(^5\)

The position of the cricothyroid membrane should be established prior to attempted intubation, as an emergency cricothyroidotomy might be required should intubation be unsuccessful. Cricothyroidotomy may be technically difficult due to a haematoma displacing the airway. The skin should be incised over the cricothyroid membrane and the anatomical structures again palpated to identify the membrane. A blade is inserted through the membrane and then twisted through 90° to open the incision. An arterial forceps is placed to open the incision. An arterial forceps is placed into the airway prior to removal of the blade and the tract enlarged. A size 6 endotracheal tube can then be inserted and the cuff inflated. The endotracheal tube is secured with tape and is cut shorter to ensure that the tube does not kink when attached to the ventilator. Correct placement is confirmed by auscultating the chest.

An unstable cervical spine without an obvious neurological injury is extremely rare in the penetrating neck setting. Gunshot wounds to the neck have a high rate of concomitant cervical spine fracture, but unstable cervical spines tend to be associated with a spinal cord injury. A hard cervical collar should not be maintained at the expense of delaying life-saving airway manoeuvres or attempts at obtaining haemostasis in the neck. Once such procedures have been completed, then the cervical collar should be fitted and spinal precautions resumed.\(^5\)

### ASSESSMENT OF BREATHING

A tension pneumothorax or haemothorax should be excluded by palpating whether the trachea is central and by auscultating the chest. Acute respiratory distress accompanied by decreased breath sounds and low oxygen saturation recordings is an indication for insertion of a chest drain on the ipsilateral side. This is performed by blunt dissection through the fifth intercostal space in the anterior axillary line. A tension pneumothorax is a clinical diagnosis and should not have to be diagnosed by chest x-ray (CXR).

### ADEQUACY OF CIRCULATION

Two high-flow lines with 14-gauge cannulae should be inserted into the antecubital fossae. Two litres of warmed crystalloid should be infused rapidly in the event of hypovolaemic shock. This is followed with emergency blood in the event of the blood pressure not stabilizing. Digital pressure can be applied to a bleeding neck wound, or a 20-FG Foley urinary catheter can be inserted into the neck wound and the balloon inflated with 5 mL of water, to stem bleeding. The lumen of the Foley catheter is cross-clamped with arterial forceps to prevent blood haemorrhaging through the urinary port. In the authors’ experience, Foley catheter balloon tamponade has been extremely effective in the haemostasis of bleeding, penetrating neck wounds.\(^1\) The patient should remain recumbent, or the neck wound must be covered with an occlusive dressing to prevent air embolism. Blood should be sent for crossmatch and a haemoglobin level. The patient is monitored with precordial electrocardiogram (ECG) leads and a non-invasive blood pressure cuff. Should the blood pressure not stabilize, neurogenic shock should be excluded as a result of a penetrating spinal cord injury. The telltale signs of neurogenic shock are an unexplained bradycardia, absence of limb movement, paradoxical respiration and priapism. A central venous line should be inserted if there is doubt about the type of shock.

### ASSESSMENT OF DISABILITY

A rapid assessment of the patient’s Glasgow Coma Score (GCS) and pupil size is made. Power in the limbs should be assessed to exclude an ischaemic stroke from carotid artery injury.

### EXPOSURE OF PATIENT

All the clothes are removed, and the patient is fully examined to avoid overlooking injuries. The patient should be logged to examine the back for penetrating injuries. The patient is kept warm.

### PLACEMENT OF TUBES AND ESSENTIAL X-RAYS

A nasogastric tube and a urinary catheter are inserted. Anteroposterior and lateral cervical spine x-rays are requested to determine the presence of spinal column injury and vertebral air that could signify a pharyngeal or oesophageal injury. Chest x-ray is done to exclude mediastinal air, pneumo- or haemothorax, and a widened mediastinum. A widened mediastinum may indicate intrathoracic great vessel or oesophageal injury.

### REASSESSMENT OF PATIENT

Haemodynamically unstable patients are taken to the operating theatre. If the patient’s condition is stabilizing, then a more thorough examination is undertaken in the secondary survey.
Secondary survey

A detailed head-to-foot examination is performed. In gunshot injuries, the entrance and exit wounds are noted, as the tract of the projectile would indicate which anatomical structures might have been injured. In the absence of an exit wound, anteroposterior and lateral cervical x-rays are requested to locate the bullet and determine the course of the tract. The wound should not be probed as this could result in massive bleeding from a vascular injury. Drainage from the wound, such as saliva, lymphatic or cerebrospinal fluid, is noted. The neck is palpated for the presence of subcutaneous emphysema. The presence of ‘hard signs’ of vascular injury, such as a peripheral pulse deficit, bruit or a large haematoma are noted. A full neurological examination is performed, and Horner’s syndrome, cranial nerve, spinal cord and brachial plexus injury are excluded.

Full history

A full history should be recorded with specific reference to the nature of the trauma. Symptoms related to oesophageal injury, such as haematemesis, dysphagia and odynophagia are noted. Dysphonia is suggestive of a vagal or recurrent laryngeal nerve injury. The past medical and surgical history is recorded.

Further investigations

Female patients of child-bearing age must have a pregnancy test done prior to further radiological examination. Special investigations such as angiography, CT scan, ultrasound and contrast studies may now be ordered in the haemodynamically stable patient. A detailed head-to-foot examination is performed. In gunshot injuries, the entrance and exit wounds are noted, as the tract of the projectile would indicate which anatomical structures might have been injured. In the absence of an exit wound, anteroposterior and lateral cervical x-rays are requested to locate the bullet and determine the course of the tract. The wound should not be probed as this could result in massive bleeding from a vascular injury. Drainage from the wound, such as saliva, lymphatic or cerebrospinal fluid, is noted. The neck is palpated for the presence of subcutaneous emphysema. The presence of ‘hard signs’ of vascular injury, such as a peripheral pulse deficit, bruit or a large haematoma are noted. A full neurological examination is performed, and Horner’s syndrome, cranial nerve, spinal cord and brachial plexus injury are excluded.

MANDATORY OPERATION VERSUS MANDATORY IMAGING VERSUS SELECTIVE PHYSICAL EXAMINATIONS AND INTERVENTION

A patient who presents with massive bleeding from a cervical wound, an expanding haematoma or a large blowing wound from a large tracheal wound clearly needs immediate exploration. But what of the patient who is haemodynamically stable and does not fulfil these criteria for immediate exploration? The optimum management of such haemodynamically stable patients has been controversial for a number of years. However, evidence-based medicine is providing a means to resolve these arguments and the clinical management of these neck injuries is becoming clearer.

Non-operative management of penetrating neck injuries was the norm prior to the Second World War, and had an associated mortality rate of 15–18 per cent. In 1944, Bailey proposed early operative intervention for penetrating neck trauma, and with the introduction of antibiotics and tracheostomy, the mortality rate was reduced to 7 per cent. In 1957, Fogelman and Stewart reported that the mortality for patients not promptly explored was 35 per cent versus 6 per cent for those undergoing immediate exploration.

This led to mandatory exploration of the neck becoming the standard of care for penetrating cervical trauma that had breached the platysma muscle. Proponents of mandatory surgery believed that the risk of missing a vascular or aerodigestive injury outweighed the morbidity and cost of a negative exploration. They argued that clinical evaluation was unreliable and diagnostic studies used to detect oesophageal and vascular injuries were not 100 per cent sensitive. In 1963, Stone and Callahan questioned the need for mandatory exploration for civilian injuries. Yet mandatory surgical exploration remained the standard of care for the next few decades. This policy was associated with a high incidence (30–89 per cent) of unnecessary neck exploration.

Proponents of selective exploration allude to the high rate of negative findings with mandatory neck exploration and the excellent specificity of special investigations such as angiography, oesophagography, oesophagoscopy and flexible laryngotracheobronchoscopy to exclude clinically significant injuries. Also many of the injuries, such as thyroid, pharyngeal and selected venous trauma, may be treated conservatively. Four prospective studies on a selective conservative approach to penetrating cervical injuries have confirmed the safety of such an approach. Demetriades et al. reported successful conservative management in 80 per cent of 335 patients in the largest published series. There were no deaths attributed to this policy. The combination of clinical and selective investigations yielded a sensitivity of 100 per cent and a specificity of 85 per cent for significant vascular and aerodigestive tract injury. Patients were clinically assessed and the direction of the tract taken into account, as well as potential structures that may have been injured. Further investigations were considered on the basis of clinical symptoms and signs. They did not consider ‘soft signs’, such as shock responding to resuscitation, non-expanding haematoma, dyspnoea, subcutaneous emphysema, hoarseness, dysphagia or minor haematemesis to be absolute indications for exploration. They concluded that the decisions about selective exploration can be made on the basis of careful initial and repeated clinical examination.

The success of this selective approach has ranged from 29 to 97 per cent in other studies. The mortality reported in the studies by Campbell and Robbs and Nga-kane et al. was not attributable to the cervical trauma, but was due to associated injuries (Table 17.1). Clinical examination and adjunctive investigations (based on clinical examination) have been shown to be able to exclude clinically significant injury at several other large trauma centres.

Therefore, the issue at hand concerning penetrating neck injuries is no longer about the safety of non-operative management, but now centres on the indications for investigations and which investigations should be performed.

CLINICAL EVALUATION

Vascular injury

The reported accuracy of clinical evaluation to detect vascular injury varies widely. ‘Hard’ signs of vascular injury include...
external haemorrhage, expanding haematoma, pulse deficit, bruit and a pulsatile haematoma. Sclafani et al.\textsuperscript{21} reported a sensitivity of 61 per cent and specificity of 80 per cent and Meyer et al.\textsuperscript{12} reported an accuracy of 68 per cent suggesting that physical examination alone was a poor predictor of vascular injury.

Others have reported that clinical examination is a reliable means of detecting vascular neck trauma. Demetriades et al.\textsuperscript{22} reported a sensitivity of 100 per cent for clinical detection of significant vascular injury, and Beitsch et al.\textsuperscript{23} found that negative findings on physical examination are highly predictive of an absence of an arterial injury.

In a recent prospective study of 59 patients undergoing routine angiography for cervical gunshot wounds, Mohammed et al.\textsuperscript{24} reported that ten patients without clinical signs of vascular injury had an injury on angiography. This finding questioned the validity of physical examination alone in the management of the stable patient presenting with a gunshot wound to the neck. Routine angiography was recommended for all gunshot wounds to the neck, even where the entrance wound is in zone 2.

Eddy\textsuperscript{25} reported on 138 patients with penetrating injuries to zone 1 of the neck in whom routine angiography was performed. The negative predictive value of a normal chest x-ray and a normal physical examination was 100 per cent in this series.

The authors’ current practice is to perform angiography in stable patients only in the presence of a large haematoma, bruit, pulse deficit, widened mediastinum on chest x-ray, or when bleeding has been tamponaded with a Foley’s catheter (see Figure 17.1). All high velocity gunshot wounds to the neck undergo surgical exploration.

### Pharyngeal and oesophageal injury

Clinical evaluation of penetrating oesophageal injury has a reported sensitivity of 80 per cent, specificity of 64 per cent and accuracy of 72 per cent.\textsuperscript{26} In our own series of 52 patients with a penetrating oesophageal injury over an eight-year period at Groote Schuur Hospital, the most sensitive sign, present in 48 per cent of patients, was prevertebral air on lateral cervical spine x-ray.\textsuperscript{27} The symptoms, signs and radiological findings encountered in these patients are listed in Table 17.2. The most common symptoms were dysphagia (29 per cent) and odynophagia (21 per cent).

### DIAGNOSTIC INVESTIGATIONS

#### Angiography

A four vessel arch angiogram with selective catheterization is the gold standard for the investigation of vascular trauma. Angiography has the benefits of identifying the site of injury.

---

**Table 17.1** Prospective studies of selective conservative management.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Observed</th>
<th>Explored</th>
<th>Negative findings</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demetriades et al.\textsuperscript{14}</td>
<td>335</td>
<td>80%</td>
<td>20%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Campbell and Robbs\textsuperscript{15}</td>
<td>108</td>
<td>82%</td>
<td>24%</td>
<td>0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Narrod and Moore\textsuperscript{16}</td>
<td>77</td>
<td>29%</td>
<td>62%</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>Ngakane et al.\textsuperscript{17}</td>
<td>109</td>
<td>97%</td>
<td>3%</td>
<td>0%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

**Table 17.2** Clinical features of penetrating oesophageal injury.\textsuperscript{27}

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>Patients</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevertebral air</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>24</td>
<td>46</td>
</tr>
<tr>
<td>Haemothorax</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Blood in nasogastric tube</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Hoarse voice</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Widened mediastinum</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Mediastinal air</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Haematemesis</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
and hence assisting with decision-making regarding proximal and distal control, delineation of crossover circulation through the circle of Willis, and identification of injuries that are amenable to endovascular management, with particular reference to the vertebral artery.

Routine angiography has been recommended for patients with zones 1 and 3 injuries, as it has been stated that these areas are difficult to assess clinically. Yet two studies with a combined total of 535 patients demonstrated that all patients with vascular injuries requiring treatment presented with symptoms (see Figure 17.2).

Most authors are in agreement that clinical examination and ancillary investigations should replace mandatory surgical exploration for zones 1 and 3 injuries. It also appears logical that if there is a suspicion of an injury in zone 2 in the haemodynamically stable patient, an angiogram should be performed to identify vertebral artery injury that can be poor in the presence of subcutaneous emphysema, and acoustic shadows of the transverse processes limit evaluation of the vertebral arteries. Similarly, the clavicle can obscure injury to the subclavian and axillary arteries.

**Endoscopy and contrast studies**

Contrast oesophagography is an excellent means to detect oesophageal and pharyngeal injury, but is ideally suited to the awake, haemodynamically stable and cooperative patient. The sensitivity of contrast oesophagography for traumatic perforation varies from 48 to 100 per cent. In the unconscious, stable, intubated patient, the contrast can be passed via a nasogastric tube which is then pulled back into the pharynx in order to image the oesophagus. A water-soluble contrast medium should be used initially. If no obvious leak is detected, then barium should be administered. Gastrografin can cause serious pulmonary problems if aspirated and is no longer used.

Rigid oesophagoscopy requires a general anaesthetic and provides limited visibility. Sensitivity of flexible oesophagoscopy is reported as 40–90 per cent. Weigelt et al. showed in a prospective study that barium swallow had 89 per cent sensitivity and 100 per cent specificity, but that flexible oesophagoscopy was unreliable in the proximal oesophagus. Wood et al. reported 100 per cent sensitivity of oesophagography, and 96 per cent specificity. They also cautioned that oesophageal and vascular injuries can be missed on neck exploration. Flowers et al. and Srinivasan et al. more recently reported 100 per cent sensitivity for flexible oesophagoscopy to detect a penetrating injury of the oesophagus.

**Computed tomographic scan**

A small prospective study of 14 patients with penetrating zone 2 neck injuries who all underwent CT scan followed by mandatory neck exploration, concluded that neck injuries could be accurately evaluated by high resolution CT scan of the neck. There were no oesophageal injuries in that study. The authors’ experience has been that CT scan is not reliable for the detection of oesophageal injuries. CT scan can provide information about the tract of a gunshot wound and the need for further investigations.

Helical CT angiography (HCTA) is rapid, does not require arterial puncture and is less expensive than conventional angiography. Several prospective series comparing HCTA with conventional angiography for diagnosing arterial injuries in the neck have reported a sensitivity and specificity as high as 90–100 per cent. The pitfalls of HCTA are the presence of artefacts, caused by bullet fragments or the shoulders of large patients, which may resemble intimal tears. Evaluation of the subclavian artery is also limited. In cases of doubtful or non-diagnostic HCTA, patients must undergo conventional angiography.

**Gunshot wounds versus knife wounds**

A higher incidence of a therapeutic operation is required in a gunshot wound to the neck as opposed to stab wounds. Even so, the majority of patients presenting with a gunshot wound to the neck can be safely managed non-operatively. Although 73 per cent of transcervical gunshot wounds to the neck are
associated with injuries to vital structures, only 21 per cent of these will require operative intervention. 43 (see Figure 17.4).

**RETIRED SHARP OBJECTS**

Patients may present with a sharp foreign body, such as a knife or screwdriver that is still in situ. These must not be removed in the Accident and Emergency Department. An anteroposterior and a lateral x-ray must be obtained to identify what vital structures may have been injured. A CT scan is very useful to provide information about the proximity of the foreign body to the oesophagus, trachea and arteries, even though there will be scatter. CT can guide the need for further investigations, but proximity of a retained sharp object to a large artery is an indication for an angiogram. Retained foreign bodies must be removed in theatre under a general anaesthetic.

**SPECIFIC INJURIES**

**Pharyngeal injury**

Hypopharyngeal injury should be suspected in all zones 1 and 2 penetrating neck injuries, particularly in the presence of dysphagia, odynophagia, dysphonia, haemoptysis, haematoma and surgical emphysema. Oedema, blood in the pharynx, or a visible perforation may be noted on flexible nasopharyngoscopy. Oesophagography is unreliable, but direct pharyngoscopy should reveal all injuries. 44 Hypopharyngeal perforations with minimal leakage on contrast study can be managed conservatively. Yugueros et al. 45 prospectively managed 14 patients with perforations of the hypopharynx non-operatively. All patients were managed with nasogastric tube feeding, antibiotics for 7 days and kept nil by mouth. All isolated pharyngeal injuries are managed non-operatively at the authors’ institution, as this is safe and effective management. The neck wound should not be sutured, but be left open to drain into a drainage bag. A contrast study is repeated on day 7, and if there is no persistent leak, the patient is fed.

**Penetrating oesophageal injury**

Penetrating oesophageal injury is relatively rare, and only between one and nine new patients present to major level 1 trauma centres per annum. 28, 46, 47, 48, 49, 50, 51 This may be due to the proximity of the oesophagus to vital vascular structures resulting in lethal vascular injury, as well as its relatively protected anatomical position.

Haemodynamically unstable patients must be taken directly to theatre to obtain haemostasis. The oesophagus can be directly examined at the time of neck exploration. Endoscopy may also be performed in theatre once bleeding has been controlled.

Haemodynamically stable patients with symptoms of odynophagia, dysphagia, haematoma, or signs of subcutaneous emphysema, blood in the nasogastric tube, leakage of saliva from the wound, prevertebral air on lateral neck x-ray, or pneumomediastinum must be investigated with a contrast oesophagogram. It should initially be a water-soluble study. In the absence of an obvious leak or a tracheo-oesophageal fistula, it can be followed by a barium oesophagram. The sensitivity of the oesophagogram is reported to be in the region of 93 per cent. 27 If the oesophagogram is negative, but there is still a strong suspicion of an injury, then this should be followed by flexible oesophagoscopy, as these two modalities combined give a sensitivity of almost 100 per cent 26 (see Figure 17.5).

CT scan may be employed as a screening tool to decide on the need for contrast oesophagography. CT can indicate the course of a bullet through the neck and demonstrate the proximity of the tract to the oesophagus. However, CT scan should not be used alone to diagnose an oesophageal injury, as sensitivity is poor.

The authors’ institution has reported on the management of 52 patients with penetrating oesophageal injuries over eight years (23 cervical, 23 thoracic and 4 abdominal). 27 Primary single layer repair with wide drainage remains the...
procedure of choice even after delayed diagnosis in stable patients. Primary repair maintains oesophageal continuity and avoids the need for multiple operations. With concomitant tracheal injury, a sternocleidomastoid muscle buttressing flap is interposed to prevent the development of a tracheo-oesophageal fistula. In the septic patient, a ‘damage control’ approach is adopted. Sepsis is initially controlled by proximal oesophagostomy, stapling of the distal oesophagus and external drainage. A feeding jejunostomy and gastrostomy can then be performed 24 hours later, once the patient has been stabilized in the intensive care unit. At a later stage, an oesophagectomy may be required, followed by reconstruction with a gastric pull up, colonic interposition or jejunal interposition.

The risk of complications related to oesophageal injury is directly related to the time interval between the trauma and definitive management of the oesophageal injury. It is therefore important to keep this time period as short as possible (see Figure 17.6).

Tracheal injury

Cervical tracheal injury is relatively uncommon and is frequently associated with oesophageal, vascular or spinal injury. Symptoms of tracheal injury include a blowing wound, surgical emphysema, haemoptysis and hoarseness. If the tracheal injury communicates with the mediastinum, then the patient may present with pneumomediastinum. If there is communication with the pleural space, then the patient may present with a tension pneumothorax. CXR may reveal surgical emphysema, a pneumomediastinum or a pneumothorax.

The initial priority is to secure an airway. Minor tracheal injuries in patients not requiring cervical exploration can be managed expectantly. The trachea can sometimes be intubated through a blowing wound in the neck. Earlier teaching that nasotracheal or orotracheal intubation should be avoided as it may aggravate an existing tracheal injury or cause a false passage appears to have been an overcautious approach. Distal tracheobronchial disruptions can be bypassed under vision with an introducer passed through a rigid bronchoscope, or by intubating over a flexible bronchoscope.

Tracheotomy is appropriate for laryngeal trauma to protect the injured larynx when it is not possible to safely pass an endotracheal tube, or in the presence of quadriplegia requiring ventilatory support. In cases of massive surgical emphysema, a tracheotomy might expedite recovery. In cases where there is communication with the pleural space and a large air leak after placement of an intercostal drain, patients will require operative intervention. Tracheal repair is achieved with interrupted sutures. When there is an associated oesophageal injury, the repair must be bolstered with a muscle flap. A sternocleidomastoid muscle flap should be used. The muscle may be pedicled either superiorly or inferiorly. The superior vascular pedicle is a branch of the occipital artery that crosses the hypoglossal nerve and enters on the deep aspect of the upper third of the muscle, while the inferior pedicle is a branch of the suprascapular artery. A tracheotomy or an endotracheal tube may be used to protect the tracheal repair in selected cases.
Carotid artery trauma

The common carotid artery is the most frequently injured vessel, and accounts for 22 per cent of all vascular injuries and 6 per cent of penetrating neck trauma. The treatment of carotid artery injury has evolved over the past few decades from routine ligation to primary repair. Primary repair of carotid artery injury was first recommended following the introduction of vascular surgical techniques during the Korean War. In 1973, Bradley et al. concluded from two autopsy studies, in which there was haemorrhagic infarction of the brain following primary carotid repair, that revascularization should not be attempted in patients with severe neurological deficits. Fear of converting an ischaemic into a haemorrhagic infarct by reperfusion, and worsening of neurological outcome has been a major concern to trauma surgeons and has fuelled the dilemma of ligation versus reperfusion. In 1978, Liekweg and Greenfield showed that patients with severe neurological deficits just short of coma had significantly better results with reperfusion. This was supported by Brown et al. in 1982 who showed that revascularization in patients with preoperative coma was indicated when ischaemia had only been present for a short period of time prior to surgery.

All patients who do not have a preoperative focal neurological deficit should undergo restoration of vascular continuity, if technically feasible. The surgeon, however, has to decide whether to repair or ligate injuries to the common and internal carotid arteries in the presence of coma and/or central neurological deficit. Based on our series of 22 patients with penetrating carotid injury over a three-year period, ligation should be reserved for coma of more than 4–6 hours’ duration, an established infarct or cerebral oedema seen on CT scan of the brain, the absence of backflow at surgery and in neurologically intact patients with vascular occlusion on angiography. Small false aneurysms, intimal defects and intimal flaps have been managed conservatively. These studies are small and the safety of a conservative approach particularly with respect to the carotid artery has not been established. Clearly, the risk of surgery should not exceed the risk of complications developing from the arterial defect. Patients managed conservatively must be followed by angiography to confirm that the defect does not increase in size.

Vertebral artery injury

With the increased availability of angiography, vertebral artery injury is being recognized more frequently. Patients may present with acute bleeding or with late complications of thrombosis, false aneurysm formation, bleeding, arteriovenous fistula and stroke. Torporoidal bleeding may be encountered from a lacerated vertebral artery. An arteriovenous fistula may present with a bruit, thrill, haematoma, neurological deficits or cardiac failure. A neurological deficit seldom occurs in the presence of a normal contralateral vertebral artery and intact collateral circulation. The mortality from an isolated vertebral artery injury ranges from 5 to 17 per cent, but increases to 50 per cent if there is an associated injury to the carotid artery. The majority of vertebral artery injuries can be managed by angiographic embolization. If the injury is discovered at emergency surgery, the vessel should be ligated. This is fairly simple if the injury is located at a point before the vertebral artery enters the foramen transversarium at the level of the sixth cervical vertebra. Once inside the canal, the artery can be ligated with ligacliips. Alternatively, bone wax may be used to tamponade bleeding, followed by angiographic embolization.

Endovascular management of arterial injury

Selective arterial embolization is the treatment of choice in a stable patient with a traumatic arteriovenous fistula involving non-essential vessels, such as branches of the subclavian and external carotid arteries, or the vertebral artery with adequate contralateral flow. The guide wire must be able to traverse the site of injury, and both the distal and proximal segments of the injured artery must be occluded so as to avoid filling of the arteriovenous fistula from the distal segment. Embolization may be achieved by a range of catheter-delivered embolic agents. Gianturco coils (coiled spring wires) can be passed via a catheter lumen and packed into vessels causing their occlusion. The vessel injury should ideally be at least 3 cm from any vital parent vessel to permit safe embolization. Embolic particles, such as gelatine sponge or polyvinyl alcohol foam, which range in size from microns to millimetres in diameter, should not be used in arteriovenous fistula as they may pass through the fistula into the pulmonary or systemic arterial systems.

Graft-covered stents are increasingly used in the trauma setting for arterial injury. These self-expanding or balloon-expandable tubular mesh devices, inserted via the femoral artery, can be used to seal off and treat post-traumatic false aneurysms and arteriovenous fistulae in essential arteries, such as the common carotid, internal carotid and subclavian vessels. An exact measurement of the proximal and distal luminal diameters is required and all arterial side-branches that may participate in the arteriovenous fistula need to be embolized prior to stent-graft deployment.

Dutoit et al. reported successful stent-graft placement in 12 patients with traumatic cervicothoracic arteriovenous fistulae. However, in the young trauma patient, stent-graft has the potential for early thromboembolism, endoleaks and later stenosis. Long-term reports of graft patency are awaited to determine the effectiveness of this form of management.

KEY EVIDENCE

- We believe that a selective non-operative approach is safe and cost-effective.

KEY LEARNING POINTS

- A definitive airway (cuffed endotracheal tube) is required in patients presenting with massive bleeding, expanding haematomas, stridor, acute respiratory distress and in unconscious patients.
• Foley catheter balloon tamponade is extremely effective in obtaining haemostasis of bleeding neck wounds.
• Prevertebral air on a lateral neck x-ray may signify a pharyngeal or oesophageal injury.
• Clinical examination with selective investigations based on clinical examination has been effective to exclude significant injuries and avoids unnecessary surgery.

REFERENCES


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PART THREE

ENDOCRINE DISEASE

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We can’t plan life. All we can do is be available for it.

Lauryn Hill

INTRODUCTION

Over the last decade, advances in molecular biology and biotechnology have provided unprecedented insights into human disorders, most notably in human cancer biology. Neoplasms arise as a result of an accumulation of inherited and/or somatic mutations of genes involved in the control of cellular growth and differentiation. Further understanding of the critical genes involved have helped to clarify pathogenetic mechanisms important in thyroid and parathyroid tumours, and thus provided novel therapeutic targets, prognostic and diagnostic markers, and are helping to identify asymptomatic individuals at risk of future cancer development through genetic screening.

This chapter aims to provide an overview of the current knowledge of molecular biology in thyroid and parathyroid tumorigenesis, and genetic testing that is available for screening and diagnosis.

THYROID TUMOURS

Aetiology of thyroid cancer

The aetiology of thyroid cancer is known to be multifactorial. Several risk factors are known to be of importance in the causation of thyroid cancer. Prolonged hyperstimulation with thyroid stimulating hormone (TSH) is believed to be important in malignant change within multinodular goitres. The presence of a solitary thyroid nodule is also a risk factor for malignancy. Another well-recognized aetiological factor in thyroid cancer is ionizing radiation. Studies have consistently demonstrated significantly increased risk of thyroid cancer in children following radiation exposure (both therapeutic and as a consequence of nuclear fallout). Genetic factors are also important. There is a definite tendency for thyroid carcinoma to occur in members of the same family.

In common with most solid tumours, thyroid tumorigenesis is believed to be a complex multistep phenomenon involving the acquisition of multiple genetic lesions that confer a growth advantage to cells. Unlike many other highly specialized cells, thyroid epithelial cells are not terminally differentiated and are thus able to proliferate in response to certain growth factors. Mutations causing altered regulation of growth factors and abnormal receptor function may play a critical role in thyroid tumour progression. Genes acting at multiple steps along growth signalling pathways can function as oncogenes when their structure is disrupted. Several oncogenes have been shown to be significantly associated with the development of differentiated thyroid cancer. Loss-of-function mutations of genes coding for growth inhibitory proteins, involved in cell cycle checkpoints or cell survival, may also contribute significantly to thyroid tumorigenesis.

During the transformation from a normal to a cancerous cell it is widely agreed that several fundamental properties have to be acquired as a result of new genetic
lesions. Genetic instability and tumour angiogenesis are critical factors in tumour progression, and have been demonstrated to play an important role in thyroid tumorigenesis.

**Growth factors in pathogenesis of thyroid tumours**

Unregulated growth signals result in cell transformation. These may arise as a result of constitutive synthesis of growth factors, constitutive activation of their receptors or the intracellular signal transduction pathways. Thyrotropin or TSH induces human thyroid cell growth and proliferation. Chronic TSH stimulation in goitres is believed to be an important factor in the development of thyroid tumours within long-standing nodular goitres. Epidermal growth factor (EGF) has also been shown to induce thyroid cell proliferation. Increased EGF and EGF receptor expression has been demonstrated in cancers compared with normal thyroid tissues. Indeed, the highest level of EGF receptor expression was observed in aggressive anaplastic tumours, and elevated EGF expression has been demonstrated to be prognostic for tumour recurrence.

Thyrocytes secrete many other growth factors (including vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF)-2), and growth promoting cytokines such as interleukin 1 (IL-1), IL-8 and transforming growth factor (TGF)-b. One study demonstrated TGF-b expression in 58 per cent of malignant thyroid tumours but not in benign tumours or normal thyroid epithelium. Further, receptors to many of these growth factors and novel receptors such as platelet-derived growth factor (PDGF) are expressed by thyroid cancer cells. Expression of both growth factor and its receptor (for example FGF-2 and its receptor FGFR1) suggests existence of mitogenic autocrine pathways that might promote autonomous cell divisions.

**Receptor defects**

**TYROSINE KINASE RECEPTORS**

Chromosomal rearrangements leading to inappropriate expression of a fusion onco-protein containing a tyrosine kinase domain (ret and trk tyrosine receptors) appear to be an important and common oncogenic mechanism in differentiated thyroid cancers. What is more interesting is the yet still unexplained specificity of this fusion mechanism for a papillary rather than a follicular subtype (for further detailed discussion see below under Ret and trk gene rearrangements).

**G-PROTEIN AND G-PROTEIN COUPLED RECEPTORS**

The G-proteins are a subfamily of GTP-binding proteins, which include ras. They are heterodimers, composed of α-, β- and γ-subunits, each encoded by distinct genes. G-proteins couple a diversity of receptors (including the TSH receptor, TSH-R) with their effectors by acting as molecular switches. Gsα is utilized widely as a positive transducer for the activation of adenylate cyclase and calcium channels.

The TSH receptor (TSH-R), a member of the seven transmembrane G-protein associated receptors, can be activated by point mutations leading to amino-acid substitutions that either abrogate the requirement for ligand or enhance responses to ligand-mediated activation. Mutations of the TSH-R are observed in many autonomously functioning thyroid nodules (AFTNs), which are characterized by progressive growth and the ability to synthesize hormones in the absence of TSH stimulation.

Activating mutations in the critical domains of both Gsα and TSH-R result in the mimicking of TSH stimulation and upregulation of adenylate cyclase activity. Transgenic studies with mice have shown persistently elevated cAMP levels (as a result of TSH driven adenylate cyclase activity) to induce thyroid hyperplasia and goitre formation.

Defects in either the TSH-R or Gsα genes are present in 50–80 per cent of solitary AFTNs. Recent studies have also demonstrated gsp mutations in non-functioning thyroid tumours. Goretzki et al. found gsp mutations in 75 per cent of thyroid tumours from Germany and 20 per cent from the United States. A few thyroid carcinomas with activating point mutations of the TSH-R gene have been reported, but these are relatively rare.

Constitutive upregulation of adenylate cyclase activity resulting from gsp and TSH-R mutations may play a potentially important role in thyroid tumour formation, but their exact contribution remains unclear (see Figure 18.1). From these findings, it is likely that these alterations are early events in thyroid tumorigenesis.
NUCLEAR RECEPTORS

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that bind to DNA as heterodimers with the retinoid X receptors. PPARγ has been shown to play an important role in regulating genes involved in adipocyte differentiation and lipid metabolism. An involvement of this nuclear receptor in thyroid cancer was discovered by the characterization of a translocation in a subset of thyroid follicular carcinomas which results in fusion of the DNA binding domains of thyroid transcription factor PAX8 to PPARγ1. PAX8-PPARγ1 rearrangements are detectable in 10 per cent of follicular adenomas and 41 per cent of follicular carcinomas, suggesting a role for this fusion protein in malignant transformation.

6More recently, mutations in the thyroid hormone receptor (TR) α1 and β1 transcripts have been reported in papillary thyroid cancers. Furthermore, gene-targeted mice with a mutant TRβ (TRβPV mice) develop invasive thyroid cancers later in life, suggesting a role for TRβ in thyroid cancer progression.

Oncogenes and tumour suppressor genes in the pathogenesis of thyroid cancer

Cancer is a complex, multistep process. However, recent years have seen major advances in understanding the role of two classes of genes that are of particular importance in carcinogenesis that provide a more substantive picture. These are oncogenes and tumour suppressor genes. By definition, an oncogene refers to an abnormal gene with a 'gain-in-function' when a normally present proto-oncogene becomes inappropriately activated through mutation. This contrasts with 'tumour suppressor genes' that represent 'loss-in-function' because of the loss or inactivation of a proto-oncogene. Proto-oncogenes are normal genes involved in cell cycle control, growth factor regulation and cell receptor function and are normally silent but can become activated or inactivated by chromosomal translocations, gene deletions or mutations, and promote uncontrolled cell growth.

Several of the known oncogenes have been consistently detected in differentiated thyroid neoplasms. Some are more strongly associated than others and, interestingly, few are limited to specific forms of thyroid tumours. The role of oncogenes in specific human cancers are developing rapidly and their biology are providing key insights into thyroid cancer biology.

RAS

The ras proto-oncogene codes for a G-protein, p-21, which is found within cell membranes and hydrolyses GTP to GDP. P21 plays a critical intermediate role in connecting the stimulatory signal from tyrosine kinases such as EGF receptor and via Raf-1 to a mitogenic cascade involving the MAP kinases. Final products act upon nuclear transcriptional factors such as c-fos and c-jun. The ras proto-oncogene appears to be part of a growth-promoting pathway in normal human thyroid as well as nodular goitre formation. Three families of ras oncogenes have been identified (K-ras, H-ras and N-ras), each located in separate chromosomal locations. Ras mutations are found in 30 per cent of human cancers, making this the most widely mutated human proto-oncogene. Activated ras has been detected previously in 20 per cent of papillary carcinomas and 33 per cent of follicular carcinomas. The consistently higher prevalence in the more aggressive and dedifferentiated follicular-type cancers may be relevant and adds further weight to the potentially important role of the ras oncogene in thyroid tumorigenesis. However, no consistent correlation between the level of ras expression and the degree of dedifferentiation or metastatic tendency has been observed.

Supportive evidence of the role of ras in thyroid cancer is available from in vitro cell line studies. Fusco et al. demonstrated K-ras- and H-ras-transfected cells undergo morphological transformation and loss of differentiation. Furthermore, injection of these cells into syngenic rats induced tumour formation.

The prevailing view is that ras activation probably represents an early event in thyroid tumorigenesis and is itself not sufficient for malignant transformation. Studies have shown ras to be present in a high proportion of the earliest forms of thyroid tumours. One study noted 50 per cent of microfollicular adenomas to contain activated ras oncogene. Others have noted normal cells immediately adjacent to RAS-containing tumour cells also harbour RAS. Furthermore, it seems that up-regulated RAS is an important feature in goitre formation.

B-RAF MUTATION

B-Raf (encoded by BRAF) is a serine/threonine kinase and is a member of the mitogen-activated protein kinase pathway, involved in the transduction of mitogenic signals from the cell membrane to the nucleus within. BRAF gene mutations have been shown to be common in human cancers. Several studies have recently identified the most common BRAF mutation, T1796A transverse mutation, in 29–69 per cent of papillary thyroid cancers. In contrast to classical genetic mutations in thyroid cancers such as RET-PTC and ras mutations, which are also apparent in some benign thyroid lesions, remarkably to date this mutation has consistently been reported to be 100 per cent specific for papillary thyroid carcinomas (PTC), with no benign thyroid neoplasms having been found to harbour BRAF mutations. Consequently, BRAF mutation has been proposed as a specific molecular marker with relatively good sensitivity for the diagnosis of PTC. Moreover, a BRAF mutation has been demonstrated to be a novel prognostic biomarker that predicts poor clinicopathological outcomes. Namba et al. reported a significant association of BRAF mutation with distant metastases and advanced pathological stages of PTC. Nikiforova et al. reported a significant association of BRAF mutations with extrathyroidal invasion and advanced pathological stages of PTC. Xing et al. demonstrated, using a novel colorimetric mutation detection method, that BRAF mutations were readily detectable in thyroid fine needle aspiration cytology (FNAC) aspirates. In a series of 48 patients undergoing thyroidectomies for cancer or suspected malignancy, they showed that 50 per cent of the nodules that proved to be
PTC on final histology were correctly diagnosed by \textit{BRAF} mutation analysis on FNAC samples performed preoperatively; there were no false positives.\textsuperscript{39} They also reported a statistically significant association of \textit{BRAF} mutation with neck lymph node metastases and higher incidence of recurrence. With multivariate analysis, presence of \textit{BRAF} mutation was shown to be an independent prognostic factor for poor survival in PTCs. Detection of \textit{BRAF} mutation in thyroid FNAC samples could be a useful diagnostic adjunctive technique in the evaluation of thyroid nodules with indeterminate cytological findings, although this requires further definition by larger studies. Further, detection of \textit{BRAF} mutation-positive patients may help identify those patients who are likely to have a poorer prognosis, allowing appropriate referral and planning for more extensive treatment.

**C-MYC AND C-FOS**

Mutations of several other proto-oncogenes, such as \textit{c-myc} (nuclear transcriptional factor family), \textit{c-fos} and \textit{c-jun} (immediate early genes), have also been demonstrated in differentiated thyroid cancers.\textsuperscript{6, 9}

The \textit{c-myc} proto-oncogene encodes a nuclear protein that binds to DNA and acts as a transcriptional factor for genes involved in growth and differentiation. Normally, \textit{c-myc} expression steadily declines as the cell cycle progresses and eventually shuts off with full differentiation and is important in inhibition of uncontrolled proliferation.\textsuperscript{40} Oncogenic activation leads to the inappropriate upregulation of this important growth/differentiation gene and has been detected in various human cancers including some thyroid tumours. \textit{c-fos} is an immediate/early gene that regulates the expression of specific target genes by binding to their regulatory sequence of DNA. Aberrant activation of this transcriptional regulator has been demonstrated in thyroid tumours.\textsuperscript{41}

Del Senno \textit{et al.} studied six thyroid carcinomas and demonstrated increased expression of \textit{c-myc} in three out of six thyroid cancers and an abnormal \textit{c-myc} product in four out of six.\textsuperscript{42} No increase in \textit{c-fos} was detected in this study. Terrier \textit{et al.} studied 23 cases of thyroid carcinoma for alterations in the expression or structure of \textit{c-myc} and \textit{c-fos} proto-oncogenes. They provided a similar figure of 57 per cent of thyroid cancers with increased expression levels of \textit{c-myc}, as well as 61 per cent of upregulation of \textit{c-fos}. They also demonstrated a prognostic correlation with the expression level of \textit{c-myc}. Those cancers with an unfavourable clinical and histological prognosis were twice as likely to demonstrate increased \textit{c-Myc} levels than those with better prognosis, a finding which has been repeated in other studies.\textsuperscript{43} These initial findings need further and more thorough evaluation.

**MET**

\textit{MET} protein is a transmembrane receptor with tyrosine kinase activity. Its natural ligand is known to be HGF/SF (multifunctional cytokine hepatocyte growth factor/scatter factor). The oncogene is constitutively activated by amplification of the gene or through mutational change.\textsuperscript{44} Oncogene activation is associated with mitogenesis, as well as motogenesis, and has been suggested to contribute to tumour aggressive and metastatic behaviour.\textsuperscript{45} \textit{MET} oncogene is seen in various cancer human types, including up to 70 per cent of papillary and 25 per cent of follicular carcinomas, although it is not detected either in medullary thyroid cancer (MTC) or in normal thyroid tissues.\textsuperscript{46}

**RET AND TRK GENE REARRANGEMENTS**

The \textit{ret} proto-oncogene is located on chromosome 10q11-2 and codes for a transmembrane protein with tyrosine kinase activity, the activity of which is normally restricted to a subset of cells derived from embryonic neural crest cells.\textsuperscript{48} It is believed to be important in neuronal cell differentiation and found to be commonly amplified in neuroendocrine tumours. This makes \textit{ret} a natural oncogene candidate for tumours of the thyroid C-cells. Indeed, point mutation of \textit{ret} is now recognized as the basis for most forms of hereditary and sporadic MTCs\textsuperscript{49} (discussed in further detail below under Medullary thyroid cancer).

The thyroid carcinoma gene, PTC, is an oncogene found in 25 per cent of papillary thyroid cancers, which was initially described by Fusco \textit{et al.}\textsuperscript{50} Subsequently, it was discovered to be a fusion between a gene of unknown function (D10S170) and the TK domain of the \textit{ret} proto-oncogene as a result of a chromosomal rearrangement that involves a paracentric inversion of the long arm of chromosome 10.\textsuperscript{51} It is now evident that \textit{ret} may undergo fusion arrangements with gene sequences other than D10S17, resulting in the constitutive activation of the RET protein kinase.

Although the \textit{ret} proto-oncogene is not expressed in normal thyroid follicular cells, the rearranged \textit{ret}/PTC oncogene is highly expressed in papillary thyroid cancer cells,\textsuperscript{52} undetectable in over 250 non-thyroidal tumours.\textsuperscript{48} PTC/ret rearrangements are specific for papillary carcinomas and have been found in 5–40 per cent of PTCs in adults and are more common in paediatric PTC, as well as in cancers from children exposed to ionizing radiation.\textsuperscript{7, 53–55} One prospective study examined thyroid FNAC aspirates for the presence of RET-PTC rearrangements in comparison with final histology following surgery. They reported only 50 per cent of papillary cancers to be positive for \textit{RET-PTC}.\textsuperscript{57} No false positive results were obtained for the 39 benign thyroid conditions, including adenomas, hyperplasia and thyroiditis. Interestingly, identification of such mutations was shown to assist in the correct diagnosis in nine of 15 cases that would otherwise have been considered indeterminate or insufficient for cytological diagnosis.\textsuperscript{57} Other studies have reported supportive data suggesting \textit{RET-PTC} detection as a marker for papillary thyroid cancers.\textsuperscript{58, 59}
Somatic rearrangements of another member of the tyrosine kinase receptor gene family, the proto-oncogene **NTRK1** which is normally restricted to neural-crest-derived cells, are also seen in papillary thyroid cancers, albeit with far lower prevalence.60 The proto-oncogene **trk** is similar in many ways to **ret** and also codes for the transmembrane tyrosine kinase receptor for neural growth factor (NGF receptor). The **trk** oncogene is also a fusion protein because of chromosomal rearrangement: inversion on the long arm of chromosome 1.61 As is the case with other TK-type oncogenes, **trk** is found in a small percentage of papillary tumours, but not detected in follicular carcinomas.

It is now evident that both **ret** and **trk** may undergo fusion arrangements with various gene sequences.52 All rearrangements result in constitutive activation of the normally functioning tyrosine kinase domain as a result of the active tyrosine kinase domain becoming spliced with a non-oncogenic gene that is normally highly expressed in the cytoplasm of thyroid follicular cells. This delivers a signal via incompletely defined pathways, which have been shown to contribute to the de-differentiation and transformation of rodent thyroid cell lines.63 As with **ras**, there is compelling evidence for the ability of **ret** (and by implication **trk**) to initiate human thyroid tumorigenesis, which in this case is along the pathway of papillary carcinoma (as opposed to follicular tumour development).

Chromosomal rearrangements leading to inappropriate expression of a fusion oncoprotein containing a tyrosine kinase domain appear to be an important and common oncogenic mechanism in differentiated thyroid cancers. What is more interesting is the yet still unexplained specificity for this fusion mechanism for a papillary rather than a follicular subtype. Complementing this observational evidence, gene transfer experiments transfecting activated **ret** gene into normal follicular cells have demonstrated proliferating colonies of thyrocytes with major phenotypic differences from those induced by **ras**, and which consist of a pattern of growth characteristic of papillary tumour.64 It seems that the ‘choice’ of initiating oncogene (e.g. **ret** versus **ras**) may determine the eventual resulting tumour phenotype and is an interesting observation warranting further investigation.

**Loss of heterozygosity and tumour suppressor genes**

Oncogenesis also frequently involves the loss of so-called tumour suppressor genes (TSGs). These genes are critical to normal cell growth and division. Loss of gene expression through mutation events allows the cell to undergo uncontrolled cell division. **P53** and **Rb** genes are classical examples of TSGs, and the loss of either gene function has been shown to be associated with most human cancer development, including thyroid cancers. Inactivating point mutations of the **p53** tumour suppressor gene are highly prevalent in anaplastic and poorly differentiated thyroid tumours but not in well-differentiated thyroid cancers.65,66 Overall, a meta-analysis reported 14 per cent of thyroid cancers to exhibit **p53** mutations.65 Mutations of the retinoblastoma (**Rb**) gene were demonstrated in 55 per cent of thyroid carcinomas but none in benign tumours.66 Twelve per cent of thyroid malignancies have been shown to harbour both **p53** and **Rb** mutations.67 Loss of chromosomal material in tumour cells are detected using PCR techniques, so called LOH, and these provide clues to potential TSG locations. These events also occur in thyroid cancers, in particular in follicular tumours. Several groups have examined thyroid tumours for loss-of-heterozygosity (LOH) to identify other potential tumour suppressor genes. There is little evidence for LOH in papillary thyroid tumours.9,68 However, a variety of chromosomal regions have been incriminated in the aetiology of follicular tumours. LOH involving chromosome 3p was shown to be specific to follicular tumours,69 and up to 14 per cent of follicular adenomas exhibited LOH at 11q13.70

**Genetic instability and thyroid cancer**

Chromosomal aberrations, both in number and integrity, were shown to be associated with tumours by pathologists over 100 years ago and have been used since to identify and stratify the aggressiveness of cancers.71 With the exception of a few haematological tumours, the majority of these chromosomal defects are not specific to tumour type but may indicate the underlying genetic instability in the cancer cells.

Several groups of researchers72-73 proposed that the low mutation rate in normal cells cannot account for the hundreds of gene defects detected in cancer cells. In 1974, Loeb et al. postulated the ‘mutator phenotype’ theory to explain this biological discrepancy. They proposed that cancer cells acquire a degree of ‘genetic instability’ as a result of mutations in certain genes involved in the maintenance of DNA integrity and fidelity during replication. The manifested increase in mutation rate in cancer cells also helps to explain the variations in gene defects seen even within specific tumour types and in part the observed heterogeneity in the subpopulation of cells seen within most solid tumours. Advances in genetic and molecular technology have provided compelling evidence for ‘mutator phenotype’ theory in human cancers. It is now widely accepted that cancer results from the accumulation of many mutations and that an underlying genetic instability is necessary for the generation of the multiple mutations that underlie cancer.

Thyroid cancers have been demonstrated to exhibit both chromosomal and intra-chromosomal instability using several molecular techniques. Allelic deletions are an indication of chromosomal instability and, in several studies of tumour LOH patterns, specific chromosomal regions such as 3p, 2p, 2q and 11q appear more susceptible to allelic loss in thyroid tumours. compared with normal thyroid tissue. Aneuploidy is a common feature of thyroid follicular adenomas (29 per cent) and carcinomas (56 per cent), as well as of many human thyroid carcinoma cell lines and, in thyroid papillary cancer, aneuploidy has been shown to be associated with higher death rates.72 A comprehensive analysis of LOH studies revealed a higher tendency to lose genetic material in follicular neoplasms, particularly follicular carcinomas, in comparison with papillary cancers, and it was suggested that a fundamental difference may exist for mechanisms controlling chromosomal instability in these two forms of thyroid tumours.68 Further, development of chromosomal instability has been suggested to underlie the progression to more aggressive phenotypes of thyroid cancer.
Microsatellite instability (MSI) has been demonstrated in thyroid cancers. One group reported 21 per cent of thyroid tumours to exhibit MSI.\(^8\) MSI was seen significantly more frequently in follicular tumours than in papillary variants. However, no difference was detected between benign versus malignant tumours. Using inter-simple sequence PCR, thyroid cancers have been shown to exhibit a high degree of genetic instability compared with colorectal tumours.\(^7\)\(^9\) Genetic instability was shown to be higher in younger patients (<43 years) compared with patients older than 43 years. Further, the level of genetic instability measured using this technique has been suggested to differentiate between benign and malignant thyroid tumours.\(^8\)\(^9\) Additionally, as an indirect measure of genetic instability, marked hypermutability of p\(_53\) has been demonstrated in thyroid cancer.\(^6\)\(^5\)

Therefore, genetic instability is a major feature in the initiation and progression of thyroid neoplasms. Further understanding of this process would provide critical insights into thyroid tumorigenesis.

### Angiogenesis in thyroid cancer

Angiogenesis is the sprouting of new blood vessels from pre-existing capillaries and is a key rate-limiting step in tumour progression and critical for metastatic spread.\(^6\)\(^8\)\(^1\) Solid tumours gain access to the host blood supply and induce their own microcirculation by stimulating in-growth of endothelial cells from the surrounding stroma.\(^8\)\(^2\) In response to appropriate stimuli, the normally quiescent vasculature becomes activated to grow new capillaries.

Thyroid cancers are more vascular than normal thyroid glands. Assessment of angiogenesis in 128 papillary thyroid cancers demonstrated a three-fold increase in vascularity in tumours compared with normal thyroid tissues.\(^8\)\(^3\) and greater mean vessel density (MVD) in malignant tumours compared with benign thyroid lesions.\(^8\)\(^4\) Further, increased risk of recurrence and shorter survival was demonstrated in those with the more vascular thyroid tumours.\(^8\)\(^5\)\(^8\)\(^6\) The finding of greater vascularization in follicular tumours compared with papillary tumours, particularly adjacent to or in areas penetrating the capsule, is consistent with the hypothesis that angiogenesis may play a more prominent role in tumour spread in follicular tumours.\(^8\)\(^4\) This is important because follicular tumours tend to spread via the lymphatic system, whereas papillary thyroid tumour spread occurs via the lymphatic system.

Increased VEGF expression, a potent pro-angiogenic growth factor, has been demonstrated in thyroid cancer when compared with normal gland and benign tumours.\(^8\)\(^7\)\(^8\)\(^9\) VEGF has also been shown to be related to thyroid tumour behaviour. Higher VEGF expression has been shown to be present in metastatic thyroid cancer compared with non-metastatic disease.\(^8\)\(^8\) Also, nodal metastases showed increased VEGF expression with respect to the primary tumour.\(^9\)\(^0\) Further, high VEGF expression has been shown to be associated with disease recurrence and poorer survival.\(^9\)\(^1\)

Increasing VEGF expression parallels increases in cell proliferation, as assessed using Ki-67 labelling index, suggesting that areas of increased cell division may be due to increased VEGF secretion, perhaps allowing increased local angiogenesis.\(^8\)\(^8\)

Taken together, angiogenesis represents an important process in thyroid tumour progression. However, further studies focusing on angiogenesis involved specifically in thyroid tumorigenesis are necessary in the hope that these will allow novel thyroid-specific therapies to be developed.

### Medullary thyroid cancer

MTC arises from the parafollicular or C-cells that produce calcitonin (CT), and accounts for 5–10 per cent of all thyroid cancers. MTC may be sporadic or hereditary. MTC is hereditary in about 25 per cent of cases. Hereditary MTC is transmitted as an autosomal dominant trait and may be either transmitted alone (FMTC) or as part of a multiple endocrine neoplasia (MEN) type 2A or 2B syndrome.\(^9\)\(^2\)

In all MTCs, there is positive immunohistochemical staining for calcitonin and carcinoembryonic antigen (CEA). Calcitonin is a small 32-amino acid peptide present in the blood. Modern immunoradiometric (IMRA) assay offers high specificity and sensitivity and are now used routinely to detect levels in the blood. Elevated basal CT levels are found in subjects with MTC, C cell hyperplasia, and rarely in patients without any C-cell abnormality. In patients with C-cell disease, CT basal levels are raised early in the disease process and the highest concentrations are observed in patients with greatest tumour burden. However, there are exceptions and there is no strict relationship between CT levels and tumour burden. Indeed, basal CT levels may be normal in some patients with MTC. In these patients, pentagastrin provocation testing is sometimes used to detect abnormal CT levels. The main clinical interest in pentagastrin stimulation testing is in subjects belonging to an MTC family in whom it may allow to schedule appropriate surgery, and to ascertain cure in MTC patients in whom basal serum CT levels is undetectable postoperatively. Measurement of serum CEA concentration may also be useful during follow up because high concentrations or rapidly rising levels indicate disease progression or recurrence.\(^9\)\(^3\)

The genetic abnormalities that may be responsible for MTC development have been mainly derived from studies in hereditary MTC syndromes. Hereditary cancers are due to germline mutations of a given gene and every cell in the body would therefore harbour the mutation and is tumour tissue specific. Germline mutations of the ret proto-oncogene has been identified in MEN 2A, FMTC and MEN 2B (see below under Inherited cancer syndromes and genetic testing).

The ret gene has 21 exons and encodes a membrane bound tyrosine kinase receptor. Upon ligand binding and activation of the receptor, autophosphorylation of the tyrosine kinase motifs results in the stimulation of numerous downstream intracellular signalling pathways. Approximately 98 per cent of all mutations causing MEN 2A are known. Further, there is a close relationship between the genotype and phenotype.\(^9\)\(^4\) The screening for these mutations, therefore, provides effective diagnostic and prognostic information (see below under Inherited cancer syndromes and genetic testing for further discussion). Mutations at known codons have been described for MEN 2B and FMTC. In MEN 2B, a mutation at...
Anaplastic thyroid cancer

Anaplastic carcinomas represent one of the most aggressive human cancers. Patients have a mean survival rate that ranges from four to 12 months and a five-year survival rate that ranges from 1.0 to 7.1 per cent. Its rarity and rapidly fatal clinical course have made it a difficult cancer to study and treat. Early studies have suggested that both hyper-TSH stimulation and irradiation may be important cofactors in this process. However, Abe et al. have demonstrated that growth and metabolic activity of undifferentiated thyroid tumours is independent of TSH function. Also, only a small minority of individuals with anaplastic cancer have a history of radiation exposure.

Whether anaplastic tumours arise de novo or require a pre-existing differentiated thyroid carcinoma (DTC) for their evolution ('anaplastic transformation') is an ongoing issue of controversy. Despite a limited understanding, anaplastic transformation or the intra-tumoural evolution of anaplastic carcinoma from pre-existing differentiated cancer has become well accepted. Many clinicians now believe that the development of anaplastic thyroid cancer is part of the natural history of untreated differentiated thyroid cancer.

Clinical evidence for the occurrence of 'anaplastic transformation' comes from the fact that anaplastic tumour evolution occurs in older individuals and often with a long history of a thyroid tumour, or a history of a previously incompletely resected tumour.

Pathological studies provide the most convincing evidence of anaplastic transformation. Multiple large cohort studies have reported significant associations of anaplastic tumours with a DTC component. Up to 90 per cent of anaplastic cancers have been found in association with DTC. Papillary carcinoma is the most commonly DTC found, although follicular and Hurthle cell tumours have also been documented.

Allelotyping studies suggest that papillary and follicular carcinomas have different genetic pathways of anaplastic transformation. Papillary tumours have a much lower prevalence of LOH than either follicular and anaplastic tumours. This suggests a fundamental difference in the underlying mechanism maintaining chromosomal stability in these tumours. LOH hotspots have been located to chromosome 16p and a tumour suppressor gene located at this locus may play an important role in anaplastic transformation.

Molecular research in anaplastic cancer has been limited and relies mainly on in vitro cell line studies. Anaplastic tumour cell lines in culture, or as xenografts in athymic mice, have provided investigators with an experimental model to study the disease biology. Mutations of the p53 gene in human neoplasia are generally regarded as late events, and appear to be relevant to the development and progression of malignant thyroid cancer. Studies have reported very low prevalence of p53 mutations in differentiated thyroid tumours whereas p53 mutations were seen predominantly or exclusively in anaplastic cancers. Codon positions 273 and 248 appear to be mutational hotspots in anaplastic thyroid cancer. This provides strong evidence that mutational inactivation of p53 may be a critical transitional step leading to progression to these aggressive undifferentiated cancers.

The important role of p53 in anaplastic tumour development has also been demonstrated in experimental studies in which reintroduction of wild-type p53 into anaplastic thyroid cancer cells led to inhibition of cellular proliferation and the induction of differentiation and cellular responsiveness to TSH stimuli.

Mutant Rb alleles have been reported in 55 per cent of thyroid cancers, but none in benign tumours. The rates of Rb mutations were similar in anaplastic and differentiated thyroid carcinomas. However, 12 per cent of cancers harboured both Rb and p53 mutations. Such double mutations appeared more frequently in advanced disease stage. It appears that Rb is an important factor in thyroid cell transformation and possibly, with p53, in tumour progression. Other genes that have been investigated and are believed to play a role in anaplastic transformation include bcl-2, β-catenin, c-myc and Nm23.

Much of the information on the molecular determinants of thyroid tumour progression remains unclear. Understanding of the underlying biology of anaplastic tumour evolution is critical for insights fundamental to the emergence of new and more effective treatments for individuals diagnosed with this lethal malignancy.

Summary

Based upon current understanding of molecular events in thyroid carcinogenesis (see Box 18.1), we may postulate a schematic picture of the sequential molecular changes which determine thyroid tumour development and progression (see Figure 18.2). The role for gsp and TSH-R mutations in thyroid cell hyperplasia and follicular adenoma formation has...
been well established. ras mutations appear to be an early event, as they are common to benign and malignant tumours. The pathways leading to follicular or papillary carcinoma are divergent. Mutational activation of ret and trk oncogenes are specific to papillary carcinomas. Conversely, loss of function of a gene on chromosome 11q13, possibly MEN1 gene, may direct the tumour clone towards a follicular phenotype. Loss of heterozygosity at chromosome 3p is specific for follicular carcinoma and implies the involvement of an important tumour suppressor gene mapping to that chromosomal region. Mutations of p53 are highly prevalent in anaplastic thyroid carcinomas and, together with mutations in the Rb gene, may represent the critical transitional step in the progression of well-differentiated tumours into these aggressive thyroid cancers. However, much of the information on the molecular determinants of thyroid tumour initiation and progression remains rather sketchy.

**PARATHYROID TUMOURS**

Primary hyperparathyroidism is a commonly detected endocrine disorder and is the most common cause of hypercalcaemia. By far the most common lesion found in patients with primary hyperparathyroidism is the solitary parathyroid adenoma, occurring in 80 per cent of patients. Multiple adenomas have been reported in 2–4 per cent of cases. Parathyroid adenomas may be sporadic or inherited as part of MEN syndromes, familial hyperparathyroidism or hereditary hyperparathyroidism with jaw tumours (HPT-JT).

**Genetic abnormalities in parathyroid tumours**

Several candidate genes have been described to be causal in this disorder. Investigations of the PTH gene, which is located on chromosome 11q15 detected restriction fragment length polymorphism (RFLP) abnormalities in sporadic parathyroid adenomas. Further analysis demonstrated the rearrangement of part of the PTH gene onto chromosome location 11q13. The protein that was overexpressed as a result of this rearrangement was designated PRAD 1 (parathyroid adenoma 1), and is a novel member of the cyclin-D family of cell-cycle regulatory proteins. The rearrangement leads to the transcriptional activation and overexpression of cyclin D1 by bringing this gene into close proximity with the regulatory region of PTH. Therefore, upon PTH gene activation, cyclin D1 gene is also stimulated, leading to growth of the clone that harbours the genetic abnormality. As many as 15 per cent of sporadic parathyroid adenomas has been shown to over-express cyclin D1.

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**Box 18.1 Summary of molecular events in thyroid tumorigenesis (see Figure 18.2)**

- A role for gsp and TSH-R mutations in thyroid cell hyperplasia and follicular adenoma formation.
- ras mutations appear to be an early event as they are common to benign and malignant tumours.
- Unclear of the earliest molecular changes that are responsible for the initiation of thyroid cancer development.
- The pathways leading to follicular or papillary carcinoma are divergent.
- Mutational activation of B-raf, ret and trk oncogenes are specific to papillary carcinomas.
- Loss of function of a gene on chromosome 11q13, possibly MEN1 gene, and chromosome 3p may direct the tumour clone towards a follicular phenotype.
- Mutations of p53 are highly prevalent in anaplastic thyroid carcinomas and, together with mutations in the Rb gene, may represent the critical transitional step in the progression of well-differentiated tumours into these aggressive thyroid cancers.
- Angiogenesis and genetic instability are important processes in tumour progression.

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**Figure 18.2 Summary of molecular events in thyroid tumorigenesis.**
The Rb tumour suppressor gene responsible for the pathogenesis of retinoblastomas is involved in the pathogenesis of various other human tumours. Allelic deletion of Rb gene has also been demonstrated in parathyroid carcinomas and in 10 per cent of parathyroid adenomas. Abnormal histological staining patterns for Rb protein in 50 per cent of carcinomas but none in the adenomas. Together, these observations demonstrate an important role for the Rb gene in the development of parathyroid carcinomas, and may help in the histological distinction of parathyroid adenoma from carcinoma.

LOH studies have revealed allelic loss of chromosome 1q32 in 40 per cent of sporadic parathyroid adenomas. Within this region of DNA, which represents about 110 million base pairs of DNA, there appears to be an important tumour suppressor gene playing a role in many sporadic adenomas.

Another genetic abnormality that appears to be important in the aetiology of parathyroid adenoma is the tumour suppressor gene associated with MEN type 1. Twelve to 20 per cent of patients with sporadic parathyroid adenomas have been shown to harbour bi-allelic defects in the MEN1 gene, which encodes a 610 amino acid protein referred to as MENIN. The 164 reported somatic mutations of MEN1 are as diverse in nature and location as observed for germline mutations responsible for the inherited MEN1 syndrome.

Parathyroid adenomas are also associated with MEN syndrome type 2a. Although c-ret mutations are responsible for MEN2a, a search for the most common mutation at codon 634 has proved to be negative, suggesting a different mechanism responsible for the development of sporadic and inherited parathyroid adenomas.

The gene causing hyperparathyroidism-jaw tumour syndrome, HRPT2, encodes for a ubiquitously expressed protein called parafibromin. As parathyroid adenomas are malignant at a higher frequency in HPT-JT than in MEN1 or MEN2, mutations in HRPT2 are probably an important factor in increased risk of parathyroid carcinoma. Shattuck et al. directly sequenced the HRPT2 gene in 21 parathyroid carcinomas from 15 patients who had no known family history of primary hyperparathyroidism or the HPT-JT syndrome at presentation. Parathyroid carcinomas from 10 of the 15 patients had HRPT2 mutations, all of which were predicted to inactivate the encoded parafibromin protein. Howell et al. detected somatic HRPT2 mutations in four of four sporadic parathyroid carcinoma samples, and germline mutations were found in five of five HPT-JT parathyroid carcinomas and may represent a marker of malignant potential in parathyroid adenomas.

INHERITED CANCER SYNDROMES AND GENETIC TESTING

Members of some families are prone to developing specific types of malignancies in the absence of identifiable carcinogen exposure. Affected members of these families may represent clustering of sporadic occurrences, multifactorial inheritance or the presence of low penetrance genes. These groupings are classified as familial cancers. Close relatives are at moderately increased risk of developing certain malignancies. However, the average age of onset is usually similar to that observed in the general population.

In contrast, in about 5–10 per cent of individuals, predisposition to a specific group of cancers is the result of a heritable mutation in a cancer predisposing gene, so called germline mutation. The at-risk individuals tend to develop tumours at an earlier age than usual and at risk of developing more than one primary tumour. In addition, the siblings and offspring of an affected individual each have a 50 per cent chance of inheriting the cancer predisposing mutation, consistent with autosomal dominant inheritance.

Multiple endocrine neoplasia type 1

MEN1 syndrome represents the combination of over 20 different endocrine and non-endocrine tumours. Thus, there is no simple definition of MEN1. A practical definition is a case with two or three main MEN1-related endocrine tumours; parathyroid adenoma, enteropancreatic endocrine tumour and pituitary tumour. MEN1 syndrome is usually inherited, although in 10 per cent of cases arise de novo. Parathyroid tumours occur in 95 per cent of MEN1 patients. Pancreatic islet cell tumours occur in about 40 per cent of patients and gastrinomas (leading to the Zollinger Ellison syndrome (ZES)) are the most common type and also

Box 18.2 Genes postulated to be involved in parathyroid tumorigenesis

- PTH rearrangements and over-expression of PRAD1.
- Retinoblastoma tumour suppressor gene deletions seen in parathyroid carcinomas and 10 per cent of adenomas.
- LOH in the chromosomal region of 1q32 suggest putative TSG is important in the development of 40 per cent of parathyroid adenomas.
- Allelic defects in MEN1 gene found in up to 20 per cent of parathyroid adenomas.
- Parathyroid adenomas are associated with MEN2a. However, the ret mutation at codon 634 responsible for MEN2a is negative in sporadic adenomas, suggesting a different mechanism is responsible for hereditary and non-hereditary forms of parathyroid adenomas.
- Mutations of the gene HRPT2, responsible for HPT-JT syndrome, has been detected in parathyroid carcinomas and may represent a marker of malignant potential in parathyroid adenomas.

Box 18.2 Genes postulated to be involved in parathyroid tumorigenesis
the most important cause of morbidity and mortality in MEN1 patients. However, with improved metabolic management deaths from ZES or HPT in MEN1 have been virtually eliminated. Approximately one-third of deaths in MEN1 cases are caused by MEN1-associated malignancies. Anterior pituitary tumours occur in about 30 per cent of MEN1 patients, with prolactinomas representing the most common type. Unlike thyroid cancer in MEN2, the MEN1-related cancers have no effective prevention or cure. The principal cancer host organs (pancreas and lung) are difficult to screen for early tumours and are not appropriate for ablative surgery.

Primary HPT is the most common endocrinopathy and is usually the first clinical expression of MEN1 in up to 90 per cent of patients, with a typical age of onset of 20–25 years (reaching nearly 100 per cent penetrance by the age of 50 years); this is 30 years earlier than that from sporadic parathyroid adenoma.118 In contrast, MEN1 is rare and represents only 2–4 per cent of all cases of primary HPT.119 Biochemical testing for HPT in MEN1 is central in the recognition of parathyroid tumours, and it has occasional application in ascertaining of MEN1 carriers. Patients with MEN1 generally have parathyroid tumours in three or all four parathyroid glands.118 These tumours are asymmetric in size and are regarded as independent clonal adenomas. The issue of which operation is optimal remains controversial.

The gene causing MEN1 was localized to chromosome 11q13 by genetic mapping studies. Further studies defined the MEN1 gene in 1997, consisting of ten exons that codes a novel 610 amino acid protein named MENIN.114 The precise function of MENIN still remains to be elucidated. Preliminary studies have shown MENIN to play a role in a large number of cellular functions through its interactions with other proteins, most notably in transcriptional regulation and genome stability.120

Over 600 germline mutations of MEN1 gene has been described and the majority (>80 per cent) of these are inactivating, and are consistent with its role as a tumour suppressor gene. More than 10 per cent of the MEN1 gene germline mutations arise de novo and may be transmitted to subsequent generations.120 Importantly, 5–10 per cent of MEN1 patients do not harbour mutations in the coding region of MEN1 gene, and these individuals may have mutations in the promoter and untranslated regions, which remains to be clarified. The mutations are diverse in their type and are scattered throughout the 1830 bp coding region with no evidence for mutation clustering as observed in MEN2. Correlations between MEN1 mutations and the clinical manifestations are absent, and this contrasts with the situation in MEN2 and ret gene (Table 18.1). Further, the MEN1-related tumours behave similarly to sporadic tumour counterparts.

MEN1 syndrome

The first step in the analysis is to identify the specific MEN1 mutation in the germline DNA derived from a peripheral blood sample (leukocytes DNA best represents the germline DNA) from the affected index case using direct DNA sequencing strategies. Because MEN1 gene somatic mutation is found in common endocrine cancers, tumour DNA is rarely used as an index of the uncommon MEN1 germline mutation (responsible for MEN1 syndrome). In most index cases of familial MEN1, a germline mutation of MEN1 will be identified. Subsequent analysis of other family members at risk is simplified by testing selectively for the MEN1 germline mutation that has already been found to be specific for that family. However, many large studies have failed to find a MEN1 germline mutation in 10–20 per cent of index cases for familial MEN1.122 Such failures are believed to be due to mutations in untested parts of the MEN1 gene or large deletions that are transparent to PCR methods. In such families with no identifiable germline mutation, haplotype analysis or genetic linkage analysis around the MEN1 locus can allow for screening for MEN1 carrier status.

When DNA-based testing for MEN1 carrier state is not helpful, individuals at a 50 per cent risk of being an MEN1 carrier (first degree relatives of an MEN1 case) should have biochemical testing (calcium, PTH and PRL) for MEN1 carrier ascertainment.

Indications for germline MEN1 testing are still under development. Testing can be offered to index cases with MEN1 or with atypical MEN1 and to their relatives. A careful assessment must be made of sporadic cases with multiple endocrine tumours to exclude those that prove unexpectedly to have familial MEN1. Candidates for testing should include any sporadic cases with two or more MEN1-related tumours. There are limited data on the frequency of an MEN1 germline mutation among the common cases with apparently sporadic tumour in one organ: parathyroid adenoma (1 per cent), gastrinoma (5 per cent) and prolactinoma (1 per cent).119 The likelihood of MEN1 mutation is higher with younger onset age for the tumour type or with tumour multiplicity in that organ. These preliminary data suggest importance should be given to testing the presumably sporadic gastrinoma (see Box 18.3 for summary guidelines for the genetic testing of MEN1 patients).

Multiple endocrine neoplasia type 2

The MEN2 syndrome describes the association of MTC, pheochromocytoma, and parathyroid tumours. MEN2 is an
autosomal dominant syndrome, and all variants show a high penetrance for medullary thyroid cancer; 90 per cent of MEN2 carriers will eventually show evidence for MTC. Three clinical variants of MEN2 are recognized: MEN2a, MEN2b and MTC-only (FMTMC). MEN2a is the most common variant, and the development of MTC (almost 100 per cent) is associated with pheochromocytoma (50 per cent) and parathyroid adenomas (20 per cent). MEN2b, which represents 5 per cent of all MEN2 cases, is characterized by the occurrence of MTC, pheochromocytoma in association with Marfanoid habitus, mucosal neuromas and intestinal autonomic ganglion dysfunction leading to multiple diverticulae and megacolon. Parathyroid tumours do not usually occur in MEN2b. MEN type 2b is the most aggressive of the MEN2 variants. MTC-only is a variant in which only MTC is the sole manifestation. MTC is the first neoplastic manifestation in most MEN2 patients because of its earlier and overall higher penetrance. Earlier studies reported mortality of 15–20 per cent when treatment was initiated after identification of a thyroid nodule. However, carrier diagnosis before adulthood allowing early thyroidectomy has lowered the mortality from hereditary MTC to less than 5 per cent.124

The likelihood of a ret germline mutation in a patient with apparently sporadic MTC is 1–7 per cent.126 Despite the modest mutation yield, all cases of sporadic MTC should be tested for germline ret mutation because of the critical clinical implications of finding a ret mutation. A germline ret mutation is more likely if the sporadic MTC is of early age onset or there is multiplicity in the thyroid gland. If there is clinical suspicion, these cases should be offered extended mutation analysis if the test for the standard exon sequencing is negative. Analysis for ret mutation in tumour tissue from an apparently sporadic case of MTC has limited value. Mutations at codon 883 and 918 (25 per cent) occur

### MTC-only is also associated with missense mutations in the extracellular domain, and most mutations are in codon 618. In contrast, 95 per cent of MEN2b is associated with mutations in codon 918 (Met→Thr) of the intracellular tyrosine kinase domain.

The aggressiveness of MTC correlates with the MEN2 variant syndrome and with the mutated ret codon. Prevention or cure of inevitable MTC is by surgery, and should be performed before the age of possible malignant progress.

### MTC genetic testing

MEN2 carrier determination is one of the few examples of a genetic test that mandates a highly effective clinical intervention. Sequencing DNA for ret mutation is effective and widely available. In 1997, a consensus was reached that the decision to perform prophylactic thyroidectomy in MEN2 should be based predominantly on the result of ret mutation testing, rather than CT testing.125 There were several unique features of MEN2 that formed this recommendation. First, early detection and subsequent surgical intervention alters the clinical course of MTC. Second, treatment of early MTC by thyroidectomy is well tolerated, even by most infants. This contrasts with complex issues involved in surgical removal of organs MEN1-associated malignancies. Third, the use of abnormal CT tests to dictate thyroidectomy led to a low (5–10 per cent), but still problematic, incidence of false positive tests. Fourth, the ret test has a higher rate of true positives and lower rates of false negatives and false positives than the CT test. Also, it facilitates even earlier thyroidectomy. Fifth, the specific ret codon mutation correlates well with clinical behaviour and guides stratified treatment.

The general issues for carrier screening is the same for MEN1 mutation testing. There are also unique features in MEN2 relevant to genetic testing (see Box 18.4). Up to 98 per cent of MEN2 index cases have an identified ret mutation. Extensive research has demonstrated a limited number of MEN2-associated mutations involving the ret exons 10, 11, 13, 14, 15 and 16. Therefore, only these exons must be tested routinely. Only if this is negative should the remaining 15 exons be sequenced (currently only available in research laboratories and large endocrine centres). If this extended ret testing is negative in the index case, haplotype analysis or genetic linkage analysis about the ret locus can be considered if the family history is suggestive of inherited MEN2. Periodic tumour monitoring should be performed in such suspected but unconfirmed MEN2 carrier patients. CT testing remains applicable for diagnosis of the carrier state in these unusual situations.

A single gene is responsible for all three syndromes, and is located on chromosome 10q11.2.94 The c-ret proto-oncogene encodes a tyrosine kinase receptor. Specific activating mutations of c-ret have been described for each of the three MEN2 variants. Thus, in 95 per cent of patients, MEN2a is associated with mutation of the cystein-rich extracellular domain of the protein receptor, with missense mutation in codon 634 (Cys→Arg) accounting for 85 per cent of MEN2a mutations.
Box 18.4 MEN2 genetic testing consensus guideline summary

- Three clinical variants of MEN2 are recognized: MEN2a, MEN2b and MTC-only (FMTC). MEN2a is the most common variant.
- The main morbidity from MEN2 is now MTC (with improved recognition and management of pheochromocytoma). MEN2 variants differ in aggressiveness of MTC: MEN2b > MEN2a > FMTC.
- To avoid missing a diagnosis of MEN2a with its risk of pheochromocytoma, clinicians should only diagnose FMTC from rigorous criteria.
- MEN2 carrier detection should be the basis for recommending thyroidectomy to prevent or cure MTC. This carrier testing is mandatory for all children at 50 per cent risk.
- When performed rigorously, ret germline mutation testing reveals a ret mutation in over 95 per cent of MEN2 index cases. It has replaced CT testing as the basis for carrier diagnosis in MEN2 families.
- The ret codon mutations can be stratified into three categories of risk from MTC. These three categories predict the MEN2 syndromic variant, the age of onset of MTC and the aggressiveness of MTC.
- Blood leukocyte testing for germline ret mutation should be performed in all cases of apparent sporadic MTC (or pheochromocytoma in young patients <40) due to the critical implications of a positive test.
- Periodic screening for other tumours in MEN2 carriers is based upon the MEN2 variant, as characterized by the ret codon mutation and by manifestations in the rest of the family.

- Level 1 (least risk for MTC): children with ret codon 609, 768, 790, 791, 804 and 891 mutations have the least risk for MTC. The biological behaviour of MTC in these patients is variable, but, in general, grows more slowly and develops at a later age. There is little consensus upon the management of these patients. Some recommend treatment as for the high risk group (level 2), others suggest thyroidectomy by ten years of age, and still others recommend periodic pentagastrin-stimulated CT testing with thyroidectomy at the first abnormal test result.

Hyperparathyroidism–jaw tumour syndrome

The HPT-JT syndrome is an autosomal dominant disorder characterized by the development of parathyroid adenomas and carcinomas and fibro-osseous jaw tumours. In addition, some patients can develop many other tumour types (renal, pancreatic and testicular).

The jaw tumours are different to the brown tumours observed in some patients with primary hyperparathyroidism, and do not resolve after parathyroidectomy. Ossifying fibromas of the jaw are an important distinguishing feature of HPT-JT and the occurrence of these can precede the development of hypercalcaemia by several decades. However, it is important to note that the parathyroid tumours may occur in isolation and without any evidence of jaw tumours. This can cause diagnostic confusion with other hereditary disorders such as MEN1. In HPT-JT, patients usually have single adenoma or a carcinoma, while MEN1 patients will often have multigland disease.

The gene causing HPT-JT, HRPT2, is located on chromosome 1q25 and encodes for an ubiquitously expressed 531 amino acid protein PARAFIBROMIN. To date, 13 different heterozygous mutations translating truncated forms of parafibromin have been reported in HPT-JT families. Although no consensus clinical guideline exists for HRPT2 genetic testing, testing for germline HRPT2 mutations are available commercially (see GeneTests, www.genetests.org).

Cowden’s disease

Cowden’s disease (CD), also known as multiple hamartoma syndrome, is a rare autosomal dominantly inherited disease characterized by the formation of hamartomas in various organs, including skin, thyroid, breast and gastrointestinal (GI) tract. Multiple trichilemmomas of the skin and mucocutaneous papillomatosis are common diagnostic features found in >90 per cent of affected individuals. Other frequent lesions are goitre and adenomas of the thyroid gland. In addition, patients with CD have an increased risk for the development of malignant tumours, including most commonly carcinomas of the breast and thyroid. People with Cowden syndrome have up to a 10 per cent lifetime risk of follicular or papillary thyroid cancer; follicular thyroid cancer is most common. Approximately 70 per cent of people with Cowden syndrome will have benign thyroid changes, including multinodular goitre, adenomatous nodules and follicular adenomas.
In the vast majority of patients with CD, the disease is caused by germline mutation in the tumour suppressor gene PTEN. PTEN is mapped to chromosome 10q23 and encodes a lipid phosphatase involved in the PI3/Akt intracellular signalling pathway. PTEN protein regulates important cellular functions including cell proliferation, cell cycle control, apoptosis and cell migration.

Approximately 133 germline PTEN and 332 cancer-associated somatic mutations have been reported in the literature to date. PTEN germline mutations are also found in patients with Bannayan–Riley–Ruvalcaba syndrome, Lhermitte–Duclos syndrome, VATER syndrome, Proteus and Proteus-like syndromes. It is evident that PTEN mutations are responsible for a variety of hereditary syndromes, all with overlapping clinical features.

Marsh et al. identified PTEN mutations in 30 of 37 (81 per cent) CD families, including missense and nonsense point mutations, deletions, insertions, a deletion/insertion and splice site mutation. Genetic heterogeneity of CD was suggested by the fact that Tsou et al. found no coding sequence mutations in 23 CD families for whom linkage to the PTEN locus had never been established.

Cowden syndrome and Bannayan–Ruvalcaba–Riley syndrome share clinical characteristics such as hamartomatous polyps of the gastrointestinal tract, mucocutaneous lesions and increased risk of developing neoplasms. Furthermore, both conditions and several other distinctive phenotypes are caused by mutations in the PTEN gene. For this reason, some have suggested that the spectrum of disorders be referred to as PTEN hamartoma tumour syndrome (PHTS).

Although no consensus clinical guideline exists for PTEN genetic testing, testing for germline PTEN mutations are available commercially (see GeneTests, www.genetests.org).

**Other inherited syndromes**

People with familial adenomatous polyposis (FAP) have a 2 per cent lifetime risk of developing papillary thyroid cancer. The average age at thyroid cancer diagnosis is 28 and women with FAP appear to be at greater risk than men. FAP is most commonly associated with an increased risk of colorectal cancer and accounts for about 1 per cent of colorectal cancer cases. People with FAP typically develop hundreds to thousands of colon polyps (small growths). The polyps are initially benign, but there is nearly a 100 per cent chance that the polyps will develop into cancer if left untreated. In FAP, colorectal cancer usually occurs by the age of 40. Individuals with FAP are also at risk for other types of cancer including stomach, small bowel, pancreas and hepatoblastoma (liver cancer seen mainly in early childhood).

Although FAP is inherited in an autosomal dominant pattern, approximately 30 per cent of people with FAP have no family history of the condition. Mutations in the APC gene cause FAP and attenuated familial adenomatous polyposis (AFAP).

Gardner syndrome, colonic polyposis with extra bowel tumours, especially osteomas, and a rather characteristic retinal lesion, is now known to be a phenotypic variant of FAP, caused by mutation in the APC gene. Herve et al. reported a case of papillary carcinoma in a 16-year-old girl with Gardner syndrome. They reviewed the literature and estimated that the incidence of thyroid carcinoma in patients with Gardner syndrome approached 100 times that of the general population. Genetic testing for mutations in the APC gene is available.

**Genetic counselling**

Although variable, depending upon the syndrome and mutation, inherited cancer risk can approach 85–100 per cent over a lifetime. There are complex medical, psychosocial and ethical ramifications of identifying individuals at risk through genetic testing. Cancer genetic risk assessment and genetic counselling is the process of identifying and counselling individuals at risk for familial and hereditary cancer. The purpose of cancer genetic counselling is to educate patients about their chance of developing cancer, help them derive personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening and cancer prevention. Informed decision making and informed consent requires understanding and integrated genetic, medical and psychosocial information. Because of the number of issues involved, comprehensive genetic testing and counselling benefits from a multidisciplinary approach including genetic counsellors, medical geneticists, surgeons, oncologists, and other relevant professionals that can help the patient address the different informational, medical and psychosocial needs.

Cancer genetic counselling process includes:

- **Personal, medical and family history**: The first step begins with the collection of a patient's personal and family history. This is often done using a questionnaire.
- **Psychosocial assessment**: An individual’s decision to seek and utilize information regarding cancer genetics is based upon a variety of factors. Assessment of the psychosocial issues is the optimal method for the clinician to appreciate all of the factors that affect risk perception and ultimately, utilization of the cancer genetic information. Further, this process also enlightens the provider on the potential impact of cancer genetic information on the client’s quality of life, educational and career goal, and other aspects of their lives.
- **Molecular testing for hereditary cancer syndromes**: Consider offering molecular testing for hereditary cancer susceptibility only when a patient has a significant personal or family history of cancer, the test can be adequately interpreted, the results will affect medical management, the clinician can provide or make available adequate genetic education and counselling, and the patient can provide informed consent. However, testing is not recommended in situations where there is a low probability of carrying a mutation given the potential psychosocial ramifications.
- **Pre-test genetic counselling and informed consent**: Informed consent is necessary for molecular testing, and involves a thorough discussion of the possible outcomes of testing, a review of the potential benefits, risks, and limitations, and a discussion of alternative testing to genetic testing. Elements of informed consent in cancer genetic risk assessment are detailed by Geller et al. In
general, genetic cancer susceptibility testing is not performed on people under the age of 18 for consent reasons. The exception includes cases where medical intervention is warranted in childhood, such as MEN2 ret testing.

The pre-test counselling required for informed consent must include a discussion about the cancer risks associated with gene mutations, including the concepts of penetrance and variable expressivity. Further, accuracy of the genetic testing for the given gene should be discussed together with possible test outcome. An important issue that must be considered is genetic discrimination. The patients considering genetic testing need to be aware of the potential consequences on insurability, and whether the results will be disclosed to any third party (such as relatives). Further information about genetic discrimination and current legislation can be found at the following websites: www.thomas.loc.gov, www.tgac.org and www.nationalpartnership.org. Some life/disability insurers now include questions regarding genetic testing on the application form. There is also the possibility of employment discrimination.

- **Disclosure of test result and post-test counselling:** Together with the delivery of the result a review of the significance of the test must be provided. Given the specificity and sensitivity of the genetic test, a discussion of how the result affects the patient’s cancer risk. Further, there must be a review of the screening recommendations and options of cancer reduction, prophylactic surgery and long-term monitoring, including the benefits, risks and limitations of these options. Appropriate referrals to other medical professionals for further discussions should be made as required.

- **Informing other relatives:** A discussion of cancer risks to other relatives and the importance of informing the appropriate family members about the genetic test result must be made. Only after written consent can the test result be shared with relatives. However, if a high-risk patient refuses to consent at-risk relatives, an ethics committee should be consulted (‘duty to warn’).

CANCER GENETICS AND GENETIC TESTING RESOURCES

GeneTests and GeneReviews: www.genetests.org
American Society of Clinical Oncology: www.asco.org
National Society of Genetic Counsellors: www.nsgc.org

KEY LEARNING POINTS

- There have been major advances in our understanding of the molecular basis for thyroid cancer. Key genes and their mutations have been demonstrated to be important in thyroid cancer biology. However, there remains much to be further elucidated.
- Our understanding of parathyroid tumour biology is less developed. Several genes have been studied (MEN1, PTH and HRPT2) and have been postulated to play an important role in the development of parathyroid tumours. However, much of this information has been gathered from the study of hereditary diseases.
- Genetic testing in endocrine disease relates to the MEN syndromes. Genetic testing plays a key role in the management of MEN type 2 and less prominent role in MEN type 1.
- ret mutational analysis is now a key investigation in the management of patients with MEN type 2. ret analysis offers a risk stratification based on the codons mutated and guides clinical management.
- Genetic counselling is important prior to any genetic testing. Informed consent is integral to genetic counselling, which aims to provide the maximum benefit both for the clinician and the patient.

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INTRODUCTION

The endocrine pathology discussed in this chapter is that affecting the extracranial endocrine system, that is the thyroid and parathyroid glands found in the anterior triangle of the neck bilaterally. This section is not intended to be an encyclopaedic treatise, more a summary overview with selective consideration of clinically important differential diagnoses. Surgical pathology is a visual subject, therefore no apology is offered for the liberal use of illustrations to supplement the text.

THYROID GLAND

The normal thyroid gland

The term ‘thyroid gland’ was first coined by Thomas Wharton in the seventeenth century to describe the gland in close proximity to the ‘shield-shaped’ thyroid cartilage. ¹, ² Embryologically, the thyroid gland develops from the median anlage and the two lateral anlagen. The median anlage starts as a thickening of the endodermal epithelium in the foregut between the first and second branchial arches at the base of the tongue close to the developing myocardium, ¹, ² which in later life constitutes the foramen caecum. The cells proliferate to form the thyroid bud and then a diverticulum, which expands and migrates from the base of tongue to lie anterior to the trachea. The track between the thyroid gland and base of tongue typically disappears by birth. The two lateral anlagen (known as the ‘ultimobranchial bodies’) develop from the caudal aspect of the fourth pharyngeal pouch supplemented by migratory neural crest elements and fuse with the median anlage as the thyroid gland descends in the neck. The median anlage forms the thyroid follicular cells and the lateral anlagen form the clear parafollicular cells (C-cells).³

The thyroid gland is the largest of the discrete endocrine organs typically weighing between 15 and 25 g (roughly 0.4 per cent of body mass), being slightly larger in women, ¹ dependent upon age, nutritional and hormonal status. Macroscopically, the normal thyroid gland presents a bilobate structure with a reddish-brown colour. The two lobes are connected by a central isthmus. A vestigial, accessory pyramidal lobe is present superiorly in 40 per cent of the population. There is a thin investing fibrous capsule, which is continuous with the pretracheal fascia. This capsule, however, is discontinuous or focally interrupted in approximately 60 per cent of individuals and extracapsular thyroid tissue is present in almost 90 per cent of glands. A variety of pericapsular inclusions, such as parathyroid tissue, heterotopic thymus, lymph nodes and autonomic paraganglia, are considered normal. Mesenchymal derived inclusions within the thyroid gland include stromal adipocytic, skeletal muscular and cartilaginous elements.⁴

Send a slide to five different pathologists and receive six different answers.

Anon
Microscopically, the functional unit of the thyroid gland is the follicle, which in the euthyroid state consists of a monolayer of cuboidal or flattened epithelial cells (thyrocytes) surrounding a central lumen containing stored colloid. The follicles are loosely aggregated into lobules (thyromeres), each containing circa 20 to 50 follicles separated by slender connective tissue septula (Figure 19.1). Intracolloidal birefringent oxalate crystals, brown cytoplasmic lipofuscin (‘wear and tear’) pigment and haemosiderin pigment are usually of incidental portent, though may be increased with age and in certain disease states. The C-cells form a minor cell subpopulation, accounting for less than 10 per cent by number, and are typically concentrated at the junction between the middle and upper thirds of the lateral lobes in a hypothetical central longitudinal axis through each lobe, corresponding to the planes of medial and lateral anlagen fusion – solid cell nests, C-cell hyperplasia and medullary thyroid carcinoma, therefore, do not ordinarily occur in the isthmus. C-cells are usually larger, more rounded, polyhedral or fusiform in shape, with paler cytoplasm than follicular epithelium.

SOLID CELL NESTS

So-called solid cell nests (SCN) are collections of non-follicular cells, found in approximately 25 per cent of resected thyroid glands, which probably represent remnants of the ultimobranchial apparatus. They are present in greater numbers in infants and children and gradually decline with advancing age. The role of SCN in the normal structure and function of the thyroid gland is incompletely understood and their biological significance remains a source of controversy and debate. Solid cell nests may harbour minimal properties of a stem cell phenotype with capacity for self-renewal and end differentiation.

Solid cell nests comprise irregularly shaped clusters of interfollicular cells delineated by basal lamina. The dominant cell component (main cell) comprises polygonal to fusiform cells disposed in solid array sometimes with an epidermoid appearance, though generally non-keratinizing, discovered incidentally in a thyroidectomy specimen indicated for partially treated Graves’ disease (H&E stain, medium magnification). (b) Such cell rests typically express pan-neuroendocrine immunomarkers, but not thyroglobulin and are thus shown here in negative relief (thyroglobulin IHC, medium magnification).

Figure 19.1 Normal thyroid gland demonstrating a lobular architecture with uniform, round/ovoid follicles. The latter contain plentiful stored colloid with fine marginal vacuolation. The parallel linear marks in the colloid (‘ripple’ or ‘wave’ effect) are an artefact of microtomy. The C-cell population is typically inconspicuous (H&E stain, low magnification).

Figure 19.2 (a) Ultimobranchial apparatus rests (solid cell nests) disposed as discrete congeries of squamoid (epidermoid) cells without keratinization, discovered incidentally in a thyroidectomy specimen indicated for partially treated Graves’ disease (H&E stain, medium magnification). (b) Such cell rests typically express pan-neuroendocrine immunomarkers, but not thyroglobulin and are thus shown here in negative relief (thyroglobulin IHC, medium magnification).
into squamous epithelium. Solid cell nests are postulated to be precursors of certain thyroid gland neoplasms, notably papillary thyroid carcinoma. They may also play a role in the histogenesis of Hashimoto’s thyroiditis, which is also associated with papillary thyroid carcinoma. Papillary thyroid carcinoma and Hashimoto’s thyroiditis, therefore, may be linked in pathogenesis via a common population of pluripotent p63 positive embryonal stem cell remnant progenitors.5

FINE NEEDLE ASPIRATION CYTOLOGY

Fine needle aspiration cytology (FNAC) is generally recognized as an effective first-line investigation in the evaluation of a thyroid swelling.6,7,8,9 In experienced hands, FNAC of the thyroid gland is accurate with a sensitivity of 65–98 per cent, a specificity of 72–100 per cent, a false-positive rate of 1–8 per cent and false-negative rate of 1–11 per cent.7,10 The non-diagnostic or inadequate rate can be as high as 28 per cent,10 but targeting by ultrasound (US) guidance can reduce the incidence of a non-diagnostic FNAC.11 US guidance is recommended in nodules with a higher chance of non-diagnostic FNAC by simple palpation. These include cystic nodules and smaller or non-palpable lesions.7 Thus, FNAC as a screening test is highly sensitive, though lacks specificity – circa 15–30 per cent of aspirates designated suspect of a follicular neoplasm are ultimately malignant, ergo the remaining majority 70–85 per cent or so of nodules are benign in the final analysis.

FNAC is substantially a screening/triage procedure for follicular carcinoma, identifying those patients who require further investigation and a primary diagnostic test for other thyroid malignancies, principally papillary carcinoma, medullary carcinoma, undifferentiated (anaplastic) carcinoma and lymphoma. The traditional wet-fixed and air-dried direct smear methodology supplemented by cell concentration techniques, such as centrifugation, filtration and cell blocks, generally remains the gold standard in thyroid FNAC in preference to the newer liquid-based technology, though with ongoing development and experience this may shift. The cytopathologist, however, can only ever be as good as the aspiration sample that he or she receives.

In spite of acknowledged cytodiagnostic pitfalls, some outlined below, the use of FNAC in the preliminary evaluation of solitary or dominant nodules reduces the use of surgery by approximately one-third, doubles the proportion of malignancies among surgical resections and increases cost-effectiveness. Serious diagnostic delay due to false-negative FNAC is uncommon where there is appropriate clinical follow up.12

Historically, the diagnostic criteria and reporting nomenclature employed have varied widely, although these have evolved to broad consensus, as epitomized by the North American National Cancer Institute (Bethesda) terminology (2007)13 stratified into six subdivisions and the parallel UK Royal College of Physicians/British Thyroid Association guidelines (2002 and 2007), the latter updated in 2009 by the Royal College of Pathologists in consultation with the British Society for Clinical Cytology and other interested parties.14 These schemata are outlined in Table 19.1. The Italian Society of Pathology and Cytopathology/Italian Section of the International Academy of Pathology classification (2007)15 substantially mirrors the UK five-tier system with a single category encompassing all borderline lesions (designated ‘follicular proliferation’ and ‘follicular lesion’, respectively). The shorthand numerical diagnostic coding intrinsic to these systems is not intended to replace a full narrative cytology report. Furthermore, the vernacular habit of grouping non-diagnostic/unsatisfactory and non-neoplastic/benign aspirates under the rubric ‘negative reports’ should be dispelled. As a fundamental principle, it is emphasized that while the presence of malignant cells is diagnostic, the absence of malignant cells can never be wholly exclusionary. The WHO classification schema (2004) for carcinoma of the thyroid gland6 is widely endorsed.

The technique for specimen preparation is summarized in Chapter 6, Head and neck pathology.

Limitations of FNAC of the thyroid gland

The follicular patterned lesion is the most commonly encountered type of thyroid FNAC specimen in clinical practice. Distinction between a hyperplastic (adenomatoid) nodule in a multinodular goitre and a follicular neoplasm may not always be achievable. The presence of dispersed colloid, monolayered sheets of bland thyrocytes and normofollicular or macrofollicular structures are more typical of hyperplasia. Dense colloid globules, paucity or absence of colloid and microfollicular configuration (Figure 19.3) tend to support neoplasia. It is necessary to focus on the predominant cytoarchitectural pattern, rather than a minor subpopulation of microfollicles, with the proviso that this approach is predicated upon adequate cell sampling. The agreed criterion for this is that samples from solid lesions should contain at least six groups of thyroid follicular epithelial cells across all the submitted slides, each composed of at least ten well-visualized epithelial cells. Note that this constitutes a minimum standard, though the degree of diagnostic confidence should increase with higher yield samples and that this threshold does not necessarily preclude a positive diagnosis of malignancy if a lesser quantum of characteristic cells is present.

Reliable discrimination between a benign adenoma and differentiated follicular carcinoma on subjective morphological grounds is now realized to be always difficult, often impossible. While the presence of high cellularity, cell crowding, tridimensional (acervate) groups, nucleiomegaly, cytonuclear atypia, three or more nucleoli per cell, irregular karyoplasm and necrosis are individually not absolute, in aggregate they tend to favour a diagnosis of malignancy. Follicular variant of papillary thyroid carcinoma (FVPTC) enters the differential diagnosis, where a scrupulous search for its characteristic nuclear morphology is indicated. The separation of minimally invasive from widely invasive follicular carcinoma on FNAC, contingent upon extent of extracapsular invasion, is obviously untenable ab initio.

Oncocytic (oxyphil) cell lesions are problematical on FNAC. Hashimoto’s thyroiditis and oncocytic (oxyphil) metaplasia in multinodular hyperplasia are generally separated by conspicuous lymphocytosis in the former
(Figure 19.4), although the degree of inflammatory cell infiltrate varies with the natural history of the disease and paucilymphocytic variants are described. The cytological distinction between Hürthle cell adenoma and carcinoma is unreliable – benign oncocyic (oxyphil) cells may display extreme pleomorphism and, paradoxically, there is often less cytonuclear variation in Hürthle cell neoplasms. Confident recognition of the rare oncocyic (oxyphil) variant of papillary thyroid carcinoma on FNAC is extremely difficult. The conclusion oncocyic (oxyphil) cell lesion or neoplasm, not otherwise specified is occasionally the best that can be achieved with a recommendation for excision, as clinically indicated. A solitary thyroid nodule composed predominantly of oncocyes on FNAC merits excision because oncocyic (oxyphil) thyroid neoplasms show on average a 30 per cent malignancy rate based on histology. Moreover, the larger an oncocyic tumour, the greater the likelihood of invasive malignancy – there is a 65–80 per cent chance of malignancy in oncocyic neoplasms exceeding 4 cm maximum dimension.

Aspirates from cystic lesions may not be fully diagnostic, particularly if there is limited or degenerate epithelial sampling. Cysts of any type tend to contain variform inflammatory cells, foam cells, pigmented macrophages and cytolytic debris (Figure 19.5). Copious dispersed colloid favours benignity, though in the absence of adequate epithelial cell content the possibility of a cystic neoplasm or cystic degeneration in a neoplasm, of which papillary thyroid carcinoma is paradigmatic, cannot be completely ruled out on FNAC microscopical appearances in isolation – up to 10 per cent of thyroid carcinomas missed on FNAC harbour a cystic component.

The diagnosis of high-grade non-Hodgkin’s lymphoma is generally straightforward with adequate FNAC material. Recognition of low-grade non-Hodgkin’s lymphoma, typically extranodal marginal zone lymphoma (‘MALToma’), however, is sometimes fraught especially if arising in the context of autoimmune thyroiditis where monomorphism of the neoplastic lymphocytes, which triggers the suspicion of neoplasia, is diluted or obscured by reactive lymphoproliferative elements. Histological examination is typically advised, particularly if more definitive subclassification is desired.

**FNAC-induced iatrogenic change**

Although FNAC is popularly considered to be a comparatively atraumatic procedure, the technique is known to induce histological changes, which may modulate or even obscure the underlying pathology and potentially mislead the unwary.

Several studies propose an incidence for FNAC-induced iatrogenic changes of close to 100 per cent. Relevant factors

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Table 19.1  Comparison of the BTA/RCP/RCPath\(^6\)–\(^8\) and Bethesda\(^15\)–\(^16\) classification systems for reporting thyroid gland fine needle aspiration cytology (FNAC) specimens together with their clinical implications.

<table>
<thead>
<tr>
<th>BTA/RCP/RCPath</th>
<th>Bethesda</th>
<th>Risk of malignancy (based on Bethesda classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thy1, non-diagnostic for cytological diagnosis</td>
<td>I, non-diagnostic or unsatisfactory</td>
<td>1–4%</td>
</tr>
<tr>
<td>Thy1c, non-diagnostic for cytological diagnosis in a cystic lesion</td>
<td>Cyst fluid only</td>
<td>Up to 10% of cystic lesions harbour malignancy</td>
</tr>
<tr>
<td>Thy2, non-neoplastic</td>
<td>II, benign</td>
<td>0–3%</td>
</tr>
<tr>
<td>Thy2c, non-neoplastic cystic lesion</td>
<td>III, atypia of undetermined significance or follicular lesion of undetermined significance</td>
<td>5–15%</td>
</tr>
<tr>
<td>Thy3a, neoplasm possible – atypia/ non-diagnostic</td>
<td>IV, follicular neoplasm or suspicious for a follicular neoplasm</td>
<td>15–30%</td>
</tr>
<tr>
<td>Thy3f, neoplasm possible, suggesting follicular neoplasm</td>
<td>Specify if oncocyic (Hürthle) cell type</td>
<td>15–45%</td>
</tr>
<tr>
<td>Thy4, suspicious of malignancy</td>
<td>V, suspicious for malignancy (papillary, medullary, metastatic, lymphoma, other)</td>
<td>60–75%</td>
</tr>
<tr>
<td>Thy5, malignant</td>
<td>VI, malignant (papillary, poorly differentiated, undifferentiated/anaplastic, medullary, squamous cell carcinoma, carcinoma with mixed features (specify), non-Hodgkin’s lymphoma, metastatic, other)</td>
<td>97–99%</td>
</tr>
</tbody>
</table>
include the nature and size of the target lesion, the calibre of the needle used, the number of passes attempted, the precise FNAC technique employed, how conscientiously such effects are sought and the interval between FNAC and excision surgery. The retrospective nature of such audit is prone to underestimate the true frequency.

The resultant secondary damage may broadly be classified into tissue damage and repair effects, tumour and tissue infarction and epithelial dislodgement/displacement phenomena. The acronym WHAFFT (‘worrisome histologic alterations following fine needle aspiration of the thyroid gland’) was originally proposed and has further been divided into acute WHAFFT and chronic WHAFFT.19

Tissue damage and repair artefact includes haemorrhage, fibrovascular granulation tissue organization and regenerative/regenerative atypia. Haemorrhagic needle tracks and associated proliferation of fibroblasts/myofibroblasts are typically pericapsular and radiate to the centre of the lesion, perpendicular to the capsule. The influx of inflammatory cells, siderophages, linear fibrosis/hyalinization, cholesterol granulomata, dystrophic mineralization, epithelial metaplasia and epithelial and endothelial atypia may on occasion be so exuberant and kaposiform as to closely mimic a sarcoma (so-called ‘post-FNAC spindle cell nodule’) (Figure 19.6).

The thyroid gland is a richly vascularized organ (receiving approximately 2 per cent of total cardiac output) and post-FNAC vascular effects include venous thrombosis, recanalization and papillary endothelial hyperplasia, sometimes to an extent to resemble angiosarcoma (‘pseudo-angiosarcomatoid’). Mitochondrion-rich oncocytic (oxyphil) cell lesions are exquisitely sensitive to ischaemia, therefore, characteristically susceptible to partial or global infarction, either spontaneously or post-FNAC. Where extensive, such infarction may render definitive histological evaluation difficult or impossible and a diagnosis of oncocytic neoplasm, not further specified may be the best that can be proffered under these circumstances. However, a minor population of better preserved tissue, the ghost-like outlines of papillae, necrotic cells or psammoma bodies, together with review of the original FNAC material may yield some insight into the underlying pathology. Immunocytochemical positivity for certain epitopes persists for a surprising time after infarction – leukocyte common antigen (CD45) and CD20 staining, for example, may reproducibly define lymphoproliferation long after tumour cells are devitalized, although antibodies such as carcinoembryonic antigen (CD66e) are more capricious and stain fields of necrotic tissue and abscess cavitation indiscriminately.

Angulated follicles and reparative stromal response, accompanied by nuclear hyperchromasia, fusiform epithelial morphology and squamous metaplasia may appear infiltrative (‘pseudoinfiltration’), and thereby merit serious consideration of follicular carcinoma, squamous cell carcinoma or mucoepidermoid carcinoma.
Developmental conditions involve the presence of normal thyroid tissue in sites outside the normal thyroid gland (heterotopia or ectopia, hamartoma and choristoma). This includes lingual thyroid, mediastinal thyroid, benign lymph node inclusions, so-called ‘lateral aberrant thyroid gland’ and sequestered (‘parasitic’) thyroid nodules. Mature adult cystic teratoma (dermoid cyst) of the ovary may show a preponderance of thyroid tissue (struma ovarii) sometimes with carcinoid elements (strumal carcinoid). The same repertoire of pathological conditions that affect eutopic thyroid gland may also be rarely encountered at these other sites (Figure 19.7).

Thyroglossal tract anomalies

Thyroglossal duct remnants persist due to failure of involuted following embryological descent of the thyroid gland. They are the most common cause of a congenital neck mass and the second most common cause of a cervical mass in childhood.

Thyroglossal duct remnants can occur at almost any site from the base of tongue to the suprasternal region, predominantly at four locations, namely intralingual, suprathyroid, thyrohyoid and suprasternal (Figure 19.8). Cysts predominate with fewer sinuses and fistulae. Counter-intuitively, follicular thyroid tissue is not a prerequisite for diagnosis. Thyroglossal duct carcinoma is rare, estimated as occurring in no more than 1 per cent of thyroglossal duct cysts and, when it supervenes, it is usually a subtype of papillary thyroid carcinoma.

Acquired conditions

Squamous differentiation

The presence of squamous epithelium is not uncommon. It is usually either an acquired, adaptive response (metaplasia) due to inflammation, or related to developmental rests of cells (heteroplasia), although may also occur in some neoplasms (differentiation) (Table 19.2 and Figure 19.9).

Non-neoplastic squamous epithelium is usually microscopically bland though may sometimes show an alarming degree of reactive/reparative cytonuclear atypia. Benign squamous epithelium generally presents the same immunophenotype as elsewhere, that is cytokeratins (notably CK5 and CK14), epithelial membrane antigen (EMA) and p63 positivity, usually with thyroglobulin, TTF-1 and carcinoembryonic antigen (CEA, CD66e) negativity. Malignant squamous differentiation, however, may not conform to this profile and anomalous epitope expression may be confounding.

Oncocytic change

Oncocytic (oxyphilic) cells are characterized by swollen, granular, mitochondrion-rich cytoplasm and may occur in both endocrine tissues and non-endocrine organs, including pituitary, parathyroid, thyroid, adrenal, lacrimal and salivary
glands, kidney, intestine, pancreas, lung and sinonasal tract. The incidence of oncocytic change increases with advancing age and may be extensive at any one site (oncocytosis). When such cells occur in the thyroid gland, they are termed ‘Hürthle cells’ (Askanazy cells). It is a purely descriptive term and does not in itself indicate biological potential – oncocytic cells occur in both non-neoplastic and neoplastic (benign and malignant) conditions (‘mitochondriomas’) (Table 19.3). Oncocytic change is a cellular adaptive process, which is believed to occur in response to pathological or physiological stress and the oxygen-sensitive nature of the mitochondria renders the cells unusually susceptible to traumatic/ischaemic injury. There is ongoing debate as to whether such oncocytic transformation is a form of metaplasia or more correctly represents a process of transdifferentiation.24 The pathogenetic basis underpinning oncocytic change is complex. The genetic events driving oncocytic change involve mutations in mitochondrial DNA and somatic mutations that affect mitochondrial function. Importantly, these changes are largely unrelated to the genetic events that result in proliferation and neoplastic transformation of thyroid follicular epithelial cells.

There is hallmark concomitant nuclear enlargement often with striking nuclear pleomorphism, coarse karyoplasm and conspicuous macronucleolation, even in benign oncocyes. The distinction between oncocytic hyperplasia and neoplasia
can be difficult, particularly in the context of thyroiditis. Note that in autoimmune thyroid disease, oncocytic change is not restricted to Hashimoto’s thyroiditis, but it may also be encountered in long-standing Graves’ disease. Oncocytic change occurring in follicular nodules and/or multinodular goitre, is conventionally regarded as hyperplastic, whereas clonality studies have demonstrated that many of the larger nodules are in fact monoclonal, thus the biologically correct approach would be to regard these as follicular adenomas.

The mitochondria themselves stain with the phosphotungstic acid haematoxylin (PTAH) method. Positive cytoplasmic immunostaining for cytokeratins (notably CK14), vimentin, antimitochondrial antibody and weakly for thyroglobulin (TG) is typical. Carcinoembryonic antigen (CEA, CD66e) reactivity is variable. Electron microscopy demonstrates abnormally configured mitochondria (Figure 19.10).

**Thyroiditis**

The various manifestations of thyroiditis are summarized in Table 19.4. These may be either non-autoimmune or...
autoimmune, the latter typified by Hashimoto’s thyroiditis and Graves’ disease and their variants. Drug-induced thyroiditis is associated with the use of a number of drugs including amiodarone, lithium, interferon-alpha and interleukin-2.

Lateral aberrant thyroid tissue

Lateral aberrant thyroid (LAT) tissue or gland describes anomalous deposits of follicular thyroid tissue in the lateral neck. Originally believed to indicate persistent lateral thyroid anlage, the modern view is that the overwhelming majority, but not all, actually represent metastatic follicular thyroid carcinoma or FVPTC, the cytonuclear morphology of which may be so deceptively bland as to be virtually indistinguishable from normal or hyperplastic thyroid parenchyma proper. Pragmatically, any such deposits lateral to the carotid sheath ought to be regarded as metastatic disease until otherwise proven. Those extracapsular deposits medial to the carotid sheath may either represent benign sequestrated (‘parasitic’) thyroid nodules, which generally recapitulate the appearances in the body of the main gland proper, or metastatic tumour. Benign thyroid tissue inclusions in cervical lymph nodes are rarely encountered and are difficult to confirm with certainty.

Hyperplastic nodules

Historically, multiple nodules as part of multinodular goitre, either incompletely capsulated or unencapsulated, are designated hyperplastic (adenomatoid or cellular colloid) nodules. One or more may predominate, thereby simulating a solitary nodule clinically and/or radiologically (Figure 19.11). They do not normally compress the adjacent gland, which often displays a similar growth pattern. Secondary retrogressive changes frequently present, sometimes extensive, include coarse fibrosclerosis (sometimes resembling a ‘radial scar’), cystic degeneration, calcification, infarction, fresh haemorrhage, haemosiderosis, siderophages, foam cells, cholesterol granulomata, endarteritis obliterans and localized inflammation. Squamous, lipocytic, chondroid, osseous and oncocytic (oxyphil) metaplasia are occasionally

| Conditions associated with oncocytic (oxyphil) epithelium in the thyroid gland. |
|-------------------------------|---------------------------------|
| **Non-neoplastic** | **Neoplastic** |
| Hashimoto’s thyroiditis | Follicular adenoma |
| Nodular hyperplasia | Follicular carcinoma |
| Long-standing Graves’ disease | Papillary thyroid carcinoma |
| Post-irradiation | Medullary carcinoma |
| Post-chemotherapy | Poorly differentiated thyroid carcinoma |
| Ageing | Undifferentiated (anaplastic) carcinoma |

Figure 19.10  Transmission electron micrograph of several tumour cells from a poorly differentiated oncocytic (oxyphil) carcinoma of the thyroid gland. Note the cytoplasmic expansion by scores of swollen mitochondria and paucity of other cell organelles. Two prominent osmiophilic macronucleoli are also plainly seen (transmission electron microscope (TEM), ultra-high magnification).
<table>
<thead>
<tr>
<th>Age</th>
<th>Sex ratio</th>
<th>Cause</th>
<th>Thyroid function</th>
<th>TPO status</th>
<th>ESR</th>
<th>Gross pathological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto's thyroiditis (chronic</td>
<td>All ages, peak 30–50</td>
<td>8–9:1</td>
<td>Autoimmune</td>
<td>Hypothyroidism</td>
<td>High</td>
<td>Symmetrical diffuse enlargement of the thyroid gland. Firm consistency, pale colour and multilobulated</td>
</tr>
<tr>
<td>lymphocytic or chronic autoimmune</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>thyroiditis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Painless). Postpartum thyroiditis</td>
<td>Childbearing age</td>
<td>Autoimmune</td>
<td></td>
<td>High</td>
<td>Normal</td>
<td>Firm to hard, tan white appearance and nodules of varying size</td>
</tr>
<tr>
<td>(subacute lymphocytic thyroiditis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Painless). Sporadic thyroiditis</td>
<td>All ages peak, 30–40</td>
<td>2:1</td>
<td>Autoimmune</td>
<td>High</td>
<td>Normal</td>
<td>Firm to hard, tan white appearance and nodules of varying size</td>
</tr>
<tr>
<td>(subacute lymphocytic thyroiditis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful. Subacute thyroiditis</td>
<td>20–60</td>
<td>5:1</td>
<td>Unknown</td>
<td>Low</td>
<td>High</td>
<td>Firm to hard, tan white appearance and nodules of varying size</td>
</tr>
<tr>
<td>(de Quervain's, giant-cell, pseudo-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>granulomatous thyroiditis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppurative. Thyroiditis</td>
<td>20–40</td>
<td>1:1</td>
<td>Infectious</td>
<td>Absent</td>
<td>High</td>
<td>Variable appearance including focal or diffuse enlargement and abscess formation. Can appear normal</td>
</tr>
<tr>
<td>(infectious, bacterial, pyogenic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thyroiditis)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riedel's thyroiditis</td>
<td>30–60</td>
<td>3–4:1</td>
<td>Unknown, sometimes part of</td>
<td>Euthyroid</td>
<td>Present</td>
<td>Thyroid replaced by dense, tan-white, firm to hard tissue, often extending into neighbouring structures</td>
</tr>
<tr>
<td>the spectrum of IgG4 sclerosing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>diseases</td>
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</tbody>
</table>
Simple papillae (papillary hyperplastic nodule) do rarely occur and the papillae tend to radiate towards the centre of the lesion (centripetal growth) (Figure 19.12). Exhaustive efforts to exclude papillary thyroid carcinoma must be pursued under these circumstances.

The concept of thyroid follicular epithelial dysplasia remains theoretical. Up to 70 per cent of hyperplastic nodules are in fact clonal proliferations and can express various markers of malignant follicular-patterned thyroid tumours. However, no morphological, immunohistochemical or molecular study to date has been able to discriminate between adenomatoid nodules, follicular adenoma and follicular carcinoma with absolute sensitivity and specificity.

TUMOURS OF FOLLICULAR EPITHELIUM

Follicular adenoma

Follicular adenoma classically occurs as a solitary benign, encapsulated tumour, which shows follicular epithelial differentiation with no evidence of either capsular or vascular invasion and neither architectural nor cytonuclear features of papillary thyroid carcinoma (Figure 19.13). It possesses a circumferential, smooth contoured or gently undulating, slender, fibrous delimiting capsule usually displaying little variation in thickness – fields of capsular augmentation warrant a conscientious search to exclude a carcinoma. Surrounding native gland may be compressed and/or atrophic. Internally, there may be a variety of growth patterns, such as normofollicular, microfollicular (fetal), macrofollicular (colloid), solid, trabecular and organoid, though the architecture tends to be fairly uniform within any individual example. Mitoses are few. Degenerative stromal changes, particularly post-FNAC, are identical to multinodular hyperplasia, but squamous metaplasia is uncommon and, where present, merits consideration of papillary thyroid carcinoma, follicular variant (FVPTC).

Histological subtypes of adenoma include solid, fetal, oxyphilic (oncocytic), clear cell, signet ring cell and lipoadenoma, defined according to the predominant growth pattern (accounting for over 75 per cent of the overall tumour). These, however, do not differ clinically or in biological behaviour from conventional follicular adenoma.

Atypical adenoma (follicular tumour of uncertain malignant potential, FTUMP) is used by some to describe follicular neoplasms, which display some worrisome microscopic features although falling short of unequivocal capsular or vascular infiltration. These include irregularly thickened capsule, partial thickness incursions into, but not completely
through the capsule, hypercellularity, increased mitoses and/or abnormal forms and nuclear atypia (Figure 19.14).

Hyalinizing trabecular tumours

Hyalinizing trabecular tumours (HTT) are a group of neoplasms originally regarded as adenomas (hyalinizing trabecular adenoma (HTA), paraganglioma-like adenoma of the thyroid (PLAT)). It has subsequently transpired that the supposed characteristic organoid growth pattern with interstitial perivascular hyalinization may also be seen focally in nodular hyperplasia plus a number of other benign and malignant thyroid neoplasms many, although not all, showing histological features of papillary thyroid carcinoma, including RET/PTC gene rearrangements. In those cases of pure HTT architecture without papillary carcinomatous morphology there appears to be a spectrum of biological potential ranging from adenoma to carcinoma, both minimally invasive and widely invasive by conventional criteria. A proportion of such neoplasms exhibit characteristic, peculiar, avid cytoplasmic Ki67 (MIB-1) immunostaining (Figure 19.15). Immunopositivity for cytokeratins, thyroglobulin and vimentin generally with negative pan-neuroendocrine marker and calcitonin staining discriminates HTT from paraganglioma proper and medullary thyroid carcinoma.

Follicular carcinoma of the thyroid

Follicular thyroid carcinoma (FTC) is a malignant epithelial tumour arising in both eutopic thyroid gland and/or
heterotopic thyroid tissue, showing follicular cell differentiation and is bereft of the characteristic features of papillary thyroid carcinoma (PTC). It accounts for 5–15 per cent of all thyroid cancers in iodine-sufficient regions. It spreads via haematogenous routes, preferentially to bone and lung with metastatic disease as a presenting feature in 11 per cent of patients. It is divided into two basic categories defined by the extent of capsular infiltration and/or presence of vascular invasion – meticulous examination of the tumour capsule and interface with native gland is consequently of paramount importance.

Minimally invasive follicular carcinoma (MIFC) is the more common variant and is characterized by microscopical transcapsular invasion and/or pericapsular vascular infiltration.\(^1\) With experience, subtle capsular transgression and/or accompanying fibrous capsular thickening may be appreciated in the gross specimen by the unaided eye (Figure 19.16), but not microinvasive capsular violation or vascular permeation.

Widely invasive follicular carcinoma (WIFC) is readily identified grossly by infiltrative, destructive, or sometimes multinodular growth, the latter often separated by fibrous bands, expanding into surrounding native gland. This may be so strikingly obviously nodular as to be mistaken for multinodular hyperplasia by the unwary, particularly if there is no clearly identifiable vestige of pre-existing capsule for reference.

The interpretation of capsular invasion remains somewhat controversial. Most authorities require full thickness capsular transgression beyond the original lesional contour (capsular invasive MIFC), whereas a minority of authors accept a given neoplasm as a MIFC if it shows only partial thickness capsular penetration. Full thickness violation is manifest as multiple foci, less commonly a single nidus, of mushrooming herniation bulging into and displacing surrounding native follicles, generally without direct, tentacular, infiltrative/permeative growth. Lateral fibrous capsular thickening (‘buttressing’) and neocapsule formation along the advancing tumour to native gland interface are paradigmatic, but not invariable. Incomplete capsular encroachment includes areas of irregular or serratiform inner capsular contour and perpendicularly dentate capsular incursions. Horizontally disposed (‘entrapped’) intracapsular follicles usually do not qualify, although they should prompt further detailed scrutiny, as should any unexplained area of capsular expansion. Circumscribed extracapsular nodules (‘satellite tumour’) may represent MIFC visualized outside the plane of connection with the body of the tumour (although such a pedicle may sometimes be impossible to demonstrate and is not mandated by some observers) or a sequestered (‘parasitic’) congerie of benign follicles; comparison of the cytological features with the main tumour bulk may aid discrimination. Artefactual capsular puncture, healing and distortion following FNAC should be interpreted with caution and the entry/exit site of perforating capsular blood vessels, where there is normally curvilinear capsular interruption, not misconstrued. Well-sampled tumours that fall short of these criteria are termed ‘follicular tumour of uncertain malignant potential’ (FT-UMP) in alternative terminology.

There is relatively good consensus as to what defines angioinvasion or lymphovascular invasion, to wit tumour penetration into medium calibre or large calibre intracapsular or extracapsular blood vessels. There should be polypoidal intraluminal growth either endothelialized with/without thrombus, although not necessarily adherent (Figure 19.17). The point of attachment of tumour to vessel wall is a prerequisite for some observers. Free-lying endoluminal nests of tumour cells may represent artefactual dislodgement of cells by surgeon or pathologist and are disallowed. Tumour cells occupying capillary-sized intracapsular vessels are of no proven clinical importance and should be discounted. Tumour within intraliteral or subcapsular vessels does not qualify. Reactive vascular endothelial hyperplasia may simulate angioinvasion and, when recognized, ought to prompt a rigorous search for vascular invasion proper. Immunostaining for vascular endothelial markers (e.g. CD31, CD34) and lymphatic endothelium (e.g. D2-40) may be helpful in selected instances. Cognizant that absolute discrimination between blood vessel invasion and lymphatic space infiltration may ultimately be impossible, the current College of American Pathologists (CAP)

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**Figure 19.16** (a) Obvious mushrooming, full thickness, transcapsular herniation qualifying as minimally invasive follicular carcinoma, easily discernible to the unaided eye during dissection. There is slight lateral capsular buttressing, but negligible neocapsule formation along the advancing margin in this example. Note that there is no universally endorsed maximum size limit for this phenomenon. (b) The same area viewed histologically corroborates collapsing impingement into perilobular native gland with no tentacular/permeative infiltration and neither significant host inflammatory nor stromal response (H&E stain, low magnification).
protocol (2009) recommends merging the two and reporting under the unifying designation of ‘lymphovascular invasion’. Capsular invasive MIFC without lymphovascular infiltration portends an extremely low risk of metastasis (less than 1 per cent). Some surgeons pursue a conservative management approach and treat these cancers by lobectomy alone with surveillance, acknowledging that there is a small risk of undertreatment in a minority of cases. The term ‘grossly encapsulated angioinvasive follicular carcinoma’ has been proposed for encapsulated tumours with any foci of lymphovascular invasion, based on the premise that access to even one or a few endothelial lined vessels confers the capacity for more aggressive behaviour with perceived higher risk of recurrence, thereby negating a designation of ‘minimal invasion’. Some authors base their definition of MIFC on the number of foci of invasion. Those tumours with a total of two foci of capsular or vascular invasion are said to show a low risk of metastasis, whereas those with four or more blood vessels involved have a higher likelihood of recurrence (47 per cent for follicular oncocytic tumours) and of metastasis (roughly 18 per cent), invoking the designation of ‘grossly encapsulated follicular carcinoma with extensive angio-invasion’ for the latter.

Widely invasive follicular carcinoma (WIFC) is an aggressive neoplasm with a high risk of distant secondaries (29–66 per cent). It displays infiltrative growth within and beyond the anatomical thyroid capsule proper, sometimes in the form of successive generations of herniating capsular transgression (Figure 19.18). Vascular penetration is common and typically widespread. A tumour size greater than 3.5 cm portends a less favourable prognosis.

Extrathyroidal extension (ETE) describes involvement of perithyroidal soft tissues by a primary thyroid carcinoma. This may be further subdivided into minimal ETE and extensive ETE. As previously noted, the thyroid capsule, though continuous with the pretracheal fascia is not a discrete anatomical structure, is incomplete or focally absent in the majority of individuals, is additionally fenestrated by lymphovascular channels and contains small nerve radicles. The histological evaluation of minimal ETE is consequently sometimes vexatious and subjective. Importantly, both adipocytes and skeletal muscle bundles may be normally encountered within the thyroid gland and may also be a component of a variety of pathological thyroid conditions. The identification of desmoplastic response, adipocytic and/or muscular impingement in close proximity to large calibre, thick-walled vessels and/or large nerve trunks, on the other hand, may be more helpful as such would not be expected within the confines of thyroid gland proper. Extensive ETE is characterized by direct infiltration well beyond the limits of the thyroid gland into subcutis, neighbouring viscera, including larynx, trachea, oesophagus, recurrent laryngeal nerve, carotid artery or mediastinal vasculature. Extensive ETE is invariably obvious, typically identified by the surgeon perioperatively.

The prognosis for those carcinomas with minimal ETE worsens referenced against those without ETE. Similarly, the survival prospects for those suffering carcinomas with extensive ETE are significantly diminished in comparison with minimal ETE. There is a dearth of evidence-based information addressing the influence of resection margin status and clinical outcome in the international literature. While knowledge of a positive margin is intuitively meritorious, scrupulous studies in large series of patients with long-term follow up analysing this have yet to be published. Similarly, there is presently no data validating the exercise of measuring the distance of tumour to closest resection margin and/or documenting close margins as an independent or co-variable prognostic index.

Oncocytic (oxyphil) cell tumours

Follicular neoplasms comprising 75 per cent or more oncocytic (oxyphil) cells are designated as such and are subclassified according to the same criteria as their non-oncocytic counterparts based upon morphology, immunohistochemical profiling and molecular markers into oncocytic (oxyphil)
adenoma, oncocytic (oxyphil) tumour of uncertain malignant potential, minimally or widely invasive oncocytic (oxyphil) carcinoma (Hürthle cell carcinoma). Oncocytic variants of papillary thyroid carcinoma, poorly differentiated thyroid carcinoma (PDTC), undifferentiated (anaplastic) carcinoma and medullary thyroid carcinoma are recognized. Focal clear cell change is common in oncocytic tumours and, where this constitutes over 75 per cent of the lesion, it is traditionally designated clear cell carcinoma. Under such circumstances, it is imperative to exclude metastatic carcinoma (renal or adrenal),34 malignant melanoma, intrathyroidal parathyroid gland neoplasms and clear cell variant of medullary thyroid carcinoma.

Grossly, they are usually single nodules (solitary oxyphil follicular tumour, SOFT) (Figure 19.19), although they may be multiple (multiple oxyphil follicular tumours, MOFT) and are sometimes associated with Hashimoto’s thyroiditis and/or conventional papillary thyroid carcinoma. A higher proportion of oncocytic (oxyphil) tumours are malignant than other follicular lesions, although when staged comparably there are reportedly no significant differences in outcome between the two. The incidence of malignancy in oncocytic (oxyphil) cell neoplasms increases with size, that is, 17, 23 and 65 per cent or more associated with maximum dimensions of less than 1 cm, between 1 and 4 cm and larger than 4 cm, respectively.35 Most examples are sporadic. Familial examples are rare and exceptionally indicate a germline mutation.36

Macroscopically, they are classically mahogany brown tumours with a propensity for ischaemic infarction, either spontaneously or post-FNAC. They may show numerous histological patterns, including papillary areas, which may morphologically overlap with oncocytic (oxyphil) papillary thyroid carcinoma. They are typified by cytonuclear atypia and mitoses, though in isolation these do not reproducibly predict biological behaviour.

Oncocytic (oxyphil) parathyroid gland neoplasms should always be considered when evaluating a potential oncocytic (oxyphil) thyroid neoplasm, as they may be indistinguishable by routine orthodox microscopy without recourse to immunostaining.

### Papillary thyroid carcinoma

Papillary thyroid carcinoma is a malignant epithelial tumour showing follicular cell differentiation with characteristic nuclear features. It accounts for approximately 80 per cent of all thyroid cancer and is also the most common paediatric thyroid malignancy. In adults it typically occurs between the ages of 20 and 50 years, with a female preponderance, with less pronounced gender bias in patients over 50 years old. It normally carries an excellent prognosis, especially in younger patients. In areas of adequate dietary iodine, papillary thyroid carcinoma usually presents as a solitary thyroid nodule. In regions of iodine insufficiency, multinodular goitre is common and papillary thyroid carcinoma can present as a more prominent or distinctive nodule. It has a propensity for lymphatogenous spread, initially to locoregional lymph nodes.

The potential macroscopical and microscopical manifestations of PTC are protean. Prototypically, it is invasive with irregular outline and either a scirrhous or granular, gritty texture often with multiloculated cystic change and colloid contents (Figure 19.20). The encapsulated follicular variant of PTC (Lindsay tumour) is usually well-circumscribed possessing a solid, fleshy cut surface, closely resembling an adenoma.

The principal defining feature of PTC is its nuclear morphology by light microscopy (Figure 19.21), thus the diagnosis of PTC is sustainable even in the absence of invasive growth. Crucially, however, the distinctive nuclear appearances may be very localized and, in an appropriate context, the diagnosis may still be entertained in their absence. Ordinarily, there is at least focal nuclear enlargement (nucleomegaly), nuclear crowding and nuclear overlap (‘basket of eggs’). Homogenization of karyoplasm (‘ground

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**Figure 19.19** A small, benign solitary oncocytic (oxyphil) cell follicular tumour (SOFT), occurring sporadically in a background of chronic lymphocytic (Hashimoto’s) thyroiditis. Despite its lack of capsule and occasional rudimentary papillae, there were no diagnostic features to suggest papillary thyroid carcinoma (H&E stain, low magnification).

**Figure 19.20** The cut surface of a classical papillary thyroid carcinoma illustrating a solid, granular appearance with adjoining encysted elements distended by inspissated colloid. The yellow punctate structures represent psammoma calcification and imparted a gritty texture.
gloss') with margination of chromatin (likened to the empty looking, pupil-less eyes of Harold Gray’s cartoon strip characters, most famously the waif ‘little orphan Annie’ and her canine companion ‘Sandy’) is characteristic, but not pathognomonic – it is not invariable, it is rarely present in FNAC and frozen sections, it may be encountered in other non-neoplastic conditions, it may be simulated by suboptimal tissue fixation (‘bubbly’ or pseudoclear artefact) and is subject to vagaries of interobserver and intraobserver reproducibility. Longitudinal nuclear grooves (‘coffee bean’) formed by redundant, folded nuclear membrane and intranuclear cytoplasmic inclusions (pseudoinclusions, vacuoles) formed by cytoplasmic herniation are typical and may be visualized on both FNAC and frozen section Figure 19.22, but again are not exclusive and may also be mimicked by intranuclear bubble artefact (‘pseudopseudoinclusions’).27

A papillary architecture is typical, although by no means universal. The papillae are often well vascularized and complexly arborescent, sometimes oedematous (hydropic), hyalinized, fibrocellular, calcified or micropapillary in configuration (Figure 19.23). Follicles are usually present, albeit with an elongated, tortuous or crenated outline, sometimes with rudimentary or abortive papillae and colloid is often densely hypereosinophilic. Intrafollicular multinucleated giant cells of macrophage/histiocyte lineage phagocytosing colloid (colloidophagy) are more often seen in PTC than in other lesions.
Psammoma bodies (laminated calcospherites) are present in roughly 50 per cent of PTCs histologically, less frequently on FNAC and are virtually pathognomonic – they must, however, be stromal in location in contradistinction to calcified, inspissated intrafollicular colloid (psammomatoid bodies or pseudopsammoma calcification) seen in normality and other disease states (Figure 19.24). Importantly, psammoma bodies may also be seen in other neoplastic and non-neoplastic conditions, both within and outside the thyroid gland. Rarely, psammoma bodies or linear scoring artefact following microtomy provide the only presumptive evidence of regressed or infarcted PTC. Multicentric PTC is common and represents either intrathyroidal lymphatic spread or synchronous primary tumorigenesis with different RET/PTC translocations.

Numerous variants of PTC have been described, none mutually exclusive within an individual tumour (Table 19.5). A single tumour is classified according to its predominant histological pattern. Most subtypes are of no prognostic significance, although tall cell, diffuse sclerosing, diffuse follicular, solid, trabecular and dedifferentiated variants (Figure 19.25) are biologically more aggressive in contrast to the encapsulated variant (where conventional infiltrative growth may not be apparent), which portends a highly favourable outcome. Increased mitoses (over two mitoses per ten high power fields) and tumour necrosis signify worse survival in PTC. PTCs measuring less than 1 cm are associated with an excellent prognosis and the outlook worsens for those tumours exceeding 4 cm. Positive lymph nodal metastasis in PTC is usually an indication for radioactive iodine therapy and the presence of extranodal spread.

### Table 19.5 Histological variants of papillary thyroid carcinoma

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<thead>
<tr>
<th>Variant</th>
<th>Classical</th>
<th>Tall cell</th>
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<tr>
<td>Follicular</td>
<td>Columnar cell</td>
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<td>Solid</td>
<td>Oncocytic (oxyphil)</td>
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<td>Encapsulated</td>
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<td>Diffuse follicular</td>
<td>Macrofollicular</td>
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<tr>
<td>Trabecular</td>
<td>Cribriform-morular (including FAP-associated)</td>
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<td>Lipomatous stroma</td>
<td>Exuberant nodular fasciitis-like stroma</td>
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<td>Spindle cell</td>
<td>Dedifferentiated</td>
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FAP, familial adenomatous polyposis.

**Figure 19.24** (a) Psammoma bodies in papillary thyroid carcinoma. These concentrically laminated concretions are stromal in location. They are often said to represent mineralized ‘tombstones’ to a mummified cell, the latter forming the initial nidus for mineral encrustation and may occasionally be large and complex in configuration. Some of these have splintered during microtomy. Any calcified deposits or other hard objects are prone to dislodgement by the microtome blade and being swept across the tissue section to give parallel linear score artefact (H&E stain, medium magnification). (b) Fine needle aspiration cytology (FNAC) from a papillary thyroid carcinoma showing two concentrically lamellated psammoma bodies mantled by vacuolated epithelial cells. Psammoma bodies are seen in 40–60 per cent of papillary thyroid carcinomas in histological sections, but in only 20 per cent of cases in FNAC specimens (H&E stain, high magnification). (c) A psammomatoid or pseudo-psammoma body composed of inspissated, partially mineralized intrafollicular colloid (H&E stain, high magnification).
extension heightens the risk of distant metastasis and death. Areas of squamous differentiation (morulae) occur in approximately 50 per cent of cases and the distinctive PTC nuclear morphology is absent from such areas. The WHO definition of tall cells in PTC is merely a preponderance of tumour cells whose height is at least three-fold (previously two-fold) greater than their width and this pattern should not be confused with columnar cell carcinoma. PTC stains immunohistochemically for cytokeratins (CK), thyroglobulin and thyroid transcription factor-1, but not pan-neuroendocrine markers. Areas of squamous differentiation lose their thyroglobulin and thyroid transcription factor-1 reactivity. A plethora of markers has been proposed to aid discrimination between follicular variant of PTC and other follicular lesions, notably high molecular weight cytokeratins (HMWCK), cytokeratin 19, mesothelium-associated antibody (HBME-1), galectin-3, Leu7 (CD57), LeuM1 (CD15), fibronectin-1, platelet-derived growth factor (CD44) and RET among others. None, individually or in combination, are entirely sensitive or specific for PTC – they may be capricious even in classical PTC. Moreover, a number of inflammatory and other neoplastic conditions may yield overlapping results.

Three independent molecular pathways are recognized in the tumorigenesis of PTC with distinct gene expression profiles, namely activation of the proto-oncogene receptor tyrosine (RET) kinase, mutation of the gene for B-raf (BRAF) and ras mutation. RET kinase activation consequent upon chromosomal translocation is collectively referred to as RET/PTC translocation and occurs in up to 60 per cent of PTCs. RET/PTC 1 fusion correlates to classical PTC and papillary microcarcinoma. RET/PTC 3 fusion is seen in tall cell and solid PTC variants plus irradiation-induced tumours. RET/PTC expression is not a feature of follicular carcinoma, poorly differentiated carcinoma or undifferentiated (anaplastic) carcinoma. Mutation of the gene for B-raf (BRAF) accompanies 29–69 per cent of PTCs, more prevalent in classical PTC, tall cell, Warthin tumour-like and oncocytic (oxyphil) variants. Follicular variant PTC harbours ras gene mutations and may show PAX8/IPPARγ translocation, but rarely RET/PTC translocation or BRAF mutations, a profile akin to that of follicular adenoma and follicular carcinoma.3

Difficulty in classifying follicular patterned lesions of the thyroid gland

The histomorphological differential diagnosis of follicular patterned lesions of the thyroid gland remains a controversial area of current diagnostic surgical pathology, hampered by relative lack of objective criteria and limited follow-up data, compounded by subjective interpretation with well-recognized interobserver and intraobserver variation, occasionally necessitating an ipse dixit diagnosis based on pragmatic constraints and experience.26

A belief among some experts that there is overdiagnosis of FVPTC38 draws some support from molecular and genetic observations. Furthermore, RET/PTC expression in some cases of follicular variant PTC show multicentric rather than diffuse alterations, suggestive of carcinomatous transformation ex-adenoma, although by convention it is recommended that the entire encapsulated lesion is arbitrarily regarded as PTC for staging purposes.28

Alternative nomenclature has been proposed to accommodate this diagnostic uncertainty and is summarized here (Figure 19.26). This provides a more descriptive schema, which may be invoked in the minority of cases where diagnostic equivocation is irresolvable by conventional morphology and the stigma of malignancy is undesired.29 Where diagnostic distinction between follicular carcinoma and papillary thyroid carcinoma is difficult, the generic rubric ‘well-differentiated thyroid carcinoma’ may be employed, although every effort to subclassify more precisely should still be made.39

Papillary thyroid microcarcinoma

Papillary thyroid microcarcinomas (papillary microtumours) are by definition less than 10 mm in diameter. They may be an incidental finding in thyroid glands removed for other

Figure 19.25 (a) Tall cell variant of papillary thyroid carcinoma. The cells are columnar, their height being at least three times greater than their width and they are not hyperstratified, in contradistinction to columnar cell carcinoma (H&E stain, high magnification). (b) Solid variant of papillary thyroid carcinoma. The small cell nests demonstrate the distinctive nuclear features. This example behaved extremely aggressively (H&E stain, high magnification).
pathology or serendipitously detected on imaging of the thyroid gland (latent carcinoma). Alternatively, they may be found retrospectively in patients presenting with metastatic disease from an initially unsuspected small primary lesion (occult or covert carcinoma). Further subdivision into tumours less than 5 mm ('minute') and 5–10 mm ('tiny') maximum dimension is of no clinical relevance. Occult and latent papillary carcinomas may or may not be microcarcinomas.

Most studies report a prevalence for latent papillary microcarcinomas of circa 5–10 per cent, but figures as high as 30 per cent or so are acknowledged. Despite their propensity for multifocality in one lobe (23 per cent), bilaterality (17 per cent) and locoregional lymph node metastasis (16 per cent), they almost always pursue an indolent clinical course with excellent prognosis, usually not requiring additional intervention. Exceptionally, however, papillary thyroid microcarcinomas behave more aggressively and the presence of two or more foci, lymphovascular invasion, extrathyroidal extension and higher risk morphology (e.g. tall cell features) may prompt more comprehensive treatment, despite tenuous long-term vindication for this. A significant number of subcentimetre papillary carcinomas occurring in children and adolescents harbour extrathyroidal extension and/or distant metastasis, prompting the CAP recommendation to restrict use of the term 'papillary thyroid microcarcinoma' to those over 19 years of age.

Morphologically, papillary microcarcinomas are usually either infiltrative and sclerotic or circumscribed but unencapsulated, located between native follicles without discernible host response (Figure 19.27). Such microscopical foci, therefore, are easily missed on cursory histological screening and are apt to mimic solid cell nests or even heterotopic thymic rests on scanning magnification.

### Poorly differentiated thyroid carcinoma

Poorly differentiated thyroid carcinoma encompasses a spectrum of heterogeneous tumours showing limited evidence of follicular cell differentiation associated with biological behaviour intermediate between differentiated (follicular and papillary) thyroid carcinoma and undifferentiated (anaplastic) carcinoma. PDTC typically arise de novo, but may occur through transformation of differentiated carcinoma

![Figure 19.26](image)

**Figure 19.26** Diagnostic algorithm for resolution of the differential diagnosis of encapsulated follicular lesions of the thyroid gland. PTC, papillary thyroid carcinoma; WDC-NOS, well-differentiated carcinoma, not otherwise specified; WDT-UMP, well differentiated tumour of uncertain malignant potential; FT-UMP, follicular tumour of uncertain malignant potential; MIFC, minimally invasive follicular carcinoma; WIFC, widely invasive follicular carcinoma.

![Figure 19.27](image)

(a) Multicentric papillary thyroid microcarcinoma (UICC/TNM pT1(m)), each deposit measuring less than 10 mm diameter. These show a sclerotic morphology. (b) Microscopical deposit of papillary microcarcinoma. This is poorly demarcated and is eliciting no stromal or inflammatory response whatsoever. Such foci are readily overlooked on cursory or low power examination (H&E stain, medium magnification).

(Figure 19.28). They may progress to undifferentiated (anaplastic) carcinoma either ab initio or after recurrence.

PDTC may be defined mainly on the basis of growth pattern. Insular (primordial) carcinoma represents the archetype
and is composed of large solid nests (insulae) punctuated by occasional primitive follicles (Figure 19.29). Minor elements of classical papillary thyroid carcinoma and/or follicular carcinoma may be recognized. Obversely, an insular growth pattern is by no means exclusive to poorly differentiated carcinoma and important differential diagnoses include medullary thyroid carcinoma, solid variant papillary thyroid carcinoma and undifferentiated (anaplastic) carcinoma.

Alternatively, PDTC may be specified according to mitotic state (exceeding five mitoses per ten high power fields, × 400) and/or comedo-like tumour necrosis. These portend a survival rate of 60 per cent at five years, irrespective of tumour architecture. Furthermore, the combination of solid growth and the presence of at least one of the following: convoluted nuclei, tumour necrosis and/or over three mitoses per ten high power fields, × 400, is a powerful predictor of poor outcome. This group constitutes the major cause of radiiodine (RAI) refractory, positron emission tomography (PET)-positive incurable thyroid carcinomas.33

Confusingly, the term ‘poorly differentiated carcinoma’ is also applied by some observers to differentiated carcinomas showing a solid, trabecular or scirrhous pattern, to tall cell papillary carcinomas and to columnar cell carcinomas. This lack of consensus may explain conflicting data as to whether a minority component of insular carcinoma in an otherwise differentiated carcinoma is an independent prognostic factor or not and, if so, at what threshold this begins to be a clinically valid observandum.

Unsurprisingly, the tumour cells demonstrate cytokeratins, thyroglobulin and thyroid transcription factor-1 immuno-positivity, but negative pan-neuroendocrine markers and calcitonin.

Columnar cell carcinoma

Columnar cell carcinoma is a rare thyroid neoplasm, which once invasive pursues a more aggressive course than other differentiated thyroid carcinomas. Where it remains encapsulated, however, there appears to be little risk of metastasis.31 There is disagreement as to whether is best classified as a distinct entity rather than a variant of papillary thyroid carcinoma. There is indeed morphological overlap between columnar cell carcinoma, the cribriform-morular variant of papillary thyroid carcinoma and also so-called familial adenomatous polyposis (FAP)-associated thyroid carcinoma (remembering that thyroid carcinomas of conventional pattern also occur in FAP patients).

This notwithstanding, the typical architecture resembles that of intestinal and endometrioid carcinomas with complex glandular, cribriform and solid growth. The individual cells are tall and columnar, but striking nuclear hyperstratification and hyperchromasia enable separation from tall cell variant of papillary thyroid carcinoma (Figure 19.30). Immunohistochemically, it is usually cytokeratin, thyroglobulin and thyroid transcription factor-1 positive.

Undifferentiated carcinoma

Undifferentiated (anaplastic) carcinoma is a highly malignant tumour typically seen in elderly patients with a female preponderance. It accounts for approximately 2–10 per cent of all malignant thyroid neoplasms,42 with a predilection for iodine-deficient regions although its overall incidence is declining.43 Undifferentiated (anaplastic) thyroid carcinoma is usually widely invasive at presentation and inoperable in roughly half of cases. It carries a high mortality and accounts for nearly a half of all deaths associated with thyroid malignancy.8 The overall median survival is four months and the five-year survival rate is less than 10 per cent. All undifferentiated thyroid carcinomas are arbitrarily UICC/TNM staged as pT4 due to their anticipated aggressive behaviour, classically showing widespread infiltration of
Medullary thyroid carcinoma (MTC) is a malignant tumour displaying parafollicular C-cell differentiation, which secretes calcitonin and often a variety of other neuropeptides. It is an uncommon tumour accounting for 5–8 per cent of all thyroid cancers. It may occur sporadically or against a background of an inherited autosomal dominant trait related to a germline mutation of the RET proto-oncogene, which cause MEN 2A, MEN 2B or familial MTC (FMTC).

Sporadic MTC is more common in females and presents at an average age of 50 years. MEN 2A presents in adolescence or young adults, while MEN 2B presents in infancy or childhood. Sporadic tumours are usually single, whereas hereditary tumours are often multicentric and/or bilateral. FMTC arises from C-cell hyperplasia, which is considered a precursor lesion and can be identified histologically with due diligence.

Regional lymph node metastasis and distant lymphogenous spread are found in 20 and 8 per cent of cases at presentation, respectively. Secondary sites of predilection include lung, liver, adrenal and bone. MEN 2B MTC generally pursues a more aggressive course than MEN 2A MTC, which in turn portends a less favourable prognosis than sporadic MTC, although for those with neoplasms confined to within the thyroid gland, overall long-term survival approaches 95 per cent, indeed many patients survive for years despite secondary systemic involvement. Micro-MTCs detected through screening are associated with a better outcome than those examples over 1 cm.

MTCs may be well demarcated or infiltrative, sometimes encapsulated (Figure 19.31). They are commonly located in the middle third of the lateral lobes, where C-cell concentration is greatest. Microscopically, they comprise solid sheets, nests and trabecula of cells separated by slender fibrovascular septa (Figure 19.33). A panoply of histological variants are seen, most of no clinical importance other than that they may masquerade as other tumours (Table 19.7). There is usually only modest nuclear pleomorphism, but necrosis may be a feature. Amyloid protein deposition is present in up to 80 per cent or so of cases (Figure 19.34) and may mineralize or elicit a foreign body granulomatous response.

The usual immunophenotype is positive for cytokeratins, calcitonin, thyroid transcription factor-1, carcinoembryonic antigen (CEA, CD66e) and pan-neuroendocrine markers. Calcitonin-depleted tumours may behave more aggressively, but almost invariably stain for CEA (Figure 19.35). Other neuropeptides may be demonstrated, including calcitonin gene-related peptide, somatostatin, ACTH, serotonin, gastrin, bombesin and histaminase, among others. A S100 protein positive subpopulation of sustentacular cells is more commonly seen in hereditary cases (Figure 19.36), potentially overlapping morphologically with paraganglioma, although paragangliomas (with the rare, anomalous exception of those involving the cauda equina) are cytotkeratin negative. It is wise to be aware that neuroendocrine

**Figure 19.30** Columnar cell carcinoma illustrating the classical, complex glandular growth pattern resembling gastric, colorectal or endometrial adenocarcinoma. The tumour cells are columnar with prominent nuclear hyperstratification (H&E stain, high magnification).

**Figure 19.31** Columnar cell carcinoma illustrating the classical, complex glandular growth pattern resembling gastric, colorectal or endometrial adenocarcinoma. The tumour cells are columnar with prominent nuclear hyperstratification (H&E stain, high magnification).

**Figure 19.32** Anaplastic carcinoma arising de novo, which is more amenable to surgical extirpation, portends a slightly more favourable outlook but is uncommon.

**Figure 19.33** A variety of other microscopical patterns are recognized and are renowned for troublesome differential diagnosis (Table 19.6). Angiolymphatic penetration is characteristic and a brisk inflammatory response is often encountered.

**Figure 19.34** While the term ‘carcinoma’ is applied, compelling proof of epithelial differentiation is not always forthcoming and the diagnosis ultimately rests upon an acceptable morphological pattern in an appropriate clinicoradiological context. Immunohistochemical staining for cytokeratin and vimentin are at least focally positive in approximately 90 per cent of cases with epithelial membrane antigen reactivity in 50 per cent of examples. Thyroglobulin, thyroid transcription factor-1, calcitonin and pan-neuroendocrine epitopes are typically negative. Diffusion of thyroglobulin from destroyed non-neoplastic follicles, however, may give rise to spurious immunopositivity. Endothelial markers (CD31, CD34 and factor VIII) may be focally demonstrated in some tumours presenting an angiosarcomatoid morphology, which may rarely prevail. Occasional cases are completely immunoinert and ultrastructural studies are seldom rewarding. Where appropriate, a haematolymphoid immunopanel should always be considered, particularly on FNAC and needle core biopsies, as so not to overlook high-grade or anaplastic non-Hodgkin’s lymphoma.
neoplasms other than MTC may sometimes express aberrant calcitonin immunoreactivity, for example laryngeal and bronchopulmonary atypical carcinoid tumours, although the latter are typically immunonegative for carcinoembryonic antigen (CEA, CD66e) and there is more often than not normocalcaemia.

Electron microscopy identifies membrane-bound electron-dense storage granules ranging from 100 to 300 nm in diameter with augmented rough endoplasmic reticulum and Golgi apparatus (Figure 19.37).

C-cell hyperplasia and neoplasia

FMTC develops in a milieu of C-cell hyperplasia and there is no recognized benign C-cell adenoma counterpart. Reactive (physiological) C-cell hyperplasia occurs with advancing age, in thyroiditis, in hyperparathyroidism, in close proximity to other thyroid neoplasms or solid cell nests and in hypergastrinaemia. There is no unanimously accepted definition of nodular (neoplastic, ‘MTC in situ’) C-cell proliferation, but over 50 C-cells per 100 field has been proposed, where there is obliteration of follicular spaces by solid, intrafollicular C-cell growth delimited by basement membrane, as demonstrated by immunostaining for collagen IV (Figure 19.38). Once there is violation of basement membrane and/or tumour-derived basal lamina reduplication, that intuitively constitutes MTC proper – the distinction between micro-MTC and intrathyroidal spread of MTC, however, may be impossible.

C-cells cannot be reliably identified by morphology on routine histological slides without recourse to calcitonin, carcinoembryonic antigen (CEA, CD66e) or pan-neuroendocrine immunophenotyping. This has, however, assumed less importance with the advent of more sensitive and specific molecular analysis looking for RET proto-oncogene germline mutations in the diagnosis of hereditary MTC syndromes.
Tumours displaying joint follicular and C-cell differentiation

The concept of mixed follicular-parafollicular carcinoma is enigmatic. Collision (combined) tumours include follicular carcinoma plus MTC and papillary carcinoma plus MTC. True follicular-parafollicular carcinoma (differentiated carcinoma of intermediate type) occurring as a genuine hybrid (composite) neoplasm is exceptionally rare. The two cell populations may either share origin from a common stem cell or be of dual clonality. The follicular component is sometimes non-neoplastic, thereby raising the possibility of implicated follicles within a slowly growing MTC. False-positive thyroglobulin staining may result from passive diffusion out of nearby native follicles or following active

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<th>Pattern</th>
<th>Major differential diagnosis</th>
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<td>Oncocytic (oxyphilic)</td>
<td>Clear cell</td>
<td>Spindle cell</td>
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<td>Giant cell</td>
<td>Squamous</td>
<td>Pseudoangiosarcomatoid</td>
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<td>(anaplastic)</td>
<td>Carcinoid-like</td>
<td>Medullary microcarcinoma (latent carcinoma)</td>
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pinophagocytosis by tumour cells, rather than endogenous synthesis proper. The conventional ontogenetic explanation proposing different origins for follicular cells and C-cells, however, fails to reconcile the observation of apparent genuine coexpression of both thyroglobulin and calcitonin in the same tumour cell. 3

OTHER NEOPLASMS AND TUMOUR-LIKE LESIONS

There are very many other less common or incredibly rare neoplasms affecting the thyroid gland of epithelial, mesenchymal, haematolymphoid, thymic, parathyroid gland and developmental origin, together with a few tumour-like lesions (Box 19.1).
Metastatic tumours

The thyroid gland is commonly affected by metastases either by direct extension from neighbouring structures, haematogenous or lymphatic spread. Local structures include the larynx or lymph nodes and common non-head and neck primary sites include bronchopulmonary, breast, malignant melanoma and renal cell carcinoma (Figure 19.39). The latter may occur metachronously following an interval of up to 19 years or be a synchronous presenting feature of the disease.34

**Figure 19.36** Medullary thyroid carcinoma in MEN 2 showing typical $\alpha$-MSH protein reactive, spindly sustentacular cells mantling small nests of secretory tumour cells ($\alpha$-MSH IHC, high magnification).

**Figure 19.37** Transmission electron micrograph depicting several tumour cells from a medullary thyroid carcinoma, occurring in a child with known MEN 2B. Numerous dense, membrane-bound neurosecretory vesicles are present in the cytoplasm (transmission electron microscope (TEM), ultra-high magnification).

**Figure 19.38** (a) Early nodular (neoplastic) C-cell hyperplasia in MEN 2, readily identified on routine staining. There is expansion of C-cells within the follicular basement membrane, but no destructive or infiltrative growth (H&E stain, medium magnification). (b) More marked and multicentric nodular (neoplastic) C-cell proliferation with follicular obliteration and interstitial expansion. This probably amounts to at least medullary carcinoma in situ, if not medullary thyroid microcarcinoma (‘microtumour’) proper (calcitonin IHC, high magnification).

The widespread adoption of FNAC has enabled broad preoperative categorization of many lesions, which by their very nature cannot be further refined by frozen section assessment, for example Thy3 follicular lesion, follicular neoplasm and oncocytic (oxyphil) neoplasm. Frozen section examination on a Thy5 FNAC lesion, definite for malignancy, is also unlikely to confer any significant benefit other than perhaps evaluation of resection margins. If the distinction between high-grade lymphoma and undifferentiated (anaplastic) carcinoma has not already been made on FNAC or needle core biopsy, then frozen section is equally unlikely to resolve this. Fleshy, solitary encapsulated lesions are likely to represent follicular adenoma or minimally invasive follicular carcinoma, but attempts to comprehensively sample the capsule in the fresh state should be resisted pending tissue fixation with a view to proper paraffin sections in order to obviate artefactual disruption and distortion of the all important pericapsular tissue planes.

The indications for perioperative frozen section examination of
thyroid gland lesions are best agreed by the relevant multidisciplinary team at a local level, taking into consideration local circumstances, individual experience and preferences together with clinical expectations.49

THYROID CANCER STAGING

The UICC/AJCC TNM classification of malignant tumours is internationally ratified, currently in its seventh edition (Box 19.2).50

PARATHYROID GLANDS

The normal parathyroid glands

Most individuals possess at least two pairs of parathyroid glands (PTG). The cephalad pair are embryologically derived from the fourth branchial cleft and are usually located over the posterior surface of the thyroid gland close to the point of entry of the inferior thyroid artery. The caudad glands are of third branchial pouch origin and typically lie over the lower thyroid gland pole, although they are more variably placed and may be found within the mediastinum or even the pericardium, consequent upon comigration with the thymus, which is similarly of third branchial pouch ontogeny. Supernumerary or heterotopic (ectopic) glandular tissue may consist of less well-formed, more diffuse cell aggregates within cervical soft tissues (parathyromatosis) often in close proximity to eutopic glands and this pattern also characterises surgically implanted gland tissue.4

The parathyroid glands secrete parathyroid hormone (parathormone, PTH), which elevates serum calcium via direct effects on kidney and bone and indirectly through the intestine. To the unaided eye, the glands are a yellow-brown colour. At operation, brown fat, yellow fat, sequestrated thyroid tissue, thymus, lymph node and autonomic ganglia may all mimic these appearances and such are not infrequently submitted for frozen section examination in
Box 19.2 UICC/AJCC TNM classification of malignant tumours of the thyroid gland (7th edn).

**Rules for classification**

The classification applies to carcinomas. There should be microscopic confirmation of the disease and division of cases by histological type.

The following are the procedures for assessing T, N and M categories:

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<tr>
<th>T categories</th>
<th>Physical examination, endoscopy and imaging</th>
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<td>N categories</td>
<td>Physical examination and imaging</td>
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<td>M categories</td>
<td>Physical examination and imaging</td>
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**Regional lymph nodes**

The regional lymph nodes are the cervical and upper/superior mediastinal nodes.

**TNM clinical classification**

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<tr>
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<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or less in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour 1 cm or less in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour more than 1 cm, but not more than 2 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm, but not more than 4 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension, limited to the thyroid or any tumour with minimal extrathyroid extension (e.g. extension to sternothyroid muscle or perithyroid soft tissues)</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour extends beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades prevertebral fascia, mediastinal vessels or encases carotid artery</td>
</tr>
</tbody>
</table>

All anaplastic carcinomas are considered T4 tumours.

| T4a* (anaplastic carcinoma only) | Tumour (any size) limited to the thyroid |
| T4b* (anaplastic carcinoma only) | Tumour (any size) extends beyond the thyroid capsules |

**N, Regional lymph nodes**

| Nx                | Regional lymph nodes cannot be assessed                           |
| N0                | No regional lymph node metastasis                                 |
| N1                | Regional lymph node metastasis                                    |
| N1a               | Metastasis in level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) |
| N1b               | Metastasis in other unilateral, bilateral or contralateral cervical (levels I, II, IV or V) or retropharyngeal or superior mediastinal lymph nodes |

**M, Distant metastasis**

| M0                | No distant metastasis                                            |
| M1                | Distant metastasis                                               |

**pTNM pathological classification**

The pT and pN categories correspond to the T and N categories.

| pN0 | Histological examination of a selective neck dissection specimen will ordinarily include six or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0. |

**Histological types**

The four major histopathological types are:

- Papillary carcinoma (including those with follicular foci)
- Follicular carcinoma (including so-called Hürthle cell carcinoma)
- Medullary carcinoma
- Anaplastic/undifferentiated carcinoma
lieu of parathyroid gland proper. Microscopically, in the
normal state, the glands are lobulated, richly vascularized and
composed of nests and/or trabecula of polygonal parenchymal
cells, that is a mixture of chief (principal) cells, water-clear cells
and oncocytic (oxyphil) cells, interspersed with adipocytes
(Figures 19.40 and 19.41). The number, size and composition
of the glands, however, are subject to wide normal and
abnormal variation (Table 19.8) influenced by age,
gender, nutritional and hormonal status. With advancing age,
congeries of oncocytic (oxyphil) cells are increasingly
encountered.

### Hyperparathyroidism

Hyperparathyroidism is defined by elevated serum PTH and is
the most common pathological condition affecting the
parathyroid glands. It is classified into primary, secondary
and tertiary forms dependent upon the identification of a
driving stimulus (Table 19.9), although the end result is an
absolute increase in parenchymal cell mass affecting one or
more glands (Figure 19.42).

In primary parathyroid gland hyperplasia, all of the para-
thyroid glands are enlarged, albeit unevenly in some cases. In

---

<table>
<thead>
<tr>
<th>Stage grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separate stage groupings are recommended for papillary and follicular (differentiated), medullary and anaplastic (undifferentiated) carcinomas:</td>
</tr>
</tbody>
</table>

#### Papillary or follicular, under 45 years

<table>
<thead>
<tr>
<th>Stage</th>
<th>Any T</th>
<th>Any N</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1a, T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T1, T2, T3</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4a</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
</tbody>
</table>

#### Papillary or follicular, 45 years and older

<table>
<thead>
<tr>
<th>Stage</th>
<th>Any T</th>
<th>Any N</th>
<th>M1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1a, T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T1, T2, T3</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4a</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
</tbody>
</table>

#### Medullary

<table>
<thead>
<tr>
<th>Stage</th>
<th>Any T</th>
<th>Any N</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1a, T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1, T2, T3</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T1, T2, T3</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

#### Anaplastic carcinoma

All anaplastic carcinoma are stage IV

<table>
<thead>
<tr>
<th>Stage</th>
<th>Any T</th>
<th>Any N</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IVA</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

#### Summary, thyroid gland

**Papillary, follicular and medullary carcinoma**

| T1 | ≤ 2 cm, intrathyroidal |
| T2 | > 2–4 cm, intrathyroidal |
| T3 | > 4 cm or minimal extrathyroidal extension |
| T4a | Subcutaneous, larynx, trachea, oesophagus, recurrent laryngeal nerve |
| T4b | Prevertebral fascia, mediastinal vessels, carotid artery |

**Anaplastic/undifferentiated carcinoma**

| T4a | Tumour limited to thyroid |
| T4b | Tumour beyond thyroid capsule |

**All types**

| Na1 | Level VI |
| N1b | Other regional |
parathyroid gland adenoma, only a single gland is enlarged, the remaining glands being of normal size or small. This is typically accompanied by marked diminution in intraglandular adipocytes and reduced or absent intracytoplasmic lipid droplets (Figure 19.43), although rarely the latter may paradoxically be more abundant in chief cells located between hyperplastic nodules. Additionally, foci of irregularly distributed stromal fat cells may persist recapitulating a rim of normal glandular tissue, which when juxtaposed to a fat-depleted hyperplastic nodule, may lead to erroneous interpretation as an adenoma – the most reliable discrimination between hyperplasia and adenoma is achieved through histological examination of multiple glands augmented by multiple sections through larger glands. If only one parathyroid gland is available for examination and proves to be enlarged and/or hypercellular, definitive pathological distinction between hyperplasia and adenoma cannot be reliably achieved.

Figure 19.40  (a) An intrathyroidal parathyroid gland presenting a normal vascularized, lobular microarchitecture comprising parenchymal cells interspersed with a normal complement of mature fat cells – these are of haphazard distribution and density. Note its clear circumscription and delicate fibrous capsule (H&E stain, low magnification). (b) A replicate section immunostained with anti-PTH antibody showing intense parenchymal positivity, in sharp contrast to the surrounding negative thyroid gland follicles acting as an internal negative control (PTH IHC, low magnification).

Figure 19.41  (a) Nests and trabecula of isomorphic chief cells forming occasional glandular lumina or so-called microfollicular/ pseudofollicular growth pattern (H&E stain, high magnification). (b) Clusters of water-clear cells displaying their characteristic clear, generally univacular cytoplasm with eccentrically displaced nuclei (H&E stain, high magnification). (c) Nodular sheets of oncocytic (oxyphil) cells illustrating their hallmark, copious, granular and densely eosinophilic cytoplasm, attributable to plentiful mitochondria. A minor degree of random nuclear pleomorphism is often encountered (H&E stain, high magnification).
Only primary and tertiary hyperparathyroidism are associated with hypercalcaemia and its attendant systemic sequelae, but all three forms may manifest with bone disease. Aberrant parathyroid hormone-related peptide (PTHrP) secretion may occur as a paraneoplastic phenomenon (humoral hypercalcaemia of malignancy) in some malignant neoplasms, notably squamous cell carcinoma of primary

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal range</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Usually 4, but ranges from 1–12</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>Length 3–6 mm</td>
<td>&gt; 6mm in any plane</td>
</tr>
<tr>
<td></td>
<td>Width 2–4 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depth 0.5–2 mm</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>Each gland approximately 30 mg – the inferior glands are often heavier than the superior ones</td>
<td>Any individual gland &gt; 60 mg</td>
</tr>
<tr>
<td></td>
<td>Total parathyroid gland mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>120 ± 3.5 mg in males</td>
<td></td>
</tr>
<tr>
<td></td>
<td>142 ± 5.2 mg in females</td>
<td></td>
</tr>
<tr>
<td>Percentage fat</td>
<td>17–50%</td>
<td>Complete absence or very marked reduction</td>
</tr>
<tr>
<td></td>
<td>Male average 20.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female average 15.6%</td>
<td></td>
</tr>
<tr>
<td>Intracytoplasmic lipid</td>
<td>Abundant</td>
<td>Absent or sparse</td>
</tr>
</tbody>
</table>

Table 19.9 Classification of hyperparathyroidism.

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Causes</th>
<th>Pathological changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Over-production of PTH due to intrinsic abnormality of one or more glands causing elevated serum calcium with depressed serum phosphate</td>
<td>PTG adenoma 85%</td>
<td>Adenoma or carcinoma changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTG carcinoma 1%</td>
<td>Chief cell hyperplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTG hyperplasia 14%</td>
<td>Reduced or absent intra-parenchymal fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sporadic</td>
<td>Diffuse or nodular changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEN 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEN 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial isolated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Familial hypocalcuric</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypercalcaemia</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Compensatory hyperplasia of parathyroid glands due to decreased serum calcium usually resulting in normocalcaemia</td>
<td>Chronic renal failure</td>
<td>Hyperplasia of all glands. May be indistinguishable from primary hyperparathyroidism.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malabsorption</td>
<td>Multinodular or diffuse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal tubular acidosis</td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>Autonomous parathyroid gland hyperfunction following secondary hyperparathyroidism</td>
<td>Any cause of secondary hyperparathyroidism</td>
<td>Very similar to secondary hyperparathyroidism, although glands are typically larger and multinodular</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May rarely be associated with adenoma or carcinoma</td>
</tr>
</tbody>
</table>
bronchopulmonary, upper aerodigestive tract and female genital tract origin, sometimes with renal cell carcinoma. Approximately 50 per cent of metastatic prostatic adenocarcinoma deposits evince anomalous PTH immunopositivity, crossreacting with PTHrP, which may prove to be a source of differential diagnostic confusion. Hypercalcaemia directly related to the osteolytic effects of bone metastasis, independent of PTHrP, may occur in mammary carcinoma and haematological malignancies. Lithium therapy prescribed for psychiatric disorders may induce a form of primary hyperparathyroidism, which abates on cessation of the drug, although parathyroidectomy may still be indicated.

Parathyroid gland adenoma

Parathyroid gland adenoma is the predominant cause of primary hyperparathyroidism. It may occur spontaneously or within the context of various syndromes. Irradiation of the neck is a potential risk factor. Excision of the abnormal gland is curative and results in normalization of biochemical indices and increased bone mineral density. Up to 10 per cent of patients relapse, sometimes after an interval of many years.

The morphological spectrum of parathyroid adenomas occurring in heterotopic sites, e.g. mediastinum, thyroid gland or oesophagus, is identical to that in eutopic locations. However, not only may they lead to unsuccessful cervical exploration, they may mimic thyroid gland adenomas or medullary thyroid carcinoma histologically.

Double adenomas may rarely occur (responsible for between 1.7 and 12 per cent of cases of primary hyperparathyroidism) and are usually bilateral. All of the patients are symptomatic and show a higher PTH level and tumour weight compared to solitary adenoma and parathyroid gland hyperplasia. Distinction from asymmetrical parathyroid gland hyperplasia, particularly in the context of MEN, is extremely difficult. The diagnosis is, therefore, only considered conclusive when follow up after removal of two abnormal glands shows no recurrence. Gene-profiling studies indicate that multiple gland neoplasia represents a distinct molecular entity.

Parathyroid gland adenomas occur more frequently in the lower parathyroid glands. The mean weight is 0.55 g, but tumours weighing as much as 53 g are recorded and, generally, the more severe the hypercalcaemia, the bulkier the adenoma. Macroscopically, parathyroid gland adenomas are well margined, soft and vary from yellow-red to orange-brown in colour (Figure 19.44). The oncocytic (oxyphil) cell variant presents a so-called mahogany brown cut surface, characteristic of such mitochondria-rich tumours at many sites. Secondary haemorrhage and/or cystic change (Figure 19.45) may be encountered, either spontaneously occurring or post-FNAC. The remaining, uninvolved parathyroid glands should be normal or reduced in size.

Microscopically, parathyroid gland adenomas are circumscribed and may be lobulated or nodular. They are hypercellular and substantially or completely bereft of intra-glandular adipocytes, with the exception of lipoadenoma. An attenuated, part-circumferential mantle of normal or compressed parathyroid gland tissue is identified in 50 per cent
or so of cases, dependent upon the planes of section examined (Figure 19.46), often near the hilum of the gland. The tumour cells may be disposed in solid sheets, cords, acini, follicles and/or microcysts. Glandular structures may contain eosinophilic colloid-like secretions and these are dPAS-positive but immunonegative for thyroglobulin. Intrafollicular or interstitial amyloid protein may rarely be deposited.

Most adenomas are composed of chief cells, though oncocytic (oxyphil) cells and/or water-clear cells are often present, either dispersed or in nodular aggregates. The chief cells of an adenoma are usually larger than their non-neoplastic counterparts present in the uninvolved rim of parathyroid tissue, where present, and in the remaining, non-neoplastic glands. They also typically possess less intracellular fat than the uninvolved tissue and the other suppressed glands. Mitoses usually number less than one per ten high power fields without abnormal forms. There may be random nuclear pleomorphism and/or multinucleation sometimes with bizarre, hyperchromatic giant cells (Figure 19.47), although in the absence of other indicators of potential malignancy these should not be misconstrued as evidence portending aggressive behaviour. Flow cytometry is of limited assistance in discriminating between parathyroid gland adenoma and carcinoma because aneuploidy is found in up to 25 per cent of histologically and clinically benign tumours.

VARIANTS OF PARATHYROID GLAND ADENOMA

Lipoadenoma (parathyroid hamartoma) is a very rare occurrence showing admixture of parenchymal cells with copious mature adipocytes, the latter accounting for 20–90 per cent of the tumour. Approximately 50 per cent of such
cases are associated with hypercalcaemia. The uninvolved parathyroid glands are normal.

**Papillary variant** is rare and apt to be mistaken for papillary thyroid carcinoma.

**Water-clear adenoma** is substantially or wholly composed of water-clear cells. It may be confused with clear cell neoplasms of the thyroid gland, including metastasis.

**Follicular variant** shows a predominant follicular (acinar) architecture often with intraglandular secretions and may be misinterpreted as a follicular thyroid neoplasm.

**Oxyphil adenoma (oncocytic adenoma)** is composed entirely of mitochondria-rich oncocyic (oxyphil) cells and may or may not be functional. It must be distinguished from nodular oxyphilic cell change with advancing age and, when intrathyroidal, from oxyphil (Hürthle) cell neoplasms of the thyroid gland.

Immunohistochemistry is occasionally valuable in the differential diagnosis between parathyroid gland adenoma and other neoplasms, notably of the thyroid gland. Parathyrocytes are cytokeratin positive and stain for many pan-neuroendocrine markers, both membrane-bound peptide products, such as PTH, chromogranin A, synaptophysin, etc., and cytosol epitopes including neuron specific enolase. Chief cells show nuclear immunoreactivity for TTF-1. Reciprocally negative staining for thyroglobulin may also be helpful. Immunostaining for antimitochondrial antibody highlights oncocytic (oxyphil) differentiation, but in itself does not discriminate between oncocytic parathyroid gland tissue and oncocytic change in other tissues. Staining for fat on frozen section is seldom of diagnostic help.

Molecular genetic studies by X-linked restriction fragment length polymorphism provide evidence for monoclonality in many parathyroid gland adenomas. Tumour-specific DNA alterations are present in the PTH gene in some cases. A minority of cases demonstrate pericentric inversion of chromosome 11, which causes translocation of the cyclin D1 gene with the PTH gene resulting in overexpression of cyclin D1 and cell proliferation. Cyclin D1 expression is identified by immunohistochemistry more frequently than this cyclin D1 gene rearrangement suggesting that other molecular factors are operant in cyclin D1 deregulation. Cyclin D1 is also common in parathyroid hyperplasia and parathyroid carcinoma. The germline mutation underlying MEN 1 is associated with some sporadic parathyroid gland adenomas. The RET proto-oncogene germline mutation underlying MEN 2 does not appear to be involved in the genesis of sporadic parathyroid gland adenomas. Other chromosomal abnormalities are detected by comparative genomic hybridization and fluorescent *in situ* hybridization (FISH) techniques.

**PARATHYROID CARCINOMA**

This is defined as a malignant neoplasm of parathyroid parenchymal cells and is responsible for approximately 0.5 to 2 per cent of all cases of primary hyperparathyroidism, although some series report as high as 5 per cent. It occurs most frequently in the fifth and sixth decades (i.e. roughly a decade younger than adenomas) with no gender predilection. Most patients are severely hypercalcaemic with active bone and renal disease at presentation, they tend to suffer worse symptoms attributable to this compared to those with adenoma and there is more often a palpable neck mass, although this presentation is by no means invariable. Initial designation as adenoma may be revised at a later time following recurrence and/or metastasis.

Parathyroid carcinoma tends to invade local structures, is slow growing and metastasizes late. Complete surgical excision at first operation affords the best opportunity for cure, although this relies upon early recognition of its malignant nature, which cannot always be achieved. Following surgery, approximately 30 per cent of patients suffer local recurrence, usually within three years. Roughly 30 per cent develop metastasis, typically late in its course, generally to regional lymph nodes (30 per cent), lungs (40 per cent), liver (10 per cent) and bone. Survival is 60–85 per cent and 40–70 per cent at five years and ten years, respectively, with an average survival following recurrence of seven to eight years. Non-functioning examples may behave more aggressively than functioning ones. Death is usually attributable to the metabolic complications of hypercalcaemia rather than overwhelming tumour burden. Repeated surgery may palliate and adjuvant radiotherapy has a limited role. The response to chemotherapy is poor. The hypercalcaemia may become refractory to medical management and specialist anti-PTH immunotherapy has proven beneficial in very severe cases (Figure 19.48), occasionally eliciting a direct antitumour effect.

The tumour size is generally larger than that of parathyroid gland adenoma with an average weight between 6.7 and 12 g, although smaller tumours are currently being identified earlier. It may be encapsulated or obviously infiltrative. There may be a soft, brown appearance indistinguishable from adenoma, or a grey-white texture. Troublesome intraoperative dissection, owing to adherence to contiguous structures, should alert the perceptive surgeon to a possibility of malignancy.

Parathyroid carcinomas may be deceptively bland or overtly malignant and anything in between – it is the biological behaviour, however, which ultimately defines parathyroid carcinoma. In rare cases, there may be no histomorphological clues to indicate potential aggressiveness. Nonetheless, first-order morphological criteria of malignancy (absolute criteria) include...
invasion into adjacent tissues and/or histologically documented metastasis. When these are absent or inconclusive, a combination of second-order facultative features (features associated with malignancy), each in themselves not fully diagnostic, are invoked (Table 19.10).

Microscopically, the capsule is often thickened and is classically contiguous with broad internal fibrous septula, dividing the tumour into irregular nodular compartments (this must be differentiated from scarring in an adenoma, secondary to spontaneous infarction, FNAC or previous surgery). Invasion beyond the delimiting capsule (Figure 19.49) may or may not be obvious (and can be mimicked by pseudoinfiltration, sequestration/benign entrapment and/or implantation of benign tissue following rupture of a parathyroid adenoma capsule). Fibrosis and haemosiderin deposition may be encountered in hyperplasia, degenerate adenomas and carcinomas. Pericapsular vascular invasion (Figure 19.50) is virtually diagnostic of malignancy (although artefactual dislodgement of cells simulating tumour embolus must be considered) but is present in only 10 to 15 per cent of cases. Perineural infiltration is also diagnostic of malignancy, but is similarly an uncommon finding. There may be a variety of growth patterns and a trabecular or rosettoid architecture favours malignancy (but is not common and not entirely specific). Diffuse growth of isomorphic cells with elevated nucleus–cytoplasmic ratio is a tocsin (Figure 19.51), as is generalized nuclear pleomorphism (in contrast to focal, random cytonuclear atypia). Macronucleolation may be conspicuous. Areas of coagulative necrosis may be seen (and should not be mistaken for ischaemic damage or haemorrhage). The interpretation of mitoses has proven controversial – mitoses are present in both hyperplasia and adenoma, although generally below one mitosis per ten high power fields (otherwise, mitotic figures may be completely absent in some metastasizing carcinomas and care must be taken to distinguish mitoses in endothelial and other stromal elements from those in tumour cells). The presence of very many mitoses and/or abnormal forms, however, is usually taken as presumptive evidence of malignant potential. There is currently no UICC/AJCC TNM staging classification for parathyroid carcinomas.53

The immunohistochemical proliferation marker Ki67 (MIB-1) is slightly higher in parathyroid carcinoma than adenoma, although there is overlap, with a proliferative index greater than 5 per cent suggestive of malignancy. Ki67 may also help in discriminating genuine mitotic figures from pyknotic nuclei (mitosoid bodies) in equivocal cases.

### Table 19.10 Microscopical criteria for the diagnosis of parathyroid carcinoma.3,49

<table>
<thead>
<tr>
<th>First order criteria</th>
<th>Second order criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of either/or:</td>
<td>In the absence of first order criteria at least two or more of the following:</td>
</tr>
<tr>
<td>1. Invasion into surrounding tissues</td>
<td>1. Capsular invasion</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2. Vascular invasion</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>3. Mitoses &gt; 5 per 10/hpf</td>
</tr>
<tr>
<td>Nerves</td>
<td>4. Broad intraleisional fibrous septa with division into nodules</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>5. Coagulative type necrosis</td>
</tr>
<tr>
<td>2. Histologically documented locoregional or distant metastasis</td>
<td>6. Diffuse growth with elevated nucleus to cytoplasmic ratio</td>
</tr>
<tr>
<td></td>
<td>7. Diffuse cellular atypia</td>
</tr>
<tr>
<td></td>
<td>8. Abundant macronucleoli</td>
</tr>
</tbody>
</table>

Figure 19.49 (a) Whole mount preparation of an oncocyty parathyroid carcinoma in a patient with MEN 2 demonstrating irregular, thick fibrous capsulation contiguous with conspicuous internal fibrous septa. This gland was adherent to surrounding structures at operation and dissected out with some difficulty (H&E stain, ultralow magnification). (b) The edge of another parathyroid carcinoma depicting an irregular, thick peripheral capsule, together with coarse intratumoral fibrous bands separating the expansile tumour nodules. This presents a broad advancing margin with surrounding soft tissues, rather than direct tentacular, permeative infiltration (H&E stain, low magnification).
Galectin-3, cyclin D1, parafibromin, retinoblastoma protein and p27 immunostaining may be of limited assistance. Cytokeratin 14 (CK14) immunoreactivity has been reported as positive in oncocytic (oxyphil) adenomas, but not in oncocytic carcinomas.

An increased incidence of parathyroid carcinoma is reported in some hereditary hyperparathyroidism syndromes. Familial hyperparathyroidism represents a clinically and genetically heterogeneous group of disorders that includes multiple endocrine neoplasia 1 (MEN 1), multiple endocrine neoplasia 2 (MEN 2), familial hypocalciuric hypercalcaemia (FHH), hyperparathyroidism-jaw tumour (HPT-JT) syndrome and familial isolated hyperparathyroidism (FIHP). Parathyroid carcinoma is seen in 10–15 per cent of the autosomal dominant HPT-JT syndrome, but it is exceptionally rare in MEN 1 and MEN 2. Early studies of FIHP suggested an increased risk of parathyroid carcinoma, although the inclusion of some patients with HPT-JT syndrome casts doubt upon this conclusion. There are no reported cases of parathyroid carcinoma with FHH.

**ATYPICAL PARATHYROID GLAND ADENOMA**

Atypical parathyroid gland adenoma (parathyroid neoplasm of uncertain malignant potential or ‘equivocal’) is a diagnostic term attributed to a parathyroid gland tumour, which displays worrisome features, although falls short of fulfilling the first-order criteria for a confident designation of malignancy. This rubric acknowledges the limitations of predicting the behaviour of an individual tumour based upon conventional histomorphological assessment (it is the pathologist, who is uncertain, not the tumour) and it is not proffered as a distinct clinico-pathological entity. Only a small minority of such atypical adenomas are expected to recur and/or metastasize and the rank importance of second-order criteria in quantifying this small risk of more aggressive behaviour has yet to be established.

Atypical parathyroid gland adenomas are generally indistinguishable from adenoma type ordinaire by the unaided eye. The most common microscopical features, ranked according to frequency, however, include intracapsular entrapment (87 per cent), intratumoral fibrosis (75 per cent), haemosiderosis (58 per cent), cyst formation (50 per cent), mitoses (25 per cent) and peritumoral fibrosis (25 per cent). The Ki67 proliferative index typically lies intermediate between adenoma and frank carcinoma. The value of ploidy studies in predicting local recurrence is based upon small studies.

Nonetheless, the use of this terminology serves to highlight those patients who merit closer surveillance, such as regular serum calcium measurements, while avoiding the stigma of a firm label of malignancy, wholly unjustified in most cases.

**OTHER PARATHYROID GLAND TUMOURS**

Paraganglioma may rarely occur at this site. Tumour-like lesions, which may on occasion enter the differential...
diagnosis, include parathyroid cysts, branchiogenic cysts and amyloidosis. Secondary neoplasms may be the result of direct extension from adjacent structures, such as larynx or thyroid, or from distant metastatic disease, most commonly of primary mammary, haematolymphoid, malignant melanoma or bronchopulmonary derivation.

FROZEN SECTION EXAMINATION

Intraoperative frozen section examination of parathyroid gland tissue in cases of hyperparathyroidism is intended to establish the nature of the excised tissue and ascertain whether it is normal or abnormal. Without knowledge of the status of the remaining glands, a more definitive diagnosis of hyperplasia or adenoma (very rarely carcinoma) cannot be proffered. Incisional biopsies render the task more difficult, as do freezing (‘ice crystal’) artefact, other technical constraints and sampling error. The process is inevitably subject to interobserver variation. Some workers advocate routine lipid stains as an adjunct to assessing intracytoplasmic fat, others do not. Oncocytic (oxyphil) cells, however, contain minimal lipid and occasional non-oncocytic hyperplastic and adenomatous parathyroyctes may retain significant lipid content. This notwithstanding, the overall accuracy of frozen section evaluation is extremely high and demonstrates good concordance with subsequent paraffin sections in experienced hands (Figure 19.53). The frozen section diagnosis of parathyroid carcinoma is understandably seldom sustainable, although alerting the surgeon to the possibility may alter peroperative management should there be other suspicious features.

The number of intraoperative frozen section examination requests in many centres has fallen, coincident with the development and refinement of preoperative imaging studies. Minimally invasive parathyroidectomy assisted by

Figure 19.53  (a) The external surface of a fresh parathyroid gland nodule, weighing 1.8 g, sent for intraoperative frozen section examination – see Figure 19.5, for comparison with the appearances of a similar fixed specimen. (b) The same nodule bivalved in the unfixed state to demonstrate ill-defined parenchymal multinodularity. (c) Frozen section histology confirms hypercellular parathyroid gland tissue devoid of intraglandular fat. The entire consultation was completed in less than 5 minutes following receipt of the specimen in the laboratory. The linear striations and folds/rents in the section are artefactual. Without knowledge of the status of the remaining parathyroid glands, this could represent either an adenoma or hyperplasia. This notwithstanding, the findings supported the clinical impression of an adenoma. Subsequent paraffin sections on routinely processed tissue serve as a quality audit (H&E stain, medium magnification).
intraoperative PTH assay has shown promising results and also reduces the burden of frozen section evaluation.

**KEY EVIDENCE**

- Accurate and timely pathological tumour subtyping, tumour grading and tumour staging underpin subsequent effective clinical management of thyroid gland and parathyroid gland neoplasia.
- Morphology remains the gold standard of histocytological diagnosis, increasingly facilitated, but not yet supplanted, by advances in ultrastructural, immunohistochemical, molecular and genetic understanding of normality and disease states.
- Advancement in diagnostic pathology has traditionally evolved along heuristic lines, assimilating observational studies with careful clinicopathologico-radiological and treatment outcome correlation at population and individual case study levels.

**REFERENCES**

9. Cooper DS, Doherty GM, Haugen BR et al. Revised American Thyroid Association management guidelines for carcinomas. Large clinicopathological studies subject to long-term follow up are still required with the anticipation that many of these controversial areas will ultimately be resolved. Until such time, traditional morphological techniques underpin the diagnosis of thyroid cancer.
- The role of ancillary immunohistochemical, molecular and genetic studies in the determination of malignancy of the thyroid gland is evolving and has yet to be fully realized in routine diagnostic practice.
- All patients newly diagnosed with medullary thyroid carcinoma should be offered genetic testing given its association with multiple endocrine neoplasia syndromes.
- The value of perioperative frozen section examination of thyroid gland lesions is disputed among pathologists and surgeons. The indications for such are best agreed by the multidisciplinary team according to local circumstances, preferences and experience.
- Parathyroid carcinoma is rare, slow growing and metastasizes late in its natural history. The diagnosis is predicated upon clinical, biochemical, imaging and pathological criteria.


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What a lot of information, all in shades of grey…

THE THYROID

There have been many advances in imaging in the last decade. Most hospitals now have access to ultrasound equipment with high spatial resolution and colour Doppler. Multislice CT has enabled the acquisition of thin section scans in a 3D data block enabling manipulation of the data to give high resolution images in any plane. Functional imaging using nuclear medicine, and in particular positron emission tomography, can assess tumour metabolism with FDG glucose positron emission tomography (PET) combined with computed tomography (CT) demonstrating areas of increased glucose metabolism with anatomical correlation.

Imaging may be used to assess thyroid morphology and function. There is no single imaging modality available presently that can adequately perform both. Ultrasound (US) is the best technique to use if the texture of the gland needs to be examined. Ultrasound penetrates bone and gas poorly. Retrosternal extension of the gland is therefore better demonstrated by CT or magnetic resonance imaging (MRI). The laryngeal cartilage framework is also poorly penetrated by US and therefore formal staging of a thyroid cancer is better performed by CT which can examine both the neck and chest. CT will however use iodinated contrast agents intravenously. MRI can be used to evaluate the neck and mediastinum with an unenhanced CT performed to stage pulmonary metastatic disease, if an iodine load will affect clinical management. The administration of intravenous iodinated contrast agents will affect radioactive iodine uptake for up to 6 weeks.

US may be used to guide fine needle aspiration of a focal thyroid mass. It can also be used to guide aspiration or biopsy of a suspicious neck node.

Thyroid scintigraphy is most commonly performed using technetium pertechnate or iodine 123 or 131. Nodules that do not take up radio-isotope are termed cold nodules. Those that are equivalent to surrounding thyroid tissue are described as warm and those that take up more radio-isotope than surrounding tissue are described as hot.

NORMAL THYROID

The normal thyroid appears of homogenous even intermediate reflectivity on ultrasound (Figure 20.1a and b). The two lobes of the thyroid can be identified with the bridging isthmus. Small hypoechoic areas which can simulate nodules are seen due to blood vessels. The flow within these structures can readily be delineated by examination using colour or power Doppler.

The thyroid is of higher attenuation than soft tissue on CT, causing it to appear brighter than adjacent muscle (Figure 20.2). This is because the iodine located within the gland has a higher atomic number than soft tissue. Calcium within bone and cartilage, or within a thyroid nodule, has a higher atomic number than iodine and will appear denser than surrounding normal thyroid tissue. The gland will enhance homogenously and thus appear brighter following intravenous contrast.
The normal thyroid on MRI has a signal intensity slightly higher than that of the adjacent strap muscles on T1-weighted sequences and is hyperintense compared to those on T2-weighted sequences (Figure 20.3). Gadolinium-based contrast agents given intravenously will enhance normal thyroid tissue causing it to appear hyperintense to muscle on T1-weighted sequences.

PATHOLOGY

Palpable thyroid nodules are present in 4–10 per cent of the adult population. However, less than 1 per cent of all cancers occur in the thyroid gland. The differentiation of a benign nodule which may require no specific treatment from a malignant nodule presents a diagnostic dilemma. At present, there is no firm consensus as to the correct evaluation of thyroid nodules. Imaging is playing an increasing role in the diagnostic evaluation of patients who either present with a thyroid swelling or with an incidentally discovered thyroid nodule. The increased incidence of neck ultrasound for other conditions has resulted in the increased diagnosis of non-palpable thyroid nodules in patients who are euthyroid and asymptomatic. The diagnostic work-up of these patients presents a particular challenge.

True cysts within the thyroid are uncommon. Cystic change may be seen within benign and malignant conditions. The presence of fluid can be identified readily on ultrasound appearing anechoic. The phenomenon of posterior enhancement will be present which is seen as a band of increased reflectivity behind the fluid containing structure (Figure 20.4). The morphology of a cyst is better demonstrated with US (Figure 20.5) than with CT or MRI. Cystic lesions will appear as areas of low attenuation (dark) on CT and will appear of low SI (dark) on T1W sequences and high signal intensity
(bright) on T2W (Figure 20.3) and STIR scans. Internal structure and wall thickness can be assessed with US (Figure 20.5). Colour flow Doppler may be used to interrogate any soft tissue nodules to try and differentiate between viable tissue and clot or debris (Figure 20.6).

A simple goitre will appear enlarged on ultrasound and may be of homogenous reflectivity but may be diffusely heterogenous and of increased or decreased reflectivity. A multinodular goitre may be generally heterogenous with more focal areas of altered reflectivity due to the nodules (Figure 20.7). These are often hypoechoic compared to adjacent normal thyroid tissue. Cystic change will result in areas of fluid causing regions of anechoic change if the fluid is simple. The presence of colloid causes multiple small foci of increased reflectivity to occur within the cyst which have bright comet tails (Figure 20.8). Haemorrhage can be seen with layering of blood products within the cyst. Colloid and haematoma will not have any abnormal colour blood flow within them. Areas of increased reflectivity can also be identified on US due to the presence of calcification (Figure 20.9) or haemorrhage (Figure 20.6). Calcification can be recognized by the apparent shadowing behind it, seen on US scan (Figure 20.9).

There are no certain ways on imaging of differentiating a benign from a malignant thyroid nodule. Radio-isotope imaging has been used to stratify the likelihood of malignancy with hot nodules being benign in over 90 per cent of cases. These are likely to be due to adenomas or hyperplasia. The risk of cancer in a cold nodule is four times that of a hot nodule but it is still more likely to be a benign lesion.

The role of ultrasound in the assessment of thyroid nodules and cervical lymph nodes to determine the likelihood of malignancy within a thyroid mass is evolving. Several features can be assessed.

**Nodule size**

The size of a nodule should be measured by placing callipers outside of any visible halo (Figure 20.10). Nodule size is not a predictor of malignancy, or of stage of disease. Kang et al. found malignancy in 57 of 198 nodules <1.5 cm and 20 per cent of these cancers were stage III. The lack of
relationship of size to stage was also found in a study that looked at 99 patients undergoing surgery for papillary cancer with primary tumours measuring <1.5 cm. Over one-third of this group of patients had disease outside the thyroid including distant metastatic involvement.

Consistency

Several US features have been shown to be associated with an increased risk of malignancy but none have been shown to be reliable indicators. The feature which has the highest sensitivity is a solid composition. A solid nodule, however, has a fairly low (15.6–27 per cent) chance of being malignant.

Calcification should not be confused with the small reflective foci with posterior comet tail artefact (Figure 20.8) which indicate the presence of colloid. The presence of microcalcifications (Figure 20.11) has the highest positive predictive value of malignancy, of 41.8–94.2 per cent. The sensitivity of this sign is low because microcalcification is only found in 26.1–59.1 per cent of cancers. A predominantly solid (<25 per cent cystic change) nodule containing microcalcification has a 31.6 per cent likelihood of being cancer whereas a predominantly cystic nodule (>75 per cent cystic change) with no calcification has a 1 per cent likelihood of being cancer. Predominantly solid nodules containing coarse calcification (Figure 20.12) are twice as likely to be malignant as those without any calcification. The significance of rim calcification is uncertain.

Number of nodules

More than one nodule is present in many patients. The presence of multiple nodules within the thyroid does not confer benignity. Each nodule should be evaluated on its own
individual US characteristics. A recent paper studied almost 3000 patients who underwent US-guided fine needle aspiration cytology (FNAC). Multiple nodules were biopsied in 360 patients. These authors concluded that the cancer risk is similar for patients with one or two nodules measuring greater than 1 cm and decreases with three or more thyroid nodules.

**Blood flow**

Colour Doppler can be used to assess blood flow in relation to thyroid nodules. Flow which is mainly internal or central is said to increase the chance of a nodule being malignant (Figure 20.13). Flow at the periphery (Figure 20.14) is suggestive of benign pathology. Some authors have suggested a grading system and combine 2D US findings with colour flow Doppler characteristics to identify those nodules that should undergo US-guided FNAC.

**Interval growth**

A rapid increase in size may be due to true growth of a nodule or may be due to haemorrhage or cystic change. Ultrasound can differentiate solid from cystic components within a mass. Both benign and malignant nodules will grow over time but rapid growth of a nodule indicates an increased risk of malignancy. There is, however, no good evidence base to quantify the rate of growth that is significant.

**Abnormal lymph nodes**

Ultrasound can also assess the morphology of cervical lymph nodes. The shape and size of a lymph node can be examined. Lymph nodes with a short axis diameter of more than 7 mm should be regarded with suspicion. The presence of an abnormal texture with loss of the normal reflective hilum, microcalcification, cystic change or abnormal colour Doppler blood flow (Figure 20.15) should prompt US-guided FNAC of that node. Any nodule within the ipsilateral thyroid lobe should also undergo fine needle aspiration. Lymph node metastases may be bigger and more conspicuous than the primary thyroid malignancy.
BENIGN THYROID DISORDERS

Graves’ disease

The thyroid appears diffusely hyper-reflective on US without nodules. An increase in vascularity is seen on Doppler interrogation (Figure 20.16). The gland appears enlarged with avid enhancement on MRI and CT. It is of decreased attenuation (density) on unenhanced CT. It will demonstrate increased tracer uptake.

Toxic multinodular goitre

Nodules and cystic change will result in areas of increased and decreased density on CT and MRI with areas of increased and decreased tracer uptake on radio-isotope studies. The presence of a toxic nodule will result in a single hot spot. Decreased uptake will be seen in the remainder of the gland elsewhere if the nodule is autonomous.

Hashimoto’s thyroiditis

The thyroid may be of normal size or enlarged. Diffuse heterogenous echotexture is present on US. Numerous poorly defined hyporeflective regions separated by fibrous bands may be seen. The presence of large nodules raises the possibility of lymphoma. The gland will appear atrophic and heterogenous due to fibrosis eventually. A heterogenous texture is seen on CT and MRI. There may be areas of increased SI on T2W images.

Riedel’s thyroiditis will give rise to low SI on T1 and T2W MRI images.

Diffuse non-toxic goitre

There is diffuse glandular enlargement with diffuse uniform or irregular reflectivity that may be increased or decreased on US.

Nodular goitre

The presence of cystic change, haemorrhage, necrosis or calcification result in diffuse heterogenous echotexture or in multiple focal nodules of decreased reflectivity. Calcifications appear as discrete areas of increased reflectivity with shadowing behind them. The gland will appear enlarged on CT and may be heterogenous, with the larger nodules seen as individual areas of decreased attenuation. The presence of colloid or haemorrhage will give rise to areas of high signal intensity on T1W MRI (Figure 20.17b) images. Calcification is not seen as well on MRI as on US and CT. The role of imaging in these patients is to demonstrate any significant extension into the mediastinum and the relationship of the goitre to the great vessels (Figure 20.17a and b). Although...
tracheal displacement and compression are clearly seen, they do not appear to necessarily correlate well with the degree of airways obstruction.

**Thyroid neoplasms**

Benign adenoma usually slowly increase in size. A sudden increase is likely to be due to haemorrhage within the lesion. Cystic degeneration is not uncommon.

**THYROID CANCER**

Papillary carcinoma is frequently multifocal and small in size. The primary lesion may therefore result in a multinodular appearance or diffuse alteration in texture or not be seen on imaging. Histologically these tumours may have calcification, haemorrhage or cystic change within them. The presence of psammoma bodies in over one-third of patients results in microcalcification which can be appreciated on US as multiple small hyper-reflective areas similar to colloid but without the comet tail (Figure 20.18). Larger solitary tumours will be appreciated as a solitary nodule. The imaging appearances are therefore variable.

The incidence of nodal metastases at presentation is higher than other thyroid tumours, occurring in up to 50 per cent of patients at presentation. These are also often small in size at presentation but, like the primary tumour, can have areas of cystic change, haemorrhage or calcification within them (Figures 20.15 and 20.18). This enables the diagnosis of a pathological node even if it is within normal size limits. The most common pattern of spread is to nodes within the anterior and posterior cervical chains but spread to the retropharyngeal nodes may be rarely seen and papillary cancer can present as a retropharyngeal/parapharyngeal mass. Metastatic spread to the lungs, bone and brain occurs less commonly.

On CT the primary and involved nodes may be of higher density due to calcification, haemorrhage or colloid (Figure 20.12). They will also enhance more than surrounding soft tissue (Figure 20.19). Cystic change will result in a reduced density. Occasionally, cystic change will result in a thin-walled cystic mass within the neck which may be mistaken for a benign cyst. CT is currently the most sensitive imaging modality for the detection of pulmonary metastases.

On MRI the nodes can have low to intermediate signal intensity on T1- and T2-weighted scans or high signal intensity (Figure 20.20) on both T1- and T2-weighted scans. The latter is thought to reflect high thyroglobulin content. Takashima and colleagues assessed 50 patients with papillary carcinoma of the thyroid, metastatic disease was present in 68 per cent of patients. Using the combined criteria of a cystic node or size of 13 mm or more (short axis

**Figure 20.18** Ultrasound scan demonstrating a small primary papillary cancer within the right lobe of the thyroid (arrow) with a larger nodal deposit (arrow). Both lesions contain small bright foci due to microcalcification.

**Figure 20.19** Contrast-enhanced computed tomography scan demonstrating an abnormal enhancing node involved by papillary thyroid cancer within the tracheo-oesophageal groove.

**Figure 20.20** Magnetic resonance scan demonstrating a small left lobe papillary cancer with enlarged heterogeneous left level IV/V nodes.
diameter) the specificity was 100 per cent, and accuracy of 82 per cent (PPV 100 per cent) but a sensitivity of only 59 per cent. A comparison study between MRI and US for staging papillary cancer was performed prospectively in 14 patients. These authors recommended the use of US as the first staging investigation because it can identify punctuate calcification and small abnormal nodes although both tests failed to identify metastatic nodes in the central group but correctly identified 14 of the 15 nodal groups outside the central group. MRI findings may contain prognostic importance in patients with locally advanced papillary thyroid cancer. Recurrence was seen in 18 of 66 patients. Multivariate analysis determined that MRI findings of tumour size and nodal metastasis were significant independent variables for disease-free survival. MRI has also been shown to be a sensitive and accurate technique for the detection of well-differentiated thyroid cancer, particularly papillary cancer (PPV 86 per cent, accuracy 85 per cent) metastatic to cervical lymph nodes in a retrospective study of 26 patients.

There is no doubt that pathological nodes may be diagnosed with US. Lymph node metastases as small as 2–3 mm can be detected when ultrasonography is performed with a high frequency probe. The majority (81.2 per cent) of malignant nodes in 20 patients with papillary carcinoma were found to be homogenous and hyperechoic (87.5 per cent) compared to adjacent sternomasoid muscle with peripheral punctuate calcification seen in 68.7 per cent. Cystic change seen on US is said to be highly suggestive of papillary thyroid cancer and cystic lymph nodes are well characterized by US and have a thickened outer wall, internal echoes, internal nodularity and septations, but may appear as a simple cyst and thus mimic a branchial cleft cyst in younger patients. Some authors have demonstrated that US can be used in the follow up of patients with thyroid carcinoma, demonstrating that US can reveal occult nodal disease in patients with normal serum thyroglobulin measurements.

A recent analysis of literature concluded that ultrasonography performed by an experienced operator is the most sensitive means of detecting neck recurrences of differentiated thyroid cancer. Some authors recommend the detection of recurrent papillary cell cancer by thyroglobulin assessment in the needle washout after US-guided FNA of suspicious lymph nodes. Preoperative neck US mapping has also been recommended for persistent/recurrent papillary thyroid cancer improving surgical outcomes.

The role of US in the initial staging of patients with differentiated thyroid cancer is not well documented. Some units suggest that neck ultrasonography should be performed routinely in all patients with differentiated thyroid carcinoma at presentation and that the examination should include not only level VI but the ‘at risk’ levels in the lateral compartment (levels III, IV and V). A study performed some years ago concluded that ultrasound was useful for preoperative investigation of thyroid papillary carcinoma but that several limitations existed, especially in evaluating extracapsular extension and regional lymph node metastasis which were underestimated in 48.1 per cent of cases. A more recent study of 590 patients with papillary microcarcinoma concluded that modified radical neck dissection was not necessary in patients without lateral node metastasis detected on US preoperatively and patients with preoperatively detected lateral node metastasis are more likely to develop recurrence in lymph nodes so careful modified neck dissection (MND) should be performed.

**Follicular cancer**

These tumours unlike papillary cancer are usually solitary lesions. On US these tumours may be iso- or hypoechoic compared to adjacent normal thyroid. The margins may be ill defined if there is extensive extracapsular invasion. There are no definite distinguishing features on imaging unless invasion into adjacent structures such as the trachea (Figure 20.21) or larynx can be identified. Vascular invasion may be seen. Lymphatic spread is uncommon, occurring in less than 8 per cent. Distant metastatic spread to lung and bone is more commonly seen. These tumours also concentrate iodine and I may be used to treat and follow up these tumours.

**Recurrent disease**

A rising serum thyroglobulin necessitates investigation of disease recurrence. Initial investigation is performed with a radioiodine scan but tumour de-differentiation may lead to decreased or lost iodine-accumulating ability. FDG PET-CT has emerged as the investigation of choice in patients with a negative radioiodine scan and raised thyroglobulin. Good anatomical imaging does however retain an important role since small volume recurrence may not be demonstrated by FDG PET.

**Medullary cell cancer**

Medullary cell tumours are derived from parafollicular or C-cells which are thought to be derived from neural crest
Many tumours express calcitonin. The tumours themselves and their metastases may calcify. They may invade locally and may spread to regional lymph nodes. Metastatic spread occurs to lungs, bone and liver. Some cases are associated with multiple endocrine neoplasia (MEN) types IIA and IIB. Medullary carcinoma does not concentrate radio-iodine and follow up is by serial serum calcitonin and carcinoembryonic antigen (CEA) measurements. Anatomical imaging is performed if recurrent disease is suspected. These neoplasms may be gallium or thallium avid. Metaiodobenzylguanidine (MIBG) may also be useful. More recently FDG PET has been shown to be useful in the demonstration of recurrent or metastatic disease, with a sensitivity of 70–76 per cent. It has been demonstrated to have a superior sensitivity and specificity compared to indium-111 pentetreotide (SMS), pentavalent technetium-99m dimercaptosuccinic acid (DMSA), technetium-99m sestamibi (MIBI), CT and MRI. Ultrasound has been shown to be superior to other imaging modalities in the detection of primary lesions within the thyroid in gene carriers of MENIIA and familial medullary thyroid cancer (FMTC). Whole body PET-CT is being used to stage metastatic disease.

**Hürthle cell tumour**

These uncommon tumours arise from follicular epithelium. There are no distinguishing imaging features. Both nodal and haematogenous spread occurs. It generally has lower iodine avidity than other differentiated thyroid neoplasms. 18F-FDG PET has been shown to have excellent diagnostic accuracy in Hürthle cell thyroid cancer patients, improving on CT and radio-iodine scintigraphy. Intense 18F-FDG is said to be associated with a worse prognosis.

**Anaplastic carcinoma**

This aggressive and rapidly fatal tumour usually presents in elderly women. They often occur in people with long-standing goitre. They grow rapidly and compress and invade the airways and oesophagus. The primary tumour is usually hyporeflective on US but often contains punctuate calcification and areas of necrosis. Lymph node involvement is common also with nodal necrosis.

**Thyroid lymphoma**

This is an uncommon condition. The thyroid may be the primary site of disease or may be involved secondarily. Patients may have a previous history of Hashimoto's thyroiditis. Tumours are not iodine avid but take up gallium. Presentation is usually with a rapidly enlarging thyroid mass causing symptoms of airway compression and/or dysphagia.
A solitary mass is more commonly seen than multifocal involvement.41

THE PITUITARY

Imaging techniques and normal anatomy

MRI is the optimal technique to image the pituitary. It has several advantages when compared to CT. Multiplanar images can be obtained with the pituitary best visualized in the coronal and sagittal planes. Multislice CT remains the imaging modality of choice in the patients unable to undergo MRI. Reconstructions can then be performed in axial, sagittal and coronal planes.

Scans need to be of high spatial resolution which necessitates thin slices with both CT (1 mm) and MRI (<3 mm). Coronal MRI allows evaluation of the sella and parasellar structures and the sagittal scans (Figure 20.24) demonstrate the midline structures well. T1 WSE MRI scans are the most commonly used. MRI scans are often obtained pre- and post-intravenous paramagnetic contrast agent administration. The intravenous contrast agents enhance areas in which the blood–brain barrier is absent or poorly developed (pituitary gland, infundibulum, median eminence, tuber cinereum and cavernous sinus). Inflammatory processes or tumour may destroy the blood–brain barrier.

The anterior lobe of the pituitary derives from Rathke’s pouch. On T1-weighted MRI it is of intermediate signal intensity similar to white matter. The smaller posterior lobe of the pituitary and pituitary stalk form the neurohypophysis which is derived from a neural downgrowth of the fetal brain. It is usually of high signal intensity on T1-weighted MRI. This is best seen on midline sagittal scans (Figure 20.24). This high signal is related to the concentration of vasopressin stored in the posterior lobe.42, 43, 44 The pars intermedia is a caudal pharyngeal outgrowth which is not well developed in humans but may be present as a small cystic space. The infundibulum or pituitary stalk extends from the mid aspect of the top of the gland towards the median eminence of the hypothalamus traversing the suprasellar cistern. The infundibulum is slightly wider at the hypothalamus and gradually narrows as it joins the pituitary gland (Figure 20.24). The width of the normal infundibulum may increase during pregnancy but should not exceed 4 mm in diameter.45, 46 It should not exceed the diameter of the basilar artery.

The size of the pituitary is variable. The average dimensions in adults are 12 mm in width, 8 mm in anteroposterior diameter and 3–8 mm in height. Normal physiological hypertrophy increases its size in adolescents and pregnant women. At puberty the pituitary gland enlarges and may reach a height of 10 mm in girls and 8 mm in boys.47, 48, 49 In pregnancy the gland increases progressively in size, reaching its maximum dimensions immediately postpartum, reaching up to 12 mm in height.50 The gland returns to normal in the second week postpartum.

The pituitary enhances homogenously following intravenous administration of contrast agent. The adjacent cavernous sinus will also enhance but fast flowing blood in the carotid arteries causes these structures to remain of very low signal intensity pre- and post-contrast (Figure 20.25).

If scans are obtained rapidly following i.v. contrast then the posterior pituitary will be seen to enhance approximately 4 seconds before the infundibulum, with the anterior lobe enhancement occurring 10–15 seconds later.51 This is due to the differing blood supply, the neurohypophysis being supplied by the inferior hypophyseal artery which arises from the cavernous portion of the internal carotid artery. The anterior lobe of the pituitary is supplied from the portal system which is derived from branches of the superior hypophyseal artery. This artery arises more distally from the supraclinoid portion of the internal carotid artery.

PITUITARY TUMOURS

Adenoma

Pituitary adenomas account for 10–15 per cent of all intracranial tumours.45 They are usually tumours of adults and are almost always benign. Tumours measuring less than 1 cm in
size are termed microadenomas (Figure 20.25) and are more of a diagnostic challenge on imaging than macroadenomas (tumours measuring > 10 mm in diameter). Approximately 25 per cent of tumours have no hormone activity. These tumours are usually diagnosed later than secretory lesions and are often diagnosed because they compress adjacent structures such as the optic chiasm producing field defects or the pituitary itself. Extension into the cavernous sinus may give rise to cranial nerve deficits. The presence of cavernous sinus invasion may be difficult to diagnose because the dural reflection of the medial wall of the cavernous sinus is thin, unlike the lateral dural reflection. Cavernous sinus invasion can be inferred if tumour extends to the lateral reflection (Figure 20.26). Asymmetry of the cavernous sinus in association with high prolactin levels has also been shown to be a good indicator of sinus invasion. Narrowing or occlusion of the carotid arteries by tumour is rare. Pituitary adenomas may expand inferiorly to present as a mass within the sphenoid sinus (Figure 20.26). Superior extension rarely causes hydrocephalus from distortion of the third ventricle and obstruction of the foramen of Munro.

An MRI grading system for pituitary adenomas has been suggested by Edal and colleagues. They have added to the Knosp–Steiner classification. They have devised five grades of suprasellar extension: grade 0 – no bulging of the adenoma into the suprasellar space; grade 1 – the adenoma bulges upwards into the suprasellar cistern but without reaching the optic chiasm; grade 2 – it reaches the optic chiasm but without displacing it; grade 3 – the adenoma displaces and usually stretches the chiasm to a variable degree; grade 4 – obstructive hydrocephalus of one or both lateral ventricles caused by tumour extension.

Infrasellar extension is described by three grades. Grade 0 – intact floor of sellar. The inferior contour of the adenoma is smooth and rounded. The floor may be expanded but there is no sign of penetration into the sphenoid sinus. Grade 1 – there is focal bulging of the adenoma as an indirect sign of perforation of the dura and floor of the sella. There may be variable filling of the sphenoid sinus. Grade 2 – tumour penetration beneath the sphenoid sinus to the rhinopharynx and/or forward to the ethmoid area and nasal cavity.

Parasellar extension is graded by these authors using the Knosp–Steiner classification in this a medial tangent – the intercarotid line (a line through the cross-sectional centres of the intercavernous carotid artery) is used to distinguish five grades: grade 0 – the normal condition; grade 1 – tumour extends up to the line; grade 2 – tumour extends to the lateral margin of the carotid artery; grade 3 – tumour extends beyond the lateral margins of the carotid artery; grade 4 – there is total encasement of the intracavernous carotid artery.

Moderate hyperprolactinaemia may be seen from stalk deviation (Figures 20.25 and 20.26) by a non-functioning tumour. Diabetes insipidus occurs very rarely. Prolactin secreting tumours are the most common functioning adenomas. They may cause amenorrhoea, galactorrhoea, infertility, loss of libido or impotence. These signs are more apparent in premenopausal women and these tumours are more likely to present at a smaller size than in men and postmenopausal women. The next most common tumours are those that produce ACTH and growth hormone. Tumours secreting growth hormone cause the clinical syndromes of gigantism in children and acromegaly in adults. ACTH secreting tumours produce Cushing’s disease. There are no imaging features to differentiate between the differing secretory adenomas but ACTH secreting adenomas are on average the smallest of all adenomas with a mean size of 3 mm. The position of the adenoma within the pituitary does to some extent depend upon that of the normal secretory cells with prolactinomas and growth hormone secreting tumours tending to be located laterally, and ACTH, TSH and LH/FSH secreting tumours lying centrally.

The most reliable imaging sign of a pituitary adenoma is a focal area of abnormal signal intensity (Figure 20.25). Pituitary adenomas are typically hypointense compared to the normal pituitary on non-contrast-enhanced T1-weighted images. A small number of lesions are isointense or hyperintense. The presence of high signal intensity within the lesion (Figure 20.27) is thought to be due to old blood within the tumour and occurs in 20–30 per cent of tumours. This is more likely to occur in macroadenomas and in patients...
receiving bromocriptine. Pituitary adenomas may present with symptoms and signs of pituitary apoplexy. Tumours which are hyperintense on T2-weighted images may be soft or partially necrotic. The acquisition of T2-weighted scans does not usually aid in the diagnosis of a microadenoma. There are several secondary and less reliable signs of a pituitary adenoma. The stalk may be deviated away from the side of the tumour (Figure 20.25). However, there have been reports of stalk deviation towards the tumour. The normal pituitary stalk may not lie in the midline and the presence of stalk deviation alone should not be taken to indicate the presence of a pituitary adenoma with almost one-half of patients having MRI of the pituitary having tilt of the pituitary stalk. There may be focal bone erosion if the tumour lies on the inferior aspect of the gland or adjacent to the dorsum sellae or a focal bulge of the superior surface of the gland.

Pituitary adenomas enhance to a lesser degree than the normal pituitary on early post-contrast scans but they may demonstrate increased signal intensity within the tumour on delayed scans making the lesion either isointense or hyperintense compared to the normal pituitary. Imaging following the administration of gadolinium-containing contrast agents has been shown to increase the sensitivity to a small degree with the majority of microadenomas being visible on pre-contrast studies. Contrast-enhanced studies are particularly useful in patients suspected of having an ACTH secreting tumour. Dynamic scanning may diagnose a small number of small lesions not seen pre-contrast or on scans obtained on a routine post-contrast scan and very delayed scans (30–60 minutes post-injection) have been shown to demonstrate otherwise undetectable lesions, with contrast being concentrated within the tumour.

The accuracy of MRI in the detection of pituitary adenomas is difficult to establish with not all patients having surgical correlation and there being a high incidence of small incidental lesions being found in pituitary glands on imaging in asymptomatic patients and at autopsy.

**DIFFERENTIAL DIAGNOSIS**

**Craniopharyngioma**

These tumours are derived from embryonic squamous cell nests of Rathke’s cleft. Most craniopharyngiomas present as a calcific cystic suprasellar mass, only rarely is the mass completely intrasellar. The calcific components of the mass may be difficult to identify on MRI but may have a mottled appearance. The cystic components of the tumour often demonstrate a high signal intensity on T1-weighted images (Figure 20.28) as well as T2-weighted images due to a higher protein content or haemorrhage within the cyst. The solid portions of the lesion are either isointense or hypointense on T1-weighted images and of high signal intensity on T2-weighted scans. The solid components show enhancement following intravenous contrast agents.

**Meningioma**

Meningiomas arising from the parasellar region can project into the sellar turcica and may thus mimic a pituitary adenoma. Intrasellar meningiomas are rare but have been reported. Typically, these lesions appear isointense on T1- and T2-weighted images. They enhance avidly and

---

**Figure 20.27** High signal intensity on this non-contrast magnetic resonance image is due to haemorrhagic products.

**Figure 20.28** Unenhanced sagittal T1W magnetic resonance image of a craniopharyngioma.
homogeneously. A tapered extension of an intracranial dural base or ‘tail’ is suggestive of a meningoma. On CT, hyperostosis of the underlying bone or dense calcification of associated dural structures is also suggestive of meningomas. The pituitary fossa is usually normal in size. The normal pituitary gland may be visible on MRI lying separate to the mass.

Other tumours

Hypothalamic hamartomas can occur in the sella and parasellar areas. Contrast enhancement should not occur in these lesions. Other rare tumours, such as parasellar granular cell tumours including myoblastomas and choristomas and infundibulomas, can present with visual loss and some degree of endocrine dysfunction. These are rare tumours originating from the neurohypophysis.

An important differential diagnosis is that of an aneurysm from the cavernous, infraclinoid or supraclinoid internal carotid artery. These may present signs of visual loss depending upon the location of the aneurysm. They may also extend into the sella and cause direct pituitary compression with resultant endocrine dysfunction. In these cases MRI is more usual than CT since CT cannot reliably distinguish an adenoma from an aneurysm or other pituitary lesion. On MRI the rapid blood flow through the aneurysm lumen causes the phenomenon of ‘flow void’. There may also be heterogeneously increased signal caused by the presence of blood products and calcification within the aneurysm.

THE PARATHYROIDGS

The parathyroid glands are derived from the third (lower pair of parathyroid glands) and fourth (upper pair) pharyngeal pouches. The majority of people have four glands but 25 per cent have more than this. The superior glands are more constant in position, lying along the dorsal aspect of the superior pole of the thyroid laterally near the recurrent laryngeal nerve. The lower glands have more varied positions, lying along the dorsal aspects of the lower poles of the lobes of the thyroid but they can lie further away at the cervicothoracic junction and even within the superior mediastinum. The normal parathyroids are difficult to visualize with US.

The main indication for imaging the parathyroid glands is during the investigation of hyperparathyroidism which is either caused by an adenoma usually affecting one gland, parathyroid hyperplasia in which all glands are involved or parathyroid carcinoma. Primary hyperparathyroidism is caused by an adenoma in 80 per cent, hyperplasia in approximately 20 per cent and carcinoma is rare, occurring in 1 per cent. In many institutions the parathyroids are not routinely imaged before the first surgical exploration. In good hands this will have a success rate of over 90 per cent.

Generally, the abnormal parathyroid gland is of lower reflectivity than the normal thyroid and the echogenic capsule will separate one from the other. Calcification is rare in parathyroid adenomas but may be seen in hyperplastic parathyroid glands and in parathyroid carcinomas. Cystic change may be seen. Most lesions (90 per cent) are hypervascular unless they are small, measuring less than 1 cm in diameter, or show cystic change. US and CT scan demonstrate high sensitivity but low specificity and are not used as the first imaging investigation.

Functional imaging of parathyroid tissue using thallium was introduced in the 1980s but has largely been superceded by the use of 99mTc-labelled isonitriles. The optimum technique at present uses 99mTc-sestamibi with subtraction imaging or washout imaging. A recent systematic review reported the percentage sensitivity (95 per cent confidence intervals) for sestamibi in the identification of solitary adenomas as 88.44 (87.48–89.40), multigland hyperplasia 44.46 (41.13–47.8), double adenomas 29.95 (–2.19 to 62.09), and carcinoma 33. This review does not separate the wash-
out and subtraction techniques. The subtraction technique (Figure 20.30) using $^{99m}$Tc-sestamibi and $^{123}$I allows the recognition of the site to be related to the thyroid tissue when the parathyroid gland is in a normal position in the neck. If there is an equivocal scan then high resolution ultrasound should be used in addition. With ectopic glands, the combined use of single-photon emission computed tomography may then provide anatomical information to enable localization of the functional abnormality. Ultrasound will not identify an ectopic gland located within the mediastinum. In these patients CT (Figure 20.31) or MRI may provide additional information if nuclear medicine investigations are equivocal. In patients who have had surgical exploration by an experienced parathyroid surgeon in a unit with an experienced nuclear medicine team and negative sestamibi imaging, it is reasonable to image the patient with $^{11}$C methionine. It is debatable whether patients with a high likelihood of secondary hyperparathyroidism should be imaged. The only possible justification is when the glands are thought to be ectopic in position. Smaller-volume parathyroid adenomas measuring less than 1 cm, those histologically poor in oxyphils and those in the upper position are less likely to be localized with sestamibi scans.

**CONCLUSION**

The next decade will see the further development of functional and molecular imaging. The use of PET-CT scanners to delineate tumour can potentially lead to more selective targeting and intensification of treatment of head and neck cancer, while reducing critical normal tissue doses. At present, tissue hypoxia may be imaged using MRI giving an insight into the likely susceptibility of tumour to radiotherapy treatment. Novel tracers are being developed such as 19F thymidine (FLT) PET which gives tumour proliferation maps and Cu (II)-diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM), F–MISO PET which can provide tumour hypoxia maps. These developments will lead to treatments being tailored to each patient using imaging to direct individual patient care.

**KEY LEARNING POINTS**

**Normal thyroid**
- No single imaging modality can assess both morphology and function.
- Thyroid nodules are commonly seen on all imaging.
- The management of thyroid nodules remains a challenge.
- Imaging cannot confidently distinguish benign nodules from malignant nodules.

**Thyroid cancer**
- US is used to assess thyroid nodules.
- Magnetic resonance and CT is used to stage known thyroid malignancy.
- PET-CT is emerging as an important investigation for recurrence and possibly in initial staging.

**Pituitary tumours**
- MRI is the investigation of choice for suspected pituitary pathology.
- Deviation of the pituitary stalk does not necessarily imply the presence of a pituitary mass.
- Calcification within a mass may not be visible on MRI.
- Meningioma and craniopharyngioma may mimic a pituitary adenoma.

**The parathyroids**
- US and CT are not used as the first imaging investigation.
- Ectopic glands may be located within the mediastinum.

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Benign thyroid disease

KRISTIEN BOELAERT, LORRAINE M ALBON AND JAYNE A FRANKLYN

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INTRODUCTION

Benign thyroid disease is common with thyroid dysfunction affecting around 2 per cent of women and 0.2 per cent of men in the UK. Hyperthyroidism is a pathological syndrome in which tissue is exposed to excessive amounts of circulating thyroid hormone, leading to a clinical picture of thyrotoxicosis. Hypothyroidism results from insufficient production and secretion of thyroid hormones. Our understanding of the effects of thyroid hormones under physiological circumstances, as well as in pathological conditions, has increased dramatically over the last two centuries and it has become clear that overt thyroid dysfunction is associated with significant morbidity and mortality. Although the evidence suggests that successful treatment of overt thyroid dysfunction significantly improves overall survival, the issue of treating mild or subclinical hypo- and hyperthyroidism remains controversial. In addition to thyroid dysfunction, enlargement of the thyroid gland affects up to 60 per cent of the population, with higher frequencies in women and the elderly. Most patients with thyroid enlargement can be managed conservatively after malignancy is ruled out, the challenge to the clinician being to identify the minority of patients with thyroid cancer who therefore require surgical intervention and additional therapies.

This chapter aims to provide an overview of the current knowledge of the management of patients presenting with thyroid dysfunction or enlargement.

HYPERTHYROIDISM

Epidemiology

In patients with hyperthyroidism, tissues are exposed to excessive amounts of thyroid hormones resulting in thyrotoxicosis. Primary thyrotoxicosis is the most common and results from pathology of the thyroid itself; secondary thyrotoxicosis results from abnormalities in the anterior pituitary gland, the site of thyroid stimulating hormone (TSH) production.

The prevalence of hyperthyroidism, defined as reduced serum TSH concentrations with raised free T4 (fT4) and free T3 (fT3) concentrations is about 2 per cent in the female UK population. The annual incidence is 0.8/1000 per year in women; much lower incidence rates are observed in men. Additionally, subclinical hyperthyroidism, defined as serum TSH concentrations below the normal reference range with normal concentrations of fT4 and fT3, is even more common. A UK survey of 1210 subjects aged over 60 years registered with a single general practice, indicated that 6.3 per cent of women and 5.5 per cent of men in the UK had low TSH levels. In the US, investigators noted hyperthyroidism in 0.5 per cent of randomly selected individuals, with subclinical disease evident in 0.8 per cent of subjects rising to 3 per cent in those aged over 80 years.
Aetiology

Hyperthyroidism has many causes. Graves' disease, an autoimmune condition caused by stimulation by antibodies directed against the TSH receptor, is the cause in most patients. The development of one or more autonomously functioning thyroid nodules that produce excessive amounts of thyroid hormones is also a common problem. Various forms of thyroiditis or thyroidal inflammation are less common but clinically important. A number of other conditions can result in hyperthyroidism and are displayed in Table 21.1. Most of these conditions have specific pathophysiological features, clinical presentation and treatment strategies.

Clinical features

The diverse effects of thyroid hormones account for the numerous and varied symptoms of hyperthyroidism. Although there is a rough correlation between the severity of symptoms and circulating amounts of thyroid hormone, patients often have greatly differing symptoms, especially elderly individuals who often have no symptoms whatsoever. In the most extreme case, this absence of symptoms has been termed apathetic or masked thyrotoxicosis.

Typical symptoms of hyperthyroidism indicate the action of excess thyroid hormone in the cell, as well as enhanced β-adrenergic activity. Patients usually have fatigue, nervousness or anxiety, tremor, weight loss, palpitations and heat sensitivity. Women may have irregular menses and decreased fertility, although frank amenorrhoea is rare. Men also can have reduced libido and sometimes painful gynaecomastia.

Clinical findings include tachycardia, warm moist skin, the presence of an enlarged thyroid and a slight tremor. Less frequent neurological findings include poor concentration and personality changes. Elderly individuals have less obvious symptoms and signs than younger patients, including a lower frequency of goitre and a higher prevalence of cardiac manifestations such as atrial fibrillation (AF), and more rarely congestive cardiac failure. About 15 per cent of elderly individuals with new onset AF have thyrotoxicosis. Conversely, a high proportion (as many as 25–35 per cent) of elderly people with thyrotoxicosis will develop AF that is resistant to treatment until the underlying thyroid disorder has been corrected. Classical symptoms and signs may not be present in all patients and the elderly in particular may present atypically. A low threshold for performing thyroid function tests is therefore appropriate.

Other indicators of hyperthyroidism include osteoporosis, hypercalcaemia, congestive cardiac failure, shortness of breath, muscle weakness, anxiety or amenorrhoea. There may be symptoms and signs suggestive of ophthalmopathy and a goitre may be present. Hyperthyroidism may also present as thyroid storm, a life-threatening situation with signs including tachycardia, AF, congestive cardiac failure, hyperpyrexia, agitation, psychosis or coma. This syndrome

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<th>Causes of hyperthyroidism</th>
<th>Pathophysiological features</th>
<th>Frequency</th>
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<td>Circulating thyroid stimulators</td>
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<td>Graves' disease</td>
<td>Thyroid stimulating immunoglobulins</td>
<td>Common</td>
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<tr>
<td>TSH secreting tumour</td>
<td>Pituitary adenoma</td>
<td>Rare</td>
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<tr>
<td>Hyperemesis gravidarum</td>
<td>Human chorionic gonadotrophin (HCG) secretion</td>
<td>Uncommon</td>
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<tr>
<td>Choriocarcinoma</td>
<td>Human chorionic gonadotrophin (HCG) secretion</td>
<td>Rare</td>
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<td>Thyroidal autonomy</td>
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<td>Toxic multinodular goitre</td>
<td>Activating mutations in the TSH receptor or G proteins</td>
<td>Common</td>
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<tr>
<td>Toxic solitary adenoma</td>
<td>Activating mutations in the TSH receptor or G proteins</td>
<td>Common</td>
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<td>Destruction of thyroid follicles (thyroiditis)</td>
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<td>Subacute thyroiditis</td>
<td>Probable viral infection</td>
<td>Uncommon</td>
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<td>Postpartum thyroiditis</td>
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<td>Drug (amiodarone) induced thyroiditis</td>
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<td>Uncommon</td>
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<tr>
<td>Acute (infectious) thyroiditis</td>
<td>Thyroid infection (bacterial, fungal, etc.)</td>
<td>Uncommon</td>
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<tr>
<td>Exogenous thyroid hormone</td>
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<tr>
<td>Iatrogenic</td>
<td>Excess ingestion of thyroid hormone</td>
<td>Common</td>
</tr>
<tr>
<td>Factitious</td>
<td>Excess ingestion of thyroid hormone</td>
<td>Rare</td>
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<tr>
<td>Ectopic thyroid tissue</td>
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<tr>
<td>Struma ovarii</td>
<td>Ovarian teratoma containing thyroid tissue</td>
<td>Rare</td>
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<tr>
<td>Metastatic follicular thyroid cancer</td>
<td>Large tumour mass capable of secreting thyroid hormone autonomously</td>
<td>Rare</td>
</tr>
<tr>
<td>Other</td>
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<td></td>
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<tr>
<td>Pituitary resistance to thyroid hormone (RTH)</td>
<td>Mutated thyroid hormone β receptor with greater expression in the pituitary compared with peripheral tissues</td>
<td>Rare</td>
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typically occurs after a precipitating event, such as trauma, childbirth, infection or surgery, in a known hyperthyroid subject, but may also arise in patients not previously diagnosed with thyroid disease. Thus, the diagnosis of thyrotoxicosis should always be considered in any patient with fever and altered mental status.¹

**Diagnosis of hyperthyroidism**

**LABORATORY DIAGNOSIS**

The single most important test is the measurement of serum TSH concentration. If this is within the normal range, then hyperthyroidism can be ruled out. The exceptions to this rule are very rare pituitary causes of thyrotoxicosis such as TSH-oma or syndromes of thyroid hormone resistance. In these cases, there may be a modest rise in TSH accompanied by a rise in fT3 and fT4.

A low TSH is not specific for thyrotoxicosis and ‘non-thyroidal’ illness or treatment with a variety of drugs may lower the TSH below the normal range, although it is still usually detectable in these circumstances. For these reasons, it is preferable to measure the TSH in conjunction with serum fT4 and, in specific cases, fT3 as well.

In most cases of hyperthyroidism, the typical picture is of undetectable serum TSH with elevated serum concentrations of fT4 and fT3. A low TSH and normal fT4 should prompt fT3 measurement as 10 per cent of cases of thyrotoxicosis are so called ‘T3 toxicosis’, with a rise in fT3 alone. This is most commonly seen in mild cases of toxic nodular hyperthyroidism or early in relapse of Graves’ disease.² It should be noted that not all laboratories perform T3 assays unless specifically requested.

Patients with hyperthyroidism often have non-specific changes in commonly requested laboratory tests. Indices of liver function are slightly raised in a minority of patients. Hypercalcaemia is present in about 10 per cent of patients, because of increased bone turnover and subsequent suppression of parathyroid hormone in serum.¹ Table 21.2 details the laboratory abnormalities found in thyrotoxicosis.

**Table 21.2** Laboratory investigations in suspected thyrotoxicosis

<table>
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<tr>
<th>Thyroid function tests</th>
<th>Elevated free T4 and/or free T3</th>
<th>Suppressed TSH</th>
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<tr>
<td>Immunology</td>
<td>Positive thyroid autoantibodies</td>
<td>Elevated alkaline phosphatase</td>
<td>Elevated calcium</td>
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<td>Biochemistry</td>
<td>Elevated calcium</td>
<td>Normal chromic normocytic anaemia</td>
<td>Long standing cases</td>
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<tr>
<td>Haematology</td>
<td>Raised ESR</td>
<td>Subacute thyroiditis</td>
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**THYROID SCINTIGRAPHY**

The 24 h radioactive iodine uptake is a measure of the iodine avidity of the thyroid gland. In most hyperthyroid states, including Graves’ disease, toxic multinodular goitre and toxic adenoma, the results are at the higher end of normal or raised. However, the test lacks specificity, since values can be high in individuals with normal thyroids and with iodine deficiency or in hypothyroid patients with Hashimoto’s thyroiditis. Also, thyroid scintigraphy lacks sensitivity because low values are seen in the various forms of destructive thyroiditis that cause hyperthyroidism (subacute and postpartum thyroiditis), as well as in hyperthyroid patients exposed to pharmacological doses of iodine. In some cases where the aetiology of thyroid hyperfunction is unclear, diagnosis can be aided by the use of scintigraphy. This imaging modality can be used to differentiate between ‘hot’ and ‘cold’ areas of increased and decreased function, respectively. There are specific scintigraphic appearances associated with different conditions (Figure 21.1).

**Graves' disease**

In iodine replete parts of the world, Graves’ disease is the most common cause of thyrotoxicosis. It is defined as a syndrome consisting of hyperthyroidism, moderate goitre, ophthalmopathy and dermopathy. In many patients, hyperthyroidism and goitre are the only features. It is more common in women than men (ratio 5:1), men are often affected later and the disease may be more severe. Its peak incidence is in the 20s and 30s, but it can occur at any age, although is uncommon before puberty. Graves' disease is more common in smokers (whose risk of the disease is almost doubled) and smoking is an even stronger risk factor for the development of thyroid eye disease.¹³

**PATHOGENESIS**

Graves’ disease is an autoimmune disorder characterized by antibodies in the circulation that are directed against the TSH receptor. These antibodies mimic the effects of pituitary TSH, thereby stimulating thyroid growth and function. Whether the disease is triggered by abnormal clones of auto-reactive T cells, or abnormal antigen presentation by thyroid follicular cells, either independently or in response to cytokines released by infiltrating T cells, is uncertain.¹³ The cause of Graves’ ophthalmopathy and dermopathy is also unknown, but cross-reactivity between thyroidal antigens and antigens in orbital and extra-orbital tissues (especially preadipocyte fibroblasts) is a strong possibility. The TSH receptor is a strong candidate, since it seems to be expressed in connective tissues in the orbit and elsewhere.¹⁴,¹⁵ A concordance rate of only 20 per cent in monozygotic twins indicates that environmental factors trigger the development of Graves’ disease in genetically susceptible individuals. These factors include life stresses,¹⁶ sex steroids, smoking,¹⁷ dietary iodine intake and immune modulators such as interferon α.¹⁸

**CLINICAL MANIFESTATIONS AND NATURAL HISTORY**

Although Graves’ disease can occur rapidly over a few weeks, in most the onset is gradual and insidious. Patients exhibit
many typical features of thyrotoxicosis and may have ‘extra-thyroidal’ signs that are not seen in other forms of thyrotoxicosis. A diffuse goitre is present in the majority of cases but the thyroid may be of normal size in around 3 per cent.1, 13 The goitre is usually symmetrical; there may be an overlying palpable thrill and a bruit may often be heard. The thrill and bruit result from the increased blood flow to the thyroid.1, 13

Graves’ disease is usually treated with anti-thyroid medication in the first instance. During the administration of adequate therapy, the disease may be quiescent but may return if compliance diminishes or dosage is inappropriately reduced. As with many autoimmune conditions, Graves’ disease is sometimes self-limiting and around 30 per cent of patients experience lasting remission after treatment.
EXTRA-THYROIDAL MANIFESTATIONS OF GRAVES’ DISEASE

Ophthalmopathy

Many patients with Graves’ disease have involvement of the eyes. Clinically evident ophthalmopathy occurs in about 50 per cent of patients, in 75 per cent of whom the eye signs appear within a year before or after the diagnosis of hyperthyroidism\(^\text{13}\) (Figure 21.2). However, imaging studies reveal evidence of ophthalmopathy, in the form of enlarged extraocular muscles in most patients without clinical signs.\(^\text{19}\) Patients who smoke are more likely to suffer eye disease of greater severity that non-smokers and hypothyroidism may exacerbate it.\(^\text{20}\) About 90 per cent of patients with ophthalmopathy have hyperthyroidism;
The remainder have autoimmune hypothyroidism or are euthyroid at presentation. The ophthalmopathy is characterized initially by swelling of the extraocular muscles, proliferation of periorbital fat and later fibrosis leading to muscle tethering. The lesions develop due to an accumulation of glycosaminoglycans and a lymphocytic infiltration of the orbital and retro-orbital tissues. The most frequent signs of ophthalmopathy (Box 21.1) are eyelid retraction or lid lag and periorbital oedema. Although a minor degree of eyelid retraction (1–2 mm) may be due to sympathetic overactivity, and can occur in patients with any type of hyperthyroidism, more marked retraction is likely to be due to Graves’ ophthalmopathy. Exophthalmos (proptosis) occurs in up to a third of patients and diplopia occurs in 5–10 per cent. Compression of the optic nerve at the apex of the orbit may cause visual loss but is rare.

Clinicians can estimate the activity and severity of thyroid eye disease using an internationally accepted scoring system. The criteria used in the most widely accepted scoring system from the European Group on Graves’ Orbitopathy (EUGOGO) is displayed in Box 21.2. Decreasing visual acuity and a loss of colour vision are ominous signs and may be caused by pressure on the optic nerve by the swollen extraocular rectus muscles or – less commonly – sheer stretch of the optic nerve. Urgent treatment is needed if permanent visual loss is to be avoided. Box 21.3 lists the indications for urgent ophthalmology referral.

Mild to moderate ophthalmopathy often improves spontaneously, and only simple measures are needed. Severe ophthalmopathy, in particular impaired vision, improves in about two-thirds of patients who are treated with high doses of glucocorticoids, orbital irradiation or both. Orbital decompression is effective in patients with optic neuropathy and exophthalmos, either as the initial treatment or after the failure of glucocorticoid treatment. The place of other medical treatments is unclear. Box 21.4 summarizes the treatment of Graves’ ophthalmopathy.

Dermopathy

This occurs in about 1–2 per cent of patients with Graves’ disease, almost always accompanied by severe eye disease. Usually occurring as a localized area of indurated non-pitting oedema over the skin of the shins and known as pretibial myxoedema, it may affect other areas of the body and areas of trauma. The skin appears raised, oedematous, nodular and discoloured with a pink or brownish tinge. Dermopathy is characterized by lymphocytic infiltration of the dermis, the accumulation of glycosaminoglycans and oedema (Figure 21.3).
Acropachy
This is very rare, occurring in fewer than 1 per 1000 patients and presents as clubbing of the fingers with sub-periosteal new bone formation seen on plain x-ray. Again, thought to arise from glycosaminoglycan accumulation, it occurs in conjunction with ophthalmopathy or dermopathy. There is no treatment.

LABORATORY DIAGNOSIS
In most patients with Graves’ disease, serum fT3 and fT4 are raised and serum TSH is undetectable. The 24-hour radioiodine uptake test usually indicates raised values, but is usually not needed to make the diagnosis. Three thyroid autoantibodies may be measured in clinical practice, those against thyroid peroxidase (TPO), thyroglobulin and the TSH-receptor. In a study of the prevalence and usefulness of thyroid autoantibodies, TPO antibodies were positive in 90 per cent of cases of Graves’ disease, thyroglobulin antibodies in 49 per cent, while TSH-R antibodies were found only in 45 per cent. Thyroid peroxidase antibodies are thus the most commonly measured antibodies in UK clinical practice.

Toxic multinodular goitre
A toxic multinodular goitre is a thyroid gland that has at least two autonomously functioning thyroid nodules that secrete excess thyroid hormone, producing typical signs and symptoms of hyperthyroidism. Most patients in the UK are more than 50 years old, although the condition is much more frequent in younger age groups in other parts of the world because of iodine deficiency. The exact cause of multinodular goitre is not known, but is probably related to mutations in individual cells that lead to clonal expansion of individual nodules with autonomous thyroid function. Due to the long natural history, an elderly patient presenting with a toxic multinodular goitre may describe the presence of the goitre many years before the thyrotoxicosis develops. In patients with underlying non-toxic multinodular goitre, pharmacological doses of iodine (e.g. from iodinated contrast agents), can lead to hyperthyroidism (iodine-induced hyperthyroidism or Jod–Basedow effect). This type of hyperthyroidism is common in areas of the world with iodine deficiency.

Patients with toxic multinodular goitre present with typical signs and symptoms of hyperthyroidism, although they may not all be present since the degree of thyroid hyperfunction is typically less marked in these subjects. It is the cardiovascular effects that predominate and these include palpitations, AF and other tachyarrhythmias. Most patients will have a goitre and multiple nodules may be palpable. Subclinical hyperthyroidism is often recorded. Compressive symptoms such as dysphagia, dyspnoea and neck pressure may occur.

Solitary toxic thyroid nodules
Solitary autonomous thyroid nodules that produce enough thyroid hormones to suppress the secretion of TSH from the...
pituitary, with consequent suppression of the contralateral thyroid lobe are called toxic nodules. They usually grow to least 3 cm in diameter before they result in overt hyperthyroidism and accounts for only around 5 per cent of cases with hyperthyroidism.\textsuperscript{33} Autonomous function has been linked to activating mutations in the thyroid receptor,\textsuperscript{34} or further downstream in the stimulatory G protein pathway linked to cyclic AMP production.\textsuperscript{35}

The frequency increases with age, and they are more common in women. Often, subclinical hyperthyroidism is evident on biochemical testing.\textsuperscript{36} Radionuclide scanning typically shows a focus of isotope accumulation with no uptake in other areas of the thyroid (Figure 21.1c).

### Treatment of hyperthyroidism

The initial approach to the hyperthyroid patient is to minimize symptoms (often with a beta-adrenergic blocking drug) and to reduce the synthesis of thyroid hormones. Three modalities of treatment exist: drug therapy, radioiodine treatment and surgery. The advantages and disadvantages of the various treatment modalities are summarized in Table 21.3. The selection of treatment depends on many factors, including the underlying aetiology, the preferences of patients and clinicians, availability of a skilled surgeon, cost and local restrictions on the use of radioisotopes.\textsuperscript{1} All three treatment modalities are associated with similar improvements in quality of life and satisfaction for patients,\textsuperscript{37} and are equally effective.\textsuperscript{38} Overt hyperthyroidism always needs treatment to avoid subsequent cardiovascular, skeletal or psychological secondary effects.

#### Table 21.3 Advantages and disadvantages of the different treatment modalities for thyrotoxicosis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thionamides</td>
<td>Rapid symptom relief</td>
<td>Risk of severe side effects</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Frequent clinic visits</td>
</tr>
<tr>
<td></td>
<td>Chance of remission</td>
<td>Common mild side effects</td>
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<td></td>
<td>No exposure to radioactivity</td>
<td>Long course of treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High chance of relapse</td>
</tr>
<tr>
<td>Radioiodine</td>
<td>Definitive treatment</td>
<td>Risk of hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Outpatient procedure</td>
<td>Radiation protection measures</td>
</tr>
<tr>
<td>Surgery</td>
<td>Definitive treatment</td>
<td>Radiation thyroiditis</td>
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</table>

**ANTI-THYROID DRUGS**

The thionamides (carbimazole and propylthiouracil) represent the mainstay of drug treatment of thyrotoxicosis in the UK. They disrupt the thyroid’s incorporation of iodine and thus control thyroid hormone synthesis. Carbimazole has a faster effect than propylthiouracil (PTU)\textsuperscript{39} and is given once daily, leading to better compliance.\textsuperscript{40} In general, PTU should only be used if patients develop adverse reactions to carbimazole or during the first trimester of pregnancy (including in women trying to become pregnant).

Patients should be started on treatment after diagnosis of hyperthyroidism is made and while awaiting specialist advice. All patients diagnosed with hyperthyroidism should be referred to a specialist.\textsuperscript{31} The starting dose of carbimazole should be 20 mg daily in a single dose, except in severe disease (i.e. $tT3$ and $tT4$ levels more than twice the upper limit of the normal reference range), when treatment should start at 30 mg daily. PTU is given in divided doses and 200 mg of PTU is approximately equivalent to 20 mg carbimazole. In general, after treatment with either drug, values of $tT4$ and $tT3$ gradually decrease to normal values over 4–6 weeks.

If a diagnosis of Graves’ disease has been established, then the patient may be offered a full course of thionamide therapy in the hope of inducing remission. Optimal duration of treatment is 12–18 months\textsuperscript{42, 43} and drug doses are titrated according to the serum concentration of $tT4$. This should be measured regularly, ideally every 4–6 weeks initially, then 8–12-weekly once control is achieved. Most patients require a maintenance dose of 5–10 mg carbimazole and 50–100 mg PTU. Larger dose requirements are suggestive of poor compliance. Thionamides do not induce remission or cure of thyrotoxicosis that is due to nodular disease. They may be used in the short term to induce euthyroidism prior to proceeding to definitive treatment with radioiodine or surgery.

Although most clinicians use thionamides alone to treat Graves’ disease, some prefer the ‘block and replace’ regimen which uses thionamides to completely block endogenous thyroid hormone production which is then replaced with thyroxine. There is no substantial evidence that the block and replace approach has any advantages in terms of remission of Graves’ disease. There is clear evidence for increased side effects (some serious), which are probably related to the higher doses of thionamides required.\textsuperscript{44}

Remission rates with thionamide drugs are less than 50 per cent, although they may be slightly higher in the elderly.\textsuperscript{38, 45} Relapse usually occurs within 3–6 months of thionamide withdrawal, in which case patients should be offered definitive treatment. Retrospective and prospective data indicate that a number of factors are associated with a poor prognosis although age, gender and goitre size appear to be the most important predictors (Box 21.5).\textsuperscript{1, 45} Once remission has been achieved, cure is likely if the patient remains euthyroid for six months, although relapse may occur after several years.\textsuperscript{46}

Side effects can occur with both carbimazole and PTU; mild side effects occur in 1–5 per cent of patients. The most common side effects are pruritic eruptions, fever, gastro-intestinal upset and arthralgias. Occasionally, the rash necessitates a swap from one drug to the other and cross-reactivity in this context is typically not a problem.\textsuperscript{1}
Propylthiouracil. Cholestatic and hepatitic forms of liver bodies in the circulation occurs mainly in patients receiving Vasculitis associated with anti-cytoplasmic neutrophil antibodies in the circulation occurs mainly in patients receiving propylthiouracil-induced liver failure and this drug is now no longer recommended as first-line treatment, except in specific circumstances. Agranulocytosis, along with hepatitis and vasculitis, are absolute contraindications to the further use of thionamides.

β-adrenergic blockers (e.g. propranolol 40 mg twice daily) are useful adjuncts to thionamides in the treatment of thyroid hormone excess. They act promptly to reduce symptoms such as tremor, palpitation and tachycardia and reduce the risk of tachyarrhythmias. They should be used cautiously in the elderly where heart failure may be present.

In patients who develop AF, anticoagulation with warfarin should be considered due to the risk of embolic complications. There have been no controlled trials of the use of anticoagulants in thyrotoxic AF, but overwhelming evidence of their efficacy in other settings argues in favour of their use unless clear contraindications exist. Approximately half of those with thyrotoxic AF will revert spontaneously to sinus rhythm; this typically occurs within three months of initiation of anti-thyroid therapy. For those who remain in AF, joint cardiological management involving specific therapy to restore sinus rhythm may be considered when the patient is euthyroid.

**Radioiodine (131I) Treatment**

Radioiodine is the treatment of choice for relapsed Graves’ disease and toxic nodular hyperthyroidism and is increasingly used as first-line therapy in Graves’ disease. Additionally, 131I treatment is used in the treatment of autonomous thyroid nodules and to induce shrinkage of benign goitres. Radioiodine is administered orally as sodium 131I in a single capsule in the outpatient setting. It is incorporated into thyroid tissue and the β-emissions result in lasting thyroid tissue damage. There is a lag effect with the maximum thyroid ablation occurring over 6 weeks to four months. Depending on the administered dose, 50–85 per cent of patients achieve euthyroidism and shrinkage of goitre around two months after therapy. Fifteen to 20 per cent of patients require a second or (rarely) third dose, given 6–12 months after initial treatment.

Many studies have shown 131I treatment to be safe and cost-effective and in terms of cancer (a concern for many patients), long-term safety has been well demonstrated. National radiation protection policies exist and include measures to avoid contamination of the home or work place with 131I including avoidance of close contact with small children, avoiding sharing utensils and sleeping alone. Although there is no national consensus regarding the most appropriate dose of radioiodine, most centres will administer a fixed dose of 400–600 MBq, which is large enough to induce cure in the majority of patients. Permanent hypothyroidism results in most patients, though this may be many years later; the incidence of 131I-induced hypothyroidism is dose dependent.

Unless the hyperthyroidism is very mild, patients should receive pretreatment with anti-thyroid drugs and 131I treatment is given when biochemical euthyroidism is restored. Thionamides are often restarted temporarily following 131I therapy to avoid exacerbation of hyperthyroidism due to radiation-related thyroiditis. The frequency of this complication is low but pretreatment to lower thyroid hormone concentrations is advisable in the elderly and those with cardiac disease. If pretreatment is necessary then carbimazole may be preferable to propylthiouracil, as there is some evidence to suggest that there is a higher failure rate of a given dose of radioiodine in patients receiving PTU around the time of 131I therapy. Whichever thionamide is used, the drug must be discontinued 1 week before radioiodine administration to allow maximum uptake into the gland. Success rates fall from over 90 per cent to under 50 per cent if the drug is continued at the time of radioiodine administration. Most centres advise discontinuing thionamides for a week before radioiodine is given and many recommend that the drug is restarted afterwards.

Following 131I administration, patients should have 4–6-weekly TSH and fT4 measurements. If biochemical hyperthyroidism persists after a six month period, it is likely that a further dose of radioiodine will be necessary. Those treated with low-dose radioiodine, males, those with severe hyperthyroidism and those with a medium to large goitre are less likely to be cured after a single dose of 131I. All patients who have received radioiodine require long-term biochemical follow up with an annual serum TSH measurement. Effectively achieved with a computerized recall system, this is essential as the incidence of hypothyroidism is significant many years after treatment with radioiodine and eventually up to 90 per cent may become hypothyroid.

Radioiodine may worsen ophthalmopathy, especially in smokers, and adjunctive treatment with corticosteroids may ameliorate or even prevent this. Most physicians delay administration of radioiodine until moderate or severe eye disease has been stable for 12 months. Those with mild eye disease are given radioiodine at the same time as a course of steroid prophylaxis.
Although most experts agree that surgery has little part to play in the initial management of thyrotoxicosis, there are instances where total thyroidectomy is a safe and effective treatment for thyroid over-activity. These include patient preference (often relating to radiation protection issues), poor response to anti-thyroid drugs, especially in pregnancy; presence of a very large goitre and presence of a coexisting potentially malignant lesion. Surgery should be performed by a skilled surgeon; complications include bleeding, infection as well as transient or permanent hypoparathyroidism and recurrent laryngeal nerve damage which occurs in 1–2 per cent of patients.

Thyroiditis

Thyroiditis refers to any inflammatory condition of the thyroid.1 The classification of thyroiditis is confusing but may be divided into those processes in which pain and tenderness develop, and those which do not have pain as a predominant feature (Box 21.6). Generally, the former rarely result in permanent hypothyroidism, but the latter often do.

Subacute thyroiditis is probably caused by a viral infection.65 Patients present with systemic symptoms, including malaise, fever and thyroidal pain, as well as tremor and heat intolerance. The thyroid gland is usually extremely tender, firm and irregular. Laboratory tests show raised inflammatory markers (ESR, CRP) and initial thyroid function tests show thyrotoxicosis with a suppressed TSH and an elevated serum T4. After 12–16 weeks, there may be a hypothyroid phase during which the damaged tissue is unable to generate thyroid hormone following which euthyroidism is generally restored.66 The course of serum TSH concentrations during subacute thyroiditis is shown in Figure 21.4. Radioactive iodine uptake is low, indicating damage to the thyroid gland. Treatment of subacute thyroiditis is supportive and includes the use of aspirin and other non-steroidal anti-inflammatory drugs. β-adrenergic blockers are useful if symptomatic in the thyrotoxic phase, but anti-thyroid drugs per se are not indicated. Permanent thyroid damage and recurrences are rare.

Subclinical hyperthyroidism

This is essentially a biochemical diagnosis consisting of low or undetectable serum TSH concentration with a normal serum fT4 and fT3 concentration. Subclinical hyperthyroidism may be exogenous as a consequence of treatment with thyroxine, or endogenous as a result of nodular thyroid disease or undetected early Graves’ disease. Exogenous subclinical hyperthyroidism is by far the most common with over 20 per cent of patients on thyroxine having low TSH values on at least one occasion.67 Potential complications of subclinical hyperthyroidism include an increased risk of AF and cardiovascular disease and loss of bone mineral density. Evidence that subclinical hyperthyroidism is a risk factor for AF is clear; indeed it has been suggested that those aged over 60 with an undetectable TSH have a three-fold increase in relative risk.68 Low TSH appears to affect long-term survival, since in the elderly population an increased mortality due to cardiovascular causes can be predicted by a single low TSH measurement.69 There is evidence that subclinical hyperthyroidism is associated with osteoporosis, especially in post-menopausal women,70 but clear evidence for an increased risk of fracture is lacking.71

The treatment of subclinical hyperthyroidism remains controversial. The increasing evidence for associated morbidity and mortality, especially in terms of cardiovascular risk, has lent support to the view that anti-thyroid treatment should be considered in those with persistent suppression of TSH and evidence for underlying thyroid disease (nodular thyroid disease or Graves’ disease), especially if associated with AF or known cardiac disease.72, 73 Crucial evidence for a beneficial effect of such treatment, i.e. reduction in AF incidence or vascular mortality in those with subclinical hyperthyroidism, awaits the results of randomized controlled clinical trials.74
Practically, it is sensible to repeat thyroid function tests on a six-monthly basis in those who have endogenous sub-clinical hyperthyroidism. Where AF and osteoporosis may have been exacerbated by excess thyroid hormone, treatment is prudent. As these patients are usually elderly, radioiodine is the treatment of choice unless contraindications exist.

HYPOTHYROIDISM

Epidemiology

Hypothyroidism results from insufficient production and secretion of thyroid hormones. This is most commonly due to disturbance within the thyroid gland itself, (primary hypothyroidism) or within the hypothalamic-pituitary-thyroid axis (secondary hypothyroidism). Box 21.7 lists the causes of primary hypothyroidism.

The prevalence of hypothyroidism in the UK is estimated at around 2 per cent of adult women and 0.2 per cent of men, rising to 5–10 per cent in women over 65.

Clinical features

An insufficiency of thyroid hormone affects every organ system in the body and the effects of hypothyroidism can be broadly divided into the generalized slowing of all metabolic processes leading to, among others, fatigue, cold intolerance and weight gain, and the tissue accumulation of glycosaminoglycans which leads to the characteristic changes such as coarse dry skin, hair loss and doughy peripheral oedema. Box 21.8 lists the manifestations of hypothyroidism.

The onset of symptoms can be insidious (particularly in the elderly), such that severe myxoedema may result. The typical patient complains of lethargy and fatigue; these complaints plus the accompanying apathy and listlessness means that ability to work is impaired. There may be a slow increase in weight despite a reduction in appetite and constipation is a common feature. Cold intolerance is typical. Patients may have a husky gruff voice attributed to ‘laryngeal cord oedema’ and resulting from oedema of the vocal cords. Menstrual periods may be heavy and a desired conception elusive. Myopathy can cause difficulty in walking upstairs or rising from a chair and numbness and paraesthesia in the hands may develop as carpal tunnel syndrome results from peripheral oedema. Occasionally, neuropsychiatric complications may develop with bizarre behaviour, so called ‘myxoedema madness’. A low threshold for thyroid function testing is necessary, since few patients have a full set of symptoms. Current consensus, however, is that routine screening is not indicated.

Aetiology of hypothyroidism

CHRONIC AUTOIMMUNE HYPOTHYROIDISM/HASHIMOTO’S THYROIDITIS

This condition is the most common cause of hypothyroidism in iodine-replete areas. It is a typical autoimmune condition, more common in females and running in families where a history of Graves’ disease may feature along with other autoimmune conditions such as vitiligo, pernicious anaemia, rheumatoid arthritis and type 1 diabetes mellitus. Although it is most common in older women, it can occur in infants as young as two years of age and is the major cause of hypothyroidism in children. The role of autoimmunity in its pathogenesis is supported by the histological finding of diffuse lymphocytic infiltration of the thyroid gland and presence of circulating thyroid autoantibodies.

Box 21.7 Causes of primary hypothyroidism

**Associated with goitre**
- Hashimoto’s thyroiditis (chronic thyroiditis)
- Iodine deficiency
- Inherited defects of biosynthesis
- Drug induced (amiodarone, lithium, phenylbutazone)
- Maternal transmission (e.g. anti-thyroid drugs)

**Not associated with goitre**
- Atrophic thyroiditis
- Iatrogenic (e.g. radiiodine, surgery, neck irradiation)
- Congenital anomaly (e.g. thyroid agenesis)

**Self-limiting**
- Transient thyroiditis
- Post partum thyroiditis
- Iatrogenic (overtreatment with anti-thyroid medication)

Box 21.8 Manifestations and laboratory findings in hypothyroidism

**Symptoms:** Weakness/fatigue, coarse dry skin, pale skin/flush (peaches and cream), periorbital oedema, loss/drying of hair, coarse facial features, constipation, cold intolerance, decreased appetite with weight gain, myopathy, peripheral oedema, intellectual impairment, slow/hoarse speech, carpal tunnel syndrome, neuropsychiatric problems, menorrhagia, ovulatory failure, galactorrhoea.

**Signs:** Palor, cool skin, characteristic facial features, peripheral/facial oedema, bradycardia, slow relaxing tendon reflexes, hoarse voice, goitre.

**Laboratory findings:** Low serum free T4 concentration, mild hyponatraemia, raised TSH concentration (if TSH concentration suppressed, consider central lesion), positive thyroid microsomal autoantibodies. Normochromic normocytic anaemia, raised serum cholesterol, triglycerides, LDL, lowered HDL (atherogenic lipid profile), raised serum prolactin.
Initially, the thyroid hypofunction may be subclinical, but may become overt with a rate of developing hypothyroidism at a rate of around 5 per cent per year. The typical goitre is moderate in size and smooth. The presence of the goitre may predate the development of overt hypothyroidism, and generally the goitre remains static or may decrease in size. Some patients present without a palpable goitre and are said to have atrophic autoimmune thyroiditis, which is thought to represent the end point of Hashimoto’s thyroiditis.  

IATROGENIC HYPOTHYROIDISM

Iatrogenic hypothyroidism may result from surgery, treatment with radioactive iodine and external beam radiotherapy in patients who have undergone treatment for head and neck malignancy. Occasionally, hypothyroidism can result from overtreatment of hyperthyroidism with anti-thyroid medication, but with close monitoring this is not common. Patients who have undergone thyroidectomy should commence thyroid hormone replacement before leaving hospital. In addition, the majority of patients treated with 400–600 MBq doses of $^{131}$I will develop hypothyroidism. External beam radiotherapy given to the neck may result in both hypothyroidism and an increased risk of thyroid malignancy, especially in children and adolescents. For patients who have had more than 25 Gy, there may be a slow onset dose dependent development of hypothyroidism. Such patients should be carefully monitored both for hypothyroidism which may initially be subclinical, and for nodular thyroid disease which may herald a thyroid malignancy.

IODINE DEFICIENCY AND THE THYROID

Worldwide, the most common cause of hypothyroidism remains iodine deficiency. In iodine-replete regions, neonatal hypothyroidism is routinely screened for in the post-natal period. Causes of neonatal hypothyroidism include thyroid gland agenesis or dysgenesis, inherited defects in thyroid hormone biosynthesis and transplacental transmission of anti-TSH antibodies (causing transient neonatal hypothyroidism).

CENTRAL HYPOTHYROIDISM

Lack of hypothalamic thyrotropin releasing hormone (TRH) or pituitary TSH may lead to hypothyroidism, although central hypothyroidism accounts for less than 1 per cent of all cases of hypothyroidism. The most common causes are pituitary tumours and the surgery/radiotherapy used to treat them. Such central causes may be distinguished from primary hypothyroidism by a normal or low serum TSH concentration that is inappropriate given a low serum fT3 and fT4 concentration. Specialist advice is required in these patients.

Treatment of hypothyroidism

Thyroine is the drug of choice for the treatment of hypothyroidism. It is absorbed from the upper small bowel with about 80 per cent efficiency, and has a long enough half-life (7 days) to allow for daily or even weekly dosing if compliance is an issue. Thyroxine is a pro-hormone which is de-iodinated in peripheral tissues to the active hormone T3.

The aim of treatment is to return the patient to a euthyroid state both clinically, as judged from symptoms, and biochemically as judged from serum TSH estimations. The majority of patients require 100–125 μg daily to achieve euthyroidism but variation exists. In those less than 50 years of age with no evidence of ischaemic heart disease, a moderate dose (typically 100 μg) may be started immediately. In older patients, or those with known cardiac disease, a starting dose of 25 μg is prudent due to the risk of exacerbating or precipitating cardiac disease because of the rise in cardiac output associated with initiation of therapy. Increments of 25 μg can be added every 4–6 weeks until TSH concentrations are within the normal range. Due to slow response of serum TSH concentrations, 4–6 weeks should elapse before measuring TSH concentration after initiating therapy or after dose adjustment. Once stable, serum TSH needs to be checked on an annual basis to ensure on-going compliance.

In those with central hypothyroidism, it is imperative that hypoadrenalism be excluded before initiating thyroxine therapy. An adrenal crisis may be precipitated if hypoadrenalism is not treated before thyroxine therapy is commenced. In central hypothyroidism, the serum TSH concentration is of no value in monitoring therapy, thus dose adjustments should be made on serum fT4 and fT3 levels alone.

A minority of subjects feel that their symptoms of hypothyroidism are not controlled on thyroxine therapy despite normal concentrations of TSH and T4. Some choose to take T3 in addition to or instead of thyroxine, although due to its rapid absorption and short half-life, it must be taken three times a day and fluctuations in thyroid hormone levels exist. At present there is no evidence to suggest advantage over T4 therapy and combination therapy with T4 and T3 is best avoided.

Subclinical hypothyroidism

This is essentially a biochemical diagnosis consisting of raised serum TSH concentrations with normal fT4 concentrations. Subclinical hypothyroidism is common, with data from population surveys estimating a prevalence of 7–8 per cent in women and 2–4 per cent in men. The prevalence rises with age to about 15 per cent in women aged over 60 years.

The aetiology may be clear from the history, e.g. previous $^{131}$I treatment or thyroidectomy. Around 60 per cent of women with subclinical hypothyroidism have positive antibodies to thyroid peroxidase. Prospective studies have confirmed that those with both positive antibodies and elevated TSH concentration are at risk of developing overt hypothyroidism at the rate of around 5 per cent per year, the risks being higher for those aged over 60 years.

Controversy exists as to who should be treated and at what point, as the potential risks of inappropriate overtreatment to bone and cardiovascular system resulting from T4 treatment have been outlined. Recent guidelines state that apart from the data relating raised TSH to cholesterol, data showing clear benefits of treatment is lacking. Many clinicians would treat if there were a consistently raised TSH over 10 mU/L and positive autoantibodies, due to the high risk of progression to overt hypothyroidism. For
asympotomatic patients with a modestly raised TSH (below 10 mU/L) or with a low or negative titre of microsomal antibodies, six-monthly or annual retesting is advised.73

THYROID DISEASE IN PREGNANCY

Hyperthyroidism and pregnancy

Postpartum, around 5 per cent of women develop thyroid dysfunction. Of those who develop postpartum thyroid dysfunction, around one-third have postpartum thyroiditis, with symptoms of thyrotoxicosis at around 12 weeks post delivery followed by a period of hypothyroidism at around 3–6 months. In some women, only the hypothyroid phase is evident and eventually there will be a return to a euthyroid state.1 About 25 per cent of such women develop permanent hypothyroidism. Recurrent postpartum thyroiditis develops in up to 80 per cent of subsequent pregnancies. Referral for specialist monitoring is advised, and annual thyroid function tests are subsequently indicated.1

Transient thyrotoxicosis may be seen in cases of hyperemesis gravidarum, the likely mechanism being stimulation of the TSH receptor by raised β-HCG levels resulting in increased production of T3 and T4. Management is supportive and anti-thyroid medication should be avoided.

Pregnancy is complicated by Graves’ disease in about 1 in 500 women.83 Recognition of Graves’ disease in pregnancy is important since untreated hyperthyroidism is associated with miscarriage, premature labour, low birthweight and pre-eclampsia.86 Diagnosis of thyrotoxicosis may be delayed as symptoms and signs may be wrongly attributed to physiological changes occurring in pregnancy.1 Treatment of thyrotoxicosis in pregnancy aims to achieve rapid biochemical euthyroidism whilst alleviating symptoms. Propranolol may be used as an adjunct but the mainstay of treatment is anti-thyroid medication, as radiiodine is contraindicated in this situation. Propylthiouracil is preferred to carbimazole as it crosses the placenta less and is associated with fewer potential teratogenic side-effects. In the rare instance of a serious adverse reaction to thionamides, surgery may be performed, preferably in the second trimester.1 Joint management with the endocrinologist, obstetrician and paediatrician is important, as there is a risk of fetal and neonatal thyrotoxicosis indicated by low birth weight, irritability and tachycardia.

Hypothyroidism and pregnancy

Overt hypothyroidism can have adverse effects on both mother and fetus with increasing risks of pre-eclampsia, placental abruption, low birth weight and an increased perinatal mortality. Considerable debate surrounds the potential effect of subclinical hypothyroidism on the unborn fetus. Recent studies have shown mild but statistically significant adverse neuropsychological effects in children born to mothers with mildly raised TSH in the first trimester.87, 88, 89, 90 Current opinion is that only targeted screening should be undertaken in high-risk patients, for example those with a personal or family history of thyroid dysfunction, a personal history of other autoimmune conditions such as diabetes mellitus, or obstetric complications known to be associated with hypothyroidism (i.e. recurrent miscarriage and preterm labour).73

During pregnancy, the requirement for thyroid hormone increases and around 75 per cent of women with treated hypothyroidism will need an increased dose during pregnancy, often by around 50 per cent. It is recommended to measure thyroid function tests around 4–6 weeks’ gestation, 6 weeks after any increase in dose of T4 and at least once per trimester. Specialist monitoring of thyroid function is indicated. Post-delivery, the dose can be reduced to prepregnancy levels and checked to ensure it remains sufficient.

THYROID ENLARGEMENT

Epidemiology and aetiology

Thyroid enlargement is common. The Framingham study in the United States indicated a 5–10 per cent life-time risk of developing a thyroid nodule,91 and the Whickham survey in the north-east of England reported a 15 per cent prevalence of goitres or thyroid nodules.2 Additionally, high resolution ultrasound can detect thyroid nodules in 19–67 per cent of individuals, with higher frequencies in women and the elderly, even when the gland is normal to palpation.22

In contrast, thyroid cancer is rare, accounting for approximately 1 per cent of all new malignant disease (0.5 per cent of cancers in men and 1.5 per cent in women), although thyroid cancer is one of the most rapidly increasing cancers.93 The majority of thyroid cancers are papillary carcinomas (72–85 per cent), with the remainder comprising follicular (10–20 per cent), medullary (1.7–3 per cent), anaplastic (< 1 per cent) and other carcinomas (1–4 per cent). Papillary and follicular carcinomas are termed differentiated thyroid cancers.93 Most patients with thyroid enlargement can be managed conservatively after malignancy is ruled out, the challenge to the clinician being to identify the minority of patients with thyroid cancer who therefore require surgical intervention and additional therapies.22

Assessment of patients with thyroid enlargement

Most patients with thyroid enlargement need no treatment after biochemical euthyroidism is confirmed and malignancy is excluded.22

CLINICAL EVALUATION

The history and clinical examination remain the diagnostic cornerstones in evaluating patients with thyroid enlargement, and in some cases may be suggestive of thyroid carcinoma.94 The physical examination should focus on inspection of the neck (including regional lymph nodes) and the upper thorax and palpation of the nodule/goitre to determine its size and nodularity. Notably, there is considerable inter- and
intra-observer variation regarding size and morphology of the thyroid.52

In many cases, however, thyroid glands harbouring malignancy are clinically indistinguishable from those that do not, and there is substantial variation among practitioners in evaluating nodules – a finding that may explain why an increasing number of thyroid specialists use imaging as part of the evaluation of thyroid nodules.52, 94 The presence of discomfort in the neck, jaw or ear and dysphagia, hoarseness or dyspnoea can occur in patients with benign thyroid nodules, and particularly in those with large multinodular goitres, but this may also indicate thyroid carcinoma. A hard and fixed nodule is suggestive of thyroid carcinoma, as is vocal cord paralysis and ipsilateral lymphadenopathy, but these clinical features are absent in the vast majority of patients with this diagnosis.52, 94

The risk of harbouring thyroid cancer is highest in men, and in those at the extremes of age.52, 94 Nodular thyroid disease is 5–10 times more common in females, whereas the rates of thyroid carcinoma are nearly equal in men and women. Therefore, the presence of a thyroid nodule in a man is more likely to reflect an underlying carcinoma.52, 94 In addition, head and neck irradiation in infancy or childhood is associated with subsequent development of carcinoma and epidemiological studies have observed increased rates of childhood papillary thyroid cancer in Belarus and Ukraine following the Chernobyl nuclear reactor accident.52, 94 Rate of growth is of importance; thyroid carcinomas are generally slow growing entities and rapid enlargement during thyroid hormone therapy is particularly worrisome.52

Overall, when the clinical suspicion of malignancy is high, thyroidectomy should be advocated irrespective of benign cytology, because the likelihood of malignancy is high. Box 21.9 lists clinical criteria suggestive of the diagnosis of thyroid cancer.

**LABORATORY INVESTIGATIONS**

Determination of the serum thyrotropin (TSH) concentration is the most used test by thyroidologists in the evaluation of patients presenting with thyroid enlargement and recent guidelines form the American Thyroid Association (ATA) and British Thyroid Association (BTA) state that serum TSH should be measured in the initial evaluation of a patient with a thyroid nodule.95, 96, 97, 98 If the TSH is below the laboratory reference range, assays for fT3 and fT4 are required in order to exclude overt hyperthyroidism (raised free T4 and free T3) or ‘T3-toxicosis’ (raised serum free T3 alone). Similarly, if TSH is raised then overt hypothyroidism must be excluded (this being indicated by low fT4 with a raised TSH concentration). Results from surveys have indicated that when TSH levels are within the normal range, subsequent assessment of circulating free thyroid hormone levels is more favoured by European physicians when compared with North American thyroidologists.52, 95, 96 Although virtually all patients with thyroid carcinoma are euthyroid, the presence of a suppressed serum TSH level (generally indicative of subclinical or overt thyrotoxicosis) does not rule out the presence of malignancy.52

Interestingly, recent studies have indicated that the presenting serum TSH concentration is an independent predictor of thyroid malignancy. The first study, evaluating 1500 patients presenting with thyroid enlargement and investigated with fine needle aspiration cytology (FNAC), indicated significantly increased odds ratios for malignancy in males, in those of younger age, in those with solitary nodules and in those with serum TSH >0.9 mIU/L.99 A further study confirmed that the likelihood of thyroid cancer increases with higher serum TSH concentration in 843 patients undergoing surgery for suspected thyroid malignancy. Moreover, the mean presenting serum TSH concentration was significantly higher in patients with stage III/IV disease compared with those with less advanced stage differentiated thyroid cancer (stage I/II).100

Anti-thyroid peroxidase measurements are measured by more than half of clinicians, but it is notable that thyroid autoantibodies are found in approximately 10 per cent of the population and autoimmunity may coexist with a thyroid nodule or goitre.52 The role of routine measurement of serum calcitonin remains controversial. This hormone is a marker of medullary thyroid carcinoma, which accounts for less than 10 per cent of all thyroid cancers and is reported to be elevated in less than 0.5 per cent of all patients with thyroid nodules.52 Early detection of medullary thyroid cancer is important but due to the presence of heterophilic antibodies, the immunometric calcitonin assay has a high false-positive rate. Again, European physicians tend to use this assay more routinely than their American counterparts.52, 95, 96 and it seems clear that if the plasma calcitonin level is found to be above 10 pg/mL, this must elicit further investigation. The routine use of measurement of serum thyroglobulin is of little value in the initial laboratory assessment of patients with thyroid enlargement because of marked overlap of measurements in those with benign and malignant disease. Guidelines from the ATA and BTA therefore state that routine measurement of serum thyroglobulin for initial evaluation of thyroid nodules is not recommended.97, 98

**DIAGNOSTIC IMAGING**

The number of imaging modalities available to determine size and thyroid gland morphology is growing rapidly. These
include ultrasonography, scintigraphy, computed tomography (CT) scanning, magnetic resonance (MR) imaging and, most recently, positron emission tomography (PET).

The most widely used form of imaging is ultrasonography, which has many favourable features including detection of non-palpable nodules, estimation of nodule size/goitre volume (e.g. to monitor the effect of therapy) and guidance of FNAC.\textsuperscript{52, 101} These advantages have led to changes in the attitude of clinicians and 80 per cent of ETA (European Thyroid Association) members, as well as 60 per cent of ATA members now routinely include ultrasonography in the initial management of patients presenting with a goitre.\textsuperscript{95, 96} Some ultrasonographic characteristics, such as hypoechoigenicity, solid nodules, microcalcifications, irregular margins, increased intranodular flow visualized by Doppler, increased ratio of anterior/posterior dimensions in transverse and longitudinal views (more tall than wide) and especially the evidence of invasion or regional lymphadenopathy, are associated with increased cancer risk.\textsuperscript{94} However, the high sensitivity of this test can also lead to the detection of clinically insignificant nodules resulting in unnecessary work-up and anxiety.\textsuperscript{52, 101} Furthermore, the low specificity of findings in most studies disqualifies ultrasound scanning from the differentiation between benign and malignant lesions and is clearly inferior to FNAC in this setting.\textsuperscript{52, 101}

Thyroid isotope imaging/scintigraphy has been used for many years and is helpful in the determination of the functionality of thyroid nodules. This technique allows the differentiation between ‘hot’ (functional) and ‘cold’ (non-functional) nodules with the risk of malignancy in cold nodules being reported as high as 8–25 per cent. However, compared with FNAC, this diagnostic tool is significantly less sensitive and specific in distinguishing benign from malignant lesions and has therefore been largely abandoned in routine practice.\textsuperscript{52, 98}

CT scanning and MRI provide high-resolution three-dimensional imaging of the thyroid gland, but neither of these methods provides advantages over ultrasound scanning in terms of detailed visualization of intrathyroidal structure. Furthermore, these methods have little value in the differentiation between benign and malignant lesions.\textsuperscript{52} Newer techniques, such as 2-deoxy-2-fluoro-D glucose (FDG-PET), are more promising in this respect but their use is limited by considerations of cost and accessibility. Tracheal imaging appears to be of limited value in the routine diagnostic work up of patients presenting with thyroid enlargement although respiratory flow loop determination is helpful in the assessment of patients with large goitres.\textsuperscript{102} Overall, FNAC is far superior to any of these diagnostic techniques and remains the current gold standard in the evaluation of patients presenting with thyroid enlargement.\textsuperscript{52, 95, 96}

**FINE NEEDLE ASPIRATION CYTOLOGY**

FNAC provides the most direct and specific information about the pathology of thyroid nodules, has an extremely low complication rate, is inexpensive and easy to learn, therefore remaining the preferred diagnostic tool by the majority of thyroidologists.\textsuperscript{95, 96} Most centres using this procedure have achieved a 35–75 per cent reduction in the number of patients requiring surgery, while at the same time doubling or tripling the malignancy yield at thyroidectomy.\textsuperscript{103}

The efficacy of this investigative tool has been evaluated in several large series which have confirmed it to be an accurate test in the diagnosis of thyroid cancer, its sensitivity and specificity ranging between 65–98 and 72–100 per cent, respectively.\textsuperscript{92, 104} The recent ATA guidelines state that FNAC is the procedure of choice in the evaluation of thyroid nodules.\textsuperscript{97}

Despite its effectiveness and diagnostic accuracy, the non-diagnostic smear (approximately 15 per cent of all specimens) remains a management dilemma. Although criteria to consider a specimen ‘adequate’ vary among institutions, a commonly accepted definition for a diagnostic sample is one that includes six or more groups of 10–20 well-preserved follicular epithelial cells per group on at least two slides.\textsuperscript{103} Inadequate sampling has been cited as the most common cause of false-negative biopsy results but repeat aspiration can augment the accuracy of the procedure.\textsuperscript{103}

Several studies have demonstrated that ultrasound guidance, compared with palpation-guided FNAC, reduces the number of non-diagnostic aspirates, thereby increasing its sensitivity and specificity.\textsuperscript{52, 94} Ultrasound-guided FNAC may be necessary for non-palpable or very small thyroid nodules, but there are no studies to demonstrate that the routine use of ultrasonography guidance improves outcome in terms of overall diagnostic rate or long-term outcome from thyroid cancer.

Guidance upon classification of cytological aspirates is provided by the BTA and ATA, as displayed in *Table 21.4.*\textsuperscript{97, 98} The action to be undertaken following cytological diagnosis of fine needle aspirates is also displayed. Cystic nodules that repeatedly yield non-diagnostic aspirates need close observation or surgical excision and if the nodule is solid surgery should be more strongly considered.\textsuperscript{97} When cytology is benign but patients belong to a high clinical risk group (Box 21.9), the decision to proceed to lobectomy may even be made with a benign FNAC diagnosis. This decision might also be made if there are pressure symptoms or rapid growth. In addition, the patient should have the choice to have the lesion removed if they so wish.\textsuperscript{98} Indeterminate cytology can be found in 15–30 per cent of FNA specimens. While certain clinical features such as gender or nodule size\textsuperscript{105} or cytological features such as presence of atypia\textsuperscript{106} can improve the diagnostic accuracy in patients with indeterminate cytology, overall predictive values remain low. Although many molecular markers have been evaluated in the hope of improving diagnostic accuracy for indeterminate specimens, at present none is recommended, because of insufficient data.\textsuperscript{97}

ATA guidelines state that diagnostic ultrasound should be performed in those patients presenting with multiple thyroid nodules as sonographic characteristics are superior to nodule size in identifying malignancy.\textsuperscript{97} Aspiration is recommended in the presence of two or more thyroid nodules larger than 1–1.5 cm, and those with suspicious sonographic features. If none of the nodules has a suspicious appearance, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodule(s) only.\textsuperscript{97} *Figure 21.5* displays a practical guide to the evaluation of patients with thyroid enlargement.
Medical management of patients with thyroid enlargement

**NON-TOXIC MULTINODULAR GOITRE**

Surgery is the treatment of choice where there is evidence of moderate to severe compressive symptoms, where FNAC of a dominant nodule is suspicious of malignancy, or where the patient prefers surgery for cosmetic reasons. Medical treatment of goitre involves the administration of radioactive iodine; the other medical option of administration of suppressive thyroid hormone is now considered outdated. \(^52\) \(131\)I treatment is given if surgery is not an option either due to age, frailty or other comorbid conditions, or because the patient refuses surgery. Radioiodine will cause a reduction in goitre size (up to 60 per cent) in most patients, with shrinkage occurring soon after treatment. The majority of patients experience relief from obstructive symptoms with dyspnoea improving in 75 per cent of those with the largest goitres, accompanied by

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**Table 21.4** Classification of cytological classification of fine needle aspirates according to BTA and ATA guidance. The action required following cytological diagnosis is also displayed. \(^{75,76}\)

<table>
<thead>
<tr>
<th>Type of lesion</th>
<th>BTA diagnostic category</th>
<th>ATA diagnostic category</th>
<th>Required action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any inadequate specimen</td>
<td>Thy1 Non-diagnostic</td>
<td>Non diagnostic aspirate</td>
<td>Repeat FNAC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>US-guided FNAC if required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Close observation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Consider surgery if solid lesion</td>
</tr>
<tr>
<td>Nodular goitre or thyroiditis</td>
<td>Thy2 Non-neoplastic</td>
<td>Benign cytology</td>
<td>Repeat aspirate after 3–6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No further diagnostic tests required</td>
</tr>
<tr>
<td>Follicular lesions</td>
<td>Thy3 Follicular lesions</td>
<td>Indeterminate cytology</td>
<td>Lobectomy or total thyroidectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Discussion between surgeon and endocrinologist required</td>
</tr>
<tr>
<td>Suspicious but not diagnostic of thyroid carcinoma</td>
<td>Thy4 Suspicious of malignancy</td>
<td>Indeterminate cytology</td>
<td>Surgical intervention for differentiated tumour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Further investigation for anaplastic carcinoma, lymphoma, metastatic tumour</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>Thy5 Diagnostic of malignancy</td>
<td>Aspirates diagnostic of malignancy</td>
<td>Surgical intervention for differentiated tumour</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Further investigation, radiotherapy or chemotherapy for anaplastic carcinoma, lymphoma, metastatic tumour</td>
</tr>
</tbody>
</table>

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**Figure 21.5** A diagnostic strategy to evaluate the solitary or dominant thyroid nodule.
an increase in cross-sectional area of the trachea of 36 per cent. Factors suggesting a favourable outcome include smaller goitres in younger patients, a shorter history of goitre and higher doses of radioiodine. In those with large goitres, large doses of radioiodine may be necessary, which, due to radiation protection legislation, can entail the hospitalization and isolation of the patient. An alternative is to fractionate therapy over a course of some months in an outpatient setting.

Side effects include hypothyroidism, which is common, the risk increasing if multiple doses are administered. The prevalence varies according to the amount of radiation exposure, with figures quoted ranging between 8 and 40 per cent at 1–2 years. Radiation thyroiditis (neck pain and tenderness) occurs in 3–13 per cent and Graves’ type hyperthyroidism associated with development of TSH receptor antibodies may occur in around 5 per cent.

There has been concern over the risk of deterioration in respiratory function in those with tracheal compression after 131I administration due to a transient increase in goitre size immediately after therapy. Studies have shown only a small decrease in tracheal cross-sectional area after therapy with no increase in upper airways obstruction. Some recommend the use of prednisolone peri- and post-131I to minimize any risks in those with severe tracheal compression but there is no evidence base for this practice.

Recombinant TSH may be used in this setting. The logic is that the higher the serum TSH, the greater the stimulus for radioiodine uptake into the goitre and the greater the chance of efficacy with a lower overall dose of radioiodine. Although preliminary results are encouraging, evidence for efficacy in volume reduction is not yet available, so recombinant TSH is not widely used at present.

Suppressive T4 treatment has historically been used to reduce goitre size. Although some studies have shown benefit, growth of thyroid nodules or goitres often resumes after discontinuation of thyroxine, meaning therapy may need to be life-long. Suppressive therapy necessarily induces a state of subclinical hyperthyroidism (suppression of TSH) with risks of atrial fibrillation and reduced bone density as previously outlined. For these reasons the use of suppressive therapy has been abandoned by most thyroidologists.

Ten to 15 per cent of solitary thyroid nodules are cystic and simple aspiration is the treatment of choice, however, recurrence rates may be as high as 80 per cent with larger lesions. For this reason, and the fact that many cysts resolve spontaneously over time, an expectant approach may be taken with small cysts less than 3 mL. Larger ones should be aspirated with FNAC performed on any residual nodule and surgery considered, as around 10 per cent of large lesions may harbour thyroid cancer.

The advent of high resolution ultrasonography has led to the discovery of small, asymptomatic and previously unrecognized thyroid nodules. These thyroid incidentalomas are usually smaller that 1.5 cm and are often diagnosed during ultrasonographic evaluation for non-diagnostic neck disorders, posing a management dilemma for the clinician. A recent consensus statement by the Society of Radiologists in Ultrasound on the management of thyroid nodules detected at sonography states that highly suspicious ultrasonographic features, such as microcalcifications, prompt a biopsy in nodules 1 cm or larger. Other suspicious features such as solid consistency promptopsy at 1.5 cm or larger, while less suspicious appearances such as mixed solid and cystic consistency should be considered for biopsy only if nodules measure 2 cm or larger. These guidelines remain controversial with endocrinologists as it has been reported that patients undergoing surgery for papillary cancers < 1.5 cm have been found to have distant metastasis. Others recommend observation for nodules smaller than 1 cm, in the absence of sonographic features of malignancy and fine needle aspiration biopsy (FNAB) for larger incidentalomas and those with features suspicious of malignancy.

The management of these incidentalomas remains controversial and clinical, as well as sonographic, follow up is generally recommended. FNAC should be performed in rapidly enlarging lesions as well as in those which exhibit suspicious sonographic features, including irregular margins and increased intranodular flow visualized by Doppler. US-guided FNAC may be necessary as the majority of nodules will be impalpable.

**CONCLUSION**

Benign thyroid disease is common with thyroid dysfunction affecting up to 2 per cent of the population. The underlying aetiology of thyroid disease in iodine-replete areas is usually autoimmune in nature. Determination of serum concentrations of TSH, fT3 and fT4 are the most important diagnostic tests to evaluate thyroid dysfunction. While there is clear evidence that overt thyroid dysfunction required treatment, the management of subclinical thyroid dysfunction remains controversial. The treatment of thyrotoxicosis is with antithyroid drugs or the administration of radioactive iodine. Hypothyroidism is treated with thyroxine replacement, the aim being to restore clinical and biochemical euthyroidism. In addition to thyroid dysfunction, thyroid enlargement is very common. Following clinical examination, all patients should have their serum TSH measured. Thyroid ultrasound is increasingly used in the assessment of thyroid neoplasia but remains inferior to fine needle aspiration biopsy in the specific detection of thyroid cancer. When thyroid malignancy is
excluded, patients with thyroid nodules require further follow up and repeat FNAB 3–6 months after the initial FNAB is recommended for benign nodules. Several clinical, biochemical and sonographic criteria can serve as an adjunct to cytological diagnosis in the prediction of thyroid malignancy and can help in the identification of patient groups who require earlier surgical referral or more regular follow up.

DEFICIENCIES IN CURRENT KNOWLEDGE AND DIRECTIONS FOR FUTURE RESEARCH

Further work on the long-term sequelae of thyroid disease, both in the fetus and in adulthood, may add to the debate on screening for thyroid dysfunction, especially in women of childbearing age. Human and mouse databases have provided powerful tools to probe many unanswered questions in thyroidology. The genetic basis for autoimmune thyroid disease is being unravelled by discovery of genetic variations associated with risk for autoimmune disease and important molecules in the disorder’s pathogenesis. Already major progress has been achieved in identifying the role of specific components of the HLA system and other immune regulatory genes such as CTLA-4 and CD40 which have functional consequences. Better understanding of the genetic mechanisms leading to autoimmune thyroid disease may lead to targeted therapies for immune modulation. Such understanding may also allow better prediction of treatment outcomes, for example response to anti-thyroid drugs and hence better tailoring of therapies for individual patients. The ability to predict outcome in Graves’ disease would be of immense clinical value.

Current research into Graves’ ophthalmopathy attempts to elucidate the precise aetiology of the condition. Newly developed animal models may have a positive impact in this field. Research into new approaches for treatment of thyroid eye disease has focused on the use of cytokine antagonists, somatostatin analogues and also on the use of antioxidants. In future, it would be expected that double blind trials involving some of these agents may begin.

Importantly we are beginning to understand the long-term morbidity, and indeed mortality, associated with thyroid dysfunction, largely vascular. This understanding will drive the development of more intensive and effective clinical management strategies and identification of those at particular risk. The relationship between subclinical thyroid dysfunction cardiovascular morbidity and mortality is a further area in need of large randomized controlled trials to guide clinicians in the management of this condition.

Future research in nodular thyroid disease will focus on ways of improving the diagnostic pathway to reduce the number of patients undergoing lobectomy for what proves to be benign disease. Current research into ultrasound and colour Doppler criteria for identification of malignancy may have a positive impact. More likely, however, is a major impact of gene expression studies allowing discrimination, perhaps on biopsy specimens, of benign from malignant disease, as well as identification of genetic and molecular markers in resected tumours which will predict potential recurrence and hence the need for intensive therapy.

KEY EVIDENCE

- The most important initial test to evaluate thyroid dysfunction is measurement of serum TSH concentration.
- Treatment of hyperthyroidism is with antithyroid drugs, radioactive iodine or surgery.
- Overt hypothyroidism requires treatment with thyroxine, the aim being to restore euthyroidism both clinically and biochemically.
- FNAB remains the diagnostic procedure of choice to detect thyroid malignancy.

KEY LEARNING POINTS

- Thionamides represent the mainstay of drug treatment of hyperthyroidism in the UK.
- Radioactive iodine administration is the treatment of choice in patients with toxic nodular goitre and in those with relapsed Graves’ disease.
- The treatment of subclinical thyroid disease remains controversial.
- All patients with thyroid nodules or enlargement should undergo serum TSH measurement.
- Patients presenting with thyroid enlargement require regular follow up.
- Some clinical, biochemical and ultrasonographic characteristics may aid in the prediction of thyroid malignancy.

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Learn the duty as well as taste the pleasure of original work.

Robert J Graves (1796–1853)

INTRODUCTION

The thyroid gland derives its name from the Greek thyreos or shield, whereas enlargement or goitre is derived from guttur the Latin term for throat.

A goitre is defined as an enlargement of the thyroid. The term is somewhat arbitrary as there is no objective measurement of size or weight that is standardized in the definition. A form of thyroidectomy was first described in China over one thousand years ago. The procedure was recognized as potentially fatal in view of the tendency to result in torrential haemorrhage. In 1866, Samuel Gross wrote that thyroid surgery should be considered as horrible butchery and that no sensible and honest surgeon would be engaged in its practice. It was not until the early twentieth century that Kocher popularized the operation. He reduced bleeding by meticulous haemostatic technique and subsequently received the Nobel Prize for his work in this area. He reported a 0.2 per cent haemorrhage rate in 1898 for the over 5000 thyroidectomies which he performed.

Thyroidectomy is performed in the treatment of, or exclusion of, thyroid cancer and in addition where benign disease gives rise to compression of the oesophagus or trachea, causing dysphagia or stridor, respectively, the treatment of thyrotoxicosis and occasionally for cosmesis.

CLASSIFICATION OF GOITRE

The World Health Organization has classified goitres according to clinical appearance into three grades:

- **Grade 0**: no palpable or visible abnormality of the thyroid.
- **Grade 1**: palpable thyroid mass that is not visualized with the neck in neutral position.
- **Grade 2**: a visual apparent mass with the neck in neutral position.

See also **Box 22.1**.

Multinodular goitre (MNG) is the most common endocrine disorder worldwide and affects 500–600 million people. The natural history of untreated, sporadic, non-toxic goitre is variable and not completely understood, but slow
growth and nodule formation is to be expected. It has been estimated that a 10–20 per cent volume increase occurs per year.\(^4\) As it enlarges, multiple areas of focal nodularity typically form. Some 5–10 per cent of MNG with continued growth may develop hyperthyroidism over a five-year period.\(^5\) Iodine deficiency is probably the most common cause, but even in iodine-deficient areas, patients are generally euthyroid with normal thyroid-stimulating hormone (TSH) and therefore it is likely that a genetic element coexists. Although the prevalence of MNG is decreasing with the use of iodine, there is still a prevalence of sporadic goitres in the United States of about 4–7 per cent and 10 per cent in the UK.\(^6,7\) Growth may be accelerated by ingestion of goitrogens, iodine deficiency, pregnancy, malignant change and the development of hyperthyroidism. Most recently, a gene located on chromosome 14 has been associated with familial non-toxic MNG and a polymorphism of codon 727 has been associated with toxic MNG.\(^8,9\)

Although MNG is relatively common in the general population, the majority of patients are asymptomatic. Generally, the growth is slow, but may occur more acutely with excessive iodine, e.g. radiographic contrast, or with medication, e.g. amiodarone. In general, surgery is necessary in extremely large MNG particularly where there is substernal extension with or without evidence of tracheal or oesophageal compression, suspicion of malignancy or the development of a toxic multinodular goitre.

**DEVELOPMENT OF SUBSTERNAL GOITRE**

There are many proposed classification systems of substernal goitre based on clinical size, relative percentage of thyroid tissue in the mediastinum, radiological appearance or pathological findings.\(^10\) None, however, is completely satisfactory or widely accepted. One accepted definition is that substernal goitre occurs when 50 per cent or more of the gland extends below the thoracic inlet.\(^11\) Although massive cervical goitres may cause tracheal displacement and narrowing, in the majority of cases the main compression of the trachea or oesophagus occurs at or below the thoracic inlet when the goitrous enlargement has resulted in substernal extension.

Substernal goitres were more common at the beginning of the last century (about 18 per cent of cases), but the widespread use of iodized salt has lead to a significant decrease.\(^12\) Currently, the incidence is of the order of 4–6 per cent in patients undergoing thyroid surgery.\(^13\) Its prevalence may yet increase due to the increased use of fine needle aspiration (FNA) for investigation of thyroid swellings and a corresponding decrease in thyroid surgery.

Initially, thyroid enlargement occurs in the neck, but when the pretracheal muscles can no longer stretch, further growth proceeds inferiorly along the path of least resistance. This may be facilitated by negative intrathoracic pressure from swallowing and inspiration, downward traction caused by normal deglutition and the pull of gravity. This mediastinal extension would appear to be more commonly seen in patients with short necks, a tendency for obesity and barrel-shaped emphysematous chest shapes. Once the mediastinal component has enlarged sufficiently to become trapped in the chest, unrestricted growth is possible because of minimal intrathoracic pressure. Thyroid nodules in the substernal component may involute resulting in cysts or haemorrhagic lesions with the potential for rapid increase in size often with pain. Rarely, this may present with acute airway obstruction.

**ASSESSMENT OF NON–TOXIC MNG**

A thorough history and physical examination is essential. In a large proportion of patients with non-toxic MNG, the patient is unaware of any problem until it is brought to their attention by a friend or relative or doctor on routine clinical examination. Symptoms may initially be non-specific, such as an irritating cough or globus-type sensation, features which will be elicited in a good history. The patient should be asked about a family history of thyroid disease, the area where the patient lives and any history of previous irradiation. Symptomatic patients may complain of symptoms related to pressure and compression of the trachea and oesophagus, and typical ones include dyspnoea, dysphagia or a tightness in the throat. Since the trachea is directly in contact with the thyroid and relatively firm and immobile, symptoms related to the airway are more common. The oesophagus is more mobile and as the goitre increases in size tends to be displaced, but not typically compressed unless the goitre affects both lobes and the oesophagus is trapped between the posterior thyroid lobes laterally, the spinal column posteriorly and the trachea anteriorly. In this situation, the patient may note significant swallowing difficulties.

The patient should be examined supine in good light with the neck fully exposed. Inspection may show an obvious goitre. In general, thyroid nodules greater than 1 cm are palpable. Typically in MNG, multiple nodules involving both thyroid lobes are apparent, but often one lobe is more affected. Clinically, the surgeon should attempt to palpate below the lower extent of the thyroid lobe to determine whether substernal extension has occurred. The development of flushing, neck vein compression and shortness of breath on raising the hands above the head for 1 minute (Pemberton's sign) is suggestive of significant substernal extension with venous compression, although false negatives are common. The use of percussion over the sternum to determine mediastinal involvement, although well documented, has not been of significant clinical value in the authors’ practice. As the thyroid lobe increases in size, it tends to displace surrounding structures and the relationship to the trachea (particularly any tracheal deviation) should be noted. In large benign goitres, the carotid artery is displaced posteriorly (Berry's sign). A neck scar indicating previous thyroid surgery may be apparent and is important in deciding further management. The finding of cervical lymphadenopathy, fixation of the mass to the surrounding structures and vocal cord paralysis should alert the physician to the possibility of malignancy.

Finally, a fibreoptic examination of the larynx should be performed. Although recurrent laryngeal nerve damage may occur due to traction by a large thyroid gland, this is a rare event and nerve palsy should suggest thyroid malignancy. Laboratory and diagnostic tests to be performed include thyroid function tests (TFT), antithyroid antibodies and serum calcium.
Ultrasound is the most commonly used investigative procedure. It provides information on the location, consistency and size of nodules. Clinically, even though a solitary nodule may be suspected, ultrasound has demonstrated that in 50 per cent of cases there are multiple nodules present. Fine needle aspiration can be performed more accurately when used in conjunction with ultrasound. Serial follow up of nodule growth can be provided by ultrasound and changes in nodular characteristics may point to possible malignancy where ultrasound-guided FNA should be of benefit. Ultrasound examination is more user dependent than other forms of imaging, such as magnetic resonance imaging (MRI) and computed tomography (CT), but is of limited value in assessing thyroids with significant substernal extension because of its inability to image contents behind the sternum.

Radionuclide thyroid scanning (scintigraphy), although less commonly used, is useful in the evaluation of a dominant nodule in a MNG as a possible focus of malignancy and to assess function of a nodule as a cause of hyperthyroidism. These scans are poorly sensitive in determining substernal extension, but may assist in determining gland functionality.

CT and MRI are useful in the assessment of the large thyroid gland where there is substernal extension and to provide information about the relationship of the gland to surrounding structures in the event of malignancy. It is important not to give iodine contrast with CT imaging, if there is concern regarding the possibility of toxic MNG as this may precipitate an acute toxic state. Similarly, an iodine load in cases of thyroid cancer may delay the ability to image and treat these tumours with radioactive iodine therapy post-surgery, although in practice this is not usually a problem.

Chest x-ray is routinely carried out and may be helpful in looking for tracheal deviation and retrosternal extension. Pulmonary function tests including flow volume loop to confirm airway obstruction are occasionally used, but not usually by experienced physicians as the other investigations used, such as CT, will provide such information.

**INDICATIONS FOR SURGICAL TREATMENT OF A MULTINODULAR GOITRE**

**Mechanical obstruction**

MNGs generally increase in size in a slow but progressive fashion. Patients may be asymptomatic despite a significant tracheal shift. Rapid enlargement, however, may occur due to haemorrhage into a cyst or with cystic degeneration. Under these circumstances, patients may complain of a feeling of suffocation, odynophagia, dysphagia or airway distress. Symptoms of acute airway obstruction may not occur until up to 70 per cent of the tracheal lumen is obstructed. Tracheal shift with no palpable goitre suggests substernal extension and, under these circumstances, the patient requires a thorough evaluation including a CT scan of the neck and thorax.

**Suspicion of malignancy**

The presence of a lump in the neck frequently gives rise to concern about the possibility of malignancy. MNGs are continuously changing in size and character and despite physician reassurance, patients may be anxious to have the mass removed. Despite such concerns, the incidence of malignancy is of the order of 5–10 per cent in MNG and is similar to that in a solitary nodule.

**Cosmetic issues**

Surgery for cosmesis is controversial and is not generally recommended because of the potential complications of the procedure together with the fact that an enlarged thyroid is being replaced with a neck scar.

**Hyperthyroidism**

Hyperthyroidism is caused by an increase in the circulating level of thyroid hormones, independent of normal
thyroid-stimulating hormone (TSH) control. All MNG patients have a potential to become hyperthyroid. Long-term follow up suggests that this toxic potential occurs in at least 20–30 per cent of cases.\textsuperscript{16, 17} It usually has a slow onset and the typical signs and symptoms of hyperthyroidism may be absent or modified in this patient cohort.

## SURGICAL TREATMENT

### Surgical anatomy of multinodular goitre

Surgical removal of a large goitre can be difficult and poses a number of problems for the surgeon. The gland surface is nodular and frequently displaces the surrounding structures. The trachea is normally relatively firm, but despite this, significant enlargement of the thyroid will lead to variable displacement to one side and even a narrowing due to pressure effects. This may be compounded by softening of the tracheal wall with the potential for airway collapse secondary to tracheomalacia. The oesophagus, although more pliable, is less likely to be displaced due to its posterior location in relation to the thyroid. The recurrent laryngeal nerves are commonly elongated and typically displaced laterally and posteriorly as the thyroid expands, however, particularly in revision cases, the nerve may lie more superficially than expected. The parathyroid glands may also be displaced and difficult to locate because of the nodularity of the gland. The enlarging thyroid will tend to displace the carotid sheath contents laterally and safe access to this area may be difficult and require division of the strap muscles. The superior and inferior vascular pedicles may also be significantly displaced, compressed and elongated. The goitre may extend between the trachea and the oesophagus and, on occasion, may extend behind the oesophagus. Goitres as they enlarge may extend into the mediastinum and therefore, knowledge of the anatomy of this region is especially necessary. After the operation, displaced structures, such as the trachea, typically shift back to a more midline position on removal of the compressing mass. Tracheal lumen narrowing due to tracheomalacia may only manifest itself following removal of the splitting effect of the enlarged thyroid leading to potential airway collapse on inspiration following extubation. Tracheomalacia is, however, uncommon.

### SURGICAL INCISION AND EXPOSURE

An anaesthetist experienced in management of the difficult airway is required. In the majority of cases, although the larynx may be distorted to one side transoral intubation is relatively easy to perform. If the trachea is narrow, an appropriate smaller calibre reinforced endotracheal tube should be used. For patients with significant airway compromise who are unable to lie supine, an awake intubation over a fibreoptic laryngoscope may be appropriate.

The patient is positioned supine with the neck extended using a suitable-sized sandbag transversely placed behind the shoulders. A transverse neck incision above the suprasternal notch in a convenient skin crease is made. The incision size may vary according to the size of the goitre, but usually extends from the anterior border of the sternomastoid muscles and typically is 6–8 cm in length. Greater incision length does not tend to improve exposure to any great extent. The surgeon should avoid placing the incision over the clavicle or on the chest wall as these scars can become unsightly with time.

The skin flaps are raised in a subplatysmal plane superio rly to the thyroid notch and inferiorly to the sternal notch. If significant compression is present, the anterior jugular veins and tributaries are larger and more prominent than usual and care has to be taken not to damage these vessels inadvertently to prevent significant bleeding. The strap muscles are opened in the midline and raised, usually by blunt dissection, off the underlying thyroid gland. Often with a large asymmetrical MNG, the midline is difficult to identify and the dissection should start at the cricoid cartilage level as this facilitates localization of the avascular plane between the strap muscles and underlying thyroid. In larger goitres, the innermost strap muscle, the sternothyroid muscle is stretched and thinned over the thyroid and it is important to delineate the medial border of this muscle to allow dissection in the correct plane between the strap muscles and thyroid capsule. Anatraumatic technique is particularly important for these large obstructive goitres, since the venous system may be compressed and significant bleeding from surface thyroid vessels may occur which is difficult to control. Access laterally and to the superior thyroid pedicle may be improved by division of the sternothyroid muscle. Although not a routine step, for access and thyroid mobilization, complete division of the strap muscles on one or both sides may be required. This is best performed by first freeing the anterior border of the sternomastoid muscles, followed by opening, by blunt and sharp dissection, the potential so-called viscerovascular space between the carotid sheath laterally and the thyroid gland and upper aerodigestive structures medially. Only the omohyoid muscle crosses this space and serves as an excellent landmark to help identify the carotid sheath contents, particularly the internal jugular vein.
This muscle may be dissected and reflected superiorly or divided and the carotid sheath contents are retracted laterally to prevent damage during division of the strap muscles. The strap muscles are usually divided more superiorly to preserve the laterally placed motor nerve supply (ansa hypoglossus). The anterior jugular veins should be ligated and divided prior to division of the strap muscles, and care must be taken not to damage branches of the middle thyroid vein laterally which may lie just below the muscle. Following division of the strap muscles, the middle thyroid vein and branches are identified and carefully ligated.

MOBILIZATION OF THE THYROID INTO THE WOUND

Many surgeons, after exposure of the thyroid gland, prefer then to identify the recurrent laryngeal nerve when performing a routine thyroidectomy. Identification of the recurrent laryngeal nerve, however, is not possible for large goitres without first mobilizing the enlarged thyroid into the wound. To accomplish delivery of the thyroid, the superior thyroid pedicle is usually exposed, and mobilized by ligation of the superior thyroid vein and artery. Visualization is helped with partial or completed division of the strap muscles. Division of the pedicle vessels is best achieved by pulling the pedicle on stretch with ligation and division of the vessels individually as close to the superior thyroid pedicle as possible to prevent damage to the superior laryngeal nerve.

Delivery of the thyroid proceeds mostly by finger dissection, which is used to disimpact the goitre trapped in the inlet and in the superior mediastinum. Gentle finger dissection is used to free the goitre circumferentially, from the surrounding soft tissues, starting anteriorly at the thoracic outlet and proceeding laterally, posteriorly and inferiorly. The dissection is facilitated by simultaneous traction on the previously mobilized superior thyroid pole. This finger dissection is, to a large extent, blind particularly when mobilizing the deeper substernal portion of the gland. It is extremely important for successful haemostatic delivery that the surgeon stays in the same capsular plane as the thyroid mass that is being mobilized. Blunt blind dissection risks inadvertent tearing of branches of the inferior thyroid vein with significant bleed and must be done in a gentle manner. It is also possible to damage the recurrent laryngeal nerve particularly by traction. Usually, the recurrent laryngeal nerve has been stretched by the thyroid enlargement, and displaced laterally and posteriorly. In cases of revision surgery, however, the nerve may be far more superficially placed in relation to the remnant thyroid swelling, having been displaced by enlargement of the so-called tubercle of Zuckerland. Gentle but continuous traction is the key to successful delivery of the goitre from the mediastinum. The use of spoon-like instruments may be helpful in facilitating delivery by breaking negative intrathoracic pressure. This instrument is particularly suited for deeper-placed goitres whose lower border is inaccessible with finger dissection. Morselization has been suggested and more recently the use of microdebriders has been described, but there is a concern regarding uncontrollable bleeding. Further mobilization and/or division of the isthmus from the underlying trachea will help in difficult delivery cases. If blunt dissection is not possible because of significant difficulties opening the planes due to adhesions, or direct thyroid extension is present suggesting malignancy, then a partial sternotomy needs to be considered (Box 22.2).

IDENTIFICATION AND PRESERVATION OF IMPORTANT STRUCTURES

Parathyroid glands

The parathyroid glands require even more meticulous attention than usual when surgery is undertaken for the management of multinodular goitres because of the increased difficulties encountered in their localization, as well as the increased risk of avascular necrosis. The superior parathyroid gland position, even with extremely large goitres, is not usually significantly displaced and it is of paramount importance, particularly if total thyroidectomy is contemplated, that this gland is identified and preserved. The authors prefer to identify this gland early in the operation after the superior pedicle has been completely mobilized. The gland is identified, deep in the wound, on the undersurface of the superior thyroid pole. It is brought into view by grasping the thyroid gland with an artery forceps at the site of the ligated vascular stump, with retraction of the gland inferiorly and laterally. The superior parathyroid gland is usually surrounded by a variable amount of adipose tissue, but has a characteristic caramel colour and is attached to the overlying thyroid tissue by variable-sized blood vessels. Dissection of the plane between the parathyroid and thyroid is usually deferred until the thyroid gland has been delivered into the wound to allow better visualization and to avoid damaging the closely related recurrent laryngeal nerve at the cricothyroid joint.

The inferior parathyroid gland is more subject to variable anatomy and displacement by the goitre. As the goitre enlarges, this gland is often found intimately attached high on the thyroid lobe. In this position, it has a more flattened appearance and may give the appearance of being embedded, due to thyroid growth, within the lobe. Careful dissection will, however, show a plane of dissection between the thyroid and parathyroid. This, together with a longer and more tenuous vascular pedicle, makes it more difficult to preserve with a viable blood supply. Identification is helped by a dry surgical field and the use of magnification loupes (2.5 power). It is important to avoid pinching, clamping or squeezing the parathyroid gland to avoid damage, which is suggested by a change in colour to a darker appearance.

As many parathyroid glands as possible should be identified and preserved before the goitre is removed from the neck. Since the vast majority of parathyroid glands receive their blood supply from the inferior thyroid artery, its main
Served in situ circumstances where the parathyroid glands cannot be premedically as close to the thyroid gland as possible. In those trunk should not be ligated, but its branches are ligated medially as close to the thyroid gland as possible. In those circumstances where the parathyroid glands cannot be preserved *in situ*, because the vascular pedicle to the parathyroid gland is compromised during surgery, they should be removed and preserved for reimplantation at the end of the operation. The parathyroid glands that require reimplantation should be divided into segments of 2 mm blocks and then implanted into a suitable muscle (usually the sternomastoid muscle). Implantation requires a meticulous technique to prevent haematoma formation within the recipient muscle, and also to avoid extrusion of parathyroid fragments from the recipient muscle before the fascia overlying the muscle is closed. The site of implantation into the recipient muscle should be marked with a non-absorbable suture. Preservation of the parathyroids *in situ* with an intact blood supply is preferable to reimplantation because transplanted glands do not always survive.

**SUPERIOR AND RECURRENT LARYNGEAL NERVE IDENTIFICATION**

The superior laryngeal nerve usually enters the larynx 1 cm superior to the entrance of the superior thyroid artery into the upper pole. Keeping the dissection close to the thyroid capsule will ensure that the nerve is not injured. It is not always necessary to expose or identify the superior laryngeal nerve; however, every attempt should be made to preserve it by dividing and ligating the superior thyroid vessels close to or on the superior thyroid lobe.

Thomusch, in a multicenter study with multivariate analysis of over 7000 patients, found that recurrent laryngeal nerve injury is associated with a number of factors including extent of surgery, repeated operations for recurrent goitres and failure to identify the recurrent laryngeal nerve at operation. Identification of the recurrent laryngeal nerve is therefore mandatory during thyroidectomy. It is usually not possible to search for the recurrent laryngeal nerve until the gland is disimpacted and delivered into the wound. To identify the nerve, a thorough knowledge of the anatomical structures and their relationship to the recurrent laryngeal nerve is required. The trachea, inferior thyroid artery, carotid artery and parathyroid glands are particularly important in nerve identification. The normally located nerve bisects the angle between the inferior thyroid artery and the trachea. It may run superiorly, inferiorly or between branches of the inferior thyroid artery and the nerve may divide into several branches particularly as it approaches the cricothyroid joint before entering the larynx. Identification of the recurrent nerve may be made more difficult due to displacement and stretching from enlargement of the thyroid. In these more difficult cases, it may be best to find the recurrent laryngeal nerve higher than usual beneath Berry’s ligament, at the cricothyroid joint, where it has a constant position even with thyroid enlargement. The recurrent laryngeal nerve is dissected free using fine mosquito forceps. Absolute haemostasis in the region of the nerve will aid in its preservation. Any overlying small branches of the inferior thyroid vein should be ligated with small clips. Use of bipolar cautery should be discouraged, while working close to the nerve as damage of the recurrent laryngeal nerve can occur from heat trauma from cautery or from traction, rather than direct division of the nerve. While tracing the nerve, care should be taken to preserve the inferior thyroid artery laterally to preserve the blood supply to the ipsilateral parathyroids. The use of intraoperative nerve monitoring may be of help to confirm the presence of the nerve, but does not take the place of careful atraumatic surgical dissection. Despite improvement in monitoring, the best results for the resection of substernal thyroid disease are obtained by an experienced thyroid surgeon rather than the occasional operator.

**EXTENT OF THYROIDECTOMY**

Controversy exists as to the extent of surgery for multinodular goitre. Three different surgical options exist varying according to the extent of thyroid gland removal, namely total, near total and subtotal thyroidectomy. Near total thyroidectomy leaves 2–4 g of thyroid tissue or a $2 \times 1$ cm piece of thyroid tissue in the tracheo-oesophageal groove. Subtotal thyroidectomy involves the removal of one lobe and the isthmus. More recently, there has been a trend towards total thyroidectomy as the surgical procedure of choice in the management of large MNGs. This prevents recurrence and it is both diagnostic and therapeutic for previously undiagnosed thyroid cancers present in the goitre. Total thyroidectomy by definition, requires lifelong thyroxine therapy and has a potential for bilateral vocal cord paralysis and permanent hypocalaemia. However, if performed in a meticulous fashion with the knowledge of the altered surgical anatomy the risks to the recurrent laryngeal nerves (RLNs) and parathyroid glands can be kept to a minimum. This is of particular importance since the surgeon is dealing with a benign condition in an asymptomatic patient.

Most surgeons would concur that total thyroidectomy is warranted where the patient presents with bilateral substernal disease. The decision is more difficult if only unilateral thyroid disease is present with little or no change on the contralateral side. Kraimps *et al.* have suggested a selectively aggressive surgical plan based on extent of thyroid disease, with the extent of surgery tailored to the extent of thyroid pathology. For bilateral thyroid disease, a total thyroidectomy is performed. If at the time of surgery difficulty is experienced in preservation of the parathyroids on the initial larger side then a near total is performed, leaving a rim of thyroid tissue posteriorly on the smaller side to protect the blood supply of parathyroid glands. For unilateral disease, a total lobectomy and isthmusectomy (partial thyroid) may be preferred, but the surgeon should realize that this operation carries an overall high rate of contralateral recurrence (in the range of 15–42 per cent) on long-term follow up, and potentially significant more complications if revision surgery is required. In view of this, more aggressive surgery, either total or near-total is particularly indicated in the younger age group and especially female patients with a family history of multinodular goitre.

**Sternotomy**

Sternotomy is reserved for goitres that cannot be delivered safely through a cervical skin incision, but is rarely required.
Although the size of the substernal goitre may make it impossible to deal with the thyroid mass through a conventional incision, more frequently the size of the goitre combined with radiological and surgical evidence of poor mobility and adherence of the goitre to mediastinal structures are what lead to the use of a sternotomy. In this procedure, a vertical incision from the midportion of the cervical incision is made vertically on the chest wall. The incision is carried down to the manubrium which is then split with an oscillating saw. Care is taken not to damage underlying manubrial contents particularly if there has been previous surgery in the area. A full sternotomy is not usually required and the sternotomy is usually angled into the second intercostal space avoiding the internal thoracic artery. The retrosternal fascia is divided exposing the mediastinal structures. The goitre can now be dissected out of the mediastinum under direct vision (Table 22.1).

PREVENTING COMPLICATIONS

The surgical wound resulting from a large MNG is much more extensive than that seen following the removal of a relatively normal-sized thyroid gland. There is usually extensive dissection of the tissue planes into the superior mediastinum, prevertebral space and into both sides of the neck. Accordingly, special attention is paid to intraoperative haemostasis. The wound is irrigated, and haemostasis is best accomplished by using bipolar diathermy, ligaclips and, on occasion, fine suture ligatures. Small amounts of oozing, particularly near the entrance of the recurrent laryngeal nerve into the larynx at the cricothyroid joint, is best managed conservatively to prevent injury. The authors prefer to use surgical haemostatic agents, such as Surgicell®, rather than risk damage from cautery. Potential venous bleeding areas may become more obvious with valsalva performed by the anaesthetist by increasing intrathoracic pressure.

For larger goitres where a large dead space is left, closed suction drains are commonly used. The wound is closed in layers, with partial opposition of the strap muscles with an absorbable suture leaving a gap inferiorly to allow bleeding from beneath the strap muscle to become obvious on postoperative clinical examination. Neck dressing, which may obscure the wound and haematoma formation, should be avoided.

POSTOPERATIVE CARE

In most instances, the patient is extubated at the end of the operative procedure. Tracheal palpation at operation may suggest tracheomalacia with the endotracheal tube being easily palpated with softening and collapse on palpation of the trachea. If there is significant concern, this should be conveyed to the anaesthetist. Any difficulty with extubation at the end of the procedure may suggest tracheal collapse and in this case the patient may be reintubated and the tube left in situ for 24 hours. In this situation, high dependence care management is usually required. Rarely is a tracheostomy required and if possible should be avoided as it may result in further weakening of the trachea.

The surgical drains are usually left in place for a minimum of 36–48 hours, and longer if the drainage is copious. Calcium metabolism is monitored carefully both clinically and biochemically, twice daily, until it has stabilized. Transient hypocalcaemia is commonly due to the initial vascular shock on the preserved parathyroid tissue and may require calcium supplementation. Factors playing a role in hypocalcaemia postoperatively include the extent of surgery, experience of the operator and the number of functioning glands left in situ. Most surgeons feel that at least two functioning glands with an intact blood supply should be left to avoid prolonged low calcium.

The majority of patients will have had a significant amount of thyroid tissue removed which results in a hypothyroid state, and thyroxine replacement therapy is usually started upon discharge from hospital. Patients undergoing partial thyroidectomy may be started on thyroxine if subclinically euthyroid, but the routine use is of dubious value in the prevention of recurrence. If carcinoma is present, thyroxine may be withheld in preparation for a whole body iodine scan to search for residual or metastatic disease.

Risk factors for recurrent nodular goitre after thyroidectomy include younger age of patient, the finding of multiple nodules (but not bilateral disease) during surgery and the extent of such surgery. Morbidity was greater after surgery for recurrent disease than for surgery for non-recurrent disease implying that total thyroidectomy in all patients with bilateral MNG, particularly younger patients, avoids many potential complications.22, 23

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<td>Aortic arch to pericardium</td>
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SUGICAL TREATMENT OF HYPERTHYROIDISM

Introduction

Hyperthyroidism is a condition in which the body is exposed to excessive amounts of circulating thyroid hormone. This increase in circulating level of thyroid hormones is independent of normal TSH feedback control. This unregulated release of thyroid hormone is more commonly found in females, and may develop suddenly or more gradually. The overt condition is usually easily diagnosed, but gradual onset hyperthyroidism in the older age group causing mainly cardiac difficulties may not be so clinically obvious. The most common cause of this condition is Graves’ disease, followed by toxic multinodular goitre and solitary hyperfunctioning thyroid nodules.

Autoimmune thyrotoxicosis (Graves’ disease) is the most common cause of hyperthyroidism, usually seen in a young age group (30–60 years) making up 70 per cent of all cases. Toxic multinodular goitre is the second most common condition accounting for between 10 and 30 per cent of cases,
and is characterized by the development of hyperfunctional thyroid nodules developing in a previous non-toxic multinodular goitre. The least common pathological process is a toxic adenoma which is a solitary hyperfunctional lesion. The incidence of toxic multinodular goitre and toxic adenoma varies considerably, being particularly common in iodine-deficient regions and sometimes referred to as Plummer's disease.

Other forms of overactivity include transient states which may be a feature of a number of thyroid conditions, including subacute thyroiditis (De Quervain's disease), early Hashimoto's disease and postpartum hyperthyroidism. This may also be seen in patients who take large amounts of iodide or thyroxine; struma ovarii, thyrotopin-secreting tumours, choriocarcinoma and amiodarone-induced thyrotoxicosis are particularly rare and may be especially difficult to diagnose and manage.

The majority of patients with hyperthyroidism are treated medically or with radioactive iodine, but surgery now plays an ever increasing part in the management of this condition.

Graves' disease

Graves’ disease is commonly attributed to a Dublin-based physician Robert Graves who described the condition in 1835, but Caleb Hillier Parry, a Bath physician, probably described the first case in 1786.24

Graves’ disease is by far the most common cause of hyperthyroidism. It is an autoimmune disease underlined by the presence of an antibody to the TSH receptor which is present in up to 90 per cent of patients. Elevated free T4 and low TSH levels are present together with a high level of antithyroid autoantibodies. Although stress or medications, particularly a family history of Graves’ disease, predisposes to the condition in susceptible subjects, there are genetic factors involved in its aetiology.25 Pathologically, the thyroid gland is diffusely enlarged, fleshy and vascular. Microscopically, the follicular epithelium is hyperplastic and a focal lymphocytic infiltration is not an uncommon finding.

As with other autoimmune diseases, Graves’ disease is most commonly found in middle-aged females, but may be seen in males and females of all ages including children. Previous history of other autoimmune diseases, and particularly a family history of Graves’ disease, predisposes to the condition. Clinical findings may vary, but commonly include features of overactivity, a diffuse goitre and ophthalmopathy.26 Classically, the patient complaints include irritability, sleeplessness, palpitations, excessive sweating, heat intolerance and weight loss. Typically, patients have tachycardia and palpitations even during sleep. On examination, patients may demonstrate exophthalmos, lid lag and a diffuse bilateral goitre which may have a palpable and audible bruit due to high vascularity. Other manifestations including exophthalmos and pretibial myxoedema (present in 4 per cent of cases) help in differentiating between Graves’ and other hyperthyroid conditions.

Ophthalmopathy may be seen alone, or appear before, during or after the patient's thyrotoxic state becomes apparent. It is due to lymphocytic infiltration of the intraorbital muscles, possibly as a cross-reactivity between ocular muscle antibodies and thyroid antigens. Six stages of ophthalmopathy are described from lid lag and retraction (stage 1) to loss of sight from optic nerve damage in the most severe cases.27

The natural history of Graves’ disease is variable. The disease may undergo spontaneous remission, however, this may not take place for many months or even years, meaning control of the conditions usually with medical therapy is required. Patients who fail to show spontaneous remission often require other forms of treatment, usually radioactive iodine or surgical intervention.

Toxic multinodular goitre

This is the second most common form of thyrotoxicosis after Graves' disease. The patients are older than the typical patient with Graves’ disease, but are predominantly female, as with Graves' disease and toxic thyroid adenoma. The history is of a long-standing multinodular goitre, and the condition develops insidiously. It is caused by autonomous hyperactivity of one or more pre-existing thyroid nodules. Symptoms are not those classically associated with thyrotoxicosis, and are commonly cardiac, particularly atrial fibrillation. Although autoimmune antibodies may be present, the titres are usually low and the condition may be differentiated from Graves’ clinically by the relatively older age group, long-standing goitre, slower onset and the absence of autoimmune manifestations, such as ophthalmopathy. Differentiation is important since, unlike Graves’ disease, spontaneous remission is not a feature, so radioactive therapy and surgery are more attractive than long-term medical therapy.

Toxic thyroid adenoma

Toxic adenoma accounts for approximately 5 per cent of thyrotoxic cases. The peak age incidence is between 40 and 60 years and is more common in females. Clinically, a solitary nodule is found in contrast to the diffuse thyroid gland swelling seen in Graves’. Pathologically, they are autonomously functioning solitary thyroid neoplasms. Rarely spontaneously infarcts may occur, but otherwise the condition will persist and always requires management. After controlling thyrotoxic symptoms, partial thyroidectomy removing the hyperfunctioning adenoma is curative. Radioactive iodine is occasionally used in patients who refuse or are poor candidates for surgery.28

INVESTIGATIONS

Suppressed TSH together with an abnormally raised T3 or T4 level is characteristic of thyrotoxicosis. A positive thyroid autoantibody level makes an autoimmune process such as Graves’ more likely, but is not an absolute requirement. Scintigraphy using technetium or iodine may be of some help in differentiating between the three common conditions associated with thyrotoxicosis. With Graves’ disease, a diffuse homogenous uptake is typical. If a cold area is seen, a fine needle aspirate possibly under ultrasound-guided conditions is warranted to rule out neoplasia. With a toxic MNG, a patchy picture is more characteristic, and with a toxic...
Adenoma a hot nodule against a suppressed background is the usual finding.

**Treatment options for hyperthyroidism**

Appropriate treatment of hyperthyroidism relies on the identification of the underlying cause. In general, there are three treatment modalities used in the management of hyperthyroidism, namely medical therapy (thionamides, beta-blockers), radioactive iodine and surgery (Box 22.3). There is no proven superior management protocol, but all patients, no matter the underlying aetiology, will require control of their toxic condition initially using medical therapy. The antithyroid drugs used most commonly are thiouracil derivatives or imidazole compounds, both of which are relatively slow in onset. Other medications may be required initially, such as beta-blockers, which control the sympathetic overdrive symptoms, such as tachycardia, sweating and tremors. Further treatment depends on the natural history of the underlying condition. With Graves' disease, the condition may vary considerably in different patients from a condition that undergoes spontaneous resolution in a relatively short period of time to life-long hyperthyroidism. Spontaneous recovery may occur in up to half of the cases, so the initial treatment of choice in the United Kingdom is usually long-term medical therapy. The drugs used fall into two main categories, namely uracil derivatives (propylthiouracil) and imidazole compounds (carbimazole). The latter in a dose of 30–60 mg daily is the most commonly used therapy, given until the patient becomes euthyroid. At that stage, the medication is reduced to a maintenance dose and continued for a variable period, usually up to 18 months to allow the thyroid to recover. Adverse reactions to medication include potential for serious bone marrow depression. A beta-blocker may also be used in the short term to control hyperthyroid symptoms.

In those patients who are poorly controlled or relapse despite adequate medical therapy, ablative therapy either radioactive iodine or thyroidectomy is considered. Radioactive iodine is a common therapy used particularly in patients with Graves' disease who fail or cannot tolerate medical therapy. Indeed, in some countries such as the United States, it may be the first line of treatment, and has potential advantages of cost-effectiveness and avoidance of surgical morbidity, hospitalization and loss of work time. The therapy is given as a capsule which is swallowed, is taken up selectively by active thyroid tissue and destroys the cells of the overactive gland. One or more courses of treatment may be required. The dose given may vary between institutes. A large percentage of patients following radioactive iodine therapy will subsequently become hypothyroid which is an expected side effect and not a complication. It is not recommended for young women who are or wish to become pregnant.

Although most patients with Graves' disease are best treated initially with medical management, surgical intervention is sometimes the preferred treatment for children, and for young women who may have reproductive concerns. Coincident carcinoma, large bulky glands, and patient preference to avoid radioactive iodine or antithyroid medica-
tions or where compliance with other treatment modalities are also reasons for surgical removal of the gland. The effect of I131 treatment on severe ophthalmopathy remains controversial, but presents another potential indication for gland removal.

In the 1990s, a different therapeutic approach was introduced, using intratissue injection of ethanol. This treatment form is relatively inexpensive, but between four and eight successive treatments are usually required to achieve success. Potential complications include exacerbation of thyrotoxicosis, fever, pain at the injection site and haematomata. Also, the treatment carries a high failure rate in bulky thyroids, all of which has meant that this therapy has not become as popular as more conventional treatments.

Spontaneous resolution is not a feature of toxic multinodular goitre or toxic thyroid goitre, and these conditions require definitive therapy. In toxic multinodular goitre, this is usually radioactive iodine followed by surgery. Occasionally, surgery is indicated as initial treatment (once the patient is euthyroid) when the goitre is large, the patient is fit and presents with obstructive symptoms, such as superior vena caval obstruction. For toxic thyroid adenoma, partial thyroidectomy is curative.

In multinodular goitre and in toxic adenoma, spontaneous or long-term medical therapy-induced remissions are much less likely to occur, making ablative therapy the treatment of choice. Radioactive iodine is a viable option to surgery, but MNG often requires multiple doses of iodine to control toxicity due to larger volume of tissue and poorer uptake. As a result, surgery is often preferred over iodine in patients who have large goitres and compression symptoms. This is especially true in younger patients.

In patients with toxic adenoma, although radioactive iodine may be given, it requires high doses of iodine and this is undesirable in younger patients. A unilateral lobectomy for toxic adenoma is curative and has minimal complications, while for multinodular goitre, total or near total thyroidectomy is required.

**Box 22.3 Treatment options for hyperthyroidism**

- Antithyroid drugs
- Radioiodine
- Surgery is an important aspect of therapy in all types of hyperthyroidism. It may be complementary to other treatments

**Indications for the surgical treatment of Graves' disease**

Thyroidectomy is an important therapeutic option in patients with Graves' disease who have failed medical therapy (Boxes 22.4 and 22.5). It is also indicated in children or young woman of reproductive age where there is a general reluctance to give radioactive therapy. It has potential benefit in patients who relapse with thyrotoxicosis after failed radioiodine therapy. It is also considered the
Surgical treatment of hyperthyroidism

The overall objective in patients undergoing thyroid surgery for hyperthyroidism is to control the toxic condition, without significant morbidity and in particular nerve damage or hypocalcaemia. There is no universally accepted treatment protocol, each patient is treated on an individual basis after assessment and explanation of the risks and benefits of the procedure. For Graves’ disease, which is by far the most common and important cause of hyperthyroidism, the present-day recommendations are to remove all or near all of the thyroid tissue accepting that the patient will require treatment for hypothyroidism. This policy recognizes that the more extensive the surgery, the more likely that the disease process would be cured. However, this has to be balanced by the potential for complications. Partial surgical resection with the treatment goal to achieve a euthyroid state is not recommended, except for toxic adenoma, because of the high chance of failure to control the toxic state.

In general, there are four choices of operation:

1. Total thyroidectomy removing all gross thyroid tissue.
2. Total lobectomy on one side with a contralateral subtotal lobectomy leaving only the smallest possible remnant of thyroid tissue posteriorly with intact blood supply to the preserved parathyroid glands (near-total thyroidectomy).
3. Unilateral lobectomy and isthmectomy. This procedure is only suitable for hyperthyroidism caused by a toxic adenoma.
4. Bilateral subtotal thyroidectomy leaving bilateral variable amounts of thyroid remnants in an attempt to have a euthyroid patient. This procedure is mostly of historical interest and is rarely performed at this time.

The literature suggests that total thyroidectomy is the most effective surgery for control of Graves’ disease. Palit et al.
performed a meta-analysis involving 35 studies of over 7000 patients with Graves’ disease treated with surgery and follow up for an average of 5.6 years. Patients treated with less than total thyroidectomy had a persistent or recurrent hyperthyroidism in 8 per cent of cases.

Hypothyroidism following total thyroidectomy is not a complication, but a natural sequela. The main complications associated with thyroidectomy include recurrent laryngeal nerve damage and potentially life-long hypocalcaemia. Permanent recurrent laryngeal nerve damage did not statistically differ between different types of surgery for hyperthyroidism. Similarly, the incidence of permanent hypocalcaemia showed no statistical difference with an incidence of 1.6 per cent for total and 1 per cent for subtotal thyroidectomy. These statistics are from international tertiary care centres with significant surgical expertise. The individual surgeon must make the decision as to the extent of surgery taking into account a number of factors, which include surgical experience and personal complication rates with regard to hyperthyroidism. The occasional surgeon should not expect similar excellent outcomes with total thyroidectomy and should consider the lesser subtotal operation or, possibly more correctly, referral to an experienced thyroid surgeon.

Experienced surgeons treating Graves’ hyperthyroidism and diffuse toxic multinodular goitre will plan a total thyroidectomy, understanding that as long as a thyroid remnant is present, recurrence of the toxic state is possible. The surgeon will pay particular attention to identifying and preserving both parathyroid glands with an intact blood supply on the initial side dissected. If the thyroid surgeon is not happy that two parathyroid glands have been preserved then a more flexible approach to the type of thyroid surgery is applied. The initial total lobectomy on one side is usually followed by a subtotal lobectomy on the opposite side. This approach leaves a small posterior thyroid remnant, the objective of which is that by preserving this thyroid remnant, the blood supply to the parathyroid glands will be preserved. Regarding recurrent laryngeal nerve preservation, total thyroidectomy, total lobectomy and contralateral subtotal lobectomy should have the same low rate of permanent damage with an experienced surgeon who identifies the nerve prior to removal of the gland.

### Surgery for hyperthyroidism

Thyroidectomy for hyperthyroidism requires a similar operation as for other conditions requiring thyroid surgery. The operation may be somewhat more difficult because of increased vascularity and/or inflammation of the thyroid. Preoperative control of the toxic state is essential together with an atraumatic technique. In particular, attention has to be given by the surgeon to identify and preserve the parathyroid glands which may be more intimately attached to the thyroid than usual. In general, although the sequence of steps for the surgery may vary, all have similar broad objectives.

### Preparation of the Patient with Hyperthyroidism for Surgery

It is of paramount importance, particularly in poorly controlled Graves’ disease, that the effects of thyroid overactivity are controlled before surgery to reduce the possibility of thyroid storm. This is caused by a massive increase in the level of free thyroid hormones in the bloodstream. Symptoms are those of extreme hyperthyroidism and may be life threatening. Reduction of thyroid vascularity is also of benefit to help the surgical procedure.

Control is probably best achieved with the input of endocrinology expertise. Initially, a relatively high initial dose of thionamide drugs is used. Once the patient is euthyroid, the dosage may be reduced or thionrine introduced. Propranolol may also be started to control symptoms of hyperthyroidism and stopped after surgery. Beta-blockers are of particular importance in patients requiring emergency thyroidectomy where there is no time to render the patient euthyroid with thionamides.

Iodine administration, such as Lugol’s iodine 5–10 drops three times daily for 7–10 days, may be used to reduce vascularity. Its effects start within 24 hours and have a maximum effect after 2 weeks. Beyond this, prolonged use of iodine will result in a worsening of hyperthyroidism.

### Reasons for Failed Control after Surgery

Following total or near-total thyroidectomy, recurrent disease suggests that thyroid tissue may have been unintentionally left behind. The locations of this tissue should be known by the thyroid surgeon to prevent recurrent disease. The most likely sites include a missed pyramidal lobe. Other sites of thyroid tissue missed include tissue associated with the superior pole, posterior to Berry’s ligament, anterior tracheal wall and adjacent to the parathyroid gland.

### Minimally Invasive Thyroid Surgery

The majority of patients who undergo thyroidectomy have surgery because of possible or definite cancer. Even with fine needle aspiration cytology used as a screening tool, two-thirds of patients prove to have benign pathology and are undergoing an unnecessary excision biopsy of the thyroid, although with the potential for cure if cancer is present, and the diagnosis may not be certain until definite pathology is available. Since thyroid pathology is relatively more common in the female population, a large proportion of these patients are young women who do not appreciate an unsightly neck scar.

Recent improvements in technology have led to minimal invasive surgery becoming the standard of care as with other surgical procedures, such as cholecystectomy. The potential advantages include less dissection, small incisions, less pain and a shorter hospital stay. Huscher et al. were the first to describe a case report of endoscopic thyroid lobectomy in 1997. Since then, a number of centres particularly in Italy and Japan have described and published on a number of endoscopic parathyroid and thyroid techniques.

In general, two main types have been popularized. The first is the ‘closed’ videoendoscopic thyroidectomy, where no neck incisions are performed. The thyroid is approached through multiple ports in the axilla, chest or breast using insufflation and similar techniques perfected in laparoscopic abdominal
operations. This procedure is lengthy and involves significant dissection in areas distant from the thyroid bed and, as a consequence is hardly 'minimally invasive'. These difficulties have meant that this type of procedure has not become popular outside a handful of centres primarily in Asia.

The second type of operation is known as 'minimally invasive video-assisted thyroidectomy' (MIVAT) (Boxes 22.6 and 22.7). This is performed through a small (1.5–2 cm) suprasternal midline incision or lateral neck incision, and does not use gas insufflation.

Selection criteria for patients undergoing this procedure include thyroid nodules less than 3.5 cm with a volume of less than 25 mL based on ultrasound to allow successful removal. The restriction on size means that only approximately 9 per cent of patients having thyroidectomy are potential candidates for this procedure. Recently, Ruggieri et al. suggested that inclusion criteria can be increased to include thyroid swelling with a volume up to 50 mL, if the neck incision size is increased to 3.5 cm.

There is no generally accepted definition of minimal invasion. The authors have found that once skin incisions for thyroidectomy are less than 3 cm, visualization and access is severely restricted. In particular with these smaller incisions, it is more difficult to identify the recurrent laryngeal nerve and parathyroids. Depending on the level of the incision, safe access and mobilization of the superior thyroid pedicle is particularly difficult. In this situation, the introduction of the endoscope allows visualization of these structures and safe delivery of the thyroid.

Thyroidectomy involves a certain number of set surgical steps. Individual surgeons may prefer to perform these in different sequences, for example delivering the thyroid gland before division of the superior pedicle, or dividing the isthmus of the thyroid before exposure of the gland.

In our opinion, MIVAT should not be considered as a separate thyroid procedure when compared to the classical ‘open’ procedure. It should be viewed as one end of a spectrum of thyroid procedures all with similar surgical manouevres and objectives, but approached through a smaller incision using the endoscope to allow identification and preservation of important structures. This restriction in surgical exposure puts a priority on an atraumatic technique with little or no bleeding.

The use of the endoscope is important in the identification of important structures and mobilization of the gland. It is not used during delivery or final removal of the thyroid. The thyroid size is the most important criteria for MIVAT inclusion, because the working space provided by the technique is limited. Miccoli et al. have popularized the midline incision less than 2 cm. Using this technique, only thyroid lesions less than 3.5 cm with a volume of less than 20 mL per lobe on preoperative ultrasound (normal size 12 mL) are suitable. Miccoli et al. also exclude patients who are found to have significant adhesions from thyroiditis. Using these criteria, Miccoli et al. found that only 10 per cent of patients undergoing thyroidectomy were eligible. The authors use less stringent criteria for inclusion. Thyroid lesions clinically less than 3.5 cm are considered for the procedure. If after mobilization of the thyroid difficulties with thyroid delivery are experienced, the incision may be extended up to 3 cm to allow safe delivery without spillage of thyroid contents. Using these criteria, up to 18 per cent of patients may be potential candidates for MIVAT. More experience with this procedure has led to the realization that excessive body mass index is also an important criteria in selection. Excessive adiposity means an increase in working distance from the skin edge, with more difficult dissection and identification of important structures, such as the parathyroid glands. The authors would also suggest that in the older patient with lax skin and well-formed skin creases, there is cosmetically little to be offered between a conventional 4 cm skin crease incision and a 2 cm incision not in a skin crease. Although Miccoli has described central neck dissection, the authors do not practise this routinely and in their hands it is a relative contraindication to the technique.

MEN carriers are uncommon, but current recommendations are that they undergo total thyroidectomy at an early stage, usually by the age of five years to avoid the potential for metastatic nodal disease and central neck dissection. Thus, MIVAT has become our procedure of choice for this condition.

Disadvantages include a learning curve, inability to palpate during the operation, a second assistant is required and the procedure is restricted to a minority of patients with thyroid pathology.

Although this procedure makes day-case thyroidectomy a possibility, the potential for life-threatening postoperative haematoma, as with any thyroid procedure, has lead to the patient being observed overnight.

### Box 22.6 Potential advantages of MIVAT

- Small incision
- Better cosmesis
- Less pain
- Short hospital stay
- Less soft tissue dissection
- MEN carriers

### Box 22.7 Disadvantages of MIVAT

- Learning curve
- Suitability
- Two assistants required and they need to be experienced
- Special instruments
- Lack of feel
- Hypertrophied scar

**Complications of surgery relating to benign thyroid disease**

Complications of surgery relating to benign thyroid disease are listed below:

1. Laryngeal nerve damage:
   - recurrent laryngeal nerve. Temporal paresis seen in approximately 6 per cent, while permanent paresis is
seen in <1 per 500 in experienced hands and should be <2 per cent for all comers.

b. superior laryngeal nerve.

2. Hypocalcaemia associated with:
   a. extent of resection
   b. recurrent goitres
   c. age
   d. gender female more likely
   e. volume of thyroid surgery
   f. Graves’ disease.

Hypocalcaemia occurs in 1–6 per cent of cases in experienced hands and the community rate is of the order of 13 per cent.

3. Haematoma occurs in 1–2 per cent of cases.
4. Wound infection occurs in 1–2 per cent of cases.
5. Tracheomalacia.

**Prevention of wound haematoma**

Haematoma is a potential life-threatening complication of thyroidectomy, the frequency of which is 1–2 per cent in large institutions, but may be higher. Preoperatively, correction of any bleeding tendencies is important and the patient should stop potential problematic medications, such as aspirin, for more than 10 days before operation. An atraumatic technique with fastidious control of bleeding is mandatory. Washing the wound copiously to get rid of clot, and the use of the Valsalva manoeuvre routinely is commonly performed to identify potential bleeding sites before completion of the operation.

Routine neck drains do not decrease the incidence of wound haematoma. Wound haematomas following thyroidectomy usually occur within 12 hours of the surgical procedure. Common sites of bleeding are from vessels associated with Berry’s ligament, but a definite bleeding point may not be found at exploration. Probably the most important aspect in the treatment of wound haematoma is early detection. In this regard, the education of nurses and junior doctors, who are most likely to first see the compromised patient, regarding the clinical features and management is of special importance. We routinely use small amounts of Surgicell to help with haemostasis. Early identification is mandatory and the patient should be returned to theatre expeditiously to allow evacuation of the haematoma.

An expanding haematoma has the potential to cause anoxia in a short period of time. In this situation, bedside decompression is required. To allow this, a clip remover and scissors should be at the bedside to allow opening of the skin, subcutaneous tissue and critically opening the strap muscles in the midline. This prevents further expansion and compromise of the airway. The patient should then be returned to theatre and undergo gas induction by an experienced anaesthetist before formal exploration and control of bleeding.

**TRACHEOMALACIA**

Postoperative airway compromise may arise after extubation due to tracheomalacia and collapse of the trachea. This may require PEEP (positive end expiratory pressure) and/or reintubation for 24–48 hours. Tracheomalacia is rare and occurs in <1.5 per cent of cases. It is important to differentiate this condition from bilateral vocal cord palsy. In most cases, despite significant compression of the trachea on removal of the offending goitre, the trachea settles back into a midline position with normal dimensions. Occasionally, an anchor suture is used to hold the trachea in position. Should the trachea remain narrowed, with the lumen less than 70 per cent its original size, consideration should be given to stenting. In rare circumstances, a tracheostomy may have to be performed (Box 22.8).

**Box 22.8 Key points in reducing complications**

- Preoperative evaluation
- Understanding anatomy
- Routine identification of the recurrent laryngeal nerve and parathyroid glands
- Meticulous haemostasis
- Most important – patience and perseverance

**KEY EVIDENCE**

- Patients with Graves’ disease treated with less than total thyroidectomy have a significant persistent relapse rate. This, together with the fact that revision thyroid surgery is associated with potentially more postoperative complications, suggests that total thyroidectomy is the preferred surgery of choice for Graves’ disease, while for nontoxic MNG, total thyroidectomy should be particularly considered with bilateral disease and in younger patients.

**KEY LEARNING POINTS**

- Multinodular goitre (MNG) is common and often asymptomatic.
- Surgery for MNG is indicated if there is evidence of compression, significant substernal extension or concern of malignancy.
- Sternal split is rarely required.
- Cosmesis is not a good indication for surgery.
- Graves’ disease is by far the most common cause of hyperthyroidism.
- Spontaneous resolution is not a significant feature of natural history in toxic MNG or toxic adenoma.
- Initial medical therapy is always indicated to control the hyperthyroid state.
Surgery is indicated for Graves’ disease in children, women of child-bearing age, large bulky glands and for cancer concern.

REFERENCES


Surgical management of differentiated thyroid cancer

JOHN M CHAPLIN, NEIL SHARMA AND JOHN C WATKINSON

There are in fact two things, science and opinion. The former begets knowledge, the latter ignorance.

Hippocrates (460–377 BC)

INTRODUCTION

Differentiated thyroid cancer (DTC) consists of a group of malignant tumours derived from the thyroid follicular cell. Thyroid cancer is uncommon, making up around 1 per cent of all cancers and DTCs (including papillary and follicular adenocarcinomas) make up around 90 per cent of all thyroid malignancy. In the United Kingdom, there are about 1200 newly diagnosed thyroid cancers a year (3.5 per 100,000 women and 1.3 per 100,000 men per year) compared with an increasing US incidence of 37,000 new cases per year in 2009. The incidence of DTC is higher in women, older patients and those with a family history or previous radiation exposure. There is evidence that the incidence of DTC, particularly papillary thyroid carcinoma (PTC), is increasing, especially in the USA and Canada although death rates in the UK and North America remain the same. Possible reasons for this are discussed later. Despite this, DTC remains an indolent disease with an excellent prognosis.

Interpreting the literature on DTC can be difficult as the disease is both uncommon, indolent and results in few deaths. The data are largely retrospective, often with inadequate follow up, and there are multiple variables and a definite outcome of any prospective trial is unlikely in any one clinician’s working lifetime. By far the most common presentation of DTC is as a solitary thyroid nodule. However, papillary and follicular thyroid cancers may present with locally invasive symptoms and signs such as a laryngeal nerve palsy, dysphagia or airway compromise, evidence of metastatic disease with palpable lymph nodes or distant spread to the bones producing a pathological fracture.

Thyroid nodules are common and occur in approximately 5 per cent of women and 1 per cent of men living in iodine-sufficient areas. Rates of up to 70 per cent can be shown by high resolution ultrasound in randomly selected individuals
although only 5–10 per cent of thyroid nodules represent malignancy. The most appropriate initial investigation of a solitary or dominant thyroid nodule is fine needle aspiration cytology (FNAC). This investigation, combined with high resolution ultrasound, has allowed the design of surgical algorithms that have been incorporated in the recently published American and British Thyroid Association Guidelines.

These guidelines advocate a multidisciplinary approach to the management of DTC with teams which include surgeons, endocrinologists, oncologists as well as nuclear medicine physicians. This allows combined, coordinated and standardized treatment that results in the best possible prognosis for the disease.

**PATHOLOGY AND CLASSIFICATION OF DTC**

Differentiated carcinomas derived from the thyroid follicular cell can be separated into two main categories. The most common type is PTC, which makes up 75–80 per cent of all thyroid malignancies. Presentation ranges from intrathyroid lesions measuring less than 1 cm in diameter called papillary microcarcinomas, through to large tumour masses with extension beyond the thyroid capsule. There are three growth patterns: pure papillary, follicular and mixed. PTC, however, is defined pathologically by the cell type rather than the growth pattern. The PTC cell is oval shaped due to nuclear changes and shows chromatin margination along the nuclear membrane giving a clear nuclear appearance known as ‘Orphan Annie’ nuclei. Similar changes in the nuclear membrane cause the other characteristic nuclear features of longitudinal grooves and inclusions that appear in PTC cells (Figure 23.1). Psammoma bodies are also present in these tumours, particularly in tumours with a papillary growth pattern. These are concentric, lamellated, calcifications caused by repeated deposition of calcium onto necrotic cells at the tips of papillae. PTC is multifocal in up to 80 per cent of cases with up to 50 per cent of these foci being in the contralateral lobe. These tumours tend to metastasize by lymphatic routes and positive nodes can be detected in up to 90 per cent of patients, although the presence of metastatic nodes is not felt to be prognostically significant. Vascular invasion is present in up to 7 per cent and distant metastases present in 5–7 per cent of cases.

In addition to the standard patterns of PTC there are a number of variants, some of which have more aggressive behaviour with respect to distant metastases and death (Box 23.1).

The second most common type of DTC is follicular thyroid carcinoma (FTC), which accounts for approximately 10 per cent of all thyroid cancers. They are more common in women and usually present in an older age group. Again, the most common presentation is with a solitary thyroid nodule. These tumours are slow growing and metastasize via the blood stream. Distant metastases in lung and bone are therefore more common than in PTC, and can be the first signs of the disease. They are not multifocal, do not invade lymphatic channels and lymph node metastases are rare.

There are two main types of follicular carcinoma: (1) Encapsulated or minimally invasive follicular carcinoma (MIFC), which essentially looks like an adenoma and is classified as a malignancy because capsular and/or vascular invasion are demonstrated histologically (Figure 23.2); (2) Widely invasive follicular carcinoma (WIFC), where the tumour diffusely infiltrates the gland (Figure 23.3). WIFC

**Figure 23.1** (a, b) Histological features of papillary thyroid carcinoma. Well-formed papillae with fibrovascular cores. Scalloping of darkly staining colloid is seen. H&E stain × 10 magnification. Papillae are lined by crowded cells with longitudinal nuclear grooves, intranuclear pseudo-inclusions, and optically clear nuclei. H&E stain × 40 magnification.

**Box 23.1 Classification of papillary thyroid carcinoma**

- PTC (papillary/follicular/mixed pattern)
- Follicular variant PTC
- Tall cell variant PTC
- Cribriform PTC
- Columnar cell variant PTC
- Papillary microcarcinoma
- Solid variant PTC
- Diffuse sclerosing variant PTC
can be subclassified into unencapsulated or encapsulated type, the latter showing extensive capsular and/or vascular invasion. WIFC tends to have poorer survival than MIFC (Table 23.1).

The difficulty with these tumours is differentiating MIFCs from adenomas and therein lies one of the great controversies of thyroid pathology and surgery. There is a lack of consensus among pathologists regarding the diagnostic criteria for MIFC. A number of criteria have been cited in the literature, including tumour invasion into/through the capsule and into the capsular vessels. Some authors feel that the diagnosis of follicular carcinoma should be made on the basis of angioinvasion and that tumours that demonstrate capsular invasion only should be referred to as ‘follicular tumours of unknown malignant potential’. These tumours have been shown to have metastatic potential. Other authors have demonstrated disease-specific mortality and distant metastatic recurrence rates of 0 per cent for MIFC with capsular invasion only. The reality probably is that those with capsular invasion only have a very small chance of metastasizing.

### Table 23.1 Outcomes of 172 patients divided into two groups based on the invasiveness of follicular thyroid carcinoma.

<table>
<thead>
<tr>
<th>Invasiveness</th>
<th>Minimal</th>
<th>Extensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at risk</td>
<td>98</td>
<td>72</td>
</tr>
<tr>
<td><strong>End of follow up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>90</td>
<td>54</td>
</tr>
<tr>
<td>Dead (from tumour)</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td><strong>Metastases at diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Distant</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td><strong>Metastases during follow up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Distant</td>
<td>4</td>
<td>18</td>
</tr>
</tbody>
</table>

Reproduced with permission from Lang et al.11

### The Thyroid Nodule

Determining which of the many thyroid nodules that a head and neck surgeon assesses are actually or potentially malignant and which require surgical excision is a complex and multifaceted task. It involves gathering as much information as possible about the nodule and then using a logical, well-defined decision-making process.

### Clinical Assessment

#### History

The majority of patients with thyroid tumours will present with a solitary thyroid nodule (Figure 23.4). The patient’s
age is very important in determining the likelihood of a solitary thyroid nodule being malignant. A truly solitary thyroid nodule in a patient under 20 years old has a 25 per cent chance of malignancy. The risk lessens in middle age to around 7–10 per cent and increases again after the age of 50 when in men the likelihood of a solitary thyroid mass being malignant is 20–40 per cent. Solitary nodules that occur at either extreme of life are more likely to be malignant. Around 10 per cent of patients with DTC will present with palpable neck node metastases and 3–5 per cent will have hoarseness or obstructive symptoms.

The other important historical risk factors in the development of thyroid cancer are radiation exposure, particularly in childhood, and a family history of thyroid disease (Box 23.2).

**Box 23.2** Factors that increase the likelihood of malignancy in a thyroid nodule

A nodule is more likely to be malignant if:

- History of neck irradiation in childhood
- Endemic goitre
- Hashimoto's thyroiditis (risk of lymphoma)
- Prolonged stimulation by elevated TSH
- Solitary thyroid nodule
- Family or personal history of thyroid adenoma
- There is a history of previous thyroid cancer
- Genetic factors –
  - Familial thyroid cancer
  - Cowden's syndrome
  - Familial adenomatous polyposis
- There is an enlarging nodule (particularly on suppressive doses of thyroxine)
- The nodule develops in a person under 14 or over 65 years of age
- The patient is male

The neck must be palpated carefully for lymph nodes; levels of involvement are VI, III, II, IV, V and I in decreasing order of frequency. Even with this knowledge, clinically involved lymph nodes can be difficult to palpate and a high degree of suspicion must be maintained.

Finally, the pharynx, larynx (and upper trachea if indicated) should be examined by direct fibreoptic endoscopy to look for vocal cord paralysis or invasion by tumour.

**Table 23.2** Classification of thyroid nodule cytology.

<table>
<thead>
<tr>
<th>Thy1</th>
<th>Inadequate for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thy2</td>
<td>Benign disease</td>
</tr>
<tr>
<td>Thy3</td>
<td>Suspicious for neoplasia</td>
</tr>
<tr>
<td>Thy4</td>
<td>Suspicious for malignancy</td>
</tr>
<tr>
<td>Thy5</td>
<td>Positive for malignant disease</td>
</tr>
</tbody>
</table>

The thyroid nodule 425

higher rate of nodal metastases. A degree of fixation to surrounding structures may be associated with extrathyroid extension.

The neck must be palpated carefully for lymph nodes; levels of involvement are VI, III, II, IV, V and I in decreasing order of frequency. Even with this knowledge, clinically involved lymph nodes can be difficult to palpate and a high degree of suspicion must be maintained.

Finally, the pharynx, larynx (and upper trachea if indicated) should be examined by direct fibreoptic endoscopy to look for vocal cord paralysis or invasion by tumour.

**Investigations**

**CYTOLOGY**

The interpretation of FNAC by an experienced cytopathologist has had a major impact in the management of nodular thyroid disease. FNAC is a safe, cheap and reliable investigation and, along with FT4, thyroid stimulating hormone (TSH), serum calcium and thyroid antibody levels together with an ultrasound scan should encompass the primary investigations in the management of thyroid nodules. The classification of thyroid cytopathology is shown in Table 23.2. A Thy5 result is only possible in papillary and medullary thyroid carcinoma where a constellation of the expected
cytological features are present. Although lymphoma and anaplastic carcinoma can be occasionally diagnosed with confidence on FNAC, a firm diagnosis is usually only made on Trucut or open biopsy. The features of PTC are listed in Table 23.3 and seen in Figure 23.5.

In follicular variant papillary tumours, there is significantly more difficulty in interpreting the cytological findings because many features overlap with those of hyperplastic nodules or follicular neoplasms (Figure 23.6). The aspirate from a lesion such as this is likely to be classified as Thy4. There are often some nuclear features suspicious for PTC, such as elongation and membrane thickening, but grooves and inclusions are frequently not seen. A lesion that has these features in the background of a mainly follicular pattern cytology is the only lesion that would justify a request for intraoperative frozen section.

The Thy3 category essentially represents lesions that have features that pathologists can only call a 'follicular neoplasm'. This reflects the fact that the diagnosis of follicular carcinoma is made only by observing capsular or vascular invasion and this cannot be determined by FNAC. The cytological features of a follicular neoplasm demonstrate a cellular aspirate with scant colloid. The cells are arranged in groups that often have a microfollicular pattern. There is frequently nuclear overlapping and although nuclear atypia can be present this does not indicate malignancy as this feature is also seen in benign follicular lesions (Figure 23.7).

Cytology representing a benign pattern (Thy2) would contain more colloid and a sparse cellular population with no repetitive microfollicular pattern and no atypical cellular features (Figure 23.8). In this situation there is still a small risk of the lesion being a follicular carcinoma. Non-diagnostic cytology (Thy1) has been shown to be malignant in up to 9 per cent of cases on permanent histological examination. The recommendation is to initially repeat the FNAC in this situation.

LABORATORY INVESTIGATIONS

Investigation of a thyroid nodule should include TSH, T3, T4 and thyroid antibodies. An elevated TSH is associated with an increased risk of malignancy. Antibodies are useful in the interpretation of the thyroid function tests, the prediction

| Table 23.3 Cytological features of classical papillary thyroid carcinoma. |
|-------------------|------------------------------------------------------------------|
| Cells             | Cellular aspirate in papillary groups, clusters or single cells   |
| Background        | Bubble gum colloid, stromal fragments, calcific debris (psammoma bodies), macrophages |
| Nuclear features  | Elongation, membrane thickening, chromatin clearing, nuclear grooves and inclusions. |

Figure 23.5 (a, b) FNAC cytological features of papillary thyroid carcinoma. (a) Neoplastic cells arranged in angulated sheets or papillae. Note the dense squamoid cytoplasm and nuclear enlargement. Diff-Quik stain™ × 40 magnification. (b) The diagnosis of papillary thyroid carcinoma rests on the identification of nuclear features which include crowding, longitudinal nuclear grooves, intranuclear pseudo-inclusions, and pale powdery chromatin. Papanicolaou stain × 40 magnification.

Figure 23.6 Follicular variant of papillary carcinoma. The follicular variant of papillary carcinoma may be difficult to distinguish from follicular adenoma or carcinoma. The diagnosis rests on identification of the nuclear features of papillary thyroid carcinoma. Contrast with benign follicular epithelium at the top left of the photograph. H&E stain × 20 magnification.
of postoperative subclinical hypothyroidism and in the assessment of the serum thyroglobulin. Preoperative measurement of thyroglobulin is not usually helpful unless the patient has had previous treatment. Serum calcium can also be considered to exclude hyperparathyroidism and to provide a baseline pre-surgery.

Radiology

ULTRASOUND

Ultrasound is useful in measuring tumour size, diagnosing multinodular goitres and excluding contralateral disease. Ultrasonography can also be used to evaluate complex cysts and can distinguish purely cystic nodules (only rarely is a cystic nodule associated with thyroid cancer). Calcification may be detected and although it occurs in both benign and malignant disease, it tends to have different features.

Scintigraphy

Scintigraphy, which has been available for longer than both computed tomography (CT) and magnetic resonance imaging (MRI), was previously routinely used for investigation of...
the solitary thyroid nodule. Iodine-123 ($^{123}$I) is probably the optimal radionuclide for thyroid imaging because of its physiological properties but, as it is cyclotron generated, cost and availability limit its use. The radionuclide technetium-99m ($^{99m}$Tc), in the chemical form of pertechnetate ($TcO_4^-$), is trapped (but not organified) by the thyroid gland in a similar manner to the iodide ion. It has a 6-hour half-life and is cheap and readily available with a low radiation dose; it is therefore now used in thyroid imaging. Pertechnetate uptake, however, is low (0.4–4 per cent) and does not always match the physiological uptake of iodide which leads to a high background activity. Nonetheless, with careful attention to scanning technique the majority of nodules greater than 5 mm diameter can be visualized on scintigraphy. False negative results are often associated with smaller lesions in the isthmus, but these are usually easy to palpate and therefore do not cause a significant problem. More than 90 per cent of lesions identified will not concentrate the radionuclide (‘cold’ nodules). These clinically solitary non-functional nodules may be an adenoma, a carcinoma or a cystic or dominant nodule in a non-palpable multinodular goitre. Truly functioning nodules (also called ‘hot’ or ‘toxic’ nodules) are highly unlikely to be malignant so this investigation is probably not cost-effective for cancer assessment. Scintigraphy is now only used to identify hot nodules in a patient with elevated thyroxine or suppressed TSH levels. A diagnostic protocol is shown in Figure 23.9.

CT of the neck and thorax is of help in assessing the extent and relationship of larger thyroid tumours, particularly those involving the larynx, trachea, pharynx, oesophagus and major vessels (Figure 23.10). It is also used to demonstrate nodal deposits in the neck and mediastinum, direct retrosternal extension and pulmonary metastases (Box 23.3).

MRI allows multiplanar imaging of the neck and has good inherent soft tissue contrast. Vessel involvement can be assessed with MR angiography. Additional advantages over CT include the fact that iodine containing contrast is not required and there is no radiation exposure. Both MRI and CT may be difficult investigations for patients with a compromised airway for whom lying flat is uncomfortable.

Prognostic factors

There are a number of prognostic factors associated with DTC and these can be divided into those related to patient, tumour and management factors. They are listed in Table 23.4.

<table>
<thead>
<tr>
<th>Box 23.3</th>
<th>Features of thyroid cancer identified on anatomical imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Extracapsular extension</td>
<td></td>
</tr>
<tr>
<td>• Contralateral lobe</td>
<td></td>
</tr>
<tr>
<td>• Vascular invasion</td>
<td></td>
</tr>
<tr>
<td>• Mediastinal involvement</td>
<td></td>
</tr>
<tr>
<td>• Pharyngeal and oesophageal involvement</td>
<td></td>
</tr>
<tr>
<td>• Laryngeal and tracheal involvement</td>
<td></td>
</tr>
<tr>
<td>• Nodal disease (levels I–VII)</td>
<td></td>
</tr>
<tr>
<td>• Distant metastatic spread</td>
<td></td>
</tr>
</tbody>
</table>

Patients under 45 years have a better prognosis and women in general do better than men. Tumours that present at advanced age generally have a poorer prognosis.29 There
is a linear relationship between the size of the tumour and prognosis\(^\text{30}\) (Figure 23.11) and the grade of tumour is also important. The tall cell variant of PTC is particularly aggressive as are those follicular tumours which exhibit extensive vascular invasion (WIFC).\(^\text{31}\) Patients with PTC fare better than those with follicular tumours. The presence of either local invasion or distant spread is associated with a worse prognosis, as are nodal metastases, particularly in elderly patients.\(^\text{15, 31}\)

**Staging**

The staging system that is most widely used for DTC is the TNM classification for malignant tumours.\(^\text{33}\) This classification is based on some of the prognostic factors listed above. There should be histological confirmation of the disease and division of cases by histological type. The current TNM (tumour, node, metastases) classification for carcinoma of the thyroid is set out in Table 23.5 and 23.6.

**Table 23.4** Prognostic factors in differentiated thyroid cancer.

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Tumour factors</th>
<th>Management factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Tumour size</td>
<td>Delay in therapy</td>
</tr>
<tr>
<td>Sex</td>
<td>Tumour histology</td>
<td>Extent of surgery</td>
</tr>
<tr>
<td>Nodal metastases (in elderly patients)</td>
<td>Experience of the surgeon</td>
<td></td>
</tr>
<tr>
<td>Local invasion</td>
<td>Thyroid hormone therapy</td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>Treatment with postoperative radioiodine</td>
<td></td>
</tr>
</tbody>
</table>

Although the current thyroid staging systems in use around the world correctly stratify mortality rates among various subsets of patients, they have their limitations. Some patients in the lowest risk groups do die of cancer, particularly if the risk groups are only stratified into either low or high. In one study, 10 per cent of patients dying of DTC had been staged as either TNM stage I or II.\(^\text{34}\) In addition, the systems that use age to stratify risk are often inaccurate in predicting the relationship between recurrence and survival since younger patients often have higher recurrence rates but lower death rates than older ones. Most staging systems have been derived from multivariant analysis and have survival as their end point. They frequently fail to consider recurrence or the effect of treatment and rely solely on information available postoperatively. Finally, recurrence free status and survival cannot be assured by low stage.

The first staging system was suggested by the European Organisation for Research and Treatment of Cancer (EORTC) in 1975 and incorporated a scoring system based on male gender, histology, “T” stage and distant metastases.\(^\text{35}\) In 1987, the Mayo clinic described the AGES classification system\(^\text{32}\) for PTC which was based on age, tumour grade, extrathyroid invasion and tumour size. The main problem with this system was that reporting of tumour grade for PTC was variable among pathologists and was available only after surgery had been performed. The following year, Cady and Rossi from the Lahey clinic introduced the AMES classification for DTC (age, distant metastases, extrathyroid invasion and tumour size).\(^\text{36}\) This system seemed user-friendly, however there still were some shortcomings: the data was retrospective, the earlier cases were incomplete with regard to tumour size and it included both papillary and follicular thyroid cancers. The Memorial Sloan Kettering (MSK) Hospital introduced the GAMES classification which is based on the size and extent of the tumour as well as its grade, the presence of distant metastases and patient gender.\(^\text{37}\) In 1992, workers at the Karolinska Institute in Stockholm added the prognostic risk factor of DNA ploidy to the AMES system and came up with the DAMES classification for PTC.\(^\text{38}\)

The Mayo clinic brought out a more elaborate staging system for PTC called the MACIS system\(^\text{30}\) (Table 23.7). This system placed patients into four groups based on their scores. Patients with a MACIS score of less than 6 had a 99 per cent chance of living 20 years. In this system there was consideration of the impact of treatment; patients who had incomplete resection of tumour could be placed in a poorer prognostic group.

The problem with many of these classification systems is that they are based on retrospective data from single institutions and have no proven advantages over the universally used and widely accepted TNM system,\(^\text{39}\) which can accurately predict survival based on a variety of prognostic factors (Table 23.8).

**MOLECULAR GENETICS OF THYROID CANCER**

The development of molecular technology over the last two decades has allowed insight into the genetic abnormalities associated with the molecular biology of thyroid cancer, although the development of novel diagnostic and therapeutic modalities is still awaited. Malignant thyroid tumours generally
have a monoclonal origin, suggesting that genetic events in a single cell account for their development. These events may involve the activation of oncogenes or the inactivation of tumour suppressor genes. **In vivo** mechanisms of action of known oncogenic pathways have been identified in transgenic mice. Several oncogenes are known to play an important role in thyroid carcinogenesis and development, for example the RET and TRK rearrangements and BRAF and RAS mutations in PTC and PAX8-PPARγ translocations and RAS mutations in FTC.

**RET/PTC**

RET is a proto-oncogene located at chromosome 10q11.2 which encodes a transmembrane tyrosine kinase receptor.

<table>
<thead>
<tr>
<th>Table 23.5</th>
<th>TNM staging for thyroid carcinoma from AJCC cancer staging manual, 7th edn, 2009.33</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour 1 cm or less in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour 1–2 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but not more than 4 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension, limited to the thyroid or any tumour with minimal extrathyroid extension (e.g. extension to sternothyroid muscle or perithyroid soft tissues)</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour of any size extending beyond the thyroid capsule and invades any of the following: subcutaneous soft tissues, larynx, trachea, oesophagus, recurrent laryngeal nerve</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades prevertebral fascia, mediastinal vessels, or encases carotid artery</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis in level VI (pretracheal and paratracheal, including prelaryngeal and Delphian lymph nodes)</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis in other unilateral, bilateral or contralateral cervical or upper/superior mediastinal lymph nodes.</td>
</tr>
<tr>
<td>cM0</td>
<td>Clinically no distant metastasis</td>
</tr>
<tr>
<td>cM1</td>
<td>Distant metastasis clinically</td>
</tr>
<tr>
<td>pTNM</td>
<td>Pathological classification</td>
</tr>
<tr>
<td>pN0</td>
<td>Histological examination of a selective neck dissection specimen will ordinarily include six or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0</td>
</tr>
<tr>
<td>pM0</td>
<td>Distant metastasis proven microscopically</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 23.6</th>
<th>Stage grouping for papillary and follicular carcinoma from AJCC cancer staging manual, 7th edn, 2009.33</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>Papillary or follicular under 45 years</td>
<td>Any T</td>
</tr>
<tr>
<td>Papillary or follicular 45 years and older</td>
<td>T1</td>
</tr>
<tr>
<td>Papillary or follicular under 45 years</td>
<td>T2</td>
</tr>
<tr>
<td>Papillary or follicular 45 years and older</td>
<td>T3</td>
</tr>
<tr>
<td>Papillary or follicular under 45 years</td>
<td>T1,T2,T3</td>
</tr>
<tr>
<td>Papillary or follicular 45 years and older</td>
<td>T1,T2,T3</td>
</tr>
<tr>
<td>Papillary or follicular under 45 years</td>
<td>T4a</td>
</tr>
<tr>
<td>Papillary or follicular 45 years and older</td>
<td>T4b</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 23.7</th>
<th>Prognostic variables for papillary thyroid carcinoma. The MACIS staging system.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Distant 'M'etastases (3)</td>
</tr>
<tr>
<td>A</td>
<td>'A'ge (3.1 or 0.08 × age)</td>
</tr>
<tr>
<td>C</td>
<td>'C'ompleteness of excision (1)</td>
</tr>
<tr>
<td>I</td>
<td>extrathyroid 'I'nvasion (1)</td>
</tr>
<tr>
<td>S</td>
<td>'S'ize (cm)</td>
</tr>
<tr>
<td>Score</td>
<td>= 3.1 + (0.3 × size) + 1 + 1 + 3.1 (0.08 × age if &lt; 40 years)</td>
</tr>
</tbody>
</table>

Reproduced with permission from Hay et al.30

The ligand for RET has recently been identified as glial cell-line neutrophic factor (GDNF). RET has been identified principally in PTC and several mutations have been identified. These are all due to specific oncogenic rearrangements of the tyrosine kinase domain of the RET gene. More than 10 RET/PTC rearrangements have been identified, many of which are seen in radiation-induced tumours. The most common rearranged forms of RET are RET/PTC1 and RET/PTC3 occurring in 60–70 and 20–30 per cent of PTCs respectively.40

The role of the RET mutation has been demonstrated in transgenic mice with targeted overexpression of RET/PTC1 and RET/PTC3. The mice develop tumours similar to human PTC. RET rearrangements are found frequently in tumours from paediatric patients and those exposed to radiation in childhood. They are more frequent in papillary microcarcinomas, classic papillary and diffuse sclerosing variant and rare in the follicular variant. RET/PTC can transform transfected follicular cells **in vitro**, which then demonstrate the nuclear features of PTC. The RET/PTC mutation was found in 60 per cent of Ukrainian
thyroid cancers after the Chernobyl accident, and RET/PTC3 was present in 19/25 of the unusual solid/follicular subset of papillary cancers seen in affected children.41

**RAS**

The RAS genes encode signal transducing proteins involved in the transduction of intracellular signalling from the cell surface to the nucleus in a similar way to G proteins. RAS activation stimulates mitosis and reduced differentiation. There are three separate RAS genes, Ki-RAS, N-RAS and Ha-RAS, and point mutations have been identified in thyroid cancers. These point mutations (usually codons 12, 13 or 61) can produce activated RAS, which is potently oncogenic. RAS mutations are uncommon in conventional papillary thyroid cancer (less than 10 per cent) but are frequently present in follicular variant PTC. RAS mutations are equally prevalent (around 50 per cent) in follicular adenomas and carcinomas. These mutations seem to predispose to development of poorly or undifferentiated carcinomas, such as anaplastic tumours. Activated RAS transfected into normal human follicular cells in vitro leads to an increase in cell proliferation, which is a key step in tumour formation.

**TRK**

TRK is an oncogene, located on chromosome 1q22, which codes for a transmembrane tyrosine kinase receptor, whose ligand is nerve growth factor. It is mutated in 10–25 per cent of papillary carcinomas. Similar to RET, the TRK gene undergoes oncogenic activation by rearrangement of chromosomes. They are less common than RET rearrangements in PTC and the incidence in post-Chernobyl PTC is around 3 per cent.

**BRAF**

The RAF proteins are serine/threonine protein kinases that are critically involved in cell proliferation, differentiation and apoptosis by signalling along the mitogen-activated protein kinase (MAPK) pathway. There are three forms: ARAF, BRAF and CRAF. BRAF is the prominent form in thyroid follicular cells and of the three it is the most potent activator of the MAPK pathway. BRAF mutations have been demonstrated in 40–70 per cent of PTC of most types, except follicular variant PTC. There is also evidence that BRAF mutations are associated with poor clinical outcome in PTC.42 They are also frequently seen in poorly differentiated or anaplastic carcinomas, particularly those with a papillary component, implying these tumours may develop from BRAF-positive PTC that dedifferentiate.43 BRAF mutations are, however, not commonly seen in radiation-induced thyroid cancers.

**PPPAX8−PPARγ**

This gene rearrangement is the result of a recurrent translocation seen in follicular lesions of the thyroid. The consequence of the translocation is fusion of the DNA of the thyroid transcription factor PAX8 to domains A–F of the peroxisome proliferation-activated receptor (PPAR). PAX8−PPARγ rearrangements are seen more commonly in follicular carcinomas compared to adenomas (53 versus 8 per cent) and are more frequent in patients with a history of radiation exposure. PAX8−PPARγ-positive follicular carcinomas are likely to be widely invasive while tumours negative for this rearrangement are for the most part minimally invasive.

**TREATMENT OF DTC**

There are many historical controversies regarding the optimal treatment of DTC, which mainly relate to the type of operation and the extent of thyroid surgery. Few dispute that the mainstay of treatment for DTC is surgery with radioactive iodine remnant ablation and thyroxine suppression. External beam radiation (and even chemotherapy) is also occasionally offered as adjuvant therapy. However, the extent of surgery is a widely debated issue and relates to lobectomy versus near-total or total thyroidectomy, particularly in low risk disease based on the prognostic indicators discussed earlier. The arguments for and against total thyroidectomy are shown in Table 23.9.45

The arguments for and against lobectomy versus total thyroidectomy also vary with the tumour type. It is recognized that PTC can be multifocal in up to 80 per cent of cases and that 50 per cent of the foci can be in the contralateral lobe.46 Despite this, local recurrence rates in tumours with PTC have been shown to be only around 5 per cent.47 The group at the MSK Cancer Centre argue strongly for conservative surgery in the form of lobectomy alone in low risk DTC, including PTC, because of the low mortality rates
Table 23.9  The arguments for and against total thyroidectomy.45

<table>
<thead>
<tr>
<th>'Total' thyroidectomy</th>
<th>'Less than total' thyroidectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioactive iodine can be used to detect and treat residual normal thyroid or local</td>
<td>Fewer complications develop</td>
</tr>
<tr>
<td>or distant metastases</td>
<td></td>
</tr>
<tr>
<td>Serum thyroglobulin is a more sensitive marker of recurrence when all normal thyroid</td>
<td>One half of local recurrences can be cured with surgery</td>
</tr>
<tr>
<td>is removed</td>
<td></td>
</tr>
<tr>
<td>The microscopic foci of cancer present in up to 30–70% of patients are eliminated as</td>
<td>Less than 5% of recurrences occur in the thyroid bed</td>
</tr>
<tr>
<td>sites of recurrence</td>
<td></td>
</tr>
<tr>
<td>Recurrent cancer develops in the remaining contralateral lobe in approximately 5–15%</td>
<td>Little clinical significance is given to multicentricity</td>
</tr>
<tr>
<td>of patients and one half of these may die of thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Recurrence is lower in patients who have undergone total thyroidectomy</td>
<td>Prognosis is good with lesser procedures</td>
</tr>
</tbody>
</table>

Facilitates accurate follow up and staging
Improved survival rates
Is the treatment of choice for multinodular goitre and thyrotoxicosis
Minimal complications of total thyroidectomy in experienced hands

(1 per cent at 20 years).48 However, little mention is made of the rates of local and regional recurrence which although may not influence survival, certainly contribute to the morbidity of the disease with respect to reoperation, further adjuvant therapy and potential complications. Analysis of a large series of patients with low risk PTC treated at the Mayo clinic over 50 years demonstrated a significant difference in local recurrence rates between those treated with bilateral lobar resection and unilateral lobectomy (2 and 14 per cent respectively ($p = 0.0001$)).49 This paper also showed a significant difference in regional recurrence rates favouring bilateral resection but no difference between the two approaches with respect to distant recurrence rates or cause-specific mortality.49 Total or near-total thyroidectomy is usually recommended because of the probable reduction in local and regional recurrence, even though there is probably no influence on survival.50

Postoperative radioactive iodine may obscure the effect of surgery, although it would seem that surgery and 131I therapy have independent effects on recurrence and cancer mortality.51

In FTC, multifocality and lymph node recurrence are not common and the arguments for total thyroidectomy versus lobectomy surround detection of recurrence with thyroglobulin levels and risks of distant disease and mortality. Usually the decision to perform completion thyroidectomy at a second operation is made once formal analysis of the ipsilateral tumour has been performed original lobectomy.52 Data from the Mayo clinic showed that in low risk FTC where vascular invasion is absent there were no distant metastatic recurrences and no cause-specific deaths.13 The authors in this series and others argue for conserva-

tive surgery in minimally invasive FTC because of the low recurrence and mortality rates.11

It is well recognized that there are difficulties with making evidence-based decisions in the management of DTC. The vast majority of patients are in the low risk category and the disease is indolent with low recurrence and mortality rates. For these reasons there are no large prospective series with adequate follow-up periods. The data available are therefore based on retrospective analysis of large groups of patients treated in single institutions over long periods of time. The data are often incomplete, and treatment strategies and quality can vary over the time the analysis occurs. Nevertheless, these data are the best that we have and surgeons treating patients with DTC must have a rational and consistent therapeutic strategy based on this evidence. In an attempt to standardize treatment, both the British Thyroid Association (BTA) in association with the Royal College of Physicians and the American Thyroid Association (ATA) have developed guidelines for the management of thyroid cancer. The BTA first published guidelines in 200253 and updated them in 2007.4 The American guidelines were first published in 199654 and last updated in 2009.5

Although there are some recognized differences between these guidelines,55 they both offer an up-to-date review of the current evidence available in the management of this complex disease. There is agreement in principle about methods of treatment, with recommendations including more use of ultrasound as both an initial investigation and at follow up, more total thyroidectomies, increased use of central neck dissection and less radioiodine. The UK guidelines6 will form the basis of the recommendations for treatment made in this chapter.

### SURGICAL TREATMENT OF DTC

Surgery is the mainstay of treatment in DTC and the main aim of initial therapy is to remove the primary tumour disease and that which has spread beyond the thyroid capsule and involved cervical lymph nodes. Other goals are to minimize treatment- and disease-related morbidity and to permit accurate staging of the disease. Thyroidectomy facilitates postoperative treatment with radioactive iodine and appropriate treatment minimizes the risk of disease recurrence and metastatic spread and caters for long-term accurate surveillance.4 Surgical options for treatment of the thyroid gland should be limited to a lobectomy (the complete removal of one thyroid lobe including the isthmus), near-total lobectomy (a total lobectomy leaving behind the
smallest amount of thyroid tissue (less than 1 g) to protect
the recurrent laryngeal nerve), a near-total thyroidectomy
(either a complete lobectomy on one side and near-total on
the other or a bilateral near-total lobectomy or a total thy-
roidectomy (complete removal of both lobes of the gland, the
isthmus and the pyramidal lobe). These operations are illu-
strated in Figure 23.12.

Traditionally, lymph node metastases have not been
thought to be a significant prognostic indicator in DTC,
but recent studies have demonstrated that this is not the
case in high risk patients (particularly those over 45 years).56
In addition, lymph node involvement has been shown to
increase the risk of local and particularly regional recurredence.56
Traditional methods of selective nodal excision
(berry picking) have been shown to result in higher rates
of recurrence than systematic compartment orientated nodal
dissection such as a selective neck dissection57 and most
institutions recommend selective or comprehensive dissec-
tion for previously untreated neck disease.

Surgical management of involved cervical lymph nodes
requires an understanding of the lymph node anatomy of the
neck and likely patterns of spread of disease to the lymph
nodes. The neck is divided into lateral and central com-
partments. Each compartment is further divided into levels as
outlined in Table 23.10 and as seen in Figure 23.13. There
are two main categories of neck dissection; a comprehensive
neck dissection involves resecting levels I–V and is sub-
classified based on the type and amount of other structures
excised; a selective neck dissection involves removing some,
but not all, of levels I–V and preservation of the internal
jugular vein, spinal accessory nerve and sternocleidomastoid
muscle. The types of neck dissection are described in detail in
Chapter 36, Neck dissection. It is well recognized that
regional metastases from PTC are most commonly found
in level VI.58 These nodes are often very difficult to palpate
and may therefore only be found at surgery or preoperatively
with imaging and possibly ultrasound guided FNAC. In the
lateral neck, in patients with palpable nodal disease, the most
frequently involved levels are II, III and IV and of these level
III is most common.59 Level II is next most frequently
involved and level IIb above the nerve is recognized to har-
bour positive lymph nodes in a significant number of
patients.59

Levels V and I are usually only affected when there is
involvement of multiple neck levels.60 In addition, multiple
levels are more frequently involved than single levels in this
group of patients.20 Recently, clinically node-negative high
risk patients (more than 45 years) have been demonstrated
to have higher rates of occult nodal involvement than low
risk patients and that even rates in patients less than 45 years
are around 30 per cent.51 There is also an increase in the
incidence of recurrence in the central compartment. Repeat
surgery in the central area is associated with a higher risk
of permanent hypoparathyroidism and recurrent laryngeal
nerve injury than central neck dissection performed at the
time of total thyroidectomy.62, 63 It is advised that level
VI node dissection should be performed at the same time
as total thyroidectomy,64 and that there is no increased
morbidity associated with this procedure.64 It is argued that
microscopic nodal disease in the central compartment can
be effectively treated by radioactive iodine. However, some
papillary carcinomas do not concentrate iodine and this
has been demonstrated particularly in the cells of older

---

Table 23.10  Cervical lymph node levels.

<table>
<thead>
<tr>
<th>Lateral compartment</th>
<th>I</th>
<th>Submental and submandibular nodes further divided by anterior belly of digastric muscle into Ia and Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
<td>Deep cervical nodes from the skull base to the level of the hyoid. Further divided by the relationship to the accessory nerve (level 2a being medial and 2b lateral)</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Deep cervical nodes from the level of the hyoid to the cricoid</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Deep cervical nodes from the level of the cricoid to the suprasternal notch</td>
</tr>
<tr>
<td></td>
<td>V</td>
<td>Posterior triangle nodes can be divided by their relationship to a plane drawn through the level of the cricoid cartilage. (Va is above and Vb is below the accessory nerve)</td>
</tr>
<tr>
<td>Central compartment</td>
<td>VI</td>
<td>Pre- and paratracheal nodes from the level of the hyoid bone above to the suprasternal notch below and the carotid artery laterally</td>
</tr>
<tr>
<td>Mediastinal compartment</td>
<td>VII</td>
<td>Superior mediastinal nodes as far as the superior aspect of the brachiocephalic vein</td>
</tr>
</tbody>
</table>
patients’ tumours, potentially reducing the efficacy of this treatment.65

SURGICAL MANAGEMENT OF THE THYROID GLAND IN PAPILLARY THYROID CANCER

Patients with cancers 1 cm in diameter or less without evidence of lymph node metastases can be adequately treated by lobectomy and thyroxine suppressive therapy. In the majority of patients with tumours greater than 1 cm, multifocal disease, familial disease, extrathyroid extension and positive lymph node involvement or distant metastases, total thyroidectomy is indicated. Total or near-total thyroidectomy is also indicated in those with a history of previous radiation exposure in childhood.4 If the diagnosis of PTC is made after lobectomy and completion thyroidectomy is required, the operation should be offered within 8 weeks of histological diagnosis. In this situation, if the risk of recurrence is judged to be low, lobectomy alone may be appropriate in tumours larger than 1 cm in diameter.4

SURGICAL MANAGEMENT OF THE NECK IN DTC

The BTA 2007 guidelines make the following grade C recommendations based on level IV data. In PTC, nodal disease in level VI discovered at surgery is treated with a central (level VI) neck dissection. If suspicious or clinically involved nodes are identified in the lateral neck and are confirmed by FNAC or by intraoperative frozen section, then a selective neck dissection incorporating levels IIa–Vb with preservation of the spinal accessory nerve (SAN), internal jugular vein (IJV) and sternocleidomastoid muscle (SCM) should be performed. The guidelines also state that node-positive FTC should be managed in a similar way. In patients with PTC and clinically uninvolved nodes but who

Figure 23.13  Cervical lymph node levels.
are deemed high-risk (i.e. any of the following features: male, age greater than 45 years, tumours greater than 4 cm diameter, presence of extracapsular or extrathyroidal disease), then total thyroidectomy and level VI node dissection should be performed.4,5

If the neck disease involves surrounding structures such as the IJV, SCM or skin, then these structures, should also be excised as part of the lateral neck dissection. Level IIb may also be addressed as there is evidence of moderate risk of these nodes being involved and recurrent disease is difficult to treat at this site.59

The options for surgery on a solitary thyroid nodule based on Thy3, Thy4 or Thy5 findings are shown in Table 23.11.

**MANAGEMENT OF EXTRATHYROID EXTENSION**

Although DTC is usually an indolent disease with a good prognosis, 8–26 per cent of patients can present with locally advanced cancer with invasion of surrounding structures, leading to increased morbidity and mortality.67, 68, 69 The presence of extrathyroidal extension (ETE) is associated with higher rates of overall recurrence and mortality than tumours confined to the thyroid,68 with local airway invasion being the cause of death in up to 50 per cent of deaths due to DTC.70

Although ETE occurs in both papillary and follicular carcinomas with equal frequency, it is seen more frequently in PTC due to its higher incidence. The prognostic risk factors significantly associated with ETE in PTC include age greater than 50 years, tumour size greater than 4 cm, non-encapsulated tumours and aggressive histological variants (diffuse sclerosing, solid, tall cell and poorly differentiated).68 The strap muscles, recurrent nerve and trachea are the most common extrathyroid structures involved in the central neck compartment; the oesophagus is less so but is usually associated with laryngotracheal invasion. In the lateral neck the SCM, IJV, carotid artery, cranial nerves X, XI, phrenic and cervical sympathetic chain can all be involved either from direct thyroid tumour extension or from extranodal extension from cervical metastatic nodes.71 ETE is associated with higher rates of lymph node metastases and distant metastases than tumours without ETE68 and it is also seen more commonly in patients who present with recurrent DTC. The MACIS and AMES prognostic scoring systems include ETE as an indicator of poorer prognosis and higher risk.

Surgery is widely recognized to be the most effective management of ETE in DTC and it is felt that complete excision of tumour results in lower recurrence rates and mortality.67 This is, however, controversial and many papers present conflicting evidence. If the invaded structure is easily resected with minimal morbidity (e.g. strap muscles or recurrent laryngeal nerve), then there is generally no argument and most authors recommend excision to obtain clear histological margins. The more difficult decision is whether to perform radical excision when there is invasion of the laryngopharynx, trachea and oesophagus, or both recurrent laryngeal nerves. Some authors recommend preservation of a functional nerve even if it is clinically invaded by tumour because complete excision of papillary carcinoma with resection of the recurrent laryngeal nerve does not improve survival over incomplete excision.72 The UK guidelines recommend incomplete excision of tumour, preservation of one or both recurrent laryngeal nerves and treatment with postoperative 131I and thyroxine suppression, plus or minus external beam radiation if both recurrent laryngeal nerves are threatened.4 Where there is superficial invasion of the laryngotraheal tree and where limited resection such as shaving leaves behind only microscopic disease, it appears that local recurrence and survival results are comparable with patients treated with completely excised invasive tumour. However, if gross disease is left behind, recurrence rates are significantly higher and survival is significantly reduced.69, 73 If there is gross invasion of the trachea or larynx, and particularly if there is intraluminal involvement, then radical resection including circumferential or partial resection of the tracheal wall and partial or total laryngectomy will reduce local recurrence rates and improve survival. An alternative to surgery is external beam radiotherapy plus or minus radioactive iodine. In patients where there is ETE, it has been shown that the addition of external beam radiation therapy offers improved locoregional control even where gross macroscopic disease has been completely excised.74 The UK guidelines recommend this treatment particularly in patients where the residual tumour fails to concentrate sufficient amounts of radioactive iodine.4

**MANAGEMENT OF DIFFERENTIATED THYROID CANCER IN PREGNANCY**

As DTC is three times more common in women and the majority is low risk disease occurring in younger people, it is...
inevitable that the head and neck surgeon will be faced with patients being diagnosed during pregnancy at some time during their career. Women presenting with a thyroid nodule during pregnancy have a higher chance of the nodule proving to be malignant than non-pregnant women. A diagnosis of DTC during pregnancy creates added anxiety with uncertainty regarding the optimal timing of treatment delivery and the impact on maternal and neonatal morbidity. Human pregnancy has been shown to accelerate the growth of thyroid cancers, but despite an increase in size of the tumours it seems that there is no impact on prognosis if treatment is delayed until after delivery compared to patients treated during their pregnancy. If a woman is diagnosed early in her pregnancy there will obviously be greater delay to treatment time if surgery is postponed until after delivery than if she is diagnosed later on. There are reports suggesting that delays greater than one year can lead to poorer prognosis.

There is significant risk to the fetus if an operation is performed during the first trimester and a higher risk for maternal vascular complications if elective surgery is performed in the third trimester. Another consideration is that postponing surgery until the postpartum period can interfere with infant care and breastfeeding protocols and can lead to further delays in treatment. Clearly, if there is symptomatic compression with airway compromise caused by the thyroid disease at any time during pregnancy early intervention is necessary. There is controversy regarding the optimal timing of surgery and authors generally recommend either performing surgery during the second trimester or to delay treatment until after delivery. Adjuvant treatment with radiiodine should be delayed until after delivery and breastfeeding is completed but suppressive doses of thyroxine are safe to use during pregnancy.

**MANAGEMENT OF DTC IN CHILDHOOD**

Although uncommon, thyroid nodules presenting in children are more likely to be malignant than in their adult counterparts. DTC frequently presents at a more advanced stage in children and young people than in adults, with a higher rate of lymph node and distant metastases and higher postoperative rates of lymph node recurrence, particularly if they are younger than 10 years old. Recurrences are also more common in patients who have positive lymph nodes and who have multifocal thyroid carcinoma. Despite these seemingly poor features, DTC in children tends to be less fatal than in adults and overall survival is significantly better even if they have distant metastatic disease. Children with a history of radiation exposure are at particular risk of developing thyroid cancer and should be followed up closely. Any nodular thyroid disease should be regarded with a high index of suspicion and treated aggressively.

The general principles of treatment are the same as in adults. A total thyroidectomy is usually recommended as management for the primary tumour site within the gland, and selective neck dissection performed for positive nodal disease. Radioactive iodine treatment is advised, particularly for patients under 10 years old, followed by vigilant follow up with thyroxine suppression and lifelong serial serum thyroglobulin levels.

**ADJUVANT THERAPIES**

The relevant adjunctive treatment modalities in DTC include radioactive iodine treatment, TSH suppression using thyroxine and external beam radiotherapy in selected cases. Details of these therapies are covered in Chapter 26, Non-surgical management of thyroid cancer, but a summary is appropriate here.

**Radioactive iodine**

A recent systematic review and meta-analysis of studies investigating the effectiveness of radioactive iodine remnant ablation in DTC suggested a statistically significant reduction in locoregional recurrence, and that ten-year distant metastatic rates were lower in patients treated with radioactive iodine remnant ablation following bilateral surgery for DTC. The data from this analysis did not allow the formulation of an optimal dose of radioactive iodine, nor could they confirm the decrease in recurrence and possible mortality in low risk patients with DTC. The BTA guidelines state that there is no indication for radioactive iodine ablation if patients have all of the following features: all tumours measuring 1 cm or less in diameter; N0, M0 tumours or MIFC without vascular invasion smaller than 2 cm in diameter; favourable histology; complete surgery and no extension beyond the thyroid capsule. Also included are absolute and relative indications for ablation, dose and safety recommendations.

**External beam radiotherapy**

As discussed above under Management of extrathyroid extension, external beam radiotherapy is indicated where there is high risk of locoregional recurrence. This includes patients with extensive extrathyroid invasion and extranodal extension even where the disease has been completely resected. Also included are older patients in whom the tumour may fail to concentrate sufficient amounts of radiiodine. It may also be used as primary treatment in selected cases.

**Thyroxine suppressive therapy**

There is evidence that doses of thyroxine adequate to suppress TSH can increase recurrence-free survival in patients with DTC and that TSH suppression is an independent predictor of recurrence-free survival. Not all studies confirm this and the evidence is certainly not as clear in low risk patients. Because of this, and the long-term risk of osteoporosis and cardiac complications, most authors now recommend that TSH is maintained at the lower limit of normal with the T4 as close to the normal range as possible.

**FOLLOW UP**

Recurrence rates in DTC are around 30 per cent over long periods and around 60 per cent of these recurrences occur...
in the first 10 years. Early detection of both locoregional and distant recurrences can lead to cure or at least favourable long-term survival if the disease is surgically resectable or takes up radioactive iodine. It is imperative, therefore, that the treating team has a surveillance strategy for patients treated for DTC.

A patient with low risk DTC is considered disease free after total thyroidectomy and 131I remnant ablation if the following criteria are fulfilled: all identifiable tumour has been resected, there is no clinical evidence of tumour, post-radioiodine scanning shows no uptake outside the thyroid bed, neck ultrasound results are negative, serum Tg antibodies are negative and Tg is undetectable (less than 1 µg/L) during TSH suppression and stimulation. It is highly likely based on recent observations with increasingly sensitive tools that these so-called recurrences are in fact cases of persistent tumour that have fallen below the threshold of detection offered by the tests available to treating surgeons and physicians.

**THYROGLOBULIN LEVELS**

Thyroglobulin (Tg) is a 660 kDa, dimeric protein produced by and used entirely within the thyroid gland. Tg is produced by thyroid follicular cells and is secreted and stored in the follicular lumen. It is also produced by DTC cells and can be used to detect residual or recurrent carcinomas following total thyroidectomy and radioactive iodine ablation of thyroid remnants. Thyroglobulin levels are less sensitive in patients who have had lobectomy or in patients who have antithyroglobulin antibodies.

It is recognized that measurement of serum Tg levels during TSH suppression with thyroxine often leads to failure to identify persistent tumour. TSH-stimulated Tg measurements with either thyroxine withdrawal or recombinant human TSH (rhTSH) are required to accurately identify recurrences. It has been demonstrated that a combination of stimulated TSH measurements and ultrasound scan has the highest sensitivity and negative predictive value for monitoring patients with DTC. In addition, it is recommended that serial stimulated TSH measurement should be the principal test in the follow-up management of low risk DTC. Serial measurements of TSH are more useful than one-off measurements and recurrence in DTC is indicated by a gradual rise in the serum Tg levels which reflects a change in the tumour mass.

**RADIOLOGICAL IMAGING STUDIES IN PATIENTS WITH ELEVATED SERUM Tg LEVELS**

Of the 30 per cent of DTC patients that recur, around 70 per cent do so locoregionally and the remainder recur at distant sites, most frequently the lungs. Imaging studies in patients with elevated serum Tg levels then should be primarily targeted to examining the central and lateral neck structures and secondarily to distant sites. The approach to detecting metastases should be the least disruptive to the patient and the most cost effective. Neck ultrasound is followed by low-dose radioiodine whole body scanning if no locoregional recurrence is detected. Other imaging modalities, such as CT or MRI should only be used to plan for surgical resection of macroscopic recurrence. F18-fluorodeoxyglucose positron emission tomography (FDG-PET) CT scans are expensive but may be useful in patients where neck ultrasound is negative, in patients who are whole body iodine image negative and Tg positive, or when there is poor uptake of radioactive iodine precluding the use of radioiodine whole body scanning.

**Neck ultrasound**

Scanning of the central and lateral neck in patients who have been treated for thyroid cancer and have an elevated Tg will demonstrate recurrence in the central or lateral nodes or in neck soft tissues in around two-thirds of cases. It is a much more sensitive investigation in detecting disease recurrence than palpation. Ultrasound is useful in differentiating malignant from benign lymph nodes as malignant nodes tend to be larger, rounder and lose their hilar characteristics. Ultrasound can also be used to guide FNAC to provide a tissue diagnosis and the needle washings can be analysed for thyroglobulin to increase the sensitivity of this test. Ultrasound is a useful imaging modality in children who have a high rate of regional recurrence and require regular surveillance because it is less invasive than other imaging modalities and is well tolerated.

**Whole body radioactive iodine scanning**

Following total thyroidectomy and radioactive iodine ablation, whole body scanning with low dose 131I is a relatively insensitive test for disease recurrence when compared to serial thyroglobulin measurement. It has the potential to miss large numbers of foci of recurrent disease in all risk groups but there is a particular concern in older patients in whom DTC has a lower avidity for radioactive iodine and in whom there is a higher risk of nodal disease and recurrence and a worse prognosis. More and more, routine whole body scanning post-ablation is being abandoned in low risk patients since the majority will have negative scans and serum thyroglobulin is a more sensitive, accurate investigative and monitoring tool. Post-treatment whole body scanning following ablative radioactive iodine treatment is more sensitive because of the higher doses used. It will reveal new foci of tumour in up to 50 per cent of patients who were negative on diagnostic scanning with a substantial number of these being distant metastases. This has led to the empirical treatment of patients with elevated serum thyroglobulin levels with ablative doses of 131I. The argument against this is that patients may be more effectively treated with targeted therapy and also that patients may be over-treated and cumulative high dose radioactive iodine treatment has some associated long-term risks. However, there may be a role for empirical treatment in patients who have particularly high Tg levels or rising stimulated Tg levels on serial testing.
FDG-PET CT scanning

Of the variety of imaging studies used to investigate patients with elevated or rising Tg levels following treatment for DTC, FDG-PET CT scanning appears to be the most sensitive test. The sensitivity in detecting metastases in DTC increases with increasing thyroglobulin levels. Studies have shown that in patients with elevated serum Tg levels and a negative diagnostic radioactive iodine whole body scan, FDG-PET CT scans can demonstrate disease that is amenable to surgery and can lead to disease-free status in a significant number of patients. In addition, FDG-PET CT scanning appears particularly useful in tumours that do not concentrate radioactive iodine where radioiodine scanning is not at all useful and where metastases have a poorer prognosis. One group of authors demonstrated the poor prognostic significance of a positive PET scan with a significant survival difference between patients that were PET positive and those that were negative. The avidity and volume of FDG uptake was also predictive of survival. F-18 FDG-PET scans are usually now performed with simultaneous CT scan to give accurate anatomical information in addition to the biological information offered by PET. PET-CT is the investigation of choice in this scenario.

A surveillance programme for patients treated for DTC therefore should include serial stimulated Tg levels either off thyroxine or after the use of intramuscular RhTSH. If the levels increase, a neck ultrasound should be performed and this can be combined with FNAC and Tg estimation on the needle washout if cytology is equivocal. If the ultrasound does not show adequate disease to explain the elevated Tg level, a diagnostic radioactive iodine scan is appropriate and if this is negative then progression to a F18-FDG-PET CT scan is appropriate.

SURGICAL MANAGEMENT OF RECURRENT DTC

It is likely that many of the recurrences seen in DTC are in fact progression of persistent initial disease that was not detected prior to primary treatment. There are a number of factors that predict for higher rates of recurrence. These can be split into patient (age greater than 60 or less than 20), tumour (size greater than 4 cm, multifocality, postoperative residual disease and lymph node involvement) and treatment (less than near-total thyroidectomy and the lack of use of radioiodine). The experience of the surgeon should also be taken into account. The majority of recurrences occur in the neck, either in the thyroid bed or in the regional lymph node basins, and the prognosis is better for these patients than it is for patients who develop distant metastases. This is mainly because locoregional disease can be treated in a multimodal fashion and treatment of distant disease is more limited. Recurrence of any sort has been shown to have a negative impact on survival and patients who develop multiple recurrences have a poorer prognosis.

Management of locoregional recurrence includes accurate detection of the site, volume and invasiveness of disease, and determination of whether the disease takes up radioactive iodine. Surgery is again the mainstay of management of local and regional recurrence, particularly with palpable disease, however there is evidence that disease detected by scintigraphy can be adequately treated using ablative doses of 131I. The issues in repeat central compartment surgery are whether the recurrence is in residual thyroid gland, nodes or invading surrounding tissues and the risk of re-operation to the recurrent and external laryngeal nerves and parathyroid glands. There are reports that demonstrate increased rates of nerve injury and hypoparathyroidism with revision central compartment surgery but there are also data that show with a systematic approach and careful technique complications can be minimized. A comprehensive compartment orientated clearance of level VI should be performed with skeletonization of the recurrent laryngeal nerves and careful preservation of the parathyroids on vascular pedicles. Recurrent nodal disease in the lateral neck is more frequent in the very young and in those who have had positive nodes previously treated, particularly those with large numbers of involved nodes. In a neck that has been previously dissected, a single focus or multiple separate foci of nodal recurrence may be treated by local lymphadenectomy, however if there has been only a ‘berry pick’ approach used then a compartment orientated selective neck dissection should be used to treat neck recurrence.

If the recurrence is not in the thyroid bed or cervical lymph nodes, then it is likely to involve one or more of the sites listed in Box 23.4.

Details of how to manage these are covered in Chapter 26, Non-surgical management of thyroid cancer, as well as the BTA Guidelines. Metastatic disease involving lung and other soft tissue areas are not usually amenable to surgery and should be treated with 131I therapy. There is no maximum limit to the cumulative 131I dose that can be given to patients with persistent recurrent disease. Extensive bony metastases are generally not curable by 131I therapy alone. For solitary or limited number of bony metastases that are not cured by 131I therapy, external beam radiotherapy, with or without resection and/or embolization should be considered in selected cases.

SURGICAL ANATOMY

It is vitally important for the head and neck surgeon to have a thorough understanding of thyroid anatomy as well as the pathology and natural history of thyroid nodules in order to be able to treat them with minimal morbidity since the majority are either usually benign or of low grade malignancy, all with an excellent prognosis. It is also important

Box 23.4 Likely metastatic sites of DTC (excluding cervical and mediastinal lymph nodes)

- Metastatic disease involving lung and other soft tissue areas
- Bone metastases
- Cerebral metastases
- Other metastatic sites
- Unknown metastatic sites
to note that the outcome of a poorly performed operation could be worse than the outcome from an untreated thyroid nodule.

The thyroid gland is made of up two lateral lobes, which extend from the sides of the thyroid cartilage down to the sixth tracheal ring. These are joined together in the midline by the isthmus, which overlies the second to fourth tracheal rings. In addition, there is often a pyramidal lobe which projects up from the isthmus, usually on the left-hand side. The gland is enclosed in the pretracheal fascia, covered by the strap muscles and overlapped laterally by the sternomastoid muscles. Superficial to the sternohyoid muscle, the anterior jugular veins cross over the central neck. On the deep aspect of the gland lie the larynx and the trachea with the pharynx and oesophagus behind and the carotid sheath laterally. On either side, there are important nerves: the external branch of the superior laryngeal nerve and the recurrent laryngeal nerve; both lie in close proximity to the gland and its blood supply. In addition, the cutaneous nerves C2 and C3 run superficial to the deep investing layer of cervical fascia and can be damaged at the time of surgery when the flaps are elevated. This results in anaesthesia of the anterior neck skin, which can be particularly troublesome to men when shaving.

The external branch of the superior laryngeal nerve lies deep to the upper pole of the gland as it passes superficial to the cricothyroid muscle in the sternothyroarvangeal (Joll’s) triangle (Figure 23.14). This triangle is formed laterally by the upper pole of the gland and the superior thyroid vessels, superiorly by the attachment of the strap muscles and deep investing layer of fascia to the hyoid and medially by the midline. Its floor is the cricothyroid muscle and its roof is made up of the strap muscles, it usually contains the external laryngeal nerve running on cricothyroid. There are three anatomical variations of the nerve described. A type I nerve (17 per cent) crosses the superior thyroid pedicle more than 1 cm above the superior thyroid pole and enters the cricothyroid muscle. In a type Ila configuration (the most common variant (56 per cent)), the nerve passes within 1 cm of the superior pole while in a type IIb variation, the external branch of the superior laryngeal nerve passes onto the cricothyroid muscle below the level of the superior thyroid pole. The type IIb nerve is the most commonly injured and the frequency of damage increases with the size of the goitre.

The recurrent laryngeal nerves run in, or lateral to, the tracheo-oesophageal groove and have a variable relationship with the branches of the inferior thyroid artery. They can run either in front of, behind or indeed between these branches. It is common for the nerve to divide into several branches before entering the larynx and there may be extralaryngeal branches as far as 3–4 cm below the inferior border of the cricoid cartilage. On the left side, the nerve ascends from the chest having circumnavigated the aortic arch. However, on the right side the nerve is more superficial, being 45° to the tracheo-oesophageal groove since it only has to pass around the artery of the 4th arch (the subclavian). On the right, it is important to remember that in approximately 2 per cent of patients the nerve may be non-recurrent and is then found more superiorly in the paracarotid tunnel where it runs with the inferior thyroid vessels en route to the larynx.

The inferior thyroid artery arises from the thyrocervical trunk, a branch of the first part of the subclavian artery. It passes medially behind the carotid artery and then pierces the prevertebral fascia medial to the carotid sheath to enter the posterior part of the thyroid gland. Additional blood supply sometimes comes from an inconstant vessel, the thyroid ima artery, which occurs in around 15 per cent of patients and arises from either the aortic arch or innominate artery (Figure 23.15).

The venous drainage of the thyroid is into the internal jugular vein via the superior thyroid vein which drains the upper pole. The middle thyroid vein drains the lateral part of the gland and there are multiple inferior thyroid veins which drain the lower pole of the gland into the brachiocephalic vein.

The parathyroid glands lie outside the thyroid capsule beneath the pretracheal fascia. In approximately 90 per cent of patients the blood supply to both superior and inferior glands is from the inferior thyroid artery and in a third of these cases there is also a significant supply through the thyroid capsule. In the remainder, both glands are supplied either by an anastomotic arch from the superior and inferior thyroid vessels or from the superior thyroid artery alone via posterior branches. The superior glands are more constant in their location and usually lie near the cricothyroid joint close to the recurrent laryngeal nerve, cephalic to the inferior thyroid artery (which is probably the best initial marker to locate them). The inferior glands are often more variable in their location, being caudal to where the recurrent laryngeal nerve and the inferior thyroid artery cross at the apex of Beahr’s triangle. In half of the cases the inferior parathyroid glands are found in and around the lower pole of the thyroid gland and a quarter may be close to, or within, residual thymus tissue. As a general rule, parathyroid glands are located symmetrically (for embryological reasons) on either side of the neck, and this is often helpful.

Figure 23.14 Joll’s triangle.

Figure 23.15 Thyroid Ima artery.
when looking for a missing gland. Most people have four parathyroids but approximately 10 per cent have more than four glands, while only 3 per cent have fewer than four glands. A healthy parathyroid usually measures on average just under 1 cm³ and is usually oval, varying in colour from light yellow in older patients to a reddish brownish colour in younger people, mainly because the fat content increases with age. It is useful to remember that in normal saline fat floats and parathyroid tissue sinks, although this is not a 100 per cent reliable test for parathyroid tissue and if there is doubt a frozen section should be performed on a small amount of gland. Parathyroid tissue can be found anywhere in the neck, including within the thyroid gland, as well as in the mediastinum where the location is usually intrathymic. Further detailed parathyroid anatomy is described in Chapter 27, Parathyroid tumours.

The primary lymphatic drainage from the thyroid is in a superior, lateral and inferior direction and follows the vascular pedicles of both the superior and inferior thyroid vessels, as well as the middle thyroid vein. The upper poles of the gland together with the isthmus and the pyramidal lobe drain superiorly, terminating in the lateral neck in levels II/III while the lateral aspect of each lobe drains into levels III and IV. The lower pole of the gland drains into the peri- and paratracheal nodes in level VI, and then onto both level IV and level VII nodes. Lymphatic drainage may also pass to nodes within the parapharyngeal and retropharyngeal spaces, but this usually tends to occur when other nodes are involved and shunting occurs, or when there has been previous treatment with either surgery or irradiation. It is very uncommon for differentiated thyroid malignancy to present initially with an isolated metastasis in the parapharyngeal space. There are also extensive communications between the lateral cervical lymph nodes in levels II, III and IV and the superior mediastinum via level VI. Subsequently, tumours in the upper pole tend to metastasize to levels II and III along the superior thyroid pedicle, in the middle third of the gland tumours spread to the perithyroid and paratracheal nodes (level VI) while those in the lower third spread predominately to the paratracheal nodes (level VI). Isthmus tumours spread most often to the pretracheal nodes (level VI). These drainage patterns are shown in Box 23.5 and Figure 23.16.

From the primary echelon nodes in the central compartment, the major lymphatic drainage is to the middle and lower deep jugular nodes (level III and IV) and to the nodes in the lower posterior triangle (level V). The lymphatic pathways to these particular nodes follow the route of the inferior thyroid artery and frequently pass deep to the carotid artery and on the left can be intimately related to terminal branches of the thoracic duct. The inferior level VI nodes then drain to the mediastinal nodes (level VII).

**SURGICAL TECHNIQUE IN DTC**

**Thyroidectomy**

When a tumour is confined to the thyroid gland without any extrathyroidal extension, or when there is simply a suspicion that a nodule may be malignant, surgery is performed in a similar manner as for benign disease. A skin incision is made in, or closely paralleling, a low anterior neck skin crease (Kocher’s incision; Figure 23.17). This is usually marked with the patient sitting up in the anaesthetic room. Flaps are raised in a sub-platysmal plane, or in a plane deep to the anterior jugular veins if the surgeon prefers to ligate these. The flaps are then sutured back, or kept open with a self-retaining Joll’s retractor. Strap muscles are either separated in the midline, elevated and retracted laterally or they are divided and retracted depending on the surgeon’s preference. One tip is to divide just deep to the sternothyroid muscle. This facilitates access, particularly to the upper pole, and can help minimize damage to the external branch of the superior laryngeal nerve. The muscle may be resutured back into

**Box 23.5 Lymphatic drainage of the thyroid gland**

<table>
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<th>Major</th>
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<tr>
<td>Middle jugular nodes – level III</td>
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<td>Lower jugular nodes – level IV</td>
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<td>Posterior triangle nodes – level VI</td>
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<tr>
<td>Pretracheal and paratracheal nodes – level VI</td>
</tr>
<tr>
<td>Superior mediastinal nodes – level VII</td>
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The lymph node groups at the highest risk of metastases from differentiated thyroid cancer are in the central compartment (level VI), lower jugular chain (levels III and VI) and the posterior triangle (level Vb).
position, or simply left which seems to have little effect on postoperative voice function. The thyroid gland is then exposed, the paracarotid tunnel entered and the middle thyroid vein divided. Dissection usually begins at the superior thyroid pole (particularly in the larger glands). The superior thyroid vessels are individually ligated and divided, and the superior pole is incrementally mobilized. Gentle downward and lateral retraction on the thyroid can be helpful during this procedure. As the mobilization proceeds, Joll’s triangle is explored and the external branch of the superior laryngeal nerve may be seen at this point and identified and preserved although it is not necessary to find it in every case. Stimulation with an electrical nerve stimulator can help with identification. The posterior branches of the superior thyroid artery are often not dissected at this point because of their importance in the blood supply to the superior parathyroid glands. At this point, a superior parathyroid gland may be found medial to the upper pole in Joll’s triangle although in 80 per cent of cases it is in its usual position, posterosuperiorly situated above the inferior thyroid artery (Figure 23.18). Attention then turns to the lower pole. Once the muscle and fascia have been elevated away from the inferior pole, the inferior thyroid veins are individually ligated and divided (Figure 23.19) and the anterior surface of the trachea exposed. It is important to realize that the recurrent laryngeal nerve can be damaged at this point. The gland is mobilized medially, both parathyroids identified together with the recurrent laryngeal nerve. The lower parathyroid is usually found below and medial to the inferior thyroid artery close to or actually within the thyrothymic ligament (Figure 23.20). The recurrent laryngeal nerve is identified (with minimal disturbance) in the thyroid bed where it makes up the third side of Beahr’s triangle, the other two sides being the inferior thyroid artery and the common carotid artery (Figure 23.21). An extracapsular dissection technique is then used on the gland across a broad front preserving the recurrent laryngeal nerve and two parathyroid glands. The assistant applies gentle but firm gradual sequential upward and medial traction using a swab (a technique known as ‘creeping’), taking care to keep out of the surgeon’s line of vision, to elevate the lobe from the thyroid bed as the capsule is being exposed. Vessels are ligated directly on the surface of the thyroid gland capsule and as dissection proceeds medially the parathyroids are noted to peel away within the fascia maintaining their blood supply (Figure 23.22). As the capsular dissection continues medially and the ligament of Berry is approached, the recurrent laryngeal nerve is seen and preserved within the fascia. At this

Figure 23.17 Low Kocher’s incision.

Figure 23.18 Position of the superior parathyroid (arrowed).

Figure 23.19 Ligation of the inferior thyroid veins.
point, and not before, the nerve may be gently exposed and then dissected up to where its various divisions enter the larynx. At the ligament of Berry, once the nerve is clear of the thyroid gland, sharp dissection on the trachea allows reflection of the lobe off the trachea to the point where the isthmus joins the contralateral lobe. This dissection of the ligament of Berry may be facilitated by the use of loupes. A Roberts clamp is placed across the gland and the lobe and isthmus excised if a lobectomy is being performed; a similar dissection is performed on the contralateral lobe for a total thyroidectomy. The parathyroids are carefully inspected and if one is particularly congested or devascularized it should be resected, morselized and placed into pockets in either the sternomastoid muscle or the brachioradialis muscle in the forearm. Some writers recommend routine reimplantation of parathyroid glands during total thyroidectomy, but there is little conclusive evidence for this. Haemostasis is established using a Valsalva manoeuvre and particular attention paid to the 'triangle of concern', which is where small blood vessels have been ligated medial to the recurrent laryngeal nerve. The triangle consists of the recurrent laryngeal nerve, the trachea and the root of the neck (Figure 23.23).

Techniques in managing extrathyroid extension

The approach here depends on the structures involved and note that more than one may be invaded.

Strap muscles: Most frequently the strap muscles are involved, and in this situation the muscles should be divided above and below the area of invasion and left attached to the gland. The approach to the gland itself is similar to above with access to the vessels and other extrathyroid structures around the attached individual strap muscles.

Recurrent laryngeal nerve: Involvement of the recurrent laryngeal nerve is not uncommon. If the nerve is non-functional prior to surgery, it can be resected without concern. If, however, it is functioning prior to surgery, all attempts should be made to preserve it. Frequently, the nerve itself will not be invaded and tumour is merely attached to the perineurium and can be carefully dissected off using sharp dissection under magnification with loupes or an operating microscope. If the nerve is clearly invaded then, functional or not, it should be resected.

Oesophagus: Although oesophageal muscle may be invaded, the lumen is only rarely involved. If oesophageal invasion is suspected clinically or radiologically, endoscopic examination of the lumen with a rigid oesophagoscope immediately prior to the surgery is essential. Placement of an oesophageal bougie or ET tube to aid identification of the oesophageal lumen while the surgeon is operating in the neck is also very helpful and can help avoid perforation.

Larynx and trachea: Preoperative assessment and endoscopy combined with imaging are crucial in managing tracheal or laryngeal compartment invasion. Complete resection of disease has been shown to be associated with improved locoregional control particularly where there is luminal invasion. The authors’ approach is as follows: Invasive disease is resected off the trachea and the extent of invasion assessed. If there is known invasion of the lumen the tracheal wall is resected through and through and, after frozen section demonstrates clear margins, the defect is assessed for closure. Several methods of repair

Figure 23.20 Characteristic position of the inferior parathyroid (indicated with forceps).

Figure 23.21 Beahr’s triangle.
are available including a patch of fascia or dermis, wedge excision and closure and segmental resection with end to end anastomosis. In the authors’ opinion, unless the defect is very small, segmental resection and end to end anastomotic repair is the most reliable method and up to 4–5 cm of trachea can be resected and closed without difficulty. Only occasionally is a suprahyoid release required.114 Laryngeal framework can be resected extensively with minimal impact on function, but once the laryngeal lumen is invaded, partial or total laryngectomy is required with the indications for the most appropriate procedure similar to those for mucosal based carcinomas. If a pharyngolaryngectomy is required, then reconstruction is usually either with free jejunum or anterolateral cutaneous thigh flap. Large vessels: The jugular vein is not infrequently invaded by nodal disease and should be resected in this circumstance. The carotid artery may be encroached upon by metastatic nodal disease within the carotid sheath in levels III and IV but the artery is rarely involved and disease can usually be easily dissected away from the adventitia without damaging the vessel wall.

**Central neck dissection (levels VI and VII)**

Nodes in level VI can lie superficial and deep to the recurrent laryngeal nerve (RLN) and tend to be more frequent in the inferior part of the central compartment. Either electively or therapeutically, a central neck dissection is usually performed with a total thyroidectomy and involves an extension of extracapsular dissection (Figure 23.24). Initially, the RLN is skeletonized from the cricothyroid joint to the level of the sternal notch with the overlying tissue laid lateral and medial. Once the nerve can be seen along its length, it is carefully elevated off the underlying tissues. Vessel loops can be used but care should be taken not to apply any traction to the nerve. The node bearing tissue is then dissected as a compartment from lateral at the IJV passing it deep to the nerve and finally resecting it off the trachea. At the lower end, the thymic remnants and associated fatty tissue and lymph nodes are dissected and removed via the neck and the trachea is then completely skeletonized. The key to preserving parathyroid function is to retain the vascular supply to the superior parathyroids while resecting and reimplanting the inferior ones. Traditionally, a central neck dissection incorporates all node-bearing tissue from the hyoid bone to the sternal notch and laterally to the carotid sheath. However, the dissection in the superior compartment does not need to be as aggressive and this allows preservation of the superior glands which have a supply either wholly from the inferior thyroid artery (ITA) or partly from the ITA and partly from...
the superior thyroid artery. Evidence suggests that this operation is associated with increased morbidity, including higher rates of recurrent laryngeal nerve damage and temporary and permanent hypoparathyroidism. One technique that reduces this risk is to divide level VI into two parts, VIa and VIb, separated by the recurrent laryngeal nerve. For small cancers in low risk patients, dissection could be confined to level VIa, greatly reducing the risks to the RLN and parathyroid glands. For high risk patients and those with large tumours, a full level VI dissection may be undertaken.

**Lateral neck dissection**

There is little role for elective lateral neck dissection in DTC. Therapeutic neck dissection will be discussed in detail in Chapter 36, Neck dissection. However, there are some particular points that should be raised in lateral neck dissection for thyroid carcinoma (Box 23.6). The incision may be either an extended conventional thyroid approach utilizing a lateral incision, or a superior extended thyroid excision overlying the cricoid cartilage. The inferior portion of level V is involved more frequently in metastatic DTC than in the more aggressive head and neck cancers. This is because, as previously mentioned, the nodal disease follows the inferior thyroid artery behind the common carotid and the internal jugular vein (Chassaignac’s triangle) and it is here that scalene nodes may be missed (Figure 23.25). On the left, the thoracic duct arches forward to enter the confluence of the IJV and innominate vein in the base of the triangle, and the sympathetic trunk is also close by. During a level Vb dissection (i.e. the region of level V below and anterior to the accessory nerve), the area must be carefully and thoroughly dissected in all cases of metastatic DTC. Level IIa (i.e. that area of level II anterior and inferior to the accessory nerve) must be cleared in every neck dissection, but if there is massive involvement of several levels, IIb may become involved and should also be cleared. Therefore a lateral neck dissection in DTC should incorporate a selective level IIa–level Vb dissection, unless there is massive multilevel disease and then a complete level II–V clearance should be performed. Access to level IV, the carotid sheath and Chassaignac’s triangle can be facilitated if needed by dividing the lower end of the sternomastoid muscle and peeling it upwards. The accessory nerve is then identified and level V below the accessory nerve along with levels IV, III and II are dissected, preserving not only the nerve but also the internal jugular vein and the sternomastoid muscle. Even then, level I does not usually need to be cleared. If there is extranodal extension and invasion of structures such as SCM or IJV, they should be excised in continuity such as in a modified radical neck dissection but again level I rarely needs to be dissected.

**COMPLICATIONS AND OUTCOME MEASUREMENTS**

Thyroidectomy is a common surgical procedure that can be associated with significant complications, including hemorrhage, infection and both temporary and permanent recurrent laryngeal nerve palsy and hypoparathyroidism. The Third National Audit Report by the British Association of Endocrine and Thyroid Surgeons confirmed that complication rates are reduced in experienced hands, and that 25 per cent of thyroid surgery in the UK was consultant led.
A complication is an unexpected adverse effect caused by thyroidectomy and this must be differentiated from natural sequelae (either temporary or permanent) which are inevitable following the operation (i.e. permanent hypothyroidism and temporary hypoparathyroidism following total thyroidectomy). Complications can be divided into early, intermediate and late, local and general and those specific to the operation.113, 114

Complications following thyroidectomy:

- early, intermediate and late;
- local and general;
- those specific to the operation.

Early complications following thyroidectomy include haemorrhage, voice change, airway obstruction and temporary hypoparathyroidism. The intermediate ones include seroma formation, infection and temporary palsy of the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve. Late complications include subclinical hypothyroidism, permanent hypoparathyroidism, permanent injury to the recurrent laryngeal nerve, the external branch of the superior laryngeal nerve, the cutaneous nerves C2 and C3 and the accessory nerve and a poor scar. Techniques employed to avoid complications are summarized in Table 23.12 and Box 23.7 and discussed in detail in Chapter 25, Avoiding complications in thyroid and parathyroid surgery.

There are a number of important outcome measurements that can be used in the assessment of treatment for thyroid cancer (Box 23.8). These data are collected prospectively by the British Association of Endocrine and Thyroid Surgeons and form part of their National Audit Report,116 allowing better quality of data for reporting results and taking informed consent. The importance of adequate low morbidity primary surgery has already been discussed along with the provision of radioiodine ablation and/or therapy, and treatment with long-term TSH suppression with regular monitoring of the serum thyroglobulin.

It is important to investigate an abnormal thyroglobulin promptly and to use local protocols which are approved by the multidisciplinary team. Because of a long natural history, the disease-free interval is important and although recurrences have been reported up to 42 years following initial treatment, late recurrences are uncommon following

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<thead>
<tr>
<th>Box 23.7 Guidelines for difficult cases</th>
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<tr>
<td>• Make an adequate incision</td>
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<td>• Do the easy side first</td>
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<td>• Always consider cancer</td>
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<tr>
<td>• Consider total thyroidectomy for many benign and malignant cases; high-risk patients may need a level VI neck dissection</td>
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<tr>
<td>• Try to identify the recurrent laryngeal nerve and parathyroid glands</td>
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<td>• Know the location of the external branch of the superior laryngeal nerve</td>
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<tr>
<td>• Consider using a nerve monitor</td>
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<tr>
<td>• Achieve good access in retrosternal goitre, do the easy side and the upper pole first, and divide the strap muscles at least on one side</td>
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<tr>
<td>• Do not hesitate to split the chest or sacrifice one recurrent laryngeal nerve if malignancy is present</td>
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</table>

<table>
<thead>
<tr>
<th>Box 23.8 Outcome measurements following treatment for thyroid cancer116</th>
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<tr>
<td>• Adequate primary surgery</td>
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<tr>
<td>• Incidence of vocal cord paralysis</td>
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<tr>
<td>• Incidence of hypoparathyroidism (temporary and permanent)</td>
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<tr>
<td>• Achievement of TSH suppression</td>
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<tr>
<td>• Provision and treatment with radioiodine postoperatively when indicated</td>
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<tr>
<td>• Regular monitoring of serum thyroglobulin</td>
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<tr>
<td>• Abnormal thyroglobulin acted upon</td>
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<td>• Disease-free interval</td>
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<td>• Quality of life</td>
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<td>• Survival</td>
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Table 23.12 Summary of important complications and avoidance measures.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Avoidance measures</th>
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<tr>
<td>RLN palsy</td>
<td>Identify the nerve early low down, use a meticulous surgical technique and consider using a nerve monitor</td>
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<tr>
<td>Damage to the EBSLN113</td>
<td>Know its course; if seen in Joll’s triangle then confirm with a nerve stimulator, avoid and ligate superior thyroid vessels individually right on the gland</td>
</tr>
<tr>
<td>Temporary and permanent</td>
<td>Identify all parathyroids, perform extracapsular dissection with preservation of blood supply and consider using loupes</td>
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<tr>
<td>hypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td>Damage to the cutaneous nerves C2 and C3</td>
<td>Lift the upper and lower flaps by staying on the deep cervical fascia. Use bipolar diathermy</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Meticulous surgical technique; doubly ligate or ligate and transfix the upper pole vessels, ligate the thyroid isthmus and close after a Valsalva. Consider using a drain</td>
</tr>
<tr>
<td>Poor scar</td>
<td>Mark correctly, ensure meticulous skin closure. Consider triamcinolone in patients with dark skin</td>
</tr>
<tr>
<td>Infection</td>
<td>Meticulous surgical technique. Consider prophylactic antibiotics in high risk cases</td>
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</tbody>
</table>
appropriate initial therapy. Common psychosocial issues relating to the anxiety of a cancer diagnosis, side effects of radioiodine treatment and the morbidity associated with major extirpative surgery are not uncommon, particularly in the young, and should be addressed by the multidisciplinary team which includes the appropriate counselling skills of a head and neck nurse and/or counsellor.

CONCLUSION

While thyroid nodules are common and cancer most commonly presents as a solitary thyroid nodule, thyroid malignancy still remains a rare entity. DTC is the most frequently seen of the thyroid cancers, and the incidence is increasing due to greater awareness and improved detection, together with an increase in surgery for benign disease and possibly greater environmental radiation exposure. Another important aetiological factor in DTC is a positive family history and although the genetics and molecular biology of these diseases are better understood than ever, effective novel therapies remain elusive.

Nevertheless, in the vast majority of cases DTC is an indolent disease with an excellent prognosis and low rates of recurrence and mortality. Several prognostic factors are recognized and among the most important are patient age, tumour size, extrathyroid extension and the presence of distant metastases. A number of prognostic scoring systems have been developed over the past three decades and although detailed analysis does support their validity, we would recommend the use of the AJCC/UICC staging system for DTC since it incorporates well-recognized prognostic risk factors, is accurate in predicting outcomes and is friendly and familiar to users because of its use in other head and neck malignancies.

The important primary investigations to exclude malignancy in a patient presenting with a solitary thyroid nodule include FNAC, T4 and TSH levels, thyroid antibodies and an ultrasound scan. Ultrasound can also be used to increase the accuracy of FNAC. There are five possible cytological outcomes of FNAC ranging from non-diagnostic (Thy1) to a definite cytological diagnosis of malignancy (Thy5). Anatomical imaging, such as CT scanning is important in investigating the extent of primary and particularly nodal disease in an established diagnosis of malignancy.

A total or near-total thyroidectomy is the appropriate operation when PTC has been diagnosed on FNAC. Following diagnostic thyroid lobectomy a completion thyroidectomy should be considered when PTC or follicular thyroid carcinoma is diagnosed.

Positive central or lateral nodal disease should be treated with selective neck dissection and in high risk PTC, elective central neck dissection may be indicated. Recurrent metastatic neck disease in a previously dissected neck may be treated by selective lymphadenectomy including single node removal. Widely invasive disease is best treated with complete resection, but morbidity should be minimized and incomplete resection with adjuvant therapy usually equates with excellent disease-free status and survival. DTC diagnosed during pregnancy is not uncommon and the prognosis is excellent despite any delay in surgical treatment until a successful delivery has been completed.

Vigilant follow up is important for the early diagnosis and management of recurrent DTC as 70 per cent of recurrences will be in the neck and therefore resectable. Serial unstimulated and stimulated thyroglobulin measurements are the mainstay of surveillance along with neck ultrasound, radioactive iodine whole body scanning and anatomical imaging where appropriate. PET-CT scanning is proving useful for those with rising Tg levels and negative 131I/anatomical scans. PET-CT scans are also proving to be valuable in those with less well-differentiated tumours that do not concentrate iodine well.

Surgery for local recurrence in the thyroid bed or central neck has increased risks of laryngeal nerve injury and hypoparathyroidism, although this is not so in the lateral neck. A comprehensive understanding of the structural and lymphatic anatomy of the thyroid gland is essential in order for safe and effective surgery to be performed. Audit of performance indicators and a multidisciplinary approach to the management of patients with DTC are required to improve outcomes in this fascinating and complex disease.

DIRECTIONS FOR FUTURE RESEARCH

Cancer is a disease of genes. Genes encoding molecules involved in regulating the growth, differentiation and function of cells are mutated, lost or deregulated in cancer. The recognition of genetic changes, and potential to correct them, are leading to exciting new modalities for the diagnosis and treatment of thyroid cancer. Many of these are in early clinical trials, and their eventual impact on mortality from thyroid cancer remains to be seen.

FNAC is an important diagnostic test in use today. Molecular techniques including reverse transcription-polymerase chain reaction (RT-PCR) have been used in an attempt to improve the accuracy of FNAC. This would be especially useful to distinguish between follicular adenoma and carcinoma, currently impossible on conventional cytological methods. There is currently no molecular marker specific enough to distinguish these, but detection of several mutations (Ras, Galectin-3 and PTTG) shows some promise. Other techniques including mass spectrometry, proteomics and gene array technology may allow accurate detection of cancer and differentiation of tumour subtypes, although further research is required.

Disease progression is currently monitored by serum thyroglobulin as well as 131I scans and clinical examination. Up to 25 per cent of patients have antibodies which interfere with the thyroglobulin assays, and make interpretation difficult. Detection of serum thyroglobulin mRNA using quantitative RT-PCR may allow this subset of patients to be analysed more accurately, although preliminary studies require further clinical validation.

Angiogenesis is the growth of new blood vessels by sprouting of existing capillaries and is essential for all tumour growth. Numerous angiogenic growth factors are
elevated in thyroid cancers including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and the angiopoietins. Bevacizumab is an anti-VEGF monoclonal antibody that already has FDA approval for use in several human malignancies including head and neck and colorectal cancers. There are several other anti-angiogenic agents in development (for example soralenib which is a VEGF receptor inhibitor) that are entering clinical trials in other solid tumours. Many of these agents may soon be applied to thyroid cancers. Indeed, there is growing in vitro and preclinical evidence for use in thyroid cancer. Several endogenous anti-angiogenic factors, including endostatin and angiostatin, have been effective at reducing or preventing tumour growth in an animal model of thyroid cancer, and may prove useful in human thyroid cancer.

Further elucidation of thyroid cancer biology has led to the development of several other therapeutic targets, and many of these are in advanced stages of clinical development. More recently, targeted therapy against tyrosine kinase receptors has gained importance in the search for novel cancer treatments. Cetuximab, a monoclonal antibody to epidermal growth factor receptor (EGFR – frequently overexpressed in many tumour types), has been thoroughly validated and is licensed for use in several human cancers including head and neck squamous carcinomas. In thyroid cancer, RET, BRAF and PI(3)K kinases appear to be rational targets for the treatment of advanced thyroid cancer. RET is involved in the formation of both medullary and papillary thyroid cancers. BRAF mutations are highly prevalent in PTC. Two small molecular compounds ZD6474 (zactima) and BAY43-9006 (soralenib) obstruct RET and BRAF signalling and are currently undergoing clinical evaluation (http://www.cancer.gov/clinical trials). Both compounds also inhibit VEGF receptors. The phosphoinositide-3-OH kinase (PI(3)K) pathway regulates cell proliferation and survival and has been shown to be hyper-activated in a high proportion of thyroid cancers. Two agents effective in inhibiting this pathway are CCI-770 (temsriolimus) and RAD001 (everolimus). Both compounds, derivatives of the macrolide antibiotic rapamycin, have been shown to have broad antitumour activity and are under advanced clinical study.

Gene therapy is the treatment of disease by the transfer of genetic material. Several vector strategies may be employed, either viral such as retroviruses, adenoviruses and lentivirus which have relatively high transfer efficiency but may have unwanted effects due to the inherent properties of the virus, or physical methods such as liposomes or injection of naked DNA, which are safer, but less potent vectors. Approaches used include introduction of p53 into p53 deficient anaplastic carcinomas, transfer of suicide genes such as thymidine kinase into cancer cells, overexpression of interleukin-2 to increase immunological antitumour activity, and increased expression of the sodium iodide symporter into thyroid cancers that have become 131I-resistant. Despite the relatively modest results of gene therapy hitherto, it is likely that these approaches will prove to be clinically useful in the medium to long term, and have the potential to transform the treatment of many cancers, including thyroid cancer.
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INTRODUCTION

Medullary thyroid cancer (MTC) is uncommon and with the exception of those who work in tertiary referral centres will rarely be diagnosed or treated by individual surgeons. MTC is unique in that it occurs as genetically determined disease in 25 per cent of cases; it occurs in the paediatric and adult setting and is associated with other endocrine tumours. MTC merits a more aggressive surgical approach than differentiated thyroid cancer. Patients with MTC require care from an experienced multidisciplinary team that includes specialist surgeons, an endocrinologist, oncologist and pathologist who meet and discuss cases regularly with a radiologist, nuclear medicine physician and biochemist, all interested in the management of thyroid cancer. Close links and involvement with personnel from a Clinical Genetics Service are essential. National thyroid cancer guidelines in the UK recommend that patients with MTC should be referred for treatment to a cancer centre.

HISTORY

Medullary thyroid cancer was first described by Hazard et al.1 in 1959. The recognition of calcitonin as a calcium lowering hormone in 1962 and its origin from the thyroid parafollicular cells, so named by Nonidez in 1932, was reported by Foster et al.2 Pearse and Polak adopted the term C cells and first described their origin from neural crest tissue.3 A child with thyroid cancer containing amyloid stroma and bilateral phaeochromocytomas was reported in 1960.4 The following year, a patient was described by Sipple with bilateral phaeochromocytomas, thyroid cancer and enlarged parathyroid gland (MEN type 2A, Sipple syndrome).5 In a series of reports Dillwyn Williams linked medullary thyroid cancer, its origin in C cells,6 association with diarrhoea,7 phaeochromocytoma8 and multiple mucosal neuromata.9 In 1968, Schimke described three patients with MTC, multiple tumours involving the buccal mucosa; two of the patients had bilateral phaeochromocytomas and abnormal facies (MEN type 2B).10 Tashjian and Melvin11 first described the production of calcitonin by MTC. MTC in three generations of a single family was reported by Cushman in 196212 in association with phaeochromocytoma and parathyroid disease.

The RET gene was first identified as a proto-oncogene in 198513 and cloned three years later.14 RET was mapped to chromosome 10 in 198715,16 and the mutations associated with MEN2A,17 FMTC18,19 and MEN2B20,21 described in 1993 and 1994.

INCIDENCE OF MEDULLARY THYROID CANCER

In the United States, about 1000 people are diagnosed with MTC each year.22 The disease accounts for approximately
3 per cent of all thyroid cancer in the USA and 5–10 per cent of paediatric thyroid cancers. SEER (Surveillance, Epidemiology and End Results) data from the USA from 1975 to 2000 indicates the maximum incidence of MTC as 4.4 per million per year in the 70–75-year-old age group, and in adolescents and young adults an incidence of less than one case/million per year. The estimated incidence of MTC in the UK is 20–25 new cases per year among a population of 55 million. In patients with nodular thyroid disease screened for MTC, the prevalence of MTC is reported as 0.4–1.8 per cent (see below under Diagnosis of medullary thyroid cancer).

**PATHOLOGY**

**C cells and calcitonin**

Medullary thyroid cancer arises from C cells that are found in the middle and upper third of the thyroid gland. These cells, of neural crest origin, will have migrated through the ultimobranchial body (branchial clefts 5 or 6). C cells produce calcitonin, a 32 amino acid peptide and calcitonin gene-related peptide (CGRP). C cells (parafollicular cells) are found adjacent to or within thyroid follicles (Figure 24.1a), between the follicular cell basement membrane and the surface epithelium. Typically, they have a polygonal or spindle shape, central nuclei and pale, granular cytoplasm. On immunohistochemical staining, C cells demonstrate marked staining for calcitonin, chromogranin, cytokeratin and carcinoembryonic antigen. Calcitonin is stored in dense cored secretory granules and released into the circulation. Circulating secretory products of MTC are listed in Box 24.1.

Calcitonin inhibits osteoclastic bone resorption and promotes calcium excretion by the kidney. Its physiological role is unclear in patients with medullary thyroid cancer, in whom calcitonin levels may be grossly elevated, and after total thyroidectomy, when levels are low, no derangement of calcium homeostasis is apparent. Calcium and pentagastatin are potent secretagogues of calcitonin. CGRP is a potent peripheral vasodilator.

**C cell hyperplasia**

C cell hyperplasia (CCH) is defined as a multifocal (diffuse or nodular) quantitative increase in C cells (Figure 24.1b). It can be found in post-mortem thyroid samples of men and women with no evidence of thyroid disease. CCH occurs as a neoplastic precursor within the setting of MEN2-associated MTC, but can also accompany sporadic MTC. Two types of CCH are described that differ in morphological characteristics: (1) neoplastic – typically nodular and diffuse and indistinguishable from invasive MTC cells and (2) reactive (also called physiological) – typically diffuse associated with hypercalcaemia, hyperparathyroidism, chronic lymphocytic thyroiditis and follicular tumours. However, in terms of clinical decision making, a purely morphological distinction between ‘physiological’ and ‘neoplastic’ CCH, independent of RET status is unwise.

**Box 24.1 Circulating secretory products of medullary thyroid cancer**

- Calcitonin
- Carcinoembryonic antigen
- Neuron-specific enolase
- Calcitonin gene-related peptide
- Katakcalcin
- DOPA-decarboxylase
- Nerve growth factor
- ACTH
- Synaptophysin
- Somatostatin
- Neurotensin
- Serotonin
- Substance P
- Corticotrophin-releasing hormone
- Vasoactive intestinal peptide
- Bombesin
- Gastric-releasing peptide

![Figure 24.1](image)

**Figure 24.1** Histological sections of thyroid stained for calcitonin. (a) Normal C cells; (b) C cell hyperplasia in MEN2A patient.
Medullary thyroid cancer

MACROSCOPIC

Sporadic tumours are usually solitary and unilateral. In patients with familial disease, tumour foci are usually bilateral and multifocal. MTC on sectioning varies in colour from grey/white to pink with varied consistency. Calcification may be present.

CYTOLOGY

Tumour cell morphology is variable; oval/round/spindle-shaped cells may be seen in clusters or as single cells with pleomorphic nuclei and eosinophilic cytoplasm (Figure 24.2a). Eosinophilic extracellular material is amyloid.

HISTOPATHOLOGY

MTC may be encapsulated or unencapsulated with extension of the tumour into adjacent parenchyma. Nuclei may be eccentric, pleomorphic with a coarse chromatin pattern, and typically there is a low mitotic rate. A wide variety of histological variants and growth patterns are seen that include papillary, follicular, squamous and oncocytic subtypes. Amyloid is seen in 80 per cent of tumours, it may be focal or diffuse. On immunohistochemistry tumour cells stain positive for calcitonin (Figure 24.2b), CGRP, carcinoembryonic antigen (CEA) and chromogranin A. Thyroglobulin staining is negative. Other peptides that may be identified include adrenocorticotropic hormone (ACTH), somatostatin, serotonin and gut hormones.

MTC is staged as described in the American Joint Committee on Cancer (AJCC) Staging Manual (Table 24.1).32

HEREDITARY MEDULLARY THYROID CANCER

Genetically determined disease accounts for approximately 25 per cent of MTC cases. Three main clinical variants are recognized that include multiple endocrine neoplasia type 2A (MEN2A), multiple endocrine neoplasia type 2B (MEN2B) and familial medullary thyroid cancer (FMTC). All are inherited as autosomal dominant disorders (Table 24.2) with age-related penetrance and variable expression. The prevalence is estimated at one in 30,000. MTC is expressed in almost all patients with MEN2 and FMTC, and is usually the first manifestation of the syndrome; the age at onset is related to specific genotypes.

Table 24.1 TNM clinical staging of medullary thyroid cancer.32

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<tr>
<th>Clinical stage</th>
<th>T0</th>
<th>T1</th>
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</table>

Figure 24.2 (a) MTC cytology obtained from fine needle aspiration of thyroid mass; (b) MTC histology showing strongly positive immunohistochemical staining for calcitonin.
Germline and somatic mutations of the RET (REarranged during Transfection) proto-oncogene located on chromosome 10q11.2 are implicated in the pathogenesis of MTC. Gain of function germline mutations associated with MEN2/FMTC are found in seven of the RET gene’s 21 exons. MEN2A accounts for approximately 85 per cent of genetically determined MTC and is associated with a mutation of codon 634 in 85 per cent of cases. At least 95 per cent of families with MEN2A have a RET mutation in exon 10 or exon 11. FMTC accounts for 5–15 per cent of hereditary cases, MEN2B accounts for 5 per cent of MEN2 cases.

RET encodes a plasma membrane bound receptor tyrosine kinase (Figure 24.3) that is expressed by thyroid C cells, cells of the adrenal medulla, autonomic nerve ganglia, colonic ganglia and parathyroid cells. The receptor consists of an N-terminal peptide, an extracellular domain important for cell-to-cell signalling (cadherin-like region) and receptor dimerization (cysteine-rich region), a transmembrane domain and two intracellular tyrosine kinase domains.

The C-terminal of RET protein has three splice variants; their various protein products have organ-specific physiological roles. Ligands of RET include glial cell line-derived neurotrophic factor (GDNF) in conjunction with a ligand-specific coreceptor (GFRα1-4), neurturin, artemin and persephin. Activation of the receptor leads to activation of various intracellular signalling pathways including c-JUN, Ras/ERK, MAPK, p38 that are involved in cell proliferation and survival, and the responses of cells to cytotoxic agents.

RET codon mutations correlate with the MTC phenotype (Table 24.2). The extracellular MEN2A 634 activating mutation induces a ligand-independent constitutive dimerization of the RET receptor which leads to abnormal cell growth, differentiation defects and cellular transformation. The intracellular 918 MEN2B mutation is associated with receptor activation in the absence of receptor dimerization by alteration of kinase substrate specificity.

Somatic mutations of RET, usually at codon 918, are found in approximately 25 per cent of sporadic MTC and linked with poorer prognosis.

### Table 24.2 | Clinical features of multiple endocrine neoplasia type 2.

<table>
<thead>
<tr>
<th></th>
<th>MEN2A</th>
<th>FMTC</th>
<th>MEN2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medullary thyroid cancer</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>10–20%</td>
<td>100%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Cutaneous lichen amyloidosis (rare)</td>
<td></td>
<td>100%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>Very rare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 24.3**  Schematic of membrane bound tyrosine kinase receptor encoded by RET.

### CLINICAL FEATURES OF SPORADIC AND HEREDITARY MTC

The average age at presentation of sporadic MTC is in the fourth and fifth decade, while MEN2A typically presents in the second or third decades, MEN2B in the first and second decades, FMTC in the fourth and fifth decades. The sex ratio is almost equal.

Local tumour growth, i.e. a thyroid mass, is normally the first indication of disease (75 per cent), usually a non-tender thyroid nodule or diffuse thyroid enlargement. MTC metastasizes early to the locoregional lymph nodes. Cervical lymphadenopathy is seen as the first presenting feature in approximately 40–50 per cent of patients. Other MTC symptoms of either local mass effect or tumour invasion include airway compromise (10 per cent), neck sensitivity (9 per cent) and dysphagia (4 per cent). Recurrent laryngeal nerve palsy is rare as a presenting feature in MTC. Diarrhoea (the specific cause of which is unknown), flushing and bone pain are reported in 20–30 per cent of MTC and reflect tumour bulk; they are signs of disseminated disease. Bloodborne metastases are evident at presentation in the liver, lungs and bone of 12–28 per cent of patients. ACTH production by MTC in rare cases will cause Cushing syndrome.

Even patients with micro-MTC have a significant incidence of extrathyroidal manifestation of the disease at presentation, lymph node metastasis in 10 per cent, distant metastases in 6.3 per cent, diarrhoea and/or flushing in 7.5 per cent.
Diagnosis of medullary thyroid cancer

Table 24.3  RET mutations associated with hereditary medullary thyroid cancer.

<table>
<thead>
<tr>
<th>Exon</th>
<th>Codon</th>
<th>Syndrome</th>
<th>Frequency of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cysteine-rich domain</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>532</td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>533</td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>609</td>
<td>MEN2A/</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>611</td>
<td>611</td>
<td>MEN2A/</td>
<td>2–3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>618</td>
<td>618</td>
<td>MEN2A/</td>
<td>3–5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>620</td>
<td>620</td>
<td>MEN2A/</td>
<td>6–8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>630</td>
<td>MEN2A/</td>
<td>&lt;1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>634</td>
<td>634</td>
<td>MEN2A</td>
<td>80–90%</td>
</tr>
<tr>
<td>634</td>
<td>635</td>
<td>MEN2A</td>
<td></td>
</tr>
<tr>
<td>635</td>
<td>637</td>
<td>MEN2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tyrosine kinase domain</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>768</td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>790</td>
<td>790</td>
<td>MEN2A/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>804</td>
<td>MEN2A/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>804,806</td>
<td>804,806</td>
<td>MEN2B</td>
<td>3–5%</td>
</tr>
<tr>
<td>844</td>
<td>844</td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>883</td>
<td>MEN2B</td>
<td></td>
</tr>
<tr>
<td>891</td>
<td>891</td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>912</td>
<td>FMTC</td>
<td></td>
</tr>
<tr>
<td>918</td>
<td>918</td>
<td>MEN2B</td>
<td></td>
</tr>
</tbody>
</table>

When the same codon appears twice, the amino acid/nucleotide sequence is different.

Phaeochromocytoma will occur in up to 55 per cent of MEN2 patients. It is most commonly associated with codon mutations at 634 and 918, but found in association with nearly all MEN2 genotypes. Phaeochromocytoma may be the first manifestation of the MEN2 syndrome in up to 25 per cent of cases; it is associated with adenomediullary hyperplasia, sometimes bilateral phaeochromocytoma, but rarely extra-adrenal or malignant disease. Annual screening for phaeochromocytoma is warranted from the age of ten years in carriers of RET mutations in codons 918, 634 and 630, and from the age of 20 years in the remainder. The average age at the time of diagnosis is the fourth decade.

In patients with MEN2A, hyperparathyroidism is reported to occur in 20–30 per cent of individuals, almost exclusively in those with mutations of codon 634 and 618. Mean age at diagnosis is 38 years. Patients are generally asymptomatic and the hypercalcaemia is often mild. Asymmetric parathyroid gland enlargement is the norm and resection of only the enlarged glands is recommended.

Rare forms of MEN2A with specific RET mutations are associated with Hirschsprung’s disease and cutaneous lichen amyloidosis (brownish plaques of multiple tiny papules, usually in the interscapular area).

Four or more MTC-affected members of a kindred without other endocrine tumours are required for the clear diagnosis of FMTC. The age at onset of MTC in this syndrome is older than seen in MEN2A and MEN2B and the phenotype is less aggressive.

MEN2B has a specific phenotype that may be apparent in infancy. The facies are typical with enlarged lips, enlarged corneal nerves. Patients with MEN2B will most likely (95 per cent) have a mutation at codon 918, 50 per cent of patients have a de novo RET mutation. Early diagnosis is essential in individuals with MEN2B because the onset of MTC occurs at a very early age. Those who have not undergone thyroidecctomy within the first year of life are likely to develop metastatic disease.

**DIAGNOSIS OF MEDULLARY THYROID CANCER**

The diagnosis of MTC in most cases will result from the investigation of patients who present with a thyroid or lymph node mass. Fine needle aspiration biopsy, alone or in combination with immunocytochemistry, electron microscopy and serum calcitonin, will result in an accurate diagnosis in most cases. When cytology is not adequate, core needle biopsy, with or without ultrasound guidance avoids the need for open biopsy in nearly all cases. A preoperative diagnosis allows for a planned surgical intervention and reduces the need for completion thyroid and/or completion lymphadenectomy.

Routine measurement of basal calcitonin in patients presenting with nodular thyroid disease is recommended by some to identify otherwise undetected MTC (Tables 24.4 and 24.5) and lead to the potential benefit of better outcome. The prevalence of MTC in this group of patients varies from 0.4 to 1.8 per cent. Basal hypercalcitonaemia will be evident in at least 1.5 per cent of screened patients. In one study, approximately 60 per cent of patients with a high basal calcitonin did not have MTC, 57 per cent of hypercalcitonaemic patients without MTC had C-cell hyperplasia. The positive predictive value of an abnormal basal calcitonin varies between studies, but for levels ≥ 20 pg/mL is reported as 23.1 per cent, for values > 100 pg/mL as 100 per cent. Pentagastrin stimulation testing (see below under Preoperative investigations) is required to confirm true positives. A positive test correlates with CCH and MTC, but false positives occur in up to 25 per cent of subjects.
PREROPERATIVE INVESTIGATIONS

Calcitonin

Serum calcitonin (CT) is a sensitive and accurate marker of MTC; an elevated basal calcitonin level confirms the cytological or histological diagnosis of MTC in a symptomatic patient. False-positive serum calcitonin levels are recorded in patients with autoimmune thyroid disease, hypercalcaemia, foregut-derived neuroendocrine tumours, and renal failure. Conversely, MTC cases with normal basal serum calcitonin are recognized.

Basal calcitonin should be measured in all patients with MTC prior to surgery. The level of calcitonin is a good indicator of disease extent: lymph node involvement may be found in patients with calcitonin as low as 10–40 pg/mL, distant metastasis and extrathyroidal growth can occur with calcitonin levels of 150–400 pg/mL.

In patients with potentially false-positive basal calcitonin levels, or when there is uncertainty about the histological diagnosis, a pentagastrin or pentagastrin/calcium stimulation test should be performed. The slow intravenous injection of 0.5 mg/kg pentagastrin and/or calcium gluconate 2 mg/kg is followed by venous sampling at 0, 1, 2, 3, 5 and 10 minutes. Peak calcitonin values are found at 1–2 minutes. The protocols for these tests and the definition of a positive test (two- or three-fold increase) or peak values >100–300 pg/mL are not standardized. Patients who have false-positive elevations of basal calcitonin will show a negative response to pentagastrin. Some patients with early MTC will have peak calcitonin values less than 100 pg/mL. Side effects of the test include nausea, chest or abdominal pain, flushing and headache. The test has a further role, particularly in the setting of clinical research, to confirm biochemical cure of MTC after surgery.

Historically, patients at risk of genetically determined MTC were screened annually using pentagastrin/calcium stimulation in order to confirm the diagnosis of CCH or MTC. The requirement to subject patients to these tests is now superseded by the combination of RET mutation analysis, basal calcitonin estimation and a better understanding of genotype–phenotype correlation and the timing of surgery.
Kindred of RET mutation-negative patients with apparent syndromic MTC and negative linkage studies will still require to undergo annual pentagastrin stimulation tests. Surgery is then proposed when the test is positive.

**Urinary or plasma catecholamines/metanephrines**

Phaeochromocytoma must be excluded prior to surgery in all patients with a diagnosis of MTC. Biochemical testing is mandatory. The absence of symptoms or hypertension does not indicate the absence of a catecholamine-secreting tumour. The absence of a family history does not preclude genetically determined disease; the patient may represent the index case of an MEN2 kindred. A 24-hour urine collection should be assayed for fractionated catecholamines, metanephrines and normetanephrines. Plasma-free normet/metanephrines can be assayed and have high sensitivity for the detection of familial phaeochromocytoma.

**Calcium**

A serum calcium level should be obtained in all MTC patients prior to surgery. The results of RET mutation analysis may not be available before operation; a high serum calcium level may indicate previously undiagnosed MEN2A in the patient. A high or inappropriate level of serum parathyroid hormone (PTH) will indicate the need for careful assessment of the parathyroid glands at the time of thyroidectomy and, when necessary, excision of enlarged glands.

**RET mutation analysis**

Even in the absence of a positive family history, MEN2 should be suspected when MTC occurs at an early age or is multifocal/bilateral. In patients with apparently sporadic MTC, the prevalence of germline RET mutation is reported as high as 7.3 per cent. All patients with a diagnosis of sporadic MTC should therefore undergo RET mutation analysis because they may represent the index case of a previously undiagnosed MEN kindred. Predictive DNA tests should be carried out under the auspices of a clinical genetics service.

DNA-based testing will identify mutations in more than 95 per cent of individuals with MEN2A and MEN2B and in about 85 per cent of individuals with FMTC. When a patient with MTC is identified as carrying a RET mutation, genetic screening should then be offered to first-degree relatives of the proband. Family members identified as gene positive may then be offered therapeutic or risk reduction surgery for MTC (see below under Surgery for MTC) depending upon their age, genotype and disease extent.

**Ultrasound**

Ultrasound imaging of the thyroid and lymph nodes may have been performed prior to diagnosis as a part of non-specific thyroid work up or to guide fine needle aspiration (FNA). It is not mandatory prior to first time surgery, although it may provide a ‘road map’ of clinically undetectable disease. Ultrasound appearances of MTC in thyroid or lymph nodes are not specific, hypoechoic tumours less than 5 mm in diameter may be discovered. Ultrasound may identify bilateral and/or multiple thyroid lesions, suggestive of genetically determined disease, enlarged and abnormal lymph nodes. Microcalcification seen in lymph nodes is probably due to amyloid.

**CT/MRI**

Preoperative assessment of the neck and mediastinum with computed tomography (CT) or magnetic resonance imaging (MRI) may alert the surgeon to the presence of extrathyroidal disease that involves the airway or oesophagus, and of lymph node enlargement outside the neck (Figure 24.6). Positive findings may result in an alteration in the surgical strategy to include planned resection of involved viscera or mediastinal lymphadenectomy requiring sternotomy. Cross-sectional imaging of the lungs and liver may reveal unsuspected distant
disease that may result in planned restriction of the extent of neck surgery. A negative examination of the lungs and liver does not preclude pulmonary or hepatic spread as small MTC metastases are often below the lower limit of resolution of the scan.

An assessment of vocal cord function should be made prior to surgery in patients with proven or suspected MTC. Invasive staging (laparoscopy, hepatic angiography) and radio-isotope scanning (131I-MIBG, 99mTc-(V)-DMSA, 111In-octreotide, 18FDG-PET) are not routinely indicated prior to first time surgery. Their use is outlined below under Localization of persistent/recurrent MTC in the investigation of patients with residual or recurrent disease. If no metastases are identified on cross-sectional imaging, and there is a high index of suspicion of liver disease, laparoscopy is indicated.

**SURGERY FOR MTC**

The aim of surgery in patients with MTC is to remove all disease in the neck, to produce biochemical and clinical cure and minimize risk of locoregional relapse. This requires meticulous total thyroidectomy and lymph node dissection in most patients. (‘Biochemical cure’ is a term frequently misused as ‘normalization’ of basal calcitonin levels after surgery. It should probably be used only when pentagastrin stimulation does not result in a significant rise in hormone levels.) Surgery should be performed with the intention to preserve recurrent laryngeal nerves, superior laryngeal nerves and parathyroid function. There is little evidence other than non-randomized retrospective studies on which to base firm recommendations for surgical treatment.

**Rationale for lymph node dissection in MTC**

Nodal metastases are common (>75 per cent) in patients with palpable MTC and occur early in the disease. Spread of MTC to lymph nodes occurs in a characteristic pattern – ipsilateral central, ipsilateral lateral, then contralateral central neck. Further spread occurs to contralateral lateral and the upper mediastinal lymph nodes. Lymph node involvement may be found when the basal calcitonin level is only minimally above the normal range. The frequency can be predicted by tumour size and ranges from 17 (pT1) to 100 per cent (pT4). Node metastases are uncommon in sporadic medullary microcarcinoma (1 cm diameter or less), but have been reported to occur in 30 per cent of patients. The pattern of metastatic node distribution in the neck is not related to tumour size. Historically, it has been considered that patients with familial MTC are more at risk of bilateral cervical node involvement because the frequency of multifocal, bilateral disease is high compared with sporadic MTC. However, central compartment node involvement is found in up to 80 per cent of patients with sporadic or hereditary disease. Ipsilateral lateral nodes are involved in 34–80 per cent and contralateral lateral nodes in 19–450 per cent of cases. The frequency of ipsilateral and contralateral lateral compartment node involvement reflects the degree of central compartment node positivity. Skip metastases (negative central and positive lateral or mediastinal compartments) are found in approximately 20 per cent of patients. Mediastinal node disease is more likely to occur in patients with positive cervical nodes and extrathyroidal extension; contralateral cervical or mediastinal lymph node involvement predicts an increased risk of distant metastases.

Standard texts describe the locoregional lymph nodes groups of the thyroid according to Robbins et al. and UICC classifications. There is, however, a lack of clarity, accuracy and confusion in the anatomical terminology of lymph node groups and the surgical procedures described in the treatment of MTC that do not allow direct comparison of outcomes or easy understanding of surgical recommendations for treatment. This may partly explain the lack of compliance with guidelines for 'best surgical practice' which result in undertreatment of many patients with MTC.

To this end, the following terms are defined:

- **Selective neck dissection.** Selective neck dissection preserves one or more of the lymph node groups removed by radical neck dissection.
- **Central compartment.** The area between the carotid arteries, the superior limit is the hyoid bone and inferiorly the suprasternal notch.
- **Central neck dissection.** Removal of lymph nodes in level 6 that include the pre- and paratracheal, precricoid (Delphian) and perithyroidal nodes. The lower limit of a level 6 node dissection, often described as the 'suprasternal notch' and the definition of level 7 nodes.

![Figure 24.6](image-url)  
*Figure 24.6 Magnetic resonance image showing bilateral cervical and infrabrachiocephalic lymphadenopathy in 17-year-old MEN2B patient following previous thyroidectomy.*
often described as ‘superior mediastinal nodes’ is unclear.

- **Lateral neck dissection.** Removal of lymph nodes in levels II, III and IV.
- **Posterolateral neck dissection.** Removal of lymph nodes in levels II, III, IV and V.

The compartment classification of Dralle et al.91 (Figure 24.7) avoids much of the above confusion. The central compartment – C1a right and C1b left – (Robbins levels VI and VII) includes the pre- and paratracheal, pre-cricoid, perithyroidal, paraoesophageal nodes extending from the level of the submandibular glands superiorly, the brachiocephalic vein inferiorly and laterally to the carotid arteries. The cervical lateral compartments (C2, right; C3, left) include cervical lymph nodes (Robbins levels II, III, IV, V) from the carotid sheath to the trapezius muscle laterally, and inferiorly from the subclavian vein to the hypoglossal nerve superiorly. The mediastinal compartment (C4) includes all lymph nodes between the left brachiocephalic (innominate) vein and tracheal bifurcation within the upper anterior and posterior mediastinum. This classification is based on surgical anatomy, is of prognostic significance in MTC and includes the mediastinal nodes below the brachiocephalic vein.

The normal recommendation for the treatment of MTC is total thyroidectomy, although sporadic disease is usually unilateral and unifocal (80 per cent). A single prospective study reported the outcome following unilateral thyroidectomy (in addition to central and ipsilateral modified radical neck dissection) in gene-negative patients with MTC and compared this with historical controls who had undergone total thyroidectomy. The extent of thyroid resection in the 37 patients studied did not influence the rate of biochemical cure.92

Total thyroidectomy and compartment orientated node dissection is associated with improved survival91 and a reduced risk of recurrence.93 Biochemical cure can be obtained in up to 95–100 per cent of patients without lymph node metastases, and in 32–45 per cent of patients with lymph node metastases.67, 77, 81 When fewer than ten lymph nodes are involved, an undetectable calcitonin level is observed in 57 per cent of patients.81

A rational approach to the primary surgical treatment of MTC without distant metastases includes:

- For the uncommon scenarios:
  - Micro-MTC when the basal and stimulated calcitonin is normal: <5 mm sporadic disease, hemithyroidectomy,94 otherwise total thyroidectomy.79, 80
  - MTC <1 cm or >1 cm in diameter when the basal calcitonin is normal and stimulated calcitonin levels are elevated – total thyroidectomy and central neck dissection (C1) (Figure 24.8).78 Patients with stimulated calcitonin levels >560 pg/mL should be treated as having palpable disease95 and considered for lateral neck dissection (C2/C3).

- For the common scenarios,
  - MTC with elevated basal calcitonin level and/or lymph node involvement – total thyroidectomy, central and lateral neck dissection (C1–C3).78
  - When preoperative imaging identifies mediastinal nodal disease or when there is a high risk of node involvement (patients with T4 tumours) mediastinal lymphadenectomy (C4) (via a trans-sternal approach) should be performed (Figure 24.9).

The addition of lymph node dissection to total thyroidectomy increases the likelihood of recurrent laryngeal nerve and parathyroid morbidity.78, 88, 96 In all patients with MTC who undergo surgery, an attempt should be made to preserve parathyroid tissue in situ or by autotransplantation. Transient hypocalcaemia may occur in up to 60 per cent of patients who undergo central compartment neck dissection.78 Permanent hypoparathyroidism after thyroidectomy and central compartment neck dissection is reported in 0.7–4.6 per cent of patients.96, 97, 98 In expert hands,
permanent recurrent laryngeal nerve palsy after neck dissection can be a very rare occurrence. In the absence of direct invasion, the sternomastoid muscle, the internal jugular vein and the accessory nerve should be conserved. Routine dissection of levels I and IIb is not required unless there are palpable/suspicious nodes at these sites. In patients with locally advanced disease, when preoperative vocal cord examination has revealed no sign of recurrent laryngeal nerve involvement every attempt should be made to dissect the tumour from the nerve/s. In patients with unilateral nerve involvement associated with extensive extrathyroidal disease, the nerve may have to be sacrificed to achieve a ‘curative’ procedure. It may not be possible to remove the entire tumour without damaging both recurrent laryngeal nerves, in which case a small residue of tumour may be left behind to protect the nerve/s.

When locally advanced disease involves the upper aerodigestive tract and/or one or both recurrent laryngeal nerves, curative excisional surgery of the tracheal wall and/or oesophagus should be considered. Although pT4 tumours have an approximately 80 per cent risk of distant metastases, survival may be prolonged. For this reason, most patients with confirmed distant metastases should undergo total thyroidectomy and central neck dissection (C1) and should be considered for resection of bulky/symptomatic lymph node disease in the lateral neck (C2 and C3) and/or mediastinum (C4).

Follow up

Thyroid hormone replacement is required and monitored and all patients with MTC require life-long review. The most useful markers of disease status are calcitonin and CEA. In some patients, the expected postoperative fall in calcitonin levels may be delayed. At each visit, a clinical and biochemical assessment should be performed as apparent biochemical cure of MTC after surgery may not be sustained. Patients with MEN2 require multidisciplinary follow up to diagnose, treat and monitor the other components of their syndrome.

PERSISTENT/RECURRENT HYPERCALCITONÆMIA AND RECURRENT MTC

The diagnosis of residual/recurrent disease is made on the basis of clinical symptoms, or signs, or an elevated/rising calcitonin. Locoregional and distant metastases from MTC occur preferentially within the first five years. Approximately 50 per cent of patients who present with palpable MTC without lymphadenopathy will develop locoregional disease even after total thyroidectomy and lymph node dissection. In contrast, a zero locoregional recurrence rate at five years is described in patients with histologically node-negative disease after compartment orientated node dissection.

When a patient presents with persistent or recurrent hypercalcitonæmia, the key issues for the surgeon are:

- Was the initial surgery less than that recommended according to best practice?
- Is the source of calcitonin in the neck (residual thyroid or lymph nodes) or mediastinum and amenable to further surgery?
- Will further surgery result in cure or improved survival?

Many patients will be found to have undergone less than optimal initial surgery: SEER data indicate that between 1994 and 2000, 15 per cent of patients with MTC had less than total or near total thyroidectomy, and between 1973 and 2002, 41 per cent had no cervical lymph node dissection and 51 per cent of patients had less than currently recommended treatment guidelines for MTC.

A conservative surgical approach has been advised by some authors for patients with persistent hypercalcitonæmia because of five- and ten-year survival rates of 90 and 86 per cent, respectively. The key issue is whether or not residual disease lies within the neck and is remediable by surgery. Reoperation in selected patients can result in normalization of calcitonin levels in 22–38 per cent of cases that persist up to ten years from surgery. Biochemical cure is most likely to occur in those patients who have previously undergone inadequate first time surgery. Reoperation may limit MTC progression. In one retrospective study,
Localization of persistent/recurrent MTC

The purpose of diagnostic imaging studies in patients with persistent/recurrent hypercalcitonaeemia is the identification of surgically remediable locoregional disease that may put the patient at risk of airway or oesophageal compression. In all other cases, in the current absence of effective/proven systemic therapy and with a clinical trial, the imaging technique will only serve to identify incurable and often untreatable metastases.

In patients with medullary thyroid cancer and elevated calcitonin levels following thyroidectomy, metastases are best detected when serum calcitonin levels are greater than 500–800 pg/mL. The most efficient detection of metastatic MTC consists of neck ultrasound, chest CT, liver MRI, bone scintigraphy and axial skeleton MRI. In-octreotide (Octreoscan) is superior to 99mTc-(V) DMSA and has a sensitivity of up to 85 per cent for localizing metastatic disease. When localization studies identify recurrent locoregional disease after appropriate first time surgery, reoperative surgery should also be performed. The presence of distant disease should not in isolation preclude surgery because even with distant metastases, bulky locoregional disease can cause significant morbidity and deterioration in quality of life, survival may be prolonged. The aim of surgery is not only to cure or significantly reduce disease bulk or symptoms, but relieve or prevent future compression of the airway and oesophagus, as well as involvement of the brachial plexus or recurrent laryngeal nerves.

MTC is responsible for 10–15 per cent of deaths due to thyroid cancer, published survival rates at five and ten years range from 69 to 97 per cent and 56 to 96 per cent, respectively (Table 24.5). More than 50 per cent of patients with sporadic MTC will die of their disease. Biochemical cure following surgery is associated with 97.7 per cent survival at ten years, survival for patients with micro-MTC is reported as 94 per cent at ten years. Combined data from 61 European Cancer Registries indicate children with medullary carcinoma thyroid have five-year survival rates of 95 per cent. Patients with advanced disease have a median survival of eight years and a third of patients with systemic symptoms die within five years.

The purpose of diagnostic imaging studies in patients with persistent/recurrent hypercalcitonaeemia is the identification of surgically remediable locoregional disease that may put the patient at risk of airway or oesophageal compression. In all other cases, in the current absence of effective/proven systemic therapy and with a clinical trial, the imaging technique will only serve to identify incurable and often untreatable metastases.

In patients with medullary thyroid cancer and elevated calcitonin levels following thyroidectomy, metastases are best detected when serum calcitonin levels are greater than 500–800 pg/mL. The most efficient detection of metastatic MTC consists of neck ultrasound, chest CT, liver MRI, bone scintigraphy and axial skeleton MRI. In-octreotide (Octreoscan) is superior to 99mTc-(V) DMSA and has a sensitivity of up to 85 per cent for localizing metastatic disease. When localization studies identify recurrent locoregional disease after appropriate first time surgery, reoperative surgery should also be performed. The presence of distant disease should not in isolation preclude surgery because even with distant metastases, bulky locoregional disease can cause significant morbidity and deterioration in quality of life, survival may be prolonged. The aim of surgery is not only to cure or significantly reduce disease bulk or symptoms, but relieve or prevent future compression of the airway and oesophagus, as well as involvement of the brachial plexus or recurrent laryngeal nerves.

**Outcome and Prognosis**

MTC is responsible for 10–15 per cent of deaths due to thyroid cancer, published survival rates at five and ten years range from 69 to 97 per cent and 56 to 96 per cent, respectively (Table 24.5). More than 50 per cent of patients with sporadic MTC will die of their disease. Biochemical cure following surgery is associated with 97.7 per cent survival at ten years, survival for patients with micro-MTC is reported as 94 per cent at ten years. Combined data from 61 European Cancer Registries indicate children with medullary carcinoma thyroid have five-year survival rates of 95 per cent. Patients with advanced disease have a median survival of eight years and a third of patients with systemic symptoms die within five years.

On multivariate analysis, retrospective follow-up studies from single centres and Swedish, US National Cancer and SEER databases indicate that younger age at diagnosis confers a survival advantage. A recent, single centre retrospective cohort study in which survival was adjusted for baseline population mortality did not confirm these findings.

Preoperative basal calcitonin levels of less than 50 pg/mL (normal <10 pg/mL) or more than 500 pg/mL may predict the likelihood or failure of surgery to achieve biochemical cure, respectively. Post-treatment calcitonin doubling time of less than six months, one year and two years indicates a worse prognosis. High preoperative CEA levels may indicate advanced disease.
Histological features that are reported to indicate worse prognosis include the presence of lymphovascular invasion, the number of positive lymph nodes, capsule invasion, disseminated tumour cells in connective tissue. Those that indicate a better prognosis include amyloid, DNA euploidy, somatostatin expression in tumour cells, absence of desmoplastic stromal reaction. A somatic RET mutation, increased disease stage, tumour size, extent of local disease, extent of lymph node involvement, distant metastases, less extensive surgery and the presence of extrathyroidal disease confer an adverse outcome.

NON-SURGICAL TREATMENT OF MTC

Adjuvant radiotherapy

Adjuvant radiation therapy has been found to be independently associated with a decreased survival, although its use is inevitably confined to those patients with a worse prognosis. External beam radiotherapy is reported to reduce local relapse in patients with limited nodal disease, in high risk patients and in those presenting with more advanced disease. It has not been shown to produce a survival benefit.

Systemic therapy

Therapeutic 131I-MIBG may provide transient, partial objective response or symptom palliation. The somatostatin analogue octreotide (DOTATOC) labelled with 90Y administered to patients with metastatic MTC that expresses somatostatin receptors can result in partial response, stable disease and survival benefit.

Combination regimes of chemotherapeutic agents that include doxorubicin, streptozotocin, 5FU and dacarbazine have been studied in small series with minimal partial response and disease stabilization in approximately 50 per cent of patients.

In vivo and in vitro studies using inhibitors of RET and FGFR4, the P13K pathway, tyrosine kinase, topoisomerase, tumour suppressor gene activation, targeted anti-CEA radioimmunotherapy and somatostatin analogue therapy provide a background for trials for patients with recurrent medullary thyroid carcinoma that include open and randomized phase II studies of ZD6474 (Zactima; Astra Zeneca), Vandetanib, Motesanib, Cabozantinib and a phase II trial of pretargeted radioimmunotherapy using anti-CEA DTPA bispecific antibody and di-DTPA-131I peptide of molecular targeted therapy. The subject is well covered in two recent reviews.

Table 24.6 Case history 1: 27-year-old male with apparently sporadic medullary thyroid cancer.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>Thyroid nodule. Referred to surgeon</td>
<td>Thyroid nodule. Referred to surgeon</td>
</tr>
<tr>
<td>2002</td>
<td>Subtotal thyroid lobectomy. Diagnosis: medullary thyroid cancer</td>
<td>Subtotal thyroid lobectomy. Diagnosis: medullary thyroid cancer</td>
</tr>
<tr>
<td>2002</td>
<td>Referred ‘… please advise as to further treatment …’</td>
<td>Referred ‘… please advise as to further treatment …’</td>
</tr>
<tr>
<td>2002</td>
<td>Calcitonin 320 ng/L (NR, 0–11.5)</td>
<td>Calcitonin 320 ng/L (NR, 0–11.5)</td>
</tr>
<tr>
<td>2002</td>
<td>Abdominal CT – bilateral adrenal masses (Figure 24.11)</td>
<td>Abdominal CT – bilateral adrenal masses (Figure 24.11)</td>
</tr>
<tr>
<td>2002</td>
<td>RET 634 mutation, i.e. MEN2A</td>
<td>RET 634 mutation, i.e. MEN2A</td>
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<td>2002</td>
<td>‘Asymptomatic’ phaeochromocytomas</td>
<td>‘Asymptomatic’ phaeochromocytomas</td>
</tr>
<tr>
<td>2002</td>
<td>Normal adrenal function. No recurrence of phaeochromocytoma</td>
<td>Normal adrenal function. No recurrence of phaeochromocytoma</td>
</tr>
<tr>
<td>2005</td>
<td>Bilateral laparoscopic adrenalectomy – cortical sparing</td>
<td>Bilateral laparoscopic adrenalectomy – cortical sparing</td>
</tr>
<tr>
<td>2005</td>
<td>Completion bilateral thyroidectomy and C1–C3 neck dissection</td>
<td>Completion bilateral thyroidectomy and C1–C3 neck dissection</td>
</tr>
<tr>
<td>2005</td>
<td>Bilateral phaeochromocytomas</td>
<td>Bilateral phaeochromocytomas</td>
</tr>
<tr>
<td>2005</td>
<td>MTC pT2N1aMx</td>
<td>MTC pT2N1aMx</td>
</tr>
<tr>
<td>2009</td>
<td>Calcitonin 5.1 ng/L (NR, 0–11.5)</td>
<td>Calcitonin 5.1 ng/L (NR, 0–11.5)</td>
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<tr>
<td>2009</td>
<td>Calcitonin 14.2 ng/L (NR, 0–18.9)</td>
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<tr>
<td>2010</td>
<td>Calcitonin 6 ng/L (NR, 0–11.8)</td>
<td>Calcitonin 6 ng/L (NR, 0–11.8)</td>
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</table>

Comments and learning points

- 2 year delay/inappropriate procedure
- Young patient with MTC = ?MEN2A
- Calcitonin level indicating at least node metastases
- ‘Asymptomatic’ phaeochromocytomas
- Index case in gene negative family
- Despite late presentation of hereditary disease
- Good outcome with ‘stable’ calcitonin at 4 years
Children and adolescents identified by RET screening to be at risk for the development of medullary thyroid cancer can be treated with prophylactic thyroidectomy before developing the disease. The timing of the intervention is modified according to genotype and the age at presentation.

Age at onset of CCH and MTC and timing of thyroidectomy

The progression of C-cell hyperplasia to MTC and subsequent lymph node metastasis occurs in an age-related, codon-specific manner:

- Children with RET codon 883, 918 mutations (MEN2B), classified as level 3, have the highest risk from aggressive MTC. Neoplastic transformation of C cells occurs in the first year of life.
- Children with RET codon 609, 611, 618, 620, 630 or 634 mutations classified as level 2 have a high risk for MTC. Neoplastic transformation of C cells occurs in the first decade.
- Children with RET codon 768, 790, 791 804 and 891 mutations are classified as level 1 or as having the least high risk.

Cohort studies that include asymptomatic carriers with no malignancy or T1 N0 tumours\textsuperscript{169} and index patients/carriers with various stages of disease\textsuperscript{170} form the basis of recommendations as to at what age prophylactic/risk reduction total thyroidectomy should be performed:

- highest risk carriers within the first year of life, preferably in the first six months;
- high risk carriers before the age of five years;
- least high risk carriers before ten years of age.

The earliest manifestation of node-negative MTC, node-positive and metastatic disease for specific RET genotypes\textsuperscript{171, 172} reveals that node-negative MTC can occur, albeit rarely, at an age earlier than that recommended for ‘prophylactic’ surgery. On that basis, decisions as to the timing and the extent of surgery should be based not only on the affected codon, but in addition the age of the patient, and the calcitonin level.

Timing of lymph node surgery

In ideal circumstances, risk reduction surgery (total thyroidectomy) should be performed before the onset of MTC, thereby reducing the need for lymph node dissection, which is associated with an increased risk of hypoparathyroidism and recurrent laryngeal nerve injury; it would be preferable to avoid this. In reality, cases often manifest when it is likely or evident that MTC is already present and occult lymph node metastasis may have occurred.

Current recommendations suggest that children with highest risk mutations (883, 918) should undergo routine lymph node dissection at the time of thyroidectomy in the first year of life. The evidence base for recommendations regarding lymph node dissection in children with high risk mutations is less clear. Although node metastasis has been identified in a child with MEN2A of five years 11 months,\textsuperscript{172} the multicentre EUROMEN study did not find node involvement prior to the age of 14 years in individuals with a 634 codon mutation.\textsuperscript{169} An evidenced-based review suggests that children with a 634 mutation should undergo lymph node dissection from the age of five years and those with mutations at codon 609, 611, 618, 620 and 630 from the ages of ten years.\textsuperscript{171} Recommendations for those with least-high risk suggest node dissection should be performed from the age of 20 years. Recent studies suggest that in the absence of clinical features to the contrary, lymph node surgery can be avoided in RET carriers with a normal basal calcitonin.\textsuperscript{173}

Results of ‘prophylactic’ surgery

Previously reported outcomes of ‘prophylactic’ surgery should be interpreted with the knowledge that MTC was often present at the time of surgery; the intervention would have been better termed ‘risk reduction’ or indeed therapeutic. By 2005, only 15 per cent of the 275 reported ‘prophylactic’ thyroidectomies performed on RET 634 children were carried out before the age of five years.\textsuperscript{174} Studies of outcome from risk reduction surgery in young patients up to the age of 21 years confirm that biochemical cure is possible and sustained at follow up in the majority of individuals. In the landmark study, at a mean
of seven years from surgery (total thyroidectomy, central neck node dissection) 88 per cent of 50 patients who had undergone surgery between the ages of three and 19 years had undetectable basal and stimulated calcitonin levels. A further report details outcome in 46 RET gene carriers (11 level 1 mutations and 35 level 2 mutations) who had undergone surgery at ages ranging from four to 21 years with a mean follow up of 6.4 years. All level 1 patients were cured. Of the level 2 patients, 24 patients had invasive disease (all pN0) at the time of surgery, five patients were not cured.

CASE HISTORIES

Illustrative case histories of two patients with MTC are given in Tables 24.6 and 24.7.

KEY LEARNING POINTS

• The care of patients with medullary thyroid cancer requires involvement of a specialist and an experienced multidisciplinary team that includes a clinical geneticist.

• All patients with MTC must undergo genetic testing for RET mutations to identify those with hereditary disease. When a patient is confirmed as a carrier of a RET mutation, further investigations should be performed to determine the presence of metastatic disease and the need for prophylactic thyroidectomy. Patients with a RET mutation should also be monitored for the development of secondary primary tumors.

• Reoperation in patients with residual or recurrent MTC in the neck results in normalization of calcitonin in approximately a third of selected patients. Genotype-phenotype correlations in genetically determined MTC provide a solid foundation on which to base recommendations for the timing of prophylactic surgery. Patients with MTC with suspected local metastatic disease to regional lymph nodes in the central compartment should undergo a total thyroidectomy and level VI compartmental dissection. When lymph node metastases are present in the paratracheal central compartment, the issue of lateral compartment node dissection is controversial.

Table 24.7 Case history 2: 42-year-old woman with sporadic medullary thyroid cancer.

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
<th>Calcitonin levels</th>
<th>Comments and learning points</th>
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</thead>
<tbody>
<tr>
<td>2005</td>
<td>Thyroid nodule. Referred to surgeon</td>
<td>Calcitonin 337 ng/L (NR, 0–4.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal thyroid lobectomy. Diagnosis: medullary thyroid cancer</td>
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<tr>
<td></td>
<td>Referred ‘… please advise as to further treatment…’</td>
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<td></td>
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<tr>
<td>May 2005</td>
<td>Calcitonin 337 ng/L (NR, 0–4.6)</td>
<td>Calcitonin level indicating at least node metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary metanephrines and catecholamines – normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RET mutation analysis – negative</td>
<td></td>
<td></td>
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<tr>
<td>October 2005</td>
<td>Completion thyroidectomy and C1–C3 neck dissection</td>
<td>Sporadic MTC</td>
<td></td>
</tr>
<tr>
<td>histology</td>
<td>MTC. pT2 pN1b single unilateral positive node</td>
<td></td>
<td></td>
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<tr>
<td>follow up</td>
<td>November 2005</td>
<td>Calcitonin 362 ng/L (NR, 0–4.6)</td>
<td>Calcitonin level indicates distant metastasis</td>
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<tr>
<td></td>
<td>April 2006</td>
<td>Calcitonin 553 ng/L (NR, 0–5.5)</td>
<td>Rapid calcitonin doubling time – poor prognosis</td>
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<tr>
<td></td>
<td>August 2006</td>
<td>Calcitonin 1005 ng/L (NR, 0–5.5)</td>
<td></td>
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<tr>
<td></td>
<td>Extensive imaging chest/neck/abdomen CT/ MRI/DOPA-PET – negative</td>
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<td></td>
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<tr>
<td>June 2007</td>
<td>Calcitonin 5060 ng/L (NR, 0–5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>June 2007</td>
<td>Multiple liver metastases on MRI</td>
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<tr>
<td>February 2009</td>
<td>Calcitonin 3300 ng/L</td>
<td></td>
<td></td>
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<tr>
<td>May 2011</td>
<td>Calcitonin 5020 ng/L (NR, 0–4.8)</td>
<td>Clinical trial of tyrosine kinase inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

466 Medullary thyroid cancer
as carrying a RET mutation, family members should be screened for the mutation. Prophylactic thyroidectomy should be offered to young gene-positive family members prior to the onset of malignancy.

- In patients with proven or suspected medullary thyroid cancer, phaeochromocytoma must be excluded prior to surgery by biochemical testing. An uneventful first operation does not preclude an ‘eventful’ reoperative procedure in a patient with a previously undiagnosed phaeochromocytoma.
- Meticulous surgery can result in biochemical cure of MTC.
- In patients with MTC, an elevated basal calcitonin and/or involved nodes and no distant metastases – total thyroidectomy and node dissection of the central and lateral neck compartments (C1–C3) should be performed.

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Avoiding complications in thyroid and parathyroid surgery

MARCO RAFFAELLI, CELESTINO PIO LOMBARDI, ROCCO BELLANTONE, CARMELA DE CREA, DAVID LESNIK, ANDRE POTENZA AND GREGORY RANDOLPH

INTRODUCTION

Although thyroidectomy is one of the most frequently performed surgical procedures worldwide, it was during the last century that it became an accepted operation. In fact, in the middle of the nineteenth century, the French Academy of Medicine banned thyroid surgery because of its high mortality rate.

Similarly in 1871, one of the pioneers of thyroid surgery, Greene, while reporting his three successful thyroidectomies, warned that the operation should be used "never for the relief of deformity or discomfort merely; only to save life."

So it was that the risk of life-threatening complications forestalled the evolution of thyroid surgery until the end of the nineteenth century. It was only after T Kocher refined and described his meticulous technique and reported his excellent results, with a mortality rate of 0.5 per cent in 5000 thyroidectomies, that thyroidectomy became an accepted procedure. It is remarkable that he was the first surgeon to receive the Nobel Prize for this accomplishment in 1909.

The history of parathyroid surgery is far more recent, with the first procedure performed by Felix Mandl in 1925.

There is no doubt that competence in thyroid and parathyroid surgery requires a mastery of basic surgical techniques and thorough understanding of normal neck anatomy, as well as the possible anatomical variations one might encounter while performing these procedures. It is currently performed with a low complication rate (<3 per cent) by experienced endocrine surgeons. Several recent reports have demonstrated that these procedures may safely be performed by residents operating under supervision and the newly established surgical consultant. However, in general, there is a significant inverse relationship between the number of procedures performed and the rate of complication. In other words, surgical skill acquired through experience plays an important role in reducing one’s complication rate. This has also been proven true in other fields of surgery.

Indeed, lower complication rates are obtained in tertiary care referral centres where these procedures are regularly performed by dedicated endocrine surgical teams.

Nonetheless, despite skill and experience, complications may occur, either as a result of surgical error or due to the
extent of patient disease. The most effective way to avoid complications in endocrine surgery is to recognize how and why they occur. Thus, the aim of this chapter is to furnish the reader not only with a list of the possible complications, but more importantly with a description of common surgical errors and techniques that will help to avoid them.

PREOPERATIVE EVALUATION

When meticulous surgical technique is employed, the occurrence of complications may be attributed, at least in part, to factors related to patient disease or comorbidity. For this reason, thorough and accurate patient evaluation is necessary at the first consultation.

A careful history that emphasizes symptoms of endocrine disease, general physical status, cardiopulmonary status, genetic abnormalities, drug intake (particularly aspirin or other anticoagulants), response to previous anaesthesia and surgery, and any previous bleeding problems are important factors to consider in any preoperative evaluation. A thorough physical examination focusing on the stigmata of mass effect on the upper aerodigestive tract and signs of thyroid and parathyroid dysfunction must always be performed. Examination of the larynx by indirect laryngoscopy provides knowledge of the integrity of laryngeal function. Although it is frequently recommended, some surgeons question its utility in patients without previous operation and no change in voice quality. However, occasionally, a paralysed cord is found preoperatively in a patient who has achieved full vocal cord compensation and a normal voice. This preoperative finding might clearly have some value with respect to surgical treatment planning, not to mention possible medicolegal implications (see below under Recurrent laryngeal nerve, p. 478).

Standard blood chemistry, including thyroid functions and a serum calcium assay, should always be performed. Documenting euthyroidism is essential, lest one risk perioperative thyroid storm in thyrotoxic patients. If concomitant primary hyperparathyroidism is detected, which is not a rarity, a complete evaluation and possible exploration of all four parathyroid glands is clearly discussed with the patient. In summary, these and other findings may inform both patient and surgeon and may also reveal the need for further preoperative medical evaluation and management.

Infection and wound healing disorders

WOUND INFECTIONS

Thyroidectomy is associated with a low risk for wound infections (0.02–0.5 per cent). Apart from normal surgical dissection prior to incision and accurate surgical field draping, no further preventive measures are usually required. As in other operations, polivinilpirrolidone (Betadine) is the preferred disinfecting solution. In patients with known differentiated thyroid carcinoma, a non-iodinated disinfecting solution should be used so as not to interfere with a post-surgical radioiodine scintiscan and ablation. No difference in frequency of postoperative wound infections has been shown with antibiotic prophylaxis. In spite of this evidence, others still recommend routine intravenous prophylactic antibiotic administration at the induction of the anaesthesia. In summary, antibiotic prophylaxis is not routinely advocated in the absence of well-known risk factors, such as diabetes, valvular heart diseases, immunodeficiency, etc. Another issue possibly related to wound infection is that of wound drainage. Some authors report that the utilization of closed suction drains reduces the amount of fluid collection in the operative bed and thus minimizes the risk of infection and abscess formation. Others do not confirm a relationship between use of a drain and the risk of wound infection. As the overall incidence of wound infection is so low, it is thought that most wound infections after endocrine neck surgery are endogenous. For this reason, surgery should be avoided in patients with acute infectious illness. Minor cellulitis usually responds well to oral antibiotics. Frank abcesses are extremely rare and require incision and drainage in addition to intravenous antibiotics.

SCAR DISORDERS

Cosmesis after thyroid and parathyroid surgery is important given the prominent location of the surgical incision, as well as the fact that the patients are frequently young females. For the best cosmetic results, a well-positioned collar incision should be made in a normal skin crease approximately 1 cm below the cricoid cartilage. Lower incisions are indeed more prone to hypertrophic scar and keloid formation because there is a higher degree of tension on the wound. This placement has another important advantage. It facilitates control and ligation of the superior pole vasculature. Over the last decade, the development of minimally invasive techniques, which are performed through small (1.5–4 cm) skin incisions, with or without endoscope utilization, has yielded even better cosmetic results compared to conventional approaches.

SEROMA

The seroma is a serum collection often associated with neck dissection during thyroid surgery. Its incidence has been reported to be between 0 and 6 per cent. When this occurs, it may be treated with repeated fine needle aspiration. However, this is associated with increased risk of infection. Drain utilization is usually suggested for its prevention, especially in cases of substernal goitre, Graves’ disease or large multinodular goitre. In case of infection, open drainage is often necessary.

POSTOPERATIVE HAEMATOMA

Postoperative haematoma remains a fortunately uncommon, but potentially serious, complication of thyroid surgery. Post-thyroidectomy haematoma is variably reported in the literature in 0.3–4.3 per cent of patients and in about 0.3 per cent of patients after parathyroidectomy. A postoperative haematoma can lead to devastating consequences with tracheal compression and subsequent hypoxia, which may then lead to brain injury and even
The term ‘compressive haematoma’ has become well known in the medical literature, indicating potential airway compromise. The exact mechanism of airway obstruction is a matter of some debate. Some authors have questioned the ability of clots to cause compression of the rigid cartilaginous trachea. They have attributed airflow compromise to impairment of venous and lymphatic drainage within the laryngopharynx resulting in oedema and obstruction.

Whatever the cause, the patient may present with respiratory distress, pain or pressure sensation in the neck or dysphagia. Signs include progressive neck swelling, suture line bleeding, dysphoea and/or stridor and possibly significant blood loss.

Intraoperative and postoperative haemorrhage may be venous or arterial in origin. It may be caused by dislodgment of ligatures, reopening of cauterized vessels, or bleeding from residual thyroid parenchyma. In some series, most of the haemorrhagic events occur early after surgery, with the patient still in the operating theatre or in the recovery room, or within the first 6 hours after the operation.

However, in other series, more than 50 per cent of patients presented with haematoma beyond 6 hours after the operation, with up to 20 per cent of patients presenting beyond 24 hours after thyroidectomy. This suggests that early discharge after thyroidectomy (<24 hours) bears the potential risk of missing some late haematomas that would require emergency evacuation. Using a decision analysis, it has been demonstrated that 54 deaths per 100 000 due to haemorrhage after thyroid operation could be prevented with 24 hours, rather than 6 hours postoperative stay.

Although it has been widely investigated, most published series have failed to definitively identify risk factors for this complication. Patient risk factors include a history of coagulation disorder such as haemophilia, von Willebrand’s disease, chronic renal failure and haemodialysis, use of anticoagulant or antiplatelet medications, etc. Preoperative optimization of these conditions prior to surgery is mandatory to avoid postoperative bleeding. Particular risk of haemorrhage associated with the underlying thyroid pathology has been postulated, but there is little evidence to support this. Toxic goitre and Graves’ disease have been associated with increased risk of postoperative haematoma. Since Lugol’s iodine solution has been proven efficacious in decreasing thyroid blood flow in toxic goitre, its utilization should be recommended in these conditions to reduce the risk of intra- and postoperative bleeding. Subternal and intrathoracic goitres, as well as reoperative procedures, have been considered risks for postoperative bleeding. Other studies failed to identify these conditions as significant risk factors.

Surgeon-related risk factors obviously include experience and surgical technique. Despite this, in most studies, high surgical volume failed to reduce the rate of postoperative haemorrhage. Moreover, operations performed by supervised residents and newly established consultants do not seem to entail a higher risk of bleeding.

Another surgeon-related factor is the surgical access. If the strap muscles are sectioned, they may represent an additional source of bleeding. Incomplete closure of the strap muscles, leaving a marginal ‘weep hole’, is widely proposed as a measure allowing early haematoma to spontaneously decompress. Care should also be taken to avoid injury to the anterior jugular veins during preparation of the flap or closure of the midline at the end of the operation. Another potential source of postoperative bleeding is residual thyroid tissue in partial resection. Recent reports showed a higher incidence of postoperative haemorrhage in patients who underwent bilateral subtotal thyroid resection.

In recent years, minimally invasive procedures for thyroid and parathyroid surgery have gained in popularity, particularly in specialized centres. Data from the literature demonstrate that the rate of major postoperative bleeding requiring surgical revision after video-assisted and endoscopic thyroid and parathyroid procedures approaches 0 per cent and only a few cases have been reported. It could be inferred that the limited dissection which characterizes these techniques may reduce the risk of this complication. These results could be biased by the strict selection criteria for these procedures. For example, with large goitres, thyroiditis, aggressive and infiltrating tumours, node metastases, and those requiring reoperative surgery or bilateral exploration are generally not candidates for these procedures.

Postoperative bleeding is preventable in the majority of patients. A meticulous surgical technique with careful haemostasis is the best means of reducing the likelihood of haemorrhage. There are several manoeuvres that can assist the surgeon in the recognition of potential bleeding sources before wound closure. Neck hyperextension should be reduced so that bleeding vessels controlled under tension may be identified prior to closure. A Valsalva manoeuvre, which increases the venous pressure and reveals potential venous bleeding sources, is also of great value. Similarly, some authors suggest briefly tilting the head of the patient down about 30° in the Trendelenburg position at the end of the operation before wound closure.

The traditional clamp and tie technique is clearly very effective for haemostasis. Additional methods include the application of surgical clips, as well as monopolar and bipolar electrocautery. Ligature and clips may become dislodged. For this reason, double ligature of prominent vessels is usually recommended. In recent years, several new technologies for haemostasis have been developed for endocrine and other head and neck operations, initially for the minimally invasive approaches. These new technological devices for haemostasis include both ultrasonic shears (Harmonic scalpel, Ethicon endosurgery) and a computer-controlled bipolar electrothermal sealing system (Ligasure; Valley Laboratory Corporation, a division of Tyco Healthcare, Boulder, CO, USA). Several comparative studies have evaluated their efficacy in thyroid surgery and have demonstrated that both instruments are safe alternatives to standard vessel ligation, with significant advantages in terms of shorter operative time. Whether these tools are effective in reducing blood loss remains to be determined.

The use of haemostatic agents (i.e. oxidized cellulose, fibrin sealant, etc.) may be useful in selected cases to facilitate haemostasis by mechanical pressure and promoting coagulum formation, thus resulting in reduced capillary ooze. Whether these agents increase the overall cost of the procedure and do no replace the need for meticulous haemostasis.

Many studies, including prospective, randomized investigations, have failed to demonstrate significant advantages in preventing postoperative haematoma with drain utilization. Other studies suggest that neither gland size, diagnosis, type of surgery, nor intraoperative bleeding
were valid justifications for the use of an external drain. Based on this, it would appear that drains should not routinely be used as a preventive measure. However, if used, they may signal the onset of bleeding and be particularly useful in alerting the nursing staff to the existence of postoperative haemorrhage. After wound closure, a smooth extubation without significant coughing or retching and adequate control of both postoperative pain and vomiting may help to avoid a sudden increase in venous and/or arterial pressure, and reduce the risk of postoperative bleeding. Pressure should be applied to the neck dressing if the patient struggles and coughs at the conclusion of the case or upon extubation. This manoeuvre could help to avoid the rise in the venous pressure at the wound site. Conversely, pressure dressings can delay identification of a developing haematoma and should be avoided. After extubation, patients should be kept with the head and the shoulders elevated (10–20°) in order to maintain a negative venous pressure in the neck.

Beyond prevention, early recognition with immediate intervention is the key for the management of this potentially lethal post-thyroidectomy complication. It is important to ensure that a member of the surgical team remains with the patient during the extubation and transit to the recovery room. Furthermore, it is important for experienced personnel to closely monitor the patient upon return to the ward in order to detect signs of significant bleeding early. One recent review stressed the importance of recognizing early signs of hypoxia, such as tachycardia, diaphoresis, irritability and confusion, in order to avoid delays in reoperation. In the event of significant airway compromise developing rapidly, bedside evacuation of the haematoma may be necessary. In such a circumstance, one must remove the superficial skin sutures and those closing the platysma to evacuate formed clots. If the patient is experiencing respiratory difficulty, it should be remembered that the supine position can exacerbate respiratory distress by increasing laryngeal oedema and may also complicate attempts at reintubation. For these reasons, intubation should be performed by experienced personnel. Inability to secure an adequate airway via intubation may result in the need for tracheotomy. Similarly, persistent laryngeal oedema after haematoma evacuation may indicate the need for prolonged intubation and systemic steroid administration and, in rare cases, tracheotomy. In a recent report from a high volume referral centre, tracheotomy was required in approximately a quarter of the patients who underwent re-exploration for haematoma (0.3 per cent of all thyroidectomies performed), although this percentage has diminished over recent years.

A liberal attitude towards re-exploration in the case of symptomatic haematoma is mandatory. Patients are best served by early definitive intervention with evacuation of the clot rather than prolonged observation. Only a small subgroup of patients with minimal swelling, lack of symptoms and no progression of their haematoma should be considered for conservative management. However, even in these cases, conservative management would prolong hospitalization time, may require weeks to months of observation until complete reabsorption, and might also impair wound healing.

At the time of re-exploration as always, protection of the structures at risk (i.e. laryngeal nerves, parathyroid glands) is paramount. Gentle irrigation and clot evacuation are mandatory. Saline solution is useful in cleaning the operative field and identifying any source of bleeding. Blind clamping of vessels is to be avoided. If no active source of bleeding is identifiable at reoperation, after all the potential sources have been adequately explored, drainage should be employed and closure should ensue.

**Superior laryngeal nerve**

Lesion of the external branch of the superior laryngeal nerve (EBSLN) may occur during thyroid surgery and may cause important voice changes, especially in professional voice users (singers, public speakers). Knowledge of its anatomy and its function is of utmost importance for thyroid surgeons. The superior laryngeal nerve (SLN) arises from the vagus nerve close to the caudal end of the nodose ganglion and descends in the neck behind the external carotid artery to the carotid bifurcation. At the level of the hyoid bone, it divides into an internal (sensory) branch and an external (motor) branch. The internal branch perforates the thyrohyoid membrane, providing sensory innervation of the pharyngeal and laryngeal mucosa from the base of the tongue to the glottis and the subglottic region. Lesions of the internal branch result in loss of sensation of the ipsilateral mucosa, determining defective sensory motor coordination of the glottis and subsequent aspiration on swallowing, but it is usually not at risk during thyroid and parathyroid procedures.

On the other hand, the course of the EBSLN is more caudal and near the superior thyroid vessels and thus it is at risk of lesion during thyroidectomy. After emerging from the SLN, the EBSLN runs in close proximity to the medial aspect of the superior thyroid artery and curves medially to provide motor innervation of the cricothyroid muscle. The function of this muscle is to lengthen and tense the ipsilateral true vocal cord. As a consequence, lesion of the EBSLN results in voice changes characterized by loss of high tone and pitch volume and fatigue after extensive use. Such changes are usually well tolerated by most patients, but may be career-threatening in voice professionals, such as singers and public speakers. The importance of this nerve for professional singers is underscored by the story of the famous opera soprano Amelita Galli-Curci whose professional career ended after undergoing a thyroidectomy for multinodular toxic goitre in 1935 performed by Dr Arnold Kegel. Indeed, after the operation she never sang well again due presumably to injury of the EBSLN.

In most patients (about two-thirds of the cases), the nerve crosses medially into the cricothyroid muscle more than 1 cm cranially to the upper pole (Cernea’s type 1). In the remaining one-third, the EBSLN runs within a distance of less than 1 cm from the upper pole of the thyroid gland (Cernea’s type 2). In one half of these patients, the nerve remains cranial to the upper pole of the thyroid lobe (type 2a). In the remaining cases, the EBSLN has a more caudal course and lies below the superior thyroid pole (type 2b). This last position involves an increased risk of inadvertent nerve injury during dissection and ligation of the vessels of the superior pole (high-risk nerves).

Several technical methods have been proposed to reduce the risk of EBSLN injury, including skeletonization and...
individual ligation of the vessels of the superior thyroid pole adjacent to the capsule and visual identification of the nerve before ligation of the superior pole. However, at present, although the importance of preservation of the EBSLN is well recognized, the need for routine visualization is still controversial, because in 12–20 per cent of the cases, the nerve cannot be visualized since it is located within the cricothyroid muscle. A recently published prospective, randomized study comparing routine identification of the nerve versus individual ligation of the vessels of the superior pole close to the thyroid capsule, failed to demonstrate a significant difference in terms of EBSLN injury between the two techniques; no definitive EBSLN palsy was found in either group. However, in absence of EBSLN identification, a meticulous surgical technique should be used to avoid injury. After careful division of the anterior suspensory ligament, the potential space between the medial portion of the superior pole and the cricothyroid muscle can be entered. The upper pole is then grabbed with a clamp or with a finger and retracted downward and outward. The connective tissue medial to the upper pole is completely opened. This allows good exposure of the vessels of the upper pole which are then individually ligated as distally as possible. Lateral and downward traction of the superior pole should put some tension on the EBSLN since it crosses the superior thyroid artery. This should aid in identification of the nerve if it is in a high-risk position. It is important to reduce the risk of EBSLN injury by avoiding en masse ligation of the superior pole. Moreover, dissection should be performed from medial to lateral.

Intraoperative utilization of a nerve stimulator has been demonstrated to be beneficial for the identification and preservation of the EBSLN. However, its utilization is not yet routine. EBSLN stimulation results in cricothyroid muscle contraction. This can help to identify the nerve during dissection of the superior pole and confirm its functional integrity at the end of the operation. It has been reported that the use of a nerve stimulator reduces the rate of EBSLN injury from 12 to 0 per cent, when compared with unaided visual identification. Nerve detection technology may be especially useful in difficult cases, such as reoperative cases and large goitres which may alter normal anatomy as a result of cephalad growth of thyroid tissue behind the vascular pedicle.

Identification and preservation of the EBSLN has been aided by video-assisted endoscopic techniques, largely due to the magnification provided by the endoscope. A recent randomized prospective study comparing voice after video-assisted versus conventional thyroid surgery has proposed a reduction in injury to the EBSLN using the former technique. Other factors may play a role in EBSLN injury. It has been reported that inappropriate use of diathermy close to the EBSLN or to the quite thin cricothyroid muscle itself can cause damage and it should be avoided. In the same way, inappropriate utilization of novel technical devices for haemostasis (Ligasure and Harmonic scalpel) close to this nerve could result in thermal injury. Cautious use of these devices is recommended when sectioning the vessels of the upper pole. When using the Harmonic scalpel, it is necessary to have the active blade far from the nerve. Moreover, one should remember that small vessels run from the superior thyroid artery into the pharyngeal constrictor and the cricothyroid muscles. As the EBSLN slips under these muscles, there is a risk of injury during cauterization of these little vascular branches. Clearly, this should be avoided.

Finally, every attempt should be made to avoid injury of the cricothyroid muscle itself. This may occur due to electrocautery or manual retraction. Indeed, lesions of the muscles may cause functional impairments similar to those related to EBSLN injury.

The reported incidence of injury to the EBSLN ranges from 0 to 20 per cent in the literature with most studies quoting a rate of < 5 per cent. The true incidence is hard to quantify because formal laryngeal evaluation is usually not performed as part of routine postoperative follow up in the absence of symptoms. In the case of unilateral paralysis, flexible laryngoscopy usually shows symmetry of the larynx at rest. During phonation, the cord on the affected side will appear shorter and bowed when compared with the normal. Inferior displacement of the affected vocal process may be seen, or, more commonly, sluggish vocal fold motion with an asymmetrical mucosal wave. This type of injury can result in rotation of the posterior glottis towards the affected side. This asymmetry will not be seen in patients with bilateral paralysis. The patients with EBSLN injury will not be able to produce high-pitch phonation because the vocal cords will not fully elongate.

Many of the symptoms or physical findings of injury to the EBSLN are subtle, especially in patients who are not professional voice users. The clinician must have a high degree of suspicion and be able to differentiate this injury from other voice disorders using indirect laryngoscopy, videostroboscopy and laryngeal electromyogram (EMG) to confirm the diagnosis. After the diagnosis is made, therapy by a speech and language pathologist should be promptly started to improve phonatory outcomes and avoid compensatory vocal abuses.

Recurrent laryngeal nerve

Recurrent laryngeal nerve palsy (RLNP) is the most feared and potentially serious complication following thyroid surgery as it may cause significant voice and airway problems. Although not all post-thyroidectomy voice and swallowing disturbances are related to laryngeal nerve injuries, symptomatic RLNP has been proved to be a major cause of impaired quality of life and to have a negative impact on job performance. It accounts for most of the medicolegal claims that are related to complications of thyroidectomy. A review of endocrine malpractice litigation, found that about 54 per cent of the adverse outcomes involved thyroid and parathyroid surgery and that about 79 per cent of these claims involved recurrent laryngeal nerve injury.

The reported rates of recurrent nerve injury range from 0 to 6 per cent, or even more frequently in some studies. About 50–88 per cent of all RLNPs are transient. Many series report an incidence of RLNP of 1–2 per cent with an incidence of permanent palsy of less than 1 per cent of cases performed by experienced surgeons. However, these are likely underestimates since only patients with significant and persistent symptoms underwent postoperative laryngeal examination in many of these studies.
Symptoms are variable, since laryngeal nerve injury is not an all-or-none problem and partial injury is more common than complete transection. Unilateral RLNP (URLNP) can sometimes be completely asymptomatic. However, most patients with URLNP do have some vocal impairment, ranging from mild vocal fatigue to severe hoarseness. In a significant percentage of patients, dysphagia for liquids and aspiration are also present. Intermittent coughing paroxysms are frequently reported and are secondary to spontaneous saliva aspiration. Dyspnoea may be apparent during exertion. URLNP is usually well tolerated, but in some patients it can be life-threatening, since aspiration pneumonia can be fatal, especially in older patients or those with impaired pulmonary function preoperatively.

Bilateral vocal cord paralysis obviously represents a potential life-threatening condition and a ‘real surgical calamity’. Indeed, it is always associated with some degree of airway impairment, ranging from acute and severe upper airway obstruction, requiring emergent reintubation or tracheotomy, to marginal dyspnoea at rest. Respiratory problems are usually more troublesome than voice changes.

Prevention of RLNP begins in the preoperative period. In all the patients who are to undergo thyroid and parathyroid procedures, examination of the larynx by indirect microscopy, and since many patients with hoarseness may not have vocal cord paralysis, this is a reliable way to preoperatively demonstrate laryngeal function. Preoperative recognition of impaired laryngeal function and RLNP is essential for the surgeon to reduce the risk of bilateral vocal cord paralysis. Moreover, vocal cord paralysis has been demonstrated to be the most accurate marker of invasive airway impairment, ranging from acute and severe upper airway obstruction, requiring emergent reintubation or tracheotomy, to marginal dyspnoea at rest. Respiratory problems are usually more troublesome than voice changes.

With regard to the invaded RLN, there is general agreement that in cases of preoperative vocal cord paralysis with macroscopic nerve infiltration by differentiated thyroid carcinoma, the nerve should be resected with the tumour. If preoperative vocal cord function is normal, the nerve should be left intact since microscopic residuum can be safely ablated with radiiodine. On the other hand, some surgeons still question the utility of routine preoperative laryngoscopy in the absence of symptoms and recommend selective laryngoscopy in symptomatic patients. Recently published guidelines make no mention of laryngeal examination in patients with thyroid nodules and carcinoma.

The risk of lesion of the recurrent laryngeal nerve exists in all neck dissections. Individual mechanisms of injury include stretch or traction, compression or crush (i.e. ligature entrapment, haematoma formation), and thermal, electrical and severing injuries (complete or partial transection). Moreover, some conditions put the nerve at a higher risk of injury (e.g. lack of identification of RLN during surgery, bilateral surgery, surgery for malignant diseases, lymph node dissection, Graves' disease and thyroïditis, previous neck surgery, subternal goitre, longer operative times or greater blood loss, reoperation for bleeding). The knowledge of the mechanism of injury and risk factors of RLNP should thus help in its prevention.

Positive identification of the recurrent laryngeal nerve is essential for preservation of its integrity and function. Until recently, some authors have questioned routine identification of RLN. Many recent studies have validated the importance of visual identification during any thyroid surgery. In their review of more than 27,000 nerves at risk, demonstrated that the incidence of temporary and permanent RLNP is significantly reduced if the nerve is identified during thyroidectomy. Moreover, they demonstrated that routine complete nerve exposure is characterized by a lower incidence of RLNP when compared with simple nerve localization and partial exposure. Indeed, they reported an average permanent RLNP rate of 0.9 per cent for localization only, 0.3 per cent for partial dissection and 0.1 per cent for extensive dissection.

One must bear in mind the possible anatomic variations in branching pattern that exist. In addition to the difference in origin and course between the left and the right side, numerous anatomic variations are well known with respect to its relationship with the inferior thyroid artery, the tracheo-oesophageal groove, the thyroid gland, and Berry's ligament. Moreover, in addition to the well-described normal patterns of extralaryngeal and intralaryngeal ramifications, the inferior laryngeal nerve (ILN) may give off branches that do not enter the larynx at all but instead connect it with other structures within the neck (sympathetic system, superior laryngeal nerve, thyroid, trachea and oesophagus). Furthermore, on rare occasions (0.3–0.8 per cent), the right ILN does not recur. In these cases, it originates from the cervical portion of the vagus nerve. Non-recurrence of the ILN results from a vascular anomaly during the embryonic development of the aortic arches, determined by the absence of the innominate artery and the formation of an aberrant right subclavian artery that arises directly from the aorta left of the midline and crosses posterior to the oesophagus. This anatomic variant is exceptionally rare on the left side.

A non-recurrent inferior laryngeal nerve has also been reported in association with an ipsilateral recurrent laryngeal nerve, in some cases even in the absence of any vascular anomaly. The surgeon should also be aware that enlarged anastomotic branches between the RLN and the cervical sympathetic chain may mimic a non-recurrent laryngeal nerve in up to 7.5 per cent of cases. Finally, another confounding condition is represented by small branches connecting a non-recurrent ILN and the stellate sympathetic ganglion with a course that is similar to that of a normally recurring ILN.

Because of the broad spectrum of anatomic variations, identification of the RLN can be difficult in some cases. The most important rule to follow during thyroid and parathyroid surgery is that no structure should be cut until the RLN is identified. Following this rule, RLN injury, and in particular transection injury, will be rare.

Several approaches have been proposed to identify the nerve. Palpation has been proposed by some as a valuable technique for nerve identification. The nerve feels like a cord or a violin string that can be rolled against the trachea. To increase tension on the RLN, this approach involves upward and medial retraction of the partially mobilized thyroid lobe. This could result in excessive stretching and consequent traction injury of the nerve, if not performed with great care.
The RLN may be identified inferiorly at the thoracic inlet using the RLN triangle, as described by Lore et al. The RLN triangle has it apex inferior in the thoracic inlet. The medial wall is formed by the trachea. The lateral wall is formed by the medial edge of the retracted strap muscles and the superior base by the lower edge of the retracted thyroid’s inferior pole. After identifying the nerve, the surgeon should trace it along its entire course. The advantage of this technique resides first of all in the fact that the RLN is identified before it branches. Thus, all branches are easily identified and preserved. Moreover, at this level, the RLN lies in soft areolar tissue, that facilitates dissection, unlike the strong, fibrous tissue of Berry’s ligament. This is of particular relevance in the reoperative cases, where the nerve should be identified out of the previous scar. Its principal disadvantage is that a long segment of the nerve is dissected, with potential risk of nerve injury by neuropraxia not to mention potential of devascularization of the inferior parathyroid glands.

Most endocrine surgeons nowadays rely on the more limited dissection of the nerve which characterizes the so-called capsular dissection. This implies division of the tertiary branches of the inferior thyroid artery, close to the thyroid capsule in order to preserve vascularization of the inferior parathyroid glands. After dividing the superior pole, the lobe is retracted medially and the posterolateral aspects of the thyroid lobe are exposed. The RLN is thus encountered at a high level in the neck, usually close to the ligament of Berry. Various landmarks have been proposed, including crossing of the inferior thyroid artery and the inferior edge of the thyroid cartilage’s inferior cornu. Actually, it is current practice to identify the nerve where it crosses the inferior thyroid artery. This approach has the potential benefits of limiting the length of the RLN dissection and focusing attention on the real ‘dangerous area’ for the RLN, i.e. the area of Berry’s ligament, and reducing the risk of jeopardizing inferior parathyroid vascular supply. On the other hand, this approach is not suitable in cases with large masses with lateral displacement of the RLN, as well as in cases with dense scar tissue as in revision thyroidectomy.

Some surgeons have called attention to the Zuckerkandl’s tubercle, a nodular thickening of the lateral edge of the thyroid lobe that is present in most patients. It usually enlarges lateral to the RLN, with the nerve appearing to pass into a cleft medial to it. Early elevation and medial displacement of the tubercle of Zuckerkandl usually allows identification of the RLN close to its entrance into the larynx. For this reason, this tubercle has been described as an ‘arrow pointed toward the nerve’. Moreover, the normal superior parathyroid glands, derived from the fourth brachial pouch, are commonly found in close association and cephalad to the tubercle of Zuckerkandl. On the other hand, in some cases, the RLN runs lateral to an enlarged tubercle of Zuckerkandl, which has been enlarging medially. In these cases, the RLN is at high risk if it is identified lower than this level.

In some situations (e.g. large substernal goitre), the RLN should be identified first at its entry point. The laryngeal entry point represents the most constant site for the RLN. The nerve can be found after superior pole reflection within or deep to the ligament of Berry, extending under the lower edge of the inferior constrictor. After its identification, the nerve should be followed downward before goitre delivery. Indeed, in case of large intrathoracic or mediastinal goitres, the RLN can be significantly displaced by the thyroid mass, in a lateral, posterior, medial or even anterior position. This last position is especially dangerous as it makes the nerve vulnerable during delivery of the thyroid lobe. It is obvious that blind finger delivery could represent a manoeuvre that risks injury to the displaced RLN. This could explain the higher RLNP rate reported for mediastinal goitre operations. Conversely, RLN identification at the level of its entrance and subsequent tracing, with progressive dissection and delivery of the thyroid lobe (the so-called ‘toboggan technique’) reduces the risk of nerve injury.

The main disadvantage of this superior approach resides in the fact that identification of the nerve occurs within the fibrous and dense ligament of Berry, which can easily bleed. Moreover, the surgeon should be aware that at this level, the nerve may already have branched. Additional challenges derive from the possible existence of a low-riding EBSL, potentially displaced by large upper poles, and from the need to avoid devascularization of the superior parathyroid, whose blood supply may depend upon the superior thyroid vessels. From a technical point of view, in such difficult cases, section of the strap muscles, and in particular of the sternothyroid muscle, can allow for a better preparation of the superior pole and easier and safer identification of the RLN at its entrance to the larynx.

It is clear that careful complete exposure allows the surgeon to prevent permanent injury. There are also some important points that should be kept in mind when performing a neck operation. The first is that the ligament of Berry represents the site of highest risk of nerve injury for several reasons. Usually, the RLN passes through this dense condensation of the thyroid capsule and is consequently fixed at this level. Excessive traction over the thyroid and the trachea during nerve dissection may result in stretching lesions of the nerve fibres. During thyroidectomy under local anaesthesia, we have observed immediate voice changes related to medial retraction of the thyroid lobe and stretching of the nerve. This underscores the particular susceptibility of the RLN to stretch injury.

Moreover, the ligament of Berry is both dense and well vascularized, along its inferior edge, from the inferior thyroid artery. These arterial branches are well known by thyroid surgeons and can cause troublesome haemorrhage during the final phase of the thyroid dissection. For this reason, meticulous dissection under direct visualization of the RLN, as well as individual ligation of small, fine arterial branches running in the ligament of Berry, are mandatory to avoid injury of the RLN in this area. If some bleeding does occur, blind coagulation should be avoided and direct ligature of the bleeding vessel should be accomplished with the nerve completely exposed. Application of small clips or small clamps and subsequent ligature with fine suture are essential. Monopolar cautery should be avoided in proximity to the RLN. Bipolar cautery is sometimes useful. To facilitate this step of the procedure, we suggest gentle downward (posterior) displacement of the RLN with atraumatic clamps or the back of scissors. This widens the space for ligature application. New technologies for haemostasis (Harmonic scalpel, Ligasure) should be avoided as well when dissecting the ligament of Berry, in order to avoid thermal injury of the RLN. Conventional ligature still represents the best approach during this step of the procedure.
The nerve itself may branch while passing through the ligament of Berry and thus surgeons should avoid clamping or cutting any portion of the ligament of Berry until he or she is completely sure that no nerve branch lies within the tissue involved.

Finally, one should remember that during less than total thyroid resection (i.e., subtotal thyroidectomy), the last portion of the RLN is not always completely visualized, regardless of whether or not its more proximal course is exposed. It is possible that the nerve runs medial to or within a crease on the surface of the thyroid remnant. As a consequence, haemostatic sutures on the remnant thyroid tissue could expose the nerve to injury. For this reason, we and other surgeons, consider total resection a safer procedure in many cases since the RLN is completely exposed in its distal course.

On occasion, despite the best efforts of the surgeon, the RLN is not identified. The rate of the unvisualized nerve is up to 12–18 per cent of the cases in recent large series. Obviously, these high rates could reflect lack of experience or technical mistakes during dissection, but some difficulties may rarely occur even in experienced hands. Moreover, anatomic integrity does not imply functional integrity and the inability to intraoperatively visualize vocal cord movement implies uncertainty with respect to postoperative functional outcome.

In recent years, several methods for RLN monitoring during neck dissection have been explored. Intraoperative nerve monitoring (IONM) has been described in the literature for nearly three decades, but it has been advocated strongly only over the last several years as a means of assisting in nerve identification and mapping to reduce the risk of injury. Several methods of IONM have been evaluated. These include finger palpation of the posterior cricoarytenoid during RLN stimulation, observation of vocal cord movement during RLN stimulation by direct laryngoscopy or through fiberoptic nasopharyngoscopy by way of laryngeal mask airway, glottic pressure/balloon transducers to detect vocal cord motion with stimulation, and intramuscular vocal cord electrodes that are placed endoscopically or through the cricothyroid membrane. Surface electrodes can be placed directly on the mucosa overlying the posterior cricoarytenoid muscle. At present, the most popular and preferred method for IONM is a technique employing endotracheal tube surface electrodes that are placed in contact with the mucosa of the vocal cord. Surface electrodes are non-invasive and may theoretically represent better recording electrodes than needle electrodes in that they sample a greater region of evoked muscle action potentials.

Some authors have described a significant reduction in both transient and permanent postoperative RLNP with the utilization of the IONM. Also, it has been recently reported that IONM is associated with improved outcomes especially in selected high-risk procedures, such as reoperative surgery, malignant disease and substernal goitre. Other studies, based on a large number of patients, failed to demonstrate significant improvement in rates of paralysis.

In other words, from all the published experiences, it is clear that IONM adds to, but does not replace, meticulous surgical technique and knowledge of the anatomy of the nerve and its variations. It is true that in the hands of experienced and dedicated surgeons, information derived from IONM could expedite surgery and render safer nerve dissection, especially in difficult cases where nerve identification and preservation can be challenging (e.g., reoperative cases, malignancy).

This has led some authors to propose selective use of IONM, mainly because of the cost involved. However, since we cannot reliably predict preoperatively which cases will be challenging, its routine use should be common practice.

This is particularly true if one considers that the most important function of IONM is its ability to prognosticate regarding postoperative neural function. In other words, nerve monitoring provides the sole possibility to intraoperatively verify nerve function. It is well known that even experienced surgeons usually underestimate actual RLNP. Electrical testing is superior to visual inspection alone. EMG activity after stimulation of the vagus nerve at the end of lobectomy confirms functional integrity of RLN. The demonstration of impaired electrical activity at the end of the first lobectomy during bilateral resection, should lead the surgeon to postpone resection of the second side and avoid the risk of bilateral nerve palsy. Moreover, RLN monitoring should be strongly considered in the presence of a preoperative RLNP, as in malignancies or reoperative cases. These aspects obviously underscore the utility of routine intraoperative nerve monitoring in all cases.

Corticosteroids are extensively used to prevent the risk of postoperative RLNP related to oedema from manipulation or stretch injury, in the case of an anatomically intact nerve. As in other operations, some surgeons empirically administer steroids during thyroid surgery in an attempt to reduce postoperative neural oedema, as well as to promote recovery of nerve function when RLNP occurs. Some authors suggest that the rate of temporary RLNP can be reduced with the use of preoperative and/or intraoperative steroids. Moreover, it has been recently demonstrated that the duration of RLNP can be significantly reduced with the use of a single dose of intraoperative steroids. As a consequence, the utilization of intraoperative steroids should be recommended, if not routinely, at least in patients where difficult nerve dissection portends a higher risk of temporary RLNP or in patients in whom intraoperative monitoring findings suggest a blunt non-contraction injury.

Management of inadvertent intraoperative division is still controversial. Primary reanastomosis can result in some functional recovery, but misdirected axonal regrowth is responsible for unintended synkinesis of the laryngeal musculature, due to reinervation of both adductor and adductor musculature. Anastomosis with an ansa cervicalis nerve graft can restore laryngeal tone and bulk, resulting in good voice. Patients with URLNP should undergo a trial of speech therapy. This is appropriate whether or not the RLN is anatomically intact. On occasion, this alone may be an adequate treatment for RLNP. However, vocal straining may lead to hyperactive compensatory mechanisms that can compromise vocal outcome after vocal cord medialization.

For minor aspiration in patients without underlying pulmonary disease, swallowing therapy can encourage compensation with the tongue base and supraglottic structures, although liquids may need to be thickened.

An algorithm for the management of patients with URLNP should be based on the degree of associated symptoms: aspiration, increased vocal effort, altered voice quality, dyspnoea on exertion and decreased quality of life.
cord medialization is usually considered urgent if aspiration pneumonia occurs or if oral feeding is considered dangerous (patients with altered pulmonary function). Endoscopic vocal fold injection of resorbable material (e.g., fat, collagen) does not compromise spontaneous functional recovery of the nerve and does not interfere with other subsequent medialization techniques. This is the technique of choice if spontaneous recovery is expected because of anatomic integrity of the RLN. On the other hand, if the URLNP is well tolerated, a waiting period combined with speech therapy is recommended. In the case of persistent unilateral RLNP after 12 months with poor voice quality, definitive vocal cord medialization by injection technique or thyroplasty is recommended. The choice of technique is a matter of the surgeon's experience and depends on the glottic configuration upon phonation (the size of the glottic gap). Arytenoid adduction performed in conjunction with medialization thyroplasty has been shown to provide good results. All of these techniques provide a good voice, eliminate aspiration and improve quality of life.

Bilateral RLNP is far more evident in its clinical manifestations than URLNP. Although voice quality may be fairly good, because of paramedian vocal cord position, most cases are recognized immediately in the postoperative period because of severe respiratory distress. The first priority is to secure an adequate airway. Immediate intubation is preferable to urgent tracheotomy in the acute setting. If the nerves are thought to be intact, the patient should remain intubated for several days and corticosteroid administered to reduce oedema. After a few days, extubation can be safely performed in a controlled setting and, if airway compromise is still present, a tracheotomy should be performed. If laryngeal motility has recovered and the airway is adequate, no further manoeuvres are necessary and safe extubation is possible. Delaying performance of tracheotomy for several days has the two-fold advantage of allowing the nerves to recover their function in the case of transient injury and avoiding contamination of the fresh surgical field with a tracheotomy.

If recovery is anticipated, observation for up to 12 months is appropriate, and the airway is usually secured by tracheotomy or arytenoidectomy, which are reversible procedures. Recently, vocal cord laterofixation has been described as a solution for avoiding tracheotomy in the acute setting, when recovery is anticipated. While multiple strategies have been used to rehabilitate the patient with bilateral vocal cord paralysis, ultimately each patient will present with a unique set of circumstances that mandate individualized care. In many cases, the simplest, most stable, and often overlooked option is the permanent tracheotomy. Patients are usually reluctant to accept such a solution. In these patients, lateralization of one cord by cordotomy or arytenoidectomy results in an improved airway and allows decannulation.

Voice and swallowing impairment in the absence of laryngeal nerve lesions

Most of the voice and swallowing alterations that occur following thyroidectomy are self-limited and not related to impaired laryngeal nerve function. These symptoms are usually dismissed by the clinician or attributed to orotracheal intubation, because they cannot be translated into objective data by appropriate diagnostic tests. Nevertheless, their presence elicits anxiety among patients if they are uninformed about the risks. These symptoms should be regarded as true complications of thyroid surgery and treated appropriately by the consulted physicians.

Recent interest in these symptoms and their possible implications on patient quality of life after thyroidectomy, especially in voice professionals, has appeared in the world literature. Subjective voice and swallowing alterations after uncomplicated thyroidectomy include a broad spectrum of symptoms, and are usually temporary and resolve relatively quickly. However, in some cases symptoms tend to persist even years after thyroidectomy. Swallowing symptoms were reported more frequently and showed a tendency to persist longer than the voice changes. In the absence of any videostrobolaryngoscopically demonstrable laryngeal nerve injury, the factors that could determine voice and swallowing disturbances seem related mainly to the normal healing process, or possibly to subclinical postoperative haematoma. After thyroid gland removal, the strap muscles become the sole support of the laryngotracheal unit, and these muscles often fuse through scar tissue formation. This results in laryngotracheal fixation with impairment of vertical movement. This problem seems more evident in the case of strap muscle division. However, a functional component related to local neck pain and an emotional or psychological reaction to the postoperative stress should also be considered as possible aetiologies. Nonetheless, in some cases, upper aerodigestive symptoms can persist for years after an 'uncomplicated' thyroidectomy. This can suggest that some symptoms may be due to an intraoperative injury of the fine anastomotic branches connecting the laryngeal nerves (RLN and the EBSLN) with the sympathetic cervical chain. Some small branches of the laryngeal nerves, together with other cervical branches, participate in the autonomic, sensory and motor innervation of pharyngeal and laryngeal structures. Injury to this perivisceral nerve plexus during thyroidectomy could underlie at least some of the postoperative discomfort, which is variable in relation to the different anatomic pattern of nerve branches. These possible mechanisms underscore the importance of meticulous surgical technique to avoid this kind of post-thyroidectomy consequence. Strap muscle division should be avoided as far as possible. Accurate haemostasis and preservation of all fine nerve branches must be a primary goal. Less extensive neck dissection, as performed in minimally invasive surgical techniques, seems related to a lesser incidence of this kind of functional voice and swallowing alteration.

Regardless of the cause, these post-thyroidectomy vocal and swallowing changes are reported frequently, and we believe that surgeons should be aware of these subjective discomforts that commonly occur following thyroid surgery. Patients must also be informed and warned about these symptoms during the preoperative counselling session for ethical as well as legal reasons, especially in voice professionals.

Hypocalcaemia and hypoparathyroidism

Postoperative hypocalcaemia is one of the most common complications of thyroid and parathyroid surgery. Moreover,
after RLN palsy, permanent hypoparathyroidism accounts for the largest number of thyroidectomy-related claims.74

Temporary hypocalcaemia has been reported to occur in 1.6–50 per cent of the patients undergoing bilateral thyroid resection and in 0–35 per cent of patients after parathyroidectomy. Permanent hypoparathyroidism results in 0–13 per cent of patients after bilateral thyroid surgery and in 0–2.2 per cent of patients after successful parathyroidectomy.23

Various factors account for these differences in the literature, such as the definition of hypocalcaemia, the type of disease, and the surgical technique. Moreover, hypocalcaemia following thyroid resection is somewhat different in origin versus that occurring after parathyroid surgery. Post-thyroidectomy hypocalcaemia is multifactorial in origin. Among the potential factors causing this decrease in serum calcium, there are postoperative hemodilution123 and calcitonin release.124 The so-called ‘hungry bone syndrome’ is also implicated in patients with hyperthyroidism or hyperparathyroidism and osteodystrophy.125

A moderate, asymptomatic hypocalcaemia is usually observed within 12 hours following unilateral or bilateral thyroidectomy, is associated with serum phosphorus decrease, and recovers spontaneously within 24 hours in most patients.123, 126 Perioperative hemodilution may be responsible for this decrease and explains its occurrence with other extracervical operations.123 This hypocalcaemia is self-limited, usually asymptomatic, and does not require supplementation.

Elevation of serum calcitonin (calcitonin leak), secondary to manipulation of the thyroid, was suspected to participate in this calcium decrease,124 but this was not confirmed in further studies.123, 125, 126, 127

Preoperative hyperthyroid status is associated with decreased gastrointestinal calcium absorption and increased osteoclast activity, with increased bone resorption to maintain serum calcium levels.128 The postoperative reversal of osteodystrophy and the accretion of calcium in bones may also contribute to the decreased serum calcium. The serum calcium generally reaches its nadir within 48 hours of surgery. The risk of hypocalcaemia is not alleviated by the correction of hyperthyroidism within a few weeks before thyroidectomy. It is correlated more closely with the pre-treatment serum levels of free thyroxine127 and with markers of bone turnover rate, such as serum alkaline phosphatase levels.123 Similarly, hyperparathyroidism is associated with osteoclast activation and increased bone resorption. After thyroidectomy or parathyroidectomy, active calcium uptake by bone may result in postoperative hypocalcaemia. These possible mechanisms of postoperative hypocalcaemia underscore the need for adequate patient preparation before surgery for hyperthyroidism. Prophylactic supplementation should be considered to avoid severe hypocalcaemia in patients with significant osteodystrophy.16

Nonetheless, it is clear that impaired parathyroid function is the major contributing factor for clinically relevant hypocalcaemia. Proper surgical technique is of the utmost importance in preserving viable parathyroid glands and several factors have been associated with impaired postoperative function.

There is a risk of iatrogenic injury to the parathyroid glands during any operation in which both lobes are explored or resected. Bilateral neck exploration for hyperparathyroidism, with biopsy of all the glands necessarily involves the risk of parathyroid gland injury. Operation for known multi-glandular disease (MEN1, MEN2A, familial hyperparathyroidism, parathyroid hyperplasia, and secondary and tertiary hyperparathyroidism) requires removal of most parathyroid tissue (subtotal or total thyroidectomy with autotransplantation). In such cases, postoperative hypocalcaemia and hypoparathyroidism to some degree are consequences of the indicated operation itself.

Susceptibility of parathyroid glands to injury during neck dissection mainly resides in their widely variable anatomical position, their relationship with the thyroid gland, and in their very delicate vascular supply. Classically, there are four parathyroid glands in close association with the thyroid, although the number and positions of the glands may vary greatly among individuals. We know that there is an incidence of about 13 per cent of a supernumerary fifth parathyroid and, at most, a 3 per cent incidence of only three glands.129

The superior parathyroid glands are derived from the fourth branchial pouch and are relatively constant in their position since they have a short line of embryologic descent and remain close to the capsule on the posterolateral aspect of the superior third of the thyroid lobe near the cricothyroid junction. This is the level of Zuckerkandl’s tubercle and is in close proximity to the RLN. The inferior parathyroid glands are derived from the third branchial pouch and descend along with the developing thymus. Therefore, they have a long line of descent and, consequently, their position is much more variable. An inferior parathyroid gland can be carried, with the thymus, into the anterior mediastinum, into the aortopulmonary window, or in the pericardium. It may also be left behind high in the carotid sheath, up to the carotid bifurcation, or even within the vagus nerve itself (undescended glands). Most inferior parathyroid glands, however, are found near the inferior pole of the thyroid in the vicinity of the thyrothymic tract. They frequently lie on the surface of the inferior pole of the thyroid, within the thyroid capsule. Despite the variability in the anatomy of the parathyroid glands, there is a frequently a symmetric arrangement in the position of the glands on the two sides of the neck. Positional symmetry of the superior glands is found in about 80 per cent of cases and in 70 per cent of inferior glands.129

As first described by Halsted in 1907,130 most of the parathyroid glands are supplied by a single, fine end-artery. There is a single arterial supply to 80 per cent of parathyroid glands, a dual arterial supply to 15 per cent, and multiple arteries to the remaining 5 per cent.131 In most cases, these arteries originate from the inferior thyroid artery. However, in 15–20 per cent of cases the superior parathyroid is supplied by a branch from the superior thyroid artery, sometimes associated with an anastomotic branch running between the superior and inferior thyroid arteries.132, 133

The incidence of parathyroid gland injury is related to the extent of the operation and to the experience of the surgeon. A higher incidence is seen after total thyroidectomy versus subtotal thyroidectomy and after subtotal thyroidectomy versus excision of a single adenoma. Other factors associated with an increased incidence of postoperative hypocalcaemia are central compartment neck dissection, reoperative cases, surgery for substernal goitre, surgery for carcinoma, and surgery for Graves’ disease.
A variety of strategies has been advocated to decrease the incidence of permanent hypoparathyroidism, including less than total thyroidectomy, intracapsular dissection, identification of the parathyroid glands with preservation of their vascular pedicle, selective autotransplantation of inadvertently removed or nonviable parathyroid glands, and routine autotransplantation of at least one parathyroid gland if not all identified parathyroid glands.

More limited thyroid resection (i.e. subtotal thyroidectomy) has been proposed to avoid inadvertent parathyroid injury. Nonetheless, at present, total thyroidectomy is still considered the optimal procedure, even in cases of benign bilateral disease.

It is now clear that the best way to avoid parathyroid damage is to clearly know the embryology and the surgical anatomy of the glands, including their blood supply, and to make every effort to preserve them in situ or to transplant one or more glands when this is not possible.

However, it should be stressed that despite the efforts of the surgeon, inadvertent parathyroid removal during thyroidectomy has been reported in 9–15 per cent of the cases, even in experienced centres according to recent reports. Even as incidental removal of one or two glands may not affect the incidence of postoperative hypocalcaemia, it demonstrates the difficulties surgeons encounter in preserving viable parathyroid glands during thyroidectomy. The incidence of intrathyroidal parathyroid glands is approximately 0.2 per cent according to autopsy studies, but this incidence rises to between 2 and 5 per cent for patients with primary hyperparathyroidism and up to 11 per cent in those with persistent or recurrent hyperparathyroidism.

The surgeon should make every attempt to preserve viable parathyroid glands in situ. Some techniques play a crucial role in preserving parathyroid glands. First of all, a bloodless surgical field is essential, because any bleeding may stain the surface of the gland, obscuring its colour which is essential for parathyroid identification. Although parathyroid glands can usually be identified based on their gross appearance, in some instances it may be difficult even for experienced surgeons to determine whether a structure represents a parathyroid gland, thyroid tissue, adipose tissue, or thymic tissue. In such cases, a liberal attitude toward biopsy and frozen section examination should be adopted.

Because of the highly variable location of the inferior parathyroid glands, inability to identify one or both of the inferior parathyroids does not necessarily indicate inadvertent removal. The glands can be located cephalad or caudal (i.e. intrathyroidic) to the site of dissection. Conversely, not identifying a superior parathyroid gland more likely signifies inadvertent removal, since it is usually located on the posterior aspect of the thyroid lobe, close to the point where the RLN enters the larynx. In other words, the surgeon should make every effort to identify and preserve superior parathyroid glands, while this may not be possible with the inferior glands in all cases. If no inferior parathyroid gland is identified in close proximity to the thyroid, no further dissection of the thyrothymic tract or the thymus itself is necessary. Extensive dissection may cause inadvertent devascularization of the inferior glands.

Once identified, the parathyroid gland should be preserved with its vascular pedicle intact as far as possible. This demands a very gentle, cautious and sometimes time-consuming dissection. The parathyroid itself should not be grasped, but gently detached from the thyroid capsule by retracting the surrounding fat which is usually present. Ligation of the most distal branches of the inferior thyroid artery usually allows for vascular pedicle preservation. Despite some reports demonstrating that truncal inferior artery ligation during subtotal thyroidectomy does not affect the incidence of postoperative hypocalcaemia and hypoparathyroidism, we (and most other authors) believe that it is necessary to ligate branches of the inferior thyroid artery in close proximity to the thyroid capsule to avoid devascularization of the parathyroid glands.

Excessive stretching of the vascular pedicle and the use of cautery should be avoided in close proximity to the parathyroid glands. Similarly, new devices for achieving haemostasis (i.e. Harmonic scalpel, Ligasure) should be avoided in close proximity to the parathyroid glands. In some cases, it may be very difficult to detach a parathyroid gland from the thyroid capsule, due to factors, such as inflammatory reaction (i.e. thyroiditis) or scarring after previous operation. In such cases, if dealing with benign disease, it is possible to perform an intracapsular dissection, with the aim of preserving the parathyroid gland in situ. Routine prophylactic central neck dissection in differentiated low-risk thyroid carcinoma is to be avoided in the absence of macroscopic involvement as it engenders a higher risk of postoperative hypoparathyroidism with arguably little patient benefit.

Identifying and dissecting the parathyroid glands during thyroidectomy does not guarantee viability. Traditionally, judgement regarding the viability of a parathyroid gland has been made based on its colour. Unless a parathyroid is markedly discoloured (dark purple/black or pallid)), it is presumed to be viable. Vascular injury to the parathyroid pedicle may be arterial or venous. Arterial ischaemia (devascularization) implies a definitive parathyroid lesion. Macroscopically, the gland appears discoloured and pale, and should be transplanted when recognized intraoperatively. Impairment of venous drainage is usually characterized by venous congestion and it is indicated by dark purple or black discoloration of the parathyroid glands. In this case, incision of the parathyroid capsule may liberate excess venous blood and usually the gland will recover its normal appearance and colour. If this does not occur, the gland should be removed and autotransplanted.

Despite the adoption of this approach, some glands may be anatomically intact, but not physiologically viable. Various methods of assessment have been adopted including the careful incision of the parathyroid capsule to assess for bleeding (knife test) and Doppler measurement of the parathyroid vessels. This latter technique has not been reproducible and has not gained widespread acceptance. On the other hand, the knife test has been advocated by some, but may have the disadvantage of inducing iatrogenic injury to the already precarious blood supply of the parathyroid gland in question.

Clearly, a reliable intraoperative method to identify patients with impaired parathyroid function could facilitate the decision to perform autotransplantation. It has been suggested that intraoperative parathyroid hormone measurement may have a role in monitoring parathyroid function, but it is generally not employed in routine clinical practice currently. As a consequence, evaluation of the
viability of parathyroid glands still relies mostly on macroscopic appearance.

Parathyroid autotransplantation during thyroidectomy was first described by Lahey in 1926. However, only after the demonstration of the viability of the transplanted parathyroid tissue in humans, was autotransplantation definitively included in the armamentarium of endocrine surgeons. Parathyroid autotransplantation is considered by most experts a useful technique for preserving parathyroid function, especially for non-viable parathyroid glands. However, strategies for parathyroid autotransplantation vary widely from a selective approach with transplantation of only non-viable or incidentally removed glands, to routine autotransplantation of one gland or even all the identified parathyroid glands. Strategies that involve routine autotransplantation are obviously characterized by a higher incidence of early postoperative hypocalcaemia, but a low rate of permanent hypoparathyroidism. Nonetheless, in recent years groups that had previously proposed routine parathyroid autotransplantation have critically reviewed their experience and now propose a more selective approach to parathyroid autotransplantation. In summary, there is no doubt that inadvertently removed or damaged parathyroid glands should undergo autotransplantation when they are recognized at operation. Intentional devascularization of all parathyroid glands should be avoided unless there is a reliable technique to ensure graft success after autotransplantation.

The technique of transplantation differs for different series. Thin sectioning (slicing) and injection of a suspension of parathyroid tissue in buffered saline into muscle have been described. Transplantation of thin sections in a muscular pocket closed and marked with a non-absorbable suture and titanium clips is the preferred option in transplantation of hyperplastic tissue, e.g. in parathyroid operations for multiglandular diseases. On the other hand, intramuscular injection of a suspension of parathyroid tissue in buffered saline seems an attractive, fast and easy option during thyroid operations.

There is also some variability in the site chosen for parathyroid transplantation. In most patients undergoing thyroid operations, parathyroid glands can be easily and safely transplanted into the sternocleidomastoid or strap muscles. In contrast, a remote site, such as the brachioradialis muscle, is more suitable for patients undergoing thyroidecmy for treatment of MEN2A (who are prone to development of hyperparathyroidism) or for aggressive malignancies such as poorly differentiated thyroid carcinoma or laryngeal cancer as these latter patients may need postoperative radiation therapy to the neck. The brachioradialis muscle is also a preferred site in patients with secondary hyperparathyroidism and multiglandular diseases (parathyroid hyperplasia, as observed in MEN1 and familial hyperparathyroidism), mainly because this facilitates evaluation of viable parathyroid tissue based on blood drawn from the forearm veins and facilitates localization and removal of parathyroid tissue in cases of recurrence. Irrespective of the site selected, it is important to histologically confirm the presence of parathyroid tissue before transplantation.

It is not clear in individual patients who have had a parathyroid transplantation and possible damage to the other parathyroid glands whether it is the transplant or possible supernumerary glands that are providing sufficient function for normocalcaemia.

In spite of all the efforts to avoid this complication, postoperative hypocalcaemia and hypoparathyroidism still occur. Temporary symptomatic hypocalcaemia is common after successful parathyroidectomy, despite the fact that minimally invasive and focused approaches have reduced its incidence when compared with bilateral neck exploration. Indeed, the targeted approaches to parathyroidectomy have the important advantage of avoiding manipulation of normal glands leading to normal parathyroid function postoperatively. In this setting, postoperative hypocalcaemia is usually self-limited and related to inhibition of normal glands by the hyperfunctioning one or to the existence of an underlying hungry bone syndrome. In any case, symptoms of hypocalcaemia are frequently observed, even in the absence of biochemical hypocalcaemia. These symptoms are usually mild to moderate and resolve spontaneously within weeks. With this phenomenon in mind, some authors propose prophylactic oral calcium administration in all patients undergoing parathyroidectomy. This is often done in order to relieve patient anxiety related to hypocalcaemic symptoms and also to allow the procedure to be performed on an ambulatory or same day basis. On the contrary, permanent hypoparathyroidism is virtually impossible in the case of focused parathyroidectomy. On the other hand, bilateral neck exploration brings with it the possibility of injury to normal parathyroid glands, especially if biopsy is obtained to confirm parathyroid origin. In such situations, patients are at risk of clinically relevant hypocalcaemia and should not be selected for outpatient surgery. Operations for parathyroid hyperplasia (total parathyroidectomy plus autotransplantation, subtotal parathyroidectomy) are obviously characterized by a higher risk of postoperative hypocalcaemia and hypoparathyroidism.

Permanent hypoparathyroidism occurs in only 0–0.5 per cent of patients after initial exploration for sporadic primary hyperparathyroidism, but is far more frequent after surgery for parathyroid hyperplasia, especially in patients undergoing total parathyroidectomy plus autotransplantation. The occurrence of permanent hypoparathyroidism is dependent on the viability of the parathyroid remnant or the parathyroid graft. Since its occurrence cannot be definitively predicted, cryopreservation of resected parathyroid tissue is usually recommended for all patients undergoing multigland parathyroid extirpation or reoperative parathyroid surgery. Cryopreserved tissue can be transplanted if permanent hypoparathyroidism occurs.

Although severe and symptomatic post-thyroidectomy hypocalcaemia is rare, it is of particular concern. Symptoms usually manifest 24–48 hours after operation and it is usually not easy to predict which patients will require oral calcium and/or vitamin D supplementation. In the absence of any reliable predictors of clinically relevant hypocalcaemia after bilateral thyroid resection, prolonged hospitalization to monitor serum calcium levels has been considered the standard of care. Conversely, current health-care practices encourage shorter and shorter hospitalizations to reduce costs. For this reason, there has been a great deal of interest in identifying perioperative factors that can predict the development of post-thyroidectomy hypocalcaemia soon after surgery, allowing for early treatment of patients at risk and
safe early discharge of patients not at risk. Calcium slopes monitoring in the early postoperative period has been demonstrated to be useful. More recently, parathyroid hormone measurement has been investigated. Several studies have demonstrated its usefulness in defining groups of patients at risk of postoperative hypocalcaemia. These patients should be treated early after surgery and are not candidates for early discharge, while those patients who are deemed not at risk can be discharged. Encouraging initial results have not been uniformly confirmed by subsequent studies. For this reason, postoperative monitoring of serum calcium levels still remains the standard of care. Another option to avoid symptomatic hypocalcaemia and to shorten hospital stay after thyroidectomy is routine prophylactic oral calcium/vitamin D supplementation.

Despite uncertain utility of calcitriol administration in the early postoperative period, we believe that supplementation should include both vitamin D and oral calcium administration in all patients. Vitamin D does not inhibit normal parathyroid gland function, but allows for a prompt recovery from hypocalcaemia. Once started, supplementation should be tapered on the basis of serum calcium levels. Intravenous calcium gluconate administration should be reserved for patients who manifest symptoms or falling levels in spite of oral therapy.

Failed exploration – recurrent and persistent hyperparathyroidism

Parathyroid operations are among the most challenging in endocrine surgery because of the large variability in parathyroid anatomy. The enlarged parathyroid gland or glands can be almost anywhere; hence the term ‘exploration’. To avoid unacceptably high failure rates, the surgeon should be familiar with normal parathyroid anatomy, but also with its variants. Moreover, he or she should be familiar with the common pathophysiology of the parathyroid diseases.

It has been demonstrated that low volume parathyroid surgeons report significantly higher rates of morbidity, most notably failed exploration. Surgery performed by experienced surgeons would avoid complication in 95–98 per cent of the cases. However, the definition of the experienced parathyroid surgeon is not entirely clear. Based on the findings of published studies, demonstrating a lower complication rate among surgeons performing more than ten operations per year, this criterion has been used to support sufficient experience.

Operative failures can be grouped into persistent hyperparathyroidism, recurrent hyperparathyroidism, and errors in diagnosis. This last occurrence is a common cause of failed exploration. The surgeon must have a working understanding of basic endocrinology if this error is to be avoided and patients spared unnecessary surgery. It should be remembered that hypercalcaemia does not always indicate primary hyperparathyroidism and it should be correlated in all cases with serum parathyroid hormone (PTH) levels. One confounding condition the surgeon should remember is benign familial hypocalciuric hypercalcaemia (BFHH).

Persistent hyperparathyroidism is the most common result of operative failure and by convention is defined as postoperative hypercalcaemia occurring within six months after initial neck exploration. Causes of operative failure and persistent hyperparathyroidism include missed adenoma due to difficult anatomy or an ectopic or supernumerary gland, failure to recognize parathyroid hyperplasia, misinterpretation of localization data or intraoperative PTH monitoring results, and parathyromatosis. Parathyromatosis is a rare but feared complication in patients with hyperparathyroidism. Capsular rupture of the pathologic gland(s) may result in parathyroid seeding and consequent disseminated growth of the seeded hyperplastic cells. This possibility underscores the importance of gentle handling of the affected glands, avoiding any capsular rupture. Grasping of the parathyroid capsule should be absolutely avoided in order to prevent this cause of persistent or recurrent hyperparathyroidism.

Recent hyperparathyroidism is characterized by at least six months of normocalcaemia after initial operation and typically indicates unrecognized, and therefore untreated, hyperplasia. It can also arise with parathyroid carcinoma, parathyromatosis, a missed synchronous or metachronous second adenoma, or recovery of a hyperfunctioning gland that was devascularized at initial dissection.

After successful operation for primary hyperparathyroidism, a significant percentage of patients show elevated levels of PTH with normal serum calcium levels (normocalcemic hyperparathormonemia). It generally resolves with six months’ postoperative treatment with oral calcium and multivitamin supplementation. In such patients, elevated parathormone seems to be a reflection of a dietary deficiency. Nonetheless, in about 1 per cent of the patients presumed to be successfully operated, this phenomenon predicts early operative failure due to unrecognized multiglandular disease. Patients with postoperative normocalcemic hyperparathormonemia should thus undergo close follow-up evaluation for recurrence.

Parathyroidectomy for primary hyperparathyroidism is associated with a success rate of 95–98 per cent. Primary hyperparathyroidism is caused by a single adenoma in most of the cases (85–95 per cent). Parathyroid hyperplasia has been reported in as many as 15 per cent of the cases, with most series reporting an incidence of 2–6 per cent. Double adenomas are present in 2–6 per cent of patients. Bilateral cervical exploration (without preoperative localization studies) with the removal of the suspected adenoma and biopsy of the normal appearing glands has long been considered the standard operation for primary hyperparathyroidism. Indeed, the requirement to clearly exclude multiglandular disease remains exploration with identification and assessment of all glands.

The only other way to exclude multiglandular disease is represented by intraoperative parathyroid hormone monitoring, which is based on measurement of serum intact PTH levels during surgery and analysed using a specially modified assay. After removal of a suspected adenoma, specific criteria indicate if further hyperfunctional glands exist. The criteria for interpretation vary somewhat between experts, but a PTH drop of more than 50 per cent of the highest pre-excision levels (and into the normal range) 5–10 minutes after parathyroid ablation are considered indicative of removal of all hyperfunctioning tissue by most.

It has been confirmed that PTH monitoring reliably predicts postoperative cure. Moreover, its introduction into clinical practice, along with improved preoperative...
localization studies (ultrasound and sestaMIBi scan) has allowed significant improvement in the surgical strategy in patients with primary hyperparathyroidism. If a single adenoma is suspected on the basis of preoperative localization studies, a minimally invasive, focused approach can be proposed with significant advantages for the patients not only in terms of cosmetic results, but more importantly in a lower incidence of postoperative complications (i.e. postoperative hypocalcaemia). At present, intraoperative PTH monitoring should be considered the new standard of care in patients undergoing parathyroidectomy for sporadic primary hyperparathyroidism.

Recurrence rates are higher (2–12 per cent) in patients undergoing parathyroidectomy for secondary hyperparathyroidism resulting from renal failure.176,177 This is usually the result of a missed gland in an unusual or ectopic location, supernumerary glands, or hyperplasia of remnant or grafted parathyroid tissue. These mechanisms highlight the need for an accurate and meticulous neck exploration in all cases and for the removal of a sufficient amount of parathyroid tissue. The decision between a subtotal and a total parathyroidectomy with autotransplantation is beyond the scope of this chapter. However, what is important in all cases of parathyroid hyperplasia is that the parathyroid remnant or graft should be carefully marked and the procedure well described in the operative report so that any possible re-exploration will have a higher chance of success, if it becomes necessary.

**KEY LEARNING POINTS**

- Complications associated with thyroid and parathyroid surgery may occur, either as a result of surgical error or due to the extent of patient disease. The aim of this chapter is to furnish the reader not only with a list of the possible complications, but more importantly with a description of common surgical errors and techniques that will help to avoid them.
- A post-operative hematoma is probably the most feared complication after thyroid and parathyroid surgery. It can lead to devastating consequences with tracheal compression and subsequent hypoxia, which may then lead to brain injury and death. The patient may present with respiratory distress, pain or pressure sensation in the neck or dysphagia. Signs include progressive neck swelling, suture line bleeding, dyspnoea and/or stridor. A liberal attitude towards re-exploration in the case of symptomatic hematoma is mandatory.
- Recurrent laryngeal nerve palsy is a potentially serious complication following thyroid and parathyroid surgery as it may cause significant voice and airway problems. Prior to thyroid and parathyroid procedures, examination of the larynx by indirect or direct laryngoscopy should be performed. About 30–40 per cent of patients with RLNP are asymptomatic, and many patients with hoarseness may not have vocal cord paralysis. Positive identification of the recurrent laryngeal nerve is essential for preservation of its integrity and function.
- Intraoperative nerve monitoring is a means of assisting in nerve identification and mapping to reduce the risk of injury. It also prognosticates nerve function postoperatively. Also, IONM is associated with improved outcomes especially in selected high-risk procedures, such as reoperative surgery, malignant disease and substernal goitre. IONM has a crucial role in the intraoperative decision-making process.
- Postoperative hypocalcaemia is one of the most common complications of thyroid and parathyroid surgery. Temporary hypocalcaemia has been reported to occur in 1.6–50 per cent of the patients undergoing bilateral thyroid resection and in 0–35 per cent of patients after parathyroidectomy. Permanent hypoparathyroidism results in 0–13 per cent of patients after bilateral thyroid surgery and in 0–2.2 per cent of patients after successful parathyroidectomy.
- Temporary symptomatic hypocalcaemia is common after successful parathyroidectomy, despite the fact that minimally invasive and focused approaches have reduced its incidence when compared with bilateral neck exploration. The targeted approaches to parathyroidectomy have the important advantage of avoiding manipulation of normal glands leading to normal parathyroid function postoperatively.
- Permanent hypoparathyroidism occurs in only 0–0.5 per cent of patients after initial exploration for sporadic primary hyperparathyroidism, but is far more frequent after surgery for parathyroid hyperplasia, especially in patients undergoing total parathyroidectomy plus autotransplantation. Cryopreserved tissue can be transplanted if permanent hypoparathyroidism occurs.
- Causes of operative failure and persistent hyperparathyroidism include missed adenoma due to difficult anatomy or an ectopic or supernumerary gland, failure to recognize parathyroid hyperplasia, misinterpretation of localization data or intraoperative PTH monitoring results, and parathyromatosis. After successful operation for primary hyperparathyroidism, a significant percentage of patients show elevated levels of PTH with normal serum calcium levels (normocalcaemic hyperparathormonaemia). It generally resolves with six months postoperative treatment with oral calcium and multivitamin supplementation. Intraoperative parathyroid hormone monitoring is a helpful tool to determine whether further hyperfunctional glands exist. It has been confirmed that PTH monitoring reliably predicts postoperative cure.
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Non-surgical management of thyroid cancer

LAURA MOSS

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Absence of evidence is not evidence of absence.
Carl Sagan, US astronomer (1934–96)

DIFFERENTIATED THYROID CANCER

There is a lack of prospective randomized controlled studies relating to the management of differentiated thyroid cancer as it is an uncommon disease with a long natural history. Many areas of thyroid cancer management remain controversial, including the indications for radioiodine ablation, the administered activity of radioiodine, timing and type of follow-up investigations, the degree and duration of thyroid-stimulating hormone (TSH) suppression, as well as indications and techniques for external beam radiotherapy. Evidence-based guidelines rely largely on retrospective and cohort studies, as well as consensus views. The recommendations in this chapter reflect common UK practice and advice from the British Thyroid Association, European Thyroid Association, the European Association of Nuclear Medicine and American Thyroid Association (ATA) guidelines.1, 2, 3, 4

131I therapy

Normal thyroid gland tissue and differentiated thyroid cancer can concentrate iodine from the circulation and 131I (an unscaled radionuclide of iodine) is taken up in the same way as stable iodine in the diet.

In practice, it is very difficult to achieve complete surgical ablation of the thyroid gland and some residual tissue is inevitably present and known as the thyroid remnant. As a rule, normal thyroid tissue within the remnant will preferentially take up the iodine compared to thyroid cancer tissue whether that is local or distant. Hence, if a large remnant is present postoperatively, the post-ablation full body radioiodine scan cannot be relied upon to exclude the presence of residual malignancy either locally in the neck or at distant sites as the iodine may be seen in the remnant only. Only when this remnant of normal thyroid tissue is ablated can you reliably expect to see any significant radioiodine uptake in sites of differentiated thyroid cancer.

INDICATIONS FOR 131I

131I aids the detection and earlier treatment of persistent/metastatic disease by destroying normal thyroid tissue; it may destroy microscopic foci of cancer in the thyroid remnant, and aids interpretation of serum thyroglobulin (Tg) measurements during follow up. It may be used for ablation of the thyroid remnant, or for treatment of residual or recurrent disease. Remnant ablation may reduce local recurrence and increase survival,5, 6 although not all reported series support these findings.7, 8, 9, 10

In the absence of published randomized trials, recommendations on 131I ablation have to be based on retrospective studies.2, 11–12, 13, 14, 15, 16–17

Postoperative radioactive iodine remnant ablation

This can be defined as the radioiodine uptake that is usually seen in the thyroid bed following a total or near total
thyroidectomy. $^{131}$I destruction of this residual tissue is called radioiodine remnant ablation.\textsuperscript{1}

The following represents the British Thyroid Association’s guidance on the indications for $^{131}$I ablation.\textsuperscript{1} It should be noted, however, that the recommendations for radioiodine remnant ablation vary slightly between the European, American and British guidelines.

- **No indication for** $^{131}$I ablation (as low risk of recurrence or cancer-specific mortality):
  - complete surgery;
  - favourable histology;
  - unifocal tumour, $\leq 1\text{ cm}$, N0 M0 or minimally invasive follicular thyroid carcinoma (FTC), without vascular invasion $<2\text{ cm}$;
  - no extension beyond the thyroid capsule.

- **Definite indications for radioiodine remnant ablation:**
  - distant metastases;
  - incomplete resection;
  - tumour extension beyond capsule, $>10$ involved lymph nodes, $>3$ lymph nodes with extracapsular spread.

- **Probable indications for radioiodine remnant ablation:**
  - less than total thyroidectomy;
  - lymph node status not assessed at surgery;
  - tumour $>1\text{ cm}$ and $<4\text{ cm}$;
  - $<1\text{ cm}$ with unfavourable histology (tall cell, columnar, diffuse sclerosing papillary thyroid carcinoma (PTC), widely invasive or poorly differentiated follicular thyroid cancers);
  - multifocal tumours $<1\text{ cm}$.

### Radioiodine therapy

This refers to administration of $^{131}$I with the intention to treat recurrent or metastatic disease\textsuperscript{4} and is indicated:

- if the primary tumour is inoperable;
- for postoperative residual neck disease;
- for distant metastases;
- for recurrent disease.

### High versus low administered activity of $^{131}$I

Administered activities of $^{131}$I between 1.1 and 3.7 GBq show similar rates of successful remnant ablation,\textsuperscript{18,19,20,21} although there is a trend toward higher success rates with higher administered activities.

The American Thyroid Association\textsuperscript{4} recommends that the minimum $^{131}$I activity necessary to achieve successful remnant ablation should be chosen.

A recent systematic review has concluded that it is not possible to reliably determine whether ablation success rates using 1.1 GBq are similar to using 3.7 GBq and advocates large randomized trials to resolve the issue and guide clinical practice.\textsuperscript{22}

In the UK in 2006, a multicentre randomized trial of high ‘dose’ versus low ‘dose’ radioiodine, with or without recombinant human thyroid-stimulating hormone, for thyroid remnant ablation following surgery for differentiated thyroid cancer was launched (HiLo Trial). The two aims are to (1) determine whether low-‘dose’ radioactive iodine (RAI) (1.1 GBq) is as effective as the standard ‘high’ dose (3.7 GBq) in ablating any remaining thyroid tissue after surgery and (2) determine whether patients given recombinant human TSH have a similar ablation success rate to those undergoing thyroid hormone withdrawal. Recruitment to this trial closed in 2010. Preliminary results suggest equivalent outcomes for all arms of the study and the final results are expected to be published in 2011.

### $^{131}$I administration procedure

Those prescribing radionuclide therapies in the UK must hold an appropriate Administration of Radioactive Substances Advisory Committee (ARSAC) certificate and the treatment must be given in appropriately designed areas.

Radioiodine is administered orally. Although it is available in liquid or capsule formulations, the latter is the preferred format as it is easier and safer to handle.

For successful remnant ablation to be achieved, the TSH level prior to the isotope administration must be elevated to $>25$–$30\text{ mU}/\text{L}$ in order to facilitate uptake of $^{131}$I by thyroid tissue. If $^{131}$I ablation can be performed approximately 4 weeks after surgery, there is no need for thyroid hormone supplementation to be commenced in the immediate postoperative period. If this is not possible, triiodothyronine (T3) 20$\mu$g three times a day should be started postoperatively and then this is withdrawn 14 days before radioiodine use to allow sufficient time for the necessary rise in TSH. Elevated TSH level stimulates the sodium iodide symporter (membrane protein involved in active transport) and hence radioiodine uptake into thyrocytes. An alternative method is to administer recombinant human TSH (rhTSH, Thyrogen\textsuperscript{185}) as an exogenous source of TSH and allow the patient to continue with thyroid hormones throughout the radioisotope treatment period. The benefit with using rhTSH is the avoidance of potential significant physical and psychological symptoms of hypothyroidism resulting from thyroid hormone withdrawal.\textsuperscript{23,24}

If the patient is already established on thyroxine they will either need to discontinue this for 4 weeks or preferably commence T3 instead at 20$\mu$g three times a day for 14 days and then discontinue this for a further 14 days prior to radioiodine. By swapping the thyroid hormones in this way, it is possible to reduce the length of time that the patient is rendered hypothyroid.

The decision whether a patient should receive $^{131}$I remnant ablation after thyroid hormone withdrawal (THW) or after rhTSH injections depends on the current licensed indications of use, the patient’s comorbidities and cost.

The current licensed indications for use are: (1) for pretherapeutic stimulation in combination with radioactive iodine for ablation of thyroid tissue remnants in patients who have undergone a near total or total thyroidectomy for well-differentiated thyroid cancer and who do not have evidence of distant metastatic thyroid cancer; (2) for use with serum thyroglobulin testing with or without radioiodine imaging for the detection of thyroid remnants and well-differentiated thyroid cancer in post-thyroidectomy patients maintained on...
hormone suppression therapy; (3) for the follow-up assessment of patients with well-differentiated thyroid carcinoma who have undetectable serum Tg levels on hormone suppression therapy.

Patient factors that would warrant rhTSH use in preference to THW include hypopituitarism, functional metastases causing TSH suppression, severe ischaemic heart disease, previous history of psychiatric disturbance precipitated by hypothyroidism, advanced disease or frailty.

rhTSH injections (0.9 mg) are given by deep i.m. injection into the buttock on days 1 and 2 with radioiodine being administered on day 3. Thyroglobulin is measured on day 5 when it reaches its maximal response.

Possible side effects include flu-like myalgia, mild nausea and headache. There is also the possibility of stimulating thyroid remnant tissue and metastases resulting in local symptoms, and consideration should be given to prophylactic corticosteroids before use if residual neck disease or metastases are known to be present.

For diagnostic 131I imaging, the method of TSH stimulation influences the optimal timing for the scan. If the patient has undergone THW the interval between administering the 131I and scanning is usually 72 hours compared to 48 hours if the stimulation is provided by rhTSH.

Serum Tg should be measured immediately prior to 131I administration if THW preparation is undertaken or on day 5 if rhTSH is used.

The usual administered activity of 131I used for remnant ablation is 3.7 GBq. However, the optimal administered activity is unknown as there are conflicting data between high and low ablation activities. For diagnostic 131I imaging, the method of TSH stimulation influences the optimal timing for the scan. If the patient has undergone THW the interval between administering the 131I and scanning is usually 72 hours compared to 48 hours if the stimulation is provided by rhTSH.

The usual administered activity of 131I used for remnant ablation is 3.7 GBq. However, the optimal administered activity is unknown as there are conflicting data between high and low ablation activities. The administered activities of 131I for therapy purposes are usually in the range 5.5–7.4 GBq. Whole body radioiodine scans are performed 2–10 days after giving radioiodine for ablation or therapy to determine the sites of radioiodine uptake and are more sensitive than diagnostic whole body scans due to the higher administered activity of radioiodine used. The timing of the scan will depend on the administered activity of 131I, the method of patient preparation (rhTSH versus thyroid hormone withdrawal) and the clinician’s choice of the residual activity at which to image the patient.

Physiological 131I uptake is seen in salivary tissue, gastrointestinal tract, and sinuses. Hürthle cell lesions are generally poorly responsive to radioiodine treatment and in particular distant metastases are often resistant to radioiodine therapy.

A preablation radioisotope scan is not routinely indicated, but it may be used to demonstrate the size of thyroid remnant. If a large remnant is seen, consideration of further surgery may be warranted. If further surgery is not appropriate it may influence the activity of radioiodine that is administered and prompt the prescription of premedication with corticosteroids prior to RAI to limit radiation thyroiditis symptoms.

If a preablation scan is performed, a low administered activity of 99mTc pertechnetate or 123I are preferred to 131I as they reduce the risk of stunning. Staining is the reduction in uptake of the 131I therapy dose as a result of the pretreatment diagnostic dose.

Thyroid hormones are started 2–3 days after radioiodine administration if the patient has been withdrawn from hormones. If the patient has been given rhTSH, they can stay on thyroxine throughout the procedure.

Prior to radioiodine administration, the total body iodine pool should be reduced. A low daily intake of iodine can increase the effective radiation dose achieved with 131I in the regions of interest. There is little consensus on the degree and the duration of dietary restriction required with each consensus guideline giving different advice, e.g. duration of the diet varies between 1 and 4 weeks with many centres using a 2-week period of restriction.

Other sources of excess iodine should be eliminated before proceeding with 131I administration, e.g. iodinated i.v. contrast and amiodarone.

### 131I toxicity

- Neck discomfort and swelling due to an inflammatory response in the remnant, residual tumour or involved cervical lymph nodes. This is most likely to be seen when there is a large thyroid remnant present. If the swelling is significant or painful, corticosteroids can be helpful. If the patient has only had a debulking procedure and gross residual thyroid tissue is present, prophylactic corticosteroids are advisable to minimize the pain and swelling associated with the inflammatory response and can be started just prior to RAI administration.
- Altered sense of taste, nausea (vomiting is uncommon and prophylactic antiemetics are not routinely used).
- Sialadenitis arises due to physiological uptake of 131I and subsequent excretion from salivary tissue. This can be reduced by encouraging patients to drink liberal quantities of fluids and possibly by encouraging salivary flow using sialogogues, such as lemon juice or sweets commencing 24 hours after 131I administration. In the long term, it is possible for tender parotid swelling to develop.
- Lacrimal gland dysfunction.
- Radiation cystitis. The risk may be reduced by maintaining a high fluid intake following radioiodine administration and during the isolation period.
- Gastritis.
- Bleeding/oedema in metastases.
- Bone marrow suppression. This reaches its peak 4–6 weeks after treatment. It is more likely in those patients who have extensive skeletal metastases or who have received prior external beam radiotherapy or chemotherapy.
- Gonadal tissue is exposed to radiation from radioiodine in the blood, urine and faeces.
  - **Male fertility**: a temporary rise in follicle-stimulating hormone (FSH) and a reduction in sperm count may be seen. High cumulative doses, e.g. > 14 GBq may reduce fertility and consideration should be given to sperm storage in high-risk cases where multiple therapeutic doses of 131I are expected.
  - **Female fertility**: no significant difference in fertility rate, birth weights or prematurity rates. Temporary alterations in the menstrual cycle may last between four and ten months in about a quarter of female patients. Increased risk of miscarriage may
If miliary pulmonary metastases are present, the patient must undergo thyroid hormone withdrawal, constipation is a common symptom of the hypothyroid state and therefore the use of laxatives may also help in reducing the gonadal tissue exposure.

- If the patient has undergone thyroid hormone withdrawal, constipation is a common symptom of the hypothyroid state and therefore the use of laxatives may also help in reducing the gonadal tissue exposure.
- If miliary pulmonary metastases are present, the patient may be at risk of developing pulmonary fibrosis especially if a high cumulative activity of radioiodine is administered. Consideration of pulmonary function test monitoring and corticosteroids immediately before and during treatment may reduce this risk. The data available are, however, fairly limited. 40-42

An increased risk of leukaemia and second cancers in organs that concentrate 131I (salivary gland, breast, bladder, colon) is seen with the risk being highest with high cumulative activities of radioiodine, i.e. greater than 18.5 GBq, and after external beam radiotherapy. 1

The risk of leukaemia is lower than reported in earlier series due to deliberate attempts to limit the total body dose and to increase the interval between radioiodine administrations, whereas the risk of second solid malignancy might be higher than previously thought. Rubino et al. 43 have reported a 27 per cent increase in overall risk of second malignancy with an absolute excess risk of 14.4 per cent for solid tumours and 0.8 per cent for leukaemias, whereas Sandeep et al. 44 reported a 30 per cent risk of second primary cancer in patients with a history of thyroid cancer.

- Good hydration, frequent micturition and regular bowel activity will help reduce the level of whole body radiation.

Consideration should be given to the use of high-dose corticosteroids before radioiodine if there is bulky neck disease or metastatic disease.

**Radiation protection issues**

Before the administration of 131I, pregnancy and lactation must be excluded. Following the administration of 131I, pregnancy/conception must be avoided for six months. 45

During the patient’s stay in the isolation room, visiting of family and friends must be restricted to non-pregnant adults. They must not directly enter the patient’s room, but must stay in a designated area outside the room and communication is often facilitated by an intercom system.

The patient’s clothing must be washed separately on their return home, unless it is heavily soiled, when storage on the hospital site or disposal may be needed. The method of transport home may be determined by the patient’s residual activity. For example, short distance travel in a private family vehicle, unoccupied by children, may allow discharge home with a higher residual activity than a longer journey via public transport where exposure to other members of the public, particularly children, may occur. Once at home, the patient must double flush the toilet; use separate cutlery and crockery, sleep alone, and restrict the time and extend the distance with their contacts. The duration of the restrictions is individualized for each patient and are longer for prolonged and close contact with children and pregnant women than they are with non-pregnant adults. Timing of a patient’s return to work will depend on the type of work undertaken, the work environment and the surrounding work personnel involved.

**TSH level**

Following total thyroidectomy, thyroxine is required to both replace thyroid hormones no longer produced endogenously, as well as to suppress TSH levels.

The initial aim is to use a thyroxine dose sufficient to suppress TSH to between <0.1 mU/L (in high-risk cases) and 0.5 mU/L (in low-risk cases). The dosage tends therefore to be larger than that used for replacement purposes following thyroidectomy for a benign aetiology. 41-43, 47-49, 50

Thyroxine in these larger doses prevents the pituitary from being stimulated to produce TSH and hence prevents stimulation of any remaining thyroid tissue, whether it is normal or malignant, with the intention of reducing the risk of recurrence, tumour progression and death.

The degree of suppression has not been tested in prospective studies and, due to concerns regarding the effects of prolonged supraphysiological thyroxine doses in low-risk cases, there has been recent interest in trying to relax the degree of TSH suppression in low-risk cases, aiming for a TSH within the lower part of the normal range. 31, 32 The European consensus statement from 2006 advocates that low-risk patients, once they have achieved apparent remission, can immediately have their dose of thyroxine reduced to achieve a serum TSH within the lower part of the normal range (0.5–1.0 mU/L), whereas high-risk patients should continue with full TSH suppression (<0.1 mU/L) for between three and five years. The American Thyroid Association 52 recommends the initial TSH suppression to be kept below 0.1 mU/L for high-risk and intermediate-risk thyroid cancer patients, while maintenance of the TSH at or slightly below the lower limit of normal (0.1–0.5 mU/L) is appropriate for low-risk patients. Similar recommendations apply to low-risk patients who have not undergone remnant ablation, i.e. serum TSH 0.1–0.5 mU/L.

When TSH is being suppressed, the free T4 (FT4) level is often seen to be above the upper limit of the normal range. Nevertheless, such moderate elevation does not commonly result in symptoms or signs of thyrotoxicosis.

The average dose of thyroxine required is in the range 150–200 μg with the dose varying depending on the patient’s age and weight.

Thyroxine is taken once daily, in the morning on an empty stomach. A number of medications can interfere with the absorption of thyroxine, so it is advisable to leave a 2-hour gap between taking thyroxine and other medications, such as calcium supplements, antacids and iron.

**Thyroglobulin**

Thyroglobulin is a glycosylated protein, which is a key substrate for biosynthesis and storage of thyroid hormones. It is
secreted by normal and cancerous thyroid cells and its release is TSH-dependent. The diagnostic sensitivity of Tg is increased when the TSH level is elevated (ideally TSH above 30 mIU/L). The Tg level may be undetectable in 20 per cent of cases in the presence of isolated lymph node metastases if it is measured while the patient is on TSH suppression therapy.

The serum Tg level is more sensitive than $^{131}$I whole body scan (WBS) in detecting recurrent or metastatic disease.

Thyroglobulin autoantibodies interfere with the ability to accurately measure and follow Tg trends. The prevalence of thyroglobulin antibodies is higher in patients with differentiated thyroid cancer (DTC) than in the general population (up to 25 per cent versus 10 per cent). There is some evidence that measuring TgAb levels and trends may be of some value in monitoring patients with thyroid cancer if the Tg cannot be relied upon in the presence of the autoantibodies. e.g. a rising trend in TgAb levels may indicate disease relapse in a patient. In order to interpret the serum Tg level, it is necessary to know the TSH level and Tg antibody level.

Serum Tg is not useful as a diagnostic test preoperatively because thyroglobulin is a product of normal thyroid tissue and can be markedly elevated by inflammatory thyroid diseases. It is therefore not specifically a serum tumour marker; however, if elevated in a patient who has previously been rendered athyroid by surgery and or by radioiodine ablation it may indicate recurrent or metastatic differentiated tumour.

Follow up

There is significant international variation in practice relating to the timing and modalities used for assessing successfulness of thyroid remnant ablation. Whole body radionuclide imaging has largely been superseded by neck ultrasound and stimulated Tg assessment in many centres.

Diagnostic $^{131}$I or $^{123}$I scans can provide useful information on the effectiveness of ablation and the need for further $^{131}$I. A follow-up scan should not routinely be performed earlier than six months following ablation. Recent data indicate that low-risk cases, after the first negative radioiodine whole body scan and cervical ultrasound, may be monitored with a stimulated Tg assessment (in the absence of interfering antibodies) without the need for a diagnostic radioiodine scan. A diagnostic whole body radioiodine scan should be performed in all other cases.

Cervical ultrasound is a sensitive method for detection of residual disease in the thyroid bed or cervical lymph nodes. In the United States and mainland Europe, it is common practice for endocrinologists to perform ultrasound in the follow-up clinic, whereas in the UK there is often a lack of access to and availability of expert cervical ultrasound in the routine follow-up clinic setting. It is essential for the ultrasound to be performed by a highly skilled operator with knowledge of thyroid cancer behaviour and not as a routine investigation by a general ultrasonographer. It is important to realize that low-risk intrathyroidal follicular thyroid cancer is very unlikely to recur in cervical lymph nodes or the thyroid bed, and therefore routine ultrasound is unlikely to detect any abnormalities in the neck if successful remnant ablation has been achieved. A raised Tg in these circumstances is therefore more likely to represent distant relapse.

For low-risk cases, if initial follow-up serum Tg is undetectable under TSH stimulation conditions then subsequent long-term, follow-up Tg assessments can be performed under TSH suppression conditions.

If the follow-up $^{131}$I scan and stimulated Tg are within normal limits the patient is kept on clinical follow up with Tg annually and there will be no need for routine radionuclide imaging unless symptoms or signs arise or Tg rises on follow up. If the scan or the Tg are abnormal the patient would be considered for $^{131}$I therapy. The usual administered activity of $^{131}$I is 3.7–5.5 GBq and this too will be followed up with repeat imaging and Tg assessment to assess response.

The TSH stimulated Tg level may remain detectable at low levels after $^{131}$I ablation. This could represent residual/recurrent cancer, but in the majority of cases represents thyroid remnant. An expectant policy in low-risk cases is recommended with repeat TSH-stimulated Tg assessment at 6–12-month intervals. In many cases, repeat assessments will reveal a gradual decline in stimulated Tg to the point of no detection, when routine follow up should then be commenced.

Thyroglobulin-positive, radioiodine scan-negative disease

This is a not uncommon scenario seen in the follow up of patients with differentiated thyroid cancer and there is controversy about optimal management.

Before assuming that the reason for the results is the presence of unidentified recurrent disease, first make sure the scan is truly negative and that there has not been any interference, e.g. iodinated intravenous contrast for computed tomography (CT) imaging, no amiodarone, no high iodine content diet. The European Consensus recommendation is that iodine containing contrast media should be avoided for two to three months prior to radioiodine administration; however, there is considerable variation in international practice relating to the optimal interval to be used between iodinated contrast-enhanced CT and the administration of radioiodine. If a patient with an elevated thyroglobulin is to be investigated with regards to localizing the site of relapse, it is important to consider this potential interference if further radioiodine treatment is being considered and alternative imaging modalities may be indicated such as ultrasound or magnetic resonance imaging (MRI).

There are two possible explanations for this situation, once a false-negative scan or false-positive Tg has been ruled out: (1) a small volume of thyroid cancer cells not taking up enough radioiodine to be shown on gamma camera images, i.e. volume of disease below the sensitivity level of the imaging modality or (2) thyroid cancer cells which are non-iodine avid, dedifferentiated or of Hurthle cell type and are unable to take up radioiodine.

There are three main approaches in this situation:

1. No action until the patient becomes symptomatic.
2. Additional investigations aiming to localize the disease recurrence and offer specific therapy (in particular surgical resection of the disease wherever
possible). Use cross-sectional imaging and radioisotope functional imaging studies to find sites of disease. If an isolated lesion amenable to surgery or external beam radiation therapy (EBRT) is found then this and RAI therapy can be considered. A possible imaging strategy is as follows:

a. Neck ultrasound/MRI of neck and mediastinum as the thyroid bed, cervical and mediastinal nodes are the most common sites of recurrence for papillary thyroid cancer. If negative:

b. CT lungs to look for micronodular lung metastases. Remember the potential for iodinated intravenous contrast to inhibit subsequent radioiodine uptake and the recommendation for delaying 131I treatment for two months. If negative:

c. ⁹⁹ᵐTc isotope bone scan. If negative, consider proceeding with a

d. ¹⁸FDG-PET/CT and consider TSH stimulation before positron emission tomography (PET) imaging as there is some evidence to suggest this increases the sensitivity.⁶², ⁶³ Other radioisotopes for imaging purposes can be used such as thallium, tetrofosmin and sestamibi, but they lack specificity for thyroid cancer.

e. ¹³¹In-labelled octreotide imaging⁶⁴ may demonstrate significant uptake in sites of tumour in a small percentage of cases and these patients may then be considered suitable for radiolabelled somatostatin analogue therapy.

f. If imaging suggests surgically resectable disease, its removal should be undertaken prior to further radioiodine therapy.

3. Empirical ¹³¹I therapy.¹, ⁶⁵, ⁶⁶, ⁶⁷

The decision on whether to proceed with an empirical dose of ¹³¹I needs to be made, bearing in mind the risk category of the patient and the rate of Tg rise. Proponents argue that a high proportion of patients will have positive post-therapy scans and or thyroglobulin response and some may achieve cure. Opponents argue that some of these patients have minimal disease and hence radioiodine is unlikely to improve survival and that treatment is associated with acute toxicity. A meta-analysis states that 50 per cent of post-therapy scans will be positive and of these positive cases 60 per cent will also show a fall in Tg.⁶⁶

**Recurrent or metastatic disease**

Between 5 and 20 per cent of patients with papillary thyroid cancer relapse in the thyroid bed or cervical nodes and surgery is the treatment of choice for such locoregional recurrence. Ideally, complete resection is recommended, but if this is not feasible, debulking is beneficial as this will facilitate greater radioiodine uptake in a smaller volume of disease.¹¹ Distant metastases develop in 10–20 per cent with pulmonary and bone accounting for the majority. If the patient has radioiodine-avid disease, then repeated doses of radioiodine are indicated provided there is evidence of symptomatic, radiological or biochemical response.

Remission can be achieved in about two-thirds of patients with neck recurrence and one-third of those with distant metastases. Remission is more likely when a limited tumour burden is present.¹³, ⁶⁸, ⁶⁹

Prognosis depends on distribution and number of metastatic sites, tumour burden (microscopic foci are more likely to respond) and age at the time of diagnosis of metastases.⁷⁰, ⁷¹ If tumour takes up ¹³¹I, then long-term survival is possible. The preferred treatment is repeated doses of ¹³¹I with administered activities ranging between 3.7 and 11.1 GBq at three to nine month intervals (usually 5.5–7.4 GBq at 6–12 month intervals).¹–⁴⁰, ⁷²–⁷⁵ The ATA guidelines⁵² recommend repeated radioiodine therapies every 6–12 months for those patients with pulmonary micrometastases, as long as there is continued evidence of response.

Empirical administered activities of ¹³¹I are generally used, but dosimetricaly calculated activities are used in some centres.⁷⁴ There is no maximum limit to the cumulative administered activity of ¹³¹I that can be used in the treatment of a patient with persistent disease.¹–⁴⁰ Normal bone marrow function is needed and reductions in the administered activity are required in the presence of renal impairment.

Extensive bony metastases are generally not curable by ¹³¹I alone. For solitary or a limited number of bone metastases, external beam radiotherapy, resection or embolization with or without postoperative external beam irradiation may be associated with increased survival.⁶⁹

**External beam radiotherapy**

The use and role of radiotherapy in differentiated thyroid cancer is debated due to conflicting results in published series. There are no randomized controlled trials and the retrospective reviews often extend over several decades resulting in considerable variation in extent of surgery and accuracy of staging investigations. Problems with selection bias are also encountered, as well as inappropriately short follow up for a disease with a long natural history.

The published data are also often lacking with regards to the radiotherapy techniques and doses used, the acute and late toxicity and study end points. The long natural history of the disease means that drawing conclusions from any treatment intervention is difficult.⁷⁵, ⁷⁶, ⁷⁷

External beam radiotherapy is infrequently used but the main indications are:

- unresectable disease;
- non-iodine avid disease;
- gross local invasion with macro- or microscopic residual;
- recurrent neck disease not amenable to surgery;
- palliation of inoperable metastatic disease.

The radiotherapy treatment volume usually includes the thyroid bed, cervical and supraclavicular nodes and superior mediastinum. Technical difficulties arise due to the irregular shape of the areas requiring treatment and their proximity to the spinal cord which is more sensitive to the effects of radiotherapy than tumour tissue and is therefore a dose-limiting structure. Without careful attention to radiotherapy planning and delivery, the patient is at risk of radiation myelopathy. The anatohysical relationship between the target area and the spinal cord makes it difficult to deliver an
homogeneous dose to the areas at risk with conventional radiotherapy techniques. It is possible that radiotherapy may reduce the uptake of radioiodine into residual thyroid tissue and therefore consideration should be given to administering radioiodine therapy before external beam radiotherapy. However, in practice, there may be a significant delay before the patient can be admitted to the isolation room for radioiodine remnant ablation and for some patients it may be advisable to proceed with external beam radiotherapy, rather than delay both treatment modalities.

Intensity-modulated radiotherapy (IMRT) allows a better radiation dose distribution to the tumour while reducing the dose to radiosensitive organs close to the target areas. This technique can also reduce the volume of non-target tissue that is irradiated to high dose and may even allow dose escalation to at-risk areas.

During radiotherapy the patient is treated supine. Due to the proximity of the area for treatment to critical structures and the need to deliver treatment accurately and precisely over a number of weeks, an immobilization shell is required to keep the patient in a reproducible position.

Radiotherapy is most often required for both the thyroid bed and the locoregional nodes, including the superior mediastinal nodes, rather than the thyroid bed alone. This results in a more complex shape and a larger volume of tissue being irradiated resulting in greater acute toxicities. The most common acute toxicities seen with external beam radiotherapy in this situation are mucositis with associated odynophagia, skin erythema, skin desquamation and laryngitis. If level I and II cervical lymph node areas need irradiating, the thyroid bed and the locoregional nodes, including the superior mediastinal nodes, should be included in the target volume. If the proximal upper mediastinum needs irradiating a wedge should be placed in the field to keep the patient in a reproducible position.

Over a number of weeks, an immobilization shell is required to keep the patient in a reproducible position. During radiotherapy the patient is treated supine. Due to the proximity of the area for treatment to critical structures and the need to deliver treatment accurately and precisely over a number of weeks, an immobilization shell is required to keep the patient in a reproducible position.

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Chemotherapy
There are no data to support the use of adjuvant chemotherapy in the management of differentiated thyroid cancer and it is also not routinely used at the onset of locally recurrent or metastatic disease. Its use is restricted to symptomatic progressive disease when surgery, radiotherapy and radioactive iodine therapy have failed. Published studies have usually only included small numbers of patients and have often had a mixture of histological tumour types within the study population.

Doxorubicin is the most extensively studied agent in advanced thyroid cancer and the most frequently used drug, with a partial response rate of approximately 20–30 per cent reported. There is no clear evidence, however, that its use increases survival. The published studies, however, include patients with variable tumour types and disease burdens and were performed prior to the routine use of high quality imaging and often have limited outcome data.

Doxorubicin in combination with cisplatin has demonstrated a higher response rate but with additional toxicity and no improvement in outcome. It has been reported that response rates to chemotherapy may increase in the presence of an elevated TSH level. However, this has been based on a small series of patients and no large studies have been conducted to address this issue more formally.

Biological agents
As radioisotope therapies and conventional chemotherapy are frequently ineffective in treating symptomatic locally advanced and metastatic thyroid cancer, new treatment strategies are being developed. These new small molecule therapies, such as tyrosine kinase inhibitors, are being targeted at problematic areas in the thyroid cancer cell growth and apoptotic pathways. The following are some of the abnormal pathogenetic mechanisms observed in thyroid cancers:

- RET gene rearrangements are present in 13–43 per cent of PTCs and 30–100 per cent of medullary thyroid carcinomas (MTC) (depending on whether sporadic, FMTC or MEN 2 related).
- BRAF mutations are seen in 29–69 per cent of PTC tumours.

These molecular alterations are now being used as targets for therapeutic strategies. A number of new agents are being investigated including sorafenib (Nexavar®) an inhibitor of BRAF, VEGFR, PDGFR-B, Flt3 and cKIT;84 sunitinib (Sutent®) a receptor tyrosine kinase inhibitor that targets PDGFR, VEGFR and KIT; axitinib (AG-013736) a selective inhibitor of VEGFRs;85 lenalidomide (Revlimid®) a derivative of thalidomide with anti-angiogenesis properties and motesanib (AMG 706), another multiple-receptor tyrosine kinase inhibitor that selectively targets and inhibits VEGFR, PDGFR, kit and RET receptors, thereby inhibiting angiogenesis and cellular proliferation.

These agents are administered orally and have a different toxicity profile compared to conventional chemotherapy. The common toxicities are:

- hypertension;
- rash;
- diarrhoea;
- prolonged QTc interval.

Other potential agents include PPARγ activators, COX 2 inhibitors, heat shock protein inhibitors, demethylating agents, histone deacetylase inhibitors, protease inhibitors and gene therapy. This is a rapidly evolving area and information on current clinical trial activity can be found at the following websites: www.clinicaltrials.gov, www.nci.nih.gov, www.centerwatch.com and www.thyroid.org.

Other radiolabelled therapies
Differentiated thyroid cancers express somatostatin receptors (mainly types 3 and 5) and a small proportion of patients may express the receptors to a significant degree thereby opening the possibility of using radiolabelled somatostatin analogues as a therapy in the metastatic setting.

Childhood
Thyroid nodules are more likely to be malignant in children. Papillary carcinoma is the most common differentiated
thyroid cancer seen, with 30–40 per cent being multifocal; 40–90 per cent of patients are found to have involved cervical nodes at initial surgery (compared with 20 per cent of adults).

Differentiated thyroid cancer tends to behave more aggressively in children younger than ten years of age and the chance of recurrence is also higher. \(^{87, 88, 131}\) Ablation is indicated for all children and adolescents with differentiated thyroid cancers > 1 cm following total thyroidectomy \(^{88, 89, 90}\) and selective neck dissection is recommended for children with positive nodes. \(^{91}\)

At presentation, 10–20 per cent have lung metastases, while bone metastases are rare (<1 per cent). Fewer than 10 per cent will die as a result of their disease.

**Management of differentiated thyroid cancer during pregnancy**

If differentiated thyroid cancer is diagnosed during pregnancy, it is essential to consider the risk to both mother and fetus of both the treatment options and the continuation of the pregnancy. Thyroidectomy in the first trimester of pregnancy is associated with a very high risk of miscarriage, but it may be performed safely in the second trimester. \(^1\) Alternatively, surgery can be deferred until after the baby is delivered provided the thyroid tumour is monitored by ultrasound and found to be stable. Suppressive doses of thyroxine are safe in pregnancy and may be considered until surgery is possible. The dosage of thyroxine may need to be increased during pregnancy. \(^92\)

Termination of pregnancy is rarely indicated.

It is necessary to avoid pregnancy for six months after radioactive iodine. \(^{44}\) There may be an increased risk of miscarriage in the first year following radioactive iodine. \(^{35, 36, 37, 93}\) It is advisable to stop breast feeding at least 4 weeks and preferably 8 weeks prior to \(^{131}\)I. \(^1\)

Pretreatment sperm banking should be considered in male patients likely to have more than two high-dose \(^{131}\)I therapy treatments (see above under \(^{131}\)I toxicity). \(^1, 34-94\) Adequate hydration at the time of treatment and several days afterwards helps prevent a decrease in sperm count. Male patients should avoid fathering a child for a minimum of four months, and ideally six months, following \(^{131}\)I.

**Follow up**

Frequency and type of follow up depends on an individual’s risk of recurrence. \(^{31, 60, 95}\) The aims of follow up are to detect tumour recurrence early, to monitor TSH suppression and to detect and manage hypocalcaemia. Protocols vary considerably between centres, but as an example the British Thyroid Association (BTA) \(^1\) suggest that following the achievement of thyroid remnant ablation, the frequency of follow up in the first two years is three to six monthly, decreasing to six to eight monthly for three years and then annually thereafter.

The recommended duration of follow up is lifelong due to the long natural history, the possibility of late recurrences, to monitor for late side effects of radioactive iodine and the consequences of supraphysiological thyroxine replacement.

**Clinical trials**


**MEDULLARY THYROID CARCINOMA**

Surgery is the main modality of treatment for this disease and monitoring of serum calcitonin postoperatively is important in establishing whether biochemical control has been achieved. The calcitonin level of many patients remains elevated after surgery and it is frequently difficult to locate the site of residual disease whether it be local or at a distant site. Blood samples taken for calcitonin must be immediately stored in ice since rapid degradation occurs at room temperature and may give falsely low results. CEA is also commonly raised and can similarly be used to monitor progress and response to therapeutic intervention.

It is presumed that by rendering a patient calcitonin negative that they will have an improved chance of long-term survival and cure; however, long-term follow up of several patient series has lead to conflicting results. Tisel et al. \(^{96}\) failed to demonstrate a survival advantage when meticulous attention to cervical lymph node dissection achieved normalization of calcitonin and many therefore advocate close clinical follow up and reserve surgery for when clinical relapse can be demonstrated. \(^{97, 98}\)

Many patients with a raised calcitonin level remain well with an excellent performance status for many years, whereas others become symptomatic over a much shorter interval. In a retrospective review of 65 patients by Barbet et al. \(^{99}\) calcitonin doubling time during follow up was a significant predictor of survival in both univariate and multivariate analyses. A calcitonin doubling time greater than two years was associated with long-term survival, whereas patients with a doubling time of less than six months all died as a result of their medullary thyroid cancer.

**External beam radiotherapy**

Due to a lack of prospective studies, the role of radiotherapy remains uncertain. It is difficult to compare reported series due to considerable differences in radiotherapy dose fractionation, eligibility criteria and often due to the relative rarity of the disease, recruitment has been over very long periods of time. Reported series also often fail to report the associated toxicity and impact on quality of life of any treatment intervention. \(^{100}\)

Radiotherapy may be indicated in the following situations: \(^{101, 102}\)

- postoperatively, when the disease was locally advanced at presentation;
- multiple involved lymph nodes;
- persistently high calcitonin/CEA postoperatively;
- bulky inoperable tumours;
- palliation of distant metastases, e.g. bone.

Routine adjuvant radiotherapy in the postoperative setting has not been shown to improve survival. \(^1, 103, 104\)
METASTATIC MEDULLARY THYROID CANCER

Many patients’ survival can be measured in years and, even in the presence of significant disease bulk, quality of life can often be good.

Distant metastases frequently involve the liver, lungs and the skeleton and may first come to light when the serum calcitonin level rises significantly. Occasionally, the first sign of the development of distant metastases may be when the patient starts to experience diarrhoea as a result of excess peptide release or symptoms related to excess hormone production. As well as experiencing frequent loose bowel actions, wheezing and flushing are also possible. Cushing syndrome may also occur. These symptoms may respond to somatostatin analogue therapy (e.g. octreotide). Chemotherapy is rarely helpful unless there is rapidly progressive symptomatic disease.

There is no curative treatment option and therefore treatment interventions are usually reserved until the patient becomes symptomatic rather than at first presentation of asymptomatic radiologically diagnosed metastases.

When assessing response to treatment, it is often difficult to demonstrate an objective radiological response even in patients who have symptomatically responded or shown a biochemical response with falling calcitonin levels, by the conventional method of measuring a decrease in the size of tumour lesions. This phenomenon is characteristically seen in MTC and is possibly due to the inclusion of amyloid and calcification within the tumour.

Unlabelled somatostatin analogue therapy for diarrhoea

Somatostatin receptors can be found on medullary thyroid cancer cells and therefore blocking these receptors can result in a decrease in the amount of peptide and calcitonin released. However, a significant decrease in tumour mass is not seen and the aim of treatment is an improvement in symptoms – diarrhoea and flushing and quality of life. Unfortunately, any recorded benefits often seem to be short lived.

If a patient responds favourably to daily subcutaneous administration of octreotide, a synthetic somatostatin analogue (starting at 50–100 μg two or three times per day and escalating according to response up to a maximum of 1500 μg daily) with a reduction in diarrhoea frequency or severity, then they can be commenced on a depot preparation. However, with prolonged use, there is a risk of tachyphylaxis developing with loss of symptomatic benefit. However, if symptom control deteriorates it is important to consider if disease progression is the cause before attributing the change to tachyphylaxis. Octreotide and lanreotide have a different spectrum of somatostatin receptor blockade. Side effects of the somatostatin analogues include gastrointestinal disturbances, such as anorexia, nausea, vomiting, abdominal pain, flatulence, diarrhoea and steatorrhoea, and rarely with long-term use gallstones may occur. Abnormalities of glucose metabolism may also occur. Local reactions at the site of administration may be seen and rotation of the injection site is recommended.

Targeted radiolabelled therapies

Once metastatic disease has been established, imaging with 123I metaiodobenzylguanidine (mIBG) or 111In octreotide may demonstrate selective uptake at sites of known tumour relapse, thereby opening up the possibility of using similar agents as targeted radiolabelled therapies.

As medullary thyroid cancer is not derived from follicular cells, it does not accumulate radiiodine.

METAIODOBENZYLGLUANIDINE

Metaiodobenzylguanidine is a guanethidine derivative, structurally similar to noradrenaline. It is transported into neuroendocrine tumour cells by monoamine transport proteins and may be useful as a therapy in a small number of cases.1–106, 107

Approximately 30–40 per cent of medullary thyroid cancers concentrate 131I-mIBG,108, 109, 110 but to date histological tumour characteristics that reliably predict isotope uptake and hence suitability for therapy have not yet been defined.

Prior to treatment, care must be taken to prevent the use of drugs that may interfere with the uptake and retention of mIBG. The following are some examples, but not an exhaustive list: tricyclic antidepressants, phenothiazines, calcium channel blockers, salbutamol and opioids.

The treatment is given in an isotope isolation room by intravenous infusion usually over a 1–2-hour period through a lead-shielded infusion system. Continuous blood pressure monitoring is required during the infusion and for a period of time afterwards, as unstable blood pressure can result. In practice, this is usually managed by slowing or interrupting the infusion, but in the case of a hypertensive crisis, intravenous phenolamine and propranolol may be required. These drugs should be immediately available during the infusion.

Prophylactic antiemetics, such as ondansetron, are indicated prior to the infusion and should be continued for 72 hours afterwards. It is advisable to insert two cannulae to allow simultaneous i.v. fluids to be given to ensure good hydration in case the patient is unable to take adequate fluids orally as a result of nausea. It is possible that the patient may experience diarrhoea, wheezing and flushing related to peptide and hormone release from the tumour. The patient remains in the isolation room for several days and will follow similar radiation protection procedures as described above under Differentiated thyroid cancer, p. 494.

Whole body gamma camera imaging is performed just before the patient is discharged home to demonstrate the distribution and intensity of isotope uptake.

A full blood count (FBC) should be checked weekly for 6 weeks afterwards as myelosuppression, particularly thrombocytopenia, can occur. This is more likely if there is widespread bone marrow involvement or if the patient has received chemotherapy.

mIBG treatment can be repeated. There are many regimes including three courses at 8–12-week intervals.

Response to treatment can be assessed in terms of symptom improvement, decreasing calcitonin levels or tumour regression on imaging. It is the former, however, which tends to dictate management decisions. Up to 60 per cent of patients
may derive symptom benefit and 30–80 per cent may achieve disease stabilization. However, these data are derived from small series.\textsuperscript{111–112, 113} mIBG is traditionally reserved until patients become symptomatic from metastatic disease and it is unknown whether its use earlier in the natural history of the disease may be beneficial, for example when there is asymptomatic elevated serum calcitonin.

Radiolabelled somatostatin analogue therapy

Somatostatin receptor imaging is reported to have a sensitivity of 50–70 per cent in localizing medullary thyroid tumour.\textsuperscript{114–115} Somatostatin analogues bound to \textsuperscript{90}yttrium or \textsuperscript{177}lutetium can therefore be used as therapy in those patients who demonstrate sufficient somatostatin analogue uptake within sites of tumour when compared to background physiological uptake. A subjective benefit may be seen after one to two treatments and this may be associated with a reduction in calcitonin/CEA and tumour stabilization. It is important to realize that a formal radiological assessment of response can be misleading. Often, overall tumour size remains static on cross-sectional imaging, even in the presence of significant radioisotope uptake, symptomatic response and biochemical response. Toxicity includes myelosuppression and nephrotoxicity. Pretreatment with an amino acid infusion can reduce binding of the somatostatin analogue to the renal tubules and hence reduce renal damage.

Chemotherapy

This is reserved for progressive and symptomatic metastatic disease.\textsuperscript{1, 80, 81, 116}

There are no randomized controlled trials. The most commonly used drug is doxorubicin, with a response rate of 20–30 per cent that is usually short-lived.

Combination chemotherapy regimens (e.g. doxorubicin with cisplatin) are no more clinically effective and can add significant toxicity.

As medullary thyroid cancer is a neuroendocrine tumour (NET), chemotherapy regimens with activity in other NETs, such as carcinoids, have been suggested, e.g. 5-fluorouracil and streptozocin.

No significant survival benefit has ever been demonstrated and therefore this treatment modality is reserved until progressive symptomatic disease develops that is difficult to palliate with other less toxic modalities.

Biological agents

Preclinical studies have shown that RET inhibition can lead to growth restraint or apoptosis in medullary thyroid cancer cell lines. As a result, there has been significant recent interest in utilizing multikinase inhibitors with activity against RET, VEGF, EGFR, PDGF and KIT in locally advanced and metastatic thyroid cancer of all histological types. They may therefore have a dual mechanism of action with a direct action on tumour cells themselves and also an antiangiogenic effect.

The toxicity profiles of these agents are different to those of cytotoxic chemotherapy agents. Common adverse events include diarrhoea, hypertension, skin rash, fatigue, headache and nausea. The side-effect profile needs to be balanced against potential improvement in disease-related symptoms, such as diarrhoea or flushing, as MTC is a slowly growing tumour in many cases.

Radiological evidence of significant disease progression along with the calcitonin doubling time, the patient’s symptoms and their performance status should all be considered before deciding if systemic therapy is appropriate and likely to provide clinical benefit.

The first TKI to get Food and Drug Administration (FDA) approval for use in unresectable locally advanced or metastatic medullary thyroid cancer was vandetanib (Zactima\textsuperscript{TM}) in April 2011. This decision was based on the phase 3, double-blind placebo-controlled ZETA study that showed an increase in progression-free survival.\textsuperscript{117}

Other oral TKIs currently being investigated include caboazonitib (XL184) and lenvatinib (E7080).

There is some evidence emerging that different RET mutations may have different drug sensitivities. For example, the codon 804 mutation seen in hereditary MTC shows in vitro resistance to vandetanib/ZD6474, but sensitivity to sorafenib.\textsuperscript{118}

Clinical trials


ANAPLASTIC THYROID CANCER

Patients with this tumour have a very poor prognosis, with the median survival being six months from symptom onset.\textsuperscript{119, 120}

External beam radiotherapy

This tumour is the least radiosensitive of the thyroid tumours. Tumour response tends to be partial even with high doses and the majority of patients still die as a result of locally progressive disease. It is also very important to appreciate that patients may spend a very significant proportion of their remaining lives undergoing treatment and recovering from its significant toxicity.

Attempts have been made to improve response to treatment by intensifying the radiotherapy regime by hyperfractionation (delivering more than the standard one fraction of radiotherapy per day) or by shortening the time period over which it is delivered (accelerated radiotherapy) and combining this with chemotherapy and in some cases surgery.\textsuperscript{121–123, 124} This intensification has in some series resulted in improved response rates, but at the cost of increased toxicity.\textsuperscript{125}
Chemotherapy

The response rate for doxorubicin is in the region of 20 per cent. The responses are often partial and of short duration. Other agents are being investigated including the chemotherapy drugs paclitaxel and combretastatin and biological agents, such as sorafenib.

Clinical trials


PRIMARY THYROID LYMPHOMA

Thyroid lymphomas constitute only 3 per cent of all non-Hodgkin lymphomas (NHL) and approximately 5 per cent of all thyroid neoplasms. They are more frequently seen in patients with a history of Hashimoto thyroiditis. The majority of thyroid lymphomas are of B-cell origin. Diffuse large B-cell lymphoma accounts for up to 70 per cent of cases, while mucosa-associated lymphoid tissue (MALT)-positive lymphoma accounts for between 6 and 27 per cent. If a diagnosis of thyroid MALT lymphoma is made, consideration should be given to performing a gastroscopy to check for involvement of the stomach as MALT lymphomas have a tendency to migrate to other areas with MALT.

The majority of patients present with cervical or mediastinal node involvement and are managed with a combination of external beam radiotherapy and systemic chemotherapy as both overall and distant relapse rates are lower in those patients receiving combined modality therapy compared to chemotherapy or radiotherapy alone. Presentation with B symptoms is uncommon.

Six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy followed by radiotherapy increases survival when compared with radiotherapy alone (35 versus 65–90 per cent). In general, the addition of rituximab, a chimeric monoclonal antibody against CD20, to CHOP chemotherapy in the management of NHL provides further benefit in survival and disease-free survival and it is therefore assumed that this also applies to primary thyroid lymphoma.

As lymphoma is a relatively radiosensitive tumour, the radiation dose required is appreciably lower than that used in the management of differentiated thyroid cancers.

Radiation therapy is most commonly given after between three and six courses of chemotherapy. The usual radiation fields either cover the areas involved at presentation only or they may be extended to include the thyroid, bilateral neck, supraclavicular regions and the mediastinum.

Radiotherapy alone may be indicated for stage Ia/M0 mucosa-associated lymphoid tissue-positive lymphoma as it tends to follow a more indolent course and a complete response of >90 per cent can be achieved with this single treatment modality. Laing et al. report 100 per cent complete response with radiotherapy, a relapse rate of 30 per cent and salvage rate >50 per cent with a 90 per cent overall cause-specific survival at five years.

KEY EVIDENCE

- I would really only recommend that practitioners are familiar with current international consensus documents/guidelines, e.g. American Thyroid Association (ATA) guidelines on management of differentiated thyroid cancer (DTC) and medullary thyroid carcinomas (MTC).

KEY LEARNING POINTS

- Differentiated thyroid cancer:
  - degree of thyroid-stimulating hormone (TSH) suppression in long-term follow up
  - possibility of moving towards lower activity of radioactive iodine (RAI).

- Medullary thyroid carcinoma:
  - importance of calcitonin doubling time

- Progressive locally advanced/metastatic disease:
  - potential role of systemic treatment in the form of tyrosine kinase inhibitors (TKI).

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Parathyroid tumours

R JAMES A ENGLAND AND NICK P MCIVOR

INTRODUCTION

Parathyroid tumours are benign in 99 per cent of cases. They usually present with primary hyperparathyroidism (HPT), normally characterized by hypercalcaemia in the presence of an inappropriate (i.e. unsuppressed) level of parathyroid hormone (PTH). Until the introduction of the automated serum autoanalyser in the 1970s, patients with these tumours typically presented late with severe symptoms or signs. Now, the majority are diagnosed in apparently asymptomatic patients with the discovery of incidental hypercalcaemia during biochemical analysis. Although making the diagnosis of HPT is normally straightforward, other causes for hypercalcaemia must always be considered and excluded.

In HPT, excess PTH is produced by the neoplastic or hyperplastic growth of parathyroid parenchymal cells. HPT is usually primarily due to a parathyroid abnormality and therefore unassociated with other biochemical influences – primary HPT. In some cases, it is due to other biochemical influences stimulating the parathyroid glands – secondary HPT. In chronic secondary hyperparathyroidism, the growth of a hyperplastic gland may become autonomous due to the resetting of the calcium receptor on individual parathyroid cells, such that the glands remain hyperplastic after the chronic stimulus has been removed. This situation is known as 'tertiary hyperparathyroidism'. Finally, HPT may be inherited as part of a MEN syndrome or less frequently in isolated form.

The vast majority of parathyroid surgery is carried out for primary HPT. The decision to operate is sometimes difficult as a significant proportion of these patients can be treated conservatively by regular monitoring and in some, symptomatic and biochemical improvement can be achieved with drugs. However, the only definitive treatment for hyperparathyroidism remains surgery and with the newer technique of targeted minimally invasive parathyroidectomy (MIP), many authors would argue that surgery should be considered in every case.

Surgery for familial hyperparathyroid syndromes is challenging because of the high incidence of multigland disease. Surgery is seldom required for secondary HPT, but those that...
THE CALCIUM–PTH RELATIONSHIP AND THE CALCIUM–SENSING RECEPTOR

There are usually four parathyroid glands in the neck (two on each side) that are responsible for maintaining the normal level of calcium in the blood specifically, and the body in general.

Normal parathyroid glands are regulated by a feedback mechanism. As the level of calcium in the blood increases, the stimulation to secrete PTH decreases and vice versa. This relationship between serum calcium and PTH is best represented by a sigmoidal curve: the PTH-Ca\textsuperscript{2+} curve. It is regulated via the parathyroid cell calcium-sensing receptor (CSR) which in turn is regulated by its coding gene and also by the 'set-point' which reflects sensitivity of the receptor. Various conditions shift the curve to the right (reduced sensitivity), e.g. lithium and chronic renal failure, while others shift it to the left (increased sensitivity), e.g. early renal failure.

The CSR lies on the surface of parathyroid cells and responds to the ambient calcium of the pericellular fluid. Aberrations in the CSR gene which regulates the expression of this receptor, influence calcium homeostasis (see Familial hyperparathyroidism, p. 512). Also, there is a receptor ‘set-point’ which reflects sensitivity of the CSR to calcium. The set-point is defined as the calcium level at half of the maximal inhibition of PTH release, i.e. 50 per cent of maximal PTH secretion. There is always some basal PTH secretion, even in severe hypercalcaemia, whereas below the set-point there is an increasing stimulation of PTH production, PTH release, and parathyroid cell replication. Various conditions influence the set-point, e.g. lithium and renal failure cause a resetting of the set-point leading to states of persisting hypercalcaemia (see Secondary hyperparathyroidism, p. 512).

PRIMARY HYPERPARATHYROIDISM

Clinical presentation

The symptoms of primary HPT are due to hypercalcaemia and are listed in Box 27.1. These can be summarized by the aphorism ‘bones, stones, groans and psychic moans’. However, 80 per cent of patients present incidentally with the finding of hypercalcaemia on routine blood testing. Their condition is often labelled ‘asymptomatic hyperparathyroidism’, but as many of the symptoms of HPT may be attributed to the ageing process, the label ‘asymptomatic’ can be hard to validate. Patients may also be diagnosed while screening for osteopenia, osteoporosis or nephrolithiasis. Very rarely, patients may present with significant bone disease (osteitis fibrosa cystica) most clearly seen on x-rays of the middle phalanges showing subperiosteal bone resorption. This presentation tends to occur more frequently in severe long-standing disease, parathyroid cancer or secondary and tertiary hyperparathyroidism.

Box 27.1 Manifestations of hypercalcaemia

- Muscle weakness
- Muscle and bone aches and pains
- Depression
- Constipation
- Tiredness
- Peptic ulceration
- Pancreatitis
- Renal impairment
- Nephrogenic diabetes insipidus
- Nephrolithiasis
- Shortened QT interval
- Band keratopathy
- Thirst and polyuria

Diagnosis of primary hyperparathyroidism

PTH hypersecretion occurring as a primary event occurs at any age, but more commonly in older patients. By the sixth decade, the incidence has risen to approximately one in 1000 in men, and one in 500 in women.

The diagnosis is usually first suspected by the finding of hypercalcaemia, although 10–20 per cent of hyperparathyroid patients may be normocalcaemic. This may be due to concomitant vitamin D insufficiency which must be screened for, or the fact that the parathyroid glands are intermittent secretors, and repeat Ca\textsuperscript{2+} monitoring or vitamin D replacement therapy in appropriate patients will normally unmask the diagnosis.

In the presence of hypercalcaemia, an ‘inappropriately’ normal or elevated PTH level is indicative of HPT. Patients with nonparathyroid hypercalcaemia virtually always have PTH values below 25 pg/mL. However, if the diagnosis is unclear, other causes of hypercalcaemia must be excluded.

The second most common cause of hypercalcaemia is cancer. There is secretion of parathyroid hormone-related peptide (PTHrP) causing the osteoclastic release of calcium and suppressing PTH. This diagnosis is normally easy to make as the tumour will be in an advanced state. However, in a clinically well, hypercalcaemic patient with a suppressed PTH, the diagnoses of malignant lymphoma and multiple myeloma must still be ruled out. PTH can be differentiated from PTHrP by a chemiluminescent assay so that primary HPT is not confused with the hypercalcaemia of malignancy. Other causes of hypercalcaemia to be borne in mind are listed in Box 27.2.

Further useful tests in the diagnosis of primary hyperparathyroidism include serum phosphate, which is normally at the lower end of the normal range and serum creatinine, as renal impairment may occur as a result of chronic hypercalcaemia. In addition, a 24-hour urine collection is useful because 40 per cent of hyperparathyroid patients at diagnosis have hypercalciuria, the remainder having normal values. Significant hypercalciuria is one of the criteria for advising surgery in asymptomatic primary hyperparathyroidism because of the increased risk of developing nephrocalcinosis or nephrolithiasis. If the urinary calcium is low, however, the diagnosis of familial hypercalcaemic hypocalciuria (FHH) must be considered (see Familial hyperparathyroidism).
A calcium/creatinine clearance ratio of >0.02 effectively rules out this diagnosis.9

### SECONDARY HYPERPARATHYROIDISM

‘Secondary hyperparathyroidism’ is so called because a chronic state of parathyroid stimulation has developed leading to parathyroid cell proliferation and thus parathyroid gland enlargement. Once the stimulus is removed, the parathyroids may return to their normal state.

Chronic stimulation of parathyroid tissue can occur from a diverse range of conditions with the most notable being chronic renal failure. Others include vitamin D deficiency, lithium therapy,10 intestinal malabsorption syndromes with inadequate absorption of vitamin D and calcium, heart failure, hypertension and long-term total parenteral nutrition (TPN).11 Depending on the stimulus and duration, secondary hyperparathyroidism can lead to states of normocalcaemia or hypercalcaemia.

#### Chronic renal failure

In all cases of chronic renal failure, there is a tendency for the kidneys to lose calcium in the urine and to retain phosphate. There is also reduced production of 1,25 dihydroxy cholecalciferol leading to reduced intestinal absorption of calcium.

In the early stages of renal failure, there is a tendency to low calcium and this subtle but persisting state leads to reduced numbers of calcium and vitamin D receptors on the parathyroid cells. This is at least partly responsible in a shifting of the CSR set-point to the right (i.e. higher levels of calcium are perceived as normal). This leads to reduced inhibition of PTH synthesis and secretion, and promotes parathyroid cell replication and thus multinodular hyperplasia, which is essentially present in all patients with chronic renal failure.12, 13 In addition, more severe secondary HPT is associated with nodular hyperplasia.12 Usually polyclonal expansion occurs, but occasionally a monoclonal population develops with the formation of an adenoma.

The increased phosphate burden further stimulates parathyroid proliferation. Also, the metabolic acidosis associated with renal failure has a direct effect on the calcium receptor to make it less responsive (i.e. less inhibitory) to PTH secretion.12

#### Vitamin D deficiency

Vitamin D deficiency is more common in dark-skinned races due to the reduced absorption of sunlight required to cause the formation of cholecalciferol. In Europe, Australia and New Zealand, the condition is most common in those of Asian origin. However, poor diet, malabsorption syndromes, gastric bypass surgery and medications, such as carbamazepine and phenytoin, may increase the risk. Typically, there is sufficient parathyroid stimulation to bring serum calcium into the normal range.

#### Lithium

The prevalence of HPT increases with duration of lithium therapy and has been assessed as being 6 per cent after 19 years.14 Also, there is less likelihood of reversal as the CSR set-point is raised.14, 15

The hyperparathyroidism induced by long-term lithium treatment is associated with unusual metabolic features: low urinary calcium excretion, absence of nephrolithiasis and normal urinary cyclic AMP excretion.16 In a 1977 study, Nielsen et al. noted that urinary calcium excretion fell by more than 30 per cent within the first week of therapy and remained low throughout the treatment period. This is thought to be due to an increase in fractional tubular reabsorption of calcium.17

#### TERTIARY HYPERPARATHYROIDISM

Tertiary HPT is simply refractory secondary HPT. In some cases of secondary HPT, the HPT can be reversed by calcitriol therapy. Other patients require pulsed intravenous calcitriol in pharmacological doses to normalize the calcium-sensing receptor set-point. However, in some, the set-point is irreversibly shifted to the right, such that there is reduced inhibition of PTH synthesis and secretion, as well as parathyroid cell proliferation.2

Tertiary HPT is typically confined to chronic renal failure, but by definition could perhaps also be considered present in HPT associated with any condition that fails to normalize upon withdrawal of the agent (e.g. lithium). In chronic kidney disease, it is present if the HPT is not reversed by a renal transplant and normalization of kidney function, but is also considered present in dialysis patients when the calcium/phosphate product exceeds 5 or PTH exceeds 100 pmol/L.

#### FAMILIAL HYPERPARATHYROIDISM

Familial or hereditary HPT is much less common than sporadic HPT, but exists in clearly defined syndromes with high penetrance (up to 95 per cent in MEN1). The early diagnosis of familial disease is important as the management differs from primary to secondary HPT. The genetic markers have engendered much interest and, while these conditions are rare, studies of the various family groups have enhanced our understanding of calcium homeostasis and of parathyroid hyperplastic/neoplastic states.18
The syndromal acronyms are FHH, ADMH, NSHPT, MEN1, MEN2a, HPT-JT, HPT-IF and are described below. The two landmark articles on these are Carling and Udelsman19 and Marx et al.20

Familial hypercalcaemic hypocalciuria (FHH), autosomal dominant mild hyperparathyroidism (ADMH), also known as familial hypercalcaemia with hypercalciuria, and neonatal severe HPT (NSHPT) are due to mutations in the calcium receptor set gene. The gene codes for the level at which the parathyroid cell calcium receptor responds to the ambient calcium. It is important to realize that normally the parathyroid cell is in a constant state of inhibition by its ambient calcium and elevation of the set-point at which parathyroid hormone is produced (reduced inhibition) leads to hypercalcaemia. Because of the altered set-point all three conditions have HPT at birth, with FHH and NSHPT representing opposite ends of the spectrum. FHH is heterozygous and associated with mild elevations in serum calcium and virtually no morbidity. The mild rise in serum calcium does not exceed the normal renal tubular reabsorption of calcium and therefore the urine has normal levels of calcium. ADMH produces higher levels of hypercalcaemia which exceeds the renal threshold and is associated with hypercalciuria and, in some cases, renal stones. NSHPT is homozygous and causes life-threatening hypercalcaemia requiring urgent intervention in the neonatal period. All three are non-neoplastic polyclonal parathyroid expansions and refractory to subtotal parathyroidectomy, although FHH requires no treatment.

The four other familial conditions are neoplastic and associated with a delayed age of onset for HPT (average age, 25–35 years). They are due to monoclonal or oligoclonal expansions within multiple parathyroid glands and therefore some can respond to less than total parathyroidectomy, although the long-term control is variable. In the case of MEN1 (formerly Werners) penetrance of the MEN1 gene mutation is high (95 per cent). Typically, these patients present with hypercalcaemia due to multigland HPT, but may also develop pancreatic and foregut carcinoids and pituitary tumours. Anything less than a subtotal parathyroidectomy is associated with high recurrence rates and many authors advocate total parathyroidectomy with autotransplantation. MEN2a (formerly Sipple’s) is associated with RET mutation (low penetrance, 20 per cent) and is dominated by the surveillance for and management of medullary thyroid carcinoma and pheochromocytoma. The usually mild hypercalcaemia may require no treatment or simply removal of enlarged gland(s).

The HPT-Jaw syndrome is a rare familial syndrome that is important for its association with parathyroid carcinoma (15 per cent) requiring a more aggressive surgical approach. The hypercalcaemia is severe.

The familial-isolated HPT (HPT-IF) syndrome combines several diagnoses and may have single or multiple gland disease.

TREATMENT POLICY

Decision-making in primary hyperparathyroidism

Primary hyperparathyroidism may be managed conservatively, medically or surgically and perhaps the most important management step is the decision as to the necessity of surgical intervention, although surgery is the only curative modality. In symptomatic patients, the decision to treat surgically is often straightforward as long as the patient is fit. If not, with concordant imaging suggesting a solitary parathyroid adenoma, local anaesthetic resection is feasible.

As the majority of newly diagnosed patients nowadays are asymptomatic, however, clinical observation is an option. The maintenance of a good state of hydration is advisable in these patients and thiazide diuretics should be avoided as they reduce calcium excretion.21 The avoidance of calcium in the diet is unnecessary as long as the serum vitamin D levels are not elevated as this does not alter urinary calcium excretion.22 In patients being treated conservatively, various drugs may to some extent control calcium and parathyroid hormone levels. Most frequently, bisphosphonates are prescribed as first-line treatment. They function by decreasing bone turnover and they also decrease serum and urinary calcium levels. Most recently, calcimimetic drugs, such as the second-generation cinacalcet, have gained in popularity. They rapidly bring about a decrease in serum PTH levels, but are expensive and currently unlicensed in primary hyperparathyroidism, although their use in renal failure patients is gaining in popularity. Oestrogen replacement therapy is also used in postmenopausal women with mild HPT, a therapy that is protective to bone density in both the lumbar vertebrae and the femoral neck.23 However, as many as 27 per cent of patients judged asymptomatic deteriorate over a ten-year period and end up requiring surgery.24 In an attempt to solve this dilemma, the National Institutes for Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases in 2002 recommended parathyroidectomy for asymptomatic patients in specific circumstances (Box 27.3).25 With this in mind, if the decision to adopt a watchful waiting approach is taken, annual serum calcium, PTH and renal function estimation, with interval bone densitometry evaluation is advisable, so that deterioration is picked up early.

Decision-making in familial hyperparathyroidism

Readers are referred to the excellent article by Carling and Udelsman19 on this specialized topic. One must remember

Box 27.3 NIH indications for parathyroidectomy in asymptomatic primary hyperparathyroidism

- Less then 50 years old
- Unable to be effectively followed up
- Serum calcium > 1.0 mg/dL above the normal range
- Urinary calcium > 400 mg/24 hours
- Thirty per cent decrease in renal function
- Complications of HPT: nephrocalcinosis, osteoporosis (T-score < -2.5 s.d. at lumbar spine, hip or wrist)
- Severe psychoneurologic disorder
that these patients are predisposed to persistent and recurrent HPT because of the persistence of parathyroid cell rests despite an apparently total (four gland) parathyroidectomy. The aims of surgery, therefore, include achieving and maintaining normocalcaemia for the longest time possible, avoiding iatrogenic hypocalcaemia and operative complications, and facilitating future surgery for recurrent disease.

**MEN1**

In this syndrome, the decision on timing of surgery can be difficult. While early intervention may avoid the long-term effects of hyperparathyroidism, it does expose the patient to the risk of recurrent HPT and of increasingly difficult revision surgeries at a younger age. Delaying surgery can allow the glands to become larger, thus facilitating the original surgery. Clearly, however, surgery is required when the effects of the disease are evident (osteoporosis, Zollinger–Ellison syndrome).

The initial surgical procedure should be either a subtotal procedure, leaving a remnant the size of a normal parathyroid gland (20–30 mg) or a total parathyroidectomy with autotransplantation of 20–30 mg of tissue. Both procedures require a meticulous search for ectopic parathyroid tissue and also a bilateral thymectomy not only to minimize the risk of persistence or recurrence of HPT, but also of thymic carcinoid tumours. Because of the fallibility of preserved and transplanted tissue and when the facilities allow, parathyroid tissue should also be cryopreserved for later transplantation if required.

**MEN2A**

The management of this condition is typically dominated by the management of medullary thyroid carcinoma. The HPT tends to be mild and occurs in only 20–30 per cent. It is usually diagnosed at the same time or after the thyroid malignancy. All grossly abnormal glands should be removed.

**Decision-making in secondary and tertiary hyperparathyroidism**

**RENAI**

Secondary HPT patients are more symptomatic than both primary and tertiary HPT, but most can be treated medically with phosphate binders, calcitriol and calcium supplementation. Medical treatment fails in about 5 per cent of patients and they become unsuppressible or autonomous requiring parathyroidectomy.  

The decision for parathyroid surgery in a renal failure patient with HPT is generally made by the renal physician to correct the biochemical abnormalities or the clinical symptoms or both. Bone pain and pruritus are likely to improve after surgery. Pruritus is one of the most disabling symptoms of secondary HPT and, although the pathophysiology is unclear, the reduction in PTH and the calcium/phosphate product must play a role. Vague symptoms, such as general muscle weakness and irritability, are improved after surgery for secondary HPT. Parathyroidectomy can also be effective treatment in the life-threatening situation of calciphylaxis. However, other vague symptoms, such as mood swings, depression, forgetfulness and fatigue, which can be expected to improve after surgery for primary HPT are variably ameliorated in patients with secondary HPT, presumably due to the continuing stimulation from chronic renal failure. Although these patients tend to improve with time, they remain symptomatic in some way, thus lowering quality of life. In tertiary HPT, where the renal failure has been corrected by transplantation, the symptomatic improvement is similar to that in the primary HPT patient.

The decision for surgery is based not only on symptoms, but also on the likelihood of calcium deposition in tissues. Deposition is likely to occur when the calcium/phosphate product exceeds 5 or when PTH reaches 100 pmol/L (normal, 1.7–7.3 pmol/L). Thus, uraemic patients in this situation are generally not put forward for renal transplantation until these parameters are improved, as the transplanted kidney is likely to fail. If oral or intravenous calcitriol is unsuccessful, then the patient is considered for parathyroidectomy. Similar parameters are used in post-transplant patients to avoid calcium deposition in the transplant.

The authors advocate total parathyroidectomy with autotransplantation of tissue into the forearm muscle or subcutaneous fat and with the cryopreservation of parathyroid tissue for subsequent grafting if the initial transplant fails. They argue that subtotal procedures may have higher rates of persistence and recurrence in a population in whom any parathyroid remnants retain an altered set-point and are therefore programmed to expand and hypersecrete. When the facilities are available, cryopreservation of surplus parathyroid tissue should proceed.

Others experienced in subtotal parathyroidectomy argue that the risk of recurrence is small and that permanent hypoparathyroidism and the long-term requirement for calcium and calcitriol should be avoided in the haemodialysis patient who is subject to potentially sudden changes in serum calcium without any functioning parathyroid reserve. The vascularized parathyroid remnant resulting from subtotal parathyroidectomy is variably defined. Some advocate leaving half of the most normal gland. However, Milas and Weber comment that ‘even leaving half’ of a typically large parathyroid gland found in patients with renal disease ‘preserves abnormal amounts of hyperfunctioning tissue’. They aim to leave a segment equal to approximately two normal parathyroid glands or approximately a 10 × 5 × 3 mm segment which they define as ‘near-total parathyroidectomy’. With this approach, these authors report a 4 per cent rate of persistent HPT and 4 per cent recurrence.

**LITHIUM**

In a study of 15 patients undergoing parathyroidectomy for lithium-induced HPT, 14 (92 per cent) had adenomas (11 single, 3 double), and one (8 per cent) had four-gland hyperplasia. In contrast, another study using intraoperative PTH (ioPTH) measurement to assess adequacy of resection in 12 patients, found that half had multifocal disease. Mean ioPTH decrease from baseline following gland resection was 74 ± 4 per cent. Although 10 of 12 patients met criteria for curative resection, only eight remained...
normocalcaemic. The other two patients, who did not meet criteria, remained normocalcaemic. Of the ten normocalcaemic patients, four had persistent elevation of PTH. The authors concluded that the incidence of multiglandular disease in lithium-induced HPT is higher than with standard HPT. They also concluded that ioPTH had a limited role in predicting durable normocalcaemia, and that bilateral neck exploration should be considered for these patients.33

In a group of 11 patients operated on by a Sydney group, a single adenoma was identified in six patients and multiglandular disease in five. All subsequently resumed lithium with one developing recurrent HPT at three years, while another after one year had increased PTH, but was normocalcaemic. They concluded that bilateral neck exploration should be performed routinely because of a relatively high frequency of multiglandular involvement, but that parathyroid resection should be limited to evident disease.34

PARATHYROID LOCALIZATION

Preoperative localization techniques

Until recently, preoperative parathyroid localization techniques were employed predominantly when an initial exploration had failed to identify a parathyroid adenoma. However, with the increasing popularity of day-case parathyroidectomy, minimally invasive parathyroidectomy (MIP), targeted resection and parathyroidectomy under local anaesthesia, preoperative localization techniques are more commonly used prior to initial neck exploration. Their routine role still remains controversial as they add both time and expense to overall patient management and many point out that an experienced parathyroid surgeon will cure 95 per cent of patients without the benefit of preoperative localization, while the most accurate localization techniques will only identify 80 per cent of parathyroid tumours at best. Proponents of localization argue that reoperative parathyroid surgery can result in recurrent laryngeal nerve palsy rates of up to 7 per cent, and successful preoperative localization brings surgical success rates at initial exploration close to 100 per cent.35

SCINTIGRAPHY

Many imaging techniques have been tried in an attempt to improve parathyroid localization. Currently, nuclear scintigraphy is seen as the most accurate localization technique. Although subtraction imaging using technetium Tc99m sestamibi or used alone in a ‘double-phase scan’ where the scan is repeated at 2–3 hours gives the best results (Figure 27.1).36, 37 The double-phase method relies on the differential washout rate of sestamibi from parathyroid tissue compared to thyroid tissue, due to the high metabolic rate of the parathyroids, particularly when adenomatous. Of the two technetium techniques, the subtraction technique is currently superior localizing solitary adenomata in 95 per cent of cases, and multigland disease in 80 per cent.38

ULTRASONOGRAPHY

Ultrasonography is also a frequently employed imaging modality when localizing parathyroid glands. Results are operator dependent, but in the best hands, solitary adenomas can be identified in 93 per cent of cases using colour Doppler.39 Ultrasound is of limited value when glands are ectopic, particularly when they are located in the mediastinum. In ectopia, nuclear scintigraphy may also be less effective as it provides a planar image and the localization of abnormal glands may be hampered by overlying structures, particularly when the lesion is below the clavicles. Under these circumstances, three-dimensional imaging techniques, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET) with either (18F)-fluoro-2-deoxy-D-glucose or (11C)-methionine are useful.

COMPUTED TOMOGRAPHY/MAGNETIC RESONANCE IMAGING

T2-weighted magnetic resonance imaging (MRI) with gadoxetate disodium is a useful investigative tool, particularly when other tests have failed or following unsuccessful exploration. It has been shown to be more sensitive than contrast-enhanced computed tomography (CT).

VENOUS SAMPLING

Rarely, when planning revision surgery and when less invasive imaging and localization techniques have failed, venous sampling is employed. This involves femoral vein catheterization and the collection of blood samples from the draining veins of the thyroid plexus (high internal jugular, low internal
jugular, brachiocephalic and subclavian from each side) and the superior vena cava. Intact PTH assays are measured from each sample and a plot of venous PTH:peripheral blood (control) PTH is tabulated. A ratio of two or greater is seen as significant. Using this technique, hyperfunctioning gland position can be predicted with 86 per cent specificity and 95 per cent sensitivity. Interpretation of results is hampered somewhat by the knowledge that the middle and inferior thyroid veins may have been ligated during the previous procedure(s). Nevertheless, it can be useful in localizing the rogue gland(s) and determining whether it is higher or lower in the neck or likely to be in the superior mediastinum.

When planning targeted parathyroidectomy, the surgeon will normally only proceed if a technetium Tc99m sestamibi scan is concordant with a high resolution ultrasound scan in localizing the parathyroid tumour. A successful resection can be effectively confirmed with the use of ioPTH, although if preoperative concordant double imaging suggests a solitary adenoma some would argue that this test is unnecessary.

**Intraoperative localization techniques**

Parathyroid localization may be further enhanced intraoperatively by the use of the gamma probe. First described as a technique useful in both gland ectopia and hyperplasia in 1995, it depends on the identification by a gamma probe of a radioisotope injected preoperatively and selectively concentrated within parathyroid tissue. Technetium 99m sestamibi tends to be the isotope of choice. The procedure depends on strict timing between radioisotope injection and time of surgery, and although not in widespread use has certainly gained some acceptance in MIP.

**METHYLENE BLUE**

The other intraoperative localization technique employed by some parathyroid surgeons is the use of intravenous methylene blue. This involves the preoperative intravenous administration of 5 mg/kg methylene blue in saline. The dye is preferentially taken up by the parathyroids particularly when adenomatous or hyperplastic, hence making their identification easier. Again, timing of infusion to surgery is crucial. The patient’s skin will have a blue hue for a few days following surgery, and there may be some nausea.

**SURGICAL ANATOMY**

Parathyroid glands are simply called ‘parathyroid’, because they are ‘next to’ the thyroid gland (Greek, para beside). They develop at weeks 5 to 6 in utero from the endoderm of the third and fourth pharyngeal pouches. There are usually two parathyroid glands on each side, a superior and an inferior, although in a series of 547 autopsies Gilmour demonstrated that 87 per cent of patients have four parathyroid glands, 6 per cent three and 6 per cent five.

The superior glands develop from the fourth pouch with the ultimobranchial bodies which form part of the lateral thyroid. Their descent in the neck is more limited and their position therefore more constant than their inferior counterparts. The superior glands lie in a plane deep to the recurrent laryngeal nerve, but during exploration their position will generally be effectively inverted by retracting the thyroid lobe medially and ‘out’ of the neck, so that it lies on top of the trachea and its dorsal aspect can be properly inspected. In 80 per cent of cases, therefore, the superior gland is visualized on or just above the recurrent laryngeal nerve at the junction of the middle third and upper third of the thyroid lobe. It is extremely unusual for a normally situated superior gland to lie below the main branch of the inferior thyroid artery, a fact useful in preoperative parathyroid localization. In ectopia, the superior gland may lie in the retro-oesophageal or retropharyngeal gutter having descended posteriomedial to the nerve. This is purely a pulsion effect due to deglutition forcing the enlarging tumour in the direction of least resistance and, in extreme cases, a superior adenoma may be found in the posterior mediastinum.

Due to their joint origin with the ultimobranchial bodies, the superior glands are more likely to become truly intrathyroidal, although inferior parathyroids have certainly been reported within the thyroid parenchyma. In addition, because of the variability in superior and inferior parathyroid development and descent, the relative positions of the parathyroid glands are occasionally reversed, i.e. the superior gland (parathyroid IV) may be more caudal than the inferior gland (parathyroid III). It is probably for this reason that some authors claim that intrathyroidal parathyroids represent ectopic superior glands, while others consider them to represent aberrant inferior glands.

The inferior parathyroids develop together with the thymus from the third pouch. Therefore, during the embryonic descent of the thymus, the inferior parathyroid is usually carried more caudal than the superior gland. The vast majority settle in the neck along this line of descent and separate somewhat from the thymus which continues into the chest leaving a thyrothymic tract in the neck in which the parathyroid is frequently situated. Most frequently located in a position caudal to the inferior aspect of the thyroid lobe, the inferior parathyroids lie in a plane superficial to the recurrent laryngeal nerve. In ectopia, their position is far more variable than the superior glands. They may be discovered as high as the carotid bifurcation and be associated with failure of thymic descent, or they may be more caudal than normal either lying within the substance of the normally situated thymus or more inferior, in the anterior or, more rarely, the posterior mediastinum. They may also be found within the carotid sheath. In 80 per cent of cases, the position of both the superior and inferior glands on each side is symmetrical, a fact that can be useful when a gland is proving hard to locate.

Finally, as the inferior parathyroids normally cross the position of the superior parathyroids during their developmental descent, both sets of glands may be extremely closely related. Therefore, a bilobed gland may be mistaken for two glands and vice versa.

The weight of a normal parathyroid gland may be 10–100 g with an average of 35–40 mg and the combined weight of parathyroid tissue averages 118 mg in men and 131 mg in women. They tend to be larger in those of AfroCaribbean origin, and increase in size with age up to the third and fourth decade. Fat content is highly variable and
unevenly distributed throughout the gland. When stimulated, parathyroid glands enlarge and their fat content decreases.

**SURGICAL PATHOLOGY**

The most common parathyroid tumour, the benign solitary adenoma, occurs with equal frequency in the superior and inferior glands. A parathyroid adenoma macroscopically appears as an encapsulated tumour which is brown in colour, and normally of a darker shade than the other macroscopically normal glands. During exploration, a parathyroid gland is normally easily differentiated from surrounding structures as it is palpably much softer than thyroid tissue or lymph nodes. It is normally approximately 5–7 mm in its maximal dimension, elliptical in shape, brownish in colour and with fine tortuous vessels on its surface. The normal parathyroid is often within, or surrounded by, a layer of fatty tissue which tends to disappear if the gland becomes adenomatous. When traumatized, a parathyroid gland will bleed freely.

Microscopically, the adenomatous portion of an affected gland is normally made up predominantly of chief cells, although rarely the tumour may consist entirely of water-clear cells. There is a suppressed rim of normal parathyroid tissue around part of the periphery of the tumour, and this is often helpful in differentiating an adenomatous gland from a hyperplastic gland, a distinction that is not always clear cut. For the diagnosis of adenoma to be reliably made and hyperplasia excluded, a biopsy of a second histologically normal gland is generally required.

Chief cell hyperplasia causes approximately 15 per cent of all primary hyperparathyroidism. This condition is a polyclonal cellular expansion resulting in proliferation of chief cells, oncocyes and transitional oncocyes in all glands, hence differing from the monoclonal expansion typical of parathyroid adenoma. Eighty per cent of hyperplasia is sporadic and 20 per cent familial, related to either familial hyperparathyroidism or a multiple endocrine neoplasia syndrome. In extremely rare instances, primary clear cell hyperplasia, which is never familial, may occur.

**INTRAOPERATIVE PTH MONITORING**

In 1987, the development of a two-site immunochemiluminescent assay for human PTH paved the way for intraoperative PTH monitoring (ioPTH) as a reliable indicator of success during parathyroidectomy. The half-life of PTH is approximately 3–5 minutes and the assay measures the intact PTH molecule with no reaction to PTH fragments, hence avoiding erroneously elevated results of earlier assays. Modifications to the assay procedure have resulted in an approximate turnaround time of 10 minutes, making intraoperative PTH monitoring a realistically useful tool, particularly in minimal access, localized and day-case resections.

The procedure of ioPTH varies slightly from centre to centre depending on the specifics of the immunoassay employed and local experience. An initial baseline blood sample is taken. This ideally is prior to the commencement of surgery (T-0), because it is recognized that manipulation of parathyroid glands intraoperatively can lead to spikes in PTH. Further samples are then taken at 5 (T-5) and 10 (T-10) minutes after removal of each gland. Operative success is predicted if either the T-5 or T-10 sample demonstrates a PTH level 50 per cent or greater below the T-0 level. The procedure indicates long-term operative success with about 95 per cent accuracy in single gland disease. However, the results in multigland disease are less reliable with false-positive decreases occurring in as many as 75 per cent of patients. In addition, recent work suggests that false-positive results, when followed up in the long term, may indicate germline mutations in the gene for multiple endocrine neoplasia, and genetic analysis of these patients is important.

The role of ioPTH in secondary and tertiary HPT is less clear cut. In renal disease, the half-life of PTH is lengthened and there is very little long-term evidence of the predictive capabilities of ioPTH. However, short-term studies suggest that using ioPTH in a similar manner to how it is used in primary HPT is useful. In addition, most work focuses on near total parathyroidectomy, or total parathyroidectomy with reimplantation. This, added to the fact that rests of parathyroid tissue when chronically stimulated by, in most instances, renal failure, can become autonomous, makes it impossible to accurately predict the completeness of the parathyroidectomy. However, recent work suggests that in total parathyroidectomy ioPTH predicts control of hyperparathyroidism, but fails to predict persistent hypoparathyroidism.

Although ioPTH has many advantages, the procedure is expensive. In many institutions, therefore, its use remains controversial and without significant cost decreases is unlikely to become uniform.

**SURGICAL TREATMENT OF PRIMARY HYPERPARATHYROIDISM**

Once the decision to operate has been made, the type of operation should be determined. In primary HPT, this decision will depend upon both the wishes of the patient and the abilities of the operating surgeon. In 80 per cent of cases, the causative lesion is a solitary parathyroid adenoma, and successful preoperative localization of such a lesion enables the surgeon to offer minimally invasive parathyroidectomy using a targeted approach. In this circumstance, parathyroidectomy under local anaesthesia is possible. The other option is the traditional four-gland exploration involving a bilateral dissection and ideally visualization of all four parathyroid glands. During this operation, the glands judged macroscopically normal are generally marked with a liga clip, and the macroscopically abnormal gland(s) removed and sent for histology. The procedure is often enhanced by intraoperative frozen section and ioPTH, the latter procedure to confirm cure following a successful dissection, or to point to the need for further exploration. Both the targeted approach and the four-gland exploration are performed endoscopically in some centres.

In 15–20 per cent of cases, HPT is caused by parathyroid hyperplasia which may be genetically predetermined. Here,
Preoperative imaging is far less effective at localizing the causative pathology and a four-gland exploration is generally appropriate. In 80 per cent of hyperplastic patients, the condition is non-familial. In this situation, a subtotal resection removing three and a half glands and leaving approximately 30–50 mg of functional tissue is the best approach as this minimizes the risk of recurrence and the need for reoperation, while preserving parathyroid function.

The technique of parathyroidectomy

FOUR-GLAND EXPLORATION

Although we have mentioned other options, the open four-gland exploration remains the most common parathyroidectomy technique.

In this ‘search and destroy’ mission, the surgeon requires an orderly and thorough approach and an understanding of the unusual positions of enlarged parathyroids.

The principles

- Dissection should be as bloodless as possible.
- The superior gland is more constant and should be identified first.
- An enlarged parathyroid is easier to identify than a suppressed normal gland.
- Variability in development means that the relative positions of the parathyroids may be reversed, i.e. a missing superior parathyroid may be caudal to an already identified inferior gland and a missing inferior parathyroid more cephalad to the superior gland.
- If an adenoma is identified and not all parathyroids found, thymic delivery can be selective and it is not necessary to remove thyroid tissue.

With the patient in a supine position, and with approximately 30° of reverse Trendelenberg to decrease venous engorgement in the neck, the neck is extended where possible by appropriate placement of a head ring and sandbag. The approach is via a standard Kocher incision that is designed to lie within Langers lines, and is situated midway between the cricoid cartilage and the jugular notch. The incision level is best marked preoperatively with the conscious patient sat in a neutral position. The incision need only be 5 cm in length in most instances. The incision continues through the platysma to the level of the superficial layer of strap muscles and the superior myocutaneous flap is then raised to a level at least 2 cm above the cricoid cartilage. The inferior flap rarely requires raising. The linea alba is then identified and the strap muscles separated. Whether the surgeon goes medial or lateral to the straps is determined by preference, but the lateral approach requires less dissection and is preferred by some.

THE MEDIAL APPROACH

The linea alba is more easily identified caudally as the central straps tend to separate to some extent inferiorly. The procedure then involves peeling the straps off the ventral surface of one of the thyroid lobes, a relatively bloodless procedure which is kept dry by medial retraction on the thyroid lobe and lateral retraction on the straps minimizing the need for sharp dissection. The middle thyroid vein, when present, is then identified and ligated/divided. It is important at this stage to visualize the ventrocaudal surface of the thyroid for the rare ventrally placed parathyroid. The procedure then involves the separation of the thyroid lobe from the many fine fibrous bands that maintain it in its anatomical position. This process is greatly facilitated by medial digital retraction of the thyroid lobe, attempting to mobilize the lobe both medially and upwards out of the tracheo-oesophageal groove and on to the trachea. Simultaneously, the strap muscles are retracted laterally to keep the fibrous bands under tension. Fibrous tissue should divide easily in a previously unexplored neck, and when this does not happen this is because the structure is in fact a small blood vessel under tension and these must be diathermized rather than cut, as the maintenance of a bloodless field is vitally important for successful parathyroid identification. Once the thyroid lobe has been mobilized on to the trachea, it is often held in place by retracting a stay suture placed through it. With simultaneous lateral retraction of the strap muscles, the search for the parathyroid glands can begin.

THE LATERAL APPROACH

A subplatysmal plane is elevated from the thyroid notch above to the sternal notch below and to the medial border of sternomastoid on each side. The lateral approach involves separating the fascia between the sternomastoid and the strap muscles and identification of the carotid sheath more deeply. The omohyoid may require division for optimal exposure. The sternomastoid is retracted laterally and the medial border of the carotid sheath is then easily dissected from the level of the superior pole inferiorly to the level of the inferior thyroid artery. This gives an excellent view of the posterior aspect of the thyroid and the tracheo-oesophageal groove. During the subsequent parathyroid search, if greater exposure is required, it is a simple matter to divide the overlying sternothyroid muscle which gives the same exposure as the medial approach (Figure 27.2).

BASIC SEARCH FOR THE SUPERIOR GLAND

The inferior thyroid artery is readily identified deep to the carotid sheath usually around the mid-part of the thyroid lobe and followed bluntly to the thyroid lobe. The recurrent laryngeal nerve is identified (see Thyroidectomy chapter). An enlarged superior gland often descends in the space behind the thyroid lobe and oesophagus and deep to the recurrent laryngeal nerve and inferior thyroid artery. Therefore, the initial inspection of this potential space (retro-thyroid/oesophageal) will frequently expose the adenoma. Should this space be empty then a more thorough dissection is employed on the posterior surface of the superior pole with the knowledge that the vast majority of superior parathyroids are within 1 cm of the cricothyroid joint. The next step is further exploration of the recurrent laryngeal nerve which is gently explored including deeply up to the cricothyroid joint. Not only does this decrease the risk to the nerve, but also the
nerve is a good constant landmark for identification of the superior parathyroid position, and the plane of both superior and inferior glands (Figure 27.3). In most instances, the superior gland will be within a fat lobule in the position described. This position is often nicely demonstrated by palpating the area with a pledget and demonstrating differential movement of a subtly darker body within the fat, often with a small vessel on its surface. Blunt dissection is employed with pledgets, mosquito forceps and bipolar diathermy division of fine vessels. Usually at this stage the surgeon will have either discovered the adenoma or a normal parathyroid gland, and a liga clip is applied. If not, the inferior gland is then sought.

BASIC SEARCH FOR THE INFERIOR GLAND

Inferior dissection proceeds with mobilization of the inferior pole and inspection particularly in the region of the thyrothymic tract. The inferior gland normally lies on or just below the inferior pole of the thyroid lobe as described, although it is ventral to the coronal plane of the recurrent nerve (Figure 27.4). For this reason, excision of an inferior adenoma can often be safely achieved without recurrent nerve identification, as long as the dissection, often with bipolar diathermy forceps, proceeds directly on the surface of the gland.

As the search continues, the tracheo-oesophageal groove is explored deep to the nerve. The examination of this area continues down to the sternal notch. Usually at this stage, both parathyroids will have been exposed, but not always. A small suppressed gland in a normal location may not be obvious, and a normal gland or an adenoma may be present in the thymus, mediastinum, thyroid or an unusual neck location. Rather than continue with further dissection that may devascularize a normal parathyroid, the surgeon proceeds to the opposite side employing the same orderly sequence of dissection and inspection.

FURTHER SEARCH STRATEGIES

After this initial bilateral exploration, in the vast majority of cases an adenoma will have been discovered and no further dissection is considered necessary even if one or more parathyroids remain hidden. The rationale for this is that a thorough exploration has been performed in all areas bar the thymus, the thyroid gland and unusual locations, such as lateral to the carotid sheath, the wall of the pyriform fossa,
elsewhere in the neck and mediastinum. The return from further dissection is likely to be small with the added risk of devascularizing a small normal parathyroid. On the other hand, if this initial exploration fails to yield an adenoma, further ordered exploration is necessary, stopping when the adenoma is found. The direction of dissection is determined by what has been found already, but the surgeon must remember that the relative positions of the glands may be reversed.

A missing superior gland is sought around the cricothyroid joint, in the retropharyngeal space down into the posterior mediastinum, on the pharyngeal musculature which is easily separated from underlying mucosa by forceps dissection, and posteromedial to the superior thyroid pedicle back to the carotid sheath and carotid bifurcation. The thyroid should also be suspected.

A missing inferior gland is sought in the thymus, the thyroid and the carotid sheath.

**THYMIC EXPLORATION**

The thyrothymic tract is followed inferiorly on one side and the thymus gently teased into the neck by dividing the fascial capsule, clamping forceps to the thymic tissue and applying gentle traction. Small gains are accepted before the forceps are reapplied to the thymus more inferiorly. This in turn is put under tension, further fascia divided, small vessels ligated, and the thymus gently lifted further into the neck. The sequence of small gains and reapplication of forceps is continued until the thyric remnant on that side of the neck is delivered (Figures 27.5 and 27.6). If the adenoma is found on one side of the thyric remnant and the opposite inferior parathyroid has not been identified, the opposite side of the thymus should be explored (80 per cent rule).

**THYROID EXPLORATION**

Exploration of the thyroid lobe includes first a reassessment to determine that all fascia has been cleared from the posterior aspect of the thyroid gland. Often a parathyroid may be subcapsular, but not truly intraglandular. Such glands may not be readily identifiable, but the bruising consequent to the initial dissection may highlight the colour and textural differences between thyroid and parathyroid tissue. The parathyroid gland may appear more brownish, reddish, blue or black (from venous congestion). Before proceeding to remove thyroid tissue, if possible the respective internal jugular veins (IJV) should be sampled for ioPTH to give an indication of which side of the neck the adenoma resides. While awaiting the assay, the surgeon should re-examine the retropharyngeal region from the hyoid level to the superior mediastinum and similarly, the carotid sheaths. The entire cervical course of the recurrent laryngeal nerve, and tissue deep to it, must be gently exposed bilaterally.

The ioPTH determines which side of the thyroid to explore and if none is available, it is the surgeon’s choice. An infra-thyroidal parathyroid is typically in the lower pole and excision of either the entire lobe or the lower two-thirds suffices. The excised thyroid tissue is then finely diced on a side table to determine whether a parathyroid adenoma is present.

**ACCEPTING FAILURE**

In the event of no adenoma being found after the initial bilateral exploration, bilateral thymic delivery and a unilateral total or subtotal lobectomy, the authors do not advocate contralateral lobectomy without definite evidence of a hidden adenoma. The wound is washed and closed with the expectation that the rogue gland is hidden deeper in the mediastinum. Imaging studies and a targeted revision procedure are likely required.

**MINIMAL ACCESS PARATHYROIDECTOMY/VIDEO-ASSISTED/LAPAROSCOPIC PARATHYROIDECTOMY**

Although the first parathyroidectomy, carried out in 1925, was under local anaesthesia, until recently the majority of procedures have been formal four-gland explorations under general anaesthesia. However, the development of ioPTH, the gamma probe and preoperative localization techniques have
paved the way for novel surgical approaches aimed at minimizing inpatient stay and patient discomfort. This is particularly so as the predominant pathological cause of primary HPT is the solitary adenoma, and hyperplasia is being recognized as an increasingly rarer entity than was first believed.

Minimal access techniques which may be laparoscopic, video-assisted or without endoscopic enhancement normally depend on accurate preoperative localization with technetium 99m sestamibi with or without the additional use of ultrasound to localize the solitary parathyroid tumour. With accurate localization, unilateral explorations and single-gland targeted excisions through incisions of 1.5 cm become realistic options. In some institutions, minimal access video-assisted parathyroidectomy enables a bilateral four-gland exploration through a single medial horizontal 1.5 cm incision. These advances have paved the way to local anaesthetic outpatient procedures producing comparable results to the traditional four-gland technique, although patient selection criteria must be firmly established for such cases and patient suitability varies from 96 to 60 per cent depending on the reporting institution.

### AUTOTRANSPLANTATION OF PARATHYROID TISSUE

To avoid the long-term consequences of hypoparathyroidism, whenever parathyroidism is considered possible after the operation, immediate parathyroid autotransplantation should occur. Some authors will routinely cryopreserve parathyroid tissue, for subsequent autotransplantation if necessary, in all patients who undergo initial neck surgery for multigland hyperplasia and those who undergo reoperation for persistent or recurrent disease.

#### Normal parathyroid

One intact parathyroid gland is all that is required to maintain calcium homeostasis. It follows that normocalcaemia can be achieved by the presence of an equivalent volume of parathyroid tissue even if in separate locations. Because the autotransplantation of a diced normal parathyroid into a vascular bed of connective tissue leads to a variable survival rate, to maximize the number of surviving parathyroid cells, any normal but devascularized parathyroid gland should be reimplemented.

The implanted cells are then under the same feedback mechanisms as they were in an intact gland. If there is initially a reduced take, one could expect that the resultant hypocalcaemia would lead to increased parathyroid cell growth, increased PTH production and increased secretion. However, in the postoperative setting, patients are not left to become hypocalcaemic. The best approach would seem to be to keep the serum calcium in the low–normal range so that there is a continuing stimulation.

#### Hyperplastic tissue

Autotransplantation of parathyroid cells in this situation differs from the above in that these cells are genetically altered to have fewer CSRs and generally also have elevated set-points. They are therefore predetermined to proliferate and to secrete a greater than normal amount of PTH for a given calcium level. They are well suited for autotransplantation.

It is recommended that approximately 60 mg of diced hyperplastic parathyroid (15–20 1-mm³ cubes) be implanted into muscle. Others advocate 30 fragments, aiming to approximate two to three normal parathyroid glands. Transplantation may be into the non-dominant brachioradialis for ease of access and facilitation of postoperative monitoring, or into the sternomastoid or deltoid. The transplantation site is marked with three liga clips orientated at 90° to one another.

Success rates are in the order of 30 per cent complete, 20 per cent partial, 40 per cent failure, 7 per cent hypercalcaemia, regardless of whether the autotransplantation is done immediately or subsequently with cryopreserved tissue. These rates remain unchanged with subsequent autotransplantation of cryopreserved tissue after an initial failure and appear to be independent of operator experience.

Recent studies suggest that implantation into subcutaneous fat is as reliable and is certainly easier to do.

### CRYOPRESERVATION

Cryopreservation must be determined prior to surgery and scheduled with the regional tissue bank which will have a strict protocol.

As the parathyroid will be stored in a freezer along with other quarantined tissue, the tissue bank will require notification of any infectious disease (AIDS, hepatitis B, hepatitis C) and the risk profile for such diseases, for example, intravenous drug user, clotting disorder, risk profile for Creutzfeldt–Jakob disease (CJD). Prior to the surgery, a questionnaire must be completed by the patient concerning the risk profile and also consent for the disposal of unwanted tissue.

The tissue bank provides small vials on ice, containing cold parathyroid medium to transport the tissue. Prior to removal of the gland for autotransplantation, the surgeon may wish to confirm that it is indeed parathyroid tissue with frozen section. If not, a small piece should still be sent in formalin to confirm its nature.

Once removed, the gland is cut into approximately 1-mm³ pieces and separated into a small number of the containers. Two 10 mL clotted blood samples for routine infectious screening are required, again because the tissue will be alongside other quarantined tissue. The containers are transferred to the tissue bank where they are placed in a controlled rate freezer, dropping the temperature 1°C per minute down to −140°C. Thereafter they are stored at −180°C in liquid nitrogen for a determined period (usually three months). If stored beyond six months, a follow-up blood sample for infectious screening is required, again to assess infectious risk.

Should the tissue be required, it is thawed by the tissue bank by placing the containers in a 37°C waterbath and gently agitating till thawed. The tissue is then washed repeatedly with a specific medium, resuspended in saline and transported to the surgeon for reimplantation.
POSTOPERATIVE HYPOCALCAEMIA

Symptoms of postoperative hypocalcaemia may develop due to a number of factors, as follows.

Temporary threshold shift

Patients with long-standing HPT, particularly with severe hypercalcaemia, may develop symptoms of hypocalcaemia even when the postoperative calcium is within the normal range presumably due to a temporary shift in what is perceived to be an optimal calcium level by nerves and muscles.

Hungry bone syndrome

Long-standing HPT causes a chronic stimulation of osteoclastic release of calcium from the skeleton. Removal of the source of elevated PTH brings about a sudden change in bone metabolism with increased calcium uptake into the skeleton leading to serum hypocalcaemia, but normal to high normal PTH levels.

Temporary hypoparathyroidism

Temporary hypoparathyroidism occurs due to manipulation and subsequent hypofunction of already suppressed parathyroid tissue leading to hypocalcaemia. In this era of miniparathyroid operations for primary HPT where dissection is confined to the adenomatous gland, injury to the other parathyroids and subsequent temporary HPT is much less frequent.

Permanent hypoparathyroidism

This can occur where a bilateral operation (single or staged) has removed or destroyed more than three parathyroid glands. In primary HPT, it is obviously more common in revision procedures where the adenoma may be the sole parathyroid remnant following earlier unsuccessful procedures. In tertiary HPT, permanent hypoparathyroidism is the aim of total parathyroidectomy (but not of subtotal).

MANAGEMENT OF POSTOPERATIVE CALCIUM LEVELS

Generally speaking, only symptomatic hypocalcaemia is treated. For those patients with an apparent threshold shift, the symptoms tend to resolve after a day or so. Either no treatment or oral calcium supplements for a week will suffice.

Hypocalcaemia whether from hungry bone syndrome or temporary hypoparathyroidism usually only lasts for days or weeks. In mild cases, calcium supplementation alone resolves symptoms, although more severe cases require calcitriol in addition.

The most complex patients to manage are those following parathyroidectomy for tertiary HPT. These cases have a threshold shift, hungry bones, permanent hypoparathyroidism and frequently autotransplanted tissue with an altered set-point.

Hypoparathyroidism is considered permanent to some degree when calcium and/or vitamin D supplementation is still required at three months.

PROTOCOL

Miniparathyroid surgery

A baseline calcium and PTH level is taken at the completion of parathyroid surgery. Further blood samples are taken according to patient symptoms. Generally, a further sample is taken the following morning either as an outpatient or inpatient.

Bilateral exploration or revision parathyroidectomy

Where there is the possibility of permanent hypoparathyroidism, serum calcium and perhaps also PTH is checked again approximately 12-hourly or twice daily. It is the trend in serum calcium that indicates the likely course of action. An initial low postoperative result may be due to dilutional effects and a further sample 6 hours later will determine whether there is a trend downwards or not. In the modern climate of day-stay and short-stay surgery, a downward trend is best managed with supplementation for a week or longer with twice weekly calcium checks. Treatment can be with oral calcium alone (1 g three times a day or 2 g twice a day) if the calcium level hovers around 2 mmol/L and above, otherwise calcitriol is added. Typically calcitriol 0.25 μg twice a day will control most, but some patients require 0.5 μg twice a day (occasionally, even more frequently).

Surgery for tertiary HPT

These complex patients are best managed on a renal ward in the perioperative period with regular input by the surgical team. On the night prior to surgery, to minimize the expected drop in serum calcium, these patients are admitted and given oral calcitriol 2 μg.

At the completion of surgery, blood should be taken for serum calcium and PTH with treatment dictated by the former. In this situation, intraoperative PTH is less reliable in assessing whether there has been complete removal of parathyroid tissue primarily because of the high initial PTH values. These are often in excess of 100 pmol/L (normal, 1.1–6.8) meaning that five half-lives or approximately 25 minutes is required before the second sample can be taken. Then there is the wait for the assay, meaning a total waiting time of 45–60 minutes. While tempting, a second sample taken after just one half-life may yield a halving of the initial PTH value yet the PTH fail to normalize due to a persisting hyperplastic parathyroid.

Following surgery and after confirmation of an aparathyroid patient, oral calcitriol 2 μg twice a day and calcium
Severe hypercalcaemia is a rare but life-threatening complication of hyperparathyroidism. As the calcium level rises, the patient complains of thirst and polyuria with general malaise. However, as the condition worsens, the patient becomes gradually more confused and the conscious level decreases, finally resulting in coma. In this rare situation, acute medical intervention is necessary to prevent death and enable the underlying diagnosis to be confirmed and treated. As a rule of thumb, a patient with an adjusted serum calcium of 3.50 mmol/L or greater should be considered a metabolic emergency.

The first treatment step should be to rehydrate the patient with isotonic saline. This will increase glomerular filtration rate and reduce sodium and hence calcium reabsorption. Serum calcium levels will also reduce due to the dilutional effect. Patients will symptomatically improve, but the effect will be short-lived. The addition of loop diuretics once rehydration has occurred can increase the rate of urinary calcium excretion, however, this must be done with care as not to exacerbate dehydration.

Second-line therapy includes the use of calcitonin due to its inhibitory effect on osteoclasts. An initial rapid decrease in serum calcium may be achieved, but this is only maintained for up to 72 hours. Glucocorticoids are also used as they inhibit vitamin D conversion to calcitriol. In rare instances, mithramycin, which is cytotoxic to osteoclasts and gallium nitrate, which inhibits osteoclast action, are used. However, bisphosphonates provide the mainstay drug therapy for the management of severe hypercalcaemia. They decrease osteoclastic bone resorption and, although their speed of onset is slower than some other therapies, their duration of action is longer, the effect of pamidronate lasting a mean 28 days. Because of their relatively slower speed of action, many advocate simultaneous bisphosphonate and calcitonin therapy.

**MANAGEMENT OF ACUTE HYPERCALCAEMIA**

1 g twice a day is continued. Serum calcium is checked 6 hours after surgery. A calcium infusion is required if serum calcium is less than 1.9 mmol/L and the oral doses may also require an increase. Regular serum checks continue.

Where autotransplantation has occurred and following discharge, serum calcium and PTH is checked twice weekly with the expectation that transplanted tissue will resume function 3–4 weeks post-surgery. Approximately 30 per cent of these patients will ultimately maintain a normal calcium level without supplementation, 20 per cent will continue to require some supplementation and 7 per cent will overproduce.

**SURGICAL FAILURE AND REOPERATIVE PARATHYROID SURGERY**

The reasons for surgical failure in order of frequency are: inadequate cervical exploration, failure to diagnose or adequately resect multigland disease, gland ectopia and wrong diagnosis. It is vitally important to maximize surgical success rates at first operation, because surgical risks increase with further surgery. In addition, revision parathyroidectomy is less successful than first surgery with success rates ranging from 65 to 98 per cent.

When failure occurs, the first step is to reconfirm the diagnosis. Other potential diagnoses, in particular FHH, pseudohyperparathyroidism and sarcoidosis must be excluded. Second, the requirement for curative surgery must be re-evaluated and its necessity reconfirmed. Patients without bony or renal complications, or normocalcemic patients with an elevated PTH, for example, may opt to be observed rather than to undergo further surgery with increased complication rates and decreased cure rates. If re-exploration is judged appropriate, the histological specimens and operative notes from the first exploration should be examined, as these will often help in pointing to the likely location of the missing gland.

Preoperatively in revision surgery, attempts at localization are mandatory. High resolution ultrasound and technetium sestamibi scanning are the most common modalities used. If a mediastinal location is suspected, contrast-enhanced CT with technetium sestamibi scanning demonstrate the best sensitivities at 92 and 85 per cent, respectively. MRI and highly selective venous sampling are also sometimes employed, and when other imaging techniques have failed 11C-methionine PET has proved useful, however, this modality is not readily available.

The operative procedure is often via a lateral approach dissecting in a plane between sternomastoid and the straps, and identifying the carotid sheath first. This avoids an approach through a densely scarred midline and enables the surgeon to localize normal landmarks early. The position and pathology of parathyroid disease varies at reoperation from centre to centre, but the overall percentage of hyperplastic glands is increased. The majority of reoperative pathologies are accessible by the transcervical approach. Akerstrom and Juhlin pooled data from eight series and the positions of glands found at reoperation are demonstrated in Table 27.1. In the event of failure to find the pathological gland(s) at reoperation, all the likely ectopic sites should be explored and if the gland is still not evident, thyroid lobectomy on the side of the missing gland is justified as is transcervical thyrectomy, if not previously performed. Ideally, ioPTH will be available and if the levels remain high, then intraoperative ultrasound and selective venous sampling are sometimes used.

Prior to reoperative surgery, the patient must be made aware of the increased risks to the recurrent laryngeal nerve, of failure and of permanent hypoparathyroidism.

<table>
<thead>
<tr>
<th>Superior glands (%)</th>
<th>Inferior glands (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal position (40)</td>
<td>Normal position (39)</td>
</tr>
<tr>
<td>Retro/tracheo-oesophageal groove (17)</td>
<td>Intrathymic (46)</td>
</tr>
<tr>
<td>Posterior superior mediastinum (40)</td>
<td>Mediastinal (not in thymus) (3)</td>
</tr>
<tr>
<td>Intrathyroidal (1.5)</td>
<td>Intrathyroidal (7)</td>
</tr>
<tr>
<td>Carotid sheath (1.5)</td>
<td>Undescended (4)</td>
</tr>
<tr>
<td>Carotid sheath (1)</td>
<td></td>
</tr>
</tbody>
</table>

Table 27.1 Percentage of parathyroid glands found in each anatomical position at reoperation.
PARATHYROID CARCINOMA

Parathyroid carcinoma (PC) is extremely rare, comprising less than 1 per cent of all hyperparathyroid presentations. Its incidence in Italy and Japan, however, seems to be higher (approximately 5 per cent). Unlike benign hyperparathyroidism where there is a female predominance, its sex ratio is the same with a median age of occurrence of between 45 and 51 years. Although rare, suspicion should be raised if calcium and parathyroid hormone levels are particularly high. The tumour is also often palpable (in 45 per cent of cases in the Mayo series), which is not the case with benign parathyroid adenoma. In addition, patients with parathyroid carcinoma tend to be more symptomatic, having a high incidence of renal dysfunction, osteoporosis and gastrointestinal symptoms. It seems that most cases of parathyroid carcinoma are idiopathic, although there are some reports suggesting that its incidence is raised in those who have undergone neck irradiation in the distant past. Molecular studies suggest that several genetic mutations are necessary in the pathogenesis of parathyroid carcinoma involving cyclin D1 on chromosome 13, the retinoblastoma and the p53 tumour suppressor genes. More recently, the HRPT2 gene has been implicated in its pathogenesis and may provide a future genetic target.

As with benign primary HPT, the only curative treatment modality for this condition is surgery. However, it is usually not possible to obtain a preoperative diagnosis of parathyroid carcinoma, and therefore for optimal outcome, intraoperative recognition is of the utmost importance.

The standard surgical treatment for this condition involves the en bloc resection of the tumour mass, together with the ipsilateral thyroid lobe and all other involved structures therefore avoiding transgression of the tumour capsule (Figure 27.7). Because of the difficulty of preoperative diagnosis, many patients require revision surgeries (60 per cent in the Mayo series). The usefulness of postoperative radiotherapy is debatable. Traditionally, PC is seen as radioresistant, but some retrospective data appear to suggest it is an effective treatment modality. Ajuvant chemotherapy seems to confer short-lived, if any, benefit.

Ultimately, patients who die of PC do so from the effects of hypercalcaemia. Local recurrences should therefore be treated by further surgical resection, and bisphosphonates and calcimimetics are useful for symptom control.

KEY EVIDENCE

- In the presence of hypercalcaemia, an ‘inappropriately’ normal or elevated parathyroid hormone (PTH) level is indicative of hyperparathyroidism (HPT). Patients with nonparathyroid hypercalcaemia virtually always have PTH values below 25 pg/mL.
- As many as 27 per cent of patients judged asymptomatic deteriorate over a ten-year period and eventually require surgery.

KEY LEARNING POINTS

- Parathyroid tumours are benign in 99 per cent of cases or more.
- Parathyroid tumours are the most common cause of hypercalcaemia. The second most common cause is disseminated malignancy which should always be remembered.
- Primary hyperparathyroidism is diagnosed in relatively asymptomatic patients in 75 per cent of cases; there are well-recognized guidelines for when to advise surgery in these patients.
- Primary hyperparathyroidism is common in the over 60s, but occurs in all age groups.
- Renal failure is the most common, but not the only, cause of secondary hyperparathyroidism.
- Tertiary hyperparathyroidism is the continuation of hyperparathyroidism, once the extraneous stimulus causing secondary hyperparathyroidism has been removed.

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INTRODUCTION

Here in this well-concealed spot, almost to be covered by a thumb nail, lies the very mainspring of primitive existence – vegetative, emotional, reproductive – on which, with more or less success, man has come to superimpose a cortex of inhibitions.

Harvey Cushing, 1912

The pituitary gland is often known as the conductor of the endocrine orchestra because of its widespread effects on endocrine function. It consists of an anterior part, the ‘adenohypophysis’, and a posterior part, the ‘neurohypophysis’. The gland is attached to the hypothalamus by the pituitary stalk. It is situated in a midline bony recess, the sella turcica, at the posterior superior corner of the sphenoid bone, a position which is in the middle of the head.

The adenohypophysis secretes a range of hormones with critical effects. Adrenocorticotrophic hormone (ACTH) acts on the adrenal cortex which secretes glucocorticoids, mineralocorticoids and androgens; thyroid-stimulating hormone (TSH) acts on the thyroid gland to stimulate thyroid hormone release; prolactin stimulates lactation; follicle-stimulating hormone (FSH) and luteinizing hormone (LH) control sexual and reproductive function; and growth hormone (GH) regulates growth before the epiphyses close and may have an effect on well-being throughout life.

The hypothalamus controls most anterior pituitary function by releasing hormones into a portal circulation which originates there and carries regulating hormones down the stalk to the cells of the adenohypophysis.

The neurohypophysis is made up of axons from the supraoptic and paraventricular nuclei of the hypothalamus which run through the stalk to the posterior pituitary. This part secretes oxytocin (causing milk ejection during lactation and uterine contraction during labour) and vasopressin or antidiuretic hormone (ADH), which stimulates the distal convoluted tubules and medullary collecting ducts in the kidney to reabsorb water.

The great majority of pituitary tumours arise within the adenohypophysis, but some arise within adjacent structures. Because most arise within the gland, this chapter concentrates on these tumours, their effects and their management.

ANATOMY OF THE PITUITARY GLAND

The gland lies in the sella turcica, a midline saddle-shaped bony recess in the posterior superior corner of the sphenoid sinuses (Figure 28.1). The anterior lobe, made up of the pars
anterior (80 per cent), pars intermedia and pars tuberalis, is quite firm yellow tissue. The neurohypophysis is adherent to its posterior aspect.

The arterial blood supply is from the superior and inferior hypophyseal arteries, which arise from the internal carotid. The anterior lobe also has its portal circulation from the medial eminence of the hypothalamus.

Bone of the sphenoid forms the anterior, inferior and posterior walls of the pituitary fossa. The lateral walls are formed by the cavernous sinuses, venous lakes which have dura mater and vein wall on their medial and lateral aspects and which contain the last part of the internal carotid arteries, the oculomotor (III), trochlear (IV) and abducent (VI) nerves, and the ophthalmic and maxillary divisions of the trigeminal (V) nerve. These sinuses are linked by connecting veins running within the anterior and inferior capsule of the gland. These connectors are important to the surgeon as they are easily opened when approaching the gland through the sphenoid and can cause troublesome bleeding. Blood from the ophthalmic veins and pterygoid plexus of veins drains into the cavernous sinuses and flows from the cavernous sinuses into the superior and inferior petrosal sinuses.

The optic nerves, chiasm and tracts are closely associated with the gland. The nerves come from the orbital apices, between the anterior and middle clinoid processes on each side, just above the carotids and merge as the chiasm just anterior to the stalk. The chiasm then divides into the optic tracts, which pass either side of the stalk to head posterolaterally around the cerebral peduncles. The relevance of this anatomy is that a superiorly expanding pituitary lesion will come into contact with these structures, causing the typical clinical presentation of visual field loss.

The anatomy of sphenoid sinus is critical for pituitary surgery. The sphenoid is occasionally not aerated at all, in which case the sella sits in the top of a solid clivus. Normally, there are two sphenoid sinuses, which open into the nose in the sphenethmoidal recesses on each side of the posterior septum. Aeration may range from minimal to highly aerated with large lateral extensions into the greater wings of the sphenoid bones. In addition to a septum separating the two sinuses, there are often additional septae within each sinus. These are valuable anatomical landmarks which can be noted on scans and used during surgery to navigate within the sinuses.

**PHYSIOLOGY OF THE PITUITARY GLAND**

This is a highly complex topic, and only a brief outline is given below, in order to allow an understanding of the pathology described in relation to the management of pituitary tumours.

### Anterior pituitary function

**PROLACTIN**

Prolactin is a 199 amino acid protein. It has a 30 minute half-life in the circulation. It has similarities to GH and serum prolactin levels are a reliable measure of the amount of circulating hormone. The normal range of circulating hormone is 60–620 mU/L and it is higher in women than men. Its main action is to stimulate and maintain secretion of milk. It is regulated mainly by inhibition from the hypothalamus by prolactin inhibitory factor (PIF) and the main PIF is dopamine. Between 12 and 28 per cent of anterior pituitary cells secrete prolactin in a normal gland. Control of secretion is complex, but raised prolactin levels, caused by a prolactin secreting adenoma (prolactinoma), may suppress the release of gonadotrophins, as well as stimulating milk secretion, and so females often present with galactorrhoea and amenorrhoea. In men, there may be no obvious effect, although suppression of gonadotrophin secretion may cause low testosterone levels and loss of libido. It is important to be aware that stalk compression, whatever its cause, can cause a mild rise in prolactin levels by preventing PIF reaching the anterior gland.

Dopamine agonists are effective in treating prolactinomas. Cabergoline is the first-line treatment for prolactinoma in most centres. It can control prolactin levels and shrink tumours.

**GROWTH HORMONE**

Between 70 and 80 per cent of GH is a single chain 191 amino acid protein. About 50 per cent of the hormone-producing cells in the anterior pituitary secrete GH. It either acts directly on cells, binding to GH receptors, or it acts indirectly by triggering production of insulin-like growth factors (IGF) which are mainly synthesized in the liver. IGF1 is the most important and unlike GH, which has a very short half-life in the circulation, IGF1 levels do not fluctuate.
quickly and relate well to average GH levels. For this reason, IGF1 levels are useful when assessing acromegaly and its treatment. GH regulation is complex, but the hypothalamus produces both GH-releasing hormone (GHRH), which stimulates GH secretion and somatostatin, which inhibits it.

**ADRENOCORTICOTROPHIC HORMONE**

Adrenocorticotropic hormone (ACTH) is a 39 amino acid peptide and it is regulated directly by circulating glucocorticoid levels and by the effect of corticotrophin-releasing hormone (CRH) and vasopressin from the hypothalamus. Glucocorticoid levels fluctuate on a diurnal rhythm, with levels being highest in the morning and lowest at night. ACTH levels fluctuate in a similar way and it is the major stimulus to the adrenal cortex, which secretes glucocorticoids, mineralocorticoids and adrenal androgens. Corticotrophic cells constitute about 6–10 per cent of the cells in the normal anterior pituitary.

**LUTEINIZING HORMONE, FOLLICLE-STIMULATING HORMONE AND THYROID-STIMULATING HORMONE**

LH, FSH and TSH are all glycoproteins with a common alpha subunit (92 amino acids) and characteristic beta subunits (115 or 112 amino acid proteins). LH and FSH control sexual function and TSH regulates thyroid function. Functioning adenomas secreting these hormones are rare.

### Posterior pituitary function

Antidiuretic hormone (ADH) and oxytocin are the hormones secreted by the posterior or neurohypophysis. ADH is the same as vasopressin. Both ADH and oxytocin are nine amino acid peptides. They are synthesized in the cells of the supraoptic and paraventricular nuclei of the hypothalamus, but individual cells in these nuclei secrete one or the other, not both. ADH acts on various receptors in the central nervous system (CNS), blood vessels, liver, adrenal cortex, uterus and platelets. Via different receptors, it acts on the anterior pituitary where it affects ACTH release, and via yet another type of receptor it affects the renal function by stimulating water reabsorption from the distal convoluted tubules and collecting ducts, hence the name ‘antidiuretic hormone’. Oxytocin acts via receptors in the uterus to cause contraction of uterine smooth muscle and via receptors in the breast to cause contraction of myoepithelial cells resulting in ejection of milk. Receptors for oxytocin have been identified at other sites, including CNS, kidney, testis and thymus.

### CLASSIFICATION OF PITUITARY TUMOURS

Pituitary adenomas can be classified in terms of function, size or histology.

### Function

The great majority of pituitary tumours are benign adenomas which can broadly be divided into functioning and non-functioning adenomas.

- **Functioning adenomas**, from the most common to the most rare are as follows:
  - prolactinoma
  - growth hormone-secreting adenoma – acromegaly and gigantism
  - ACTH-secreting adenoma – Cushing disease and Nelson syndrome
  - TSHoma
  - Gonadotrophinoma.

- **Non-functioning adenomas**. These are more common than functioning adenomas and they present either by being large enough to compress adjacent structures or by causing pituitary hormone deficiency, or a combination of these. Of course, functioning adenomas can also be large enough to exert pressure on adjacent structures.

- **Incidental lesions** found on imaging for another indication. ‘Incidentaloma’ is a term used to describe the increasing number of adenomas identified in patients who have a head scan for other reasons. These imaging abnormalities may or may not prove to be significant, but depending on the size and imaging characteristics of the lesion, may merit investigation to exclude a functioning adenoma and at least continued surveillance (see below under Epidemiology and incidence).

### TUMOUR SIZE

Tumour size is important when considering treatment. Pituitary adenomas are often described in terms of size:

- microadenomas, up to 10 mm in their largest dimension;
- macroadenomas, larger than 10 mm.
- the term ‘mesoadenoma’ is sometimes used to describe tumours of intermediate size (10 mm).

Of greater importance in larger tumours is their extent. Hardy and Somma’s graded pituitary tumours on a scale of 0 to 4, where 1 and 2 are adenomas confined to the fossa, 3 has localized invasion and destruction of the sella and 4 has more extensive invasion and expansion beyond the sella. Extrasellar extension is described by further grades A to E. This classification is relevant to the surgical strategy as larger tumours require more extensive surgery to cure them and this is discussed below under Surgical approaches.

### HISTOLOGY

Tumours used to be defined by the staining characteristics of the granules in the cells on haematoxylin and eosin staining into chromophobe, eosinophil (prolactin and GH) and
basophil (ACTH, TSH, LH, FSH) tumours. However, with modern immunohistochemistry, histology can define type of hormone in the adenoma – for instance, a tumour may be described as corticotrophinoma (containing ACTH granules) or a somatotrophinoma (containing GH granules). It is interesting to note that adenomas may contain more than one hormone and positive immunohistochemistry does not always coincide with tumour function.

**OTHER LESIONS ARISING IN AND ADJACENT TO THE PITUITARY**

A range of other lesions can arise at this site. Below is a list of some of these, and this illustrates the diversity and the need for expert imaging and investigation in such cases. Many have particular characteristics on magnetic resonance imaging (MRI) and computed tomography (CT) which can be identified by an expert radiologist. Pituitary function may not be disturbed by these lesions, but if it is, function tends to be impaired:

- Rathke's pouch cyst
- Craniopharyngioma
- Chordoma
- Meningioma
- Carotid aneurysm
- Plasmacytoma
- Glioma
- Epidermoid cyst
- Dermoid cyst
- Nasopharyngeal carcinoma
- Metastatic cancer
- Granulomas.

**EPIDEMIOLOGY AND INCIDENCE**

Pituitary adenomas account for about 12 per cent of primary brain tumours and the incidence in various studies ranges from 0.6 to 2.8 tumours/100,000 population per annum.2 Some studies show females to be more frequently affected than males, but this is not consistent. Non-functioning adenomas and prolactinomas are most common, with GH adenomas and ACTH adenomas third and fourth.

Post-mortem studies show a much higher incidence of adenomas – between 1.5 and 25 per cent, with an overall figure of 9.4 per cent.2 Ten per cent of these were found to be multiple. This puts the finding of an incidental adenoma on a head scan into context.

Primary malignant tumours of the pituitary are extremely rare.

**CLINICAL PRESENTATION OF PITUITARY LESIONS**

As stated above, pituitary tumours present in one or more of three ways:

- Endocrine disturbance, caused by the effects of excess or deficient pituitary hormone secretion.

- As a space-occupying lesion spreading out of the pituitary fossa and compressing or invading adjacent structures.

- As an incidental finding on imaging of the brain.

The presentation of each type of pituitary tumour will be described in more detail under the individual tumour types.

**INVESTIGATIONS**

**Pituitary imaging**

MRI and CT scanning have made enormous advances over the last few decades. Modern MRI gives a wealth of information about the soft tissues in and around the pituitary gland at little risk to the patient. T1-weighted images with and without contrast and T2-imaging are most valuable. CT scanning obviously exposes the patient to significant doses of x-rays, but provides a wealth of detail about the bony anatomy when this is needed. Imaging of the pituitary is used to demonstrate the following:

- **Normality.** MRI gives details of the size, shape and intensity of the gland. On T1-weighted imaging without contrast, the normal posterior pituitary is hyperintense in 90 per cent of children, but is less reliably so in adults. This is because the neurosecretory granules contain phospholipids which are bright on T1. MRI also demonstrates the sphenoid sinus (air filled and so black on all weightings) and bone marrow (bright on T1) within the clivus very well. CT defines the bony margins of the fossa and identifies bone asymmetry, expansion or erosion if present.

- **Abnormality within the gland.** MRI is best for identifying an abnormality within the gland. On this modality, the intensity of an adenoma is either iso- or hypointense. On T1-weighted imaging with gadolinium, an adenoma will usually appear darker than the adjacent gland initially, because circulation is swifter to the normal gland than to the adenoma, but this may reverse in a delayed scan, where the adenoma may be bright after the contrast has moved out of the normal gland. T2-weighted imaging will demonstrate cerebrospinal fluid (CSF) in the suprasellar cistern, a cyst in the gland if its contents have the appropriate signal characteristics, or a partially empty sella. CT is not likely to be useful in microadenomas. The presence of an abnormality in the gland must be treated with caution in light of the following:
  - A 10 per cent incidence of asymptomatic pituitary adenomas in the general population.
  - Small functioning adenomas may not be visible on standard MRI (about 25 per cent of Cushing adenomas cannot be seen on MRI). There is evidence that with improving techniques, imaging will become more accurate.3

- **Abnormality adjacent to the gland or extending beyond it.** Once again, MRI is likely to show most detail. Extension into the suprasellar cistern, chiasmal compression and cavernous sinus invasion will all be
seen on T₁-weighted imaging with contrast. The carotid arteries in the cavernous sinuses are seen clearly as flow voids. The optic nerves are easily seen after they have left the orbital apices, as is the optic chiasm. Invasion of the sphenoid sinus will be visible on all modalities of MRI and CT will show bone thinning or destruction when a tumour invades the sphenoid bone or sinuses.

The availability and quality of MRI means that this may be the only imaging needed, but some surgeons prefer to have imaging to demonstrate cortical bone detail clearly. Cortical bone is not seen clearly on MRI and so CT can be used to acquire this information. Both types of imaging can then be used by image guidance systems during surgery. This is helpful to guide the surgeon in the nose and sinuses. Angiography of any type is seldom required for pituitary adenomas because the carotids are seen clearly as flow voids on MRI and it is extremely unusual for a pituitary adenoma to affect the carotid arteries. If the signal characteristics of a lesion in or adjacent to the pituitary are in any way atypical of adenoma, an experienced neuroradiologist will advise on the differential diagnosis and any further types of imaging which should be used to define the nature of such a lesion. In many instances, MRI alone or MRI and CT are sufficient to make the diagnosis of whichever lesion is arising in this area (see the list of ‘other lesions’, above under Other lesions arising in and adjacent to the pituitary).

Endocrine investigations

The detail of the endocrine investigations needed to diagnose and assess pituitary function and abnormality will vary, dependent on the clinical diagnosis. The standard endocrine tests for pituitary function will measure plasma cortisol, urinary free cortisol, prolactin, growth hormone (GH), IGF1, LH, FSH, TSH, thyroid hormone levels, and plasma testosterone levels.

VISUAL FIELD TESTING

This is essential if there is suprasellar extension and the tumour reaches the optic nerves or chiasm. Documentation of the visual fields will demonstrate if the tumour is causing visual impairment, and provides a record which can be used to show the effect of surgery on the loss. Intracavernous tumours do not give rise to visual field problems but if any patient complains about visual disturbance, it is wise to document their visual fields preoperatively.

TREATMENT OPTIONS

If a pituitary tumour is suspected, it is important to investigate it as described above. The options for treatment will depend on the type of tumour, the overall health of the patient and how the tumour is affecting the patient. Treatment options vary for each type of tumour, as described below, but in general the options are:

- watchful waiting, with serial MRI;
- surgery;
- radiotherapy;
- medical treatment;
- combinations of these options.

NON-FUNCTIONING ADENOMA

Presentation

A non-functioning adenoma (NFA) can come to light for the following reasons:

1. Symptoms due to compression of the optic nerves and chiasm. If this is the presentation, the patient will usually be referred with the results of visual field testing showing the visual field loss. If the patient comes from an ophthalmologist, they may well have had MRI as well.
2. Symptoms of pituitary hypofunction, being investigated with a scan which demonstrates a pituitary adenoma.
3. An incidental finding when a patient has a scan for another reason ( incidentaloma).

Investigation

VISUAL FIELD ASSESSMENT

If the patient has not had formal assessment of the visual fields, this will need to be accurately documented.

IMAGING

This will provide a great deal of valuable information for the surgeon about the adenoma.

- Size and extent. MRI will define the extent of the tumour and what structures are compressed or invaded by it. Obviously, if the tumour is causing visual disturbance, it will have grown upwards out of the fossa, but it may have invaded one or both cavernous sinuses or the sphenoid sinuses, or all of these structures. Its extent has important implications for planning the surgery and the more extensive the tumour, the more difficult it is to clear it completely at operation. Bone destruction may be evident on MRI, but CT will give more detail. This can be very important, for example it is valuable to know if the posterior clinoid processes and posterior wall of the pituitary fossa have been eroded by the adenoma, because if they have, there is nothing hard between the posterior capsule of the gland and the brain stem and basilar artery.

- Shape. A tumour may be a concentric enlargement, it may have a ‘cottage loaf’ shape or it may invade laterally or inferiorly. The waist in the cottage loaf is usually caused by the superior extent of the tumour pouting out through the diaphragma sellae. The superior part of a concentric tumour may descend into the fossa more readily during surgery than the upper part of a ‘cottage loaf’.
Consistency. MRI will often give some indication as to the consistency of the tumour. This is useful, because it is easier to remove cystic or ‘soft-centred’ tumours. If the tumour is tough and fibrous or proves to be adherent to the cavernous sinus during surgery, it is more difficult to remove completely. ‘Soft-centred’ tumours are often homogeneous or even have a slightly enhancing rim on T1-weighted imaging with gadolinium with a homogeneous, hypointense centre. A heterogeneous signal on MRI may give the surgeon an indication that the tumour is going to be more fibrous and ‘tough’, making dissection and good clearance more difficult.

ENDOCRINE FUNCTION

It is essential to investigate pituitary endocrine function in the presence of a pituitary adenoma. A significant proportion of these patients are partially or totally deficient in anterior pituitary function. Any deficiencies identified can be treated prior to surgery if appropriate. If the presentation is as an emergency, the surgeon should be aware that the patient may be cortisol deficient and it is essential that this deficiency is treated urgently.

Prolactinomas may present as NFAs, particularly in men, and so a serum prolactin should be measured and a diagnosis of prolactinoma considered if the prolactin is greater than 2000 mU/L. If the patient has a prolactinoma, urgent treatment with a dopamine agonist should be considered because this is highly effective.

Treatment

Surgery is effective if needed to relieve the local pressure. This is described below under Surgical approaches, p. 537. If the adenoma is truly non-functioning, there is no medical treatment. Radiotherapy is effective but slow to act and is subject to its own complications. Recurrence post-surgery can be treated by further surgery with a good prospect of controlling the tumour.

Follow up

When a non-functioning adenoma is treated surgically, tumour removal may be partial or total. Most of these tumours are large and benign, and total removal may be unachievable or excessively risky. In that event and even with apparently complete removal, they can recur.

Routine follow up should include the following.

POSTOPERATIVE ENDOCRINE ASSESSMENT

The recovery of endocrine function that was deficient pre-operatively is unpredictable, but on occasions recovery occurs. Surgery may also cause further loss of endocrine function and so full assessment of pituitary function should be undertaken postoperatively. Sometimes postoperative symptoms will give a good indication of lost or returning function. For instance, persistent diuresis occurs if the patient has developed diabetes insipidus, and if a woman’s periods return, it is likely that LH and FSH secretion has recovered. It is important to assume that a patient is glucocorticoid deficient postoperatively until they have passed a short synacthen test which confirms a normal adrenocortical response to ACTH.

HISTOLOGY

Clearly, histological examination of the removed tissue is essential to confirm the diagnosis. It may also give some indication of the growth rate of the tumour, if there is a high mitotic rate and the Ki67 index is high.

IMAGING

Recurrence of NFAs will depend on the degree of clearance obtained at surgery and the nature of the tumour. In view of this, it is recommended that all NFA patients should be rescanned. The timing of the first postoperative scan is at the surgeon’s discretion. The authors rescan at about four to six months post-surgery, when healing is complete, and then serially at intervals of months or years to assess for evidence of recurrence. If there is persistent tumour on the scan and it starts to grow and if further treatment is considered necessary, the treatment options are further surgery or radiotherapy or both. This management avoids radiation for the majority of patients in whom the NFA never recurs.

FUNCTIONING ADENOMAS

These include the following:

- Prolactin-secreting adenoma – prolactinoma
- Growth hormone-secreting adenoma – acromegaly
- ACTH-secreting adenoma – Cushing disease
- TSHoma
- Gonadotrophinoma.

Prolactinoma

PRESENTATION

In women of reproductive age, a prolactinoma is most likely to present with secondary amenorrhoea and galactorrhoea. This is because high prolactin levels suppress gonadotrophin release and stimulate milk secretion. In men, they may cause no obvious symptoms, but gonadotrophin suppression may cause loss of libido or impotence. Prolactinomas are the most common functioning pituitary adenomas. They can vary from microadenomas to large macroadenomas which may even be invasive and very rarely truly malignant. The larger tumours can give rise to the same symptoms as a NFA.

INVESTIGATION

Serum prolactin levels will be elevated to over 2000 mU/L. In larger tumours, the levels may well be >10 000 mU/L.
Gonadotrophin and testosterone levels may be low. Full endocrine assessment is important. Occasionally, tumours secrete both prolactin and GH.

TREATMENT

Medical treatment is effective to treat prolactinoma. Dopamine agonists lower the prolactin levels and shrink the tumour in most cases. Cabergoline is the drug of choice and is usually commenced at a low dose twice weekly and increased until a suitable response occurs. The effect on prolactin levels can be measured in the blood and tumour size can be monitored with serial MRI and serial visual field testing if there is visual field loss initially. Surgery is only indicated if one or more of the following applies:

- The tumour does not respond to medical treatment, either with a failure of prolactin levels to drop, or the tumour to shrink or both. Typically, the levels drop quite rapidly, but tumour shrinkage occurs over a longer period.
- The patient cannot tolerate medical treatment.
- The tumour expands, causing sudden loss of vision or other intracranial complications. This may be sudden, due to haemorrhage into an adenoma.
- Occasionally, a large tumour may shrink so much that a CSF leak develops and needs closure.

Should surgery prove necessary, it is important to screen the patient for cardiac valve disease, because this can arise from dopamine agonist treatment.\(^7\)

It is important to check the serum prolactin in all patients presenting with what is thought to be a non-functioning adenoma, because some of these may be prolactinomas. In the event that the serum prolactin is significantly elevated, unless there is an immediate indication for surgery, such as sudden loss of vision, giving a dopamine agonist may well be effective in shrinking the tumour avoiding unnecessary surgery.

Acromegaly

PRESENTATION

The clinical picture in acromegaly is of enlargement of the hands, feet, soft tissues and bones of the face. Patients note these features, but the onset is typically insidious, and so it is often someone other than the patient who notices the change and triggers medical interest. Headaches, excessive sweating, snoring, nasal symptoms (an association with nasal polyposis), tight rings, enlarging feet, the onset of diabetes, hypertension and muscle and joint pains are all features of the condition. Family photographs can often help in identifying the onset of this disorder. Excessive secretion in childhood results in gigantism and following fusion of the epiphyses, acromegaly.

INVESTIGATIONS

Growth hormone is a protein with a half-life of a few minutes. There is a diurnal variation in the secretion, but in addition to this, the hormone is secreted in pulses. GH antagonizes insulin and its secretion is suppressed by a high blood sugar. If this condition is suspected, growth hormone levels should be measured during an oral glucose tolerance test (OGTT), because in normal people high glucose levels suppress GH levels below 0.6 \(\mu\)g/L and if GH levels remain persistently high during this test, it is diagnostic. IGF1 (insulin-like growth factor 1) is produced in the liver in response to circulating GH and this is useful because it has a long half-life. Elevated IGF1 levels are strongly supportive of a diagnosis of acromegaly.

MRI of the pituitary fossa will usually demonstrate an adenoma, which may be anything from a microadenoma to a tumour spreading well beyond the limits of the gland.

TREATMENT

It is important to treat acromegaly. This condition is associated with a significantly increased risk of premature death if left untreated, due to a variety of causes, but mainly due to vascular disease and cancer.

Surgical

In this condition, surgery remains the treatment of choice in most centres. If the tumour is fully surgically accessible and there is normal gland in the fossa, it is possible to cure the disease and retain normal function. In microadenomas, surgical cure is obtainable in more than 85 per cent of tumours. Where tumours are larger or more invasive, the cure rate drops.

Medical

Somatostatin suppresses the secretion of GH, and somatostatin analogues are now available. These are quite short-acting drugs which have to be administered by injection, but once the treatment has been established and proved effective in controlling symptoms, depot preparations requiring just one injection every few weeks can be used. Tumour regression is variable and not very reliable, but somatostatin analogues are effective in lowering GH levels and will often rapidly relieve the patient’s symptoms.

Radiotherapy

Radiotherapy has a role, as in other pituitary tumours, but given the slow-growing and benign nature of these tumours, the action on tumour size and hormone secretion is slow, taking years to show its full effect.

FOLLOW UP

Endocrine assessment is essential to assess the effect of treatment on growth hormone and IGF1 levels. These should fall following surgery. As with preoperative assessment, growth hormone levels should be measured during an oral glucose tolerance test, and should be low at rest and suppress to less than 0.6 \(\mu\)g/L on the OGTT. Surgery ideally cures the disease and preserves other normal pituitary function, but this does not always happen, and so all anterior pituitary function should be assessed postoperatively and any deficiencies treated as appropriate.
Postoperative imaging is of value in assessing the removal of the adenoma and the presence of tissue within the fossa, but it is of secondary importance from the point of view of the patient, because restoring normal GH levels and maintaining this state of affairs is the goal of treatment. Life-long follow up is essential, because there is an incidence of a late recurrence in acromegaly.

Cushing disease and Nelson syndrome

PRESENTATION

‘Cushing syndrome’ is the term used to describe the clinical features of this condition whatever the source of glucocorticoid excess. This may be from an adrenal tumour, a pituitary tumour, an ectopic tumour secreting ACTH or due to medication with glucocorticoids. ‘Cushing disease’ is the term used when this is due to an ACTH-secreting adenoma in the pituitary. Whatever the cause of hypercortisolaemia, the presentation is similar. The effects of glucocorticoids on the body are wide ranging and the typical clinical picture is of increasing central obesity with a moon face and a buffalo hump, peripheral wasting with associated muscle weakness, skin changes which may include acne, hirsuitism, striae, easy bruising and easily damaged skin, bone demineralization which may cause pathological fractures, hypertension and diabetes. Untreated, this is a lethal disease, but once again the onset is usually insidious and the diagnosis is often missed early in the disease.

Nelson syndrome is included here because this arises in some patients who have adrenalectomy for Cushing disease without the pituitary adenoma being treated. The effect of adrenalectomy under these circumstances is to remove the inhibitory effect of high circulating levels of glucocorticoids on the adenoma, so it may undergo rapid growth giving rise to a larger more invasive ACTH-producing adenoma. The clinical features of Nelson’s are hyperpigmentation (due to high levels of ACTH and associated hormones) in the presence of a rapidly expanding pituitary tumour in a patient who has had an adrenalectomy. The treatment is hypophysectomy in combination with radiotherapy if this has not already been used, but the cure rate is low.

INVESTIGATIONS

Adrenocorticotrophic hormone regulates glucocorticoid secretion and glucocorticoids are essential for life. Pituitary ACTH secretion is partially regulated by direct feedback of circulating glucocorticoid levels and partially by CRH and vasopressin. However, the diagnosis of Cushing disease may be complicated by ectopic secretion of ACTH, typically from a neuroendocrine tumour. Normally, glucocorticoid levels have a characteristic diurnal rhythm, with levels being highest in the morning and lowest at night. ACTH levels regulate this and fluctuate in a similar way.

Endocrine assessment

Because ACTH is a 39 amino acid protein with a short half-life, it is easier to measure plasma cortisol and 24-hour urinary-free cortisol levels when assessing pituitary/adrenal function.

- The loss of diurnal rhythm can be detected by measuring plasma cortisol levels at 9 a.m. (normal 180–550 nmol/L) and midnight (normal <130 nmol/L). In normal people, an overnight dexamethasone suppression test – a low dose of dexamethasone (2 mg) at night – will suppress plasma cortisol levels the next morning and this can be used to exclude a diagnosis of Cushing syndrome.
- Because ACTH may also be secreted by ectopic sources, such as neuroendocrine tumours, and such tumours give rise to a similar clinical picture, the diagnostic pathway needs to include a method of distinguishing between Cushing disease and syndrome. The behaviour of tumours secreting ectopic ACTH differs from that of pituitary adenomas because most ectopic tumours do not suppress in the presence of high circulation levels of glucocorticoids. Because the management is obviously radically different, it is essential to distinguish between ACTH arising from a pituitary adenoma and from an ectopic source. The dexamethasone suppression test has traditionally been used to distinguish between normal, where suppression occurs with a low dose of dexamethasone, pituitary adenomas, which suppress with high-dose dexamethasone and most ectopic adenomas which do not suppress at all. However, this is not infallible.
- If there is doubt remaining, giving the patient a dose of corticotrophin-releasing factor (CRF) will cause a rapid rise in ACTH in Cushing disease, but does not usually make any difference if the ACTH is from an ectopic source.
- Finally, the current preferred technique is to do inferior petrosal sinus sampling (IPSS) for ACTH during a CRF test. If there is a significantly greater rise in ACTH in the inferior petrosal sinuses than in peripheral blood, this indicates a pituitary source of ACTH.

This is a complex field and any surgeon treating this condition needs to work in close collaboration with a specialist endocrine team.

Imaging

These adenomas are usually small and may be undetectable on imaging. MRI is most useful and most adenomas are less than 1 cm. As stated above, a significant proportion cannot be clearly identified on MRI. This leaves the surgeon dependent on the endocrine results to make the diagnosis, but the presence of an abnormality on MRI does not guarantee that the ACTH secretion is arising from that abnormality, for the reasons stated above under Epidemiology and incidence.

TREATMENT

As stated, this is a dangerous condition with a high mortality rate if left untreated. The treatment options are surgery, medication and radiation, but in Cushing disease, pituitary surgery is the main option. Medication, using Metyrapone, suppresses the symptoms by blocking the peripheral effects of
glucocorticoids, but this is not a definitive treatment. Radiation is not used alone, as the onset of effect is too slow and unpredictable.

**FOLLOW UP**

The ideal outcome is a cure for the disease with maintenance of normal pituitary function. This requires excision of the adenoma with preservation of sufficient normal gland to function adequately. Even if this is achieved, recovery of normal ACTH secretion in the pituitary remnant takes months because in Cushing’s this will have been suppressed by the disease. For this reason, patients should be given replacement hydrocortisone at physiological doses post-operatively and this should not be stopped until there is evidence of recovery of adequate ACTH secretion. Follow up will always include a full endocrine assessment in case there has been collateral damage to pituitary function.

Imaging is of secondary significance in the follow up of Cushing disease, but is essential if further surgery is being considered.

In our hospital, the optimal indicators for a good outcome are:

- an identified adenoma on preoperative imaging;
- histological confirmation that the tumour has been excised;
- a plasma cortisol which is undetectable on blood testing in the early postoperative period when the patient is off all steroids. This is measured on the 4th postoperative day.

Even if all these criteria are satisfied, we have had three patients whose Cushing’s recurred. This once again emphasizes the fact that these patients all need life-long follow up from an endocrine service.

**Other pituitary adenomas**

TSHomas are rare functioning adenomas which present with hyperthyroidism. In a hyperthyroid patient who does not have suppression of TSH, this diagnosis should be considered. Treatment may be surgical or medical, because somatostatin analogues are useful in this condition.

Gonadotrophinoma is a diagnosis which is usually made on immunohistochemistry, so most patients with this diagnosis present as if they had non-functioning adenomas.

**Other lesions in and around the pituitary**

These have been listed above under Other lesions arising in and adjacent to the pituitary. Such lesions may present in a similar way to a non-functioning adenoma, as a space-occupying lesion in or near the pituitary fossa. Imaging may suggest the diagnosis, and often the neuroradiologist reporting the scan will identify features atypical of a pituitary adenoma and characteristic of an alternative diagnosis, such as calcification in a craniopharyngioma or a meningeal tail in meningioma. The presence of clinical signs, such as an ophthalmoplegia, should alert the clinician to the possibility of a diagnosis other than pituitary adenoma, because pituitary adenomas very seldom give rise to symptoms or signs caused by invasion or destruction of adjacent structures. The treatment of such lesions may be surgical, but this is a decision which should only be made when the diagnosis is clear.

**HYPOPHYSECTOMY**

**Contraindications for surgery**

**GENERAL CONTRAINDICATIONS**

General contraindications include:

- **Uncontrolled disease**, for example severe Cushing disease where the patient’s condition could be improved by controlling their hypertension or diabetes.
- **Poor general health** where the patient is at significantly increased risk from the anaesthetic or surgery. Coexisting medical conditions should be optimally treated.
- **Risk of haemorrhage** is an important consideration. Any anticoagulant, including aspirin, should be stopped. If the patient is on warfarin and this cannot be stopped, hypophysectomy is contraindicated.

**LOCAL CONTRAINDICATIONS**

- **Abnormal anatomy**, such as a solid sphenoid, needs to be considered, but it is not a contraindication. Abnormal position of the carotid arteries can occur and needs careful consideration. Image guidance is valuable in these situations.
- **Local infection**, such as sinusitis or nasal vestibulitis, needs to be eliminated or optimally treated before surgery to minimize the risk of meningitis.

**PATIENT INFORMATION AND CONSENT**

All pituitary surgery is performed in specialist centres and often patients are aware of the diagnosis and treatment options by the time they are first seen in a specialist clinic. Patients may have information on their condition or have searched the internet. However, a detailed individual explanation is always necessary, whatever the patient’s state of knowledge. It should include the following:

- A careful explanation of the treatment options, with the benefits and shortcomings of each, including the consequences of no treatment.
- For surgical consent, the surgeon needs to explain:
  - the reason why surgery is the preferred option;
  - the nature of the operation;
  - the risks;
  - the likely outcomes and chances of these being achieved;
– the complications and their consequences;
– the likely time off work;
– what follow up is required and why, how and by whom the patient will be followed up and for how long.

Supporting literature is valuable and is available from the Pituitary Foundation (www.pituitary.org.uk).

PREOPERATIVE INVESTIGATIONS

The patient should be as fit as possible preoperatively. The preoperative assessment for each condition is described above, but the patient should be fully assessed with regard to their medical history and any abnormal physical findings and any pre-existing conditions should be treated to avoid or minimize the risk of problems in the perioperative period. Both Cushing’s and acromegalic patients have significant increased risk of cardiac problems, hypertension and diabetes mellitus and this should be assessed and optimally treated before surgery. Dopamine agonists are also recognized to be associated with a risk of cardiac valve anomalies and so patients on these drugs should be assessed for this possibility.7

Preparation for surgery

- Nasal preparation. Bleeding can be minimized by using vasoconstrictors to reduce bleeding and improve access. Topical vasoconstriction (e.g. xylomatazoline 0.1 per cent spray) to the nasal mucosa and injection of local anaesthetic with adrenaline (lignocaine 2 per cent with 1:80 000 adrenaline) achieves this.
- General anaesthesia is obviously essential. It is useful if the anaesthetist is able to raise the CSF pressure when requested, to push the upper part of the gland into the fossa during the dissection of a macroadenoma.
- Positioning. The patient’s head must be stable, but does not need to be fixed. If image guidance is being used, this needs to be set up appropriately.

SURGICAL APPROACHES

The pituitary has been approached from many different routes over the history of this surgery, but the basic requirements of any approach are the following:

- There must be adequate access to the gland and tumour.
- Intraoperative complications – the surgeon must be able to control bleeding and CSF leak.
- The approach must minimize complications intraoperatively and postoperatively.

The two main routes to the pituitary gland are trans-sphenoidal and transcranial. The first is now the method of choice in the vast majority of cases. Morbidity is significantly lower in trans-sphenoidal surgery and recent technical developments particularly in imaging, video technology, image guidance and instrumentation such as surgical debriders have resulted in the endoscopic trans-sphenoidal approach being the preferred technique. A transcranial approach is still indicated if there is an intracranial portion of tumour which is inaccessible from below.

Endoscopic transnasal route to the sphenoid sinus

ENDOSCOPIC TRANSNASAL ROUTE

This approach is particularly applicable since the introduction of Hopkin’s rod endoscopes to nasal surgery. These instruments come in various angles of vision, but for this surgery 0° and 45° are ideal. The advantage of using this system is that the surgeons’ vision is the view at the tip of the endoscope. Perspective is altered, but the angle of vision is dramatically wider than down a microscope. Ideally, two surgeons work together, one holding the endoscope and another instrument such as a sucker, the other using one or two other instruments as required. Both surgeons work from a television screen, and so it is essential to have a high quality video system attached to the endoscope and an efficient means of keeping the tip of the endoscope clean to maintain illumination and visibility. This is very much a team activity.

- The middle turbinate is lateralized.
- The spheno-ethmoidal recess and the sphenoid ostium are then identified.
- The anterior wall of the sphenoid is removed inferiorly, widening the ostium. The same is done in the other nostril.
- The surgeon makes an incision in the posterior septum about 1 cm anterior to the rostrum of the vomer, does a subperiosteal dissection of the rostrum, which is then removed. Septal bone is useful if the surgeon wishes to repair the defect in the anterior wall of the pituitary fossa with bone. A long-shafted drill is important to get good access where the bone is thick.
- Bone and mucosa are then removed to obtain a clear view of the interior of the sphenoid sinuses. A surgical debrider is very useful for this purpose.

Advantages

- This is a simple rapid approach with minimal bleeding in a well-prepared nose.
- This provides a very similar approach angle as the transseptal approach without the dissection involved – it can be used through both nostrils.
- There is no risk of damage to nasal skeleton and so no risk of postoperative nasal deformity.

Disadvantages

- This technique requires two people who are familiar with the technique and the equipment.

THE TRADITIONAL TRANS-SPHENOIDAL APPROACHES

1. Trans-septal route. This route follows the subperichondrial and subperiosteal plane to the
rostrum of the vomer, which is removed to gain entry to the sphenoid sinuses. This plane can be entered through an SMR (submucous resection) incision in the nasal septum or through a sublabial incision in the mouth. It is an excellent approach, but requires careful dissection. When using retractors in the wound and a microscope, this approach is useful, but it has been superseded by the endoscopic approach, which provides much better visibility in the sphenoid and pituitary fossa.

2. **Transethmoidal route**. This approach requires an incision from the medial end of the eyebrow, curved round the medial aspect of the orbit, inferiorly to the level of the upper edge of the piriform aperture of the nose. Care must be taken to make this incision well anteriorly, away from the medial canthus to avoid webbing of the scar. The approach is then through a window in the medial wall of the orbit, through the ethmoid complex to the sphenoid to gain an excellent view of the pituitary fossa. This view is maintained using a Talbot retractor (the same orbital blades as the Ferris Smith, but the self-retaining system is as for a mastoid retractor). This is the shortest route to the pituitary gland. It allows vision through the ethmoids and instrumentation through the nose and there is a wider view of the operative field than with a trans-septal approach. This is particularly advantageous if there is extensive disease in the sphenoid sinus or clivus. There is no risk of destruction of the anterior nasal septum or deformity of the external nose. The disadvantages of this approach are a facial scar, however minimal, more bleeding during the approach, and a poorer superior view within the pituitary.

With extensive experience of all these approaches, the authors’ preference is for the endoscopic approach. This requires two surgeons, and painstaking attention to maintaining illumination and visibility, but the benefit for the surgeon is a much better view of the operative field. The benefit for the patient is a technique with the lowest morbidity and a shorter hospital stay. The other approaches have specific advantages and are available if indicated. For instance, the transethmoid approach can be useful for extensive lesions within the sphenoid sinus and clivus.

Given that most pituitary surgery has a low morbidity, it is increasingly important that the surgeon takes care of the nasal structures. Nasal septal perforations, postoperative crusting, collapse of the nasal skeleton with the associated nasal deformity and unsightly facial scarring are now all avoidable complications of this surgery.

### INDICATIONS FOR TRANSCRANIAL APPROACH TO THE PITUITARY GLAND

- If there is a large intracranial element of the tumour which is unlikely to be accessible by a trans-sphenoidal approach, then this approach should be considered. Tumours with a ‘cottage loaf’ or ‘hour glass’ shape are theoretically more difficult to remove from below, but normally they are amenable and so this appearance is not a contraindication to trans-sphenoidal surgery.

- If the surgeon suspects that the tumour is not an adenoma, but some other pathology such as a craniopharyngioma or meningioma, trans-sphenoidal surgery may well be inappropriate. However, the scope of the endoscopic skull base surgery is advancing so fast that many lesions previously considered inappropriate for this technique are becoming part of the normal repertoire.

Occasionally, a dual approach, either simultaneously or as a staged procedure, is necessary. Obviously, any approach to the pituitary from above is strictly a neurosurgical procedure.

### TRANS–SPHENOIDAL HYPOPHYSECTOMY

The structures are described as the surgeon encounters them in this approach.

- **The sphenoid sinuses** are very variable in size and shape, and are normally asymmetrical. MRI and CT allow the surgeon to have a map of the route to the gland. Poor aeration of the sphenoid sinus has been quoted as a contraindication to surgery by this route, but with modern imaging, even unaerated sphenoid sinuses seldom pose a problem. Image guidance systems provide further assistance in this situation, but intraoperative x-rays are of value in the absence of image guidance.

- **The optic nerves** and the **internal carotid arteries** usually create indentations in the roof and lateral walls of the sphenoid sinuses. These are visible to the surgeons using the endoscope. Seldom does either cause a problem, but the surgeon should know their location from the MRI prior to starting surgery, and the images should be on display in theatre during surgery. If they or the pituitary adenoma are in an abnormal location and the bone over these structures is thought to be dehiscent, a CT scan is valuable. The optic nerves and chiasm are at some risk when the surgeon is operating above the pituitary fossa, although they lie outside the gland. They are seldom visible to the surgeon using a microscope, but they may well be visible with the endoscope and can be avoided.

- The thickness of the **anterior bony wall of the pituitary fossa** is inversely related to the degree of aeration of the sphenoid sinuses. In a well-aerated sphenoid or an expanded fossa, it may be dehiscent or paper thin so that it will crack with gentle pressure, allowing it to be dissected off the dura and removed. With thicker bone, the preferred techniques are a drill or a bone-penetrating laser. Once the pituitary fossa is open, its posterior limit (the dorsum sellae) is palpable with a pituitary dissector. This provides useful guidance on the anatomy of the fossa during surgery, but occasionally large tumours erode the dorsum sellae, in which case such a manoeuvre is inappropriate.

- The **dura mater** lines the pituitary fossa and forms a tough fibrous layer which is encountered as soon as the bone of the anterior bulge of the gland is removed. This has to be cut to enter the gland. Sharp dissection, diathermy or a laser can be used. Deep to this is a
thinner layer of pituitary capsule, which can also be opened or the surgeon may choose to develop a plane between normal gland and the tumour capsule. It is important to be through the dura, or the surgeon may find that the dissection is in the plane of the intercavernous connecting veins which may result in brisk venous bleeding.

- The cavernous sinuses lie lateral to the pituitary gland, but their interconnecting veins are directly in the way of the surgeon. These may be visible in the dura, in which case the surgeon may be able to avoid them. Bleeding can be controlled with gentle pressure and haemostatic sponge (Lyostypt®) or similar material. If the tumour extends laterally into one or both cavernous sinuses, it can be removed, at least partially, with blunt ring dissectors such as Hardy's dissectors, angled suction or a combination. More caution is required if the internal carotid artery is surrounded by tumour. Given the nature and contents of cavernous sinuses, great caution is advisable when dissecting laterally. It is wise to refer to the scans, to check the relationship between the tumour, the internal carotid artery and the cavernous sinus. The III, IV, V and VI cranial nerves can also be damaged at this point, although this is uncommon.

- The normal anterior pituitary gland is quite firm, pale yellow tissue with a lobular structure. Adenomas are very variable in macroscopic appearance. Occasionally, they pop out as a discrete nodule, but more often there is an area of softer, sometimes discoloured gland. Macroadenomas are often bulky pinkish grey soft tumours (much of which will go up the sucker to leave a cavity), the walls of which consist of soft adenoma. This can be removed by gentle blunt dissection in all directions using purpose designed dissectors. The common varieties are the Angel-James and Hardy dissectors. If there is a large superior extension of adenoma, raising the intracranial pressure will push the tumour down into the fossa from where the surgeon can remove it. The anaesthetist can do this by raising the intrathoracic pressure. Using 0° and 45° endoscopes passed into the pituitary fossa, angled suction and angled dissectors, tumour that is not visible from outside the fossa may become visible and can be removed, particularly if it is soft. Some surgeons use a lumbar canula and infuse an appropriate solution to raise CSF pressure.

- The pars posterior of the pituitary, lying at the back of the gland, is often well seen on T1-weighted MRI because of its fat content. It can be displaced by an adenoma. It is seldom involved in the disease process and care should be taken to leave it intact to avoid diabetes insipidus.

- When operating at the upper edge of the gland, the diaphragma sellae, the pia arachnoid attached to the upper surface of the gland, is a very delicate bluish membrane which has a venous pulsation in it. This is very easy to perforate and may be dehiscent. When dissecting in this plane, it is usual to see CSF seeping from it. If torn, a free flow of CSF occurs. As the dissection is taken posteriorly, the stalk of the gland can be seen penetrating the diaphragma.

- Once the surgeon has removed all or part of the gland and considers the operation within the fossa is complete, the means of closure depends on the presence or absence of a CSF leak. When there is no leak, the surgical defect used for the approach is closed gently, using synthetic material such as a gelatin sponge (Gelfoam® or similar) or collagen sponge (Lyostypt®). Surgical practice varies at this stage of the operation, but the authors’ preference is to use collagen foam in the fossa, a piece of bone from the nasal septum to repair the fossa itself and sphenoid mucosa on the outer aspect of the fossa. The opening in the fossa is covered with more Lyostypt, then the sinus is filled with Nasopore impregnated with bismuth and isodorm paraffin paste (BIPP). This avoids the need for a nasal pack, which is a great benefit to the patient.

In the event of an obvious CSF leak, a more comprehensive repair is required. The authors have two methods, the first is a patch of material such as Surgisis (Cook Medical, Bloomington, IN, USA) and bone flake repair of the anterior wall, with a Lyostypt (B Braun Biosurgicals, Tuttingen, Germany) and DuraSeal (Covidien, Basingstoke, UK) or Tisseal (Baxter Healthcare, Compton, UK), covered with Nasopore (Polyganics, Groningen, The Netherlands), as described above. The second is a vascularized septal flap to cover the front of the pituitary fossa. In the presence of a persistent leak, the vascularized septal flap is now the preferred closure technique.8

### POSTOPERATIVE MANAGEMENT

A protocol for the management of patients in the perioperative period is very valuable. This needs to cover the hormonal requirements of the patient, prevention of infection, fluid balance, the prevention of complications and their early detection and treatment. The protocol should be agreed with the involved endocrinologist and microbiologist. It should cover the following.

#### Steroid replacement

Our standard policy is to cover all patients for the perioperative period with hydrocortisone, giving 150 mg in divided doses on the day of surgery, reducing to 15 mg in the morning and 5 mg in the afternoon by the 5th day. Patients are all discharged on a maintenance dose of hydrocortisone 15 and 5 mg, as above, and instructed to stay on this all the time until they are reassessed at 4 weeks. A short synacthen test is performed at about 4 weeks and, if this indicates sufficient adrenal function, hydrocortisone is stopped. Patients treated for Cushing disease need a higher replacement dose and are reduced to and discharged on 20 mg at 9 a.m., 10 mg at noon and 10 mg at 4 p.m.

#### Antibiotic cover

Perioperative use of antibiotics is important in this surgery because the approach is through a contaminated field.
Prophylactic antibiotic use should be agreed with the local microbiologist and be part of the hospital antibiotic policy. CSF penetration is useful, and the first dose must be given early enough to ensure that there is an effective circulating level of antibiotic at the time the gland is opened and dissected. The duration of antibiotic cover is the perioperative period only, unless there is an indication to continue it for longer, such as a persistent CSF leak through the pack.

Neurological observations

All patients should be fully alert and orientated as soon as they have recovered from the general anaesthetic. The neurological status of the patient should be observed and recorded regularly for the first 12–24 hours to detect any developing intracranial complications as soon as they occur.

Fluid balance and the management of diabetes insipidus

An accurate fluid balance record must be maintained from the time of surgery. Diabetes insipidus (DI) is likely to occur when the pars posterior or pituitary stalk has been traumatized during surgery and may be transient in up to a third of patients, but is persistent in up to 9 per cent.\(^5\) The diuresis normally begins on the first postoperative day, but a diuresis can occur for reasons other than DI, and so it is essential to monitor the serum electrolyte levels daily and ensure that the serum sodium level is greater than 140 mmol/L before treating a diuresis with synthetic ADH (DDAVP). If the patient is passing high volumes of dilute urine, DDAVP 1 μg subcutaneously will control this rapidly. Regular doses are seldom required. DI is usually transient, but if it persists and continues to require treatment, DDAVP injections can be replaced with ADH analogues given either orally or as a nasal spray. If it is necessary to confirm that the diuresis is indeed DI, urinary and plasma osmolality should be measured. The other problem of fluid balance which may arise in the postoperative period is the syndrome of inappropriate ADH secretion (SIADH). This causes water retention and a fall in plasma sodium levels. The patient may develop a range of symptoms including confusion and convulsions. Treatment is by strict fluid restriction.

Management of postoperative CSF leakage

The purpose of the absorbable nasal dressing is to hold the repair to the pituitary fossa in place while the pituitary fossa heals and becomes sealed from the nose. Although healing takes months to complete, there is usually an effective seal within days of surgery.

If there was no CSF leak on the table, this is very unlikely to occur during the postoperative period. If there was a leak during surgery, the surgeon will have repaired it, but in a proportion of patients the leak may persist, or start during the postoperative period. It may resolve spontaneously, but if it persists for more than a few days, it is wise to repair it to avoid the risk of meningitis. The approach is simple because it has already been done at the first operation. The techniques are described above.

DISCHARGE FROM HOSPITAL

The patient is discharged home when well enough and when any diuresis has settled or been controlled. Serum urea and electrolytes should be normal. If there was a visual field defect before surgery, postoperative visual fields may be measured prior to discharge. In Cushing disease, a plasma cortisol level of less that 20 nmol/L (undetectable) in the early postoperative period is a significant indicator of surgical cure. This needs to be measured with the patient off all hydrocortisone for 12 hours. Discharge medication should include hydrocortisone or the equivalent in physiological doses unless the surgeon is certain that the patient has sufficient ACTH. The patient must remain on hydrocortisone until adequate adrenal function has been confirmed, must understand the importance of this medication and must carry a Steroid Card, in the event of accident or hospital admission.

COMPLICATIONS OF SURGERY

Intraoperative complications

HAEMORRHAGE

The most common source of troublesome bleeding is the intercavernous connecting veins in the anterior capsule of the gland, which are easily controlled by packing. Haemorrhage from an internal carotid artery is a rare but potentially lethal complication if the artery is torn. This must be avoided by knowing where the arteries are from the scans and using only gentle blunt dissection when working in the gland. Should this complication occur, immediate packing to control the bleeding and transfer to an interventional neuroradiological facility are vital, to use endovascular techniques to identify and control the bleeding vessel.

CEREBROSPINAL FLUID LEAK

If a CSF leak arises during surgery, it is repaired at the time. If it persists or recurs postoperatively, it needs to be repaired before discharge, as described above.

Early postoperative complications

- Diabetes insipidus is discussed above under Fluid balance and the management of diabetes insipidus.
- Meningitis is rare, but serious. Antibiotic prophylaxis is always used, but neurological observations are done to enable early detection and prompt treatment of this complication.
- Significant intracranial haemorrhage is very rare. If it is suspected from the clinical signs, it constitutes a neurosurgical emergency and should be investigated with early scans and intervention to stop the bleeding.
Pneumocephalus. Air may enter the CSF space if there is a connection into the nose. If suspected, it can be seen on a plain x-ray or CT scan. Nurse the patient flat, and if it persists, early repair of the defect is necessary.

Late postoperative complications

- Anterior pituitary deficiency. This is detected on postoperative endocrine assessment and needs to be adequately treated with replacement therapy.
- Persistent diabetes insipidus is a recognized complication. It needs to be treated with replacement antidiuretic hormone. It presents in the early postoperative period and often it settles, but in some cases it persists and necessitates life-long replacement therapy.
- Failure to cure the endocrine disorder. Pituitary surgery has a failure rate. In most cases, the abnormal levels of hormone will fall, but may not reach the criteria for cure. There is often a corresponding improvement in symptoms. The decisions on the need for and nature of further treatment are best made within the multidisciplinary team.
- Nasal and sinus complications are increasingly rare with endoscopic surgery, but sinusitis can arise. Trans-septal surgery can damage the nose and septum. Transethmoidal surgery causes a scar, which may be unsightly, and it can also result in a frontal sinus mucocele.
- Recurrence of the tumour can occur many years later. The postoperative protocol for these patients includes long-term follow up.

Treated functioning adenomas can be monitored by measuring the relevant hormone levels. In most cases, a good early response to surgery is a strong indication of cure, but this is not invariable.

Non-functioning adenomas are followed up by repeated MRI. They may regrow very slowly, hence the need for life-long follow up. Further treatment may be indicated with surgery or radiotherapy or both. The role of radiotherapy to these lesions is discussed below.

Surgical outcomes

In functioning adenomas, success or failure can be categorized into four categories:

1. Cure with normal pituitary function. In this case, the patient’s symptoms resolve and their biochemistry returns to normal, with normal pituitary function. If the patient had partial or complete hypopituitarism preoperatively, return of normal function may occur, but is unpredictable.

2. Cure with partial or complete hypopituitarism and requirement for replacement therapy. Once again, the patient’s symptoms resolve, but they will be on life-long replacement medication for the persistent deficiencies. One of the current debates in the postoperative period is growth hormone deficiency.

Some patients are symptomatic from GH deficiency and improve if they are given a replacement dose of GH.

3. Failure to cure, but otherwise normal pituitary function. Further treatment will be required for the relevant hormone excess.

4. Failure to cure, but with partial or complete hypopituitarism. Further treatment and replacement therapy are required.

For non-functioning adenomas causing symptoms due to compression of adjacent structures, cure can be defined as:

- resolution of the clinical features – return of normal visual fields, subjective improvement in vision, resolution of headache.
- reduction in size or complete removal of the tumour on imaging, and no regrowth of the tumour on serial imaging over time.

Revision hypophysectomy

The best chance of curing a pituitary adenoma is at the first operation. However, if cure is not achieved and the surgeon and endocrinologist feel that revision surgery is the best option, this should be done. If the first operation was a microadenectomy, removal of all the remaining gland is likely to be appropriate unless the surgeon can easily identify an adenoma in the gland remnant, excise it and leave some normal anterior pituitary tissue. All series quote substantially lower cure rates and higher rates of hypopituitarism and increased complication rates in revision surgery.  

Role of radiotherapy in pituitary adenomas

Radiotherapy can be delivered by external beam, gamma knife, cyber knife and stereotactic conformal radiotherapy to treat pituitary tumours. Radiotherapy is seldom used as first-line treatment, but it is effective and can be used as the sole or main treatment to cure pituitary adenomas, as well as an adjunct to surgery if indicated. It is mainly used where the alternatives are contraindicated (too unfit for surgery) or as an additional therapy where the tumour is not amenable to total surgical removal, where biochemistry or imaging indicate recurrence, or in special situations such as following adrenalectomy for Cushing disease, where radiotherapy to the pituitary reduces the risk of Nelson syndrome.

The effect is gradual over a period of years and so if it is used as the primary treatment, symptomatic control may be needed while the effect of treatment develops. It has potential side effects too. 4 Important among these are:

- a long-term incidence of hypopituitarism (13–56 per cent);
- a risk of optic neuropathy or rarely, brain necrosis;
- a secondary risk of tumours arising in the irradiated field;
- an increased risk of cerebrovascular accident.

Role of radiotherapy in pituitary adenomas 541
For these reasons, radiotherapy is reserved for the following patients:

- Those with postoperative regrowth of non-functioning adenomas showing signs of further growth on serial imaging. Fifty per cent of NFAs will regrow after surgery if there is residual tumour on imaging, and about 20 per cent will regrow even if there is no evidence of tumour on postoperative imaging. Long-term follow up and serial imaging will identify those patients who need further treatment. Radiotherapy is effective in controlling NFAs following surgery.
- Those with functioning adenomas which have not been cured by surgery or show evidence of relapse, either on biochemical assessment or imaging or both. Here the options may include medical therapy, revision surgery, radiotherapy or combined treatment.
- Patients who have had adrenalectomy for Cushing disease. This may prevent them from developing Nelson syndrome.
- Patients who need treatment but are unfit for surgery.

THE FUTURE FOR THE SURGICAL MANAGEMENT OF PITUITARY TUMOURS

- Improved preoperative imaging of adenomas. This particularly applies to Cushing disease and it may be that MET-PET and high resolution MRI will prove successful here.
- Intraoperative MRI is becoming available and does allow assessment of the tumour during surgery. This will hopefully become less expensive, more available and accurate over time.
- Improved instrumentation for surgery. Rigid endoscopes allow the surgeon to see round corners within the pituitary fossa. The next advance will be the generation of instruments which allow the surgeon to see and operate round these corners to remove parts of large adenomas which are currently inaccessible through the sphenoid.

KEY EVIDENCE

- Endoscopic surgery offers significant advantages over traditional approaches and should be considered in all patients undergoing pituitary surgery.

KEY LEARNING POINTS

- Pituitary surgery is only one facet of the management of diseases of the pituitary gland. It requires a multidisciplinary approach

including endocrinologists, radiologists, surgeons, pathologists and radiation oncologists.

- Imaging has made enormous strides in the last two decades and improved accuracy in preoperative imaging has contributed significantly to improved outcomes. Intraoperative imaging is likely to improve outcomes in the next decade.
- Endoscopic surgery offers significant advantages over traditional approaches and the use of the operating microscope, for the following reasons:
  - reduced surgical morbidity
  - extended scope of surgery
  - improved surgical outcomes.

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INTRODUCTION

The oral cavity is the uppermost part of the digestive tract. It starts at the mucocutaneous junction of the lips (the vermilion border) extending posteriorly to the junction of the hard and soft palate superiorly, anterior fauces laterally and the junction of the anterior two-thirds and posterior third of the tongue inferiorly.

The oral cavity is lined by stratified squamous epithelium of varying degrees of keratinization. Primary tumours of the oral cavity may be derived from the mucosa, salivary glands, neurovascular tissues, bone or dental tissues. Over 90 per cent of tumours of the oral cavity are squamous cell carcinomas.

Globally over 300 000 people are diagnosed with oral cancer each year and it is the eighth most common malignancy. Oral cancer is more common in males, patients usually presenting in their sixth and seventh decade of life (Figure 29.2), although the incidence of oral cancer in young people seems to be increasing.

Smoking and alcohol consumption are the major aetiological factors in the development of oral cancer, oral cancer being considered largely preventable (Figure 29.3).

If oral cancer is detected when it is confined to the oral mucosa five-year survival rates exceed 80 per cent, decreasing to 40 per cent for those with regional disease at presentation and 20 per cent if distant metastasis has occurred (Figure 29.4).

Early presentation with oral cancer is associated with an improved prognosis and less extensive treatment in attempt to cure the patient. Research is required regarding selected or opportunistic screening for oral cancer, but at present there is insufficient evidence to support screening.

The management of patients with oral cancer requires a concentration of medical expertise and resources. For the patient to receive optimal management, a truly multidisciplinary approach is required.

PATIENT WORK UP

History

The work up of a patient with suspected oral cancer starts with a detailed accurate history. The patient’s symptoms...
should be documented and a thorough history of each symptom clarified. A short systematic review should be included, asking specifically for symptoms suggestive of metastatic disease or synchronous aerodigestive tract tumour.

The patient’s medical history, including medications and allergies, should be recorded. A frequently neglected aspect of history taking is the patient’s social history. Patients with oral cancer are likely to face the prospect of major surgery, radiotherapy or chemoradiotherapy. The social circumstances of a patient will significantly influence management decisions. Support packages instituted early in the patient’s management may help with timely delivery of care and increased patient compliance. If it is anticipated that free flap reconstruction may form part of the treatment plan, then direct questions regarding proposed donor sites should be asked, such as hand dominance, intermittent claudication or chronic chest disease.

Examination

While taking a history from a patient, the clinician should make note of such things as the patient’s mobility when they
enter the room, the patient’s affect, dysarthria or clues to smoking and drinking habits.

The formal examination should ideally be conducted in a dental chair with good lighting. The neck should be systematically palpated for cervical lymphadenopathy. Using two dental mirrors to help with retraction and visualization, the oral cavity and oropharynx should be examined in their entirety in a systematic manner. All patients should undergo nasendoscopy if there is a high index of suspicion that they have oral cancer. A dental examination should form part of the initial consultation so that dental treatment may be started early in anticipation of surgery or radiotherapy.

Occasionally, pain or trismus may limit the examination; in these circumstances an examination under anaesthetic should be conducted.

Investigations

Investigations conducted at the initial consultation will depend on the clinician’s suspicion that the patient may have oral cancer. Simple investigations that may be conducted at the first appointment include:

- photographs (Figure 29.5);
- incisional biopsy of mucosal lesions;
- fine needle aspiration cytology (FNAC) of suspicious lymphadenopathy;
- orthopantomogram (Figure 29.6);
- chest radiograph;
- electrocardiogram;
- routine bloods – full blood count, urea and electrolytes, liver function tests and clotting.

Biopsy should always be conducted prior to definitive treatment, preferably by a senior member of the team. The biopsy site should be at the periphery of the lesion to include a sample of normal mucosa. A large, deep biopsy may give information regarding depth of invasion and hence the potential necessity to conduct a neck dissection. It has been demonstrated that if tumour thickness on biopsy is \(4.2\) mm, then the final tumour thickness is usually greater than \(3.5\) mm, suggesting an elective neck dissection may need to be considered. Unfavourable tumour factors, such as perineural spread, vascular permeation and a noncohesive
invasive front are indicators to the probability of positive margins and long-term prognosis. Unfavourable features may lead one to consider wider surgical margins where feasible so as to reduce local recurrence (accepting that these same features suggest a poorer long-term prognosis), while balancing the quality of life issues raised by conducting such a resection.

Once oral malignancy is confirmed histologically, additional investigations may be conducted.

**STAGING OF THE DISEASE**

- Computed tomography (CT) ± CT of the chest (Figures 29.7 and 29.8)
- Magnetic resonance imaging (MRI) (Figure 29.9)

- Ultrasound (USS) of the neck or primary ± USS-guided fine needle aspiration (FNA) of suspicious lymphadenopathy (Figure 29.10)
- Positron emission tomography (PET) (Figure 29.11).

There has been much debate regarding the extent to which an individual is screened for second aerodigestive tract tumours or metastatic disease. To subject a patient to major head and neck surgery and an extended hospital stay is clearly inappropriate in the presence of established distant disease, however extensive surgery may be an excellent mode of palliation. Currently, screening for distant metastases is indicated in patients with multiple cervical nodes, recurrence, second primary or advanced disease. The modality of choice for screening is a CT chest, although $^{18}$FDG-PET may

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**Figure 29.7** Computed tomographic scan demonstrating squamous cell carcinoma invading the right mandible.

**Figure 29.8** Computed tomographic scan of the chest demonstrating metastasis of oral squamous cell carcinoma to the right lung.

**Figure 29.9** Magnetic resonance image of the tongue demonstrating squamous cell carcinoma of oropharynx and base of tongue.

**Figure 29.10** Ultrasound-guided fine needle aspiration sampling of an abnormal cervical node.
The routine use of panendoscopy in the work up of the patient with oral cancer is not warranted. Once the patient has had appropriate investigations, the tumour may be staged using the TNM (tumour, node, metastasis) system (Tables 29.1 and 29.2).13

**PLANNING OF RECONSTRUCTION**

The most appropriate reconstruction will be determined by multiple factors, notably characteristics of the primary site and the anticipated defect, the medical and social history of the patient and donor site characteristics. The reconstructive surgeon should have the ability to raise or harvest many different types of local, regional or distant flaps when dealing with head and neck malignancy. Focused examination or investigations regarding proposed reconstruction include:

- Allen’s test of the vascular supply to the hand if a radial free forearm flap is anticipated (Figure 29.12).
- Magnetic resonance angiography (MRA)/angiography of the leg vessels, if composite fibula reconstruction is anticipated (Figure 29.13).
- Thorough examination of the chest and abdomen if a DCIA (deep circumflex iliac artery) free flap is anticipated.
- Doppler ultrasound of potential perforator flap donor sites (Figure 29.14).
- CAD/CAM (computer-aided design/computer-aided modelling) models, if complex composite reconstruction is anticipated (Figure 29.15).
- Dental impressions for all maxillary tumours.

**Table 29.1** TNM staging of oral tumours: AJCC Cancer Staging Manual.13

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**Table 29.2** Stage grouping of oral tumours: AJCC Cancer Staging Manual.13

Figure 29.11 Positron emission tomographic scan demonstrating squamous cell carcinoma of the right oropharynx and left cervical nodes.
ANAESTHETIC ASSESSMENT OF THE PATIENT

It is advisable to liaise with the anaesthetist early in the patient’s treatment plan. Investigations that may help assess the patient’s fitness for anaesthetic include:

- echocardiography;
- exercise tolerance test;
- nuclear cardiac perfusion scan;
- lung function tests.

The patient should be seen by the dietician early in management for dietary advice. Early consideration should be given to a percutaneous endoscopic gastrostomy\(^{14}\) or a radiologically inserted gastrostomy to supplement feeding, particularly if radiotherapy is anticipated. Nasogastric feeding may be more appropriate if the surgery anticipated is not complex and the need for postoperative radiotherapy unlikely. It is beneficial if the patient meets the speech and language therapist, and counsellor prior to definitive treatment starting.

Once the patient has been thoroughly worked up, a discussion should occur with the whole head and neck team to formulate an appropriate treatment plan. The proposed treatment should then be discussed with the patient and informed consent gained. Informed consent should be tailored to the individual and results achieved in the operating unit. The general success rate of microvascular free flap surgery is greater than 95 per cent, however 5–15 per cent of patients may require return to theatre for complications such as flap compromise, haematoma or infection. It should be remembered that the perioperative mortality rate for major head and neck surgery is 1–3 per cent. Patient’s age alone should not rule out major surgery and microvascular reconstruction,\(^ {15}\) as it is the patient’s comorbidity that primarily influences the incidence of postoperative complications\(^ {16,17}\) and prognosis.\(^ {18}\) The benefit of major microvascular surgery

Figure 29.12  Allen’s test demonstrating good vascular return to the hand following release of digital occlusion of the ulnar artery.

Figure 29.13  Magnetic resonance angiography of the lower limbs demonstrating vascular anatomy prior to fibular free flap harvest.

Figure 29.14  Doppler ultrasound of perforators prior to harvest of a scapula-thoracodorsal artery perforator flap.

Figure 29.15  CAD-CAM model of mandible demonstrating planned resection and precontoured, prelocalized reconstruction plate.
in patients with an Adult Comorbidity Evaluation Index 27 of grade 3, unstable angina, respiratory disease with breathlessness at rest, etc., should be carefully considered.

**SURGICAL ACCESS**

The ultimate aim of surgical resection is removal of the tumour with adequate margins. For the majority of oral tumours, this may be achieved via a peroral route with good retraction and lighting.

Patients with trismus, microstomia, large or posteriorly based oral tumours may require additional access procedures to ensure adequate clearance of the tumour.

**Mandibulotmomy**

Bone resection is no longer an acceptable method of improving access to oral tumours. A mandibulotomy gives good access to large or posteriorly located tumours. An orthopantomograph (OPG) is required prior to conducting this procedure to demonstrate the dental anatomy of the area. Typically, the procedure is accompanied with a lip split. Mandibulotomy without lip split has been described, however access is not as great as when a lip split is conducted.

The neck dissection incision is extended anteriorly to split the lip. Multiple incision designs have been proposed for the lip split. An incision around the chin prominence tends to make the prominence more pronounced, a vertical incision over the chin point producing a more cosmetic result. Incorporation of a chevron between the chin prominence and vermilion aids closure and breaks up the scar. The intended incision should be marked and temporary tattoos created with needle and ink at the vermilion to ensure accurate reappraisal at the end of the procedure.

The osteotomy should be conducted anterior to the mental foramen so to preserve labial sensation. The preferred site for the osteotomy is the paramidline area (between the lateral incisor and canine) since the distance between the tooth roots is greater and an osteotomy in this area preserves the attachments of geniohyoid, genioglossus and digastric, only mylohyoid requiring division. If the distance between the lateral incisor and canine roots is insufficient to accept a saw blade, then the lateral incisor should be removed and the osteotomy conducted through the socket to minimize the possibility of osteoradionecrosis should a tooth be damaged. Once the site of osteotomy is established, miniplates are adapted and applied to the mandible bridging the proposed osteotomy site. The plates are then removed and the osteotomy conducted using a fine reciprocating saw blade. The mandible and cheek flap may now be retracted laterally and superiorly giving excellent access to the posterior oral cavity and oropharynx (Figure 29.16).

The nonanatomical position adopted by the temporomandibular joint (TMJ) during this procedure does not give rise to long-term TMJ dysfunction. The osteotomy is plated with the preadapted and drilled plates at the end of the procedure, ensuring the occlusion is accurately preserved (Figure 29.17).

**Visor approach and lingual release**

This approach is generally reserved for when bilateral neck dissections are to be performed. The visor approach may also be appropriate for recurrence or second primary tumours in patients who have received previous radiotherapy to the mandible. The visor approach avoids facial incisions, the incision being located in a cervical skin crease. A mastoid to mastoid visor flap is elevated in the subplatysmal plane to the lower border of the mandible. An intraoral mucosal incision is made in the lingual gingival sulcus from the posterior molar on one side to the posterior molar of the other. In edentulous patients, the incision is made on the alveolar crest. The mylohyoid, geniohyoid, genioglossus and digastrics are detached from the lingual aspect of the mandible allowing the floor of the mouth and tongue to be dropped into the neck (Figure 29.18).

Care should be taken to ensure the lingual and hypoglossal nerves are not injured during the dissection. The reattachment of geniohyoid and genioglossus muscles at the end of the procedure is important to reconstitute the floor of the mouth. This may be facilitated by drilling holes in the
lower border of the mandible through which securing sutures are passed.

Excellent access may be achieved without the necessity of a lip split, however the expected gain in cosmesis has not been proven and this technique is associated with significantly greater functional deficit postoperatively compared to lip split and mandibulotomy.

Upper cheek flap

The upper cheek flap may be required to augment access to large or posterior maxillary tumours. The cornea of the eye should be protected in all patients. Anterior tumours requiring improved access may be approached via a modified Weber–Ferguson incision without extension. The modified Weber–Ferguson approach is essentially an upper lip split extending into a lateral rhinotomy incision. It is imperative that the incision is marked out accurately and temporary localizing tattoos are created prior to starting the procedure. The lip split is usually conducted along the philtral dimple to the base of the columella. The incision extends laterally along the floor of the nose, then follows the alar crease to its superomedial end before continuing to a point 6–8 mm medial to the medial canthus. The incisions are deepened to bone and the cheek flap raised in the subperiosteal plane, preserving the infraorbital nerve, unless it is to be sacrificed on oncological grounds. Elevation of the flap requires a mucosal incision in the gingivolabial and gingivobuccal sulcus to a point where the flap incision merges with the resection margins of the tumour (Figure 29.19).

Greater access is afforded by extending the modified Weber–Ferguson incision either with a subciliary incision (Diffenbach extension) or medial canthal incision (Lynch extension).

SURGICAL MARGINS

The ultimate aim of surgical resection is adequate clearance of the tumour. Inadequate clearance of tumour results in increased local recurrence and decreased long-term prognosis (Figures 29.20 and 29.21). Indications for postoperative radiotherapy (PORT) include positive or close margins, however despite PORT, local recurrence rates do not approach those in which adequate clearance is achieved at the primary operation.

Increasing resection margins in the region of the head and neck potentially results in increased functional and cosmetic deficit. Resection margins of up to 2 cm have been advocated, however such margins result in significant functional deficit following the resection of even the smallest of tumours. Three-dimensional, 1 cm resection margins have been demonstrated as acceptable when dealing with oral and oropharyngeal tumours. By adopting 1 cm surgical margins, account is taken of the shrinkage that occurs post-resection, so ensuring >5 mm pathological margins. It should be remembered...
that the use of 5 mm as a cut-off point for ‘clear’ margins is arbitrary and purely represents a margin that is considered acceptable.\textsuperscript{28} It is vitally important to continually reassess margins visually and by palpation during tumour resection. If approaching the resection of a tumour with curative intent, then reconstructive considerations should not influence the tumour resection.

Comparison of published data regarding the incidence of positive margins and their influence on survival or local recurrence is complicated by the variable definition of a positive margin.\textsuperscript{29} The definition of a positive margin ranges from invasive tumour at the margin,\textsuperscript{30} tumour within 1 mm\textsuperscript{26} and tumour within 5 mm.\textsuperscript{24} The UK Royal College of Pathologists have issued guidelines suggesting clear margins if the histological clearance is $>5$ mm, close margins if 1–5 mm and positive margins if $<1$ mm.\textsuperscript{31}

The incidence of positive margins for tumours of the oral cavity has been demonstrated as being higher than other head and neck sites,\textsuperscript{30, 32} potentially due to its complex anatomy and three-dimensional shape. Large tumours, perineural spread, vascular permeation, a noncohesive invasive front or cervical metastasis are all associated with a greater risk of failing to achieve clear margins.\textsuperscript{25, 33} These features suggest that close or involved margins potentially reflect a more aggressive tumour.\textsuperscript{25, 26}

The incidence of close or involved margins following tumour resection may be greater than 60 per cent depending on tumour site and size (Figure 29.22).
Invariably, it is the deep margin that is close or positive, however close deep margins do not necessarily require adjunctive treatment. The use of ultrasonography to aid in determining deep margin resection has been described.

Frozen sections are not routinely used by many surgeons, reasons cited being potential cost, inability to reliably prevent positive final margins and poor relocation of biopsy site should the result be positive. Ninety-nine percent of American head and neck surgeons routinely use frozen section intraoperatively, however overreliance on frozen section may result in undertreatment of tumours.

When conducting a bony resection, a 1 cm margin should be achieved. It has been demonstrated that it is unusual for extension of tumour in bone to exceed the overlying soft tissue extension.

BUCCAL CARCINOMA

Surgical anatomy

The buccal mucosa is the mucosal lining of the inner surface of the cheek. The area extends from the oral commissure anteriorly to the retromolar trigone posteriorly. The junction between the buccal mucosa and retromolar trigone is an arbitrary line drawn from the maxillary tuberosity to the distobuccal aspect of the mandibular third molar (or its anticipated position if not present).

The inferior and superior boundaries of the area are delineated by the mandibular and maxillary gingivobuccal sulci, respectively.

The buccal mucosa is not exposed to masticatory loads and so is covered by a lining mucosa with nonkeratinizing stratified squamous epithelium. The mucosa is firmly attached to the underlying buccinator muscle. Minor salivary glands are located within the cheek. The parotid duct pierces the buccinator muscle to enter the oral cavity adjacent to the first maxillary molar tooth.

Sensory innervation to the area is via the buccal branch of the mandibular division of the trigeminal nerve. Lymphatic drainage of the site is via the ipsilateral facial and submandibular nodes to the deep cervical chain. The thickness of the cheek, from mucosal lining to external skin, is 1–3 cm.

Epidemiology

The buccal mucosa is the most common site for oral cancer in South East Asia, up to 40% per cent of oral cancers arising at this site. This contrasts with North America and Western Europe where buccal carcinoma only accounts for 2–10% per cent of oral carcinomas. The consumption of betel quid is socially and culturally embedded in the countries of South East Asia and is responsible for the difference in site predilection. The ingredients of betel quid (paan/paan masala) varies throughout South East Asia. The main ingredients include the Piper betel leaf, slaked lime, spices, tobacco and areca nut. For many years, the tobacco content alone was credited as being the carcinogenic agent in betel quid, however it is now recognized that the areca nut is also carcinogenic, as well as being the main aetiological agent in oral submucous fibrosis. Individuals who consume betel quid frequently have a preference regarding which side they chew betel, this corresponding to the side of tumour development. There is a strong association with smoking and alcohol consumption in populations where betel chewing is not prevalent.

The male-to-female ratio in Western countries approximates 1:1, however in South East Asia the ratio reflects the consumption of betel quid. In India, the male-to-female ratio is approximately 4:1, however in the Taiwanese population, where betel quid use occurs primarily in the male population, the ratio may be as high as 27:1.

Buccal carcinoma typically occurs over the age of 40 years, although it may occur in younger patients, particularly when associated with the habit of betel chewing.

Presentation

Buccal carcinoma may be described as verrucous, exophytic or ulceroinfiltrative in character (Figures 29.23 and 29.24).

Figure 29.23 Squamous cell carcinoma buccal mucosa of verrucous appearance.

Figure 29.24 Squamous cell carcinoma buccal mucosa of ulceroinfiltrative appearance.
Patients may present with pain, an intraoral mass, ulceration or trismus. Patients who chew betel often have areas of erythroleukoplakia of the buccal mucosa or submucous fibrosis and consequent trismus, making the detection of invasive squamous cell carcinoma difficult. Advanced buccal carcinomas may extend into adjacent sites to include external skin, mandible or maxilla.

It is not unusual for patients to present with advanced disease, 40 per cent or more presenting with stage III/IV disease.40, 41, 46 Palpable lymphadenopathy on presentation may be as high as 57 per cent for T3/4 lesions. Occult nodal metastasis may be present in 26 per cent of those who are clinically N0 at presentation.40, 41, 46, 47 Tumours greater than T2, are poorly differentiated, have a poor lymphocytic response47 or are thicker than 5 mm47, 48 are more likely to demonstrate cervical metastasis. Tumours are usually well differentiated.40, 49

Work up

Biopsies of buccal carcinomas should be of sufficient depth to help the pathologist give an indication of depth of invasion, since this will help decide on management of the neck. Buccal carcinoma may rapidly extend to adjacent sites, thus accurate imaging is required. Most patients will require MRI/CT imaging, augmented with ultrasound scan if necessary to help in the assessment of depth of primary and cervical lymphadenopathy.

Treatment

PRIMARY SITE

Traditional treatment of buccal carcinoma is surgery with PORT for selected patients.41, 45 T1/2 disease can typically be resected perorally, however T3/4 disease may require facial access incisions and bony resection of the maxilla and/or mandible.

The primary tumour should be resected with a 1 cm margin26 and up to 2 cm if skin is involved.50 The buccinator muscle should be included as the deep margin at the very least.50 The parotid duct may need to be repositioned or ligated.49 External skin should be taken with the specimen if there is any evidence clinically or on imaging that it is involved. Partial maxillectomy or mandibular resection (rim or segmental) may be required.

Small T1 tumours may be resected and reconstructed by primary closure. Healing by secondary intention may be considered, however postoperative trismus may be anticipated unless vigorous mouth opening exercises are conducted. Split thickness skin grafts may be used, the use of silicone sheets to stabilize the graft being useful.51 The use of a skin graft to reconstruct deeper resections may leave a very thin cheek with potentially poor aesthetics. Local flaps such as the buccal fat pad or temporoparietal fascial flap may be used for reconstruction if tumour extension does not compromise their use. Microvascular free flap reconstruction with a radial free forearm flap or anterolateral thigh flap52 restores the thickness of the cheek and if external skin is involved, the flaps can be bipaddled to provide reconstruction of mucosal and skin surfaces. T4 tumours requiring segmental resection of the mandible may require composite free flap reconstruction. Reconstruction with a radial free forearm flap has been shown to give better postoperative mouth opening than reconstruction with a split skin graft or buccal fat pad (Figures 29.25 and 29.26).53

Radiotherapy as a single treatment modality for T1/2 tumours has been advocated,54, 55 however, a change of practice from radiotherapy to surgery at Memorial Sloan Kettering was associated with improved prognosis.56 Brachytherapy or external beam irradiation may be considered.

NECK

Regional spread of disease in buccal carcinoma is usually to the ipsilateral level I and II lymph nodes.57, 58 Patients with palpable lymphadenopathy or pathological nodes on imaging should have a comprehensive neck dissection, although if pathological nodes are only located in level I, a level I–III selective neck dissection (SND) may be considered.59 Nodes in the region of the facial artery as it crosses the mandible should be removed with the neck dissection specimen.

Patients with T2 or greater primary tumours or tumours with a thickness >5 mm should have an elective neck dissection.61, 62 Some institutions will conduct an elective neck
Table 29.3  Recurrence of buccal carcinoma.

<table>
<thead>
<tr>
<th>Local (%)</th>
<th>Regional (%)</th>
<th>Locoregional (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>53</td>
<td>28</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 29.4  Five-year survival for stage I–IV buccal carcinoma.

<table>
<thead>
<tr>
<th>I (%)</th>
<th>II (%)</th>
<th>III (%)</th>
<th>IV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>78</td>
<td>66</td>
<td>62</td>
<td>50</td>
</tr>
<tr>
<td>71</td>
<td>60</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>83</td>
<td>71</td>
<td>57</td>
<td>42</td>
</tr>
</tbody>
</table>

dissection (END) if the tumour is 3–4 mm thick or if histological examination of the tumour demonstrates lymphatic infiltration.41

PORT

The indications for postoperative radiotherapy to the loco-regional area are similar to other sites, notably two or more nodes in the neck, extracapsular spread (ECS), positive margins or stage III/IV disease.46 The beneficial role of PORT in selected patients with buccal carcinoma has been demonstrated by several authors.61, 62 Some authors suggest that PORT should be considered even in stage I and II disease,40, 46 or tumours greater than 10 mm thick.61

Recurrence

Recurrence rates for buccal carcinoma are 26–80 per cent,40, 41, 43, 46, 47, 49 usually occurring within two years (Table 29.3).

Involvement of the parotid duct and buccinator have not been found to be significant indicators of recurrence.60 Factors that influence recurrence include tumour thickness47, 48, 63 and tumour differentiation.49

Prognosis

Buccal carcinoma is considered by many to be particularly aggressive. Five-year survival figures vary depending on population studied and treatment modality (Table 29.4).41–46

Factors that potentially influence survival include regional metastasis,41, 44 extracapsular spread,41 tumour thickness > 5–6 mm,47, 48 skin involvement,43 positive margins,43 stage45 and recurrent disease.47

Epidemiology

The floor of mouth is a common site for oral cancer, 18–33 per cent of oral cancers developing at this site.26, 68, 69, 70, 71 It is thought that the high incidence of cancer at this site may be due to pooling of saliva with dissolved carcinogens or lack of keratinized epithelium.72 Within the anatomical site, tumours are more likely to occur anteriorly.73, 74, 75

Floor of mouth carcinoma occurs more frequently in men,70, 71, 74, 76, 77 the age at diagnosis usually being in the sixth to seventh decade.70, 76, 77 Floor of mouth cancer, as does oral cancer at all sites, has a strong association with smoking72 and the consumption of alcohol.76

Presentation

Since the floor of mouth is a relatively small anatomical area, tumours frequently extend into adjacent sites notably the tongue or mandible.78 Patients may present with a sore lesion, ulceration or obstructive submandibular gland symptoms.79 Leukoplakia of the floor of mouth may be considered a premalignant condition with an annual transformation rate of 1–2.9 per cent,80, 81 the demonstration of carcinoma within an excised leukoplakia not being uncommon.80

Stage at presentation varies considerably between institutions, although approximately 50 per cent present with advanced disease (Table 29.5).82, 83 Cervical lymphadenopathy is present in 17–45 per cent of patients on presentation,70, 71, 74, 82, 83 up to 22 per cent of those clinically N0 at presentation having occult metastasis.70, 77, 82, 83 Depending on the location of the tumour, up to 28.6 per cent of patients may have bilateral nodal involvement.71, 82 Many tumours of the floor of mouth are well or moderately differentiated.74

FLOOR OF MOUTH CARCINOMA

Surgical anatomy

The floor of mouth is the mucosal lining of the anterior and lateral floor of the mouth. The area is bound anteriorly and laterally by the attached mucoperiosteum of the mandibular alveolus. The lateral floor of mouth is bound posteriorly by the anterior tonsillar pillars. Medially, the floor of mouth merges with the ventral and lateral aspects of the tongue.

The floor of mouth is lined by nonkeratinizing stratified squamous epithelium similar to the buccal mucosa, but with a less dense submucosa. Underlying the mucosa lie minor salivary glands, the sublingual glands, submandibular ducts, hypoglossal nerves, lingual nerves and genioglossus muscles. These structures are located in an area bound by the mylohyoid muscle laterally and hypoglossal muscle medially. The submandibular ducts enter the mouth anteriorly either side of the lingual frenum.

Sensory innervation to the area is by the lingual branch of the mandibular division of the trigeminal nerve. Lymphatic drainage of the lateral floor of the mouth is via the ipsilateral submandibular nodes to the deep cervical chain. Lymphatic drainage of the anterior floor of mouth is via the submental nodes to both the left and right deep cervical chains.66 Lingual lymph nodes in the floor of mouth, above the mylohyoid, may have implications regarding the management of tumours of the floor of mouth.38, 67
Work up

Work up of patients with floor of mouth tumours should follow that of any patient with oral cancer. Particularly important in larger floor of mouth tumours is assessment of invasion of the base of tongue or mandible. The loose connective tissue of the floor of mouth presents a poor barrier to local spread.

Treatment

PRIMARY SITE

The need for aggressive treatment of floor of mouth carcinomas is well recognized.84

Surgical resection with a 1 cm margin should be achieved if surgery is the preferred treatment modality. Even in the best surgeon’s hands, positive or close margins may be seen in up to 47 per cent of resections,76,78 despite the use of intra-operative frozen section.71 Many floor of mouth tumours are infiltrative with indistinct edges, possibly explaining the high incidence of positive margins.71 Further resection is advocated if margins are positive.71 Although 1 cm margins are considered by most surgeons to be adequate, extended 2 cm margins have been advocated by some.85

The early extension of floor of mouth tumours into the tongue or mandible is demonstrated by the fact that many patients require rim or segmental resection of the mandible.70 Surgical resection of the floor of mouth in the majority of circumstances will involve resection of part of the submandibular ducts. Typically, the ducts will be resected at the resection margin, well away from their orifice, however in smaller resections at least 3 mm length of duct proximal to the orifice should be taken to ensure surgical clearance of carcinoma or dysplasia that may extend along the duct.86 Management of the submandibular ducts is of great importance if a neck dissection is not being conducted with consequent removal of the submandibular gland. Stricture of the duct in the presence of a functioning gland may give rise to obstructive symptoms of the gland and difficulty in differentiating the potential submandibular gland swelling from cervical disease. The ducts should be transected obliquely to minimize stricture formation and repositioned at the margin of resection, ideally being stented.87 Alternatively, the ducts may be found proximal to the resection margin, a longitudinal incision made and the duct ‘marsupialized’ to the floor of mouth mucosa. Uninvolved branches of the lingual nerve should be identified and preserved.

Small resections may be left to heal by secondary intention or a split thickness skin graft applied (Figures 29.27, 29.28 and 29.29). A more substantial reconstruction may be achieved using local nasolabial88 or facial artery musculomucosal flaps,89 however an edentulous segment is required when using both of these flaps to accommodate their pedicle. If a neck dissection is required and surgical facilities allow, microvascular reconstruction provides a far more flexible reconstructive option, without necessarily prolonging operative time if a two team approach is adopted (Figures 29.30 and 29.31).

The radial free forearm flap is an ideal reconstructive option for floor of mouth defects, easily being converted to a composite flap if segmental resection of an edentulous mandible is required. Prefabricated fasciomucosal free flaps have been described in oral reconstruction,90 however their role in oncological reconstruction is questioned. The fibula osteocutaneous flap provides superior reconstruction if a

Table 29.5 Floor of mouth carcinoma stage at presentation.

<table>
<thead>
<tr>
<th>Stage I/II (%)</th>
<th>Stage III/IV (%)</th>
<th>Country</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>57</td>
<td>n = 9970</td>
<td>United States</td>
</tr>
<tr>
<td>50</td>
<td>50</td>
<td>n = 28071</td>
<td>United States</td>
</tr>
<tr>
<td>15</td>
<td>85</td>
<td>n = 14476</td>
<td>United States (tertiary referral centre, 45 previously treated elsewhere)</td>
</tr>
<tr>
<td>76</td>
<td>24</td>
<td>n = 20774</td>
<td>France</td>
</tr>
<tr>
<td>49</td>
<td>51</td>
<td>n = 32073</td>
<td>United States</td>
</tr>
<tr>
<td>64</td>
<td>35</td>
<td>n = 24882</td>
<td>United States</td>
</tr>
</tbody>
</table>
segmental resection is anticipated in a dentate patient, although like the composite radial free flap, flexibility of the skin paddle is limited. The scapula osteocutaneous flap with two skin paddles, or one skin paddle and muscle left to mucosalize, provides an excellent reconstruction of large defects involving mucosa, bone and external skin. Radiotherapy techniques (brachytherapy or external beam) for T1/2 primaries have been shown to provide results similar to surgery. The proximity of the floor of the mouth to the mandible is of concern when using brachytherapy, since up to 8.5 per cent of patients treated with this modality require segmental resection of the mandible due to osteoradionecrosis within 10 years.

Several units have described a change in practice from brachytherapy to surgery as the primary treatment modality due to the risk of complications. T3/4 lesions are best treated with surgery and postoperative radiotherapy.

Regional spread of disease in floor of mouth carcinomas is usually to the ipsilateral level I to III lymph nodes, involvement of multiple levels not being unusual. Lesions towards the midline may spread to both sides of the neck, hence bilateral neck dissections should be considered. The presence of lingual lymph nodes has raised the concept of incontinuity neck dissection in an attempt to reduce local recurrence and improve survival. Resection of the tumour accompanied with the complete clearance of the floor of the mouth, preserving mylohyoid, hyoglossus and genioglossus if possible, so clearing the lingual lymph nodes would seem an acceptable method of managing lingual lymph nodes.

The decision to conduct an elective neck dissection has been related to tumour size or depth of invasion. Lesions that are T2 or greater should have an elective I–III/IV selective neck dissection, although elective neck dissections have been advocated for T1 lesions.

Tumour thickness of 4 mm is often used as a ‘generic’ critical thickness, greater than which an elective neck dissection is indicated, since the risk of occult metastasis is greater than 20 per cent. It has been demonstrated that the risk of cervical metastasis of floor of mouth tumours exceeds 20 per cent in tumours as thin as 1.5–2 mm. Using a thickness of 1.5 mm may result in up to 32 per cent of patients requiring END based on thickness criteria.

The indications for postoperative radiotherapy to the locoregional area are similar to other sites, notably two or more involved nodes in the neck, extracapsular spread, positive margins or stage III/IV disease.

The beneficial role of PORT in selected patients with floor of mouth carcinoma has been demonstrated.

Recurrence

Recurrence rates for floor of mouth carcinoma are 26–55 per cent, usually within the first two years.

Factors that influence recurrence include tumour size, margin status and tumour thickness, and advanced nodal disease.
Prognosis

Overall five-year survival for floor of mouth carcinoma is 52–76 per cent (Table 29.6).\textsuperscript{70, 71, 77, 82} Factors that potentially influence survival include nodal status,\textsuperscript{71, 82} thickness,\textsuperscript{94} margin status and recurrence.\textsuperscript{71}

TONGUE CARCINOMA

Surgical anatomy

The oral tongue is the freely mobile anterior two-thirds of the tongue. The oral tongue is demarcated from the base of tongue by the circumvallate papillae posteriorly. The tongue may be subdivided into the tip, dorsum, lateral borders and ventral surface. The ventral and lateral surfaces are in continuity with the floor of mouth, having a lining mucosa with nonkeratinizing stratified squamous epithelium. The dorsum and tip of tongue are lined by specialized gustatory mucosa, with a thick, primarily keratinized epithelium. The mucosa of the tongue overlies the intrinsic muscles of the tongue, in addition to the four paired extrinsic muscles of the tongue – genioglossus, hyoglossus, styloglossus and palatoglossus.

Motor innervation to muscles of the tongue is via the hypoglossal nerve, except palatoglossus which is supplied by the vagus nerve. Sensation of the tongue is supplied by the lingual nerve, a branch of the mandibular division of the trigeminal nerve. Taste sensation of the oral tongue is supplied by fibres of the facial nerve that run with the lingual nerve before passing to the chorda tympanic branch of the facial nerve.

Lymphatic drainage of the lateral borders of the tongue is to the ipsilateral cervical nodes; however, drainage of the midline, tip and base of tongue occurs bilaterally. The blood supply to the tongue is provided by the paired lingual arteries, the third branches of the external carotid artery. During resection of posterior tongue lesions, the contralateral vascular pedicle should be preserved if the tongue tip is to be maintained.

The tongue is a complex structure with an important role in mastication, deglutition and speech.

Epidemiology

In populations where tobacco chewing is not endemic, the oral tongue is one of the most common sites for oral cancer, 22–39 per cent of oral cancers developing at this site.\textsuperscript{26, 69, 98}

Within the site, most tumours occur in the middle third of the tongue,\textsuperscript{99, 100} commonly on the lateral aspect, followed by the ventral aspect of the tongue. Only 4–5 per cent of tongue carcinomas occur on the dorsum of the tongue.\textsuperscript{101}

Tongue cancer occurs slightly more frequently in males,\textsuperscript{99, 102, 103, 104, 105} the age at diagnosis usually being in the sixth to eighth decades,\textsuperscript{99, 103, 104} 90 per cent of patients being greater than 40 years of age.\textsuperscript{102} The male-to-female ratio has decreased in recent years, possibly due to increased alcohol consumption by females.

Smoking and alcohol consumption is common among patients with tongue cancer,\textsuperscript{102} up to 70 per cent describing significant tobacco and alcohol use.\textsuperscript{99}

Presentation

Patients with oral cancer may present with several symptoms notably pain, ulceration or a lump on the tongue.\textsuperscript{99, 102, 104, 106} Lesions of the oral tongue are more likely to be symptomatic than lesions of the base of the tongue, although despite this many patients still present with a four- to six-month history of symptoms prior to seeking medical advice.\textsuperscript{102, 104, 107} The majority of patients with cancer of the oral tongue present with stage I/II disease,\textsuperscript{99, 102, 103, 106} which contrasts significantly with cancers of the base of the tongue that are usually stage III/IV at presentation.\textsuperscript{102} Clinically positive cervical lymphadenopathy at presentation is in the region of 21–34 per cent.\textsuperscript{99, 103, 105} Occult cervical metastasis has been demonstrated in up to 53 per cent of patients with tongue cancer,\textsuperscript{99, 104, 107, 108} being related to tumour thickness.\textsuperscript{109} Tumours arising on the lateral aspect of the tongue tend to be thicker than those of the ventral aspect of the tongue.\textsuperscript{105} Up to 4.5 per cent may have occult cervical disease in the contralateral neck.\textsuperscript{104} Clinical examination, CT and MRI have relatively poor sensitivity at determining cervical lymphadenopathy.\textsuperscript{105, 110}

The majority of tongue tumours are well to moderately differentiated on histological examination.\textsuperscript{99, 102, 103, 106}

Work up

As with many sites, management of the neck is frequently determined by tumour thickness. Tumour thickness can be assessed accurately with intraoral sonography, or immediate sonography of the resected tumour prior to proceeding to a neck dissection if access to the neck is not required for reconstructive purposes.

Biopsies should endeavour to include the deep margin of the tumour in addition to mucosa at the periphery of the
tumour. Deep biopsies may give an indication of tumour depth, but also multifactorial histological malignancy grading of the most dysplastic areas of the invasive front may help in assessing the risk of cervical metastasis.\textsuperscript{105}

**Treatment**

**PRIMARY**

Resection of the tumour with a 1 cm margin in three dimensions should be conducted if surgery is the treatment of choice. The use of ultrasonography to aid in assessment of surgical clearance had been advocated,\textsuperscript{39, 111} particularly for the deep margin. Frozen section is not routinely used in many units. Even with apparently adequate margins during surgery, 10 per cent of resections may demonstrate histologically positive margins.\textsuperscript{99}

The aim of reconstruction of the oral tongue following resection is to ensure maximum function of the residual tongue tissue, since the complex function of the tongue cannot be replicated with current reconstructive techniques.\textsuperscript{112} Preservation of the tip of the tongue, while maintaining oncologically sound resection margins, helps maximize postoperative function.\textsuperscript{113}

The use of monopolar electrocautery, ‘cutting’ through mucosa changing to ‘coagulation’ when in muscle, or the harmonic scalpel helps reduce bleeding during the resection, however this is at the cost of lack of feel afforded by the use of scalpel or scissors. If both lingual vessels are resected, then the viability of the tip of tongue remnant should be carefully assessed. Sacrifice of both hypoglossal nerves results in a nonfunctioning tongue tip.

Small lesions may be removed with a laser and allowed to heal by secondary intention (Figures 29.32 and 29.33). T1 and small T2 primary tumours may be excised with a vertical wedge and the defect closed primarily, if the defect does not extend to significantly include the floor of mouth. Many larger lesions benefit from free flap reconstruction of the defect, usually with a radial free forearm flap, although the anterolateral thigh free flap is being used more frequently (Figures 29.34 and 29.35).

The skin paddle of the chosen free flap should be fashioned so as not to restrict residual tongue function and should hopefully augment swallowing. Typically, the reconstruction should be of the same size, or slightly smaller than the defect created by the resection. Care should be taken in the design of the flap when the defect extends to include...
adjacent sites, such as the soft palate or floor of mouth. The mobile tongue and floor of mouth should be ‘separated’ in the reconstruction to minimize restriction of movement of the residual tongue. Thin radial free flaps may have their bulk increased by extending fascial flaps beyond the skin island, the fascial flaps then being folded and buried underneath the epithelial reconstruction.

Reconstruction of large resections may be accompanied by measures aimed to improve postoperative function, such as static laryngeal suspension to the mandible and cricoarytenoideus myotomy.

Once the specimen is removed, it is examined for clearance and orientated for the pathologist, a digital photograph being useful.

Radiotherapy as the primary treatment modality has been advocated since it conserves tongue volume and morphology, brachytherapy being considered preferable to external beam radiotherapy. Osteoradionecrosis of the mandible is a recognized complication of brachytherapy of the tongue, up to 9 per cent developing some form of osseous complication. The use of brachytherapy to the primary site requires either surgery or external beam radiotherapy to the neck in an elective or therapeutic manner. When surgery is not conducted as the primary treatment valuable prognostic information is lost, since the primary tumour is not examined histologically. This makes the decision as to whether to conduct an END more difficult. It has been suggested that surgery is superior to brachytherapy in the management of stage I/II tongue cancer. By conducting surgery as the primary treatment modality, radiotherapy is kept in reserve for either poor prognostic indicators of the resected specimen, for management of recurrence or management of second primaries which commonly occur at a later date.

NECK

Tumours of the tongue initially metastasize to levels I and II, lateral tongue tumours frequently metastasizing directly to level II nodes. Involvement of level V nodes, in the absence of positive nodes in levels I–IV is rare, however it is not unusual for nodes in level IV to be involved. Hence even in elective neck dissections levels I–IV should be dissected.

Like floor of mouth tumours, the presence of lingual lymph nodes should be considered and either an in-continuity resection with the neck specimen or clearance of tissue above the mylohyoid conducted.

Bilateral neck dissections should be considered in tumours that extend to or beyond the midline.

The management of the neck in larger primary tumours is usually straightforward since the neck is accessed for microvascular or pedicled flap reconstruction of the primary site. Management difficulties arise with smaller tumours amenable to peroral resection and local closure.

It has been proposed that the increased incidence of nodal metastasis associated with tongue carcinoma may be due to contraction of tongue muscles promoting entry of cancer cells into the lymphatics. It is thought that mechanism by which tumour thickness is related to cervical metastasis is that thicker tumours have access to wider lymphatics in which tumour emboli can form more readily.

Although tumours arising on the lateral aspect of the tongue tend to be thicker than those of the ventral aspect of the tongue, this may not manifest as a greater risk of cervical metastasis, since the ‘critical thickness’ for tumours of the floor of mouth is less than other oral sites.

Elective neck dissection or elective neck radiotherapy should be considered for tumours thicker than 3–4 mm, or greater in dimension and T2 or greater in dimension and T1 tumours that demonstrate poor histological features (poor differentiation, double DNA aneuploidy or degree of differentiation at the advancing front).

Elective neck dissection significantly improves loco-regional control. It has been demonstrated that conducting an END reduces regional recurrence from 47 per cent in ‘watch and wait’ patients to 9 per cent if END is conducted.

END has been shown by some to improve five-year survival, the five-year survival of patients undergoing therapeutic neck dissection following a ‘watch and wait’ policy being 35 per cent, as opposed to 69 per cent when an elective neck dissection is conducted. Others, however, have not demonstrated a survival advantage.

PORT

PORT has been advocated for positive margins, multiple cervical nodes, extracapsular spread in the neck, stage III/IV disease, perineural spread or tumours thicker than 9–10 mm even in the absence of other features. Based on involved margins, ECS of cervical nodes or multiple positive nodes, 62 per cent of patients receiving surgery as the primary treatment modality may require PORT.

Local failure following PORT to tongue tumours has been demonstrated to be higher than comparable floor of mouth tumours, leading some to suggest higher doses of PORT should be considered for tongue tumours.

Recurrence

Recurrence rates for oral tongue carcinoma are 10–50 per cent, usually being locoregional. Similar to other sites, recurrence usually occurs within the first two years.

Factors that influence local recurrence include tumour thickness and the presence of perineural spread. It has been proposed that recurrence of thicker tumours is related to difficulty in assessing deep clearance intraoperatively compared to assessing mucosal clearance.

Patients younger than 40 years have been demonstrated to be significantly more likely to develop locoregional failure, although this does not influence survival. Ten per cent of patients who have developed a tongue tumour will develop metachronous second tumours of the oral cavity.

Prognosis

Tumour thickness, the presence of perineural invasion, cervical metastasis or dysplasia at the
resection margins have all been demonstrated to influence prognosis. Patients with tumours greater than 9 mm thick have been shown to have a five-year survival of 66 per cent compared to 100 per cent survival for tumours less than 3 mm thick (Table 29.7).

**RETROMOLAR CARCINOMA**

**Surgical anatomy**

The retromolar trigone is a triangular area of mucosa that overlies the ascending ramus of the mandible. The base of the triangle is in the region of the mandibular third molar inferiorly, the apex being adjacent to the maxillary tuberosity superiorly. The area is bound by the buccal mucosa laterally and the anterior tonsillar pillar medially. The retromolar mucosa is not exposed to masticatory loads and so is covered by a lining mucosa with nonkeratinizing stratified squamous epithelium, similar to the buccal mucosa. Sensory innervation to the area is by the buccal branch of the mandibular division of the trigeminal nerve. Lymphatic drainage is to the ipsilateral submandibular and deep cervical nodes.

**Epidemiology**

The retromolar trigone is a relatively unusual site for carcinoma of the oral cavity, only 6–7 per cent of oral carcinomas arising at this site. The disease is more common in males and like other sites is typically a disease of older individuals. In common with other oral sites, there is a strong association with smoking and alcohol consumption.

**Presentation**

Patients typically present late with pain, trismus, otalgia and lingual paraesthesia.

Since the retromolar trigone is an anatomically small site, tumours often extend to involve adjacent subsites: buccal mucosa (84 per cent), oropharynx (14 per cent), masticator space, involving the medial pterygoid, masseter, temporalis, mandibular branch of the trigeminal nerve (22 per cent). Bone involvement of the mandible and/or maxilla is present in 12–34 per cent of retromolar tumours, although a higher incidence of up to 75 per cent has been reported. The posterior maxilla is more frequently involved than the mandible when bone invasion occurs.

Retromolar carcinoma usually presents as advanced disease, 55–73 per cent having stage III/IV disease at presentation. Spread to regional lymph nodes occurs in 26–56 per cent of patients at presentation, having occult cervical node involvement.

Tumours of the retromolar trigone are usually well or moderately differentiated.

**Work up**

The complex anatomy of the retromolar region and the frequent extension of retromolar carcinoma make accurate preoperative imaging essential. CT has been demonstrated to have a high specificity, but low sensitivity for predicting mandibular bone invasion of retromolar carcinomas. MRI is considered the imaging modality of choice for retromolar tumours due to its ability to accurately stage the disease and demonstrate accurately anatomical relationships of the tumour, although mandibular invasion may still be hard to define.

**Treatment**

**PRIMARY**

The treatment of choice for retromolar tumours is surgical resection with pre/postoperative radiotherapy or chemoradiotherapy dependent on the stage of the tumour and histological findings. Radiotherapy as a sole treatment modality for retromolar carcinoma has been demonstrated to be associated with significantly worse recurrence rates and disease-free survival, although others have been unable to demonstrate this significance. The debate regarding the use of surgery or radiotherapy as the primary treatment modality is hampered by the lack of data regarding tumour thickness in this anatomical site. It is recognized that tumours in this site may be T3 in size, but superficial in nature.

Resection should be achieved with a 1 cm margin in all planes. It is recognized that the incidence of positive margins following resection of retromolar tumours is higher than other oral sites.

Small tumours of the retromolar trigone may be resected via a transoral route, however the posterior location of retromolar tumours and frequent extension of disease into adjacent anatomical sites often necessitates a mandibulectomy to facilitate access. Extensive tumours extending into the masticator space may require a cervicofacial incision, parotidectomy, ± zygomatic osteotomy and preservation of

<table>
<thead>
<tr>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
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<tbody>
<tr>
<td>65%</td>
<td>54%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Overall 5-year survival.

### Table 29.7 Tongue prognosis.

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>82%</td>
<td>65%</td>
<td>54%</td>
<td>22%</td>
</tr>
<tr>
<td>n = 322 (mainly radiotherapy)</td>
<td>n = 297 (mainly surgery)</td>
<td>n = 448 (brachytherapy only)</td>
<td></td>
</tr>
</tbody>
</table>

Overall 5-year survival. DSS, disease-specific survival.
the facial nerve for access, or an anterior approach including maxillectomy.135

Defects following the resection of small mucosal tumours may be left to heal by secondary intention, however larger lesions require reconstruction to prevent trismus. Simple reconstructive methods include use of a split skin graft or buccal fat pad reconstruction (Figures 29.36 and 29.37).

Tongue flaps and masseteric flaps have been described, however they lack flexibility and may be compromised in anything but the smallest of tumours.128

Given the low negative predictive value of CT for bone involvement and the high incidence of bone involvement demonstrated in retrospective series, a low threshold for bone resection should be adopted. A posterior marginal mandibulectomy (including coronoid) conducted via a visor or lip split soft tissue flap is oncologically safe in patients with no history of previous radiotherapy and no radiological signs of cortical bone involvement.127, 136 Patients demonstrating cortical bone involvement on imaging, or who have previously received radiotherapy should have a segmental mandibular resection. A posterior maxillectomy should be conducted when indicated.

The combination of mandibulotomy and posterior marginal mandibulectomy for large soft tissue lesions should be avoided in view of the increased risk of osteoradionecrosis, a segmental resection being warranted in these circumstances.137

Pedicled myocutaneous flaps, such as the pectoralis major flap, are stretched to their limit at this anatomical site, often resulting in delayed healing.127 The use of the radial free forearm flap or anterolateral thigh flap provides excellent reconstruction of larger soft tissue defects in the retromolar region, it being important to pay particular attention to flap design in this area. Where the resection involves the soft palate, the combination of free flap and superiorly based pharyngeal wall flap should be considered to minimize nasopharyngeal reflux.

Reconstruction following segmental resection should ideally be with free tissue transfer, such as the fibula, scapula or DCIA flaps. Since radiotherapy will almost certainly be indicated following segmental resection, the use of vascularized bone flaps results in more predictable healing with lower risk of nonunion/resorption.127 The use of reconstruction plates and purely soft tissue cover is particularly prone to failure in the retromolar region.138

Large tumours extending into mandible, maxilla, soft palate, tongue base and buccal mucosa require careful consideration regarding reconstructive options. Dual free flaps may provide ideal soft tissue and bony reconstruction, but at the increased risk of complications. The scapula flap is versatile enough in thin individuals to be able to reconstruct these extensive defects (Figures 29.38, 29.39 and 29.40).

NECK

Lymphatic spread to the neck is usually to levels I and II in the absence of detectable lymphadenopathy, however involved nodes in levels III–V may occur in the presence of nodes in levels I and/or II.130

Unlike tumours at other sites, there are few data correlating tumour thickness to incidence of cervical metastasis. An END (levels I–III/IV) is indicated for any tumour bigger than T1,123, 127, 130, 136 or where access to vessels in the neck is required for reconstruction.

PORT

Up to 58 per cent of patients may require postoperative radiotherapy/chemoradiotherapy,123 an indication of the typically advanced nature of retromolar carcinomas.

Recurrence

Local and/or regional recurrence may occur in 20–37 per cent,123, 124, 125 depending on primary treatment modality and stage of disease on presentation. Recurrence usually occurs in the first two years.130

Prognosis

Factors influencing survival are stage, involvement of the masticator space123 and cervical metastasis,123, 125, 130 mean
survival in patients with masticator space involvement being 38 months.123 Patients receiving surgery combined with radiotherapy have been demonstrated to have a significant survival advantage over patients receiving radiotherapy alone (Table 29.8).124

MAXILLARY ALVEOLUS AND HARD PALATE

Surgical anatomy

The maxilla comprises the maxillary alveolus and the hard palate. The osseous alveolar process supports the maxillary dentition, being covered by a mucoperiosteum with a stratified squamous epithelium. The maxillary alveolus merges laterally with the buccal mucosa and lips at the gingival sulcus and medially with the hard palate. The alveolar process extends to the upper end of the pterygopalatine arches posteriorly. The hard palate lies within the horseshoe shape of the maxillary alveolus, merging imperceptively with the alveolar mucosa. The hard palate has minor salivary glands located in the submucosa, 33 per cent of palatal tumours being derived from salivary epithelium.139 Posteriorly, the hard palate merges with the soft palate at the posterior edge of the palatine bone. Sensory innervation to the maxillary mucosa is by branches of the maxillary division of the trigeminal nerve. The nasopalatine nerve supplies the anterior hard palate, passing through the incisive foramen, the posterior palate being supplied by the paired greater palatine nerves that pass through the greater palatine foraminae. Lymphatic drainage is to the ipsilateral cervical nodes via the submandibular nodes or potentially the retropharyngeal nodes in posteriorly located tumours.

Epidemiology

Squamous cell carcinoma of the maxillary alveolus represents 3.5–6.5 per cent34,69 of oral cancers, being approximately one-third as common as mandibular alveolar carcinoma. Carcinoma of the hard palate is very unusual representing only 1–3 per cent140,141 of oral cancers. Aetiological factors include tobacco use and alcohol consumption. Palatal carcinoma is particularly associated with reverse smoking, a habit practised in parts of India by women.142,143,144

Patients tend to present in their sixth to seventh decade of life.140,143,145 There is an even distribution between the sexes, except where reverse smoking is practised when there is a greater frequency in females.143
Patients may present with pain, ulceration, loose teeth or poorly fitting dentures. Symptoms of advanced disease may include infraorbital paraesthesia, trismus or nasal obstruction. Most patients present with stage I or II disease.

Eight per cent of patients with carcinoma of the hard palate or maxillary alveolus present with cervical lymphadenopathy, a further 27 per cent having occult metastasis.

Work up

The surface extent of a maxillary carcinoma may be relatively easy to determine from clinical examination alone, however extension into the maxillary antrum and beyond requires additional imaging. Extension of tumour through the pterygoid plates into the masticator space may render a tumour inoperable. CT scans and MRI are complementary in the assessment of maxillary tumours.

Intranasal examination with a nasendoscope should be conducted to determine the extent of the tumour through the floor of the nose or medial antral wall.

All patients should have impressions taken for the provision of a temporary obturator, even if free flap reconstruction is anticipated. In the unfortunate situation of free flap failure, the presence of presurgical models will make prosthetic salvage considerably easier. If prosthetic reconstruction is to be considered from the outset, then early consultation with a prosthodontist is required.

Treatment

PRIMARY

Anaesthesia is usually accomplished with an oral tube, a tracheostomy only being considered for larger resections or free flap reconstruction. Patients requiring an upper cheek flap for access should have their eyes protected with corneal shields or temporary tarsorraphies.

The surgical goals that apply to hard palate and maxillary alveolar tumours are the same as those at other sites, notably surgical clearance of 1 cm in three dimensions. Small tumours may be approached perorally, however larger tumours may require an upper cheek flap or midfacial degloving to augment access.

Once the mucosal incisions have been completed, the soft tissues are elevated in a subperiosteal plane away from the tumour to allow access for bone cuts. Teeth may need to be extracted to allow osteotomy cuts and minimize postoperative complications. The use of a fine reciprocating or sagittal saw allows accurate bony resection. Care should be taken to avoid tooth roots. If the margins of resection extend posteriorly, the specimen may be disarticulated from the pterygoid plates with a curved osteotome. Posterior dissection may be completed with large curved scissors. The posterior dissection in the region of the pterygoids should be the last part of the resection due to the bleeding that occurs in this area. An ipsilateral coronoidectomy should be conducted to minimize impingement of the coronoid on the prosthesis or flap reconstruction. Defects that are to be reconstructed with a prosthesis should be lined with a split skin graft (Figures 29.41, 29.42 and 29.43).

Surgical closure of small maxillectomy defects may be achieved with local flaps, such as buccal fat pad, temporalis flaps or facial artery musculomucosal flaps. Large defects may require soft tissue or composite free tissue transfer (Figures 29.44, 29.45 and 29.46).

### Table 29.8 Retromolar prognosis.

<table>
<thead>
<tr>
<th>I (%)</th>
<th>II (%)</th>
<th>III (%)</th>
<th>IV (%)</th>
<th>Overall 5 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>74</td>
<td>75</td>
<td>43.6</td>
<td>60%</td>
</tr>
<tr>
<td>I–III, 83</td>
<td></td>
<td>IV, 61</td>
<td></td>
<td>Overall 5 year 69% (DSS)</td>
</tr>
</tbody>
</table>

DSS, disease-specific survival.

![Figure 29.41 Case 8: Alveolar squamous cell carcinoma anterior maxilla.](image1)

![Figure 29.42 Case 8: Surgical defect following resection.](image2)
The use of an appropriate defect classification system allows for planning of reconstruction and communication with colleagues.

**NECK**

Historically, regional spread from maxillary tumours has been considered low, however this may be due to coregistration of hard palate and alveolar tumours such as sinonasal tumours. Cervical metastasis has been demonstrated in 35 per cent of patients with hard palate or maxillary alveolar carcinomas, an elective I–III neck dissection being considered appropriate for lesions of T2 size or greater. Consideration should be given to clearing the facial lymph nodes when conducting a neck dissection for maxillary tumours.

**PORT**

Postoperative radiotherapy has been suggested for T3 or greater disease, positive margins, perineural or perivascular invasion or multiple cervical nodes, particularly if they demonstrate extracapsular spread.

**Recurrence**

Locoregional control of hard palate and alveolar tumours following initial therapy is in the region of 40–45 per cent, increasing to 68 per cent following secondary intervention. Salvage of local recurrence may be achieved in 33 per cent and regional recurrence in 71 per cent. Over 90 per cent of recurrence occurs within the first two years, similar to other sites.

**Prognosis**

Five-year absolute survival for hard palate carcinoma is 57 per cent, five-year survival for alveolar carcinoma being 49 per cent. Tumour stage and presence of cervical metastasis influence long-term survival.

**MANDIBULAR ALVEOLUS**

**Surgical anatomy**

The mandibular alveolus represents that part of the mandible that is ‘intraoral’. The osseous alveolar process of the mandible supports the dentition and is covered by a
mucoperiosteum. The mandibular alveolus merges laterally with the buccal mucosa/lips at the gingival sulcus and medially with the floor of mouth. The alveolar process extends to the retromolar trigones posteriorly. Sensory innervation to the mandibular alveolus is by the mandibular division of the trigeminal nerve. Lymphatic drainage is to the ipsilateral submandibular and submental nodes to the deep cervical chain. Lymphatic drainage towards the midline may be bilateral. Following loss of the dentition, there is considerable resorption of the alveolar process, leaving only a thin strip of attached mucoperiosteum on the crest of the mandible between the floor of mouth and buccal mucosa.

Epidemiology

Squamous cell carcinoma of the mandibular alveolus represents 7.5–17.5 per cent of oral cancers, although it represents up to 30 per cent of oral cancers in the Japanese population. Mandibular alveolar carcinoma is three times more common than maxillary alveolar carcinoma. Rarely, primary intraosseous carcinomas may occur, being derived from residues of odontogenic epithelium within the mandible. The use of tobacco, particularly chewing tobacco, and alcohol is associated with alveolar carcinoma.

Patients tend to present later in life in their seventh decade, the disease being slightly more common in males.

Presentation

The most common presenting symptom is pain, occurring in 54–86 per cent of patients. Patients who are dentate may note loosening of teeth while edentulous patients may note a change of fit of their dentures. Labial paraesthesia may be a presenting feature in up to 14 per cent of patients. Unfortunately, patients still present with a history of delayed healing of an extraction socket in up to 28 per cent of cases. The majority of lesions of the mandibular alveolus are located posterior to the canines, extension to the floor of mouth or buccal mucosa being common. Alveolar tumours are staged by their size until there is invasion of tumour through cortical bone into marrow space when the tumour becomes T4. Cervical lymphadenopathy is present in 24–32 per cent of patients at presentation, usually to levels I and II, 15 per cent of patients having occult metastasis. Up to 94 per cent of patients have evidence of bone involvement clinically. Most tumours at this site are usually well or moderately differentiated.

Work up

The most important aspect of working up mandibular alveolar tumours is to determine the degree of bone involvement since this determines the extent of tumour resection.

Treatment

PRIMARY

Mandibular alveolar carcinoma is considered a surgical disease. Invariably, some degree of bone resection is required, 6–7 per cent requiring soft tissue resection only. Small alveolar carcinomas with no clinical evidence of significant bone involvement may be resected via a peroral approach and a marginal mandibulectomy, aiming for a 1 cm soft tissue and bony margin. Larger tumours with obvious bone involvement require segmental resection and extraoral access incisions. Segmental resection should also be considered for small tumours abutting a mandible previously treated with radiotherapy, massive soft tissue tumours adjacent to the mandible, involvement of the inferior dental nerve or intraosseous tumours (primary or secondary). Marginal mandibulectomy is preferable to segmental resection whenever oncologically acceptable. If a marginal resection is conducted, then reconstruction may usually be achieved by primary closure (Figures 29.47, 29.48 and 29.49).

More extensive mucosal defects may require reconstruction with a skin graft; local flaps such as the FAMM (facial artery muscular mucosal) flap, nasolabial flap or buccal fat pad; or microvascular free tissue transfer to achieve acceptable soft tissue closure. Segmental mandibular resection should be accompanied with composite microvascular free flap reconstruction whenever feasible (Figures 29.50, 29.51, 29.52 and 29.53).

The use of a recognized mandibular defect classification helps surgeons plan appropriate reconstruction and communicate effectively with colleagues. The H, C, L, o, m, s classification system accurately describes mandibular surgical defects.

NECK

Regional spread of mandibular alveolar tumours is usually to the ipsilateral level I–III nodes. Elective neck dissection is
indicated in tumours T2 in size or greater or any tumour with demonstrable bone invasion, clearance of levels I–III being adequate. Lesions overlying the symphysis are thought to be associated with a higher risk of cervical metastasis and may require bilateral neck dissections. It has been argued that a staged neck dissection should be considered if histological examination of the primary tumour demonstrates bone involvement. A more extensive neck dissection should be conducted in the presence of confirmed cervical metastasis, level V requiring treatment.

PORT
Indications for postoperative radiotherapy include positive margins (soft tissue or bone), multiple positive nodes or extracapsular spread.

Recurrence
Recurrence rates for mandibular alveolar carcinoma at two years are 13–25 per cent. Higher recurrence rates are associated with increasing T stage and positive resection margins.

Prognosis
Overall five-year survival for lower alveolus carcinoma is 50–60 per cent, disease-specific survival being 73–80 per cent.
Cervical metastasis has been demonstrated to significantly reduce prognosis for lower gingival carcinoma.\textsuperscript{156} Increasing T stage (and particularly tumours greater than 3 cm),\textsuperscript{151} bone involvement (cortical or cancellous)\textsuperscript{151} and positive resection margins\textsuperscript{150, 151} are associated with decreased prognosis.\textsuperscript{150, 151} Tooth extraction at the site of primary tumour does not influence prognosis.\textsuperscript{150, 151}

**MANAGEMENT OF THE MANDIBLE**

Tumours of the mandibular alveolus, the floor of mouth, buccal mucosa or retromolar trigone may involve the bone of the mandible. Involvement of the mandible has significant consequences regarding management of the patient.\textsuperscript{150} Several questions need to be answered when managing a patient with potential mandibular involvement.

**How does squamous cell carcinoma invade the mandible?**

Squamous cell carcinoma (SCC) invades the mandible either in an invasive or erosive manner.\textsuperscript{154, 157} Invasive tumours demonstrate fingers or islands of tumour advancing deeply into bone with no obvious osteoclastic activity. Erosive tumours have a broad advancing front with osteoclast activity and connective tissue between the tumour and bone, although as the depth of invasion increases, they may become more erosive in character. Large, deeply invading tumours are more likely to demonstrate an invasive pattern of spread and involve the mandible.\textsuperscript{154, 158}

Tumours enter the mandible at the point of contact,\textsuperscript{154, 159} usually the junction of the attached and reflected mucosa, whether the patient is edentulous or dentate. The mandible should be considered at risk at any point where tumour is in contact and this is taken into account when planning resection. Clinical fixation of the tumour to bone is not necessary for bone invasion to occur.

It has been demonstrated that it is primarily the size and extent of the tumour that dictates the pattern of spread once in bone rather than anatomical features, such as the inferior alveolar nerve or periodontal ligament. Preferential spread within the mandible via the inferior alveolar nerve or medullary space is rare,\textsuperscript{154, 160} justifying 1 cm margins.

Tumours demonstrating an invasive pattern of spread are more likely to give rise to cervical metastasis with extracapsular extension,\textsuperscript{154} an indication of their more aggressive nature.

**How do we detect bony invasion?**

Preoperative imaging of the mandible is necessary to determine if bone resection is required, and if so the appropriate type of resection.\textsuperscript{161}

At present, there is no single investigation that can reliably predict bone invasion (Table 29.10). An OPG radiograph should be requested for all cancer patients. This plain radiograph is not only useful for demonstrating bony invasion, but also for assessing mandibular height, dental anatomy and dental pathology. It should be remembered that plain radiographs do not detect initial invasion until 30 per cent demineralization has occurred, giving rise to reduced sensitivity.\textsuperscript{162} Clinical examination and OPG alone are probably inadequate for accurate assessment of mandibular invasion.\textsuperscript{162}

Axial MRI views with T1 and STIR fat suppression are very sensitive for imaging the primary site of oral cancer with an adequate specificity.\textsuperscript{163} Bone scintigraphy or

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**Table 29.10** Mandible imaging.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>82</td>
<td>61</td>
</tr>
<tr>
<td>Plain films</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Computed tomography\textsuperscript{61}</td>
<td>75</td>
<td>86</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>85</td>
<td>72</td>
</tr>
<tr>
<td>Single photoemission computed tomography</td>
<td>97</td>
<td>65</td>
</tr>
<tr>
<td>Bone scintigraphy</td>
<td>93</td>
<td>74</td>
</tr>
</tbody>
</table>

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**Figure 29.52** Case 11: Postoperative occlusion and intraoral fibula skin paddle.

**Figure 29.53** Case 11: Postoperative orthopantomogram demonstrating fibula flap *in situ*. 
single-photon emission computed tomography (SPECT) may be considered in equivocal cases. When bone involvement is equivocal on preoperative imaging, then periosteal stripping looking for cortical bone disruption at the time of resection may help the clinician plan the resection.

How do we manage bone involvement?

A rim resection/marginal mandibulectomy should be considered for T1/2 tumours with early invasion (< 5 mm) and adequate bone height of the mandible (dependent on preoperative imaging, clinical examination and periosteal stripping). Traditionally, rim resections have been conducted horizontally, however with the understanding that tumour may enter the mandible at any point of contact it becomes apparent that the saw cut should be angled to accommodate this. Marginal resections in the retromolar region may include the coronoid process. Every effort should be made to preserve the inferior alveolar neurovascular bundle when conducting a marginal resection in an edentulous mandible so as to minimize the risk of avascular necrosis and iatrogenic fracture postoperatively. The anterior and posterior margins of a rim resection should be curved so as to minimize the risk of iatrogenic mandibular fracture postoperatively. Rounding of the edges of the rim resection also minimizes the risk of iatrogenic mandibular fracture postoperatively. The anterior and posterior margins of a rim resection should be curved so as to minimize the risk of iatrogenic mandibular fracture postoperatively. The surgeon should aim for a 1 cm margin of the soft tissue tumour, as it is highly unusual to get a positive bone margin in the absence of a positive soft tissue margin.

Usually, intraoperative assessment of bony margins is not conducted, however techniques for frozen section analysis of cancellous and cortical bone have been described.

What are the quality of life implications?

Rim resection of the mandible maintains bony continuity and hence is usually associated with an excellent functional and cosmetic outcome. The rim resection in addition to maintaining the structural integrity of the mandible also usually preserves sensation of the lower lip and muscular attachments. With modern reconstructive techniques, the Andy Gump deformity should no longer be encountered.

Patients’ quality of life following mandibular resection is influenced by many factors, such as site of bony resection, type of bony resection, the soft tissue resection, type of reconstruction, adjunctive radiotherapy, etc.

It is recognized that whenever oncologically sound, a rim resection should be the resection of choice. However, it has been demonstrated that there is little or no difference in quality of life between a rim resection and segmental resection with composite microvascular free tissue transfer, particularly when the resection is greater than 4 cm.

**LIP CANCER**

**Epidemiology**

Cancer of the lip is the most common malignant tumour affecting the head and neck and its clinical behaviour is similar to that of skin cancer. Incidence rates vary and examples are 13.5 per 100 000 in Oceania, 12 per 100 000 in Europe and 12.7 per 100 000 in North America. The factors commonly cited as important in lip cancer are solar radiation, tobacco smoking and viruses. The rate of lip cancer appears to be directly related to the amount of sun exposure and its incidence increases towards the equator. It is much more common in men than women, with a 95:5 ratio. The main aetiological factor of solar radiation means that the lower lip is much more commonly affected than the upper lip. Ninety per cent of tumours arise in the lower lip with 7 per cent occurring in the upper lip and 4 per cent at the oral commissure. Squamous cell carcinoma is the most common histological tumour type, followed by basal cell carcinoma. The most common non-squamous form of lip cancer arises from tumours of the minor salivary glands, with the upper lip being more commonly involved than the lower lip. The distribution of lip cancer is shown in Figure 29.54.

**Figure 29.54** Distribution of lip cancer.
Clinical characteristics

The clinical presentation of cancer of the lip is usually that of an exophytic crusted lesion with variable invasion into underlying muscle (related to the size of the primary tumour). The adjacent lip often shows features of actinic sun damage such as crusting, colour change, thinning of the lip and various associated areas of leukoplakia (Figure 29.55).

The staging of primary cancer of the lip is similar to that of the oral cavity and is shown in Table 29.11. Tumours less than 2 cm are staged as T1, 2–4 cm as T2, >4 cm as T3 and tumours with invasion of deep soft tissues, adjacent bone or skin are staged as T4.

Investigations

Imaging of early stage tumours of the lip is usually not indicated. However, advanced tumours of the lip (particularly if they are adherent to the adjacent mandible) require CT imaging or MRI to allow complete staging and treatment planning with regard to resection margins which may include adjacent jaw bone.

Treatment

Early stage lip cancer can be treated equally well by surgery or radiation therapy. The five-year crude survival rates for surgical treatment are around 75–80 per cent for T1 to T2 tumours, dropping to 40–50 per cent for T3 and T4 tumours. The presence of cervical nodes at presentation is a poor prognostic indicator. About 15 per cent of patients fail initial therapy and this usually presents as local or regional failure.

FACTORS AFFECTING CHOICE OF TREATMENT

Treatment is guided by the anatomical position of the tumour and also by associated patient factors. Small lesions are managed by simple surgical excision and primary closure. Equally good results are achieved with external beam radiotherapy (which may be more acceptable in elderly patients). Larger lesions of the lip require more consideration with regard to reconstruction techniques. The amount and type of reconstruction necessary will relate to the extent of lip resection and whether adjacent tissue can be used with a good aesthetic outcome. The functional outcome of the repair with regard to lip sensitivity and muscle function also needs to be taken into consideration. The general physical and medical and psychological condition of the patient is important in deciding between primary surgery and primary radiotherapy.

REPAIR OF LIP DEFECTS

Ablation and reconstruction should ideally be performed at the same time. It is important to remember that the lip should have sensation, motion, prevent drooling, permit speech and have a reasonable cosmetic appearance. Whenever possible, full thickness skin flaps (skin, muscle and mucosa) should be used. The repair should provide sufficient mucosa contiguous to the commissure to avoid contracture.

LIP SHAVE AND MUCOSAL ADVANCEMENT

Superficial field change lesions affecting the external vermilion of the lip, such as leukoplakia or actinic keratoses, are best managed by a lip shave and mucosal advancement. With extensive premalignant changes, the entire vermilion surface of the lip may require excision. Following adequate excision of the vermilion border, the mucosa of the residual labial sulcus aspect of the lower lip is mobilized down to the gingival buccal sulcus. The blood supply to this tissue is maintained via its lateral margins. A horizontal relieving incision in the buccal sulcus is often required to allow sufficient mucosal advancement. The undermined mucosa is now advanced to the edge of the previous vermilion excision and accurate alignment restores the vermilion border. The advanced mucosa is sutured to the remaining lip with interrupted resorbable monofilament sutures. An application of chloramphenicol ointment prevents scaling of the lip during healing and irritation from the sutures. The patient is warned that an initial loss of sensation will return over the

<table>
<thead>
<tr>
<th>Table 29.11</th>
<th>TNM definition of lip cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>Description</td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but not more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e. chin or nose</td>
</tr>
</tbody>
</table>

T, primary tumour.
course of a few months. Following treatment, advice on the use of sun block to the lip to prevent recurrence of the original problem is given.

LOWER LIP

The techniques for treating defects of the lower lip are summarized in Figure 29.56, and described in detail below.

Infiltrating lesions of the lower lip affecting less than one third

Small lesions invading into the adjacent muscle are amenable to a wedge excision. A through and through surgical defect is thus created. In closing the defect, the vermilion is temporarily approximated with a resorbable suture. This allows the underlying muscle to be closed in two layers. The external skin is closed with an interrupted monofilament and the labial and intraoral wound is closed with a resorbable suture. The excision can also be completed using a W-plasty or half W-plasty to avoid the bottom of the excision encroaching on the crease line of the chin (Figure 29.57).

Lower lip defects one-third to two-thirds

Defects of the lower lip over one-third require a different surgical approach. The dimensions of the lip resection require the introduction of tissue from the other lip by means of an Abbe or an Abbe-Estlander flap or rotation of tissue from the adjacent lip via a Karapandzic. 181, 182, 183, 184

**Abbe-Estlander flap**

The Abbe-Estlander staged reconstruction requires the development of a triangular full thickness flap from the upper lip. The width of the flap is one-half to two-thirds the horizontal length of the lower lip defect, with the vertical dimension of the flap being the same as the surgical defect. The flap is pedicled on the labial artery with the full thickness incision extending within 2–3 mm of the vermilion border. With the flap mobilized, initial inset into the defect is completed in a layered fashion flap (Figure 29.58). Two to three weeks after the harvest of the flap, the pedicle is divided and the final insetting of the flap is completed. Care is taken to reconstruct accurately the white line. The Estlander modification of the cross-lip flap is used to reconstruct the oral commissure. (An Estlander flap is a laterally based Abbe flap that is used when defects affect the commissure.) The commissure is thus rotated when the tissue is transferred to the defect in the lower lip. The patient needs to be placed on a soft diet while the transposed flap takes. Venous compromise of the flap is usually due to leaving too thin a bridging pedicle or too tight a closure. A few sutures should be removed in the early stages to see if this reverses the venous compromise, or consideration to the use of medicinal leeches to deal with the venous stasis needs to be undertaken. The bridging pedicle is divided under local anaesthetic after 2–3 weeks.

**Karapandzic flap**

The Karapandzic flap is useful for defects involving more than two-thirds of the lower lip where the defect is in the midline. 185 The main advantage of the Karapandzic flap is that the nerve and blood supply to the underlying orbicularis oris muscle is retained and the underlying orbicularis muscle is rotated so that a sensate functional lip reconstruction occurs. The tissue is rotated from the nasolabial region and this tissue is shifted medially and rotated into the lower lip. The lateral incisions of the Karapandzic flap follow the nasolabial skin creases. Resection of the tumour on the lower lip is performed in the usual manner and then the skin
incisions for elevation of the Karapandzic flap are made. It is important to avoid division of the muscle fibres containing the neuromuscular control of the orbicularis under the skin. To aid mobilization, mucosal incisions are placed in the gingival labial and gingival buccal sulcus on each side. The flap is elevated in a subcutaneous plane remaining superficial to the orbicularis oris muscle. Sufficient length in the mucosal incisions must be performed to permit medial mobilization of both flaps for a midline closure. The repair of the defect begins with the vertical midline closure of the lower lip with approximation of the vermilion border by a temporary nylon suture. The advanced muscle in the orbicularis oris is closed in the midline followed by external skin closure. Following this, reapproximation of the suture line between the advanced cutaneous margin of the flap and the residual cutaneous margin of the chin and nasolabial region is undertaken (Figure 29.59). The larger the defect, the tighter the reconstructed lip will be, and thus a certain amount of microstomia can be present following Karapandzic flap reconstruction. This is more easily accommodated in the elderly edentulous patient where there is a certain amount of skin laxity. The restricted oral aperture will stretch gradually over the course of a few months and the stretching can be augmented by physiotherapy.

**Lower lip defects greater than two-thirds**

With larger defects of the lower lip, reconstruction requires either large cheek flaps to be advanced to repair the defect or the use of free tissue transfer. The common forms of cheek flap include the bilateral Gillies fan flaps or the Bernard–Webster cheek flap reconstruction. In the Gillies fan flap, a full thickness incision is made around the commissure extending on to the upper lip at the nasolabial fold. The advanced muscle in the orbicularis oris is closed in the midline followed by external skin closure. Following this, reapproximation of the suture line between the advanced cutaneous margin of the flap and the residual cutaneous margin of the chin and nasolabial region is undertaken (Figure 29.59). The larger the defect, the tighter the reconstructed lip will be, and thus a certain amount of microstomia can be present following Karapandzic flap reconstruction. This is more easily accommodated in the elderly edentulous patient where there is a certain amount of skin laxity. The restricted oral aperture will stretch gradually over the course of a few months and the stretching can be augmented by physiotherapy.

**Abbe flap.** (a) T1 squamous cell carcinoma, right lower lip; (b) outline of excision marked on lower lip and rotation flap on upper lip; (c) the tumour has been excised; (d) the upper lip rotation flap has been raised. Note the anterior limit of the incision at the vermilion border; (e) the upper lip rotation has been inserted into the lower lip and the donor site repaired; (f) three weeks later, just prior to incising the pedicle.
In the Bernard–Webster flap, Burrows triangles are formed at the edge of the lower lip excision. Incisions are extended laterally from the base of the defect. The buccal mucosa from the base of the excised Burrows triangles are rotated inferiorly over the free margin of the triangle and used to reconstruct the lateral vermilion of the lip. The two flaps are advanced medially, the triangles closed and the flaps are approximated in layers (Figure 29.61).

Free tissue transfer is required for lip reconstruction when the total remaining lip or adjacent rotated tissue is insufficient to create a reasonable circular and symmetrical mouth. Often these defects include cheek, skin and underlying mandible. In this case, a radial artery free forearm flap using the palmaris longus tendon to suspend the lower lip is used. This reconstruction technique, however, is insensate and immobile and merely provides a static platform for the mobile upper lip to close against. The flap is used as a double paddled flap rotated on the underlying palmaris longus tendon. The skin and contour match is not as accurate as when using adjacent rotated tissue. The lip can remain ptotic and may require wedge excisions a few months following reconstruction to improve the lip tone, allowing the formation of an adequate seal with the upper lip. Similarly, fascial slings may be required to maintain lip closure.

UPPER LIP

In the upper lip, defects again can be divided into: less than a third, one-third to two-thirds and greater than two-thirds to complete defects. The techniques for treating them are summarized in Figure 29.62.

Defect involving up to a third of upper lip
Similar to lower lip defects, wedge excisions and advancement flaps can address upper lip defects which involve up to one-half of the width of the upper lip. Care is taken to respect the relevant aesthetic subunits. Defects of less than a third in the midline can be closed primarily.

Defects between one-third and two-thirds
These can be reconstructed with cross lip flaps from the lower lip. Perialar crescentic advancement flaps can be used to disguise the advancement of the upper lip when the advancement encroaches on the medial part of the nose.

Defects greater than two-thirds of the upper lip
A Burrow-Diffenbach reconstruction can be performed. The Burrow-Diffenbach flap replaces upper lip defects by utilization
of laterally based advancement flaps. Bilateral perialar crescentic excisions are required to provide adequate advancement.

NECK DISSECTION IN LIP CANCER

Squamous cell carcinoma of the lip does not appear to be as lethal as squamous cell carcinoma at other sites in the oral cavity. The favourable survival rate of lip cancer is often due to the early stage of the presentation of tumours and most large series in the literature show that the majority of patients have small lesions without palpable cervical metastases. The local recurrence rate is low due to the relative ease of surgical excision and even re-excision because of local failure leads to salvage in 75–80 per cent of patients. The incidence of synchronous cervical metastases increases as the size of the primary tumour increases. The primary lymphatic drainage of the lower lip is to the submental and submandibular level Ia and Ib cervical lymph nodes. Neck dissection is generally not performed in the absence of clinically suspicious cervical lymph nodes as less than 5 per cent of patients are likely to develop recurrence in the neck following treatment of the primary lesion.

RADIOTHERAPY TECHNIQUES

Various studies have shown that for small tumours, radiation therapy can achieve a cure rate equivalent to that obtained surgically. However, the cosmetic results of radiation therapy to the lip may not be as satisfactory as surgical excision and repair. Surgical excision of small lip tumours involves relatively minor surgery, often under local anaesthetic and may be therefore less burdensome for the patient than a course of radiotherapy.

EXTERNAL BEAM THERAPY

The lower lip is one of the few ideal sites for orthovoltage x-ray therapy. Using a single anterior field a fractionated course of 50 Gy in 15 fractions over 3 weeks is given.

Table 29.12 Tumour thickness and survival rate in lip cancer.

<table>
<thead>
<tr>
<th>Tumour size (cm)</th>
<th>Five-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>&lt;2</td>
<td>84</td>
</tr>
<tr>
<td>&lt;3</td>
<td>58</td>
</tr>
<tr>
<td>&lt;4</td>
<td>67</td>
</tr>
<tr>
<td>&gt;4</td>
<td>62</td>
</tr>
</tbody>
</table>

Presence of nodal disease and five-year survival: N+ 61%; N0 89%.

BRACHYTHERAPY

192-iridium brachytherapy can be used in the treatment of lip cancer. Patients can be treated twice a day for 4–5 days with a total radiation dose between 40 and 45 Gy in eight to ten fractions. The Paris system is often used, where needles are placed horizontally and parallel to the mucosa of the lip with 9 mm spacing between them.

PHOTODYNAMIC THERAPY

Photodynamic therapy can also be used to treat primary cancer of the lip. The light sensitizing drug, such as photothrin, is given intravenously followed 4 days later by a single nonthermal illumination of the tumour using a light dose of 20 J/cm² with an irradiance of 100 mW/cm² (Figure 29.63). This form of treatment yields complete response rates comparable to those published for surgery or radiotherapy. As this treatment works by a cold photochemical process producing apoptosis and vascular shut down, less scarring should occur compared to radiotherapy and surgery. However, clinical experience suggests that some scarring does occur with larger lesions and the problems of light sensitivity and pain following treatment may limit its general application. However, the lack of tissue memory for photodynamic therapy means that, unlike radiotherapy, this treatment can be given on a number of occasions.

Survival rates for lip cancer

The survival rates for lip cancer are shown in Table 29.12.192

Key Evidence

- Although screening for cancer has proved effective for some major cancers there is no evidence to support screening for oral cancer.
- The routine use of panendoscopy in the work up of patients with oral cancer is not warranted, however a computed tomography (CT) scan of the chest is indicated in most patients.
- Management of the primary tumour involves surgical resection and appropriate reconstruction. Radiotherapy (brachytherapy) may be considered for accessible, well-
demarcated lesions not adjacent to the mandible.
- Patients should be offered elective neck treatment if characteristics of the primary tumour suggest there is a greater than 20 per cent risk of occult nodal metastasis, although entry into appropriate clinical trials should be offered.

KEY LEARNING POINTS

Buccal carcinoma
- The most common site for oral cancer in South East Asia.
- Associated with betel/paan consumption.
- Good surgical reconstruction is required to prevent postoperative trismus.
- Up to 26 per cent have occult nodal metastasis at presentation.
- Consider elective neck dissection if tumour >4 mm thick.

Floor of mouth carcinoma
- One of the most common sites for oral cancer.
- Leukoplakia of the floor of mouth has a 1–2.9 per cent annual malignant transformation rate.
- Careful consideration should be given to management of the submandibular ducts.
- Anterior lesions may require treatment of both necks.
- Tendency for cervical metastasis to occur in thinner tumours than other sites.

Tongue carcinoma
- One of the most common sites for oral cancer.
- Usually presents as stage I/II disease.
- Elective neck dissections should include levels I–IV because of skip metastases.
- Reconstruction should maximize function of the residual tongue.

Retromolar carcinoma
- Represents 6–7 per cent of oral carcinomas.
- Frequently presents as stage III/IV disease with extension into adjacent sites.
- Accurate preoperative imaging is required to determine the extent of disease.

Maxillary alveolus and hard palate
- Carcinoma of the maxillary alveolus is three times less common than the mandibular alveolus.
- Carcinoma of the hard palate represents only 1–3 per cent of oral cancers.

- Palatal carcinoma is associated with reverse smoking.
- All patients should have dental impressions as part of their work up.
- Some degree of bone removal is nearly always required.

Mandibular alveolus
- Represents approximately 10 per cent of oral cancers, although it represents up to 30 per cent in the Japanese population.
- Ninety-four per cent of tumours involve bone.
- Alveolar carcinoma is a surgical disease requiring a rim or segmental resection of the mandible.

Management of the mandible
- Bone involvement may be by erosion or invasion.
- Bone involvement occurs at any point where tumour contacts bone.
- Magnetic resonance imaging, computed tomography, single-photon emission computed tomography and periosteal stripping are complimentary in assessing bone involvement.
- Bone margins should be dictated by overlying soft tissue margins.
- Rim resection should be conducted when oncologically acceptable.

Lip cancer
- Lip cancer arises mainly as a result of solar radiation.
- Surgical reconstruction usually involves local rotation flaps.
- Neck metastases are unusual.
- Radiotherapy is reserved for elderly and medically unfit patients.

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For there is nothing either good or bad, but thinking makes it so.

William Shakespeare, *Hamlet*, Act 2, Scene 2

**INTRODUCTION**

The nasopharynx is located behind the nasal cavity and above the oropharynx. The nasopharynx, also known as the post-nasal space, is located in the centre of the head. It is a region where thorough clinical examination is not easy and it is even more difficult to expose the region adequately for surgical resection of malignant lesions. Its connection with the middle ear through the Eustachian tubes and its vicinity to the skull base and the cranial nerves further demonstrate its crucial, functional and structural importance in otorhinolaryngology. The investigatory procedures and the treatment strategies used in lesions in the nasopharynx are quite different from those used in other pathologies in the head and neck region.

**SURGICAL ANATOMY**

The nasopharynx is the upper one-third of the pharynx and is separated from the oropharynx below by the soft palate. Anatomically, it is the space situated behind the nasal cavities and its mucosal lining starts immediately behind the posterior choana. It is actually located in the centre of the head and is more than 10 cm from the skin surface of the head in all directions. The undersurface of the body of the sphenoid bone forms the roof of the nasopharynx which slants downwards to form the posterior wall in front of the arch of the atlas and upper part of the body of the axis vertebra. The floor of the nasopharynx is formed by the upper surface of the soft palate which separates the nasopharynx from the oropharynx below. The lateral wall of the nasopharynx is formed by the opening of the Eustachian tubes superiorly and the upper part of the superior constrictor muscle inferiorly. The orifice of the Eustachian (auditory tympanic) tube is delineated by an incomplete cartilaginous ring, the deficient portion is in the inferolateral aspect. The medial portion of the cartilaginous ring elevates the overlying mucosa to form the medial crura. The slit-like space formed by this medial crusa and the posterior wall of the nasopharynx is the fossa of Rosenmüller.

The muscular wall of the nasopharynx is formed by the superior constrictors lying deep to the pharyngobasilar fascia. The fascial sheets join to form a median raphe which extends from the skull base downwards along the entire posterior pharyngeal wall. The lymph nodes that drain the nasopharynx lie in the retropharyngeal space outside the pharyngobasilar fascia and in front of the prevertebral fascia. The cranial nerves IX, X, XI and XII, the carotid sheath and the sympathetic trunk traverse the parapharyngeal space which is lateral to the superior constrictor.

The roof of the nasopharynx is lined by pseudostratified ciliated epithelium while the posterior wall is lined with stratified squamous cells. The epithelium has a well-defined basement membrane and there is abundant lymphatic tissue in the lamina propria. This lymphoid tissue forms the pharyngeal tonsil or adenoid in children.

Branches of the internal maxillary artery supply the nasopharynx and venous drainage is to the pterygoid plexus, then to the facial and internal jugular veins. The sensory nerve supply of the region is from branches of the maxillary nerve. The lymphatic supply of the nasopharynx drains...
into the retropharyngeal lymph nodes. Efferent lymphatics from these nodes and those that come directly from the nasopharynx drain to the deep cervical lymph nodes. The lymphatic drainage then passes down the neck nodes in an orderly fashion, from the high neck nodes to the lower ones.

**PATHOLOGY**

Both benign and malignant lesions are seen in the nasopharynx. Congenital pathologies such as dermoid cysts, teratomas and encephalocele are uncommon and usually seen in neonates or children. They frequently present with nasal obstruction and breathing disturbances. The diagnosis is usually arrived following investigations such as imaging studies and endoscopic examinations.

**BENIGN TUMOURS**

Most benign tumours in the nasopharynx arise from the minor salivary glands in the nasopharynx. Occasionally, a juvenile angiofibroma presents as a vascular mass in the nasopharynx. Benign tumours arising from the epithelial linings of the nasopharynx are relatively uncommon.

For minor salivary gland tumours, the presenting symptoms are increasing nasal discharge and nasal obstruction. The diagnosis is usually confirmed with biopsy during endoscopic examination with the finding of a lobulated mass in the nasopharynx.

**Angiofibroma**

Juvenile nasopharyngeal angiofibroma (JNA) occurs in male teenagers and is a benign but locally aggressive tumour. The tumour contains both vascular and fibrous elements intermingling together. The patient presents with nasal obstruction and epistaxis, one symptom usually predominates and this depends on the proportion of either of the two elements present. Recurrent epistaxis, which can be severe, is usually the presenting symptom. The origin of JNA is the posterolateral aspect of the roof of the nasal cavity in the region of the sphenopalatine foramen. When the tumour increases in size, it may extend into the pterygopalatine fossa and then posteromedially into the nasopharynx or it may enlarge laterally into the infratemporal fossa. Other routes of expansion include superiorly eroding the sphenoid sinus or anteriorly into the maxillary sinus. Growth into the orbit through the inferior orbital fissure will lead to proptosis and in some cases extension superiorly into the middle cranial fossa is observed.

On macroscopic examination, the angiofibroma is lobulated in appearance and its consistency ranges from spongy to a varying degree of firmness depending on the proportion of vascular tissue and fibrous component that forms the tumour. Microscopically, tumour is unencapsulated and formed by numerous blood vessels of varying calibre coursing through a fibrous tissue stroma. The thickness of the muscular coat of these vessels varies and in general elastic fibres in these vessels are lacking, thus the ability to retract is reduced.

This lack of contractile tissue is the pathological reason for frequent episodes of epistaxis once a minor vessel starts to bleed. These clinical features of repeated epistaxis and nasal obstruction in a male adolescent, together with the finding of a vascular mass in the nasopharynx, clinches the diagnosis.

Imaging studies are required to confirm the diagnosis and to assess the extent of the tumour. The pathognomonic feature of this tumour on plain x-ray consists of bowing of the anterior wall of the maxillary sinus anteriorly and the erosion of the base of the medial pterygoid plate. Angiography reveals typical vascular tumour blush with multiple sources of blood supply and for large tumours bilateral supply is not uncommon. The internal maxillary artery and its branches are usually the principal feeder.

**Treatment**

Localized minor salivary gland tumours of the nasopharynx can be transnasally removed with the assistance of the endoscope. In cases of recurrent tumours or large tumours that occupy the entire nasopharynx, a transpalatal excision of the tumour may be required. In view of the benign nature of these tumours, a close but clean surgical resection margin is adequate for eradication of the pathology.

As the location of the angiofibroma is behind the maxilla, the most direct approach for its removal is from the front. Removing the medial wall of the maxilla will enhance its exposure and facilitate its removal. This can be performed following a lateral rhinotomy incision or midfacial degloving approach. Once the tumour is exposed it can be removed with blunt dissection. With the application of the endoscope, which greatly aids visualization of the region, complete removal of the tumour can be achieved. As the angiofibroma is a vascular tumour, preoperative selective embolization is one option to reduce blood loss during resection. Selective cannulation of the feeders of the tumour should be carried out 48 hours prior to the resection. Although the embolization procedure has a small risk of leading to cerebral ischaemia, in established centres the benefit outweighs the risk.

**MALIGNANT TUMOURS**

**Lymphoma**

The nasopharynx has abundant lymphoid tissue and this forms the superior part of the Waldeyer's ring of lymphoid tissue. Thus one of the differential diagnoses of any malignant lesion in the nasopharynx is lymphoma. Diffuse B-cell lymphomas are most common and the symptoms are those of a mass in the nasopharynx, nasal obstruction, middle ear effusion or epistaxis. The biopsy of the tumour should include fresh unfixed tissue to allow immunostaining to give a definite diagnosis.

**Salivary gland malignancies**

Minor salivary gland tumours include the adenoid cystic carcinoma, mucoepidermoid carcinoma and adenocarcinoma.
Macroskopically, they appear as polypoid masses and present with typical mass effects and epistaxis. They have a tendency to infiltrate the surrounding structures, such as the fifth cranial nerve and pterygoid muscles, thus patients may present with facial pain and trismus. The diagnosis is usually confirmed by biopsy.

Miscellaneous malignant tumours

Sinonasal carcinomas, malignant mucosal melanomas arising from the nasal lining and chordoma, may extend to involve the nasopharynx. The symptoms are nasal obstruction and epistaxis related to the tumour bulk and superficial ulceration of the tumour. Chordomas are malignant neoplasms arising from notochord remnants located at the sphenoid region. Patients with chordoma present with a mass in the nasopharynx originating from the clivus region (the posterior wall) of the nasopharynx. In addition to mass symptoms, chordomas involve the cranial nerves.

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma arising from the epithelial lining of the nasopharynx. It is the most common malignancy in the nasopharynx found in the inhabitants of southern China, North Africa and Alaska.

The neoplastic cells are frequently found intermingled with lymphoid cells and thus it was previously known as lymphoepithelioma. It is commonly located at the fossa of Rosenmüller (the pharyngeal recess, located medial to the medial crus of the Eustachian tube). In most regions, NPC is an uncommon head and neck neoplasm, and its age-adjusted incidence for both sexes is less than one per 100,000. However, geographical clusters are observed, for example a recent reported incidence of NPC in Hong Kong was 20 to 30 per 100,000 (males) and 15 to 20 per 100,000 (females), respectively. Even for those Chinese who have migrated to Southeast Asia or North America, the incidence of NPC remains high. The incidence of this malignancy among second and subsequent generation Chinese born in North America is lower compared to those born in southern China. This suggests that genetic, ethnic and environmental factors may all have a role in the aetiology of this malignancy, although the significance of each factor varies.

Pathology

The NPC cells are basically squamous cell carcinoma with minimal differentiation. In 1978, the World Health Organization (WHO) categorized NPC into three histological types (Figure 30.1):

1. Type I is the typical keratinizing squamous cell carcinoma, similar to those found in the rest of the upper aerodigestive tract.
2. Type II is non-keratinizing squamous carcinomas.
3. Type III is the undifferentiated carcinomas.

In China and endemic areas, around 2 per cent of patients with nasopharyngeal carcinoma have type I, 3 per cent type II and 95 per cent type III. The corresponding distribution of histological types in North America and other regions is 25, 12 and 63 per cent, respectively.

Biopsies obtained from the NPC sometimes show a mixed histological pattern and the recent WHO classification has taken this into account. The histological types of NPC are now defined either as squamous cell carcinomas or non-keratinizing carcinomas; the second group is subdivided into differentiated and undifferentiated carcinomas. Only the non-keratinizing variant is associated with Epstein–Barr virus (EBV) infection. This classification has been shown to bear prognostic significance. The undifferentiated NPC have a higher local tumour control rate with therapy although the incidence of distant metastasis is also higher.

Clinical features

In general, patients suffering from nasopharyngeal carcinoma are younger than patients with other types of head and neck malignancy. The median age of patients with NPC on presentation is 50 years.

The symptoms of patients suffering from NPC are related to the anatomical location of the primary tumour and its metastasis. The common symptoms can be grouped into four categories: (1) Nasal symptoms: progressive nasal obstruction, epistaxis and blood-stained post-nasal discharge. (2) Otological symptoms: hearing loss, otalgia, otorrhoea and tinnitus are the results of the Eustachian tube dysfunction caused by the tumour bulk in the nasopharynx and its possible lateroposterior extension to the paranasopharyngeal space. The type of deafness on presentation is mostly conductive and this is the result of middle ear effusion following the impaired tubal musculature interfering with the opening of the auditory tympanic tube. (3) Neurological symptoms: related to cranial nerve involvement. The prevalence of cranial nerve palsies on presentation is around 20 per cent. When the tumour extends superiorly to affect the lateral wall of the cavernous sinus, then the cranial nerves III to VI might be affected and with lateral extension of the tumour into the paranasopharyngeal space, cranial nerves IX to XII might be affected. The cranial nerves most frequently affected are the third, fifth, sixth and twelfth. (4) The fourth group of symptoms on presentation is the presence of a painless mass in the neck. Fifty per cent of patients have an enlarged lymph node in the neck on presentation. The neck node usually appears in the upper part of the neck, ipsilateral to the primary tumour. Bilateral lymph nodes are occasionally obscured and when present are usually bulky (Figure 30.2).

Systemic symptoms common with other malignant tumours, e.g. anorexia and weight loss, are infrequently seen. Occasionally, the patient may complain of bone pain which signifies distant metastasis.

Many of the symptoms related to early NPC are non-specific and trivial, and frequently escape notice. Patients often only seek medical attention when the disease has progressed to an advanced stage. There is a case for improving early diagnosis so that the outcome of the therapy could be improved.
Diagnosis

The diagnosis of NPC hinges on clinical suspicion – per nasal endoscopy and CT and MRI scanning. A positive EBV antibody titre or the detection of EBV DNA in blood are also useful. Cervical lymph nodes should be biopsied by ultrasound-guided fine needle aspiration cytology.

Epstein–Barr virus antibody levels and DNA copies

EBV is a double-stranded DNA virus belonging to the family of herpes virus. It is widely present and the majority of the population has been infected by the time they reach adulthood.12 Cells of nasopharyngeal carcinoma contain multiple copies of EBV genome, several EBV-specific antigens are also expressed.13 The immunological response to the various EBV antigens helps to characterize the different types of EBV-associated diseases, ranging from infectious disease to malignant tumours.

In NPC the level of IgA in response to early intracellular antigen (EA) and viral capsid antigen (VCA) are much higher than those detected in the general population. Such serological profiles have been used as an indicator towards the diagnosis of undifferentiated NPC.14 The IgA anti-EA has been shown to be more specific while IgA anti-VCA is more sensitive for the diagnosis of NPC.13 The value of EBV serology in the early diagnosis and screening of the population was studied in 9699 subjects cross-checked against the cancer registry and death registry for a 15-year period in Taiwan. The difference in the cumulative incidence of nasopharyngeal carcinoma increased between seropositive and seronegative individuals with prolonged follow up.

As EBV is closely associated with NPC cells, then the EBV DNA is released into blood on lysis of the NPC cells. Circulating free EBV DNA has been found in the serum of patients with NPC.15 The number of copies of EBV DNA in the blood of these patients increased during the initial phase of radiotherapy suggesting that more viral DNA is released into the circulation after cell death following radiation.16 The quantity of free plasma EBV DNA can be

Figure 30.1  WHO histological classification of nasopharyngeal carcinoma. (a) Type I keratinizing squamous cell carcinoma; (b) type II non-keratinizing squamous cell carcinoma; (c) type III undifferentiated squamous cell carcinoma.
measured by real-time quantitative PCR and this is related to the stage of disease with high copies more commonly detected in advanced stage,\(^\text{17}\) however its value in the early detection of recurrent locoregional NPC is limited.

The quantity of EBV DNA measured before and after treatment is also an important predictive factor of outcome. One study reported patients with post-treatment EBV DNA above 500 copies/mL had a higher chance of developing relapse and death.\(^\text{18}\) Another study reported pre-treatment EBV DBA above 4000 copies/mL in stage I–II patients was associated with a higher risk of distant failure.\(^\text{19}\) These results suggested that pre- and post-therapy EBV DNA may provide important prognostic information which allows clinicians to define a high risk patient group that warrants more aggressive treatment.

**Imaging studies**

The development of cross-sectional computed tomography (CT) and magnetic resonance (MR) imaging have revolutionized the diagnosis, evaluation and treatment of NPC. The extent of the primary tumour and its involvement of adjacent structures can be clearly determined (Figure 30.3). The presence of cervical metastasis can also be determined (Figure 30.4). These imaging studies have improved the accuracy of staging and have also allowed radiotherapy planning and treatment.\(^\text{20}\)

It has been shown recently that better treatment results, especially the reduction of side effects, can be achieved with intensity modulated radiotherapy (IMRT). This therapeutic modality employs composite CT-MR images,\(^\text{21}\) and enables radiotherapy to be targeted even more accurately onto the tumour while at the same time sparing adjacent tissue.

**MAGNETIC RESONANCE IMAGING**

MRI is superior to CT in displaying both superficial and deep nasopharyngeal soft tissues and differentiating tumour from normal tissue. Its multiplanar capability also gives a three-dimensional impression of the tumour (Figures 30.5, 30.6, 30.7). MRI can demonstrate the infiltration of muscle by tumour laterally (Figure 30.8) and superiorly to affect the cavernous sinus (Figure 30.9). It is also useful in the detection of the presence, location and extent of paranasopharyngeal and cervical nodal metastases (Figure 30.10).\(^\text{22}\) MRI, however, is of
limited effectiveness in evaluating the extent of bone involvement.

**COMPUTED TOMOGRAPHY**

CT is useful for detecting bone skull base erosion by tumour (Figure 30.11). CT can also identify the paranasopharyngeal extension of the tumour which is one of the most common modes of extension of NPC, and perineural spread through the foramen ovale as an important route of intracranial extension. Perineural spread through the foramen ovale is the explanation for cavernous sinus involvement without skull base erosion.

**OTHER IMAGING STUDIES**

Imaging studies to detect distant metastases at diagnosis are less successful in early disease (scale 1) in patients with advanced disease (N3); staging with chest x-ray, bone scan and liver ultrasonography is indicated. The reactive policy of imaging only when patients have symptoms of distant metastasis is the best policy.

Both CT and MRI are not sensitive in detecting residual or recurrent disease following radiation or chemoradiation. Positron emission tomography (PET) is more sensitive than CT and MRI in detecting persistent and recurrent tumours in the nasopharynx (Figure 30.12).

**Endoscopic examination and biopsy**

Endoscopic examination provides valuable information on mucosal involvement and tumour extent and allows guided biopsy. The endoscopic examination, however, cannot
determine deep extension or skull base involvement of the tumour. The endoscopic examination and biopsy can be carried out under local anaesthesia using both flexible and rigid endoscopes.

**FIBREOPTIC FLEXIBLE ENDOSCOPE**

A fibreoptic flexible endoscope with a suction and biopsy forcep channel should be used. Flexible biopsy forceps are small however, and this limits the amount of tissue obtained. As the carcinoma cells may lie submucosally, the biopsy forceps should pierce the nasopharyngeal mucosa and be inserted deep to ensure a good biopsy. The optical image obtained with the flexible endoscope is slightly inferior to that of the rigid endoscope. The flexibility of the scope and its incorporated biopsy forceps channel are the main advantages (Figure 30.13).
RIGID ENDOSCOPE

A 4 mm Hopkins rod rigid endoscope provides a better optical image. Endoscopes with different visual angles can be used for inspection of different regions in the nasopharynx. The rigid endoscopes that are frequently used include the 0° and 30° lens scopes (Figure 30.14). The rigid endoscope can be inserted through either nasal passage to reach the pathology in the nasopharynx, a biopsy forceps can be introduced either alongside the endoscope or via the opposite nostril so that biopsy is taken under direct vision.

Staging of nasopharyngeal carcinoma

There are a few staging systems for NPC. The American Joint Committee on Cancer Staging and/or UICC system is used in

Figure 30.12  Positron emission tomography (PET) showing residual tumour in the nasopharynx after chemoradiation (arrows).

Figure 30.13  Flexible endoscopic view of nasopharynx. (a) Scope through the left nasal cavity, showing a tumour (C) in the left fossa encroaching onto the medial crura of the Eustachian tube (ET). (b) Scope through the right nasal cavity, showing a polypoid tumour (C) arising from the right fossa, attaching to the medial crura of the Eustachian tube (ET).
north America and Europe, while the Ho’s staging system is more frequently preferred in Asia. The nodal classification in Ho’s system has been shown to bear prognostic significance, but its stratification of the T stages into five sectors differs from most other staging systems.

There is a need to incorporate the various prognostic factors into the staging system, a revised AJC/UICC staging system was published in 1997. T1 stage in the new system included tumours that are localized in the nasopharynx, and T2 stage covered tumours that had extended to the nasal fossa, oropharynx or paranasopharyngeal space. The T3 stage included tumours that had extended to the skull base or other paranasal sinuses. The new T4 stage covered tumours that had extended into the infratemporal fossa, orbit, hypopharynx and cranium or to affect the cranial nerves. A slightly modified staging system was put forward in 2009. When the primary tumour extends to the oropharynx or the nasal cavity, it is still staged as T1; only when the tumour extends laterally into the parapharyngeal space is it T2. The N and M staging remained unchanged (Table 30.1). For cervical nodal staging the size of the lymph nodes were also taken into consideration, in addition to the laterality of the cervical nodes. Stage N1 under the new system referred to unilateral nodal involvement which is less than 6 cm in diameter. Stage N2 includes bilateral nodal disease that are less than 6 cm in diameter. All the N1 and N2 nodes should be in the upper part of the neck not reaching the supraclavicular fossa. Stage N3 referred to lymph nodes larger than 6 cm (N3a), or nodes that had extended to the supraclavicular fossa (N3b). The new staging system has enabled patients to be staged more precisely, and has been shown to be effective in predicting survival (Table 30.1).

**Treatment**

**RADIOThERAPY**

The primary treatment modality for locoregionally confined nasopharyngeal carcinoma is radiotherapy as the tumour is radiosensitive.

Nasopharyngeal carcinoma has a tendency of early spread to paranasopharyngeal and cervical lymphatics, hence prophylactic nodal treatment is mandatory and radiotherapy can cover these areas adequately. The outcome of NPC patients who are treated with radiotherapy has improved significantly in the past four decades; this has increased from a low five-year survival rate of 25 per cent in the 1950s, to 50 per cent in the 1970–1980s, and then to 75 per cent in the 1990s.

For effective treatment of nasopharyngeal carcinoma, the radiation target volume includes the nasopharynx and also the paranasopharyngeal space, oropharynx, base of skull, sphenoid sinus, posterior ethmoid sinus and posterior half of maxillary antrum. Cervical nodal irradiation is mandatory even in clinically node-negative patients due to the high incidence of neck relapse in the absence of prophylactic nodal irradiation. As the nasopharynx is a small region, NPC frequently crosses the midline and metastases to contralateral cervical nodes are not uncommon, thus the radiation field has to cover the upper two-thirds of the neck on both sides.

Employing high megavoltage radiation, a dose of 65–70 Gy is normally given to the primary tumour, 65–70 Gy to the involved neck nodes, and 50–60 Gy to the node-negative neck. Conventional two-dimensional treatment planning and radiotherapy use two or three large fields to cover the primary ± upper neck and one or two fields to cover the lower neck (Figure 30.15). Treatment is usually delivered using single fraction daily and five fractions per week. It is important to avoid any significant interruption during treatment as this will reduce the overall efficacy of radiotherapy.

In order to further enhance the tumour control by radiotherapy, a variety of radiotherapy techniques and strategies have been employed. Based on the dose-volume-response relationship, one strategy is to escalate the target dose by additional boost treatment using different techniques, such as small field conventional or three-dimensional conformal radiotherapy, brachytherapy and stereotactic radiosurgery. To improve the efficacy of treatment, the application of intracavitary brachytherapy to deliver a boost dose for T1 and T2 tumours after radiotherapy has been...
used. This has been reported to improve the tumour control rate by 16 per cent.\textsuperscript{44} Altered fractionation has been used to overcome tumour radioresistance. This, however, is not always beneficial.\textsuperscript{45} In another study of accelerated fractionation, a shorter course of six fractions per week produced satisfactory tumour control without a significant increase in toxicity.\textsuperscript{46}

The most important advance in radiotherapy in the past decade is IMRT. This complicated technique allows the delivery of a highly conformed dose of radiation to the target through the optimization of intensity of multiple beams. Following image acquisition, with CT as a slice thickness of 2.5–5 mm, the clinician then contours the target volume and important critical structures on the images (\textbf{Figure 30.16}). The desired dose parameters and dose-volume constraints are then entered into a computer and a treatment plan is then generated. The advantages of IMRT include the ability to deliver highly conformal radiotherapy to irregular targets. This is useful if the target volume wraps around critical structures such as the brain stem and spinal cord, as sometimes seen in nasopharyngeal carcinoma. Other advantages include the ability to treat primary and regional lymphatics in one volume and the ability to deliver a simultaneous integrated boost. The superior dose distribution and sparing of normal tissues with IMRT when compared to three-dimensional conformal radiotherapy for boost or salvage treatment of nasopharyngeal carcinoma has been demonstrated.\textsuperscript{47} IMRT has already achieved excellent local control rates for newly diagnosed NPC, with reported rates

\begin{table}
\centering
\begin{tabular}{l}
\textbf{Tumour in nasopharynx (T)}
\hline
T1 & Tumour confined to the nasopharynx or extends to oropharynx and/or nasal cavity \\
T2 & Tumour with parapharyngeal extension \\
T3 & Tumour invades bony structures and/or paranasal sinuses \\
T4 & Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, or orbit \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\begin{tabular}{llll}
\textbf{Regional lymph nodes (N)} & \\
NX & Regional lymph nodes cannot be assessed \\
N0 & No regional lymph node metastasis \\
N1 & Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa \\
N2 & Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa \\
N3 & Metastasis in a lymph node(s) \\
N3a & greater than 6 cm in dimension \\
N3b & extension to the supraclavicular fossa \\
\hline
\textbf{Distant metastasis (M)} & \\
MX & Distant metastasis cannot be assessed \\
M0 & No distant metastasis \\
M1 & Distant metastasis \\
\hline
\textbf{Stage grouping} & \\
Stage 0 & T1s & N0 & M0 \\
Stage I & T1 & N0 & M0 \\
Stage II & T1 & N1 & M0 \\
 & T2 & N0 & M0 \\
Stage III & T1, T2 & N2 & M0 \\
 & T3 & N0, N1, N2 & M0 \\
Stage IVA & T4 & N0, N1, N2 & M0 \\
Stage IVB & Any T & N3 & M0 \\
Stage IVC & Any T & Any N & M1 \\
\end{tabular}
\end{table}

\textbf{Figure 30.15} Simulator film of two-dimensional treatment plan for nasopharyngeal carcinoma. A large treatment volume (outlined by grey line) which included many normal structures.
Both concurrent and adjuvant chemotherapy in the study arm, and reported an absolute improvement of survival of 31 per cent at three years. Subsequent randomized trials conducted in endemic regions have confirmed the benefits of concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma, although different regimens and schedules were being employed in these studies. However, the one study that employed the same chemotherapy regimen used in the Intergroup study showed no survival benefits. Nevertheless, current evidence indicates that concurrent chemoradiotherapy has a major role in advanced stage nasopharyngeal carcinoma. Combined induction and concurrent chemotherapy may have the added benefit of rapid tumour shrinkage prior to radiotherapy, and excellent control can be achieved using this approach in advanced T stage NPC.

COMBINED CHEMORADIOTHERAPY

Nasopharyngeal carcinoma has a high incidence of distant metastases and local failure still constitutes another important cause of failure. Chemotherapy may contribute to the successful management of these problems. However, some cases of recurrent and metastatic disease showed response to chemotherapy with occasional long-term survivors and good performance status with little comorbidity. Many randomized trials have been conducted to explore the benefits of combined chemoradiotherapy in NPC. Most studies employ cisplatin-based regimens with the main difference between the various trials being the timing of chemotherapy in relation to radiotherapy: before (induction), during (concurrent) or after (adjuvant) radiotherapy.

Four randomized phase III studies comparing induction chemotherapy followed by radiotherapy versus radiotherapy alone in nasopharyngeal carcinoma have been reported. None of these studies have demonstrated survival benefits. Two of these studies were recently updated and although significant improvement in disease-free survival in the chemotherapy arm was observed, overall survival was not improved. Only two adjuvant chemotherapy phase III studies have been reported, and both showed no survival benefits.

Concurrent chemoradiotherapy in recent years has emerged as the treatment of choice for locoregionally advanced nasopharyngeal carcinoma, largely due to the positive findings of the Intergroup 0099 trial which was the first randomized trial to demonstrate survival benefit with the concomitant use of chemotherapy and radiotherapy in nasopharyngeal carcinoma. The Intergroup trial employed both concurrent and adjuvant chemotherapy in the study of 92–97 per cent at 3–4 years. Apart from improvement of tumour control, IMRT may also reduce the risk of late complications, especially in those patients with early stage disease.

COMPLICATIONS OF CHEMORADIOTHERAPY

Although treatment of NPC with radiotherapy or concurrent chemoradiation yields good response, there are many complications that can adversely affect the quality of life of patients. Xerostomia is almost universal after conventional radiotherapy and this leads to dry mouth, poor oral hygiene and dental caries. Hearing impairment is also frequently seen and may be related to the combined effects of direct radiation insult to the hearing apparatus, persistent disturbance of Eustachian tube function and chemotherapyy-induced ototoxicity. Soft tissue fibrosis following radiotherapy may lead to restriction of neck movement or mouth opening, often accompanied by discomfort. Cranial nerve palsies are usually due to incomplete healing of damage caused by tumour; although cranial nerves (especially CN IX, X, XI and XII) can also be damaged by radiation. Dysphagia can be due to cranial nerve palsies or pharyngeal stricture. Hormonal insufficiency can develop due to damage to the hypothalamic-pituitary axis or end organs such as the thyroid gland. Carotid artery stenosis can develop following neck irradiation and may result in cerebral ischaemia. The more serious sequelae are damage of higher functions that lead to memory loss, cognitive dysfunction, and neuropsychological dysfunction. This can occur with or without radiological evidence of temporal lobe necrosis (Figure 30.17).

The advent of conformal radiotherapy such as IMRT has the potential of reducing late radiation problems by reducing the dose delivered to critical structures. For example, it is possible to prevent xerostomia by selectively sparing the parotid glands using three-dimensional conformal radiotherapy or IMRT (Figure 30.18).

Persistent and recurrent disease

Despite the efficacy of chemoradiotherapy as the primary treatment modality for NPC, some patients still develop persistent or recurrent tumour. To attain good salvage results for those patients who develop local or regional failure, early detection and treatment is essential. This early detection can be achieved through clinical examination and serological evaluation during follow up.
It is important to document any residual disease after radiotherapy as many will still be amenable to salvage treatment. Follow-up endoscopy at 6–8 weeks and imaging at 10–12 weeks after completion of radiotherapy or chemoradiotherapy is recommended to document tumour responses. Timing of this clinical assessment is important: assessment carried out earlier than 6 weeks is not recommended due to the occasional presence of slowly regressing tumours, whereas malignancy detected after 10 weeks usually represents viable tumour and salvage treatment is indicated. 

After documentation of complete remission, regular clinical and imaging follow up is also recommended for the detection of locoregional recurrences since those recurrences when detected early are more amenable to salvage treatment. Regular examination of the nasopharynx by mirror and endoscopy should be performed as part of follow up every 4–6 months during the initial 3–5 years of follow up. CT and/or MR imaging of the nasopharynx should also be performed every six months.

Detection of circulating cell-free EBV DNA may also be useful in detecting relapse, especially distant metastases. EBV DNA may also serve as a tumour marker for monitoring of treatment response and follow up, but it is less useful in detecting local recurrence than distant metastases as up to one-third of patients with locoregional recurrence do not have elevated EBV DNA copies. Late recurrence of nasopharyngeal carcinoma is not uncommon and may actually represent second primary, hence long-term follow up is necessary.

Residual or recurrent tumour in the neck nodes after chemotherapy and radiotherapy is notoriously difficult to confirm. Various imaging studies might suggest the presence of disease while fine needle aspiration (FNA) cytology biopsy can detect malignant cells in at most 50 per cent of the patients, even at experienced centres. This low yield on FNA is because the enlarged lymph nodes are not entirely replaced by tumour cells, there is a great deal of fibrosis; and in some lymph nodes only clusters of tumour cells are present. For residual or recurrent tumour in the nasopharynx, FDG-PET has been reported to be better than CT. The presence of malignant disease can usually be confirmed with endoscopic examination and biopsy. When the disease remains localized in the nasopharynx, salvage treatment should be given whenever possible (Figure 30.19). Patient survival after salvage treatment for extensive disease remains poor, but is still better than those who were managed conservatively. Even for those patients who had locoregional tumour, salvage therapy should be considered for the selected group who can tolerate the therapeutic measures.

**METASTATIC CERVICAL LYMPH NODES**

Following chemoradiation for NPC, the incidence of isolated failure in the neck lymph nodes is less than 5 per cent. The metastatic cervical lymph node might present as persistence or reappearance of the nodes after complete resolution following the initial chemoradiation. Lymph nodes which respond to the initial treatments such as radiotherapy or chemoradiation will take roughly three months to become negative clinically.

As already stated, it is notoriously difficult to confirm the presence of malignant cells in nodes after radiotherapy or chemoradiation. Fine needle aspiration is frequently not helpful and sometimes, clinically enlarged nodes may not harbour malignant cells. If the presence of metastatic cancer can be confirmed in the cervical lymph nodes or there are imaging features suggestive of disease or clinical progression of lymph nodes, then salvage therapy is indicated.

Persistent or recurrent nodal disease managed with a further course of external radiotherapy has an overall five-year survival rate of 19.7 per cent. Surgical salvage (radical neck dissection) has a five-year tumour control rate of 66 per cent in the neck and a five-year actuarial survival of 37 per cent. The rationale for radical neck dissection in persistent or recurrent neck disease, even single lymph nodes is: (1) serial whole specimen section studies of curative radical neck dissections revealed three times more positive nodes than...
clinically evident; (2) over 70 per cent of the nodes exhibited extracapular spread; (3) 30 per cent of positive nodes were lying close to the spinal accessory nerve.79

In some cases cervical lymph nodes at presentation are already of a significant size to suggest extensive extracapsular spread (Figure 30.19). The extension beyond the confines of the lymph nodes can involve surrounding neck structures such as the overlying skin (Figure 30.20) and muscle carotid sheath. For these patients, even after radical neck dissection, removing all macroscopic tumour, the resection margins would be close and there might be microscopic residual disease. After-loading brachytherapy delivered to the tumour bed following radical neck dissection has been shown to be useful. In this situation, nylon tubes are placed on the tumour bed accurately at the time of the neck dissection (Figure 30.21). The overlying skin has to be removed as it will not survive further radiation from the brachytherapy. A skin flap is used to cover the tumour bed and bring in new blood supply and thus decrease the risk of necrosis. Adjuvant brachytherapy in extensive neck diseases allows a similar tumour control rate to that achieved when radical neck dissection alone was performed in less extensive neck disease.86

DISEASE IN THE NASOPHARYNX

Reirradiation

External reirradiation of NPC with curative intent is often undesirable given the large numbers of critical structures in the vicinity of the primary radiotherapy field. Whenever possible, brachytherapy or stereotactic radiosurgery should be considered for reirradiation of treatments. Reported five-year survival rates after external reirradiation using the conventional technique range from 8 to 36 per cent.85, 87, 88 A high incidence of late complications, mostly neurological
damage and soft tissue fibrosis, is commonly seen after external reirradiation. The use of three-dimensional conformal radiotherapy and more recently IMRT has improved the outlook of patients receiving external reirradiation. In one study using three-dimensional conformal radiotherapy for retreatment of nasopharyngeal carcinoma, the five-year local control rate was 71 per cent but the actuarial incidence of major late toxicities was still high with at least grade 3 toxicities in 100 per cent and grade 4 in 49 per cent at five years. Several preliminary reports using IMRT for re-irradiation of nasopharyngeal carcinoma also reported good short-term control with a relatively low incidence of severe late toxicities.

Chemoradiotherapy may also improve treatment outcome in locally recurrent nasopharyngeal carcinoma. One study employed induction chemotherapy to shrink the tumour volume followed by reirradiation using IMRT and reported 75 per cent local control rate at one year. Another study employed concurrent chemoradiotherapy and reported a one-year progression-free rate of 42 per cent. In patients with advanced local recurrence in which treatment planning for reirradiation is difficult, induction rather than concurrent chemotherapy is preferred as the former may allow tumour shrinkage to take place and thus facilitate subsequent radiotherapy planning and whole target coverage.

Stereotactic radiosurgery

The technique of stereotactic radiosurgery involves the localization of a small target which is irradiated by multiple convergent beams providing a large single dose of radiation. The technique was originally developed for the treatment of functional neurological disorders, but was later found to be useful for vascular malformations, benign intracranial/skull base neoplasms and cerebral metastases. Stereotactic radiosurgery has also been used in nasopharyngeal carcinoma to deliver a boost dose after a second course of radiotherapy or as a salvage treatment for local recurrence (Figure 30.22). Stereotactic radiosurgery alone can achieve local control rates of 53–86 per cent for locally recurrent nasopharyngeal carcinoma. For recurrent disease confined to nasopharynx or adjacent soft tissues, the reported local control rate at two years was 72 per cent. When stereotactic radiosurgery was administered as a boost dose after reirradiation, the three-year control rate ranged from 52 to 58 per cent. Based on these results, there is strong evidence indicating that radiosurgery is an effective salvage treatment for local failures of nasopharyngeal carcinoma. There are, however, no data comparing the relative efficacy and complications of radiosurgery with other salvage treatments. In practice, the selection of treatment modalities depends mainly on the extent of disease and expertise available. For recurrent disease confined to the nasopharynx or adjacent soft tissues, results of radiosurgery appear to be comparable to brachytherapy or surgery, and can be considered as a treatment option. The advent of intensity-modulated radiotherapy appears to have improved the outcome of recurrent nasopharyngeal carcinoma. Reirradiation using IMRT is recommended for patients with extensive local recurrence while reserving radiosurgery as a boost treatment or for further recurrence. Although most series reported a relatively low risk of late

Figure 30.21  Computed tomography (axial view) showing that the enlarged right neck node has infiltrated the overlying neck skin (arrow).

Figure 30.22  (a) Clinical photograph showing the placement of hollow nylon tube (arrow) over the tumour bed after radical neck dissection. The overlying skin was removed with the radical neck dissection. (b) The cutaneous defect in the neck was covered with the pectoralis major myocutaneous flap.
complications following radiosurgery, massive potentially fatal haemorrhage remains the most severe form of complication.\textsuperscript{99} Massive haemorrhage after radiosurgery is usually due to radiation damage to the carotid artery, often as a result of using a large fraction dose and high cumulative dose. To minimize the risk of haemorrhage, radiosurgery should only be used in the absence of direct tumour enca-
sement of the carotid artery.

Brachytherapy
When brachytherapy is used, the radiation dosage is highest at the source and decreases rapidly towards the periphery. This enables a high dose of irradiation to be delivered to the residual or recurrent tumour while surrounding tissue receives a much smaller dose. Brachytherapy radiation also delivers radiation at a continuous low dose rate, which gives a further radiobiological advantage over fractionated external radiation.

Intracavitary brachytherapy has been used traditionally for nasopharyngeal carcinomas.\textsuperscript{100} With this method, the radiation source is placed either in a tube or over a mould and then inserted into the nasopharynx (Figure 30.23). The irregular contour of the nasopharynx and the variable dimensions and location of persistent or recurrent tumours make it difficult to position radiation sources accurately in the nasopharynx. To circumvent this problem, radioactive interstitial implants have been used to treat small localized residual or recurrent tumour in the nasopharynx.

Radioactive gold grains (198Au) have been used as an interstitial radiation source. Gold grains can be implanted into the tumour either transnasally under endoscopic guidance\textsuperscript{101} or using the split-palate approach.\textsuperscript{102} The latter approach gives the surgeon a direct view of the tumour, its location and its extent in the nasopharynx. This enables the precise implanting of the gold grains permanently into the tumour.

Using a soft palate split in the midline and to one side of the uvula, the mucoperiosteum over the hard palate is lifted. The attachment of the soft palate to the posterior edge of the hard palate is detached and the tumour in the nasopharynx is exposed (Figure 30.24). The palatal wound is then closed in layers. During the closure, a thick lead shield is used to reduce the radiation dose to the body of the surgeon and the patient’s eyes are protected with a lead glass (Figure 30.26).

As brachytherapy is effective over short distances it is used only for shallow tumours localized in the nasopharynx and without bone invasion. The split palate implantation of gold grains as a brachytherapy source has provided effective salvage with minimal morbidity (Figure 30.27).\textsuperscript{103} Where gold grain implants were applied to treat persistent and recurrent tumours after radiotherapy, the five-year local tumour control rates were 87 and 63 per cent, respectively, and the corresponding five-year disease-free survival rates were 68 and 60 per cent, respectively.\textsuperscript{104}

Nasopharyngectomy
When persistent or recurrent tumour in the nasopharynx is too extensive for brachytherapy or has extended to the paranasopharyngeal space, then surgical salvage may be an option. Nasopharyngectomy can achieve salvage in selected patients.

Adequate surgical exposure to allow oncological extirpa-
tion of tumour in the nasopharynx region is a technical challenge. A number of approaches have been described including the infratemporal approach from the lateral aspect,\textsuperscript{105} transpalatal, transmaxillary and transcervical approaches from the inferior aspect,\textsuperscript{106, 107} and an antero-
lateral approach.\textsuperscript{108} The overall mortality associated with all these salvage surgical procedures is low. As all patients have undergone previous radical radiotherapy, meticulous tissue handling during surgery is essential for satisfactory healing.

The choice of the surgical approach to carry out the nasopharyngectomy depends on the location and extent of the tumour in the nasopharynx. For localized tumour in the lower part of the posterior wall of the nasopharynx, the transpalatal approach is usually adequate. The disadvantage of this approach is that the lateral extent of resection is limited. When the main tumour bulk is located in the paranasopharyngeal space, lying close or lateral to the
Figure 30.26 During closure of the palatal wound, the bodies of the surgeons are protected by a lead shield (arrow) and the eyes are protected by a thick lead glass mounted on the shield (arrows).

Figure 30.25 (a) Endoscopic view showing the Eustachian tube opening (arrow), the shallow tumour in the nasopharynx (arrow heads) and the tip of the gold grain introducer (solid arrow). (b) The surgeon on the left examines the tumour in the nasopharynx with the flexible endoscope (arrow) and the clinical oncologist standing on the right inserts the gold grains into the tumour with the introducer (arrow). (c) The cartridges of gold grains and the introducer.

Figure 30.27 Plain x-rays showing the implanted gold grains (arrow). (a) Lateral view; (b) anteroposterior view.
internal carotid artery, then the lateral infratemporal fossa approach is applicable. The limitation of this approach is that many structures have to be mobilized in order to obtain an adequate exposure. The various other anterior and inferior approaches may give adequate visualization of the tumour but do not allow the resection of the tumour from all sides in

Figure 30.28 Schematic axial view computed tomography. (a) The dotted lines mark the osteotomies on the maxilla. (b) The maxilla is swung laterally but remains attached to the anterior cheek flap (arrow). Pterygoid plate and the posterior part of nasal septum can be removed. (c) Whole nasopharynx exposed after the maxilla is swung laterally and removing the pterygoid plates and posterior part of nasal septum.

Figure 30.29 (a) Weber Ferguson facial incision extends between the central incisors onto the hard palate. (b) The midline palatal incision turns laterally behind the maxillary tuberosity.
an oncological fashion. As most nasopharyngeal carcinoma is closely associated with the crura at the opening of the Eustachian tube, a curative oncological resection should always include these structures. Serial sectioning of nasopharyngectomy specimens has shown that the persistent or recurrent nasopharyngeal carcinoma exhibits extensive submucosal extension and a wide resection of the nasopharynx is essential in order to achieve a favourable outcome.

As most of the residual and recurrent nasopharyngeal carcinoma in the nasopharynx affects the fossa of
Rosenmüller and the crura of the Eustachian tube, the anterolateral or maxillary swing approach is a common route for surgical salvage. The procedure applied for salvage nasopharyngectomy was first reported in 1991 (Figure 30.28). The facial incisions start with the Weber–Ferguson incision as for maxillectomy and this is continued between the central incisor teeth onto the hard palate in the midline and then turned laterally along the attachment of the soft palate to the hard palate (Figure 30.29). The soft tissue over the anterior wall of the maxilla is lifted to expose a small portion of the bone for osteotomy (Figure 30.30). The osteotomy goes through the anterior wall of the maxilla below the floor of the orbit and includes the lower part of the zygomatic arch. The hard palate is divided in the midline and a curved osteotome used to separate the maxillary tuberosity from the pterygoid plates (Figure 30.31). After the osteotomies, the maxilla is dropped down but remains attached to the anterior cheek flap (Figure 30.32). The maxilla can be swung laterally as an osteocutaneous complex to expose the nasopharynx and the paranasopharyngeal space (Figure 30.33). This wide exposure allows persistent or recurrent tumour in the region to be removed en bloc (Figure 30.34).

Patient selection is crucial as surgical salvage in the form of nasopharyngectomy is only indicated for tumours localized in the nasopharynx without infiltration of the skull base or internal carotid artery. As long as the residual or recurrent tumour can be removed adequately, i.e. when the surgical margins are negative, the long-term aesthetic and functional results are satisfactory (Figure 30.35). The five-year actuarial control of tumours in the nasopharynx has been reported to be 74 per cent and the five-year disease-free survival rate is around 56 per cent. As all these patients have undergone radical radiotherapy, they develop morbidities such as trismus and occasionally palatal fistula. Palatal fistula risk can be minimized by avoiding placing the soft tissue incision in the same plane as the osteotomy over the hard palate (Figure 30.36).

Recently, resection of a small tumour localized at the posterior wall of the nasopharynx has been reported using endoscope and instruments inserted through the nasal and oral cavities. The rigid endoscopic instruments limit the en bloc removal of larger or laterally located tumour. For small tumours located over the lateral wall but not extending into the paranasopharyngeal space, they might be resected adequately using the versatile endowrist of the da Vinci robot. The camera and the robotic arms are inserted from the inferior aspect with a split palate approach.

For a successful salvage of localized small tumour in the nasopharynx, brachytherapy or surgery could be considered. The choice of approaches of surgical salvage of recurrent nasopharyngeal carcinoma depends on the location and extent of the tumour. For those tumours involving skull base or those that are too extensive for surgery, stereotactic

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**Figure 30.35** Postoperative photograph at 1.5 years after the operation. (a) The facial wound has healed and is nearly invisible (arrows). (b) All the teeth on the side of the swing have survived.

**Figure 30.36** (a) The palatal incision is modified to go along the root of the upper alveolus. (b) The palatal flap (arrow) is raised so that the osteotomy (dotted line) of the hard palate is not in the same plane as the incision on the palate.
radiation or intensity modulated radiotherapy could be tried and this is sometimes combined with chemotherapy.\textsuperscript{114}

**KEY EVIDENCE**

- Epstein–Barr viral DNA determination has been established as a diagnostic means for nasopharyngeal carcinoma, especially for early stage disease.
- Concurrent chemoradiation employed for the treatment of advanced stage nasopharyngeal carcinoma has improved survival outcome when compared with radiation alone.
- Salvage surgery for residual or recurrent disease either in the neck or in the nasopharynx gives satisfactory results with limited morbidity.

**KEY LEARNING POINTS**

- Nasopharynx is anatomically difficult to examine.
- In southern China the most common malignant pathology is nasopharyngeal carcinoma.
- Imaging studies determine the extent of the pathology while the diagnosis of nasopharyngeal carcinoma has to be confirmed with biopsy through endoscopic examination.
- The primary treatment modality for early stage nasopharyngeal carcinoma is radiotherapy and for advanced stage concurrent chemoradiation.
- For residual or recurrent nasopharyngeal carcinoma in the cervical lymph nodes, the optimal salvage is radical neck dissection.
- For residual or recurrent nasopharyngeal carcinoma in the nasopharynx, the optimal salvage is nasopharyngectomy.

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Pharynx: oropharynx

JARROD HOMER AND GUY REES

INTRODUCTION

Arguably, patterns of incidence and treatment have changed the management of oropharyngeal cancer more than any other site of the head and neck in the last decade. The incidence of squamous cell carcinoma (SCC) in the oropharynx has increased greatly over this period of time, more than other sites of the upper aerodigestive tract (UADT). This has mainly been due to the rise in non-smokers with human papilloma virus (HPV)-induced tumours, something that has been described as an ‘epidemic’. At the same time, there has been an increase in the practice of chemoradiotherapy, with a decrease in radical surgery and postoperative radiotherapy (RT). HPV-induced tumours are particularly radiosensitive. These issues, together with the introduction of transoral laser resection techniques, means that decision-making in oropharyngeal cancer is complex and a significant challenge to the multidisciplinary team.

SURGICAL ANATOMY

The oropharynx includes the soft palate, tonsillar fossae, tongue base and the pharyngeal walls from the level of the soft palate to the level of the epiglottis caudally. The most distinguishing anatomical characteristic is the location for most of Waldeyer’s lymphatic ring, including the palatine and lingual tonsils. Other pertinent features include a complex muscular structure that is critical to speech, mastication and swallowing and a rich blood supply.

The oropharynx extends from the level of the hard palate superiorly to the level of the hyoid bone inferiorly. Its anterior limit is the anterior faucal pillar, but this is contiguous with the retromolar trigone. It is divided into the following components:

- The anterior wall, which is made up of the base of the tongue posterior to the foramen caecum, the vallecula and the lingual surface of the epiglottis; it is bounded by the pharyngoeiglottid folds.
- The lateral wall, which is made up of the anterior pillar (palatoglossus), posterior pillar (palatopharyngeus) and the pharyngeal palatine tonsil.
- The roof, which is formed by the soft palate containing the two heads of palatopharyngeus, the levator palati, the tensor palati and the palatoglossus. The oral surface of the soft palate is in the oropharynx and the nasopharyngeal surface is part of the nasopharynx.
The posterior wall, which extends from the level of the hard palate to the level of the hyoid and is anterior to the second and third cervical vertebrae. This consists of the superior and middle constrictors and the buccopharyngeal fascia, which separates it from the prevertebral fascia.

The tongue base, or posterior tongue. This is made up of the genioglossus muscle, which is attached to the hyoid. The base of the tongue is contiguous with the vallecula, which is the roof of the pre-epiglottic space.

Like the rest of the UADT, the oropharynx is lined with squamous epithelium. However, there is abundant lymphoid tissue particularly in the palatine tonsil and also lingual tonsil of the tongue base. These can be affected in head and neck lymphoma. The soft palate is especially rich in minor salivary glands and is a site of minor salivary gland tumours.

### FUNCTION

The oropharynx plays a central role in speech and swallowing. Movement of the soft palate modifies the size and shape of the resonating cavities, influencing vowel production. Closure of the soft palate prevents food regurgitating into the nose. The base of tongue modulates the production of vowels and consonants because of its obstruction of the vocal tract. Movement and the bulk of the base of the tongue forces the food bolus into the oropharynx, powering this phase of swallowing and helping protection against aspiration.

### PATHOLOGY

#### Oropharyngeal tumour histological types

SCC is the most common malignancy and forms 90 per cent of the tumours in this region. Non-Hodgkin’s lymphomas account for 8 per cent and minor salivary gland tumours for 2 per cent. With regard to squamous cell carcinoma, the frequency of affected sites is tonsil/lateral wall (60 per cent), tongue base (25 per cent), soft palate (10 per cent) and posterior wall (5 per cent).

#### Lymphoma

These consist almost entirely of non-Hodgkin’s lymphoma. The histological classification, staging and relative site incidence of these lymphomas are described in Chapter 4, Assessment and staging (Table 31.1). Lymphomas particularly affect younger patients, and usually occur in the tonsil or tongue base.

#### Minor salivary gland tumours

On the soft palate, most minor salivary gland tumours are benign pleomorphic adenomas. Elsewhere in the oropharynx, however, malignant tumours are the rule, with adenoid cystic and mucoepidermoid tumours being the most common. Adenoid cystic tumours invade perineural lymphatics and there is a rich source of tumour spread in this area along the greater and lesser palatine nerves and the inferior alveolar nerves.

### Table 31.1 TNM and overall staging of oropharyngeal tumours.

| TNM and staging |
|-----------------|-----------------|-----------------|-----------------|
| T: Primary tumour | Primary tumour cannot be assessed | N0 | M0 |
| T1 | No evidence of primary tumour | N0 | M0 |
| T2 | Carcinoma in situ | N1 | M0 |
| T3 | Tumour 2 cm or less in greatest dimension | N1 | M0 |
| T4 | Tumour more than 2 cm but not more than 4 cm in greatest dimension | N0, T1 | M0 |
| T4 | Tumour more than 4 cm in greatest dimension | N0, T1 | M0 |
| T4 | Tumour invades adjacent structures, e.g. pterygoid muscles, mandible, hard palate, deep muscle of the tongue, larynx | N0, T1 | M0 |

Stage grouping

| 0 | T1 | N0 | M0 |
| 1 | T2 | N0 | M0 |
| 2 | T3 | N1 | M0 |
| 3 | T3 | N0, T1 | M0 |
| 4 | T4 | N0, T1 | M0 |
| Any T1,2,3 | N2 | M0 |
| Any T1,2,3 | N3 | M0 |
| Any T | Any N | M |


*New inclusion.
TREATMENT

Minor salivary gland tumours of the oropharynx are treated with primary surgery. Small benign and low grade tumours of the soft palate can often be treated by narrow margin transoral laser excision. Elsewhere in the oropharynx, minor salivary gland tumours are more likely to be high grade malignant and are generally treated with primary surgery, in the same manner as a squamous cell carcinoma in the same location, as described later in this chapter. Postoperative radiotherapy tends to be the rule due to high grade features. These tumours are discussed in more detail in Chapter 37, Salivary gland tumours.

SQUAMOUS CELL CARCINOMA

Epidemiology and HPV

The true incidence of oropharyngeal cancer is difficult to determine because the term oropharyngeal cancer is often used to include oral cavity cancer. Most true oropharyngeal cancers are captured in the ICD-10 codes, C01 (base of tongue), C09 (tonsil) and C10 (oropharynx). The crude incidence rates of these groups combined in the UK in 2006 were 3.6 (males) and 1.2 (females)/100 000/year and have steadily increased in the previous decade. This is similar to the incidence in the US. There is consistent evidence of increasing incidence of oropharyngeal squamous cell carcinoma (OPSCC) in many different countries, and the rate of increase is itself increasing.

Like other UADT squamous cell carcinoma, the most significant aetiological factor is tobacco, alcohol to a lesser degree but with significant synergy between the two. The effect, however, of HPV-16 has been profound on OPSCC. It is this effect that is responsible for the increase in incidence of OPSCC over the last decade or more, so much so that now as much as 50 per cent of OPSCC is thought to be HPV-induced. Recent rises in the incidence of tonsillar cancer have paralleled the rise in the proportion of HPV-positive cancers. This has led to claims of a developing ‘epidemic’ of HPV-induced OPSCC with most cancers in the near future being HPV-induced, in the same way as cervical carcinoma. Moreover, this increase is particularly marked in younger patients (typically 40–60 years) and in non-smokers.

HPV-16 infection is spread by orogenital sex and typically presents earlier than smoking/alcohol-induced tumours. There is much to suggest that HPV-induced SCC is distinct from its smoking-induced counterpart at every level. This is summarized in Table 31.2.

There is a lack of consensus as to how to define an OPSCC as HPV-induced. The different definitions and biomarkers used reflect the variability in the exact frequency of HPV-induced tumours from series to series. The most robust biomarker is arguably a combination of proof of HPV infection and integration into the host genome (e.g. in situ hybridization) AND proof of downstream activity of HPV E7 protein overexpression of p16.

A summary of the issues around HPV and OPSCC can be found in Adelstein’s monograph. While it remains unclear as to how exactly treatment should be modified according to HPV status, there has been much progress in integrating HPV status together with stage and smoking history to define low, intermediate and high risk groups.

TUMOUR PROGRESSION

Local progression

Local progression is discussed below under Patterns of presentation.

<table>
<thead>
<tr>
<th>Table 31.2 Characteristics of HPV-induced OPSCC.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td>Epidemiology</td>
</tr>
<tr>
<td>Aetiology</td>
</tr>
<tr>
<td>Histopathologic morphology</td>
</tr>
<tr>
<td>Genomic profile and gene expression</td>
</tr>
<tr>
<td>Clinical behaviour and prognosis</td>
</tr>
</tbody>
</table>
Lymphatic metastasis

Lymph node metastases at presentation are common in OPSCC, with over half of patients having clinical or radiological evidence of cervical metastasis, and around a third of patients diagnosed as cN0 having pathologic evidence of lymph node metastasis.\(^{14, 15}\) The lymphatic drainage from the oropharynx is mainly to levels II, III and IV.\(^{15, 16}\) Frequencies of involvement of different levels are shown in Table 31.3. It should be borne in mind that, by virtue of such data coming from patients undergoing neck dissection, there will be a bias towards patients with cN+ necks, and these are therefore not representative of patients staged with cN0 necks.

It also drains into the retropharyngeal (RP) nodes, which need to be considered in the assessment of disease in this area.\(^{17}\) The risk of metastasis to RP lymph nodes depends on subsite, a meta-analysis of papers suggests risk of RP lymphadenopathy being 19 per cent for soft palate; 12 per cent for tonsil; 6 per cent for base of tongue and 21–57 per cent for posterior pharyngeal wall tumours (including hypopharynx).\(^{18}\) The prognostic impact of positive RP lymph node metastasis is disputed, some authors showing an adverse impact\(^{19, 20}\) and others not.\(^{14, 21}\)
A particular feature of OPSCC is the propensity to metastasis to the contralateral neck, this occurring in up to 30 per cent of patients overall in one series. The subsites in which this is mostly likely to occur are the soft palate, base of tongue and posterior pharyngeal wall. However, even tonsil cancers have an approximate rate of contralateral nodal spread of 10 per cent.

**Distant metastasis**

As distinct from other head and neck tumours, as many as 8 per cent of patients will have distant metastases which are apparent at presentation. This is probably due to the rich lymphatic drainage of the oropharynx, which leads to a higher incidence of local and hence distant metastases. Distant metastasis will occur at some stage of the disease in 15–20 per cent, with 80 per cent of such cases being apparent within two years of diagnosis, and is most commonly to the lungs (around 50 per cent) followed by bone and liver, these being relatively common for this site compared to other head and neck sites. Patients who present with advanced disease, particularly more advanced cervical lymph node metastases, are at increased risk of distant metastasis (DM), as are patients who recur locally. However, of those patients who achieve locoregional control, only around 5 per cent will go on to develop DM.

**Second primary**

One in three patients with oropharyngeal tumours will, at some time, develop a second primary, so it is important to consider the presence of a synchronous second primary, especially if contralateral nodes are found.

### PATTERNS OF PRESENTATION

OPSCC tends to present in one of three ways: (1) symptoms from primary disease with or without lymph node metastases; (2) lymph node metastasis with clinically detectable OPSCC primary; (3) lymph node metastasis with unknown primary. With the introduction of PET-CT in patients with an unknown primary cancer, the vast majority of these are, in fact, OPSCC. Fifty per cent of patients have palpable metastatic nodes at initial presentation, with another 25 per cent having occult disease in a clinically N0 neck.

### Lateral wall tumours

These are the most common tumours (50 per cent) and usually involve the tonsil. They may spread anteriorly and upwards to the retromolar trigone and on to the buccal mucosa, as well as into the tongue base. If they erode deeply, they involve the pterygoid muscles producing trismus and pain. Further posterolateral invasion will involve the parapharyngeal space and structures including the carotid sheath (carotid artery, internal jugular vein and vagus nerve), the sympathetic chain, the styloglossus, the stylopharyngeus. Disease here is usually contiguous with lymph node metastases. Anterolateral extension can involve the angle of the mandible and the inferior alveolar nerve, especially in elderly patients, since in the edentulous mandible the inferior alveolar nerve is more superior than usual. Inferiorly, these tumours can extend down the lateral pharyngeal wall into the piriform sinus.

Tonsil primaries, especially in the inferior pole, are often submucosal and difficult to detect on examination.

### Tongue base

These are the next most common oropharyngeal tumours (40 per cent). As above, early tumours are often submucosal and difficult to detect. Symptoms frequently do not appear until the lesions are at an advanced stage, by which time tumours often have crossed the midline and through the genioglossus. In doing so, the oral tongue and floor of the mouth can be involved. Spread can also be posterior and inferiorly into the vallecula, the epiglottis and hence into the supraglottis and the pre-epiglottic space.

### Soft-palate tumours

Carcinoma of the soft palate occurs almost exclusively on the anterior surface. As the tumour progresses, it will involve the nasopharynx and superior pole of the tonsil. Further progression may involve the palatine nerves and the back of the maxillary antrum. A particular feature of these tumours is aggressive, not uncommonly bilateral lymph node metastases, in association with very little primary tumour volume.

### Posterior wall tumours

These are relatively unusual and often are associated with contiguous submucosal spread in a superior and inferior direction to involve the nasopharyngeal or hypopharyngeal posterior wall. In the untreated patient, the prevertebral fascia often acts as a barrier to spread. The majority of patients present late and usually complain of a sore throat, otalgia or dysphagia.

### Table 31.3

Frequency of lymph node level involvement in patients with OPSCC (adapted from Buckley and Feber and Shimizu et al).

<table>
<thead>
<tr>
<th>Lymph node level</th>
<th>N (from 6 series)</th>
<th>Total number of neck dissections</th>
<th>Frequency of cervical metastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>406</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>222</td>
<td>406</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>406</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>77</td>
<td>406</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>406</td>
<td>6</td>
</tr>
</tbody>
</table>
EXAMINATION

Key considerations when examining a patient with possible OPSCC are that: (1) a systematic upper aerodigestive tract examination, including fibre-optic endoscopy should be performed; and (2) the tongue base should be additionally palpated (as many tumours here are submucosal).

INVESTIGATION

Radiology

The role of radiology in the assessment of oropharyngeal tumours is discussed in Chapter 42, Principles of radiotherapy. In general, MR imaging is preferred to CT, particularly for assessing tongue base and parapharyngeal spread. Mandible invasion can be assessed by CT or MR with high sensitivity (combined with clinical examination).

As with all UADT cancers, it is mandatory to image the thorax with CT to ascertain distant metastasis and/or second primary cancers.

Cytology

Patients who present with a neck mass will have fine needle aspiration cytology at initial assessment. This can be carried out under ultrasound guidance for increased diagnostic accuracy, as well as for staging information.

Biopsy

This is generally performed under general anaesthetic, as part of a systematic panendoscopy, the latter to exclude any UADT second primary tumours. As well as a means of obtaining definitive histology, the primary tumour is accurately staged and an assessment of whether it is surgically resectable can be made (and by what means). If the diagnostic biopsy/endoscopy is not carried out by a surgical oncologist, this may need to be repeated in order to make a decision about treatment with regards to surgery.

With regard to tonsil tumours, the preferred means of biopsy is a deep incisional biopsy, rather than tonsillectomy. Performing a tonsillectomy at diagnostic stage often means that it is difficult to judge the margins of any remaining tumour for later definitive surgical resection, either open or transoral. Therefore, a well intentioned tonsillectomy as a debulking procedure might exclude the possibility of definitive primary surgery while achieving nothing oncologically. Nevertheless, if there is not an obvious tumour, then tonsillectomy will be necessary. This applies to the context of evaluating an unknown primary, when 'blind' biopsies will also be carried out of the tongue base, and there is a strong argument for bilateral tonsillectomy also. This is discussed in more detail in Chapter 35, Management of an unknown primary carcinoma.

TREATMENT POLICY

General comments

The treatment of OPSCC has changed considerably over the last two decades. In the 1980s, surgical resection and reconstruction for patients with advanced tumours was the rule, with postoperative radiotherapy, on the basis that this approach offered the best chance of disease-specific cure, particularly for more advanced disease. Patients with early disease or those not suitable for this were given RT.

The 1990s saw the introduction and increasing use of definitive concomitant chemoradiotherapy (CRT), which offers better survival compared to RT. Initially, this was seen as a better way of treating patients who would otherwise simply have RT. However, even before the popularization of CRT, there was some suggestion that definitive RT offered comparable survival with better function. For example, results from definitive RT (twice daily in some), with planned post-RT neck dissection in a series of 490 patients, yielded the following oncologic results: local control T1 87 per cent, T2 82 per cent, T3 70 per cent, T4 43 per cent; disease-free survival I 89 per cent, II 89 per cent, III 87 per cent, IVa 69 per cent, IVb 61 per cent.

With the additional advantage of concomitant CRT, the balance has fallen to CRT over surgery and this has now become the standard of care for most patients with OPSCC.

While the results of CRT for early OPSCC seem to be excellent, the results for more advanced OPSCC are disappointing. The overall survival in a series of 48 patients was 84 per cent for T1–2 OPSCC and 27 per cent for T3–4, treated with concomitant CRT.

Intensive modulated radiotherapy (IMRT) may reduce morbidity without oncologic compromise.

CRT has evolved to be generally in the form of induction chemotherapy, with three cycles of TPF (docetaxel–cisplatin–5-fluorouracil) and then concurrent chemoradiotherapy with platinum. With the additional advantage of concomitant CRT, the balance has fallen to CRT over surgery and this has now become the standard of care for most patients with OPSCC.

However, some have questioned the major toxicity of this treatment approach and the encouraging oncologic results may, in part, reflect the increasing influence of HPV-induced OPSCC. The acute toxicity and late effects of chemotherapy and RT are significant in terms of mucositis, haematological toxicity, long-term dysphagia and dependence of feeding tubes.

In Bonner et al’s trial of radiotherapy versus radiotherapy and cetuximab, the effect of cetuximab was most pronounced in OPSCC. This observation, coupled with the possible overtreatment of HPV OPSCC with conventional chemoradiotherapy, has led to proposals for using cetuximab with radiotherapy for OPSCC, especially HPV-induced tumours.

In the last decade, transoral microsurgery has gained popularity as a means of carrying out effective oncologic resection with much less morbidity. This has been in the form of CO2 laser transoral microsurgery, but recently, transoral robotic surgery (TORS) has attracted interest, particularly for oropharyngeal resections. Most patients treated by transoral microsurgery have postoperative RT or CRT. The oncologic results appear promising, with a disease-free survival of 94 per cent in one series of 71 tongue base OPSCC (18 per cent T1; 51 per cent T2; 21 per cent T3), as do the functional results with no patients requiring tube feeding.
With regard to neck disease, there has been a parallel evolution. In the 1980s, most patients with clinically evident neck disease (certainly N1) would be treated with a comprehensive neck dissection, whether the primary was treated with surgery or not. The introduction of CRT saw this being used for definitive treatment of N2 and even N3 disease, if the primary was being treated in the same fashion. Initially, this would generally be followed by planned post-CRT neck dissection, for N2 and N3 disease. This has given way to an increasingly acceptable policy of definitive CRT with neck dissection only if there is clinical or radiological evidence of residual disease. Thus, it has become routine practice to perform a positron emission tomography-computed tomography (PET-CT) scan after CRT to guide the need for neck dissection.

Options for definitive treatment of OPSCC are shown in Table 31.4.

### Treatment of the neck

Patients with clinical and/or radiologic evidence of neck metastases (cN+) should have a comprehensive neck dissection or CRT. As alluded to above, if CRT is used for definitive treatment of the N+ neck, it is increasing practice for that to be followed by PET-CT and only neck dissection if there is clinical or radiologic evidence of residual disease.

A comprehensive neck dissection can be done as part of primary tumour surgery, or before definitive RT/CRT. The role of selective neck dissection for N+ disease is more controversial. However, there is growing evidence to suggest that level 5 can be spared, if there is no preoperative evidence of involvement and there is no multiple lymphadenopathy (i.e. N1 or N2a). Quality of life studies indicate improved pain scores if level 5 is not dissected. Similarly, in cases staged below cN2b, level 1 can be modified so as not to include perifacial lymph nodes.

### Treatment of the contralateral N0 neck

Contralateral metastases are a feature of all OPSCC subsites to a degree and clinicians should be alert to this. The contralateral neck should be treated as for the ipsilateral N0 neck for tumours arising in the soft palate, posterior pharyngeal wall and/or near midline, large tumours (T4) and advanced ipsilateral nodal involvement (N2b, N3) due to the high frequency of lymph node metastases. For other tumours, in most cases it will remain untreated (by surgery

<table>
<thead>
<tr>
<th>Table 31.4 Overview of treatment options for OPSCC.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>RT</td>
</tr>
<tr>
<td>RT/CRT</td>
</tr>
<tr>
<td>CRT</td>
</tr>
<tr>
<td>CRT</td>
</tr>
<tr>
<td>Trans-oral surgery ± RT/CRT</td>
</tr>
<tr>
<td>Open surgery ± RT/CRT</td>
</tr>
</tbody>
</table>

CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; ND, neck dissection; OPSCC, oropharyngeal squamous cell carcinoma; PET-CT, positron emission tomography-computed tomography; RT, radiotherapy.
or RT) in the absence of clinical or radiologic suspicion of involvement. In a series of 642 patients treated with ipsilateral RT (mostly T1–2), only 3.5 per cent failed in the contralateral neck.54

**Functional considerations**

Percentage tongue base resected and total volume resected are most often correlated with swallowing function.55 In patients closed with a flap, the excess bulk of the flap compared to the size of the defect is related to a poorer outcome with swallowing. The best outcomes are for patients with no flap closure. The use of postoperative radiotherapy worsened swallow, on a dose-related level.

Twenty patients with stage III/IV oropharyngeal cancer were treated by surgical extirpation, free flap and postoperative radiotherapy.56 Average time to decannulation was 15 days. Thirteen of 20 started oral intake before RT (average 19.5 days); by four months after surgery 10/20 took all food orally and ten were tube fed (6/10 managing some oral intake).

There is a tendency to worse swallowing outcomes in patients with advanced T stage and with base of tongue rather than tonsil subsite of disease.

**SURGICAL RESECTION**

**Open techniques**

There are three technical considerations in open surgery for the oropharynx: access technique (generally via mandibulotomy or transcervical); reconstruction; and mandibulectomy (see Table 31.5).

### Mandibulectomy

Advanced tumours of the lateral oropharynx, particularly when extending into the retromolar trigone of the oral cavity, may require segmental or rim mandibulectomy. This should be anticipated on clinical or radiological grounds. The operative technique, including reconstructive issues, are discussed in Chapter 51, Defect-based reconstruction: mandible and oral cavity.

### Access techniques

The two main access techniques are via paramedian mandibulotomy or transcervical/pharyngotomy. Lateral mandibulotomy should not be used mainly because the inferior alveolar nerve is divided, which renders the lower lip insensate and leads to drooling.

Paramedial mandibulotomy is used for access for lateral oropharyngeal wall (± lateral tongue) tumours, or tongue base cancers extending laterally. For small tongue base tumours, an elegant posterior approach is via a lateral pharyngotomy. This can be extended by removing the ipsilateral hyoid bone. The functional results from this approach are superior to mandibulotomy.57

Any incisions which relate to access must consider the levels required for neck dissection, which will usually be at least level II, III and IV for the N0 neck, or otherwise a modified radical or radical neck resection. Such an operation

<table>
<thead>
<tr>
<th>Technique</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access</strong></td>
<td></td>
</tr>
<tr>
<td>Paramedian mandibulotomy</td>
<td>Standard access technique for most oropharyngeal tumours</td>
</tr>
<tr>
<td>Lateral mandibulotomy</td>
<td>Rarely used. Sacrifices inferior alveolar nerve and places osteotomy in radiotherapy field</td>
</tr>
<tr>
<td>Lingual release</td>
<td>Unusual approach for oropharyngeal resections. Offers little extra compared to transoral approach</td>
</tr>
<tr>
<td>Lateral pharyngotomy</td>
<td>Very useful technique for tongue base tumours without significant lateral extension, with good functional results57</td>
</tr>
<tr>
<td>Midline suprahyoid pharyngotomy</td>
<td>Unusual approach</td>
</tr>
<tr>
<td><strong>Reconstructive</strong></td>
<td></td>
</tr>
<tr>
<td>Radial artery free flap</td>
<td>Generally the flap of choice, as it is pliable enough to reconstruct the three-dimensional nature of the oropharynx, and can be modified to optimize palatal closure56</td>
</tr>
<tr>
<td>Anterolateral thigh free flap</td>
<td>Reduced donor site morbidity. Increased bulk compared to RAFF may be preferable when there is significant tongue base resection</td>
</tr>
<tr>
<td>Pectoralis major myocutaneous flap</td>
<td>Not ideal for the oropharynx, as it is generally at the limits of the arc of rotation, and the weight tends to make it pull inferiorly</td>
</tr>
<tr>
<td>Other pedicled flaps</td>
<td>Several local pedicled flaps can be used and have been described. For a tumour to be large enough to warrant an open resection and reconstruction rather than CRT or a transoral approach, these will often be inadequate. Examples include sternomastoid myofascial flap, buccal mucosal transposition flap, lingual flap, temporalis flap</td>
</tr>
<tr>
<td>None</td>
<td>Many defects can be primarily closed or left to heal by secondary intention</td>
</tr>
</tbody>
</table>

CRT, chemoradiotherapy; RAFF, rectus abdominus free flap.
facilitates exposure of the major vessels, which will provide the facility for microvascular free transfer. The oropharynx is a difficult area to reconstruct, given its three-dimensional complexity and the need for sensation. The principles for reconstruction are discussed in Chapter 51, Defect-based reconstruction: pharynx.

**Paramedian mandibulotomy**

- Tracheostomy – it is standard to perform tracheostomy as part of any open OPSCC resection, in order to protect the airway from postoperative obstruction at the resection/reconstruction site and from aspiration. This is generally performed at the beginning of the operation through a separate small incision.
- Incision – usually involves a lip split with paramedian mandibulotomy and access via a mandibular swing (Figure 31.2). It is important to preserve the mental nerve to ensure that lower lip sensation remains intact. The incision can be extended into the neck as either a modified Schobinger or a ‘T’ on its side.
- Neck dissection is carried out, the type and selectivity depending on individual circumstances. It is important to preserve all candidate vessels, where possible, for microvascular anastomosis, assuming that a free flap reconstruction will be employed. This includes the lingual-facial trunk, superior thyroid artery, (occasionally) transverse cervical artery, internal jugular vein and facial vein. The neck dissection may be left pedicled on the parapharyngeal space adjacent to the primary tumour to allow for a primary neck dissection single specimen, or can be taken separately.
- Mandibulotomy – the periosteum of the mandible is cleared either side of the mandibulotomy site, usually at or around the lateral incisor or canine tooth. The mental nerve is identified and preserved. The mandibulotomy can be either between tooth roots or through one. The exact location depends on the OPG XR assessment (i.e. through an appropriate socket after extraction or between two roots that diverge, allowing enough room). The inner periosteum is also cleared but only immediately around the mandibulotomy site. The mandibulotomy is planned as a stepped incision and is pre-plated with titanium plates and screws beforehand. The bone cuts can be done with a reciprocating or an oscillating saw.
- Tumour access and resection. The mandible is then swung laterally, as the mylohyoid and anterior belly of digastric are cut, whilst making a mucosal incision in the gingival mucosa towards the retromolar trigone (it is important to leave enough mucosa on the mandible-side for later closure). The lingual and hypoglossal nerves are identified and preserved. At this point, the access depends on the exact location of the tumour. Generally, dissection will be performed around the tumour medially via glossotomy, while lateral dissection will extend from the retromolar trigone, around the anterior faunal pillar to the soft palate. The external carotid artery and internal carotid artery can be followed superiorly in the parapharyngeal space, as this marks the deep aspect of the tumour dissection. The pterygoid muscles can be resected at the deep margin also.
- Reconstruction is performed, usually with a radial artery free flap for most OPSCC.
- Closure.

**Lateral pharyngotomy approach**

A neck dissection incision (as above) with a selective or modified radical neck dissection is performed as required. In dissection of level 1, the lingual artery is dissected, ligating any posterior branches feeding the inferior tonsil or tongue base, clipping branches to posterior tongue. Following this, the hypoglossal nerve is dissected from the anterior edge of the carotid artery to the hyoglossus muscle. Elevation of the nerve away from the tongue base area akin to a clothes line and elevation away from posterior tongue over hyoglossus allows access to the tongue base without compromise to motor innervation of the mid and anterior tongue. Inferior to the hypoglossal nerve, and above the superior thyroid artery, the internal branch of the superior laryngeal nerve is encountered. Careful dissection of this nerve is essential to reduce the risk of denervation and loss of sensation of the ipsilateral supraglottic larynx.

At this stage, attention passes to the hyoid bone. Periosteal dissection of bone from midline to greater cornua is performed with separation of digastric, mylohyoid and hyoglossus from hyoid. The ipsilateral hyoid is resected from the lesser cornua to the apex of the greater cornua. More extensive tumours will require resection of the entire ipsilateral hyoid. Incision through the base of hyoid into ipsilateral vallecula with a hockey-stick extension posterolaterally allows exposure of the lower pole of tonsil, and base of tongue. Transoral digital palpation of the tumour allows approach to the tumour without transection of the lesion directly and maintenance of tissue margins.

Once the pharyngotomy is made, direct view of the tumour with controlled margin resection is made in three dimensions.

Dependent upon the volume of tissue resected, the pharyngotomy can be closed and the defect left to heal by secondary intention. In larger defects, local mucosal flaps can be developed from the tongue base and pharyngeal wall to close the defect. Some defects may require free flap closure – most probably a radial forearm free flap, with vascular access to the superior thyroid artery and internal jugular vein close by for anastomosis.

**Midline vallecula approach**

In the case of midline tongue base, following bilateral level I and II anatomical dissection and bilateral dissection of the lingual arteries and hypoglossal nerves, a suprapharyngeal release of geniobathy, mylohyoid and hyoglossus muscles with transoral digital palpation allows incision into the apex of the vallecula from one tonsillolingual sulcus to the opposite sulcus. Retraction of the tongue base into the neck allows direct resection of the tumour with three-dimensional marginal control. Tissue closure may occur primarily with small defects, or with tongue/pharyngeal flaps from larger defects.
The use of a free flap to repair a defect in the entire tongue base is associated with significant loss of swallowing function requiring a PEG tube and persistent swelling requiring prolonged tracheostomy tube dependence.

**Lingual release approach**

In the case of large tonsillar or tongue base tumours, especially those requiring a free flap closure, a lingual release allows excellent tumour exposure, direct margin control in three dimensions of the primary tumour and more straightforward free flap insertion and vascular anastomosis.

The release commences with transoral exposure of the tumour using plastic cheek/lip retractors and a bite block with silk suture retraction of the tongue. Incision of oral mucosa allowing a cuff of mucosa and mylohyoid muscle to remain on the inner surface of the mandible is made. This allows maintenance of vascular supply to the mandible and eases muscle and mucosal repair with a watertight seal at the end of the procedure. Following myomucosal incisions laterally, the genial tubercle muscles and the anterior

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*Figure 31.2* Lip split incision (a) with paramedian mandibulotomy and a mandibular swing (b). Panel (b) reproduced with permission from Aug KK, Harris J, Wheeler R et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *New England Journal of Medicine* 2010; 363: 24–35.
attachment of the anterior bellies of the digastic muscles are divided, again leaving a cuff of muscle/tendon attached to the inner surface of the mandible to allow postresection repair. At this point, there should be a through and through defect from the oral cavity from one retromolar space to the other and the entire tongue will be dropped out into the neck. Pulling forward on the tongue allows the entire oropharynx to be visualized for controlled tumour resection. In the case of tonsillar extension of the tumour, transoral release of the tonsil from the soft palate and resection lateral to the superior constrictor muscle, anterior to the buccopharyngeal raphe and inferior to the retromolar trigone, allows the tonsil to drop out into the neck in continuity with the tongue base. Resection of the inferior-medial extension of the tumour is now performed with three-dimensional marginal control.

One benefit of this approach is that the ipsilateral hypoglossal and lingual nerves may be preserved if not invaded by tumour, and vascular control of external carotid vessel branches can be achieved. Second, insertion of a free flap is straightforward with closure of inferior and posterior mucosal surfaces with the tongue in the neck and then with the tongue returned to the oral cavity, repair of the flap to soft palate and superior pharynx can be achieved under direct view. Muscle and mucosal closure allows a watertight seal and avoids the possibility of postoperative fistula formation. In addition, muscle closure returns the normal diaphragm function of mylohyoid supporting tongue movement and returns the genioglossoptomy anatomy to normality with stability of the airway and larynx.

**Tissue reconstruction**

Tissue reconstruction in oropharyngeal defects follows the standard ‘ladder’ approach, as with other tissue sites.

Generally speaking, the simplest closure which achieves watertight closure without tension and maximal retention of organ function directs the technique used.

Small lesions may be closed primarily, following the principles above. Medium-sized defects of the tonsil and tongue base which do not expose major vessels may be left to heal by secondary intention. A combination of fibrotic scar contracture and re-epithelialization of the defect allows excellent functional recovery in most cases. There is a small risk of secondary bleeding, which may require return to theatre, and the patient should be alert to this possibility.

Larger defects, and especially those associated with major vessel exposure or direct communication with the neck as a through and through defect, will require myomucosal closure. This may be achieved in some cases by use of local myomucosal flaps, such as the buccinator flap, posterior tongue flap, lateral pharyngeal flap or superior constrictor advancement flap. In these situations, a palatopharyngoplasty may reduce the risk of velopharyngeal incompetence. Larger defects where these local approaches are insufficient for tissue coverage will be repaired with free flaps. In general, lateral pharyngeal defects may be commonly closed with a radial forearm flap or, in thin patients, an anterolateral thigh flap. In general, it is helpful not to design the flap to completely replace three dimensionally the tissue resected, but to slightly reduce the flap size, allowing a slightly more constricted closure. The ideology here is that the flap is insensate, immobile and stiff, and minimizing the size of this non-functioning portion of the oropharynx will improve postoperative oropharyngeal functionality. It is vitally important not to leave the pharynx overly constricted, or to make the closure too tight, increasing the risk of impaired mucosal breakdown and fistula formation. Flap design needs to be three-dimensional in design, allowing palate, pharynx and tongue base to be maintained in normal anatomical configuration after flap repair, maintaining functionality.

**TRANSORAL SURGERY TECHNIQUE DESCRIPTIONS**

The two main access approaches are:

1. Boyle Davis gag – mainly for tonsillar, palatal and limited tonsillolingual tumours.
2. FK retractor system – useful for base of tongue tumours, inferiorly extending lateral pharyngeal tumours.

At the time of initial tumour evaluation at panendoscopy, a trial of exposure of the tumour with the above systems is made. Biopsies of the primary tumour and marginal tissues are taken and evaluation of the mobility of the tumour is made. Particular note is taken of deep invasion of tonsillar tumours through the superior constrictor and anterior invasion behind the pterygomandibular raphe into the medial pterygoid muscle and ascending ramus of the mandible. Invasion anterior to the medial pterygoid muscle inferiorly brings the tumour into contact with the lingual nerve, inferior alveolar nerve, nerve branch to mylohyoid and to the perioestem of the body of the mandible. Examination of the tongue base to assess the extent of tumour spread across the tongue base and inferiorly to the apex of the vallecula, hyoepiglottic ligament and pre-epiglottic space is made. Palpation for tumour extension deeply into genioglossus, and inferolaterally into styloglossus, as well as palpation of the carotid vessels through the posterolateral oropharyngeal mucosa and for retropharyngeal nodes posteriorly, is made. Elevation and inspection or transnasal rigid endoscopic assessment of the superior portion of the lateral pharyngeal wall is made to look for extension into the salpingopharyngeus and up to the Eustachian tubal orifice.

These features are critical to achieve a clear margin resection and avoiding untoward neural and vascular injury and to identify areas of extended resection including marginal mandibulectomy. In addition, the requirement for reconstruction is made – none, mucosal advancement, buccinator myomucocutaneous flap or free flap.

At the time of resection surgery, tracheostomy may be electively planned for large transoral resection with associated modified radical neck dissections and free flap reconstruction. Patients with smaller tumours requiring no or local flap closure may be managed by extubation on the table with a covering nasopharyngeal airway or remain intubated in ICU overnight and electively extubated the following day.

During the neck dissection, elective ligation of the posterior lingual artery branch(es) to the tongue base and
ascending pharyngeal artery may be associated with reduced risk of primary and secondary bleeding.

The use of dilute adrenaline (1:200 k) to the tissue surrounding the tumour acts to maintain a clear surgical field and a heat sink to reduce thermal injury to non-resected tissue during electrocautery or laser resection.

The tumour may be resected with a CO₂ laser, set at 10–15 watts superpulse continuous mode via a microslad on an operating microscope or a hand-held attachment using operating loupes (2.5–3 × magnification). The use of electrocautery using a switching pen with a guarded tip or Colorado needle, set at 20 joules cautery and 40 joules cutting, allows an extended and maliable attachment to be used, reaching margins tangential to the line of sight. Bipolar cautery and ligaclips are used to seal small and larger vascular structures.

Commonly, tumours may require alteration of the angle of view, requiring replacement of retraction systems to access the three-dimensional nature of the tumour. At all times the operator must be clear as to the volume of the tumour and surrounding structures. It is commonplace to dissect immediately along the adventitia of the carotid artery, and to dissect across the tongue base to identify the lingual artery and ligate it.

For superiorly based tumours (palate and tonsil), a superior to inferior approach is used, maintaining a view of the depth of the tumour and allowing the field to be kept clear of blood. For tongue base lesions, the medial and inferior edges of the tumour may be exposed using the FK retractor, resecting perpendicular to the epithelial surface. Following replacement of the retractor, the lateral and anterior margins are exposed and the other two sides of the box cut are made with resection of the tumour, taking care of the third dimension margin.

In the case of tonsillar tumours, an incision at the level of the buccopharyngeal raphe in the vertical plane, extending superiorly across the soft palate with an adequate mucosal margin, and across the tonsillolinguall sulcus with a similar margin, is made.

At this point, deepening the incision through the superior constrictor muscle allows entry to the space. In this area, loose areolar tissue and fat is encountered with vessels crossing the space from lateral to medial. These may be ligated, harmonic scissor coagulated or bipolar diathermied appropriate to the size of the vessel. Continual assessment of the deep margin of tumour resection is made, and dissection of the space posteriorly with scissors or an artery clip allows exposure of the internal carotid artery. Dissection medial to the artery allows the tumour flap to be elevated to the posterolateral pharyngeal wall and the posterior mucosal incision can be made, again with appropriate margins. It is the author’s preference to take frozen section tissue of superficial and deep margins to allow confidence in clear tumour resections. It is noted that other centres may take the primary tumour directly to the pathologist at this stage, and with coloured inking of the specimen, allow frozen section margins to be taken of the resected tumour with a similar outcome.

In the case of tongue base tumours, the use of the FK retractor system allows access to the apex of the vallecula and lateral pharyngeal wall. It is critical to have a clear idea of the depth of invasion of the tumour to plan an adequate depth to tumour resection. This is achieved by a combination of radiologic review and palpation of the tumour on the table. The asymmetric blade is positioned to allow complete visualization of the ipsilateral hemitongue base. The author uses electrocautery to release the tumour from the base of the tonsil, with a clear margin, extending across the level of the ipsilateral circumvallate papillae to the midline, and then inferiorly to the apex of the vallecula. The anterolateral quadrant of the dissection is the critical point of exposure as this is where the lingual artery and two medially directed transverse tongue base branches are encountered. Knowledge of the anatomy of this area through cadaveric dissection practice and training in a centre with a regular approach to this area is vital at this time to avoid transgression of the arterial branches. Inferomedial retraction of the tumour with dissection in the line of the pedicle allows the lingual artery to be identified and ligated with ligaclips if required for tumour resection. Similarly, the two medially directed tongue base branches are similarly ligated. Once vascular control is achieved, the mucosal incision laterally is taken down to the pharyngo-epiglottic fold and across the apex of the tongue base to the midline. At the pharyngo-epiglottic fold, there is a constant arterial vessel passing in the fold medially towards the apex of the vallecula. This will also require ligacclipping. At this point, the resection allows clearer visualization of tumour boundaries, achieving with direct transoral view. This improves the accuracy of tumour resection and manipulation of the specimen and vessels, making the surgery easier to perform. Third, the ‘robotic surgeon’ operating through two hand controls allows the ‘manual assistant’ to grasp, cut, ligate and suction in the field simultaneously. It would be very difficult for a standard transoral procedure to take place with four surgeons’ hands working on the tongue base!

Whatever way the tumour is resected, haemostasis with intraoperative vasalva is checked and titanium clips are used adequately to seal all major vessels. Following tumour resection of the tonsil or tongue base, and establishment of haemostasis, Surgi-Flo or Surgicell Fibrillar may be placed over the deep resection surfaces to allow small vessels’ coagulation to occur and minimize surface oozing.

The requirement for tissue repair is now made. Essentially, extended tonsil tumour resections may not require any closure, behaving like a normal tonsillectomy with healing by secondary intention. Resection involving the soft palate at risk of developing velopharyngeal incompetence should be closed using a posteriorly based buccinator artery myomucosal flap (BAMMF) or palatal island flap (PIF). Tumours involving exposure of mandibular bone should always be covered, usually using a BAMMF to avoid issues of
osteoradionecrosis following the planned postoperative radiotherapy. Lesions of the tonsil extending into tongue base will benefit from a BAMMF to reduce tethering and tongue mobility issues. Because this flap is neurotized, sensation of this important area is maintained. It is not critical to close small tongue base lesion resections (less than 30 per cent surface) as these will also mucosalize similar to tonsil lesions.

Tumours extending widely onto the lateral pharyngeal wall whose resection exposes carotid vessels or where oral secretions may contaminate the neck around the great vessels should be repaired. Small defects may be covered with the BAMMF, but larger lesions will require a radial forearm free flap.

It should be noted that these larger lateral pharyngeal resections will probably be through and through resections with contact to the neck dissection. This situation will commonly occur if high level IIa or lateral retropharyngeal nodes are resected at the time of the neck dissection. In some centres, staging of the surgery with primary resection is followed by a neck dissection at a 1-week interval, allowing tissue healing to start to close the primary defect prior to the neck dissection. It is the author’s preference to close pharyngeal defects which expose the carotid artery as indicated above, however. At the time of neck dissection, the use of the posterior belly of digastric muscle and stylohyoid muscle to close the defect will reduce neck contamination.

When tumour invasion extends into the mandible and is visible radiologically preoperatively, or evident at the time of surgical resection, it should be treated by segmental mandibulectomy. This will usually require a fibula or deep circumflex iliac artery osseomyocutaneous flap repair.

As can be seen from the above, most lesions will not require free flap closure, and those that will should be predicted from preoperative imaging and panendoscopic tumour assessment.

Most patients will require a period of at least 4 days nil by mouth with NET feeding, and then assessment by a speech pathologist to commence liquid diet intake. Patients with mandibulectomy and free flap closure often will require a prolonged period of nutritional support, especially as they will have significant deterioration of swallowing with adjuvant radiotherapy. These patients should be planned to have a PEG tube insertion prior to the resection surgery, as there will be a deterioration in swallowing related to radiotherapy and planned PEG insertion will avoid delays and interruptions in delivery of radiotherapy.

Those patients who require a tracheostomy will commonly have staged decannulation starting at day 4–5 postoperatively.

The surgical approach indicated above would be expected to allow one modality (surgery) treatment to be definitive in approximately 10 per cent of patients, and to avoid the need for chemotherapy in postsurgical treatment in 30–40 per cent of patients. The subsequent de-escalation of treatment in a planned, histologically directed manner allows tumour control and minimizes treatment-related morbidity.

POSTOPERATIVE RADIOTHERAPY AND CHEMORADIOThERAPY

The principles and indications for postoperative radiotherapy and chemoradiotherapy are discussed in Chapter 44, Postoperative radiotherapy in head and neck cancer and Chapter 45, Chemoradiation in head and neck cancer. The indications after OPSCC resection are no different from other primary tumours. Most pN+ and T>2 OPSCC are treated with postoperative radiotherapy, with specific adverse features being treated with postoperative CRT, these being, extra-capsular invasion and positive surgical margins, although many would also include other adverse features, such as perineural or lymphovascular invasion. After transoral resections of the oropharynx, most patients have postoperative RT or CRT, with results that appear to be comparable to open surgery and postoperative radiotherapy.

RADIOTHERAPY AND CHEMORADIOTHERAPY TECHNIQUES

The radiotherapeutic technique chosen depends on whether or not the tumour is well lateralized. If there is a central tumour, or a large, lateral one which either crosses or even encroaches on the midline, there is a high probability of bilateral nodal involvement. In such cases, the whole width of the neck must be irradiated, whereas for small, laterally placed tumours, treatment of a limited volume can be effective. Such a set-up enables the contralateral mucosa and parotid gland to be spared, and therefore it causes much less morbidity.

Carcinomas of the tonsil or lateral wall

SMALL TUMOURS WITHOUT NODES

Before considering small-volume treatment for a lateral oropharyngeal tumour, it is essential that its limits have been precisely identified at examination under anaesthesia, and that any clinically occult extension has been excluded by a CT scan. As in the case of oral cavity tumours, it can be helpful for treatment planning if the tumour margins are marked by the insertion of inert metal seeds, which are used to indicate the position of the tumour on radiographs. For T1 or T2 squamous carcinoma of the tonsil or fauces which do not extend significantly into the base of tongue or parapharyngeal area, and where there is no lymphatic spread, small-volume treatment is appropriate. Two ipsilateral fields are used (Figure 31.3), a posterior oblique and an anterior oblique. Wedges are used to ensure that a homogeneous dose distribution is achieved (Figure 31.4).

The fields extend from the level of the hard palate superiorly down to the hyoid. Their anterior border is through the central part of the tongue and their posterior limit is through the vertebral bodies. The volume encompassed therefore includes the primary tumour with an adequate margin and the jugulodigastric and parapharyngeal nodes, and extends to the midline. For T1–2N0 tumours it is not necessary to irradiate the lower neck prophylactically. The patient is planned lying supine in a shell with the mouth closed. A simulator check film is taken as a permanent record of the intended treatment, and portal verification films are taken or megavoltage imaging is performed to ensure that treatment is executed as planned. A dose of 55 Gy in 20 fractions over 4 weeks or its equivalent is given, using 4–6 MV x-rays from a linear accelerator.
EXTENSIVE LATERAL TUMOURS AND SMALLER ONES WITH NODES

To embrace the primary tumour adequately and upper deep cervical nodes bilaterally a pair of lateral parallel opposed fields is used. Their margins are essentially the same as described for more limited tumours. Care is taken to ensure that these are extended if necessary to cover any direct tumour extension or nodal involvement. Although in most circumstances radiotherapists attach great importance to achieving a homogeneous dose distribution, the oropharynx provides an exception. If the tumour is confined to the tonsillar region and does not infiltrate the base of tongue or extend on to the palate, it is possible to weight the treatment, giving a greater dose to the affected side and an adequate prophylactic dose to the contralateral nodes. If there is palpable nodal enlargement, the lower neck is also treated. An anterior field is used, the upper border of which matches the lower border of the parallel opposed fields. If the lymphadenopathy is bilateral, then both sides of the lower neck are treated. A single anterior field covering the width of the neck is used and a midline block is required to shield the cervical cord. If there is extensive or bulky nodal disease, primary surgery with postoperative radiotherapy is usually preferred. Nonetheless, primary radical radiotherapy is sometimes appropriate, in which case it may not be possible to achieve adequate coverage without including the spinal cord in the high-dose volume. A two-phase technique, similar to that described for piriform fossa carcinoma (Chapter 42, Principles of radiotherapy), enables the dose to the cord to be kept within safe limits. In such circumstances the likelihood of cure is slim, but radical treatment may be attempted as it is sometimes successful. A dose of 55 Gy in 20 fractions over 4 weeks is often given, but for the reasons set out in the section on supraglottic carcinoma (Chapter 42, Principles of radiotherapy), many radiotherapists prefer a more protracted fractionation schedule.

Carcinoma of the base of tongue

The technique here is similar to that described above for bulky lateral wall tumours, or those with nodes. The inferior margin of the lateral fields should, however, be lower to cover actual or potential spread into the supraglottis. In addition, if the tumour is confined to the tongue base, the upper margin is placed below the level of the hard palate and the patient is treated with the mouth open and the tongue depressed. This enables the mucosa of the roof of the mouth to be spared to some extent. Treatment of nodal disease and selection of a fractionation schedule are as indicated above.

Sometimes, a brachytherapy boost can be given to the primary tumour using looped iridium wires, as described in Chapter 42, Principles of radiotherapy.

Carcinoma of the soft palate

In most cases this is treated by evenly weighted parallel opposed lateral fields, as described for extensive lateral wall tumours. In the rare event of finding a small T1 squamous carcinoma, interstitial therapy alone may be chosen. The principal advantage of this approach is that because the treatment volume is small, the reaction will be minimized. Implantation is a particularly valuable treatment method when irradiation of a previous primary tumour has limited the scope for further external beam radiotherapy.
REFERENCES


22. Northrop M, Fletcher GH, Jesse RH, Lindberg RD. Evolution of neck disease in patients with primary squamous cell carcinoma of the oral tongue, floor of mouth, and palatine arch, and clinically positive neck


Cancer of the hypopharynx remains a dismal disease that poses a therapeutic challenge to the treating physician, with an extremely high incidence of morbidity and distant metastases.

Ferlito (2001)

INTRODUCTION

Hypopharyngeal cancer is uncommon in the United Kingdom, 10 per million per year, with the majority of patients presenting with advanced primary and metastatic disease. Patients with hypopharyngeal cancers usually present with significant comorbidities: respiratory, cardiac and nutritional, which may restrict the therapeutic options. The selection of treatment is dependent on the stage of disease and a thorough understanding of cancer spread and its natural history. Frequently, the relief of symptoms may be the best therapeutic intent allowable, and maintenance of nutrition and airway, with relief of pain is all that can be realistically achievable. However, in selected patients aggressive treatment will result in cure of disease, but may result in significant life-long morbidity, particularly voice and swallowing, which will require support and rehabilitation.

ANATOMY

The hypopharynx is interposed between the oropharynx superiorly and the upper oesophagus inferiorly, with the larynx located anteriorly. In the adult, the hypopharynx extends from the hyoid bone (fourth cervical vertebrae) above to below the cricopharyngeus muscle, lower border of the cricoid cartilage (sixth cervical vertebrae). The cervical oesophagus extends from the lower border of the cricoid cartilage into the thorax. The hypopharynx includes the posterior pharyngeal wall, the piriform fossae or sinuses, and the postcricoid area or space (Figure 32.1 and Table 32.1).

The wall of the hypopharynx is composed of four layers:

1. An inner mucosal lining of stratified squamous epithelium over a loose stroma.
2. A fibrous layer of pharyngeal aponeurosis.
3. A muscular layer formed by the inferior constrictor muscle and, in the upper part by the distal portion of the middle constrictor. The most distal fibres of the inferior constrictor condense into the cricopharyngeus muscle; just proximal to this muscle on the posterior wall is an area of relative weakness known as Killian's dehiscence.
4. An outer layer of fascia that derives from the buccopharyngeal fascia.
The piriform sinus is divided into a superior or membranous part, and an inferior or cartilaginous part. The thyrohyoid membrane bounds the superior aspect of the piriform sinus laterally, through which passes the internal branch of the superior laryngeal nerve. Sensory innervation of this area synapses with the jugular ganglion, along with sensory nerves of the external auditory canal (Arnold’s nerve), which accounts for the referred otalgia frequently encountered with the patient presenting with tumours of the piriform sinus. The lower portion of the piriform sinus is bounded by the ala of the thyroid cartilage. The terminal branches of the recurrent laryngeal nerve pass through the fibres of the cricopharyngeus muscle and the posterior cricoarytenoid muscle and the posterior cricoarytenoid muscles of the larynx. Motor and sensory innervation of the hypopharynx occurs via the pharyngeal plexus, which is formed by branches of the cranial nerves IX and X. The arterial supply arises from branches of the superior thyroid arteries along with collateral vessels from the lingual and ascending pharyngeal arteries.

Lymphatic drainage of the hypopharynx terminate in lymph nodes along the jugular vein (levels II, III and IV) and appear to a lesser extent in the nodes along the spinal accessory nerve (level V) and even less frequently in the submandibular area (level Ib). Significant lymphatic drainage occurs from the posterior pharyngeal wall and drains to the retropharyngeal lymph nodes. Lymphatics from the inferior part of the piriform sinus, the postcricoid area and the upper oesophagus often drain to the nodes along the recurrent laryngeal nerves to the paratracheal lymph nodes (level VI).

Table 32.1 Hypopharynx – UICC anatomical descriptions (C12, C13).

<table>
<thead>
<tr>
<th>Anatomical description</th>
<th>Description</th>
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<tr>
<td>C13.0</td>
<td>Pharyngo-oesophageal junction (postcricoid area) extends from the level of the arytenoid cartilages and connecting folds to the inferior border of the cricoid cartilage, thus forming the anterior wall of the hypopharynx.</td>
</tr>
<tr>
<td>C12.9</td>
<td>Piriform sinus extends from the pharyngoepiglottic fold to the upper end of the oesophagus. It is bounded laterally by the thyroid cartilage and medially by the hypopharyngeal surface of the aryepiglottic fold, the hypopharyngeal surface of the arypepiglottic fold (C13.1) and the arytenoid and crico cartilages.</td>
</tr>
<tr>
<td>C13.2</td>
<td>Posterior pharyngeal wall extends from the superior level of the hyoid bone (or floor of the valleculae) to the level of the inferior border of the cricoid cartilage and from the apex of the piriform sinus to the other.</td>
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</table>

PATHOLOGY AND CLASSIFICATION

Macroscopic pathology

The majority of tumours present as ulcers and are widely infiltrative. They have a tendency to extend submucosally and also to metastasize to the local lymph nodes.

Histopathologic types

The most common (90 per cent) histologic type of cancer is squamous cell carcinoma. Other malignant tumours present in a similar manner either with ulceration or as a non-ulcerative swelling: malignant minor salivary gland tumours, lymphomas and sarcomas.

Epidemiology

The hypopharynx is an uncommon site of tumours, the majority being malignant, and accounts for less than
10 per cent of all squamous cell carcinomas overall. The overall incidence in the Western world is one per 100,000 per year. There is a high incidence in Northern France of 14.8 per 100,000 per year, which accounts for 18 per cent of head and neck cancer seen. The distribution macroscopically of hypopharyngeal cancer varies geographically, with tumours of the piriform sinus being the most common subsite in North America and Europe, and postcricoid lesions more common in Northern Europe and the UK (Table 32.2).

The mean age at presentation is 60 years. Piriform sinus and posterior pharyngeal wall carcinomas demonstrate a male dominance, 5–20:1. Postcricoid lesions unlike other sites, shows a moderate female preponderance 1.5:1.

### Aetiology

As with all head and neck cancers, there is a significant association with alcohol and smoking, acting synergistically. Postcricoid carcinoma is associated with previous irradiation exposure, and sideropenic dysphagia, with up to 10 per cent having a history of Plummer–Vinson, Kelly–Patterson Brown syndrome.

### SECOND PRIMARY CANCER

Hypopharyngeal cancer patients are at risk of having a synchronous or metachronous cancer. Little work has been reported on this topic. In a series of 38 patients treated surgically\(^1\) who had a cancer in their upper oesophagus or hypopharynx, 14 had multiple primaries in addition to their main primary cancer. They reported that synchronous, previous metachronous and subsequent metachronous carcinomas occurred in 26, 17 and 8.5 per cent of instances, respectively. Twenty of the 25 (80 per cent) multicentric carcinomas were invasive. This finding lends weight to the concept of total pharyngolaryngectomy as the treatment of choice for hypopharyngeal cancer because it includes all the condemned upper pharyngolaryngeal mucosa. A similar study in the UK,\(^2\) has shown that patients with a hypopharyngeal cancer have a greater than 20 per cent chance of developing a second primary cancer. Half of all will present within two years of the index tumour diagnosis. Another publication\(^3\) reports that there is an excess risk for the development of a second primary cancer in the upper aerodigestive tract and lung following initial hypopharyngeal cancer, but no excess risk was observed in organs outside the respiratory tract and/or the upper aerodigestive tract.

They recommend that stopping smoking and alcohol consumption, as well as increased consumption of citrus fruits should be recommended as a means to reduce the risk of second primary cancer.

### Routes of primary tumour spread

Cancer of the medial wall of the piriform sinus may spread superficially towards the aryepiglottic folds and arytenoids. It also may infiltrate deeply into the larynx, to include the cricoarytenoid joint area. Involvement of the paraglottic and pre-epiglottic spaces frequently explains the frequency of early vocal cord fixation.\(^4\) Involvement of the recurrent laryngeal nerve beneath the mucosa of the piriform sinus may also fix the hemilarynx. Tumours of the lateral wall spread rapidly to the ala of the thyroid cartilage and thereafter to involve the lobe of the thyroid gland.

Cancers of the postcricoid space frequently invade the posterior cricoarytenoid muscles and the cricoid and arytenoid cartilages. The apex of the piriform sinus terminates in the postcricoid area and is often invaded early. Advanced tumours may totally encircle the hypopharyngeal lumen.

Cancer of the posterior pharyngeal wall usually presents as an ulcer that infiltrates the whole of the posterior wall both superficially and deeply, and may involve from the nasopharynx down to the upper oesophagus. Tumours may spread to involve the prevertebral muscles and the retropharyngeal space, and may spread laterally to involve both piriform sinuses.

### Regional metastases

In more than 80 per cent of patients, tumours spread to involve the local lymph nodes are detected on physical examination or by imaging at first presentation. The lymphatics fluid flows mostly via collectors into the lymph nodes of levels II and III. A direct relationship to level I has not been detected. Drainage to involve level IV occurs frequently. The lymphatic drainage of the posterior pharyngeal wall occurs mainly first into the retropharyngeal lymph nodes, and accounts for over 40 per cent of cases.\(^5\)

In hypopharyngeal cancers, because of its advanced stage at presentation and its involvement or extension to cross the midline, the risk of contralateral metastases is high, with histological identification of tumour in more than 20 per cent of cases treated surgically\(^4, 5, 6, 7\) and supports the therapeutic decision to treat both sides of the neck, either by surgery or by radiotherapy in the N0 neck.\(^8\) Other areas of lymph node drainage that require specific attention, when evaluating and considering the treatment of patients with hypopharyngeal cancers include retropharyngeal and parapharyngeal nodes,\(^9, 10\) paratracheal nodes\(^11\) and mediastinal nodes.\(^12\)

### Distant metastases

Distant spread has been reported in up to 3 per cent of patients who present for treatment of a hypopharyngeal cancer, and related to site – piriform sinus, advanced T stage,

<table>
<thead>
<tr>
<th>Table 32.2 Geographical distribution of hypopharyngeal cancers.</th>
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<tbody>
<tr>
<td><strong>United States</strong></td>
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<tr>
<td>Posterior pharyngeal wall</td>
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<tr>
<td>Piriform sinus</td>
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<tr>
<td>Posterior space</td>
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\(\text{N0 neck}\)
as well as the presence of nodal metastases. The most frequent sites involve the lungs, liver, bones and brain. However, as the cancer progresses, distant metastases are a common feature of hypopharyngeal malignancy. The majority of patients at presentation have advanced disease when diagnosed.\(^{33, 14}\)

### CLASSIFICATION

- **T1**, Tumour limited to one subsite of hypopharynx and 2 cm or less in greatest diameter.
- **T2**, Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm, but not more than 4 cm in greatest dimension, without fixation of hemilarynx.
- **T3**, Tumour more than 4 cm in greatest dimension, or with fixation of hemilarynx.
- **T4a**, Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue (prelaryngeal strap muscles and subcutaneous fat).
- **T4b**, Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures.

The nodal classification for the hypopharynx is the same as for other regions in the head and neck, resulting in similar stage groupings of disease into early and late stage, depending on T and N stage.

### PATIENT EVALUATION

#### Presenting symptoms

Patients with cancer of the hypopharynx commonly present with a history of sore throat, dysphagia, referred otalgia, hoarseness and/or a neck mass. Dysphagia, while common, commences with a vague pain or discomfort in the throat, and may be associated with problems with swallowing of saliva initially, then food (usually solids), then followed by difficulty with fluids. Severe dysphagia and otalgia are signs of advanced-staged disease that involve the lower regions of the piriform sinus/postcricoid area and the upper oesophagus. Hoarseness is not uncommon with cancer of the hypopharynx and may be due to invasion of the larynx or paralysis of the recurrent laryngeal nerve. Dysphonia is uncommon in the early stage, but when present suggests that the larynx is extensively involved or may be due to bilateral recurrent nerve involvement, resulting in bilateral vocal cord fixity. This progressive difficulty with swallowing results in weight loss and hyponatraemia – adding to the associated comorbidity of patients who present with advanced head and neck cancers.

Cervical adenopathy is frequent at the time of presentation and is most often detected at level IIa and III. Thus, in patients who present with palpable cervical adenopathy, who may have a sore throat, otalgia and with known risk factors (smoking and drinking), a tumour located in the hypopharynx needs to be excluded.

### Clinical assessment

The assessment of patients with a hypopharyngeal cancer begins with a global evaluation of their general health – nutritional status and anaemia. Also, requiring assessment are their social habits, such as chronic smoking and excessive alcohol intake, which may have an effect on their respiratory and hepatorenal systems. Evaluation of the airway for patency and possible dyspnoea and hoarseness may suggest a large tumour involving the supraglottis or even the subglottis or the trachea.

Evaluation of the primary tumour can be performed by indirect and direct examination of the hypopharynx recording the subsites involved, whether the vocal cords are mobile or paralysed. Next is palpation of the neck, to determine the presence of enlarged lymph nodes, and record their number, size and distribution. Also, during neck palpation, it is possible to assess laryngopharyngeal mobility on the cervical vertebrae. Extension of the tumour to the prevertebral muscles when early causes loss of laryngeal crepitus indicating significant oedema or swelling around the hypopharynx, usually associated with a large tumour.

### Endoscopic assessment

Almost every clinic has a flexible fibreoptic nasolaryngoscope which is used widely to evaluate patients who have head and neck pain, as well as throat symptoms. Frequently, a tumour of the hypopharynx is first diagnosed in this way, and the extent of the lesion can be assessed. Movements of the vocal cords can be noted, together with any distortion, swelling or ulceration suggesting involvement of the larynx, as well as narrowing of the laryngeal or upper tracheal airway. The transverse extent of hypopharyngeal cancers can usually be determined by flexible endoscopic examination, whereas evaluation of the vertical extent is difficult if not impossible with any degree of accuracy. This is particularly challenging when the tumour is located in the postcricoid region. One useful tip is to get the patient to swallow the endoscope into the oesophagus and during gentle withdrawal of the viewing end, the lower end of the tumour can be evaluated.

The vertical extent of the tumour is best evaluated by the use of the rigid endoscope, however, this procedure requires the use of a general anaesthetic. The larynx can be lifted forward opening the lower end of the hypopharynx for inspection and facilitates biopsy to be performed. Sometimes, the use of bougies to dilate the stenosed tumour segment may be required to evaluate the lower extent, as well as estimating the vertical length. This procedure is traumatic and bleeding can occur, obstructing the view, and may increase the possibility of perforation.

### Imaging studies

The aim of imaging studies is to determine the exact three-dimensional extent of tumour involvement, to detect the presence of locoregional neck metastases, to detect pulmonary metastases or synchronous second primary, so as to allow the patient’s therapy or treatment to be optimized. The lateral soft tissue radiograph may be a good screener in a busy clinic,
to determine the urgency of patients’ investigation, in that patients with hypopharyngeal upper oesophageal cancers will have expansion of the prevertebral soft tissue, the space between the tracheal air column and the cervical vertebral bodies. In some large tumours, involvement of the trachea or vertebral bodies themselves may be visible.

**CONTRAST STUDIES OR BARIUM SWALLOW**

Performing a barium study may not be appropriate because of the potential risk of aspiration and also may not with any degree of accuracy identify any mucosal irregularities, so it may need to be modified by the radiologist. By using a modified Valsalva or Toynbee manoeuvre, it is possible to distend the hypopharynx and allow the barium to coat the mucosa, thus increasing the surface area covered by the barium suspension. The longitudinal extent of the hypopharyngeal cancer has been shown to be a significant prognostic indicator, however, the lower end of the tumour is notoriously difficult to predict with accuracy on contrast studies. Should a perforation or a pharyngotracheal fistula be suspected, then a non-ionic and low osmolar water-soluble contrast agent should be used to minimize the resultant chemical pneumonitis and pulmonary oedema.

**COMPUTED TOMOGRAPHY**

Computed tomography (CT) is currently the most frequently employed imaging study used to evaluate the extent of hypopharyngeal cancers (Table 32.3). Its use can identify the tumour itself, the surrounding structure (larynx, thyroid) and assessment of the likely involvement of the cervical nodes. The primary tumour may extend or invade in all directions; a piriform sinus tumour may invade medially into the larynx or laterally to or through the thyrohyoid membrane. Also, in all subsites whether the tumour has crossed the midline, it is imperative to evaluate the upper and lower extent of the tumour, which may involve the oropharynx above or below the oesophagus. One of the limitations of CT is that it is difficult to differentiate between tumour and soft tissue oedema.

**MAGNETIC RESONANCE IMAGING**

Magnetic resonance imaging (MRI) is superior to CT scanning at demonstrating soft tissue abnormalities such as prevertebral fascia invasion. The limitations of MRI in the hypopharyngeal imaging are that it is time consuming and images can be blurred because patients have a tendency to swallow excessive saliva. Also, metallic implants, such as cardiac pacemakers and intracerebral aneurysm clips, are a contraindication to the use of MRI as an imaging technique.

**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomography (PET) when used with the contrast fluorine-18-fluoro-deoxy-glucose (FDG) has a high sensitivity in the detection of occult, residual and recurrent tumours, but has a low specificity. While contrast CT and MRI remain the mainstay of initial radiological evaluation, imaging usually upstages the tumour at presentation. After treatment, including surgery and/or chemoradiotherapy, using CT and MRI to differentiate residual and recurrent tumour from oedema and scarring may be impossible. The combination of PET and CT increases the specificity and is increasingly being used to image post-treatment cases. Other newer imaging modalities, such as diffusion-weighted imaging (DWI), MR spectroscopy and MRI with super-paramagnetic iron oxide (SPIO) contrast agent are reported to be useful and should be employed more widely in difficult cases.

**CURRENT MANAGEMENT PHILOSOPHY**

The optimal treatment for hypopharyngeal cancer depends on the stage at presentation. For early disease, radiotherapy and surgery achieve similar results. For advanced disease, radical surgery followed by radiotherapy may be applicable when the tumour stage is operable in selected patients. Many hypopharyngeal cancer patients present with significant comorbidity, thus limiting the choices of available treatment. The functional outcome following treatment is important and the appropriate therapeutic measure chosen should be ‘cost-effective’ in that the treatment duration should be short and the associated morbidity minimal. In a review of treatment of hypopharyngeal cancer as practised in the United States in the 1980s and 1990s, survival was best for surgery only (50.4 per cent), similar with combined surgery and irradiation (48 per cent), and worst for irradiation only (25.8 per cent). However, the appearance of active chemotherapy regimens has shifted many paradigms in head and neck oncology, and no more so than the treatment of hypopharyngeal cancer (Box 32.1). The tendency to avoid removal of the larynx has led many clinicians to assess preservation strategies using up-front or concurrent chemotherapy with irradiation as an alternative for candidates for surgery. The evidence-based management of hypopharyngeal cancer in the UK has been summarized as of practice in 2001. It was suggested that early disease be managed by organ-sparing techniques – both surgical and non-surgical. Radical surgery in early cancer is not justified on available evidence.

A retrospective review of whether radiotherapy or surgery alone as primary treatment results in any survival advantage when applied to a retrospective population-based study of 595 patients from Ontario, Canada, treated between 1990 and
1999, has been reported. Three different methodological approaches were used for the survival analysis, including a restricted cohort study, a matched case–control study, and natural experiment study across defined geographical regions. The authors report that there was no survival advantage for either radiotherapy/salvage surgery or surgery/postoperative radiotherapy. It must be commented that there has been no analysis of the modern inclusion of chemotherapy to the treatment regimen. However, a more recent commentary on the widespread use of primary chemoradiotherapy as a laryngeal organ-preserving protocol when applied to hypopharyngeal cancer (extralaryngeal sites) lacks a paucity of randomized controlled trials comparing non-operative treatments to the gold standard of surgery followed by postoperative radiation for adverse pathological features, as the likelihood of a successful surgical salvage does not translate to extralaryngeal sites compared to that of larynx cancer.

Useful and practical guidance has recently been developed by the Scottish Intercollegiate Guidelines Network (SIGN). These are clear, comprehensive and well referenced.

Early hypopharyngeal carcinoma is relatively unusual (Figure 32.2a,b). Treatment options include radical surgery, conservation surgery and radiotherapy with or without induction or concurrent platinum-based chemotherapy. At present, there are no randomized controlled trials comparing these treatment modalities. It is noted that surgery and radiotherapy are equal modalities for cure with equal morbidity for early hypopharyngeal cancers. However, there is a paucity of well-designed prospective clinical trials to support this statement because early hypopharyngeal cancer occurs infrequently and, therefore, does not frequently appear in the reported large series.

Cancer of the hypopharynx is known to invade insidiously, and the presence of submucosal spread is considered an indication for wide resection, well beyond gross clinical margins. If practised in small tumours, this will result in an extensive surgical procedure. As a result, the frequent reporting of pathologic specimens with incomplete excisions has resulted so that when advocating surgical treatment for larger tumours, it is considered best that radiotherapy is given postoperatively. Thus, currently, because of the likely risk of complications and loss of laryngeal function when treating advanced surgically curable disease, patients are now recommended to consider treatment with concurrent chemoradiotherapy. Should the hypopharyngeal cancer recur...
or persist after such treatment, then salvage surgery consisting of total pharyngolaryngectomy with neck dissections may be feasible. This programme is generally associated with a poor prognosis. When one reviews large patient series of consecutive patients with hypopharyngeal cancer, up to 25 per cent of patients are considered untreatable for a variety of reasons, such as comorbidity, inoperability, second primary cancer, and refusal to consent to treatment.26

SURGICAL PATHOLOGY

The results of radical surgery for hypopharyngeal cancer have remained poor with a five-year survival rate with postoperative radiotherapy in the range of 25–40 per cent. The main cause of failure is thought to be due to submucosal extension of the primary tumour. Poor survival is associated with the high rate of involvement of the cervical nodes, as well as the resection margins and usually presents within two years of treatment, the overall five-year survival rates being in the region of 30 per cent in stage III/IV.27, 28

In a series from Hong Kong,29 using whole organ serial sections, submucosal tumour extension was found in 58 per cent (33 of 57) and most (67 per cent) could be detected grossly at the time of surgery. These investigators recommend that surgical resection margins should be 3 cm inferiorly and 2 cm both superiorly and laterally. However, it is agreed that the extent of invasion into the laryngeal framework and the surrounding tissues after radiotherapy is unpredictable. Thus, conservative surgery is considered unsafe.

In another study,30 they looked at radial clearance in resected hypopharyngeal cancer. It was considered important to be aware that tumours can infiltrate into the muscular wall of the pharynx and the laryngeal cartilage. A total of 56 per cent of patients had a radial clearance of <1 mm, but the incidence of local recurrence was only 19 per cent, and occurred usually in the upper and lower margins of resection. This narrow margin would appear sufficient as long as the patients were treated with postoperative radiotherapy. Naturally as wide a margin as possible is to be recommended.

Treatment of the thyroid gland in hypopharyngeal cancer is dependent on the clinical and radiologic findings at tumour assessment. However, in certain circumstances, total thyroidectomy has been advocated in resection of postcricoid and upper oesophageal cancer. It is recommended that resection of the thyroid isthmus and lobe ipsilateral to the tumour be removed in cancers of the piriform sinus. Because many of these patients currently are treated in addition by chemoradiotherapy, the possibility of hypothyroidism and hypocalcaemia needs to be considered during each and every visit for the duration of the patient’s life.31

SURGERY FOR HYPOPHARYNGEAL CANCER

A classification for surgery of the hypopharynx is important (Table 32.4) to discuss the specific procedures available when treating patients with a tumour involving specific sites or areas within the hypopharynx.32 It is recognized that in many patients with advanced disease, the site of origin of the tumour is impossible to determine because frequently all

Table 32.4 Classification of surgery on the hypopharynx.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tr>
<td>Internal excision</td>
<td>CO₂ laser or ‘cold steel’</td>
</tr>
<tr>
<td>External excision (with or without flap repair)</td>
<td>Partial pharyngectomy/partial laryngectomy</td>
</tr>
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<td></td>
<td>Partial pharyngectomy/total laryngectomy</td>
</tr>
<tr>
<td></td>
<td>Total pharyngolaryngectomy</td>
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<td>Extended pharyngolaryngectomy</td>
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three subsites are involved with tumour (Figure 32.3). A classification of defect repair has been suggested, but does not consider preservation of the larynx, and is best used by surgeons when describing repair of pharyngeal defects.33

A review of the reconstructive options used in the UK found that the use of the stomach pull up was the most commonly used method, but the jejunal free flap was becoming increasingly more popular because of its associated lower morbidity and mortality.34

SURGICAL TECHNIQUES

Internal excision

The operative technique of transoral partial hypopharyngectomy is well established, and current preference is to use the endoscopic technique with the carbon dioxide laser.35, 36
A spreadable supraglottoscope is used for exposure of the hypopharynx in the orally intubated patient. In patients whose tumour has spread caudally to involve the oropharynx or even nasopharynx, a mouth gag is also used. In lesions involving the posterior wall of the hypopharynx, a resection line is drawn around the tumour with the laser at the beginning of the procedure, followed by performing a deeper incision made using the laser approximately 1 cm cranial to the superior border of the tumour, until the prevertebral fascia is reached. Using this incision, the complete or total tumour volume along with all of the layers of the pharyngeal wall is dissected off the prevertebral fascia using the CO₂ laser, exactly like a scalpel or scissors, while remaining inside the excision borders marked initially. Because grafts do not cover the wounds adequately, healing is by most usually by secondary intent, taking about 3–4 weeks to granulate and heal. In such cases, the need for a tracheostomy and nasogastric tube feeding is seldom required.

The lateral and medial hypopharyngeal walls of the piriform sinus can be treated in a similar manner. If blood vessels of more than 0.5 mm are encountered, they are grasped with an alligator clamp, which is insulated except for the jaws, coagulated, and then divided by the laser. Postcricoid tumours are only resected, if the tumour is limited to one arytenoid and the cricoid cartilage is not infiltrated. Also if the apex of the piriform sinus is involved or low postcricoid cancer, access may be difficult or impossible to view, and if resected with safe margins, patients are at high risk of developing pharyngeal stenosis, which may require further surgery. Complications reported with the use of laser excision include local infection, emphysema, pharyngocutaneous fistula, postoperative bleeding, dyspnoea due to oedema or stenosis, swallowing difficulties and aspiration problems, including pneumonia.

**External excision**

**PARTIAL PHARYNGECTOMY ± PARTIAL LARYNGECTOMY ± FLAP REPAIR**

Cancer of the posterior pharyngeal wall and some cancers of the lateral wall of the piriform sinus may be small enough to employ local excision via a lateral pharyngotomy approach and primary repair with skin, free tissue or allowed to heal by secondary intent. However, these patients need to be carefully selected so that the larynx can be preserved, with minimal morbidity. The types of tissue described which have been selected so that the larynx can be preserved, with minimal morbidity. The types of tissue described which have been used in such defects have included radial forearm, platysma muscle flap and pectoralis myocutaneous flap.

Many investigators have advocated the use of partial laryngeal surgery with partial pharyngectomy. Ogura and Mallen described select patients who had cancer of the medial wall of the piriform sinus without involvement of the apex, who were suitable for treatment with partial laryngopharyngectomy. They advocated entering the hypopharynx away from the clinically evident tumour, permitting surgical exposure of the lesion, while preserving as much pharyngeal wall as possible for subsequent reconstruction. The extent of the laryngeal resection depends upon the degree of involvement by the piriform sinus primary and may range from subglottic laryngectomy to resection of the arytenoid.

The use of the supracricoid hemilaryngopharyngectomy was popularized in the mid-1960s and was indicated for tumours of the supracricoid upper part of the piriform sinus and carcinomas of the lateral wall with normal mobility of the vocal cord.

The use of near-total laryngectomy has also been advocated for more advanced cancer of the piriform sinus, which includes both the lateral and medial wall sites, with or without fixation of a vocal cord. This procedure, recently reported has resulted in preservation of speech and aspiration-free swallowing in the majority, thus many patients may avoid a permanent tracheostoma.

**TOTAL LARYNGECTOMY AND PARTIAL PHARYNGECTOMY – PRIMARY WITH AND WITHOUT FLAP CLOSURE**

In the vast majority of patients worldwide who have cancer of the hypopharynx, the prime subsite location is the piriform sinus. Surgical treatment of these cancers requires total laryngectomy and partial pharyngectomy. Indications for this procedure include involvement of the apex of the sinus, partial involvement of the postcricoid mucosa, and invasion of the thyroid cartilage or the presence of a paralysed hemilarynx.

After total laryngectomy with partial pharyngectomy, it is possible to close the pharynx primarily if the narrowest width of the pharyngeal remnant is 1.5 cm relaxed or 2.5 cm stretched in the absence of tumour. This amount of residual pharyngeal tissue is sufficient to restore swallowing function.

When there is less than 50 per cent or <2.5 cm of mucosa stretched after removal of a hypopharyngeal tumour, then the remaining mucosa needs to be supplemented by a ‘patch technique’ using either a free tissue flap, such as a radial forearm or a pectoralis myocutaneous flap; this will minimize the possibility of a fistula and subsequent pharyngeal stenosis. It is considered that using a ‘patch technique’ in such circumstances results in better swallowing function than repair of a full circumferential defect, the use of residual pharyngeal tissue will maintain accurate length and better physiology (Figure 32.4).

The concept of hypopharyngeal reconstruction must deal with restoration of not a simple tubed conduit but a complex arrangement of constrictive and propulsive forces with fine sensory circuits. The chosen surgical approach should aim to achieve both complete removal of tumour and re-establishment of two primary functions: swallowing and phonation. To date, the use of free flaps represents the first choice for both partial and total oncologic hypopharyngeal reconstruction, and pedicled flaps should be considered only when free flaps are contraindicated by general and vascular conditions.

**TOTAL PHARYNGOLARYNGECTOMY AND FLAP REPAIR**

The need for complete excision of the hypopharynx, in addition to a total laryngectomy, is based on the circumferential extent of the tumour and the presence of
tumour inferiorly in the postcricoid area, extending towards or involving the cervical oesophagus. The hypopharynx is a funnel-shaped tube, with a larger upper circumference that narrows down towards the pharyngo-oesophageal junction. Hence, cancer at the lower end of the hypopharynx and upper oesophagus requires a complete circumferential resection and repair. The surgical defect thus created requires a tubular replacement which can be skin, skin and muscle (a myocutaneous or free tissue), viscus (either free jejunum, caecum, greater curve of stomach with omentum or a pedicled stomach) or colon graft.

The problems or difficulties associated with primary and secondary (salvage) hypopharyngectomy are different and the surgical defects require differing management and realistic expectations, not only by clinicians but by the patients and their carers. Patients considered for salvage are a high-risk group in terms of both operative morbidity and survival. It has been proposed that the use of the gastro-omental flap because of its anatomical, physiological and immunological properties is the ideal reconstructive technique in repair of surgical defects, especially for hypopharyngeal cancers, when considered after failed primary treatment having used chemoradiotherapy. Patients with nodal metastases, extracapsular spread and poorly differentiated tumours are likely to succumb to their disease and should be selected for adjuvant therapy when possible.

The ideal reconstructive technique for circumferential defects of the hypopharynx and upper oesophagus should have as many of the following attributes as possible: adequate surgical margins, especially the inferior margin; low rate of stenosis or fistula formation; short time to swallowing; normal sounding of conversational speech; ability of tissue to withstand postoperative radiotherapy with or without chemotherapy; simultaneous harvesting at the same time as the excisional surgery to reduce time ‘on the table’; short hospitalization; and surgeon team experienced with the procedure and handling of complications.

CERVICAL LYMPH NODES

In view of the high propensity of metastases to cervical lymph nodes in patients suffering from hypopharyngeal cancer, attention to these is as important as resecting and repairing the primary defect. The method of treating the likely cervical nodal metastases will depend on the method of primary treatment whether it is surgery, or radiotherapy ± chemotherapy.

For patients with no palpable cervical lymph nodes, then selective neck dissection removing the lymph nodes at levels II, III and IV should be performed with resection of the primary tumour. When cervical nodal disease is palpable, then a modified neck dissection should be considered. Nodal disease along the paratracheal gutter should be sought for when the primary tumour is located low in the piriform sinus or postcricoid space. Occasionally, the upper mediastinum will need to be approached and a mediastinal neck dissection performed.

THE THYROID GLAND

Involvement of the thyroid gland in hypopharyngeal carcinoma is difficult to predict preoperatively, unless there is gross invasion seen on imaging studies. In early disease confined to one side, e.g. piriform fossa carcinoma, a hemithyroidectomy can be performed on the involved side preserving the contralateral thyroid. If the patient receives postoperative radiotherapy, hypothyroidism may still result and thyroid function should be monitored.

In more advanced disease, total thyroidectomy is usually required. The indications for total thyroidectomy have been summarized when surgically managing laryngeal and hypopharyngeal cancers including the presence of subglottic extension of more than 2 cm, cricoid cartilage invasion and perithyroidal soft tissue involvement. The significant morbidity from this does not usually arise from removal of the thyroid whose function can be simply replaced with thyroid hormone supplements, but from resection of the parathyroid glands and the resulting hypocalcaemia. In these cases, careful titration of 1-alpha calcidol against calcium levels should result in normal calcium levels, but can be difficult to achieve and may be disturbed by comorbidity or intercurrent illness. In all cases, the aim should be to preserve one of the parathyroid glands, which may be difficult with extensive neck disease. If possible, the parathyroid gland should be left in situ, but if removed can be reimplanted into the sternomastoid muscle.
COMPLICATIONS

Complications associated with surgery for hypopharyngeal cancer may occur either during or after the operation. The problems may be grouped in relation to the procedure of resection or reconstruction. Early recognition of these is mandatory if successful discharge from hospital is to be anticipated.

Resection-related problems

BLEEDING

Intraoperative bleeding during the resection can be controlled easily as the neck is wide open! Bleeding from the carotid artery requires prompt attention and appropriate suturing of the defect in the wall, or ligation of a branch as appropriate. More extensive defects may require a venous patch, or even a bypass temporarily to maintain blood flow while the defect is controlled. Consideration to repairing an arterial defect by use of a vein bypass may be occasionally required to excise tumour adherent to the carotid system.

Bleeding intrathoracically during blunt dissection of the oesophagus may be profuse and sometimes may even be fatal, if the aorta or a large branch is avulsed. Bleeding from the azygos vein if injured can be torrential, and direct visualization of the bleeding area or vessel may be very difficult to view and additional access may be required with appropriate use of suction and light, as a matter of urgency. The anaesthetist should be advised should bleeding occur, as it is important that the patient’s blood pressure is maintained, either by giving blood or plasma expander. A torn azygos vein can be approached by extending the abdominal incision into a right anterior thoracotomy incision, by retracting the right lung, allowing identification of the azygos vein and ligation. With experience, this vein can be dissected under direct vision, using thorascopic techniques and the vein ligated, so avoiding this complication.

Bleeding from the jugular vein in the neck can be controlled by pressure and, with appropriate assistance, the defect can be ligated, avoiding the possibility of air embolism.

DAMAGE TO THE POSTERIOR WALL OF THE TRACHEA

Injury to the posterior wall of the trachea may occur during separation of the posterior wall from the upper part of the oesophagus. This is likely when the tumour of the hypopharynx indents the oesophageal wall and has invaded the wall of the oesophagus, or in the clinical situation when the patient is being salvaged from previous treatment, such as radiotherapy. During the separation, the cuff of the endotracheal tube or the tracheostomy should be deflated to reduce the distension of the posterior tracheal wall. When the posterior tracheal wall is damaged in the upper portion of the trachea, it can be repaired from the neck wound. When the tear is more distal and cannot be repaired from the neck, then the repair procedure requires better access.

Injury at a lower level above the carina, can occur when mediastinal dissection is being performed. When the damage is through the lower trachea, the anaesthetist may notice that they are unable to maintain ventilation pressures, and gas will leak through the tear. An upper midline sternotomy, sometimes with retraction of the trachea with paratracheal traction sutures, may allow for the trachea to be presented into the neck, so that the tear can be sutured. Occasionally, a thoracotomy may be required to gain access. The endotracheal tube may be pushed further down to the level of the carina, to bypass the damaged area and maintain ventilation. Should a ventilation leak persist, then it may be necessary to insert a pneumonectomy double ventilation tube into each main bronchus to maintain ventilation. The damaged tracheal wall can be repaired directly, but usually involves drawing the cartilaginous rings posteriorly together to gain an air seal, or a partial pleural or pericardial flap can be sutured into the defect to reinforce the weakened area. Also, bringing the stomach into the neck will provide additional support to the repaired posterior tracheal wall.

Intraoperative problems

TENSION AT THE ANASTOMOSIS

This problem occurs and depends on the type of tissue used for repair and the technique and size of the surgical defect.

When a patch technique is being used, the current preferred flaps available include the myocutaneous flap, free jejunal graft, free gastro-omentum or stomach. When a pedicled flap is used, tension of the muscle pedicle must be avoided so as to minimize tension on the anastomosis. With jejunum, an adequate length is essential and should be sutured under adequate tension so there is minimal redundant tissue. The jejunal lumen is usually too small to fill the defect at the oropharynx, so additional diameter can be achieved by making an incision on the anti-mesenteric border to increase the lumen size.

When the stomach is used, it is usually brought up through the posterior mediastinum as this is the shortest route and will allow for maximum length of stomach to be achieved. Other ways to increase length are to reduce the tension at the pharyngogastric anastomosis by mobilizing the pharynx, or increasing the length of the stomach. Also, if the opening into the fundus of the stomach extends anteriorly about 1–1.5 cm distal from the free border, this will give additional length posteriorly, the tongue will always be mobile enough to be sutured more caudal, or alternatively a lingual flap can give additional length. If the stomach will not reach the oropharyngeal defect, then it is recommended that a gastrostomy be created in the neck as high as is possible, the orostome closed and then wait for 2–3 weeks and re-explore the wounds and see if further mobilization is possible. Alternatively, an additional graft may need to be piggy-backed to repair the short segment.

LEAKAGE FROM THE PHARYNGEAL RECONSTRUCTION

Leakage may manifest during the early and the late recovery phase. The causes associated with other fistulae apply here, such as previous radiotherapy, poor nutrition and techniques of closure (Figure 32.5).
developed recurrence of his symptoms six years later, and was found to have cancer in the residual pouch. Treatment was by excision of the pouch with the carcinoma followed by external beam radiotherapy.

Use of radiotherapy with or without chemotherapy

Although radiotherapy alone is effective, concurrent chemoradiotherapy has become the treatment of choice for those patients able to tolerate treatment, as a survival benefit of around 16 per cent has been demonstrated on meta-analysis. Neck node metastases to levels II, III and IV are common in hypopharyngeal carcinoma and the N0 neck is usually treated either by selective neck dissection, if surgery is the primary modality of treatment, or radiotherapy. The N+ neck is considered below.

Treatment of advanced hypopharyngeal carcinoma is challenging. Options include radical surgery or non-surgical organ preservation strategies. Radiotherapy alone has little chance of controlling advanced disease and the outcomes are poor. Induction chemotherapy with cisplatin and 5FU followed by radical radiotherapy, for those with a complete response, gives similar survival figures to historical controls having radical surgery and post-operative radiotherapy. More recently, the concurrent administration of chemotheraphy and radiotherapy has increased in popularity for those patients able to tolerate the treatment. Subsequent publication of a number of randomized studies and meta-analyses indicates increased laryngeal preservation rates after concurrent platinum chemotherapy and radiation. This regimen has also resulted in improved survival in non-resectable disease. Novel agents, such as the monoclonal antibody cetuximab and its analogues, have shown significant improvement in locoregional control and disease-free survival when added to conventional radiotherapy in randomized studies. Altered fractionation radiotherapy, either hyperfractionation or acceleration, can improve locoregional control when an increased overall dose of treatment is given, but this may result in an increase in early and late side effects.

As indicated above, nodal metastases to levels II, III and IV are common in hypopharyngeal carcinoma and the N0 neck is usually treated actively. Patients with low volume neck disease (N1), particularly those with nodes <2 cm in diameter and no evidence of necrosis on imaging studies can be treated in the same way as the N0 neck, with selective neck dissection if the primary treatment is surgery or extension of the radiotherapy treatment fields to include the neck. Advanced neck disease (N2 or N3) is usually resected. The extent of surgery should be tailored to the extent of disease, preserving the accessory nerve and internal jugular vein if possible, but not at the risk of leaving disease in the neck. This strategy can be used with early or advanced disease at the primary site and irrespective of the treatment of the primary site.

Assessment of the primary site and the neck after organ preservation strategies is vital to determine whether surgical salvage is required. Clinical examination and outpatient endoscopy should be carried out on all patients at regular intervals following treatment to assess tumour response.

Figure 32.5 A pharyngocutaneous fistula, following an attempt at primary partial pharyngeal closure.
Persistent pain or dysphagia should alert the clinician to the possibility of residual disease. Much of the hypopharynx is hidden and endoscopy under general anaesthetic may be required. Imaging modalities, such as CT and MRI can give an indication of response to treatment, but are a crude indicator of disease eradication. PET scanning has increased in popularity over the last decade as it measures glucose uptake in metabolically active residual carcinoma cells. It must be carried out at least 8 weeks after the completion of treatment and has a higher specificity than CT alone for residual disease.82, 85 If positive, a concerted effort can be made to locate the residual disease and treat appropriately.

MORBIDITY AND QUALITY OF LIFE

Two major problems for patients treated for hypopharyngeal cancer are breathing and swallowing.84 As commented above, early hypopharyngeal cancers are uncommon, with the majority of patients having advanced stage disease at presentation. Patients treated surgically will result in a pharyngo-laryngectomy and result in a tracheostoma and difficulty with their swallow. Minimal problems with swallowing in patients who have had a gastric transposition are reported. As a consequence of laryngectomy, they will require altered voicing techniques such as electrolarynx or tracheo-oesophageal (TEP) puncture. Much has been written about TEP voice restoration in laryngectomy patients, but a lesser quality of voice and increased risks of complications are associated with patients who have extensive replacement of their hypopharynx by free tissue or viscus flaps.85, 86, 87 Swallowing is also a major problem either in the early phase with fistulae or in the late period with stricture formation.88, 89, 90

Patients who are treated by radiation or chemoradiation have associated complications, including mucositis and swallowing problems. The incidence of mucositis and, as a consequence, swallowing problems, is high, but varies depending on tumour location, radiation dose and schedule, and the use of concomitant chemotherapy.91, 92 Problems with swallowing may interfere with all three phases of swallowing, and the following have been observed in studies using a modified barium swallow: reduction of posterior tongue base movement, reduced tongue strength, impairment of laryngeal elevation, pharyngeal stasis, piriform and vallecular residue, and aspiration. Interestingly, pre-treatment swallowing abnormalities became severe following treatment, suggesting that chemoradiotherapy did not produce any new swallowing abnormalities, but exacerbated pre-existing ones.93 Dysphagic patients tend to be isolated and depressed as they cannot comfortably participate in social activities, such as going out to dinner, because of fear of embarrassment. In a retrospective survey of patients who had a modified barium study and responded to quality of life (QoL) questionnaires, the degree of anxiety and depression was correlated with dysphagia severity. Patients who required prolonged tube feeding because of aspiration had the worst QoL.94 Once chronic dysphagia occurred, it rarely returned to normal in studies with sequential modified barium studies for monitoring long-term dysphagia.95 In addition, pharyngeal or oesophageal stenosis occurred late (more than one year) after chemoradiation, and required repeated dilatations, thereby increasing treatment morbidities.96 Thus, the management of patients following treatment of hypopharyngeal cancers requires the care of a multidisciplinary team, involving not only doctors but physicians, speech and language therapists, dietitians and psychologists.97

Salvage after initial curative treatment

Relapse-free survival of patients who have a cancer located in the hypopharynx is strongly related to the localization and initial tumour stage; 25 per cent of relapses remain undetected by patients themselves. To detect relapse at an early stage, oncologic follow up should be performed at close intervals during the first three years. The use of PET-FDG has helped to increase likely detection of persistent and/or recurrent disease, and should be performed 12 weeks after completion of treatment, but beware of the possible confusion with chondronecrosis. Sadly, most of these relapses are already incurable at the time of diagnosis. In a recent analysis of treated cases of hypopharyngeal cancer, the median relapse-free survival was 45 months.98 Another analysis of the ‘natural history’ of hypopharyngeal cancer from Canada,99 reports that up to 20 per cent of patients after curative treatment had residual disease, recurrences tended to appear in the first year and 50 per cent of first recurrences included distant metastases. Overall, 47 per cent of patients were disease free at three years, but eventually 64 per cent of patients died of their cancer.

SUMMARY

The treatment of hypopharyngeal carcinoma remains one of the most challenging areas of head and neck cancer management. Patients often present late with advanced disease and significant co-morbidity. Appropriate decision-making is helped by careful clinical and radiological assessment of the patient and tumour, and discussion with colleagues in a multidisciplinary team environment. There is little hard evidence to guide treatment decisions due to the paucity of well-conducted randomized trials, but the addition of chemotherapy to organ-preservation strategies has improved survival. One of the hardest decisions to make with a patient is to follow a non-curative pathway and institute active palliation with symptom support, but for many with advanced disease this is the appropriate course of action.

KEY EVIDENCE

- The majority of patients when diagnosed with hypopharyngeal cancer have advanced stage disease with evidence of advanced local disease T3/T4,80 regional involvement of level II, III, IV, paratracheal and retropharyngeal lymph nodes (> 80 per cent)5, 9, 11 and involvement of contralateral lymph nodes (> 20 per cent)6 and
KEY LEARNING POINTS

- There is a high risk of synchronous and metachronous second primary tumours.
- Treat the neck in all cases – 80 per cent are N+ at the time of presentation.
- Submucosal spread is common – surgical margins should be 3 cm inferiorly and 2 cm both superiorly and laterally.
- Prevent tracheal tears by deflating the cuff of the endotracheal tube when dissecting the trachea from the oesophagus during gastric transposition.
- Consider the addition of chemotherapy to organ-preservation treatment strategies and post-operative radiotherapy.

REFERENCES


**FURTHER READING**


INTRODUCTION

Laryngeal cancer is the eighteenth most common cancer in the UK. It has an incidence of 6.2 per 100,000 males and 1.3 per 100,000 females, resulting in approximately 1800 cases a year.\(^1\) In recent years, there has been a small decrease in incidence, seen in males only. Incidence is strongly related to age, and is rare before 40 years of age. Laryngeal cancer incidence also has a strong socioeconomic association, being twice as common in the more deprived groups compared to the more affluent groups. There is also a wide geographic variation, being highest in Scotland and the north of England, mirroring the socioeconomic profiles. A recent comparison of head and neck audits involving more than 4000 patients in Scotland and south and west England found that there was significantly more laryngeal cancer presenting at an advanced stage in Scotland than south and west England.\(^2\)

Tobacco smoking and alcohol are the main risk factors for laryngeal cancer, and their effects are synergistic.\(^3\) Smoking is the main risk factor for glottic cancers, whereas alcohol appears to be the bigger risk factor for supraglottic tumours. Recently, a large study has shown the relative contributions of smoking and alcohol to the risk of head and neck cancer in the population. This shows that the population attributable risk is multiplicative and is 89 per cent for laryngeal cancer; being almost half due to tobacco alone and half due to tobacco and alcohol combined, and a small percentage due to alcohol alone.\(^4\)

Within the larynx, tumours may arise from the vocal cords (glottic), superior to the vocal cords (supraglottic), or from below the vocal cords (subglottic). This subclassification of site of origin is historical but serves to allow comparison of tumours between individuals as part of the ‘TNM’ classification (see Table 33.1). In practical terms, however, in all but the very early stage tumours the allocation of a tumour to a subsite is highly subjective. Tumours do not adhere to subsites and indeed the definition of most T2 stages and beyond involve two subsites or more. Definition of the site of origin is subjective and is generally concluded at initial examination without the benefit of detailed imaging. Despite this, it is of value to allocate an index primary site to allow relevant discussion in the patient’s management.

The most common site is glottis (approximately 49 per cent) followed by supraglottis (16 per cent). Eighty-five per cent of tumours are squamous carcinomas.

In recent years, there has been a significant change in the philosophy behind the treatment of laryngeal cancer. Previously, radiotherapy was the mainstay of treatment for most early and low volume tumours, and total laryngectomy for advanced disease. Partial laryngectomy was performed in a few selected cases in a few specialist centres. Increasing application and popularization of endoscopic resection techniques and organ preservation strategies, coupled with improvement and increased availability of imaging techniques, such as PET scanning, has resulted in a considerable

It is not the years in your life but the life in your years that counts.

Adlai Stevenson
change in approach to management considerations by head and neck multidisciplinary teams.

Previous treatment strategies resulted in overall survival of approximately 84 per cent at one year, 64 per cent at five years and 54 per cent at 10 years. This is an increase of 3.3 per cent every five years since the 1980s, and is mainly due to improvement in survival of affluent groups.

SURGICAL ANATOMY

The principal bony and cartilaginous structures in the larynx are the hyoid bone, thyroid cartilage, the cricoid cartilage and the trachea, each being attached to the surrounding structures. Within the larynx are the arytenoids, positioned on the cricoid, and the epiglottis. The cartilages, with the exception of the epiglottis, may have degrees of differential ossification. These structures are further interconnected by a series of membranes, ligaments and muscles with whole assembly being covered by an overlying epithelium (Figures 33.1, 33.2 and 33.3).

It is from this epithelium that dedifferentiation may occur and result in an invasive tumour. The epithelium within the

### Larynx

| T Categories for laryngeal cancers from UICC: TNM classification of malignant tumours |
|----------------------------------|-----------------|----------------------------------|
| **Supraglottis**                | T1              | One subsite, normal mobility      |
|                                  | T2              | Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis; without fixation |
|                                  | T3              | Cord fixation or invades postcrioid area, pre-epiglottic tissues, paraglottis space, thyroid cartilage erosion |
|                                  | T4a             | Through thyroid cartilage; trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus |
|                                  | T4b             | Prevertebral space, mediastinal structures, carotid artery |
| **Glottis**                     | T1              | Limited to vocal cord(s), normal mobility |
|                                  | T1a             | One cord                           |
|                                  | T1b             | Both cords                         |
|                                  | T2              | Supraglottis, subglottis, impaired cord mobility |
|                                  | T3              | Cord fixation, paraglottis space, thyroid cartilage erosion |
|                                  | T4a             | Through thyroid cartilage; trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus |
|                                  | T4b             | Prevertebral space, mediastinal structures, carotid artery |

| **Subglottis**                  | T1              | Limited to subglottis              |
|                                  | T2              | Extends to vocal cord(s) with normal/impaired mobility |
|                                  | T3              | Cord fixation                       |
|                                  | T4a             | Through cricoid or thyroid cartilage; trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus |
|                                  | T4b             | Prevertebral space, mediastinal structures, carotid artery |

### Table 33.1

- **Larynx**
  - **Supraglottis**
    - T1: One subsite, normal mobility
    - T2: Mucosa of more than one adjacent subsite of supraglottis or glottis or adjacent region outside the supraglottis; without fixation
    - T3: Cord fixation or invades postcrioid area, pre-epiglottic tissues, paraglottis space, thyroid cartilage erosion
    - T4a: Through thyroid cartilage; trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus
    - T4b: Prevertebral space, mediastinal structures, carotid artery
  - **Glottis**
    - T1: Limited to vocal cord(s), normal mobility
    - T1a: One cord
    - T1b: Both cords
    - T2: Supraglottis, subglottis, impaired cord mobility
    - T3: Cord fixation, paraglottis space, thyroid cartilage erosion
    - T4a: Through thyroid cartilage; trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus
    - T4b: Prevertebral space, mediastinal structures, carotid artery
  - **Subglottis**
    - T1: Limited to subglottis
    - T2: Extends to vocal cord(s) with normal/impaired mobility
    - T3: Cord fixation
    - T4a: Through cricoid or thyroid cartilage; trachea, soft tissues of neck: deep/extrinsic muscle of tongue, strap muscles, thyroid, oesophagus
    - T4b: Prevertebral space, mediastinal structures, carotid artery

Sagittal section across the larynx looking laterally.

Figure 33.2 The framework of the larynx.
lateral in the ventricle. It is widely regarded that the vocal folds anteriorly and laterally act as the point of division of lymphatic drainage and as such have very little lymphatic drainage themselves. With such a clear division of origin, regional lymphatic drainage is clearly demarcated, namely:

- supraglottis – via superior laryngeal vessels to levels II and III;
- anterior glottis and subglottis – through cricothyroid ligament anteriorly to level VI and laterally to level IV;
- posterior glottis and subglottis – through cricotracheal membrane to the paratracheal nodes in level VI and laterally to level IV.

Chijiwa et al. describe the importance of paraglottic or cricoid involvement in patients with glottic carcinoma and the significantly increased occurrence of lymph node metastases in this group.

**PRESENTATION**

The cardinal symptom of laryngeal cancer presentation is hoarseness. There is not any particular type of hoarseness which is more indicative of cancer than a benign aetiology. However, the hoarseness is frequently persistent with resumption of a normal voice occurring extremely rarely. With increasing size of an intralaryngeal lesion, vocal cord mobility may be reduced with a subsequent breathy component to the voice. As the volume of the tumour increases, less of the laryngeal airway remains patent. This increases turbulence, and stridor ensues. Associated symptoms may include dysphagia, choking attacks, odynophagia, otalgia and weight loss.

**DIAGNOSIS**

**Clinical examination**

In a patient presenting with hoarseness, visualization and assessment of their larynx while they are awake is essential.

This is generally carried out in the outpatient setting, traditionally by indirect laryngoscopy using a mirror. Although this technique has almost universally been replaced by fibreoptic naso-laryngoscopy as the standard for laryngeal assessment, it may still be of value in assessing the tongue base or in those patients who cannot comply with nasal instrumentation.

Fibreoptic nasolaryngoscopy can be carried out following installation of topical local anaesthesia, such as co-pheynylcaine, or without any anaesthesia using a lubricating gel. The advantage of fibreoptic nasolaryngoscopy is that the tongue base and posterior and lateral pharyngeal walls can be visualized and an impression of the pyriform fossa obtained, in addition to a detailed examination of the larynx. It is important to conclude the most likely subsite of origin of the index tumour. Thereafter, the extent of the tumour should be described in detail with particular regard to the laryngeal subsites. The tumour area is effectively a surrogate for a volume assessment, which is confirmed by subsequent computed tomography (CT) scanning or magnetic resonance imaging (MRI). An accurate commentary on the macroscopic appearance of tumour involvement of the subsites allows provisional T stage categorization, although this will be confirmed later at examination under general anaesthesia.

The main advantage, however, is in the assessment of the mobility of the vocal cord, which is pivotal in the determining T staging. It is important that this is carried out in a fully awake patient, as it is inaccurate if carried out in a sedated patient, for example when awakening from general anaesthesia. Mobility is categorized into fully mobile, reduced mobility, or fixed. This assessment can sometimes be difficult due to the vocal cord being obscured by the tumour mass.

 Videostroboscopy is not an essential part of examination, but it may have a role in early stage lesions. The detail of the vocal cords can be highlighted with the use of the rigid endoscope. Subtle movement deficits within the vocal cords may then be elucidated by using the videostroboscopic function. The theory is that as the malignancy involves more structures of the larynx, the dysfunction of the vocal cord will increase, culminating in complete involvement of the intralaryngeal musculature with marked reduction in the movement, or fixation, of the vocal cord. The advantage of this instrumentation is that intralaryngeal detail can be recorded.
and is of specific relevance when contemplating partial laryngeal surgery either by an endoscopic or external approach.

**Imaging**

The main imaging modality for staging the larynx is CT scanning. Usually, it is used to complement direct examination of the larynx when staging laryngeal cancers. Fine slice CT scanning provides a detailed impression of the extent of the tumour, in particular the inferior extension, invasion of the paraglottic and pre-epiglottic spaces and/or extension through the thyroid cartilage to the paralaryngeal soft tissues. It can also identify possible nodal metastases. Extending scanning down to the chest will also identify abnormalities in the lung, the most common site of distant metastases and second primary tumours in this patient group.

It should be noted that MRI has a better sensitivity, but less specificity, for laryngeal cartilage invasion. Therefore, when there is concern about invasion of the laryngeal cartilages, an MRI scan may provide additional useful information. A further indication for the use of MRI is concern about involvement of the tongue base.

Ideally, scanning should be performed before examination under anaesthesia as the manipulation of the tumour and the larynx by direct laryngoscopy may result in inflammatory changes around the tumour, with the possibility of upstaging of the tumour. When assessing imaging of a laryngeal tumour, consideration should be given to the following:

- the subsites involved, including extension across the mid line, and the approximate volume;
- paraglottic and pre-epiglottic space extension, as this can upstage the tumour;
- laryngeal cartilage invasion – especially the outer cartilage invasion, which upstages the tumour to T4. It can sometimes be difficult to be certain if this has occurred, because of differential ossification of the thyroid cartilage. In general, the only way of concluding that there is unequivocal invasion is if there is tumour lateral to, i.e. ‘outside’, the thyroid cartilage;
- the subglottis and anterior subglottic wedge which can be particularly involved in anterior commissure tumours, and may result in upstaging the tumour significantly;
- an examination of pyriform fossae and postcricoid region should also be made;
- tongue base involvement;
- assessment of the neck, including the central compartment (level 6), for nodal metastases.

If there is any suspicion of lymph node involvement then this can be confirmed, or refuted, by ultrasound scanning with sampling by fine needle aspiration cytology or core biopsy as appropriate.

**Examination by microlaryngoscopy**

Once a laryngeal lesion is identified, a full examination of the larynx and surrounding sites is necessary for staging. This is usually undertaken under general anaesthesia to allow close examination of the tumour, its depth, its relations, and to obtain a histological biopsy. When examining a laryngeal tumour, assessment of the surrounding structures should be undertaken. This is especially important for the pyriform fossae and postcricoid region. Tumour can extend through the aryepiglottic folds into these sites, resulting in an upstaging of the tumour and a change of the management plan. Assessment of the extension into the base of tongue and vallecula should also be made.

The ideal form of anaesthesia allows examination of each of the subsites while at the same time maintaining the delivery of the anaesthetic gaseous agents. When examining all aspects of the larynx, including the subglottis, it is best to use a Venturi type of delivery of entrained air and an appropriate microlaryngoscope. There are many types of microlaryngoscope but essentially they are of a design with a proximal lumen which can accommodate the many and varied microlaryngeal instruments and with a distal lumen which sits in the supraglottic larynx displaying the appropriate mucosal surfaces of the larynx. The illumination is fiberoptic and delivered distally. One such laryngoscope is the ‘Dedo’ laryngoscope (Pilling) which satisfies the above criteria very well and is currently in regular clinical use.

Due to patient anatomical issues such as the length of their neck, and upper dentition, it is not always possible to visualize all areas of each of the subsites of the larynx. It is mandatory to achieve this in patients in whom there is a clinically obvious lesion or in whom there is a high level of suspicion. To obtain this, an anterior commissure laryngoscope is used. This scope must be available for all microlaryngoscopy cases, as it may be the only method of intubating a patient with a large laryngeal lesion, and can often obviate the need for a surgical tracheostomy, especially in the emergency situation. The key features of this type of laryngoscope are that it is smaller in each of the main dimensions of the laryngoscope. Namely, it is shorter and narrower but of a similar shape. This allows the laryngoscope to be positioned through a gap in the upper dentition, or gain access to the supraglottis in prominent dentition. The difficulty with it is the diameter of the proximal end, which does not allow ease of use of the microlaryngeal instruments. This is even more problematic when trying to use the CO₂ laser through it, the difficulty on this occasion being the alignment of the laser beam onto the target area. A further problem is the use of the Venturi system with this laryngoscope as it is not possible to fix it to the laryngoscope as the surgical access is then obscured. To allow access in the non-laser cases, fine bore laryngeal intubation can be used with a system attached to the insufflator. The tube sits in the posterior commissure and allows near total access to all parts of the larynx. An example of this type of tube is a Hunsakker tube, which has the added advantage of having a portal through which to measure the patient’s CO₂ levels. It is imperative, however, that a CO₂ laser is not used if there is any kind of endotracheal tube in the airway other than a specified laser tube.

Irrespective of the instrument used, each laryngeal subsite must be inspected thoroughly. It is best to start by identifying if there is an obvious lesion. The ventricle, false cords and the remainder of the supraglottis must be examined, and may present difficulties for examination. This may require
retraction of the false cords with examination of all aspects of the ventricle. The most difficult area to obtain a complete assessment is the laryngeal surface of the epiglottis, and in particular the petiole. The reason for this is the introduction of the endoscope which obscures the area. To overcome this difficulty, the endoscope should be introduced to the level of the anterior commissure and then withdrawn slowly, gradually exposing the mucosal surface of the petiole and laryngeal surface of the epiglottis.

When a tumour is present, it is necessary to map it out carefully in relation to all of the areas of the larynx and surrounding structures. It is best to start by deciding (estimating) from where the tumour has originated. This is known as the index primary site. Although it is of importance for reference for treatment and epidemiological reasons, in high volume tumours it can be difficult to determine the epicentre of the tumour. On some occasions, this is not possible and the tumour is registered as ‘indeterminate’.

Having established the index site, the involvement of all the surrounding structures is noted in detail. This should be considered in all directions within the larynx with attention paid to the subglottis, particularly anteriorly, the anterior commissure, the ventricles, and the petiole and all areas of the supraglottis. The tumour extension out with the larynx is then described – the most commonly involved areas being the aryepiglottic fold into the pyriform fossa, the epiglottis into the vallecula, and the subglottis into the trachea.

To examine these areas comprehensively, telescopes should be used. Hopkins rods are a form of telescope which can be coupled to a video camera system to allow accurate recording of the tumour. The optical system uses angles of 0, 30 and 70 degrees to allow differing perspectives of the laryngeal subsites. They are of particular value in the glottis, subglottis and ventricle. The 70 degree telescope is invaluable in early laryngeal malignancy, particularly if endoscopic resection, with or without, the CO₂ laser, is planned. It allows accurate assessment of the volume of the lesion and its position on the glottis, thereby allowing accurate planning and resection of the tumour while preserving as much of the laryngeal structures as possible.

Using the camera, linked to the telescope, the lesion can be digitally recorded and reproduced for informed discussion at clinicopathological and multidisciplinary team meetings. This ensures that all health care professionals in the MDT are able to appreciate the extent of the tumour, and acts as a focus when discussing further management. It is advisable to attach a ‘hard copy’ of the photo of the lesion as a permanent record in the patient’s case notes. Photos can also be attached to the pathology request form.

**PRINCIPLES OF MANAGEMENT OF LARYNGEAL CANCER**

The management of laryngeal cancer depends in the first instance on the stage at presentation. However, a variety of other factors are also involved in the decision-making, including the patient’s age, comorbidities, surgical access issues, the skills and preferences of the treating multidisciplinary team and, importantly, the wishes of the patient.

**Early laryngeal cancer**

For T1 N0 and T2 N0 lesions, the options for treatment are mainly radiotherapy or transoral endolaryngeal surgery. For a small number of patients, there is the option, or need, for open partial laryngeal surgery. This is now undertaken infrequently following the introduction of transoral endolaryngeal laser surgery.

It should be noted that there have been no direct comparisons of the efficacy of the two main treatment modalities, radiotherapy and endoscopic laryngeal surgery. However, on examining the literature, including cohort studies, they appear to have very similar cure rates. For example, Moreau⁹ reported on a review of the literature on CO₂ laser surgery for T1 and T2 glottic squamous cell carcinomas (SCCs). They found a 6.5 per cent recurrence rate in the series of 400 cases; 10 out of the 26 recurrences required total laryngectomy with an overall survival rate of 99 per cent. Ambrosh et al.⁴ reported on a series of 48 cases of supraglottic stage 1 and stage 2 SCCs, demonstrating a five-year control rate of 100 per cent for T1 tumours, and 89 per cent for T2 tumours, and a five-year recurrence-free survival of 86 per cent. Similarly, many radiotherapy cohort studies report excellent success rates for early laryngeal cancer.¹⁰

There are relative advantages and disadvantages for each of the modalities. For endolaryngeal surgery, advantages include treatment in a single sitting, minimal absence from employment, certainty of removal of the specimen and the ability to assess margins surgically. Importantly, it also allows further laryngeal surgery or radiotherapy in case of recurrence. The disadvantage of transoral laser surgery is that it can affect the voice quality and access is sometimes difficult. It is also requires a general anaesthetic, and may need repeated operations, for which patients may not be fit.

The main advantage of radiotherapy is that it is potentially achievable in patients with poor reserve. In addition, it has been thought to have better voice outcomes. This hypothesis is based on the principle that the laryngeal structures are being ‘preserved’: The flaw to this is that at the time of presentation the laryngeal structures will already have been destroyed to a certain extent by the malignant process. In addition, radiotherapy is in itself a radical treatment so it will have a deleterious effect on the structures. To date, definitive comparison of voice outcomes between the two treatment methods has not yet been possible. However, a study has shown that quality of life outcomes for the two modalities appear to be similar.¹¹

While reported control rates after open partial laryngeal surgery for small tumours are probably as good as the other modalities, there is only a very limited role for open partial surgery for T1 and small T2 tumours. This is because the approach carries more morbidity with poorer outcomes than transoral laser surgery. Its only conceivable role would be for a patient whose access transorally is not possible, and who has refused radiotherapy. In addition, there may also be a limited role in low volume recurrences following radiotherapy.¹² Due to the small numbers of cases being performed, these operations should be undertaken by someone with specialized interest in open partial surgery.
Advanced laryngeal cancer

The main options for the treatment of advanced laryngeal cancer currently are total laryngectomy or chemoradiotherapy. Other options used less commonly include partial open laryngectomy, near total laryngectomy and laser CO₂ transoral surgery.

LARYNGECTOMY

The first total laryngectomy was reportedly carried out in 1873 by Billroth. Since then, it has been the standard by which other treatments are compared. This is because it results in excellent local and regional control of the cancer. However, it results in considerable effects on voice production and communication, as well as resulting in psychological effects due to disfigurement and the production of an end stoma. This has led to the development of organ preservation treatments. Interestingly however, some cross-sectional studies have shown no difference in the quality of life between patients who have had total laryngectomy and those who have had radiotherapy or conservation surgery. This suggests that any treatment of advanced laryngeal surgery considerably affects the function and overall quality of life of patients.

OPEN PARTIAL LARYNGECTOMY AND TRANSORAL LASER SURGERY

Other surgical options for the treatments of advanced laryngeal cancer include open partial laryngectomy, near total laryngectomy and laser CO₂ transoral surgery. These techniques are not suitable for the majority of advanced laryngeal patients. However, they do have an important role in selected patients with selected pathologies such as liposarcomas or neuroendocrine tumours.

Options include partial and supracricoid laryngectomy for certain moderately sized (T2 and small T3) primary or recurrent tumours involving one half of the larynx or for those limited to the supraglottis, with no paraglottic space involvement respectively. Laccourreye et al. reported on 21 T2–T4 laryngeal SCCs treated with supracricoid partial laryngectomy, with a local control rate of 95 per cent and a laryngeal function preservation rate of 90 per cent over five years. In addition, CO₂ laser transoral surgery has also been used for advanced laryngeal and hypopharyngeal squamous cell carcinomas. For example, Iro et al. reported a series of 141 supraglottic carcinomas, eight of which were T3 and T4 – over 50 per cent of whom also received postoperative radiotherapy. He reported a five-year disease-free survival of 75 per cent for stage 3 and 45 per cent for stage 4. Steiner et al. reported on 96 stage 3 and 4 hypopharyngeal SCCs with five-year overall survival of 37 per cent.

However, it should be noted that the above management options are not standard treatment options, and that they need to be recommended within the context of a multidisciplinary team discussion. Furthermore, these operations should only be carried out by surgeons experienced in conservation laryngeal surgery. Such cases should be referred to regional centres and nominated surgeons to ensure that there are surgeons who are performing adequate numbers of such operations.

LARYNGEAL PRESERVATION CHEMORADIOLOGY

The first generation of larynx preservation chemoradiotherapy trials appeared in the 1990s, and randomized patients into surgery and radiotherapy or to induction chemoradiotherapy cycles of cisplatin/5FU. Patients who responded to chemotherapy then received radiotherapy, with possible salvage surgery. If they did not respond to the chemotherapy, they received surgery and postoperative radiotherapy. Generally, the results of these studies showed no significant difference in survival between the two treatment arms. The larynx was preserved in 56 per cent of patients undergoing the experimental chemoradiotherapy arm.

In 2000, Pignon et al. published a meta-analysis of the first generation of larynx preservation chemoradiotherapy trials. In the main, they included T3 laryngeal and hypopharyngeal cancers. There was no statistically significant difference in overall survival. However, it is important to note that there was a trend to benefit from surgery (hazard ratio 1.19 intervals 0.97–1.46). Surgery ± radiotherapy resulted in overall survival of 45 per cent compared to an overall survival from chemoradiotherapy of 39 per cent. On the other hand, 56 per cent of those who survived with chemoradiotherapy managed to avoid laryngectomy, giving an overall laryngectomy survival rate of 23 per cent at five years. Patients treated with chemoradiotherapy had almost double the local recurrence rate, but less distant metastases than the patients treated with surgery. Analysis of laryngeal cancer patients separately from hypopharyngeal cancer patients showed that laryngeal cancer patients in the surgical arm demonstrated a risk reduction of 32 per cent. This suggests that advanced laryngeal tumours would be better treated with surgery than chemoradiotherapy. On the other hand, hypopharyngeal cancer patients showed no difference in survival between the two modalities of treatment.

Furthermore, the meta-analysis showed that the overall survival benefit from chemotherapy in addition to radiotherapy was 4 per cent at five years. Concomitant chemotherapy resulted in an 8 per cent overall survival benefit, compared to a 4 per cent overall survival benefit from neo-adjuvant chemoradiotherapy. Adjuvant chemoradiotherapy resulted in no overall survival benefit. These findings have resulted in the adoption of concomitant chemoradiotherapy as the standard regimen for delivery of chemotherapy when treating laryngeal and pharyngeal cancers. Recently, an update of this meta-analysis confirmed an overall survival effect of 6.5 per cent for concomitant chemoradiotherapy.

The second generation of laryngeal preservation trials were published in 2003. The RTOG 91-11 trials showed that both concomitant and neo-adjuvant chemoradiotherapy with cisplatin resulted in no statistically significant differences in survival compared to radiotherapy alone. However, laryngeal preservation was highest with concomitant chemoradiotherapy (84 per cent) compared to neo-adjuvant chemoradiotherapy (72 per cent) and radiotherapy alone (67 per cent). On the other hand, concomitant chemoradiotherapy resulted in significantly worse acute toxicity compared to induction and chemotherapy and radiotherapy alone.

Third generation organ preservation trials have now started reporting. They show that the addition of doxicetel to standard induction chemoradiotherapy with cisplatin and 5-fluorouracil results in significantly higher survival rates.
More studies are required to prove the superiority of these enhanced induction regimens compared to standard concomitant cisplatin regimens. It should also be noted that oncological alternatives to chemoradiotherapy also exist. A meta-analysis by Bourhis et al. in the *Lancet* in 2006 showed that hyper-fractionation and accelerated fractionation without total dose reduction results in better local regional control compared to radiotherapy alone. These altered regimens can be used in patients who would not tolerate chemotherapy.

Laryngeal preservation strategies are clearly an attractive option. However, the concept of organ preservation is not clearly defined. There has been little research into what constitutes a preserved larynx. From an oncological perspective, the effects of the therapy are generally reported by assessing the local toxic effects, such as mucositis and xerostomia. Although this level of toxicity is used to compare various therapeutic regimes, it should not be regarded as the sole assessment of organ preservation. Organ preservation is not merely the presence of the organ in situ, but it also has to have useful function, however that might be defined. As such, an assessment of end organ function would be appropriate. This can be achieved relatively easily by using patient-centred, patient report questionnaires, addressing voice (VoiSS, VHI), swallowing (MD Anderson Dysphagia Inventory) and quality of life (University of Washington or FACT). This is of considerable importance and is an area of clinical research which needs to be addressed.

**MANAGEMENT OF NODAL METASTASES**

For early laryngeal cancer, the risk of metastases, especially for glottic cancer, is negligible. Therefore, the nodal basins are not treated electively, unless there is clinical evidence of metastases.

In advanced laryngeal tumours, there is a high risk of occult nodal metastases, of up to 60 per cent, especially when the supraglottis is involved. Therefore, in the N0 neck, the primary echelon nodes are treated electively either by radiotherapy or surgery. The risk of occult metastasis in a lesion confined to the glottis is only 10 per cent. Therefore, elective treatment for a N0 neck is not indicated for this subsite.

For the N1 neck, if treatment of the primary is by surgery, then treatment is by selective 2–4 neck dissection, followed by chemoradiotherapy where appropriate. If the primary is being treated by chemoradiotherapy, then treatment of the nodal metastases can also be performed by chemoradiotherapy followed by assessment of the neck. In advanced nodal disease (N2 and N3 disease), if the primary is being treated by surgery then a modified radical neck dissection should be performed with consideration of postoperative radiotherapy or chemoradiotherapy. Increasingly, some are carrying out selective neck dissections instead. If the primary is being treated by chemoradiotherapy, further treatment is controversial. The options are a neck dissection or treatment followed by assessment with a PET CT scan. Currently, a multicentre PET Neck trial is taking place in the UK examining this question.

**DECISION-MAKING IN THE MANAGEMENT OF LARYNGEAL TUMOURS**

It should be noted that there are multiple factors involved in decision-making process for treatment. These include:

- Tumour stage and characteristics: the presence of laryngeal cartilage invasion suggests the need for a laryngectomy. Nodal metastasis also affects the type of treatment required.
- Patient’s comorbidity: patient comorbidity affects the degree to which they can be treated. Cardiac disease precludes the use of cisplatin and may mandate carboplatin or fractionated radiotherapy.
- Patient’s lifestyle and social support network may also strongly affect the choice of treatment modality. Patients who require the use of their voice, e.g. for teaching or in meetings, may wish to have organ preservation treatment. Self-employed patients may choose laryngeal conservation surgery over radiotherapy for early laryngeal tumours due to the convenience of a shorter treatment course with less absence from work.
- The expertise of the treating centre can also affect the treatment that is offered. Some of the alternative surgical treatment options should not be offered by occasional operators.
- Finally, the patient’s preference is of utmost importance. It should be noted that there may be up to a 70 per cent discordance between patients’ and clinicians’ preference in the decision on treatment modality, as demonstrated by List et al.

**SURGICAL TECHNIQUES**

**Principles of surgical treatment of an early suspicious laryngeal lesion**

Diagnosis of the cause of an abnormality in the larynx, most frequently arising in the glottis, requires the acquisition of representative tissue while ensuring minimal damage to the underlying and surrounding structures of the larynx. This is a frequent challenge to the laryngologist.

In Figure 33.4, a lesion, suspicious of being malignant can be seen to be arising from the right vocal cord. Ideally, the surgical procedure would not only treat the lesion but would also ensure that there is a representative specimen for histological examination. The key considerations in this situation are the position and the volume of the tumour. Extreme care must be taken when the excision might involve the anterior commissure. Webbing can occur even when there has been very little damage to the contralateral mucosa. Such a result can affect voice quality considerably, as any significant degree of webbing will result in dysphonia. If the lesion is in the anterior two-thirds of the vocal cord, then once again care must be taken as excessive damage will result in deficiency in the vocal cord structure or scarring, with subsequent abnormality in its vibration.

The key is to carry out a dissection which will preserve the integrity of the vocal ligament. Furthermore, it must be possible to visualize the lateral margin and thereby achieve a...
Dissection margin. If each of these criteria can be satisfied, then the lesion in its entirety can be excised with care. To achieve this, it is necessary to use fine instrumentation, such as that produced by Bouchayeur (Microfrance). Some laryngologists use the technique of hydrodissection to delineate and facilitate the plane of dissection by injection of saline into the submucosal space, Reinke’s space, thereby allowing the dissection to remain superficial to the vocal ligament.

In the majority of appropriate cases, however, dissection proceeds by incision of the mucosa either posteriorly or laterally to the lesion. This allows entry into Reinke’s space, thereby allowing the dissection to remain superficial to the vocal ligament.

In the majority of appropriate cases, however, dissection proceeds by incision of the mucosa either posteriorly or laterally to the lesion. This allows entry into Reinke’s space, thereby allowing the dissection to remain superficial to the vocal ligament.

The technique will be described in relation to glottic lesions, although a very similar technique applies to supraglottic and subglottic lesions.

The patient is placed in a supine position, the general anaesthesia being delivered via an intravenous infusion, with muscle relaxant, and the patient being maintained oxygenated using a Venturi entrainment system. The most frequently used laryngoscope is the ‘Dedo’ laryngoscope, the

Figure 33.4 (a) T1A right vocal cord; (b) right vocal cord following excision of T1A.
design of which is suitable because of the shape of the distal end in conjunction with the distal fibreoptic illumination. In patients who need repeated microlaryngoscopies, as in this clinical situation, an individually manufactured laser mouth guard, which is laser resistant, should be used if possible. The laryngoscope is placed in the supraglottis, displaying all areas of the glottis. The laryngoscope is suspended with the larynx view maximized by applying pressure to the cricoid or fixing it with some adhesive tape. Updated photography with digital capture is carried out using 0, 30 and 70 degree Hopkins rods (Figure 33.6).

Having tested that the CO₂ laser system is functioning correctly, it is set at the optimal setting. This is often dot size of 1 mm, exposure time of 0.1 second, and a power of 5–10 watts, in a repeated mode. This can be modified by reducing the power or putting it onto single fire. The tumour is held using aspirating forceps and retracted medially. The laser incision commences posteriorly, or posterolaterally, the laser plume being aspirated through the aspirating forceps or through the aspirating portal on the laryngoscope. The dissection proceeds while maintaining at least a 1 mm margin. On occasion, it may not be possible to visualize the entire lesion and so to achieve this it may be necessary to remove the ipsilateral false cord, known as a ventriculotomy. This can be simply achieved by vapourizing the false cord, but care should be taken not to disrupt the surface appearances of the glottic lesion so that an accurate macroscopic resection can take place. Dissection proceeds from posterior to anterior, although one must be constantly aware of the three-dimensional perspective of the resection. The mucosal margin is relatively obvious and so therefore should be the maintenance of a 1 mm excision margin. Resection of the deep margin is more difficult. It can be judged by the appearance of the submucosal structures, which in the case of the true vocal cord, are the vocal ligament and the vocalis muscle. If there is any significant bleeding, this can be arrested by use of one of the bipolar systems. A disposable variety is that designed for intranasal use. Its end is fine enough for most bleeding points and is used in conjunction with a separate microlaryngeal metal suction. Alternatively, a combined suction monopolar diathermy, such as that produced by Steiner, could be used.

The problematic area during the dissection of the lesion is the anterior commissure. It is well recognized that there is a significant effect on the quality of voice if the endoscopic resection involves the anterior commissure. It is necessary to ensure that the anterior subglottis is resected adequately while ensuring that there is no unnecessary sacrifice of the anterior commissure mucosa.
Having completed the resection, it is useful to view the resection site by once again using the 0, 30 and 70 degree Hopkins rods. This ensures that the operator is satisfied with the macroscopic clearance and that there is no gross disease remaining. Furthermore, the photograph of the resection site facilitates discussion at the multidisciplinary team meeting.

Previously, ‘standard’ practice involved taking a series of samples for frozen section examination at selected areas around the resection site to ensure that the excision is complete. A useful way of recording the sites of these is to annotate a stylized larynx diagram and photograph it, with the clinical images, for clinicopathological discussion. However, there are difficulties using a frozen section strategy. First, there can be considerable difficulty with the histopathological processing of frozen section samples, not only because of the size but also with the difficulty in interpreting the cellular appearance following the thermal effects of the laser. Second, there is reluctance by surgeons to remove a large specimen for frozen section as it may compromise the quality of the postoperative voice. It is highly debatable as to whether there is significant value from frozen section assessment or whether it is a case of ‘treating the surgeon’. At the UK consensus meeting on the endoscopic management of early laryngeal cancer it was concluded that the use of frozen sections was not required routinely.27

The resected specimen requires a detailed and accurate pathological assessment. The standard approach would be to ‘pin the specimen’ using a cork base and pins around the edge of the specimen. Unfortunately, this destroys the accuracy of the assessment of the margins. If no base is used, orientation is extremely difficult. This can be overcome by mounting the specimen on an organic mount which can be subsequently sectioned. A good example of this is to use dehydrated cucumber as the organic mount.28

The cucumber is prepared by removing the skin and cutting the cucumber into 5 mm thick transverse sections. The seeds are removed from the centre, leaving a triangular appearance with the sides of the ‘triangle’ being of the approximate dimensions of the vocal cords. The cucumber is then dehydrated by placing it in absolute alcohol for 24 hours and repeating the process for two further 24-hour periods. The cucumber is stored in absolute alcohol and can be removed as required. The specimen is mounted onto the cucumber using histoacryl tissue glue. To ensure correct histological orientation, the lateral border of the specimen is marked using black ink. Having been allowed to dry for a few minutes, the mounted specimen is placed in a container with standard formalin solution. Gross pathological assessment starts by photographing the gross specimen and mount and printing an A4 copy. This allows an accurate recording of where the transverse sections are made. The histopathological sections are examined sequentially and so an accurate map of the tumour and its margins can be made. By using the diagram, it is possible to delineate where there are ‘near’ or ‘involved’ margins. This allows targeted further resection to be carried out if necessary, achieving adequate margins while at the same time minimizing the amount of tissue resected and thus minimizing the effect on the patient’s voice.

Once the patient has been discharged from hospital, voice therapy by speech and language therapists should be carried out. Close monitoring of the larynx is necessary and should be carried out every month for the first 12 months, looking for any recurrent, or persistent, intralaryngeal pathology or any change in the vocal cord mobility. Electively, there should be repeat microlaryngoscopy with detailed examination of the larynx under general anaesthesia, paying particular attention to any area or subsite which was of concern at the initial resection. There are no accepted guidelines about the frequency or timing of check microlaryngoscopy. It will depend on confidence of a clear margin at the initial histological examination and the level of suspicion in individual cases. If routine monitoring is to be carried out, then it should probably be approximately 2–4 months post-endoscopic resection. Should there be a recurrence, then a decision has to be made regarding further treatment, namely further surgical excision or radical radiotherapy. This decision is based on the definitive histopathology and the volume, site and stage of recurrence.

**Technique of total laryngectomy**

**PREPARATION**

Preparation of the patient for total laryngectomy is important and should involve the speech and language therapists at an early stage. This allows them to advise the patient on the sequence of events postoperatively and how they can cope with the communication issues, ultimately advising on the self care of the tracheo-oesophageal voice prosthesis. Part of this process is offering the patient the opportunity to meet a patient who has had a laryngectomy to allow an insight and an opportunity to ask questions.

Prior to the procedure being performed, routine haematological and biochemical investigations are carried out. These should include full blood count, urea and electrolytes, liver function tests and thyroid function tests. Thyroid function should be assessed as at least a hemi-thyroidectomy will be performed in conjunction with the total laryngectomy.

Patients who have advanced high volume laryngeal cancer may have marked airway compromise due to obstruction of the airway by the tumour and reduced vocal cord mobility. Although in most circumstances it is possible to maintain the airway by CO2 laser or microdebrider tumour debulking, in some situations it is necessary to carry out a tracheostomy to ensure a safe airway. Some series have reported that there is an increased incidence of tumour, and in particular stomal, recurrence in those patients who have required a tracheostomy.29 However, others have discounted this. In an attempt to minimize the risk of stomal recurrence, it is necessary first to carry out the tracheostomy as high as possible in the trachea and should be around the level of the first tracheal ring. Second, when the laryngectomy is carried out the specimen is excised by including the tracheostomy with a ‘cuff’ of skin of the tracheostomy site included in it. Third, a thorough level six dissection should be carried out. This should minimize the risk of tumour recurrence as one of the main reasons for stomal recurrence is the deposit of tumour in paratracheal lymph nodes in level six.

**ANAESTHESIA**

The patient is anaesthetized using a reinforced endotracheal tube, the tube fixed in the midline and connected to the
ventilator by taking the connecting tubing over the patient’s head. This allows the dissection to proceed and the tube to be changed during the procedure. In general, the endotracheal tube is removed at the point of larynx removal and replaced by a preformed tube, such as a Montandon tube. The timing of this tube change is dependent on the progress of the procedure but is generally once the trachea has been entered and just prior to larynx removal.

**Surgical Approach**

The horizontal skin incision is made in the midcervical region at around the level of the cricoid cartilage, extended over the anterior border of sternocleidomastoid bilaterally and curved gently superolaterally. It should be positioned so that the tracheostomy can be placed in the inferior flap with a sufficient bridge of skin between the superior edge of the tracheostomy and the incision, this being of the order of 2 cm.

The use of the eponymously named ‘Gluck–Sorenson incision’ is an alternative approach. Once again midcervical, but this time lower, more ‘U’ shaped, and running into the proposed tracheostome. This incision is convenient to close but care has to be taken as there is a three-point junction at either side of the stoma. Such an incision is of value when a tracheostomy has been carried out to relieve obstruction preoperatively. The aim is to excise the skin around the tracheostomy and the tract to the trachea in these patients. This tracheostome resection, combined with a superolateral extension, effectively produces a Gluck–Sorenson incision.

If a neck dissection is to be carried out at the same time as the laryngectomy, the extent and the direction of the incision will depend on the levels of lymph nodes being cleared. However, most of the time, the neck dissections can be performed through the same incision as the laryngectomy.

**Mobilization**

Following an appropriate incision, the skin flaps are elevated with the platysma in continuity, so maintaining the vascularity of the flap. As there is little platysma in the midline the subplatysmal flap is best elevated by commencing it laterally. This flap is elevated easily by sharp dissection using a scalpel, probably best with a number 10 blade, and by dissecting directly onto the deep aspect of the platysma muscle. This is best achieved by traction on the flap by the assistant using initially a cat’s paw and thereafter a rake retractor, and with countertraction of the soft tissues by the principal operator.

When in the correct surgical plane, as might be expected, the flap elevation is relatively bloodless. Involvement of the platysma by tumour occurring unexpectedly should be relatively rare as detailed pre-operative imagining is mandatory. It is sensible, however, to elevate the flaps with particular care when overlying the index primary site as extralaryngeal spread may have occurred. The elevated flaps can be retracted by either sewing them in a retracted position or using some kind of elasticated retractor.

Having exposed the larynx, the aim of surgical removal is to resect the tumour while maintaining the maximum amount of residual mucosa and, to a lesser extent, muscle. To achieve this, it is necessary to mobilize the larynx and disconnect it from its blood supply, the pharynx, the tongue base and the trachea. When considering this, it is also necessary to decide if a total thyroidectomy will be performed; for example, when there is extensive tumour around the anterior commissure, the petiole or anterior subglottis. In other words when there is a high chance of ‘escape’ of the tumour out of the larynx through the cricothyroid membrane. In the majority of patients, there will be a preponderance of tumour to one side of the midline and it is the hemi-thyroid of this side which will be resected, with preservation of the contralateral lobe on its inferior vascular pedicle.

Mobilization will be discussed without reference to any form of neck dissection being performed. The most appropriate plane to establish first is in the paralaryngeal, parapharyngeal space between the carotid sheath (containing the internal jugular vein, the carotid arterial systems and the vagus nerve) and the constrictor muscles attached to the pharynx and larynx.

This space is entered by sharp dissection in a direction parallel to the constrictors and with division of omohyoid in the tendinous mid-portion. Dissection proceeds superiorly and inferiorly to the level of the thyroid. Superiorly, the pedicle is identified as a branch of the external carotid artery, the superior thyroid artery and is divided as it enters the larynx as it pierces the thyrohyoid membrane. The artery is best transfixed and divided. The superior thyroid vein is taken separately as are any other remaining vessels.

If the hemi-thyroid is to be resected with the tumour specimen on this side, then dissection proceeds inferiorly with division of the inferior thyroid pedicle. Prior to identifying the pedicle, the inferior strap muscles are divided inferiorly. These are sternohyoid and sternothyroid muscles. The inferior thyroid artery is easily identified as a branch of the thyrocervical trunk. Once again, this is divided and transfixed. The inferior venous drainage from the hemithyroid is present around the lateral and inferior aspects of the thyroid and is divided with the vessels being tied or clipped with stainless steel clips. Dissection proceeds onto the trachea with clearance of soft tissue from it, thus clearing the level six lymph nodes.

On the contralateral side, mobilization takes place in a similar fashion. There are no hard and fast rules about which order mobilization should occur. This is dependent on the presence of concurrent neck dissection and the extent of the index tumour.

The technique is then repeated on the contralateral side. The paralaryngeal, parapharyngeal space is identified and entered by sharp dissection, with division of omohyoid with this space being opened posteriorly down to the level of the prevertebral muscles. The superior vascular pedicle is divided in a similar fashion to the contralateral side.

Inferiorly, the strap muscles, sterno-hyoid and sternothyroid muscles are divided as inferiorly as possible and reflected by sharp dissection from the anterior surface of the capsule of the thyroid gland until the hemi-thyroid has been exposed completely. The thyroid gland is transfixed and divided in the midline. The hemi-thyroid is elevated from the trachea by sharp dissection and bipolar diathermy, this ensures that the thyroid gland and the ipsilateral parathyroid glands are preserved on their vascular pedicle.
Any lymph nodes from level six should be included with the laryngeal resection.

RESECTION

At this stage, it is timely to enter into the trachea to establish a secure airway before proceeding to the laryngeal resection.

Having ensured that the soft tissue has been cleared from the trachea, the anaesthetist frees the taped fixation of the endotracheal tube prior to removal. The trachea is entered by sharp incision anteriorly, probably at the space between the second and third tracheal ring. The exact level will depend on the extent, and in particular the subglottic extent of the index tumour. Clearly, if there is any significant extension into the subglottis an appropriate margin will be needed. If following resection inspection of the larynx reveals a close margin, another tracheal ring can be excised to ensure an adequate margin. Prior to tracheal entry a stay suture, using a relatively heavy suture such as 2/0 sutures, is placed in the lateral wall of the trachea at the level of the proposed incision. As the trachea is entered, the endotracheal tube is retracted by the anaesthetist to a level just proximal to the tracheostomy and can be watched by the operator. This allows the patient’s ventilation to be maintained throughout. An appropriate endotracheal tube is inserted with a pre-formed tube probably being the most appropriate. A good example of this is a Montandon tube. With this in place, anaesthesia is continued through this tube.

The larynx has had the external infrahyoid muscles divided and has been mobilized from its vascular supply. The areas of connection which remain are at the trachea and tongue base.

Dissection proceeds by removing the larynx from the tongue base by using the monopolar diathermy or scalpel dissection of the suprahypoid muscles in the midline. It is important to ‘stay on the hyoid’ during this dissection until all of the muscle has been divided. By so doing, any damage to the hypoglossal nerve on either side should be avoided as the nerve lies superomedial to the hyoid. It is extremely important to maintain the integrity and function of the hypoglossal nerve as paralysis significantly compromises voice and swallowing rehabilitation post-laryngectomy.

The muscles are removed from the greater and lesser horns of the hyoid until the superolateral aspect of the hyoid has been exposed. The medial aspect of the hyoid is mobilized by using curved Mayo scissors.

The pharynx has to be entered, bearing in mind at all time that the tumour has to be resected with an appropriate margin, at least 1 cm macroscopically, while at the same time maximizing the amount of mucosa which remains. This is of importance to ensure there is minimal tension in the pharyngeal repair and voice and swallowing rehabilitation is maximized.

The pharynx is entered by continuing the dissection at the level of the hyoid in the midline at the genioglossus and proceeds until the vallecula is entered. An alternative is to enter the pharynx from a lateral approach. The epiglottis edge is palpated and dissecting scissors are aimed just posterior to the edge and directed medially and the mucosa opened. The advantage of the lateral to midline approach is that the mucosa can be seen clearly, of particular importance when the lesion arises from the supraglottis or there is involvement of the pyriform fossa. The mucosa is divided in the vallecula and the pharynx opened fully thus maintaining symmetry of dissection.

Before proceeding further, it is necessary to divide the constrictors from the thyroid cartilage, approximately 1 cm anterior to the posterior edge of the thyroid cartilage, using a scalpel or monopolar diathermy. The muscle is elevated from the cartilage and around its posterior edge.

Removal of the larynx proceeds from superiorly and by retracting the epiglottis anteriorly, holding it with tissue holding forceps such as ‘Alices’ or ‘Babcocks’. This places the pharyngeal mucosa on a stretch. If the lesion is intralaryngeal then the mucosa is divided along the lateral border of the epiglottis parallel to the aryepiglottic folds, aiming towards the superior horn of the thyroid cartilage. This proceeds into the pyriform fossa bilaterally by taking the larynx forward and dividing the mucosa, bearing in mind to preserve as much mucosa as possible on the contralateral side to the lesion, while carrying out an effective mucosal resection ipsilaterally. Maintaining symmetry, mucosal division is carried out immediately post-crccoid. By completing the incision, mobilization of the larynx from the cervical oesophagus is carried out by retracting the larynx and dissecting the cervical oesophagus from it, by scissors or blunt dissection. It is facilitated by pulling the larynx superiorly and maximizing the amount of trachea mobilized by blunt dissection of the soft tissues. The larynx is disconnected from the trachea by dividing the trachea at the level of the tracheostomy and bevelling the incision posteriorly.

Cricopharyngeal myotomy can be carried out at this stage by vertical incision through the muscle down to the mucosa, leaving the mucosa intact. Whether this is necessary or not is dependent on the experience, and preference, of the head and neck team and the benefit of the procedure to the voice rehabilitation outcomes.

STOMA CREATION

At this point, it is worthwhile creating the end stoma for the trachea. An appropriate incision has to be made for the stoma between the horizontal incision for the laryngectomy and the sternal notch, approximately half way between, leaving an appropriate bridge of skin superiorly, 15–20 mm in breadth. The opening for the stoma should be an ellipse/oval in shape, with the larger axis horizontal. The crucial aspect is that the skin to mucosa has to be aligned in such a fashion that the stoma remains open and there is no concentric scarring and subsequent closure of the stoma. To achieve this, the tracheal mucosa is positioned at least 5 mm above the skin edge. This should maintain it in an everted position. To prevent the concentric scarring, a bilateral ‘v’ plasty can be used as a primary procedure. When designing the ellipse of skin excision two small triangles of skin are preserved at the lateral edge of the oval (Figure 33.7). These are then inserted into the two lateral incision in the trachea of similar ‘height’ to the skin triangles. This is an extremely effective method of ensuring the stoma size and shape and facilitates tracheo-oesophageal voice prosthesis use.
Closure of the pharynx is an extremely important issue and should be carried out meticulously. The aim is to ensure that the mucosal edges are inverted throughout the length of the closure. The amount of residual mucosa will clearly depend on the extent of the pharyngeal resection and so the line of mucosal closure may vary. Individual surgeons have personal preferences on the optimal way of closing, ranging from horizontal to ‘T’ shaped to vertical. Rather than adhering to a standard shape of closure, it is probably more rational to close as it most naturally wishes to come together while doing so with no tension in the surrounding tissues. Closure should be with an absorbable suture and is probably best as interrupted for the first layer. This allows the mucosal edges to be accurately approximated with appropriate tension. The second layer can be continuous, by picking up the serosa and ensuring that the suture line is inverted. Finally, the cut edges of the constrictors are approximated, without excess tension, using the same absorbable suture.

Drains are inserted bilaterally, size 18 gauge, fixed and attached to continuous suction once the skin has been closed. The skin and subcutaneous tissues are closed in two layers. The first layer is the apposition of the platysma layer. The second layer can be continuous, by picking up the serosa and ensuring that the suture line is inverted. The skin is closed using staples.

Postoperative care following laryngectomy

Routine postoperative measures should be instituted. These should include the following:

1. Adequate fluid replacement until tracheogastric feeding has been established.
3. Intravenous antibiotic cover. There has been considerable debate about the type, dosage and frequency of the antibiotics which are used. SIGN guideline review recommends antibiotic prophylaxis, covering aerobic and anaerobic organisms, for 24 hours.
4. Tracheostomy tube should be left in situ, with the endotracheal cuff deflated, and oxygen delivered in a humidified format. This should be removed as soon as possible.
5. The patient should be nil by mouth. Enteral feeding is commenced via the stomagastric tube when the gastrointestinal tract is receptive. This generally starts in the first or second postoperative days, when any pharmacologically induced ileus has settled.
6. Routine blood tests should be carried out, initially full blood count, calcium levels and later thyroid function tests. It is unlikely that the calcium levels will be affected significantly in those cases where only a hemi-thyroidectomy has been carried out. Patients may have insidious onset of hypothyroidism.

Figure 33.7 Stomaplasty technique.

TRACHEO-OESOPHAGEAL TRACT CREATION

Once the stoma has been created the set up for the tracheo-oesophageal voice prosthesis should be considered. It is only in rare circumstances that a voice prosthesis would be inserted via a secondary tracheo-oesophageal puncture. Mostly the debate is whether to create a tracheo-oesophageal puncture at the time of laryngectomy and fit a voice prosthesis at a later date or to insert a tracheo-oesophageal prosthesis during the laryngectomy. The former strategy is carried out by taking a pair of curved forceps, such as a ‘Cushing Cairns’, passing them into the cervical oesophagus, position anteriorly, and then cut down onto them. The forceps are advanced and tent up the posterior tracheal mucosa, approximately 5 mm inferior to the mucosal edge and cut down onto it. A size 14 nasogastric tube is grasped by the forceps and delivered posteriorly into the oesophagus and advanced inferiorly into the distal oesophagus.

Postoperatively feeding can be commenced through this tracheogastric tube. This will act as the final conduit for the tracheo-oesophageal voice prosthesis. The advantage of this strategy is that it allows the tracheo-oesophageal fistula to heal fully and so the fitting of the voice prosthesis can be carried out accurately. Alternatively, a voice prosthesis can be inserted at the time of laryngectomy and feeding carried out through a nasogastric tube placed through it. This has the advantage of not needing a valve inserted at a later date. However, the disadvantage is that the inserted valve may not be the most appropriate size and could potentially be damaged by the insertion of the tracheogastric tube. The choice of which strategy to adopt is dependent on the local expertise and preference.
after a few months, especially if they receive postoperative radiotherapy. It is imperative to monitor thyroid levels as significant proportions are having a salvage laryngectomy post-radiotherapy or chemoradiotherapy.

7. Fitting of a tracheo-oesophageal voice prosthesis
occurs at approximately 2–4 weeks once the stoma has healed and the interparty wall has settled to it near final size. Some fit the voice prosthesis 7–10 days after surgery.

PATHOLOGICAL ASSESSMENT

At the time of the operation, most surgeons would want to assess the macroscopic clearance of the total laryngectomy procedure in relation to the extent of the laryngeal tumour. It is imperative that the ‘formal’ excision margins are not compromised by any per-operative examination. To achieve this, the most effective way of assessing the endolaryngeal extent is to ‘split’ the larynx posteriorly between the arytenoids and through the cricoid cartilage. This allows the tumour to be visualized and the main margin, i.e. that in the trachea, to be assessed.

The excised larynx, with or without an attached neck dissection, is placed in a container with formalin. In general, it is preferable to ‘pin out’ the specimen so that the larynx can be examined in relation to the associated levels of lymph nodes. The neck specimen should be annotated either by marking the cork onto which the specimen has been pinned or by attaching ‘dog tag’ number labels. When requesting pathological assessment, key elements of the history should be stated. These include previous radiotherapy ± chemotherapy, smoking status, clinical staging including vocal cord mobility and specific areas of concern such as areas of potentially close excision margins.

At pathological assessment, the specimen should be photographed macroscopically prior to sectioning. Essentially, the larynx can be sectioned in the sagittal, coronal or axial planes, or a combination of them depending on the area being examined. From an ideal surgical anatomical perspective, the most effective method would be to section the larynx from the glottis inferiorly in the axial plane and superior to this in the sagittal plane. This would allow the most appropriate examination of the laryngeal spaces, but most of all the pre-epiglottic space. In general, however, most larynges are sectioned throughout in an axial plane. To allow sectioning to take place, the laryngeal specimen has to be decalcified and this, in conjunction with the definitive histological examination, can take several weeks. This is not only important when considering the potential requirement for postoperative radiotherapy but also in advising the patient that it may be some time before this is known. Radiotherapy is considered when there is concern about the excision margins or the metastatic tumour volume in the cervical lymph nodes. In general, if the excision margins are less than 5 mm, then radiotherapy is considered.

Excision margins have to be interpreted with care. During the orientation of the excised specimen, there is only a certain amount of margin which is possible as a result of the anatomical structures. For example, anteriorly the skin or subplatysmal layers must be the anterior extent and so this is the anterior margin. Equally the margins, or free edge, in the pyriform fossa can be difficult to orientate. It is essential that following full assessment, preferably in conjunction with the clinician, that the full extent of the tumour, including detailed assessment of lymph nodes, numbers of nodes, their appropriate levels and the presence, or otherwise, of extracapsular spread, are stated. These various aspects when combined must be noted as a pTNM staging. Such a staging is regarded as the ‘gold standard’ with which to compare all aspects of management, for example determining the sensitivity and specificity of key investigations such as CT or MR scanning, or evolving techniques such as PET CT. It is imperative that there is regular audit of the validity of the pathological assessments and staging conclusions. It is incumbent on each head and neck multidisciplinary team to ensure that they are satisfied with their clinicopathological processes.

SALVAGE SURGERY

As part of an effective organ preservation strategy, it is mandatory to have surgical resection as the main salvage treatment modality. There are effectively two forms of index primary treatment which may need surgery should there be persistence or recurrence.

Post-endoscopic resection

As part of the endoscopic resection strategy it is necessary to reexamine or reoperate on individuals depending on the certainty and security of the initial resection. Separate from this, however, is the small group of patients in whom there is recurrence of the disease following a period of the patient having been disease free. If there is a recurrence, great care has to be taken in restaging the recurrence, with this effectively meaning that the original assessments are repeated. If there is low volume recurrence, then it may be possible to carry out endoscopic resection. If not, then radiotherapy, total laryngectomy, or in rare circumstances, partial laryngectomy, are carried out.

Post-radiotherapy or chemoradiotherapy

With the increased use of ‘organ preservation’ strategies using radiotherapy, and ever increasing chemoradiotherapy regimes, surgical resection needs to be employed should there be recurrence or persistence at the index site, the neck, or both. These situations may be challenging, not only during the surgical resection but also in the healing process.

The principal procedure employed is total laryngectomy. There are no specific issues which need to be addressed except to maintain a meticulous surgical technique and be aware of potential areas where the healing may be compromised. Particular attention needs to be paid to the skin, where on occasions new tissue is needed in the form of a myocutaneous flap or free tissue transfer. Care also needs to be taken with pharyngeal repair and closure. Use of a muscle-only pectoralis major pedicled flap, laid over the pharyngeal
repair, improves healing of both the pharynx and the overlying skin.

There has been increasing use of endoscopic resection techniques when there is ‘low volume’ recurrence following radiotherapy or chemoradiotherapy. There are questions surrounding the applicability of the technique for curative intent in radio recurrent situations. However, it is of value when there is a palliative intent or where the patient is unfit or unwilling to undergo total laryngectomy.

STOMAL RECURRENCE

Recurrence of malignant tumours in or around the stoma following total laryngectomy is a specific and difficult problem to manage. There has been a longheld belief that this can be associated with a pre-laryngectomy tracheostomy. This would appear to be the case and hence the requirement for excision of the tracheal cuff of skin and soft tissues during laryngectomy.

The principal cause of stomal recurrence is the persistence of disease in lymph nodes in the central compartment or paratracheal region. If it occurs then the most effective way of managing it is by surgical excision with appropriate reconstruction, and postoperative radiotherapy if possible. This should only be undertaken for limited, small volume disease, mainly situated above the ‘3 to 9 o’clock’ line. Large recurrences, and those below this line, have a very poor prognosis despite resection. Resection will involve the trachea, levels six and seven, and possibly part of the manubrium.

Horizon scanning

Transoral robotic surgery of the larynx: transoral robotic surgery has recently been performed for oropharyngeal lesions. There is also some preliminary work on glottic surgery using the robot in dogs. There have been early reports regarding using this technique in humans. This may become an established procedure in due course.

KEY EVIDENCE

- Laser microsurgery is an effective treatment option for early laryngeal cancer.\(^9\)
- The addition of chemotherapy to radiotherapy improves survival of advanced head and neck cancer by approximately 6 per cent.\(^19\)
- Supracricoid laryngectomy is an effective treatment for a small selected number of patients with laryngeal cancer.\(^15\)

KEY LEARNING POINTS

- Thorough assessment using a combination of imaging and examination under anaesthetic is essential for planning and treatment.
- Early laryngeal cancer can be treated with single modality treatment: either transoral surgery or radiotherapy.
- Advanced laryngeal cancer can be treated with combined modality: either surgery and postoperative chemoradiotherpay or primary chemoradiotherapy.
- Laryngeal cartilage invasion is usually an indication for laryngectomy.
- Partial laryngectomy techniques can be used for a few selected primary and recurrent laryngeal cancers, and should be undertaken in specialist centres.
- Elective treatment of neck nodes is usually indicated in advanced supraglottic or transglottic laryngeal cancer.

REFERENCES


INTRODUCTION

One of the most important prognostic factors in head and neck cancer is the presence or absence, level and size of metastatic neck disease. Many tumours of the head and neck will at some stage metastasize to lymph nodes and a number of factors control the natural history and spread of disease.

Several controversies exist about the management of malignant neck disease, with varying practices on choice, timing and combination of treatment modalities. This is primarily due to the paucity of high level evidence to many treatment paradigms, but this trend may be reversing with some randomized controlled trials and systematic reviews published in the last decade and a few more in progress. However, many organizations have generated guidelines following rigorous evidence-gathering exercises, suggesting best management practices based on available evidence in many countries.

This chapter identifies the evidence base and discusses the principles of management of metastatic head and neck squamous cell carcinoma (HNSCC) at initial presentation, residual disease following treatment and recurrent neck disease. It also outlines major clinical controversies regarding the management of the neck in relation to when to treat, how much to treat and which modality to use. It reviews tumour biology behind metastatic disease, the various rationales for assessment, as well as methods for elective and therapeutic treatment and focuses on quality-of-life issues. The management of tumours other than HNSCC (i.e. salivary gland and thyroid tumours) are not covered in this chapter.

TUMOUR BIOLOGY AS RELATED TO METASTASES

Significant progress has been made in understanding at the molecular level the processes that trigger the metastatic cascade. Tumours do not have primary lymphatics and cancer cells were thought to gain access to the lymphatic system through pre-existing lymphatic vessels near the tumour. Recent studies on animal models have shown that solid tumours can induce lymphangiogenesis. In the context of HNSCC, intratumoral and peritumoral lymphangiogenesis has been correlated with lymph node metastases. Vascular endothelial growth factor (VEGF)-C and VEGF-D, secreted by the tumour, have been shown to play an active role in lymphangiogenesis by binding to VEGF receptor-3, a tyrosine kinase receptor, expressed on the surface of lymphatic endothelial cells (Figure 34.1). This pathway is also the focus for research into antilymphangiogenetic therapeutics.
The metastatic potential of primary tumours varies considerably, even among tumours of the same site and extent. One factor that affects the metastatic potential is the genetic make up of the tumour. Metastatic primary tumours have been shown to express distinct signature genes that set them apart from non-metastatic tumours. This metastatic profile includes genes related to the extracellular matrix, adhesion, motility and protease inhibition. The products of these genes help local invasion and spread into the intra- and peritumoral lymphatics, which is the next essential step in the metastatic cascade. This is facilitated by three molecular events: (1) Cellular adhesion molecules, such as E-cadherin, responsible for tissue architecture and differentiation, are downregulated, making the cancer cells free to migrate. (2) Integrins are adhesion receptors that provide a linkage between the cell cytoskeleton and the extracellular matrix. Overexpression of integrins is associated with increased cellular motility and the production of matrix metalloproteinases (MMP 1, 2, 3, 9 and 14) that act upon the matrix to enable cancer cell migration. (3) Cellular proliferation, motility and protease inhibition. The products of these genes help local invasion and spread into the intra- and peritumoral lymphatics, which is the next essential step in the metastatic cascade. This is facilitated by three molecular events: (1) Cellular adhesion molecules, such as E-cadherin, responsible for tissue architecture and differentiation, are downregulated, making the cancer cells free to migrate. (2) Integrins are adhesion receptors that provide a linkage between the cell cytoskeleton and the extracellular matrix. Overexpression of integrins is associated with increased cellular motility and the production of matrix metalloproteinases (MMP 1, 2, 3, 9 and 14) that act upon the matrix to enhance migration. The MMPs are produced both by tumour and stromal cells, lending credence to the important role that the ‘soil’ plays in the metastatic cascade. A meta-analysis pooling data from 710 patients indicated that MMPs played a significant role in metastatic behaviour. Cathepsins are lysosomal endopeptidases with a similar role in promoting metastases. (3) Active migration of cancer cells into lymphatics is driven by the production of autocrine and paracrine cytokines, mediated by integrin receptors. Tumour cell homing to lymph nodes is probably mediated by L-selectin, a migratory cell–cell interaction molecule. In summary, a variety of genotypic (e.g. p53 and MET oncogene mutation), phenotypic (e.g. E-cadherin downregulation) and micro-environmental (e.g. expression of VEGF-C) processes conspire to facilitate what is probably an inefficient process.

The milieu in the node is hostile to the cancer cells, with the preponderance of immune effector cells and cytokines. The immunoresistant clones are thus selected out for establishing metastases. Once adapted to the lymphatic nodal environment, these cells can invade the rest of the lymphatic system with little need for further adaptation.

The exact role of the regional lymph node system in the spread of HNSCC has yet to be fully defined, although it is established that they are not simple mechanical barriers, but are involved in conferring anti-tumour immunity, primarily through cytotoxic T lymphocytes. However, defects in the antigen-presenting machinery of the cancer cells and reduced expression of HLA class I antigens are the mechanisms that have evolved to avoid detection by immune effector cells. Toker described four distinct growth patterns of squamous cell carcinoma (SCC) within cervical lymph nodes:

1. Following initial cancerous deposits in the subcapsular sinus, growth within the affected node takes place, replacing the architecture of the node before ECS occurs. Ultimately, ECS occurs by the direct penetration and destruction of the capsule, or by the arrest of further underlying capsular or juxtacapsular lymphatics.
2. Metastatic deposits extensively infiltrate the lymphatic sinuses, leaving the germinal centres and trabeculae intact. ECS occurs by the direct penetration and destruction of the capsule, or by the arrest of tumour emboli in underlying capsular or juxtacapsular lymphatics.
3. A less common pattern involves the deposition of a malignant embolus within the subcapsular sinus together with the simultaneous arrest of tumour within capsular or juxtacapsular lymphatics. This results in the coincident and equivalent proliferation of cancer both within and outside the node.
4. Another uncommon metastatic pattern is where capsular or juxtacapsular emboli grow with no intranodal cancer. In these instances, ECS can occur much earlier in the natural history of the disease process.

Metastatic involvement of various lymph node regions usually progresses from superior to inferior in an orderly fashion, but it has been shown that in some situations lymph node groups can be bypassed, leading to 'skip metastases'. Once tumour cells arrive at a draining lymph node, they can proliferate, die, remain dormant or enter the circulation.

### Behaviour of disease within the cervical lymph nodes

Multiple afferent lymph vessels bring lymph into the lymph node, branching extensively in the capsule of the node. Several variations exist in the way afferent vessels interface with the node, and this is important in understanding patterns of lymph nodal infiltration and why extracapsular spread (ECS) can occur earlier in the natural history. While the afferent channels may penetrate the capsule and discharge the lymph into the subcapsular sinus, many run obliquely into the capsule, while others travel along the capsule for considerable distances before penetrating it. Valves are often found in these afferent channels that run on the capsule, forming a network of capsular lymphatics.

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### Haematogenous spread

From the node, efferent channels leave the hilum to join the terminal collecting trunks (the right and left lymphatic ducts) and then drainage is into the venous system. However, there are other routes whereby cancer cells can access the bloodstream and these include entering directly from a node. Vascularization of tumours usually occurs when growths are greater than 0.1–1 mm in size and following this, rapid rates of neoplastic growth and increased rates of vessel invasion can occur. These may be released as single cells, cell clumps or a thrombus fragment containing tumour cells. The success of implantation is determined by both tumour and host factors. In the context
of HNSCC, disseminated and circulating tumour cells in the bone marrow and venous blood occur at a low frequency compared to other tumour sites (one to five cells per $6 \times 10^7$ leukocytes).\textsuperscript{10, 11} Owing to very small numbers of cells in the circulation, low levels of tumour-specific markers and heterogeneity of marker gene expression transcripts, work in this field has been hampered. However, using highly sensitive and specific techniques and a panel of tumour markers, circulating tumour cells have been demonstrated in the setting of HNSCC and shown to predict disease-free survival.\textsuperscript{10, 12}

### CLINICAL IMPLICATIONS OF METASTASES

The presence of regional lymph node metastases acts as an indicator of the ability of the primary tumour to metastasize locally and to distant sites, rather than acting as an instigator of distant metastases on their own. This is because lymph node involvement indicates a host response which is permissive for the development of metastases, not only in the regional lymph nodes, but also to distant sites. Therefore, the degree of lymph node involvement should be regarded as an indirect index of the systemic tumour burden. Therefore, elective removal of regional lymph nodes serves as a biopsy staging procedure to ascertain whether or not metastatic disease is present and to identify high risk patients who might benefit from systemic adjuvant therapy, but is not expected to diminish the metastatic potential. This means that, like breast cancer, tumour-free survival depends more on the biology of the tumour present at the operation rather than the extent of surgery. This explains why patients with metastatic lymph nodes in HNSCC have a significantly reduced chance of survival when compared with those who are disease free.\textsuperscript{13}

It has long been recognized that systemic spread can occur early in many solid tumours and this includes HNSCC. The question that one must ask is, ‘If cancer is a systemic disease, how can cure ever be effected?’ Traditional teaching has been to offer wide margin radical surgery to the neck, with the premise that patients who have a large number of occult positive nodes fare better since these nodes are discovered earlier. This philosophy is now being questioned with regard to locoregional disease being cured with locoregional treatments, since recent advances mean patients are now living longer only to die more frequently of second primaries or distant metastases. Overall survival has not changed significantly.

It becomes clear from the above discussion that the spread of HNSCC to the regional lymph nodes indicates an aggressive tumour where the tumour–host balance has swung in favour of the tumour. While there are structural and immunobiological mechanisms that may affect tumour lysis within the lymph node itself, in a certain proportion of cases, systemic spread occurs early on. This can take place by lymphaticovenous or haematological routes. These processes of spread and tumour arrest can be affected by previous treatment. As the systemic immunosuppressive effects of multimodality head and neck cancer therapy are taken into consideration, both the number and the complexity of modalities that are used become ever more important.

### NECK LEVELS

It is useful to introduce the concept of neck levels here. In 1981, the Memorial Sloan-Kettering Hospital published a number of levels or regions within the neck which contain groups of lymph nodes representing the first echelon sites for metastases from head and neck primary sites.\textsuperscript{14} These levels have been widely accepted and currently six neck levels are recognized, with level VII being outside the neck and referring to the chain of parapharyngeal nodes below the suprasternal notch to the level of the innominate artery. These neck node levels (Figure 34.2) along with their respective boundaries are described in Table 34.1.\textsuperscript{15} Levels I, II and V can be further subdivided into (a) and (b). These subdivisions were introduced to recognize certain areas in the neck that have a biological significance independent of the

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**Figure 34.2** The lymph node levels of the neck.
<table>
<thead>
<tr>
<th>Level</th>
<th>Clinical location</th>
<th>Surgical boundaries</th>
<th>Radiological boundaries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Submental triangle</td>
<td>S, Symphysis of mandible&lt;br&gt;A (M), Left anterior belly of digastric&lt;br&gt;P (L), Right anterior belly of digastric</td>
<td>Nodes above the level of lower body of hyoid bone, below mylohyoid muscles and anterior to a transverse line drawn through the posterior edge of submandibular gland on an axial image</td>
</tr>
<tr>
<td>Ib</td>
<td>Submandibular triangle</td>
<td>S, Body of mandible&lt;br&gt;I, Posterior belly of digastric&lt;br&gt;A (M), Anterior belly of digastric&lt;br&gt;P (L), Stylohyoid muscle</td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>Upper jugular</td>
<td>S, Lower level of bony margin of jugular fossa&lt;br&gt;I, Level of lower body of hyoid bone&lt;br&gt;A (M), Stylohyoid muscle&lt;br&gt;P (L), Vertical plane defined by accessory nerve</td>
<td>Superior and inferior limits as described under surgical boundaries. Nodes posterior to a transverse plane defined by the posterior surface of submandibular gland and anterior to a transverse line drawn along the posterior border of the sternomastoid. Note: Nodes lying medial to the carotids are retropharyngeal and not level II</td>
</tr>
<tr>
<td>Ib</td>
<td>Upper jugular</td>
<td>S, Lower level of bony margin of jugular fossa&lt;br&gt;I, Level of lower body of hyoid bone&lt;br&gt;A (M), Vertical plane defined by accessory nerve&lt;br&gt;P (L), Posterior border of sternomastoid muscle</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Mid jugular</td>
<td>S, Level of lower body of hyoid bone&lt;br&gt;I, Horizontal plane along inferior border of anterior cricoid arch&lt;br&gt;A (M), Lateral border of sternohyoid muscle&lt;br&gt;P (L), Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus</td>
<td>Superior and inferior limits as described under surgical boundaries. Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries</td>
</tr>
<tr>
<td>IV</td>
<td>Lower jugular</td>
<td>S, Horizontal plane along inferior border of anterior cricoid arch&lt;br&gt;I, Clavicle&lt;br&gt;A (M), Lateral border of sternohyoid muscle&lt;br&gt;P (L), Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus</td>
<td>Superior and inferior limits as described under surgical boundaries. Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries</td>
</tr>
<tr>
<td>Va</td>
<td>Posterior triangle</td>
<td>S, Convergence of SCM and trapezius muscles&lt;br&gt;I, Horizontal plane along inferior border of anterior cricoid arch&lt;br&gt;A (M), Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus&lt;br&gt;P (L), Anterior border of trapezius muscle</td>
<td></td>
</tr>
<tr>
<td>Vb</td>
<td>Posterior triangle (supraclavicular)</td>
<td>S, Horizontal plane along inferior border of anterior cricoid arch&lt;br&gt;I, Clavicle&lt;br&gt;A (M), Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus&lt;br&gt;P (L), Anterior border of trapezius muscle</td>
<td>Nodes posterior to a transverse line drawn on each axial scan through the posterior edge of the SCM</td>
</tr>
<tr>
<td>VI</td>
<td>Anterior compartment</td>
<td>S, hyoid bone&lt;br&gt;I, sternal notch&lt;br&gt;A (M), common carotid artery&lt;br&gt;P (L), common carotid artery</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>Superior mediastinum</td>
<td>S, sternal notch&lt;br&gt;I, innominate artery&lt;br&gt;A (M), common carotid artery&lt;br&gt;P (L), common carotid artery</td>
<td></td>
</tr>
</tbody>
</table>

A, anterior; I, inferior; L, lateral; M, medial; P, posterior; SCM, sternocleidomastoid; S, superior.
larger zone that they lie in. For instance, level Ia is rarely involved in malignant processes excluding the lip, anterior floor of mouth and midface. The prognostic significance of level Vb involvement is grave and thus merits the subdivision. The rationale behind subdivision of level II is discussed below under Elective neck treatment.

**NECK DISSECTION TERMINOLOGY**

Standardized neck dissection terminology that was first produced by the American Academy of Otolaryngology and Head and Neck Surgery in 1991 has been updated by the Committee for Neck Dissection Classification of the American Head and Neck Society in 2002 and is widely used (Table 34.2). There is an increasing trend to divide neck dissections into two broad types with subdivisions: (1) comprehensive (removal of levels I–V) and (2) selective neck dissection (SND) (less than five levels).

The previous division of SND into named subtypes has been superseded by recommendations that the levels or sublevels removed during SND be precisely stated in the operation notes. There is an even greater need for this in the chemoradiation era, where specific levels may need to be cleared along with some non-lymphatic structures, leading to calls for further modification of the terminology. The term ‘elective neck dissection’ (END) is used to describe any type of neck dissection that is performed on the neck that is clinically and radiologically free of disease.

**REGION–SPECIFIC LYMPHATIC DRAINAGE**

There are approximately 150 lymph nodes on either side of the neck. The normal range in size is from 3 mm to 3 cm, but most nodes are less than a centimetre. Within the upper deep cervical nodes in level II, the largest node is often called the jugulodigastric node and is situated within the triangle formed by the internal jugular vein, facial vein and posterior belly of the digastric muscle. It is important because it receives lymph from a wide area which includes the submandibular region, the oropharynx and oral cavity. The jugulo-omohyoid node are situated at the junction between the middle and lower cervical group (low level III/high level IV) where the omohyoid muscle crosses the internal jugular vein and receives lymph from a wide area which includes the anterior floor of mouth, oropharynx and larynx. It is important to realize that contralateral neck spread may occur early in those tumours situated in or near the midline.

- The nasopharynx, nasal cavities and sinuses drain via the junctional nodes into the upper deep cervical nodes (levels II and III) having passed through retropharyngeal or submandibular lymph nodes.
- The oropharynx similarly drains into the upper, middle and lower deep cervical nodes (levels II, III and IV) again either directly or via the retropharyngeal nodes. Within these areas of deep lymph node collections in the neck, certain nodes can reach quite large proportions.
- The oral cavity has a wide area of drainage and this is important because there is often free communication between the two sides of the tongue. This means that the normal acts of mastication and swallowing facilitate tongue massage and can promote both early and rapid lymphatic spread directly to low in the neck. The posterior parts of the oral cavity either drain directly into the upper deep cervical nodes (level II/III) or indirectly via the submandibular nodes (level Ib). More anterior parts of the oral cavity and tongue also drain to these nodes but, in addition, may drain to the submental nodes (level Ia) or directly to the jugular nodal chain (levels II–IV). The tongue especially is known to cause ‘skip metastases’ to level IV.
- The larynx drainage is separated into upper and lower systems based on its embryological origins, with a division that occurs at the level of the true vocal cord. The supraglottis drains through vessels which accompany the superior laryngeal pedicle via the thyroid membrane to reach the upper deep cervical nodes (levels II/III), with a greater tendency for bilateral nodal drainage. The lower system drains directly into the deep cervical nodes (levels III/IV) through vessels which pass through or behind the cricothyroid membrane and also into the prelaryngeal, pretracheal or paratracheal nodes (level VI), before reaching the deep cervical nodes.

The region-specific drainage translates well into clinical practice and it is possible to predict the site of a primary tumour based upon the distribution of cervical metastases.
and vice versa. In a landmark study of 1155 patients with previously untreated HNSCC published by Lindberg in 1972, the topographical distribution of clinically evident cervical metastases was set out. This identified distinct patterns of spread to the neck based on the primary site. Histological proof of this concept was produced in 1990 by Shah, in a series of 1119 neck dissections.

It is widely accepted that patterns of subclinical microscopic metastases follow a similar distribution. The high incidence of occult metastases in tumours of the oral cavity, pharynx and the supraglottic larynx forms the basis for SND and removal of the echelon lymph nodes which are the most likely sites of initial metastatic deposits. The echelon nodes for each site are as follows: levels I, II and III for the oral cavity, levels II, III, IV for the larynx and pharynx, and levels IV, VI and VII for the thyroid gland. For the parotid gland, the first echelon lymph nodes are the pre-auricular, periparotid and intraparotid lymph nodes along with those in levels II, III and the upper accessory chain (level Va). For the submandibular and sublingual gland, the echelon lymph nodes lie in levels I, II and III.

**METASTATIC BEHAVIOUR IN THE PREVIOUSLY TREATED NECK**

Treatment modalities can affect tumour–host equilibrium in unpredictable ways and these include surgery, radiotherapy and chemotherapy.

Surgery can undoubtedly mechanically alter the locoregional tumour environment. Considerable gaps between lymphatics mean that collateral channels form, and the ability to do this relates to the nature of connective tissue through which the lymphatics must grow. These mechanical effects can alter patterns of lymphatic metastatic spread and divert lymph flow to the contralateral neck and sometimes even cause retrograde spread. Surgical scarring can trap tumour cells, although this may not always ultimately lead to established local recurrence. It seems sensible to suggest that gentle handling of cancer tissues may decrease the amount of exposure that a surgical wound gets to free cancer cells and as such minimize the potential for any growth.

Lymphoid tissue and circulating small lymphocytes are sensitive and very small doses of radiotherapy (as low as 2.5 Gy) may produce a detectable decrease in the peripheral lymphocyte count. Suppressor T cells are also thought to be particularly radiosensitive. There is evidence in the literature that the systemic cellular immune response is significantly compromised following locoregional radiation therapy (RT) in head and neck cancer patients. Radiation is associated with changes in the regional lymph nodes and lymphatics in general. Thus, within a few days of starting RT, there is a decrease in the numbers of lymphocytes within lymph nodes and thickening of the walls of both lymph nodes and blood vessels can be noted. Some of these changes explain why previous RT can cause lymphatic obstruction and shunting of lymph both into the subdermal vessels and also to the contralateral neck. All of the above lead to unpredictable changes in the pattern of lymphatic drainage, and thus, the echelon levels described above for the various sites will not be applicable to disease recurrence following treatment.

**OCCULT NODAL DISEASE**

The term ‘occult disease’ is used to describe the presence of metastases in the neck nodes that cannot be clinically or radiologically identified. This falls into two categories: (1) occult metastases that can be identified on light microscopy and (2) micrometastases measuring less than 2 mm that need special histological techniques (immunohistochemistry, step serial sectioning and molecular analysis) - for identification. The incidence of occult disease as assessed by routine histological examination varies by the site and stage of tumour (Table 34.3), but use of molecular techniques to look for metastatic disease will increase the incidence rates.

The natural history and the clinical significance of occult metastases is an important, yet largely unanswered question.

<table>
<thead>
<tr>
<th>Primary site</th>
<th>T-stage</th>
<th>N0%</th>
<th>N1 %</th>
<th>N2–N3%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Floor of mouth</strong></td>
<td>T1</td>
<td>89</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>71</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>56</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>46</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td><strong>Oral tongue</strong></td>
<td>T1</td>
<td>86</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>70</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>52</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>24</td>
<td>10</td>
<td>66</td>
</tr>
<tr>
<td><strong>Retromolar trigone</strong></td>
<td>T1</td>
<td>88</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td><strong>anterior faucial pillar</strong></td>
<td>T2</td>
<td>62</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>46</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>32</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td>T1</td>
<td>8</td>
<td>11</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>16</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>12</td>
<td>9</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>17</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td><strong>Soft palate</strong></td>
<td>T1</td>
<td>92</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>64</td>
<td>12</td>
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<td>T3</td>
<td>35</td>
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<td></td>
<td>T4</td>
<td>33</td>
<td>11</td>
<td>56</td>
</tr>
<tr>
<td><strong>Base of tongue</strong></td>
<td>T1</td>
<td>30</td>
<td>15</td>
<td>55</td>
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<td></td>
<td>T2</td>
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<td>T3</td>
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<td></td>
<td>T4</td>
<td>16</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td><strong>Tonsillar fossa</strong></td>
<td>T1</td>
<td>30</td>
<td>41</td>
<td>30</td>
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<tr>
<td></td>
<td>T2</td>
<td>32</td>
<td>14</td>
<td>54</td>
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<td>T3</td>
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<td>18</td>
<td>52</td>
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<tr>
<td></td>
<td>T4</td>
<td>10</td>
<td>13</td>
<td>76</td>
</tr>
<tr>
<td><strong>Supraglottic larynx</strong></td>
<td>T1</td>
<td>61</td>
<td>10</td>
<td>29</td>
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<td></td>
<td>T2</td>
<td>58</td>
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<td>T3</td>
<td>36</td>
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<td></td>
<td>T4</td>
<td>41</td>
<td>18</td>
<td>41</td>
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<tr>
<td><strong>Hypopharynx</strong></td>
<td>T1</td>
<td>37</td>
<td>21</td>
<td>42</td>
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<td></td>
<td>T2</td>
<td>30</td>
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<td>49</td>
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<td>T3</td>
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<td>54</td>
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<tr>
<td></td>
<td>T4</td>
<td>26</td>
<td>15</td>
<td>58</td>
</tr>
</tbody>
</table>

Table adapted from Lindberg and Shah.
Neck dissection may arrest progress of some cancer cells. However, a lymph node may be negative on examination because either cancer never reached it or if it did, it was not retained or indeed was destroyed. This has led to several controversies in the management of the occult neck. It is important to address this question because this affects whether or not the disease needs to be treated and by what method. Observational data suggest that the conversion rate from the N0 to the N+ neck without neck treatment is similar to the incidence of pathological positive nodes in END specimens (around 30 per cent). There is no doubt that occult neck disease does have the potential to manifest itself, but it is impossible to predict with reasonable certainty in individual patients. This is one of several arguments that justify the elective treatment of the occult neck. The clinical significance is discussed in depth below under The N0 neck.

**MICROMETASTASES AND ISOLATED TUMOUR CELLS**

Micrometastases are deposits of cancer cells between 0.2 and 2 mm in size. Presence of micrometastases upstages the neck status (pN1mi). One of the many goals of translational research in cancer has been to refine disease prediction by detecting tumour-specific molecular alterations in histological normal tissues either at resection margins or identifying 'sub-pathological' metastases in regional lymph nodes. Specific clonal genetic changes seen in tumour cells can be used as molecular markers for their detection in lymph nodes. However, the heterogeneity seen in HNSCC, like other solid cancers, precludes the use of a single tumour specific marker. Thus, these studies are dependent on the amplification of less specific epithelial genes or a panel of their transcripts.

Several molecular markers have been used to identify the presence of 'subpathological' metastases in lymph nodes. Using immunohistochemistry, micrometastases can be detected in between 5 and 25 per cent of tumour-positive elective neck dissections of clinically N0 necks, with upstaging occurring in up to 12 per cent of patients. Results using techniques such as quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR) can be obtained within 2 hours of tissue harvesting.

The clinical significance of micrometastases is undetermined. Prospective studies have used different markers and techniques to assess micrometastases and have arrived at diametrically opposite conclusions. In the absence of a universally acceptable marker or a battery of markers, it will be difficult to design clinical trials. Because of the unknown prognostic significance of micrometastases or indeed implications for additional postoperative treatment, the extra work involved in discovering it on a routine basis is not currently justified.

Isolated tumour cells (ITC) are defined as malignant deposits within lymph nodes that measure ≤0.2 mm in greatest extent or appear as single cells or small clusters of <200 cells, detectable on standard processing or immunohistochemistry, that show no evidence of metastatic activity. Unlike micrometastases, the presence of ITCs does not upstage the pathological stage, with their presence being denoted as pN0[i+].

**CYSTIC NECK METASTASES/BRANCHIOGENIC CARCINOMA**

Cystic neck metastases are usually of oropharyngeal origin, with the most common site being the tonsil. Human papilloma virus-related tumours are usually associated with cystic metastases. These patients tend to have a better prognosis than their non-cystic counterparts. This has been reported as branchiogenic carcinoma in the past. Any diagnosis of branchiogenic carcinomas should be viewed with scepticism. The majority of branchiogenic carcinomas are in fact cystic metastases from oropharyngeal carcinoma, most commonly originating in the tonsils, and not true carcinomas arising in a branchial cleft cyst.

A diagnosis of branchiogenic carcinoma arising from the branchial system can only be made if the criteria in Box 34.1 are fulfilled. One could add to this list that the tumour should be human papilloma virus (HPV)-negative, as identification of HPV would point to an oropharyngeal origin.

**PROGNOSTIC NODAL FEATURES**

There are a number of features of metastatic cervical nodal disease which indicate a poor prognosis (Box 34.2). However, much of the data used to arrive at these conclusions are retrospective. Lefebvre et al. looked at the impact of various regional factors on regional recurrence and distant metastases. This study with 1330 patients showed that irrespective of T staging, ECS, three or more positive nodes and positive level IV nodes doubled the risk of regional recurrence and trebled the risk of distant metastases.

<table>
<thead>
<tr>
<th><strong>Box 34.1</strong> Criteria for the diagnosis of branchiogenic carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The carcinoma should be demonstrated as arising in the wall of the branchial cyst.</td>
</tr>
<tr>
<td>• The tumour should occur in line running from a point just anterior to the tragus along the anterior border of sternomastoid muscle to the clavicle.</td>
</tr>
<tr>
<td>• The histology should be compatible with an origin from tissue found in branchial vestiges.</td>
</tr>
<tr>
<td>• No evidence of high risk human papilloma virus should be identified in the tumour tissue.</td>
</tr>
<tr>
<td>• No other primary should become evident within a five-year follow up.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Box 34.2</strong> Prognostic nodal features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Site, size and number</td>
</tr>
<tr>
<td>• Low neck nodes</td>
</tr>
<tr>
<td>• Extracapsular spread</td>
</tr>
<tr>
<td>• Morphology</td>
</tr>
<tr>
<td>• Bilateral and contralateral spread</td>
</tr>
</tbody>
</table>
**Extracapsular spread**

There is a general consensus that the presence of ECS in a lymph node is associated with a poor prognosis. Both prospective and retrospective evidence suggests that ECS decreases survival rates by approximately half compared to those patients whose tumour was confined to the nodes. Also, patients who have occult involvement of nodes and ECS statistically do worse. A meta-analysis concluded that perinodal spread adversely affected five-year survival, with a summarized odds ratio of 2.7. Some workers have noted that invasion of the soft tissues of the neck by tumour lowers treatment success rates by 80 per cent. Other studies show that patients with ECS are at increased risk of local recurrence, distant metastases and that the time to recurrence is shorter. It is likely that ECS may have a differential impact depending on the primary sites. For instance, Oosterkamp et al. showed that ECS adversely affected survival in laryngeal cancer by increasing the risk of metastases nine times, compared to a three times greater risk in patients without this finding.

Currently, it is not clear whether or not ECS represents an increase in tumour burden or an increase in tumour aggressiveness. As previously discussed, Toker demonstrated that a primary deposit of tumour emboli within the node capsule may lead to ECS occurring quite early in the metastatic process and as such may represent an anatomical variation rather than an aggressive tumour. In addition, not all nodes within a neck dissection specimen show ECS and there may be a threshold volume of ECS above which the prognosis is poor.

The literature almost universally recommends that the standard treatment if ECS is detected following surgery is to add postoperative radiotherapy or chemoradiation, even for those who have only one node involved. Currently, based on level 1 evidence, many centres recommend adjuvant chemoradiation in the presence of extracapsular spread. The pattern of spread of malignant disease to the neck depends upon both patient and tumour factors. These are identified in Box 34.3. The site of the primary tumour is important with some sites having a higher incidence of ECS.

**Retropharyngeal nodes**

Tumours that are associated with these nodes include primary disease of the oropharynx, paranasal sinuses and pyriform sinus, as well as advanced primary tumours at any site together with massive unilateral or bilateral neck disease, which presumably involves retropharyngeal nodes due to shunting from obstructed lymphatic ducts or channels. Retropharyngeal node invasion is almost always a radiologic diagnosis. There are a number of reports in the head and neck literature that associate the presence of retropharyngeal nodes with a very poor prognosis, but a recent study of 51 patients concluded otherwise.

**Clinical staging**

The joint UICC/AJCC classification for regional cervical lymphadenopathy, published in 2009 is the current system used for staging (Table 34.4). A classification system is essential for documentation of disease extent, comparisons of results between centres and stratifying patients for inclusion into trials. This is based not only on the presence or absence of cervical lymphadenopathy, but also the size, number and laterality of the lymph nodes. It applies to all head and neck tumours apart from those arising from primaries of the nasopharynx, thyroid gland and mucosal melanomas.

**Limitations of the current staging system**

The staging system is primarily anatomical and does not take into account very important prognostic factors such as concurrent comorbidity, HPV status in oropharyngeal cancers, the presence of vascular invasion and ECS in lymph nodes. It also does not take into account the level of the lymph nodes, and the worse prognosis conferred by some nodal groups, e.g. retropharyngeal nodes.

Furthermore, clinical staging gives great weight to laterality whereas pathological studies have shown that bilateral nodes, particularly if they are small (<3 cm), do not carry any worse prognosis than N1 nodes at certain sites, i.e. supraglottis. For other sites, contralateral and bilateral nodes carry a dismal prognosis and, as such, probably deserve an N3 grouping. This scheme does not allow independent classification of massive nodes on both sides of the neck which are often fixed and almost universally fatal.

**Table 34.4** TNM classification of regional nodes.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N1</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm, but not more than 6 cm in greatest dimension or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm, but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension</td>
</tr>
</tbody>
</table>

Note: Midline nodes are considered ipsilateral nodes.
metastases, both palpable and otherwise, at presentation (Table 34.3). Neck metastases usually present as neck masses, usually firm to hard on palpation. They may be mobile or fixed to surrounding structures, usually determined by the degree of ECS.

**ASSESSMENT OF CERVICAL LYMPHADENOPATHY**

Any patient with a head and neck primary tumour requires careful assessment of the neck. This begins with a full clinical examination which may be supplemented by an examination under anaesthetic. Further assessment of the neck with fine needle aspiration cytology and radiological imaging can help confirm or refute the diagnosis. Occasionally, an open biopsy may be required.

**Clinical examination**

Clinical examination remains an important initial method of assessing regional lymph nodes. Clinical examination of the neck has a variable diagnostic accuracy. Based on a systematic review, physical examination has a sensitivity of 74 per cent, specificity of 81 per cent and an overall accuracy of 77 per cent. This can be particularly difficult in necks that are difficult to examine, i.e. for restaging or in short, stocky necks. In these instances, nodes may go unnoticed until they reach a considerable size. In addition, some regions are inaccessible, such as the retropharyngeal area.

**Fine needle aspiration cytology**

In the presence of palpable disease and a proven primary, treatment will usually be directed towards the assessment of the neck disease rather than confirming that a metastasis is present by fine needle aspiration cytology (FNAC). However, in many cases it is beneficial to perform an FNAC on a palpable node since a positive result is often back before assessment under anaesthesia can be performed. Few surgeons would ignore a clinically palpable node in the presence of proven primary disease, even if the FNAC shows no evidence of malignancy. The technique is particularly useful in the assessment of a palpable node when searching for an unknown primary as the cytological aspirate can be subjected to tests that may help in the search for the primary tumour. For example, evidence of human papilloma virus or Epstein–Barr virus transcripts (or their surrogate markers) will point to a primary site in the oropharynx or nasopharynx, respectively.

**Ultrasound scan**

This technique can detect the presence of malignant cervical lymph nodes with sensitivity rates between 70 and 90 per cent. When combined with FNAC, this figure increases to 90 per cent. The technique may require an ultrasonographer to be present in the outpatient clinic, is operator dependent and labour intensive. However, more clinicians are integrating portable ultrasound machines into the outpatient practice, and perform the procedure themselves. The addition of power Doppler to assess vascular flow and molecular analysis of the aspirate does improve on these figures. It should be noted that there are no absolute criteria for differentiating benign from malignant disease, but absent hilar echoes and increases in short axis length are generally considered to be features of metastatic neck nodes.

**Computed tomography**

The diagnostic accuracy of computed tomography (CT) scanning in detecting malignant cervical lymphadenopathy is higher than clinical examination. The range of non-malignant cervical lymphadenopathy is 3 mm up to 3 cm, but most authors recognize that nodes greater than 1 cm in size on CT may contain metastatic disease. The criteria used for categorizing metastatic deposits include lymph nodes with short axis diameter larger than 1 cm, cluster of three or more borderline enlarged nodes larger than 0.8 cm, and nodal necrosis or patchy enhancement within the nodes. A meta-analysis of CT versus physical examination with 647 neck dissections showed CT to have a sensitivity of 83 per cent with a specificity and overall accuracy of 83 per cent. This figure has remained stable in a more recent meta-analysis. The detection of malignant disease is based on the fact that as cancer invades the lymph node, its size, shape and characteristics change so that as it enlarges, its centre dies and appears necrotic, and there is a thin rim of inflammation around the edge which shows up on scanning as rim enhancement.

It is important to realize that the two most difficult areas in imaging head and neck cancer are the detection of low volume

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**Box 34.3 Factors implicated in pattern of metastatic nodal disease**

- Tumour site
- Tumour size
- Tumour thickness
- Previous treatment
- Tumour recurrence
lism difficult. On its own, 18FDG-PET has inferior sensitivity, limited morphological information, making the exact anatomical localization of an area of increased glucose metabolism difficult. However, the major drawback of this technique is the increased uptake of the glucose analogue FDG can be imaged. However, the presence of distal metastases, otherwise not detected on conventional scanning may be picked up on PET imaging, leading to a more palliative approach. This can help more treatment resources to be directed to those who are more likely to do well following locoregional treatment.66–67 High sensitivity (90–95 per cent) and specificity (95–99 per cent) rates have been observed in the pretreatment setting.66, 67, 68, 69 However, lack of high quality prospective evidence about the impact the imaging has on the outcome and cost–benefit has delayed widespread use. CT-PET detection rate for nodes less than 1 cm is reported at 71 per cent.70 Thus, this modality has poor detection rate (0–30 per cent) in the setting of the N0 neck.71–73

Currently, the widespread role of CT-PET is confined to detecting the occult primary and for assessment of residual and recurrent disease following surgery and irradiation. If a primary site is not immediately apparent on clinical examination, all efforts must be taken to identify the primary site. Where the primary site remains undiscovered, a larger mucosal field may need to be radiated to cover all possible sites, thus increasing the morbidity. This is best done in a manner that maximizes the diagnostic efficacy of all modalities. Prospective and retrospective studies have shown that CT-PET scans will detect a primary site in between 25 and 60 per cent of patients in whom no primary is evident on clinical examination and using conventional radiology74–75 and combined with panendoscopy and biopsy, a primary will be identified in about 50 per cent of patients. CT-PET scans are best done prior to the panendoscopy to reduce false-positive rates. Our suggested algorithm for investigating an unknown primary is set out in Figure 34.3. It is worth noting that false-positive results are common in the first few weeks after treatment and scans should be deferred until at least 8–12 weeks after completion of treatment. The scan has a high sensitivity (100 per cent) and negative predictive value (98–100 per cent) in the evaluation of the post-treatment neck, and these figures also hold good on meta-analyses.78 Based on this finding, its use has been recommended to avoid salvage neck surgery following chemoradiation (see below under The chemoradiated neck), and for restaging recurrent tumours.79 Based on this finding, its use has been recommended to avoid salvage neck surgery following chemoradiation (see below under The chemoradiated neck), and for restaging recurrent tumours.79

In general, this diagnostic procedure is best avoided as an initial diagnostic modality. However, in situations where
FNAC is not available, equivocal or non-diagnostic, or when the results suggest either a lymphoma or an anaplastic carcinoma, or when a primary site is occult, it may be necessary. There is no evidence in the literature that an open biopsy alters the prognosis, as long as correct treatment is instigated within 6 weeks. Any incision should be made to facilitate the removal of the scar via a subsequent standard neck dissection incision and previous surgery may mean that vital structures, such as the sternomastoid muscle, may have to be sacrificed due to scar tissue.

Sentinel node biopsy

The sentinel node biopsy (SNB) is a diagnostic technique used to assess the presence of occult metastatic disease in the N0 neck. The SNB concept is based on the principle that identification of the echelon nodes and assessing them for metastatic spread will provide information regarding the status of the rest of the neck. Using radioactive probes and/or blue dye around the tumour site, the first to third echelon nodes are identified with the help of gamma cameras and peri-operative hand-held probes; these nodes are subsequently harvested and analysed for tumour deposits. From a pathological point of view, these nodes undergo a much more comprehensive analysis (step-serial sectioning, immunohistochemistry) as missing a small deposit in the node could result in a wrong decision to not treat the neck. The assumption here is that if these echelon nodes are negative for secondary deposit, it is unlikely for the rest of the neck to have metastases, thus avoiding further treatment to the neck.

It has been shown in patients with early-stage malignant melanoma that selective lymphatic dissection performed after confirmation of positive sentinel node(s) is therapeutically equivalent to elective lymphatic dissection. Although the technique is considered standard for melanoma in non-head and neck sites as well as breast cancer, in the head and neck the technique suffers from a number of inherent problems. The head and neck lymphatic drainage can be variable with skip metastases, collateral channels are often present and the technique potentially involves the violation of oncologic principles. In addition, the technique is operator dependent with a recognized learning curve and there is an inherent risk of facial nerve damage when assessing parotid nodes. Its role would only be mainly in the treatment of disease within the oral cavity and oropharynx as injection of the tracer around laryngeal and hypopharyngeal tumours is very cumbersome and satisfactory injection all around the tumour is difficult, if not impossible, to perform. A multicentre trial showed that SNB procedure is reproducible in early oral cavity and oropharynx tumours with good sensitivity rates. A diagnostic meta-analysis incorporating a decision analysis model demonstrated pooled sensitivity rates for the SNB procedure using radionuclides from all published studies to be 92 per cent. When compared to elective neck dissection, the decision analysis model showed that the cumulative outcomes (including recurrence and mortality) for SNB were poor by about 1 per cent. The outcomes did not take into account the morbidity caused by the procedures. Within the head and neck, its use remains to be established outside trial settings. A Europe-wide multicentre trial is now underway to establish the role and efficacy of this modality in oral cancer. Other prospective trials are also in progress in the United States.

Pathology

The head and neck pathologist has the final say in the assessment and staging of cervical lymphadenopathy. Following neck dissection, the specimen should be pinned out on a board and orientated as to the levels, or the specimen separated into respective levels before presenting it to the pathologist. It will then be examined to assess the total number of lymph nodes in the specimen, the number that are positive, the levels that are involved along with the presence or absence of ECS, vascular and lymphatic permeation. Within the current UICC/AJCC classification, histological examination of a selective neck dissection will ordinarily include six or more lymph nodes and examination of a radical neck dissection will include ten or more lymph nodes. Standardization of pathological reporting is essential in order to compare data across centres and to facilitate comparative audit and there is currently a standardized reporting form, which has recently been produced by the Royal College of Pathologists.83

**Figure 34.3** Algorithm for investigating an unknown primary with neck metastases.
After controlling for patient and tumour factors, the treatment of metastatic neck disease is usually decided by the stage of neck disease as identified by the joint UICC/AJCC classification for regional cervical lymphadenopathy.\(^4\) The following section discusses treatment of neck disease for each N stage. It is worthwhile identifying the broad areas where there is a lack of high level evidence and controversy exists (Box 34.6). Most of these topics are being actively investigated and the treatment paradigms are evolving.

It is worth reiterating a few important general principles regarding neck spread when discussing the surgical management of metastatic neck disease. (1) In the untreated neck, patterns of spread may be predictable. (2) In the N0 neck, occult disease is usually found within the first echelon lymph node drainage basin. This permits the principle of selective neck dissection. (3) Previous treatment alters drainage patterns significantly. (4) Patients with palpable neck disease are more likely to have non-palpable spread in other levels.

**TREATMENT OF METASTATIC NECK DISEASE**

**Box 34.5 Prerequisites for studies reporting outcomes of treatment for neck disease**

- Homogeneity in disease presentation (untreated necks, recurrent disease, etc.).
- Disease control at the primary site.
- Nodal status verified by rigorous histological examination where possible.
- Standardized assessment of treatment response.
- Clear presentation of regional control rates and disease-specific survival.
- Adequate follow-up period.

**Box 34.6 Controversies in the management of metastatic neck disease**

- Significance of occult disease in cervical lymph nodes
- Clinical significance of micrometastases
- Treatment of the N0 neck: elective versus therapeutic
- Role of selective neck dissection in N1 disease
- Role of the sentinel node biopsy in N0 disease
- Role of chemoradiation in advanced neck disease
- Role of superselective neck dissection in the irradiated neck
- Role of neoadjuvant chemotherapy in neck disease
- Optimal treatment for suspected or established bilateral neck disease
- Management of the difficult, inoperable or untreatable neck
- Use of salvage surgery and reirradiation in recurrent neck disease
- Quality of life following single and multimodality treatment for neck disease

**The N0 neck**

Historically, evaluation and treatment for the N0 neck has been one of the great dilemmas in head and neck surgery and its treatment today is still controversial. The problem that faces the head and neck oncologist is whether or not to treat the neck electively. The reason why elective treatment to the N0 neck has been proposed is that retrospective evidence from elective radical neck dissection (RND) specimens suggests there is a high incidence of subclinical disease for SCC affecting the oral cavity, pharynx and supraglottic larynx. As shown in Table 34.3, the likelihood of there being involved nodes depends not only on the site of the primary disease, but also on tumour size and histological differentiation. The controversy extends to when and how the N0 neck should be treated.

There are a number of treatment options for the N0 neck. These include the following:

- elective surgery;
- elective radiotherapy;
- adopting a policy of ‘wait and see’;
- elective neck investigation.

**Elective neck treatment**

Proponents of elective neck treatment maintain it prevents some cancer-related deaths because untreated neck disease can shed tumour into the vascular or lymphatic system and produce distant metastases. Unfortunately, only distant metastases which are seeded from developing nodal disease can be prevented by elective neck treatment and since spread can occur by other routes, or at inception of tumour, then quite clearly the argument for elective treatment is weakened.
EVIDENCE FOR ELECTIVE NECK TREATMENT VERSUS OBSERVATION

Five randomized prospective trials that have examined the issue of elective neck treatment are summarized in Table 34.5. Four compared surgical clearance of the neck, and one elective neck irradiation, with observation. The bulk of this level 1 evidence is based on cohorts with oral cavity primaries.

As can be seen, only one trial, favoured elective neck treatment. Careful five-year follow-up detected no difference in survival between the two groups in the French trial, but in the delayed treatment group, tumour problems or the patient’s general condition precluded an operation when nodes were palpable in two patients, one of the objections to adopting a policy of ‘wait and see’ for N0 disease. In addition, more than 50 per cent of patients in both arms received radiation, which may have contributed to the lack of difference. Although the trial by Fakih et al. showed no difference in control rates between the arms, it must be noted that the results reported were one-year survival data, despite a median follow-up period of 20 months. Chi-square tests were used to compare the proportion who were disease free at one year and no actuarial methods were used. Careful perusal of this trial shows that patients who underwent elective treatment did well in all comparisons, without achieving statistical significance. A recent randomised trial from Hong Kong by Yuen et al. with 71 patients showed no difference in disease-free survival between the groups. However, the observed group had a significantly higher incidence of regional recurrences, which were picked up on close surveillance and successfully salvaged. This group had earlier published significantly better five-year disease-free survival in a retrospective cohort who had been compared to observation alone. The major difference is close follow-up in the observation arm, leading to earlier identification of neck metastases. It must also be noted that all these studies are not adequately powered.

In addition to the trials by Vandenbrouck et al., Yuen et al. and Pointon and Gleave, other studies support a wait and watch policy for the N0 neck. D’Cruz et al. found no differences in the three- and five-year disease-free survival in a retrospective cohort of 359 patients (200 observed versus 159 treated with END) who had early tongue cancer. Leyland et al. looked at the influence of neck disease on the outcome in a large retrospective cohort of 3887 patients with SCC at all subsites in the head and neck. The results suggested that close observation with subsequent salvage in the event of recurrence produced statistically similar disease-specific survival to elective treatment, be it radiation, surgery or combined modality. This approach can be complemented by meticulous follow-up using ultrasound-guided cytology and salvage when appropriate. These studies seem to support the contention that elective treatment of the neck is not prophylactic in that it does not prevent cancer-related deaths or improve survival. Currently, multicentre prospective randomised trials designed to address this question in oral cavity cancer are in progress in the United Kingdom and in India.

However, many retrospective studies and recently, other prospective non-randomized studies, including an evidence-based review, that have looked at the treatment of the N0 neck in oral cavity carcinomas, suggested improved outcome when the neck was electively treated. A ‘wait and watch’ policy will result in 25–35 per cent of patients presenting with overt disease, needing therapeutic neck treatment, although the results from the randomized trials quoted above suggest a much higher conversion rate. Control rates in this scenario approximate 30–50 per cent, leading to around 15 per cent of patients who have progressive disease. This figure is still higher than the widely accepted 5–7 per cent failure rate where the neck is electively treated. In the presence of only limited high-level evidence for a watch and wait policy, the general consensus in the literature is to err on the side of caution and it is prudent to treat the neck when the risk of occult spread is more than 15–20 per cent. The latter figure is derived from a rather simplistic decision analysis model performed in the 1990s, which showed that at a threshold occult metastatic rate of 20 per cent, the morbidity of treatment is offset by its benefit, and is widely accepted. It must be noted that the surgical treatment considered in the model was radical neck dissection. Many surgeons and oncologists would perform elective neck treatment for lesser probability (5–15 per cent) of occult metastases. The Scottish Intercollegiate Guidelines Network also espouses elective treatment of the neck in this scenario.

Currently, both elective neck dissection and irradiation are viewed as prophylactic treatments, but if one recognizes the significance of occult neck disease as a marker of the ability of

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>No. patients</th>
<th>Primary site</th>
<th>Positive necks</th>
<th>Disease-free survival (%)</th>
<th>Follow up (years)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pointon and Gleave88</td>
<td>ENI</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>80</td>
<td>2</td>
<td>NS</td>
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<tr>
<td></td>
<td>OBS</td>
<td>105</td>
<td>–</td>
<td>–</td>
<td>65</td>
<td></td>
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<tr>
<td>Vandenbrouck et al.84</td>
<td>END</td>
<td>39</td>
<td>Oral tongue</td>
<td>19</td>
<td>NA</td>
<td>5</td>
<td>NS</td>
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<td></td>
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<td>END</td>
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<td>72</td>
<td>3</td>
<td>(p = 0.04)</td>
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<tr>
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<td>13</td>
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<td>Fakih et al.86</td>
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<td>Yuen et al.87</td>
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<td>Oral tongue</td>
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<td>11</td>
<td>87%</td>
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</table>

END, elective neck dissection; ENI, elective neck irradiation; NA, not available; NS, not significant; OBS, observation.
any individual tumour to metastasize thereby providing a significant prognostic indicator of eventual distant metastases and the possible need for systemic adjuvant chemotherapy, then only surgery can provide the histological data to give this information (Box 34.7).

Choice of treatment modality for the N0 neck

Although there are no prospective trials, retrospective data from studies with large numbers suggest that elective neck dissection and irradiation are equally effective in controlling subclinical disease. The choice of treatment modality is dictated by numerous factors, including physician and patient choices, quality-of-life issues and how the primary site is managed. When the primary tumour is being treated with radiotherapy, then elective treatment should be with radiotherapy to at least the first echelon lymph nodes (or the whole neck) and where midline extension occurs, treatment should be bilateral. If the primary tumour is being treated with interstitial brachytherapy then the neck may be treated electively with either surgery or irradiation. When the primary tumour is treated with surgery, then elective neck surgery should be carried out since it provides further information for clinical staging, lymph nodes in the area are cleared to give access to vessels for reconstructive purposes, local recurrence rates may be reduced and survival enhanced. The appropriate levels to be dissected out in an SND are based on the site of the primary tumour and this is discussed under Elective surgery below. Figure 34.4, summarizes our recommendations for management of the ipsilateral N0 neck.

ELECTIVE SURGERY

The pros and cons of elective neck surgery are set out in Boxes 34.8 and 34.9 below.

The concept of therapeutic equivalence of selective neck dissection and comprehensive neck dissection for elective treatment of the neck is widely accepted and based on prospective studies, there is little justification for a comprehensive neck dissection in this setting. Levels II–IV need to be cleared for laryngeal and hypopharyngeal cancer. For patients with oral cavity cancer, SND of at least levels I–III should be carried out, with the addition of level IV for tongue cancers. Levels II–IV are recommended for oropharyngeal cancers. There appears to be little advantage in dissecting level V for any of the mucosal primaries electively. Excellent local control rates can be obtained with SND, with recurrence rates of around 5 per cent with the primary controlled.

Current work focuses on selecting the levels that need to be dissected in the elective setting. For example, clearance of level IIb during SND involves dissection in a relatively narrow field...
and significant retraction of the sternomastoid muscle is needed. It is likely that the accessory nerve can be subjected to traction injury and segmental devascularization, causing shoulder dysfunction. Prospective studies have shown that SND causes a small, but significant impairment to the shoulder function. The incidence of isolated metastases in this level is very low at 0.3 per cent. Prospective studies have shown little oncologic benefit in clearing this level in laryngeal cancer as the occult metastatic rate is low at 0.4 per cent, but higher incidence rates are seen in oral cavity (3.9 per cent) and oropharyngeal (5.2 per cent) cancer, needing clearance of this level. Whether preservation of level IIb necessarily leads to improved shoulder outcomes needs to be verified in prospective studies. Other reviews have promoted evidence to suggest that level IV need not be dissected in patients with N0 supraglottic and glottic squamous carcinoma.

END can undoubtedly serve as a biopsy and a subsequent indicator of the risk of systemic disease since local neck and distant metastases are manifestations of the same process and represent the ability of the tumour to metastasize in an individual host.

### ELECTIVE NECK IRRADIATION

Retrospective evidence suggests that external beam radiation of approximately 40–50 Gy to the clinically N0 neck will control occult metastases in more than 90–95 per cent of cases. In addition to the prospective study identified, other retrospective studies evaluating its role in the treatment of patients with SCC of the oral cavity and tongue did show that elective neck irradiation improves locoregional control and may prolong survival in some cases. This is based on the observed rate of conversion of N0 to N+ necks after elective neck irradiation (3–15 per cent) and the expected rate of appearance of nodes when the neck is observed, based on a 20–40 per cent histological incidence of occult neck disease. However, this assumes that all occult lymph node cancer deposits are clinically significant and evidence from other studies suggests this is not necessarily the case.

### ELECTIVE NECK INVESTIGATION

Another option in the N0 neck is to consider elective neck investigation. Could a radiological investigation such as CT, MRI or ultrasound demonstrate malignant cervical lymphadenopathy at the subclinical stage and if so, could a treatment plan be adopted on the basis of these scans? It would seem that many of the arguments levelled against neck dissection could be levelled against elective neck imaging. If false-positive results are inevitable in the presence of inflammatory neck nodes and false negatives do occur, then imaging could play no role in the routine evaluation of the N0 neck. Treatment should be based upon the understanding of the natural history in question and currently it is probably cheaper and as effective to offer elective treatment to those high-risk patients who need it and ‘wait and see’ in the others. This will avoid large numbers of unnecessary CT scans and subsequent inevitable inappropriate surgery. It is perfectly reasonable to adopt a policy of ‘wait and see’ in low-risk necks, i.e. carcinoma of the glottis or the gingiva, but for those who are high risk, waiting for the neck to develop from N0 to N1 may have a detrimental effect on the patient unless scrupulous follow-up policies are instituted.

The follow-up protocol for the observation arm in the randomized trial by Yuen et al. included three-monthly ultrasonograms of the neck for the first three years. This policy led to earlier diagnosis of neck recurrences and prompt salvage with no decrease in disease-specific survival. Van den Brekel et al. evaluated the outcome of observing the clinically N0 neck in high-risk patients (mainly oral carcinoma) using ultrasonographic-guided (US) FNAC for follow up after transoral excision. Patients were followed up for between one and four years using palpation and US-FNAC. The high salvage rate (71 per cent) was attributed to a strict follow-up policy using US-FNAC and concluded that a policy of ‘wait and see’ was justified. Other studies and reviews have come to similar conclusions.

### The contralateral N0 neck

In the setting of a unilateral primary and ipsilateral metastases, data suggest that the contralateral neck has a very high incidence of occult metastases, between 30 and 70 per cent, especially in supraglottic hypo- pharyngeal and oropharyngeal tumours. In the presence of advanced primaries at high risk of occult spread, contralateral neck treatment is warranted. Recurrence in the untreated contralateral neck has been shown to be the most common cause of failure in supraglottic cancer, with improved local control and two-year survival when dis- sectected. There is no benefit in clearing level IIb in the contralateral N0 neck for any primary site.

### The N+ neck

Management of the N+ neck is continuously evolving as more and more data are accrued. Traditionally, advanced neck disease has needed a combination of surgery and radiation therapy for control of disease. The treatment
offered to the neck often depends on the modality used to treat the primary site, as seen in the suggested algorithms for patients undergoing primary surgery (Figure 34.5) and primary chemoradiation (Figure 34.6).

SINGLE PALPABLE METASTASIS IN THE IPSILATERAL NECK LESS THAN 3 CM IN DIAMETER (N1)

Similar to the N0 neck, the choice of modality is usually dictated by the treatment to the primary site. Where the primary is treated with irradiation, the neck is also covered in the field. ECS is uncommon in this stage and since the survival figures are good, conservation neck surgery is feasible. It is important to remember that in palpable neck disease, all five levels may be involved and should usually be dissected. In the majority of cases, the accessory nerve can be preserved, enabling modified radical neck dissection (MRND). Based on assessment of the best available evidence, there is no evidence that RND achieves better survival figures than MRND.

It is widely accepted that single treatment modality gives good control rates for N1 neck disease, although review of large databases suggests that there may be survival advantage to adding RT even for N1 necks. As approximately 50 per cent of clinically N1 necks are upstaged after pathological assessment, many patients subsequently require postoperative radiation. Single modality usually suffices to control N1 neck disease, with both radiation and surgery having equivalent control rates.

SELECTIVE NECK DISSECTION IN THE N1 NECK AS PRIMARY TREATMENT

The role of SND in the N+ neck is less controversial today than it was two decades ago. There is no doubt that the morbidity of a neck dissection arises largely from level V dissection and there is a low incidence of nodal involvement at this level unless two or more levels (especially level IV) are involved. There is a clear pathological basis for SND in N1 and N2a disease. The proponents for a ‘less than five level’
Concurrent chemoradiation (given for treating the primary site) offers excellent control rates.\textsuperscript{138, 139} No treatment is required in the event of a complete response, but partial responders merit a neck dissection. The type of neck dissection for partial responders is discussed below.

**Concurrent Chemoradiation Therapy for the N1 Neck**

Concurrent chemoradiation for N1 disease argue that the distribution of metastases within first echelon lymph nodes in non-palpable disease can be applied to early palpable disease. However, this sort of surgery requires considerable expertise and is not recommended for the trainee surgeon.

Byers \textit{et al}.\textsuperscript{131} looked at the outcomes of SNDs in 517 patients. They found that recurrence rates in patients with N1 disease were 5.6 and 35.6 per cent with and without postoperative radiation, respectively. Other retrospective studies also vouch for the efficacy of the SND alone in the N1 neck, as long as adjuvant treatment is provided if the disease is upstaged following surgery or other adverse factors exist.\textsuperscript{132, 133, 134, 135, 136, 137}

Prospective studies are yet to be performed to evaluate this further, but on the basis of a large body of retrospective evidence, it can be concluded that SND may be sufficient treatment for N1 disease confirmed on pathological examination. We recommend that where there is doubt regarding the spread and extent of disease, it is better to perform a comprehensive procedure the first time around.

**Ipsilateral Large Node (\(>3–6\) cm, N2A) or Multiple Unilateral Nodes (N2B)**

The treatment depends on the management of the primary and if deemed operable, the neck should be treated with comprehensive neck dissection. If possible, a MRND sparing the accessory nerve gives equivalent control rates to a RND.\textsuperscript{37, 140–141} Larger neck nodes are at a greater risk of ECS, and following primary surgery are best treated by postoperative adjuvant treatment (Box 34.10). Analysis of large databases show that adjuvant radiotherapy confers a 10 per cent absolute increase in five-year cancer-specific survival and overall survival for patients with lymph node-positive HNSCC compared with surgery alone.\textsuperscript{142} Recent randomized controlled trials performed in Europe and the United States confirm the clear benefit provided by adjuvant chemoradiation in the presence of ECS.\textsuperscript{38, 143–144} If the primary site is being irradiated, and incomplete response ensues, a neck dissection is warranted. Patients who achieve a complete response may not need surgical salvage and the rationale behind this is discussed in more detail below under The chemoradiated neck. This group represents advanced disease and retrospective and prospective studies clearly show that if primary surgery is performed, postoperative adjuvant therapy is required to achieve good regional control rates.

**Bilateral and Contralateral Nodes (N2C)**

Patients with bilateral neck nodes are uncommon and occur overall in about 5 per cent of head and neck cancers. The common primary sites involved are the tongue base, supraglottic larynx and hypopharynx. Conventionally, the presence...
of bilateral neck disease was thought to be a grave prognostic sign and this was indicated historically in its staging. However, subsequent careful pathological studies have shown that, in certain instances, this is not so. The prognosis is determined more by the size, number of nodes and by the presence or absence of ECS within the neck rather than by pure laterality. This is particularly true for the supraglottic larynx and in those patients where the bilateral nodes do not feature massive and multiple nodes, treatment can be worthwhile using conventional surgery. Conservation neck surgery may be possible on the less involved side and postoperative radiotherapy will usually be administered. The decision to treat will often be helped by the location and size of the primary site. Laryngeal tumours with extralaryngeal spread and bilateral nodes are often eminently treatable with laryngectomy and appropriate neck dissection, but patients with an extensive tongue base tumour and bilateral cervical lymphadenopathy will usually be inoperable at presentation. Patients with bilateral nodes when one side is fixed are usually incurable.

**MASSIVE NODES (＞6 CM, N3)**

The presence of massive nodes is again an uncommon event occurring in patients with head and neck cancer. Only 5 per cent of all patients will present with N3 neck disease in the United Kingdom. It is important to realize that many nodes that do reach 6 cm in size are often fixed to the skin and/or underlying structures. The decision whether or not to operate depends upon the stage and site of the primary site, presence or absence of fixation, what the node is fixed to, the experience of the surgeon and the needs of the patient. The incidence of true fixation of neck masses is often difficult to determine from the literature with reported figures up to 30 per cent. Fixation to the mandible, sternomastoid muscle or muscles in the midline may not represent as much a problem as fixation to the brachial plexus or carotid artery. These patients are at high risk of distant metastases and may present a special group where CT-PET scans may be warranted to fully evaluate this problem.

Long-term control rates are poor and the benefit of treatment must be carefully weighed against the morbidity caused by it, including the chances of control at the primary site. Radical treatment is warranted in patients who have less advanced disease at the primary site, and has been shown to achieve long-term control. Combined modality therapy leads to better control rates, although recent studies report similar control rates by reserving surgical salvage for clinical or radiologic evidence of residual disease. In many patients, palliation will be the best option.

### The unknown primary

There is no consensus on the management of squamous cancer arising from occult primaries. Options include primary surgery (comprehensive neck dissection) followed by radiotherapy (plus chemotherapy where indicated) to either the ipsilateral involved neck alone or to the bilateral neck and mucosa of the upper aerodigestive tract. Alternatively, primary chemoradiation to the neck or to the neck and all mucosal sites can be delivered, with surgical salvage as discussed above. Extending the radiation field to encompass all possible mucosal primary sites results in lower locoregional failure at five years (27 versus 51 per cent for ipsilateral irradiation), but has no advantage in terms of disease-free survival and emergence of primary cancer, but is associated with increased toxicity. This entity is discussed in further detail in Chapter 35, Management of an unknown primary carcinoma.

### The difficult neck

The scenarios that present a difficult neck are set out in Box 34.11.

**Box 34.11 The difficult neck**

- Difficult to assess
- Short stocky neck
- Retropharyngeal nodes
- Recurrent disease
- Involvement of vital structures

**CAROTID INVASION**

In current day practice, most tumours that present with clinical and radiological signs of invasion are likely to be radiorecurrent. Indications for considering carotid resection include clinical evidence of fixation of the tumour to the carotid, invasion confirmed on imaging, and encroachment of tumour which encompasses more than 270 degrees of the vessel wall. Luminal invasion is rare and pathological evidence of invasion, limited to the adventitia, is seen in only 40–50 per cent of resected arteries.

The plan to resect the carotid should always be a preoperative decision and almost never should a situation arise where this is contemplated for the first time peri-operatively. Preoperative work up is essential to plan the resection. Balloon occlusion of the artery with single photon emission computed tomography (SPECT) is performed to prognosticate the possibility of neurological deficit following resection. If the test shows adequate crossflow and does not cause symptoms, permanent occlusion can be performed with coils pre-operatively, with resection being performed 2 weeks later. Intraoperative ligation without reconstruction is fraught with a high risk of complications owing to the haemodynamic instability that can occur. This is likely even in those patients who demonstrate good crossflow and a stump pressure of more than 70 mmHg. If the crossflow is inadequate, reconstruction is necessary to reduce chances of neuroligic complications. Most studies report using the saphenous vein graft.
A high operative morbidity (33 per cent hemiplegia) and mortality (12 per cent) has been quoted from work undertaken in the 1980s, but recent studies where resection and reconstruction of the carotid artery is performed have shown much lower figures. A review of 148 patients published between 1987 and 1998 demonstrated combined major neurological morbidity and mortality rates of 10 per cent.

It is well recognized that in untreated patients with HNSCC, the carotid artery may not often be involved even when massive disease is present in the neck and that neck dissection may be possible. However, in the presence of radiological evidence of invasion, surgeons have traditionally opted to resect the carotid. In a review of 90 patients with documented radiological evidence of invasion, Ozer et al. showed that this need not be the case and in over 70 per cent of cases dissection of the carotid is feasible and the tumour can be removed without recourse to carotid resection.

Traditionally, carotid resections were regarded to be unrewarding in HNSCC from the point of either achieving locoregional control or improving survival. A review of the literature in 1992 reported a two-year survival rate of 22 per cent following carotid artery resection. This study has been criticized for failing to identify those patients who had been treated previously, for not distinguishing between the treatment of isolated neck recurrence compared with recurrent disease at the primary site, as well as the neck. Aggressive disease in a radiated neck may be associated with residual tumour following resection and there is high risk of systemic disease; thus resection of the carotid artery was thought not to affect the natural history of the disease. Papers published in the last decade suggest that poor outcomes are especially seen in patients who have had previous radiation. Those patients with demonstrable carotid invasion who undergo primary surgical resection with or without reconstruction of the carotid may have a much superior outcome, with control rates between 30 and 50 per cent at five years.

There may be a subgroup of patients who present with bulky neck disease and carotid invasion, who are best managed by primary resection and reconstruction with adjuvant radiation. This is often a difficult scenario and decisions should be made after careful consideration of the morbidity and mortality of the procedure, patient expectations and the expertise of the treating team.

THE IRRADIATED N0 NECK WITH RECURRENCE AT THE PRIMARY SITE

Very few studies have addressed this question, but have happily arrived at the same conclusion. There appears to be no increased risk of occult metastases in this setting and SND is oncologically adequate to clear the neck.

THE CHEMORADIATED NECK

Organ-preservation protocols have established a firm place in head and neck oncologic practice. Using concurrent chemoradiation, they aim to avoid resection and thus sacrifice of the organ where the primary is sited, even for advanced primaries. The following discussion assumes that the primary site has been controlled in all instances.

Although histological evidence of residual disease has been demonstrated in only 40–45 per cent of partial responders, few centres would argue against salvage neck surgery in this setting. The extent of the procedure remains a point of controversy as it is rare to find viable disease in levels that are clinically negative.

However, there is no universal agreement on how the advanced neck should be dealt with following chemoradiation when a complete response is obtained. Pathologic examination of the neck dissection specimen reveals residual disease in up to 25 per cent of patients who have achieved a complete response, but the presence of tumour cells does not indicate that they are viable. Some studies show a clear benefit in regional control when planned neck dissection is undertaken even in the presence of complete response. However, prospective studies of patients with a complete response as assessed radiologically have mature long-term clinical follow up and show very low regional relapse rates that are comparable to the regional failure rates reported in planned neck dissection series.

Several studies have demonstrated the high sensitivity and negative predictive value of CT-PET imaging to assess residual disease in complete6, 165, 166 and partial responders, 167 performed at least 8 weeks after treatment. Earlier scanning increases false-positive results and is not recommended. A recent meta-analysis showed that highest sensitivity results are seen in studies performing CT-PET 10 weeks after treatment. This has been used as a decision-making tool in recommending neck dissection after chemoradiation, with surgery being limited to cases where there is evidence of uptake. The literature has slowly shifted towards a non-surgical management for patients who experience a complete response, with some international groups endorsing this in consensus statements. Emerging data suggest some role for an SND or even a lesser procedure (superselective neck dissection) in this setting when a complete response is obtained.

We recommend that necks staged N2 undergo conventional imaging between 8 and 12 weeks and that the decision is made for the surgical salvage in partial responders. Complete responders can be observed. Where there is access for CT-PET imaging, this can be used to decide if neck salvage is required, assuming all quality control assurances are met. For N3 necks, as the incidence of residual disease is high, we would recommend neck salvage irrespective of the response (see Massive nodes ( > 6 cm) above). In the absence of sufficiently sensitive diagnostic techniques, it is prudent to perform a comprehensive neck dissection in N2–3 necks, regardless of the response. Metastases from nasopharyngeal carcinomas are excluded from this recommendation, and observation alone will suffice when a complete response is obtained even with N3 disease.

The timing of neck dissection after chemoradiation has not been systematically assessed. Nodes tend to regress at variable rates after irradiation. Bataini et al. suggested an interval of at least 8 weeks for nodes 6 cm and less and longer periods (16–20 weeks) for those greater than 6 cm. Pathological studies have shown that metastatic disease can be demonstrated in 30 per cent of necks after chemoradiation, despite clinical and radiological evidence of complete response, but this does not correlate with the clinical outcome of low (5 per cent) recurrence.
This may be due to non-viable cells and the fact that many of the dissections were done 4–6 weeks after treatment. The neck is best assessed between 8 and 12 weeks as discussed above and salvage offered following this. Surgical procedures on necks after chemoradiation are fraught with more complications.

**TREATMENT OUTCOMES**

Regional recurrence rates in the pN0 neck are consistently good between 3 and 7 per cent, largely irrespective of the modality of treatment. Recurrence rates following therapeutic neck treatment will vary depending on other factors, such as control of the primary site, ECS and the stage. Where the primary tumour has been controlled, overall recurrence rates range from approximately 10 per cent for N1 disease without ECS, 20–30 per cent for N2 disease and up to 85 per cent for N3 disease, although some series quote better results. In many cases of N3 disease, the primary site remains uncontrolled.

**RECURRENT NECK DISEASE**

Recurrence in the neck following previous treatment carries a gloomy prognosis. In accordance with the natural history of HNSCC, the majority of recurrences occur within the first two years of treatment. Various considerations including status of the primary site, extent and nature of recurrence, distant metastases and comorbidity dictate the treatment. Thus, a comprehensive investigation of the general status of the patient and distant metastases should be performed. Many of these masses will be fixed to vital structures which will negate extensive surgery. In patients who present with unresectable disease, reirradiation with or without chemotherapy should be considered, particularly in those who present more than two years since their previous treatment. Evidence of partial repair of radiotherapy-induced spinal cord subclinical damage and newer radiotherapy delivery techniques (intensity-modulated radiotherapy (IMRT), tomotherapy, protons) that allow better sparing of neurologic structures at risk make this a realistic option in a larger number of patients. If surgery is possible, wide resections should be undertaken and postoperative radiotherapy given. If the patient has already received postoperative irradiation, then further radiotherapy using brachytherapy may be given when margins are close or when complete resection was not possible. About one-third of patients will be untreatable at presentation.

**Recurrence in the ipsilateral untreated neck**

In this situation, neck dissection is usually the preferred treatment with or without postoperative radiotherapy based on the histology. This group of patients do relatively well and local control rates between 50 and 60 per cent can be expected. Alternatively, irradiation with surgical salvage may be used along the principles described above.

**Recurrence in the contralateral untreated neck**

A proportion of patients in whom metastases occur on the untreated contralateral side of the neck some time after a dissection on the other side may be salvaged, provided there is no recurrence at the primary site. In a retrospective review of 2550 patients, Spector et al. concluded that delayed metastases occurring on the untreated contralateral side were associated with significantly better salvage rates (42.5 per cent) than the ipsilateral previously treated neck (17 per cent).

**Recurrence in the previously treated neck**

Radical radiotherapy can be used if there is recurrent disease in the neck developing after previous surgery, which was not followed by postoperative irradiation. Owing to scarring from previous treatment, the neck stage is often N2a or more at presentation and ECS occurs in the vast majority of patients.

A multi-institutional review studied 77 patients with cervical recurrence on the treated side, in the setting of a controlled primary. The review found that attempting salvage was useful in selected patients, giving a 33 per cent control rate at three years. Results were better when surgical salvage was performed, but this probably reflects the low disease volume. Salvage rates were significantly better in the previously radiated neck rather than the neck treated by previous surgery, with disease-free intervals being 46 months and eight months, respectively.

**Nodal recurrence after combination treatment**

The prognosis is extremely poor in those patients who suffer a neck recurrence following previous surgery and radiotherapy, with median disease-free intervals of four months. This clinical situation is often associated with distant metastases. However, the presence of such disease in the neck causes distressing symptoms, such as pain or bleeding, together with offensive fungation and in selected cases further treatment may be appropriate. This includes wide excision of the tumour and the overlaying skin, flap reconstruction and brachytherapy. In very selected cases, reirradiation may be an option. Evidence of partial repair of radiotherapy-induced spinal cord subclinical damage and newer radiotherapy delivery techniques (IMRT, tomotherapy, protons) that allow better sparing of neurologic structures at risk make this a realistic option in a larger number of patients.

**IMPACT OF NECK TREATMENT ON QUALITY OF LIFE**

The issues that relate to quality of life and the treatment of metastatic neck disease are discussed below.
Elective surgery versus irradiation of the N0 neck

There are no studies comparing quality of life between these two treatments and there is very little morbidity associated with a well-executed SND. This is because vital structures are preserved and level V is not usually dissected. In contrast, a strategy of uniformly irradiating both sides of the neck to try and decrease the likelihood of occult cancer growth may be associated with numerous problems since radiation does not always control occult neck cancer. The fate of recurrent cancer in an electively irradiated neck is much more difficult to salvage and isolated recurrence in the contralateral neck is extremely unlikely. In addition, treatment options for second primary tumours are diminished when wide field radiotherapy has been applied to both sides of the neck and there are no prospective randomized studies which demonstrate a survival disadvantage when the N0 neck is observed. In summary, the quality-of-life issues relating to elective irradiation appear less transparent than those for elective surgery and should not be underestimated when prescribing its use. Further studies are awaited.

Impact of neck treatment on the shoulder

Neck surgery for node-positive disease usually involves a five level dissection and there are quality-of-life issues that relate both to the extent of the dissection and which tissues are sacrificed (i.e. accessory nerve, sternomastoid muscle and the internal jugular vein). Shoulder problems are greater in patients undergoing a RND as opposed to a MRND. Despite preserving the accessory nerve in MRND, dysfunction occurs due to the nerve being devascularized and stretched. The fewest problems are seen in patients undergoing an SND. It is noteworthy that SNDs that clear levels II to IV can also affect the shoulder by stretching the accessory nerve during dissection of the submuscular recess (level IIb). Quite clearly, if level V is not dissected, this may improve quality of life. However, it must be noted that the trade-off for not dissecting all five levels may be the subsequent morbidity of postoperative radiotherapy, which does contribute to shoulder dysfunction.

The use and extent of radiotherapy to the neck

While the effects of neck surgery are confined to the neck, radiotherapy fields often include the salivary glands and some of the viscera, leading to side effects such as mucositis and xerostomia. Use of IMRT has allowed parotid sparing techniques. Results from randomized controlled trials indicate that IMRT does improve quality of life, at least in the early years. In addition, the evidence that both sides of the neck need to be irradiated in well-lateralized primaries postoperatively is flimsy since the incidence of contralateral neck disease is relatively uncommon. Unfortunately, many oncologists continue to routinely prescribe bilateral postoperative radiotherapy to the neck.

In our efforts to improve quality of life and reduce the traumatic psychosocial impact, a number of specialist centres are now in the process of balancing science with ethics and the human experience with a surge of quality of life (QoL) research and, hopefully, an evidence-based rationale to guide us in the future. Until a major therapeutic breakthrough takes place, reducing physical treatment morbidity, improving patients, overall quality of life and minimizing the psychosocial impact of therapy will continue to present our greatest challenge in the practice of head and neck surgery.

FUTURE RESEARCH

The quality and quantity of randomized trials of surgical techniques for metastatic neck disease are acknowledged to be limited. There are several problems that make running surgical trials a difficult prospect. Further research should involve the integration of modified randomized trials with prospective audit and quality control studies. The following are areas where further work needs to be addressed:

- Imaging of low volume disease
- Significance of occult cancer in the neck
- Molecular detection of occult neck disease and its significance
- Sentinel node biopsy for occult neck cancer
- Selective neck dissection for palpable disease
- Assessment of the chemoradiated neck
- Superselective neck dissection for residual disease after chemoradiation
- Management of the contralateral neck
- Quality of life should be investigated following various treatment modalities
- Centralization with specialization and appropriate data collection should improve research, audit and quality control.

KEY EVIDENCE

- Where rigorous, close and frequent clinical and radiologic follow up can be assured with the resources for rapid intervention when necessary, it appears that observation of the N0 neck for early oral tongue squamous cell carcinoma offers equivalent regional control rates to elective neck dissection. Where this management policy cannot be ensured, selective neck dissection is more appropriate.
- Selective neck dissection alone offers equivalent control rates to modified radical neck dissection in histologically confirmed N0 and N1 neck disease.
- Following neck dissection, adjuvant radiation is necessary to enhance regional control rates in the presence of adverse histological findings.
- In the presence of extracapsular spread, the use of concomitant cisplatin during adjuvant radiation increases tumour control and overall survival.
In selecting treatment options, quality of life is important considerations.

A key determinant in the choice of modality to manage neck disease is the treatment given to the primary site.

Elective neck dissection is as effective as elective irradiation in controlling regional disease.

Selective neck dissection is adequate in the management of N0 necks.

Modified radical neck dissection is as good as radical neck dissection in regional control.

Adjuvant radiotherapy or chemoradiotherapy is indicated for surgically managed N2 and N3 disease, and for N1 disease with poor prognostic features.

Management of the neck following chemoradiation continues to evolve. Neck salvage for complete and partial responders should be based on availability of local imaging expertise.

In selecting treatment options, quality of life issues are important considerations.

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INTRODUCTION

The definition of an unknown or occult primary carcinoma is the presentation of metastatic neck lymphadenopathy without the development of a primary lesion within a subsequent five-year period. The diagnosis is, however, one of exclusion and consequently depends upon the diligence exercised in the search for a primary tumour. Failure to identify an occult primary has been attributed to spontaneous regression of the primary tumour possibly as a result of autoimmune destruction, although the exact reason is unknown. The term ‘carcinoma of unknown primary origin’ (UPC or CUP) should be used if no evidence of primary tumour is found after adequate clinical examination, fibreoptic endoscopy, imaging investigations which include fluorine 18-labelled deoxyglucose positron emission tomography (FDG-PET) ideally with CT fusion imaging (FDG) PET-CT and biopsy of putative mucosal sites.

The presentation of metastatic carcinoma involving neck nodes without clinical evidence of a primary tumour is an unusual scenario and accounts for only 2–3 per cent of patients with head and neck malignancy. Metastasis most commonly occurs to nodal levels II and III with less frequent involvement of levels I, IV, V and VI. Squamous carcinoma is the most common histological tumour type and poses the greatest diagnostic dilemma because of the large number of primary upper aerodigestive sites from which nodal metastases may arise. The prognosis for these patients is relatively good with five-year survival rates exceeding 50 per cent, irrespective of the management strategy. Isolated supravacular nodal involvement is almost invariably related to malignant disease arising below the clavicles, with the most likely origin of squamous carcinoma being from lung and oesophagus and adenocarcinoma from thyroid, breast, gastrointestinal and gynaecological tracts. Such tumours have discrete histological and immunohistochemical characteristics and are outwith the remit of this discussion.

DIAGNOSIS

When a patient presents with an isolated neck mass, a thorough clinical history with emphasis on smoking and drinking habits and clinical examination are essential, including a full ear, nose and throat (ENT) assessment with nasendoscopic examination of the upper aerodigestive tract.

Metastatic nodal disease in level I is most commonly associated with a primary tumour of the lip, anterior tongue, anterior floor of mouth and buccal mucosa and, in patients from the Indian subcontinent, there may be a history of betel nut or paan chewing. The majority of patients presenting with a level II/III mass will have a primary tumour of the tonsil or tongue base and so particular attention must be paid to the examination of these areas. It must be emphasized that bulky neck nodes can present in conjunction with a very small primary tumour of the tonsil or a submucosal tumour of the tongue base. Additionally, the skin in the head and
Traditionally, anatomical imaging with computed tomography (CT) and magnetic resonance imaging (MRI) of the head and neck, was the next diagnostic step of the process and while they remain important techniques for the staging of established disease, (FDG) PET-CT, which will be discussed in detail later in this chapter, should now be considered to be the optimal diagnostic investigation. This must be undertaken before examination under general anaesthesia and biopsy of putative mucosal sites, because if scanning is performed after biopsy, subsequent swelling and inflammation may result in FDG uptake and confound interpretation.

Examination under general anaesthesia should then be performed. This consists of pharyngolaryngo-oesophageoscopy and careful palpation of the tongue base. PET-CT may assist in targeting a specific structure for biopsy. However if PET-CT is negative and there is no obvious primary on endoscopy, tonsillectomy, tongue base biopsy and biopsies of the postnasal space and pyriform fossa should be performed. The nasopharynx is of particular importance in patients whose nodal metastasis lies in level V and in those with an undifferentiated histology. Tonsillectomy is recommended because up to 25 per cent of tumours are found at this level.7 8 Traditionally, tonsillectomy ipsilateral to the nodal metastasis has been recommended, however contralateral spread from occult tonsilar lesions may be as high as 10 per cent, consequently bilateral tonsillectomy will offer a higher diagnostic yield.9 Tongue base biopsy will subsequently reveal an additional 10–15 per cent of occult primaries. Biopsy of the tongue base can be difficult and many occult carcinomas are submucosal. Consideration should be given to performing a wedge biopsy, cutting deeply into the tongue base rather than just using cupped forceps.

A note of caution is warranted in a patient presenting with a presumed branchial cyst over the age of 40, particularly if they smoke and drink alcohol. The diagnosis must be treated with considerable suspicion even if FNAC is reported as being benign. If subsequent histological examination reveals squamous carcinoma, the diagnosis will most likely be metastatic squamous carcinoma from the upper aerodigestive tract most commonly from the tongue base or tonsil. Malignant transformation in a branchial cyst is extremely unusual and should never be assumed as the definitive diagnosis. Therefore, branchial cyst in the >40-year-old group should be considered as a patient presenting with an unknown primary.

Conventional processes of clinical examination, panendoscopy, CT and/or MRI followed by panendoscopy with biopsy have been shown to reveal the primary site in over 40 per cent of patients initially diagnosed with neck node metastatic squamous carcinoma of unknown primary origin10 and is further improved with (FDG) PET and more recently (FDG) PET-CT. Diagnostic accuracy may also be enhanced using laser-induced fluorescence endoscopy in parallel with conventional panendoscopy and biopsy. In a study of 13 patients reported by Kulapaditharam et al.11 the identification rate of an occult primary was increased from 15.4 to 38.5 per cent.

**GENETICS AND MOLECULAR ANALYSIS**

Undifferentiated carcinoma is a special example in which the diagnosis of nasopharyngeal carcinoma can be strengthened by the detection of Epstein–Barr virus in the lymph node metastasis either by polymerase chain reaction (PCR) or in situ hybridization, techniques which have sufficient sensitivity to detect the virus in FNAC12 or in core biopsy. Serology combining IgA with early antigen serology will also provide a high degree of sensitivity and specificity when type III nasopharyngeal carcinoma is suspected.

Genetic alterations in apparently normal tissue from putative primary sites should be identical to those from a metastatic lymph node and can be defined by microsatellite identification. This technique has been used successfully by Califano et al.13 where 10 of 18 patients demonstrated identical molecular abnormalities in apparently benign mucosa from surveillance biopsies. The technique may prove clinically useful in patients with an unknown primary squamous cell carcinoma and warrants further assessment. Cytomorphological characteristics, such as monolayered papillary fronds with intranuclear cytoplasmic inclusions in thyroid papillary carcinoma; large, polygonal, keratinized cells with a low nuclear/cytoplasmic ratio in perioral cancers; and numerous naked nuclei with marked lymphocytic infiltrates in nasopharyngeal cancer could possibly be utilized for presumption of primary site in cases of UPC. In a retrospective review of 133 cytologically diagnosed carcinomas, the accuracy rate of presumption of primary sites was 100 per cent in thyroid papillary carcinoma (6/6), 83 per cent in perioral cancer (24/29) and 77 per cent in nasopharyngeal cancer (26/34), but low in other malignancies.14

**Positron emission tomography**

Positron emission tomography using 18-fluorodeoxyglucose (FDG) PET is a promising disease detection modality because of its ability to differentiate between tissue with a high rate of metabolism, such as tumour, inflammation or infection, and tissue with a low metabolic rate, for example scar tissue. The technique is being increasingly used to detect occult primary lesions which other conventional methods have failed to identify.

Historically, the data have been somewhat heterogeneous with results which have been misleading and frequently
contradictory. Detection rates for single modality FDG-PET following conventional procedures, including anatomical imaging have been variable with reports ranging from 14 to almost 50 per cent.\textsuperscript{15, 16} This wide range can also be attributed to small sample sizes and varied definitions of UPC. Fogarty et al.\textsuperscript{17} have reported a series of 21 patients with UPC who underwent FDG-PET. A potential primary tumour was detected by the procedure in eight patients, although none was considered unequivocally PET-positive. Only one case was pathologically confirmed, in five this could not be confirmed, of which three had no evidence of primary disease within a subsequent two-year period. The authors concluded that FDG-PET did not add significantly to conventional comprehensive investigations as previously discussed. In contrast, a similar-sized prospective study performed at Christie Hospital, Manchester, drew differing conclusions recommending routine use of FDG-PET scans in the management of patients with unknown head and neck primary carcinoma. In this study, a primary site was identified in nine out of 25 patients with UPC on the basis of positive FDG-PET scans. Although 42 per cent of patients had a positive PET scan, only 33 per cent had a true positive PET scan confirmed by histopathology (three out of nine patients). The rate of true negative scans was very high at 88 per cent (14 out of 16 patients). Although, an occult primary was detected only in a small number of patients, nearly a third of the patients studied had abnormalities on PET scans in terms of locoregional disease and distant metastases in 23 and 6 per cent, respectively.\textsuperscript{18} Similar conclusions were drawn by Bohuslavizki et al.\textsuperscript{19} in a study of 28 patients with UPC. Sixteen out of 28 patients showed increased tracer uptake corresponding to potential primary tumour sites. Of these, nine tumours were found suggesting that approximately a third of patients may benefit from the procedure. Wong et al.\textsuperscript{20} reported treatment-related benefits of FDG-PET scans in nine out of 17 patients (53 per cent) with UPC. Of concern, in one series reported by Greven et al.,\textsuperscript{21} the apparent false-positive rate was as high as 46 per cent which could have significant implication should the technique be used to select treatment options. Higher false-positive rates in some studies could be attributed to the fact that the PET scans may have been performed after the biopsy.\textsuperscript{18} FDG-PET has been summarized as having a positive predictive value of 56 per cent, a negative predictive value of 86 per cent and an overall accuracy of 69 per cent.\textsuperscript{22} However, the benefit of FDG-PET scans is not only limited to identifying a primary tumour, as the detection of advanced locoregional disease or distant metastases can significantly alter management in terms of modifying radiotherapy fields from unilateral to contralateral neck or changing treatment intent from radical to palliative.\textsuperscript{18, 20}

The more recent advance using CT cross-sectional image co-registration with (FDG) PET specifically using a single scanning device termed ‘PET-CT’ has provided more detailed anatomical localization of FDG avid tissue and together with improved scanning technology may prove to offer greater sensitivity, selectivity and specificity (Figure 35.1). Fakhry et al.\textsuperscript{23} reported a prospective study of 20 patients with UPC who underwent PET-CT scan, and concluded the sensitivity and specificity of PET/CT to be 70 per cent. Additionally, the use of PET-CT fusion imaging has also significantly reduced the number of false-positive results.\textsuperscript{24}

A recent meta-analysis of (FDG) PET-CT from the Netherlands has reported data from 11 studies comprising 433 patients with unknown primary carcinoma. Overall primary detection rate was 37 per cent, with sensitivity of 84 per cent and specificity of 84 per cent, however there was considerable heterogeneity of results between individual studies.\textsuperscript{25} A negative PET/PET-CT result clearly does not preclude the requirement for panendoscopy under anaesthesia and biopsy of putative sites, including deep biopsy of the tongue base.\textsuperscript{26}

It is important to emphasize that if biopsies have been undertaken prior to PET scanning, false-positive uptake will occur at the biopsy sites and PET-CT scanning will need to be delayed for up to 6 weeks thereafter. Such delay is unacceptable in the time course of the patient’s treatment.

**CLINICAL MANAGEMENT**

Despite extensive investigations, a primary tumour will nevertheless remain elusive in approximately 60 per cent of cases. Management of patients with UPC presents a clinical dilemma due to the lack of evidence-based treatment, exclusion of most patients from randomized clinical trials and rarity of the disease. Controversies in the management of patients with UPC, range from types of neck dissection to be performed, fields of radiotherapy (whether ipsilateral neck only, whole neck or additional panmucosal fields), role of chemotherapy, to sequencing of radiotherapy and neck dissection. The optimal management strategy for patients with UPC is yet to be defined. Therapeutic options include excision biopsy of involved lymph nodes, neck dissection, radiotherapy, chemoradiotherapy or radiotherapy with salvage neck dissection. The only randomized phase III study (EORTC-24001-22005) looking into the selection of the target volume for postoperative radiotherapy in patients with cervical lymph node metastases from UPC closed in July 2004 with very poor accrual.

**Surgical management of the neck**

Modified radical neck dissection is the most commonly used technique for management of nodal metastatic disease. The procedure can be considered definitive if the histological specimen reveals no more than two involved nodes without evidence of extracapsular spread. Postoperative radiotherapy will then be unnecessary and an active surveillance policy for the occult primary carcinoma can be safely adopted avoiding definitive treatment to putative mucosal sites and consequent treatment-related morbidity.

There is evidence to support the use of radiotherapy alone for management of the neck following the excision of a single metastatic node without recourse to neck dissection, with 88–100 per cent control rates quoted in the literature.\textsuperscript{27, 28} A Canadian retrospective study of 61 patients with UPC compared outcomes after panmucosal radiotherapy, preceded by either biopsy (67 per cent) or neck dissection (23 per cent). There was no statistically significant difference in eight-year overall survival between patients who had biopsy (FNAC or
excision biopsy) or neck dissection (64.8 and 67.6 per cent, respectively). They concluded that definitive radiotherapy to the neck and potential mucosal sites is effective in achieving good local control rates, whether preceded by neck dissection or not. A retrospective review of 106 patients with UPC demonstrated a reduction in mucosal and neck recurrences with the addition of radiotherapy, but failed to show a survival improvement. Coster et al. reviewed records of 117 patients with UPC and concluded that patients with N1 neck disease with no extracapsular extension can be managed by surgery alone. However, they recommended postoperative radiotherapy for patients with a pathologic stage N2 or higher or with evidence of extracapsular extension.

However, the present authors would advise definitive modified neck dissection following excision biopsy in all cases, because recurrent disease in the irradiated neck usually presents as a diffuse tumour infiltrate for which successful salvage rates are low. An exception to this would be where the nodes are small (<2 cm) and where there is no evidence of extracapsular spread. For N2 and N3 disease, the consensus at the present time is for dual modality therapy, involving both neck dissection and radiotherapy. Both neck dissection followed by postoperative irradiation to the neck, and

Figure 35.1 (FDG) positron emission tomography–computed tomography (PET-CT) images showing 'occult' carcinoma of left tonsillar fossa subsequently confirmed by biopsy and level II lymphadenopathy.
radiotherapy followed by an interval neck dissection are acceptable.

**Irradiation limited to the involved neck**

The most commonly used techniques employ either an anterior radiation field or anterior–posterior parallel opposed fields to encompass the clinical target volume of the lateral neck nodal compartments and to exclude the midline structures, thereby reducing mucosal toxicity. Sinnathamby et al.\(^{31}\) reported their series of 69 patients treated between 1983 and 1992. Sixty-three patients were treated with radical radiotherapy, 23 by radiotherapy alone and 40 with surgery and postoperative radiotherapy, with only four patients having surgery alone. The actuarial incidence of primary mucosal occurrence at ten years was 30 per cent, which is consistent with most other series. A retrospective study of 144 patients by Wier et al.\(^{28}\) compared 85 patients receiving radiotherapy to the neck only, with 59 patients who were treated with irradiation to both neck and mucosa. Primary tumours developed in only 8 per cent of the former group and in 2 per cent of the latter. While they reported a trend towards improved survival in those receiving neck and mucosal irradiation, the difference was no longer evident once the extent of nodal involvement was taken into account. Their overall five-year survival rate was reported as 41% with no significant difference between the two groups. The authors cautiously suggest that radiation to the involved nodal region alone may be adequate.\(^{28}\) These data corroborate the earlier much quoted work from the Middlesex Hospital, London reported in 1990 in which 83 unselected patients at that centre over a 30-year period were treated with radiotherapy to the neck alone, 58 with radical intent for which the overall five-year survival was 40%. Only 7% subsequently developed a primary tumour above the clavicles, supporting the argument for avoidance of routine panmucosal irradiation in this circumstance.\(^{32}\)

**MANAGEMENT OF THE PUTATIVE PRIMARY SITE**

When there is a clear indication for postoperative irradiation to the neck, the choice of management strategy becomes considerably more challenging. Irradiation of lateral neck structures will largely preclude irradiation of subsequently occurring primary sites, particularly those which lie in the midline because there will be considerable overlap with radiation fields required to treat a primary site. The management choice will be either to treat putative mucosal sites by panmucosal irradiation, or alternatively by selective mucosal irradiation, using techniques which will also include the involved neck, or alternatively to irradiate the involved neck alone. Postoperative neck irradiation requires a dose of 60–63 Gy over 6–6.5 weeks, or biological equivalent,\(^{33}\) is well tolerated with mild acute toxicity primarily short-term skin erythema and confers a low risk of associated long-term toxicity.

Panmucosal irradiation requires doses of 50–60 Gy over 5–6 weeks encompassing nasopharynx, oropharynx, hypopharynx and larynx, and in contrast causes considerable morbidity.\(^{34}\) Acute mucosal toxicity is usually severe and patients frequently require enteral support with nasogastric or PEG (percutaneous endoscopic gastrostomy) feeding. Symptomatic xerostomia is unavoidable with conventional two- or three-dimensional CT treatment planning and results from irradiation of both major and minor, mucosal, salivary glands. When the probability of an occult nasopharyngeal tumour is low, selective mucosal irradiation avoiding this site can be employed and reduces mucosal dryness, although xerostomia may nevertheless remain significant.

At present, all data are retrospective and there are no completed randomized trials. Published reports can be broadly divided into those which propose elective panmucosal irradiation and into those which suggest that avoidance of irradiation to mucosal sites is a safe alternative incurring significantly less morbidity.

The Danish Society for Head and Neck Oncology reported their series of 277 patients from five oncology centres with unknown primary carcinoma treated radically between 1975 and 1995. The majority, 224 patients (81 per cent), received panmucosal irradiation, 26 patients (10 per cent) ipsilateral neck irradiation and 23 patients (9 per cent) neck surgery alone. The five-year actuarial risk of emergence of the primary was significantly higher in the surgery only group, 54 per cent, compared to those treated with surgery and radiotherapy, 15 per cent. When comparing panmucosal with ‘neck only’ irradiation, the five-year actuarial control rates were 51 and 27 per cent, respectively, although the number of patients was small in the latter group.\(^{7}\) A smaller study from Reddy and Marks\(^{35}\) compared 36 patients treated with panmucosal and bilateral neck irradiation to 16 patients who received irradiation to the ipsilateral neck alone. Occurrence of a primary tumour at five years was 8 versus 44 per cent, respectively, and contralateral neck node control 86 versus 56 per cent suggesting superior control rates for more comprehensive irradiation. Patient numbers are small, however, the study is noteworthy because electrons were used to treat the neck only, avoiding incidental irradiation of midline structures and to the contralateral neck, which can occur with photon (x-ray) beam techniques. Earlier reports from the University of Florida and from Institut Curie, Paris, have also alluded to the efficacy of mucosal radiotherapy for eradicating occult primary tumours, although neither included data from nonirradiated patients.\(^{34, 36}\)

**RECENT ADVANCES**

**Intensity-modulated radiotherapy**

Intensity-modulated radiotherapy (IMRT), a new technique for delivering tumoricidal radiation doses to mucosal sites, yet permitting a reduction in dose to sensitive structures including major salivary glands, is still in the early stages of implementation in the UK.
A comparison of IMRT versus conventional radiotherapy treatment plans for six patients undertaken by Bhide et al.37 at the Royal Marsden Hospital has shown improved radiation coverage of the mucosa including nasopharynx with a significant reduction of dose to the parotid gland contralateral to the involved neck, thereby reducing the risk of severe xerostomia.

Results with IMRT in patients with unknown primary carcinoma have been encouraging as recently reported by Memorial Sloan-Kettering Cancer Center for a series of 21 patients. Two-year regional progression-free survival, distant metastasis-free survival and overall survival were 90, 90 and 85 per cent, respectively. The incidence of acute grade 1 xerostomia was 57 and 43 per cent for grade 2 xerostomia. Salivary function improved over time, however dysphagia as a result of oesophageal stricture occurred in three patients all of whom improved following oesophageal dilatation.38 A group in Ghent has reported similar results using IMRT compared to their historical controls treated with conventional radiotherapy. Grade 3 acute dysphagia was 4.5 compared to 50 per cent. By six months, grade 3 xerostomia was 11.8 per cent in the IMRT group and 53 per cent in the historical controls. There were no cases of late grade 3 dysphagia in the IMRT patients. Control rates and the emergence of a subsequent primary tumour were equivalent.39

Inclusion of the nasopharynx in nasopharyngeal carcinoma (NPC)-endemic China has resulted in high control rates and a low risk of development of a primary.40 Nevertheless, inclusion of the nasopharynx increases the dose to the parotid gland even using IMRT37 and selective mucosal irradiation should still be considered in patients with a low risk of NPC.

**Chemoradiotherapy**

Concurrent chemoradiotherapy is now a standard nonsurgical management option for patients with locally advanced head and neck cancers. The role of chemoradiotherapy for patients with UPC has not been fully established. Shehadeh et al.41 reported a benefit in locoregional disease control with postoperative radiotherapy with concurrent cisplatin (100 mg/m² given 3 weekly) in 37 patients with UPC. The majority of patients in this cohort had greater than N2b disease (71 per cent) and extracapsular spread (68 per cent). After a median follow up of 42 months, regional and distant recurrences were noted in 5 and 11 per cent of patients, respectively. Substantial acute and late morbidities were seen, particularly incidence of grade 3/4 mucositis in 46 per cent and xerostomia in a third of patients.41

**CONCLUSIONS**

- Modified neck dissection is recommended for all patients with UPC with cervical lymphadenopathy outside the context of a clinical trial.
- Postoperative selective or panmucosal radiotherapy is indicated for most patients with advanced operable neck disease.
- IMRT should be considered to be the optimal radiotherapy technique in order to maximize coverage of putative mucosal sites and to spare major salivary gland tissue.

**FUTURE RESEARCH AND DEVELOPMENT**

Issues in the management of patients with UPC continue to remain unresolved. With the current lack of randomized clinical trials for UPC along with a reduced incidence of these tumours, the clinical management of these patients remains challenging. The majority of evidence used to guide investigations and management of these tumours is limited to small retrospective case series.

- Is definitive neck dissection sufficient for patients with N1 and N2a disease, avoiding the need for elective mucosal irradiation (EMI) and its associated morbidity?
- The optimal field for elective irradiation is yet to be defined – whether selective irradiation of the ipsilateral neck is adequate, or is panmucosal or selective mucosal irradiation required for an improvement in disease-free survival and overall survival?

**KEY EVIDENCE**

- There is no level I evidence for guidance in managing the UPC patient. Data are at best level II.
- PET-CT has been shown to have a key role in the management of patients presenting with UPC, and should precede putative biopsy.
- Postoperative selective or panmucosal radiotherapy is indicated for most patients with advanced operable neck disease.
- Strategies for the use of new treatment technologies, IMRT and modified radiation fractionation, are largely based upon extrapolation of data accumulated for the treatment of known sites of head and neck squamous carcinoma.

**KEY LEARNING POINTS**

- Unknown primary carcinoma is an unusual clinical scenario and accounts for only 2–3 per cent of patients with head and neck malignancy.
Involvement of nodal levels I–IV is almost exclusively associated with occult upper aerodigestive tract primary squamous carcinoma, with level II being the most common site.

CT, MRI or (FDG) CT-PET scans should be performed prior to biopsy in order to guide subsequent biopsy and to avoid imaging artefacts or false-positive results with PET scans.

The only tumour marker of clinical value is Epstein–Barr virus serology. Positive EBV serology should be followed on by multiple biopsies of the nasopharynx in the search for an occult primary.

The usefulness of FDG-PET scans in the diagnostic pathway of patients with UPC has been reported with varying degrees of success. Careful analysis of all available data reveals that FDG-PET can alter management in up to a third of patients with UPC. Simultaneous image coregistration PET-CT should be considered optimal.

There is good evidence to recommend tonsillectomy, but the evidence for tongue base and nasopharyngeal biopsy is less compelling.

Definitive modified neck dissection should be performed in all patients with UPC after either FNAC or biopsy.

Panmucosal radiotherapy has demonstrated a reduction in primary site occurrence without any improvement in overall survival. Associated morbidity is high, in particular grade 3/4 mucositis and xerostomia.

Radiotherapy-related morbidity may be reduced if selective mucosal irradiation is undertaken, most commonly by exclusion of the postnasal space within the clinical target volume in patients who present with nodal involvement of levels I–IV.

IMRT should be considered to be the optimal technique for radiation dose delivery.

For panmucosal radiotherapy, a dose of 50 Gy in 25 daily fractions, five fractions per week is sufficient for control of occult primary disease.

Nodal stage is the most important risk factor for local relapse.

Chemoradiotherapy in patients with UPC should be considered when neck nodes have extracapsular spread or when resection margins are positive.

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Neck dissection

RENÉ LEEMANS, SIMONE EELENSTEIN AND VINIDH PALERI

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… most meaningful progress is made in small increments. The reality today concerning neck dissections is a good example.

Robert M Byers

INTRODUCTION

Neck dissection has proved to be an essential and central procedure in the treatment of head and neck cancer. The neck dissection procedures performed today are the result of many years of refinements and modifications of the first description in the English language by Crile in 1906.1

The history of neck dissection is fascinating and several historical figures mark the rationale of neck dissection in its present form. Concepts of cervical lymph node metastases and the incurability of the disease dawned on surgeons in the mid-nineteenth century with publications as early as 1847 by Joseph von Chelius.2 In 1880, Theodor Kocher introduced the Y-shaped incision which is still in use today, thus allowing for wide resection of lymph node metastases.3 In the following years, surgeons such as Packard advised the excision of the submandibular lymph nodes and Sir Henry Butlin advocated elective dissection of the cervical lymph nodes in the treatment of tongue cancer.4 A publication in 1888 by Jawdyński, a Polish surgeon, went unnoticed due to its publication in his native language. This article is the first in which a lymph node dissection procedure, later known as radical neck dissection, is described.5 One should note that Jawdyński also ligated the carotid artery due to mass tumour invasion. As mentioned previously, the landmark article of what later became known as the classical radical neck dissection was published in 1906 by George Washington Crile Sr from Cleveland.1 This paper, which in fact is a sequel to a previous publication of his in 1905,6 is the first well-documented paper including many clear drawings in which the systematic en bloc dissection of lymph nodes in head and neck cancer is described. Ever since, the name of George Washington Crile has been synonymous with radical neck dissection (RND). Subsequently, in 1951, Hayes Martin from Memorial Hospital New York, NY, popularized the radical neck dissection with a step-wise description of the technique.7

A decade later, in 1963, the Argentinian Osvaldo Suárez, introduced the first systematic approach to functional neck dissection (FND).8 However, as the paper was written in Spanish, the article went largely unnoticed in English-speaking countries. Suárez demonstrated lymph nodes to be within well-defined fascial compartments and thus introduced the possibility of performing a cervical lymph node dissection while preserving certain structures. Ettore Bocca from Italy saw Suárez in action and published a detailed article in English on the technique of FND in 1964.9 Together with César Gavilan from Spain, they adopted FND as a new approach to the neck in 1969.10

Due to new insights into lymph drainage pathways, other modifications were also developed during the 1960s, such as the modified radical neck dissection (MRND) and selective neck dissection (SND). Increasing knowledge of the topographical distribution of metastatic lymph nodes with various primary sites permitted evolution of less radical techniques.11,12 In these techniques, selective lymph node groups that have the highest risk of containing metastases are removed and they are mainly associated with names such as Richard Jesse, Alando Ballantyne and Robert Byers from Houston.13
CLASSIFICATION

The increasing variation in surgical techniques created the need for a classification system. The American Academy of Otolaryngology—Head and Neck Surgery, jointly with the American Society for Head and Neck Surgery, produced a standardized classification system in 1991. An update was published in 2002, which brought further consensus in the description of the modified and selective neck dissection. It must be emphasized that a comprehensive knowledge of the neck nodal levels and their boundaries is necessary to understand the classification system. This is discussed in Chapter 34, Metastatic neck disease.

The updated system of neck dissection classification identifies four categories:

- **Radical neck dissection** involves removal of lymph nodes in levels I–V and three non-lymphatic structures including the accessory nerve, the internal jugular vein (IJV) and the sternomastoid muscle.

- **Modified radical neck dissection** removes lymph nodal groups levels I–V, but preserves one or more of the three non-lymphatic structures that are routinely sacrificed in a radical neck dissection. The structure that is preserved should be specifically named, for example, spinal accessory nerve, internal jugular vein.

- **Selective neck dissection** is a procedure where one or more of the lymph node groups are preserved in addition to the non-lymphatic structures. The dissected levels or sublevels that are removed should be identified within parentheses, e.g. SND (I–IV).

- **Extended radical neck dissection** involves removal of one or more additional lymphatic and/or non-lymphatic structures(s) relative to a radical neck dissection, e.g. level VII, retropharyngeal lymph nodes, hypoglossal nerve, carotid artery, skin of neck, etc. All additional structures should be identified within parentheses.

Procedures that dissect all five levels (RND and MRND) are also commonly referred to as ‘comprehensive neck dissections’.

NECK DISSECTION IN THE TWENTY–FIRST CENTURY

Several factors have led to an enormous change in the kind of operations performed to deal with metastatic neck disease in the present day. A greater understanding of the patterns of metastatic disease for the various primary sites and the recognition that no head and neck primary site spreads to all five levels, combined with the paradigm shift from the Halsedian principles of cancer management has meant that the RND is performed less frequently than ever. In the authors’ practice, five level neck dissections (usually MRND) are currently limited to patients presenting with clinical neck disease (staged N2b and higher) in the setting of oral cavity cancers and for advanced laryngeal and hypopharyngeal cancers where surgery is used to deal with the primary site as well. With evidence emerging to support SND even for N2a disease, it is very likely that five level dissections will be used only in highly select patients. Even within the spectrum of SND, studies now question the need to remove select levels and based on the primary site.

The advent of the chemoradiation era has also led to a considerable change in the practice of oncologic surgery to eradicate neck disease. Bulky neck disease (N2a and N3) used to be the common indications for RNDs. The increasing evidence base supporting primary chemoradiation has led to a reduction in the use of primary surgery to deal with metastatic neck disease for several primary sites, notably the oropharynx. A significant proportion of these patients experience complete response and recent evidence suggests that complete responders, following appropriate investigation, may not need salvage surgery.

Increasing experience with operating on the chemoradiated has resulted in the recognition of two key facts: (1) Lymph nodes occupying neck levels that had no evidence of disease involvement and remain clinically negative after chemoradiation rarely harbour occult metastases. (2) Chemoradiation causes significant scarring that makes for challenging surgery, especially for the novice surgeon. Partial responders demonstrating residual disease can be managed by less extensive procedures which are associated with less morbidity with equivalent oncologic efficacy. In addition, a five level neck dissection after chemoradiation causes significantly more scarring that can lead to greater functional impairment with no benefit.

The above has resulted in new surgical procedures for residual disease which cannot be classified under the existing system. The less extensive neck dissection procedures in partial responders include dissections of one or two levels, called superselective neck dissection (SSND) or ‘nidulectomy’, sometimes with concurrent sacrifice of non-lymphatic structures; for instance, a 2 cm-sized residual node in level II following chemoradiation for a tonsil primary tumour that has responded completely may need clearance of levels II and III along with sacrifice of the adherent sternomastoid and cannot be classified under the current system. This has led to calls for further modification of the existing neck dissection terminology. These issues are discussed in greater depth in Chapter 34, Metastatic neck disease.

All of the above have conspired to significantly change the experience accrued by current trainee head and neck surgeons compared to the past where a five level neck dissection was one of the first operations taught to gain familiarity with neck anatomy. Today, a trainee is more likely to perform a modified radical or a selective neck dissection than a radical procedure. The former procedures need an astute grasp of anatomy and more mastery of surgical skills as they involve operating with restricted exposure, in scarred fields while preserving key structures.

Preoperative preparation

The patient should be prepared as for any major operation, with adequate evaluation by the anaesthesiologist before surgery. The patient’s operative field should be shaved. Preoperatively, the patient is advised about risks and possible complications (see Chapter 11, Complications and their management). A patient undergoing unilateral neck dissection as a solitary procedure does not usually require a tracheostomy. A tracheostomy may be indicated when the
primary tumour is dissected in continuity with the neck, especially in instances where the mandible is split for access. It may also be advisable to perform an elective tracheostomy in patients who are undergoing a bilateral neck dissection. Prophylactic antibiotic regimes of 24 hours’ duration, covering aerobic, anaerobic and Gram-negative bacteria, based on local sensitivities, are mandatory for clean-contaminated surgery. Their use is advised in clean major oncological head and neck surgery. A urinary catheter can be eschewed if the sole procedure to be performed is a neck dissection.

The following description of neck procedures assumes that several conditions are met: patients are fit for a major surgical endeavour and fully understand the risks of the procedure, the metastatic lesion is resectable, and the primary tumour is controlled or will be addressed concurrently, unless there are over-riding palliative indications for the procedure that have been discussed with the patient and preferably in a multidisciplinary setting. Distant metastases are not necessarily a contraindication for surgery if it is judged that locoregional control will be obtained by the surgical procedure and the benefits outweigh the risks.

**Position of the patient during surgery**

The patient is laid supine on the operating table and intubated. The authors prefer for the patient not to be paralysed in case a need arises to use nerve stimulators during the procedure. The head is turned to the opposite side and is hyperextended, resting on a head ring. A sandbag, or a towel, pillow or inflatable rubber bag, is placed under the shoulders in order to obtain the desired surgical position of the neck. The upper end of the operating table is elevated to approximately 30°, which decreases the amount of blood loss during surgery and further extends the neck.

A disinfectant surgical solution is applied, with ample margins, to prepare the operative field before draping the patient. Draping may vary according to hospital custom. In general, two horizontal drapes and two vertical drapes are fixed to the skin. Basically, when draping the surgical field the following ipsilateral landmarks should remain visible: mastoid tip, ear lobe, body of the mandible, midline of the chin, suprasternal notch, clavicle and region of trapezius muscle insertion.

A scrub nurse as well as two surgical assistants, one in front of the surgeon and one at the patient’s head, is usually present. Few general instruments are used for the operation.

**Type of incision**

A number of eponymous incisions have been described (Figure 36.1). The choice for a specific incision is based on a variety of factors, including personal preference, previous radiotherapy or surgery, the site of the primary tumour and its resection.

The following are the main goals that should be achieved by the skin incision:

- assure adequate vascularity of the skin flaps;
- adequate exposure of the surgical field;
- consider the localization of the primary tumour;
- adequate protection of the major vessels if the sternocleidomastoid muscle is resected;
- consider preoperative factors, such as previous radiotherapy;
- consider as well as facilitate reconstructive surgery, if needed;
- include previous surgical fields (scars, incisions for biopsies, etc.);
- produce acceptable cosmetic results.

Variations of the classical Y-incision (Crile), such as the Gluck, Schobinger, Conley or Martin incision, were used commonly for the excellent exposure they provide, but have the drawback of a trifurcation point or narrow flaps which are prone to breakdown, especially in previously radiated necks. Other alternatives such as the utility incision, hockey stick incision and the apron flap also give good exposure, while avoiding trifurcation points. The McFee incision with two horizontal limbs limits exposure, but has a low incidence of wound dehiscence.

When a neck dissection is performed on a planned basis or for salvage after radiation, it is very unlikely for all five levels to be dissected, thus limiting the need for extensive exposure. A smaller vertical, hockey stick or horizontal incision, based on the levels that need extirpation, will suffice in some selected cases.

When an extensive neck dissection is performed for salvage after chemoradiation, it is advised that myofacial flaps are used to prevent wound breakdown and further complications.

**Generic steps for all neck dissections**

After positioning and draping of the patient, the desired incision is drawn using a marking pen or ink. The incision should provide adequate exposure and therefore suitable access to the complete operative field. There are four areas of special attention that define the limits of the dissection, and adequate exposure of these areas may constitute the difference between failure and success (Box 36.1 and Figure 36.2). The goal of surgery is to resect both visible and occult disease, and it is in these corners that further occult disease may lurk. Also, when marking the desired incision, care should be taken not to place three-point junctions over the carotid artery.

Before making the incision, slight scratch marks can be made at right angles across to the incision or matching dots can be made/tattooed at three or four points with the tip of an intramuscular green needle dipped in ink, in order to facilitate placement of critical sutures.

The incision is made with a blade No. 10 through the skin down to and through the fibres of the platysma muscle. During the incision, the assistant helps apply adequate traction and countertraction to the skin. The skin flaps are elevated using the platysma muscle as identification of the correct dissection plane. Keeping the platysma muscle into the elevated skin flap ensures appropriate blood supply to the skin flaps and also increases the strength of the wound in the postoperative period. In certain situations, it may be necessary to keep the platysma in the dissection specimen due to tumour invasion, and in these cases it is often wiser to resect the overlying skin as well. In the cranio-posterior part of the neck, the fibres of the sternocleidomastoid muscle insert...
Figure 36.1 Various incisions for neck dissection.
directly into the skin, and the appropriate plane of dissection is less easily found.

Raising the skin flaps is made easier if the assistant places double skin hooks or a rake retractor under the platysma and applies upward traction. Also, countertraction should be applied to the specimen and, still using the knife, the dissection can be continued in the subplatysmal plane. Dissection along the subplatysmal plane results in very little bleeding.

When the upper skin flap is raised, care should be taken to preserve the marginal branch of the facial nerve. If possible, although of less clinical importance, the cervical branch of the facial nerve can also be spared. Both branches supply tension to the lower lip; the marginal branch supplies the muscles of the corner of the mouth, while the cervical branch supplies the platysma muscle that crosses the mandible and is inserted into the corner of the mouth. Both branches emerge from the lower pole of the parotid gland, curve around the angle of the mandible, cross the facial vessels and then run parallel – approximately at a finger breadth – to the body of the mandible. At the level of the submandibular gland, the marginal mandibular branch is found immediately superior and the cervical branch lateral to the gland. Next, the branches both curve upwards and cross the mandible (Figure 36.3).

One should always bear in mind that neck dissection is an oncological procedure with the goal of cancer cure and this should not be compromised by preserving the nerve. Specifically, if nodal disease is present in the close proximity of the nerve branches, then they should be dissected.

If a McFee incision is being used, the next step is to make the lower skin incision and the lower and middle skin flaps are elevated. Following the subplatysmal plane, the lower flap is easily elevated, and the middle skin flap (also referred to as the bridge) is elevated by dissecting both from the caudal as well as from the cranial field of dissection.

If a trifurcate incision is being used, then the anterior and posterior skin flaps are next to be elevated. Care should specifically be taken when the posterior flap is elevated as it is the most difficult of the three flaps to be raised. This is due to the insertion into the skin of the cranial fibres of the sternocleidomastoid muscle, as well as absence of the platysma muscle over part of its extent, causing the appropriate plane of dissection to be less easily found. The flap is easily made too thick or too thin, and it is easiest to achieve uniform thickness by holding the flap both between retractor and fingers. The posterior flap is elevated to the anterior border of the trapezius muscle. The trapezius muscle constitutes the posterior limit of dissection and it should be exposed from mastoid tip to the clavicle. Due to the hyperextended and rotated position of the patient, the trapezius muscle is lax and it can therefore be more difficult to find. One should remember that the accessory nerve runs through the posterior triangle at a superficial level and is therefore close to the plane of dissection and it is sometimes injured at this point in modified neck dissection procedures. Even though the accessory nerve is resected in a radical neck dissection, the surgeon should be aware of its trajectory, and it is a safe custom to identify the nerve before resecting it.

Once the skin flaps have been raised and adequate exposure is obtained to the aforementioned corners of sternation, the flaps, if desired, can be sutured to the drapes. The flaps should be preferably protected with a moist gauze or sponge to keep them in good condition.

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### Box 36.1 Four areas of special attention during neck dissection

- Lower end of internal jugular vein
- Junction of lateral border of clavicle with lower edge of trapezius
- Upper end of internal jugular vein
- Submandibular triangle

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**Figure 36.2** Skin flaps raised showing the four areas of special attention.

**Figure 36.3** Cervical and marginal branches of the facial nerve.
Despite the diminished role of RND in head and neck surgical practice, this is discussed first as a description of radical neck dissection provides greater insight into the neck levels and regional anatomy.

**Surgical boundaries and indications**

The surgical field has the following boundaries: superior, the inferior border of the mandible; anterior, the contralateral anterior belly of the digastric muscle, the hyoid bone and the sternohyoid muscle; inferior, the clavicle; and posterior, the anterior border of the trapezius muscle.

The indications and contraindications for radical neck dissection are set out in Box 36.2.

**Box 36.2 Indications and contraindications for radical neck dissection**

Indications for radical neck dissection:

- Significant operable neck disease (N2a, N2b, N3) with tumour bulk near to or directly involving spinal accessory nerve and/or internal jugular vein
- Extensive recurrent disease after previous selective surgery or radiotherapy
- Clinical signs of gross extranodal disease

Contraindications for radical neck dissection:

- Untreatable primary tumour or unresectable neck disease (i.e. encasement of internal carotid artery, brachial plexus, prevertebral fascia)
- Patient unfit for major surgery
- Distant metastases
- Simultaneous bilateral neck dissection (preserve one internal jugular vein!)

**FIRST AREA OF SPECIAL ATTENTION: THE LOWER END OF THE INTERNAL JUGULAR VEIN**

According to personal preference and institution, the dissection can be started at any chosen point, some surgeons like to locate the accessory nerve first, but usually dissection is started at the lower end in the first (lower end of internal jugular vein) or second area (junction of the lateral border of the clavicle with the trapezius muscle) of special attention.

Opinions differ as to whether the lower end or upper end of the main draining vein from the operative field should be ligated first; ligation of the lower end prevents transport of possible tumour emboli into the bloodstream by manipulation of the tumour, but ligation of the lower end of the internal jugular vein causes distension above the ligature rendering dissection more difficult.

Usually, the lower end of the internal jugular vein is approached first by continuing the dissection along the upper border of the clavicle from trapezius muscle to the suprasternal notch. The supraclavicular nerves and vessels (such as the external jugular vein) are divided as well as the sternocleidomastoid muscle. The internal jugular vein lies between the sternal and clavicular heads of the sternomastoid muscle, and dividing the muscle fibres just above the clavicle reveals the vein. This can be done by using blunt-tipped scissors, isolating the muscle by pushing the scissors under the muscle and then keeping the scissors in place to protect the underlying vein, the muscle can be cut (Figure 36.4). After dividing the sternocleidomastoid muscle, the blueness of the internal jugular vein can be seen as the vein lies encompassed within the carotid sheath. The carotid sheath contains the internal carotid artery, the internal jugular vein, the vagus nerve and usually also branches of the ansa cervicalis.

The carotid sheath is opened and the internal jugular vein is exposed for at least a few centimetres in order to allow for adequate access for ligation. The position of the vagus nerve is verified before ligation of the internal jugular vein. Three ligating sutures, i.e. vicryl 0/0, are placed around the vein: a ligature and an additional transfixion at the lower end and a ligature at the upper end of the vein remaining within the dissection specimen (Figure 36.5).

The vein can be easily damaged during dissection, either when dividing the overlying sternocleidomastoid muscle or when the vein itself is manipulated for its dissection. Damage to the internal jugular vein, but also to small contributing vessels in its proximity, can lead to alarming bleeding during which it is of the utmost importance to remain calm and instruct the assistant not to grab the bleeding vessel with artery forceps or use diathermy as this will enlarge the hole in the vessel. The trick in stopping the bleeding is to apply pressure with a finger or apply arterial clamps and then ligate the vessel. If a large hole occurs or the vein is torn, adequate finger pressure should be applied and the patient should ideally be placed in the Trendelenburg position before...
clamping and ligating the vein, as the main danger of a torn internal jugular vein is not the blood loss but the possibility of an air embolism.

When performing neck dissection on the left side, one should be alert in the angle between the internal jugular vein, subclavian vein and the clavicle because of the thoracic duct. The thoracic duct passes medial to the jugular vein, then posterior to it and finally curves around to enter the junction of the internal jugular and subclavian vein (Figure 36.6). One should note that when performing dissection on the right side, a similar but much smaller duct (accessory duct) is encountered.

After ligation of the vein, the carotid artery and vagus nerve are carefully retracted medially allowing for dissection of the internal jugular vein and its associated lymph nodes. It is of great importance to bear the position of the sympathetic chain in mind – deep to the carotid artery – and it should be preserved.

Once the internal jugular vein has been tied, the dissection extends laterally towards Chaissaignac’s triangle, which is defined as the triangle between where the longus colli and scalenus anterior attach to the tubercle of C6 (Chaissaignac’s or carotid tubercle) with the subclavian artery as the base (Figure 36.6). Here are found the scalene nodes (which should be removed) and the main jugular lymph duct that terminates here on the left side with the thoracic duct, and it is at risk of being damaged. If the duct is damaged, noticeable by extra clear fluid welling up into the dissection area, the source should be found and transfixed. At the end of the operation, it is important to return to this point and check that there are no further leaks. Occasionally, not one large duct but a convolute of lymphatic vessels is found in this area and the utmost care should be taken to prevent chyle leakage.

SECOND AREA OF SPECIAL ATTENTION: JUNCTION OF CLAVICLE AND ANTERIOR BORDER OF TRAPEZIUS

Next, the dissection proceeds towards the second area of special attention formed by the junction of the trapezius muscle and the clavicle (Box 36.3). One way to do this is, having tied off the internal jugular vein (Figure 36.7), move directly towards the second area and begin the dissection at the lower end of the trapezius muscle. The fatty tissues in the supraclavicular region are divided and care should be taken not to pull these tissues from behind the clavicle into the neck. While the fat is retracted upwards, the inferior belly of the omohyoid muscle is encountered and, according to institutional preference, it is either cut or ligated and it can then be retracted upwards.

Deeper to the omohyoid, the transverse cervical artery and vein are found as they run laterally across the floor of the posterior triangle. They are normally ligated, and in some instances the artery is spared as a possible anastomosis for free flap reconstruction purposes. Both the artery and particularly the vein have small branches across the anterior border of the trapezius muscle. These vessels can often be the source of bleeding during dissection of the posterior triangle, particularly in the short thick neck if they retract into the fat below the trapezius muscle.

Dissection is then continued further, either sharp or blunt with a swab, on to the underlying level of the prevertebral fascia overlying the scalene muscles. Directly beneath the prevertebral fascia, the phrenic nerve and the brachial plexus are seen and, as long as the fascia is not breached, these structures are protected. The phrenic nerve descends from lateral to medial through the neck over the anterior scalenus muscle and the brachial plexus emerges from between the
medial and anterior scalenus muscles. If bleeding occurs in this part of the dissection, bipolar diathermy should be used because of the proximity of the nerves. The supraclavicular dissection is continued to the anterior border of the trapezius muscle and here the dissection proceeds in an upward direction, thus dissecting the posterior triangle of the neck. A note of caution should be made not to exert excessive traction when dividing the supraclavicular tissue as it is possible to inadvertently pull the subclavian vein out of the upper chest with obvious consequences.

Dissection of the posterior triangle

The dissection continues upwards following the anterior border of the trapezius muscle to the uppermost point of the triangle at the mastoid tip where the trapezius and sternocleidomastoid meet. By following the anterior border of the trapezius, but dissecting on to the prevertebral fascia, the posterior triangle can be cleared. Particularly in patients with a short thick neck, the volume of fatty tissue dissected increases and the clearance of the posterior triangle can be a major problem area for the inexperienced surgeon.

It is however, often thought easiest to dissect the posterior triangle working from the mastoid tip downwards to the clavicle; at the tip of the dissected triangle, the layer of tissue is still thin and it is easier to identify the desired dissection plane. The anterior border of the trapezius muscle constitutes the lateral border of the dissection and the floor of the posterior triangle is formed by the prevertebral fascia overlying the deeper muscles of the neck: the splenius capitis

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**Box 36.3 Critical steps in radical neck dissection: the lower neck**

- Divide the lower end of the sternocleidomastoid muscle in the first area
- Isolate and ligate the internal jugular vein
- Look for and avoid damage to the thoracic duct and branches of the jugular lymphatic duct in Chaissaignac’s triangle
- Remove scalene nodes
- Divide and retract the omohyoid muscle upwards
- Mobilize the fat pad overlying the prevertebral fascia
- Identify and preserve the brachial plexus
- Identify and preserve the phrenic nerve
- Deal with the second area
(cranially) and the levator scapulae. The prevertebral fascia is left intact. The method of dissection used is one of personal preference, varying from scissors to sharp scalpel dissection, or in some instances blunt, with the aid of dry gauze.

As a matter of routine, the accessory nerve should be identified before dissection of the posterior triangle. As the nerve runs in the roof of the posterior triangle, it is often identified by the surgeon early during neck dissection when the skin flaps are raised.

Several methods can be used to identify the accessory nerve, based on its anatomical trajectory and surgical landmarks. The accessory nerve innervates the trapezius muscle and the nerve exits from its trajectory through the sternocleidomastoid muscle, approximately at the junction of the upper and lower two-thirds of the sternocleidomastoid and runs in a caudolateral direction to the anterior border of the trapezius. The exit point of the nerve from within the sternocleidomastoid muscle can be predicted by the rule of thumb that it is located approximately 1 cm above Erb’s point, the point where the great auricular nerve winds from behind the muscle on its route to supply the skin over the parotid gland. Another way to identify the accessory nerve, but often thought more difficult, is to locate it at its entry point into the anterior border of the trapezius muscle a few centimetres above the clavicle. The dissected tissues are retracted forward and the retraction is hindered by branches of the cervical plexus (C2, C3 and C4). These branches emerge immediately posterolateral to the carotid artery and internal jugular vein and enter the dissection specimen. To enable further retraction, the branches are cut; however, some surgeons prefer to spare the branches of C3 and C4 contributing to shoulder function if the accessory nerve is divided.

The dissected tissue now hinges on the mastoid and skin insertions of the sternocleidomastoid muscle; these are dissected as well as the lower lobe of parotid gland at the level of the angle of the mandible. The mass of the sternocleidomastoid muscle varies considerably; it can be particularly bulky in patients with a short, thick neck. It is of great reassurance for any surgeon to remember that no structures run between the sternocleidomastoid muscle and the posterior belly of the digastric muscle and if these landmarks are defined, the muscle can be divided safely.

**THIRD AREA OF SPECIAL ATTENTION: THE UPPER END OF THE INTERNAL JUGULAR VEIN**

The posterior belly of the digastric muscle – often referred to as the resident’s friend – is cleared and, using a Langenbeck retractor, it can be retracted superiorly exposing the internal jugular vein and the accessory nerve (Figure 36.8). The accessory nerve runs along with the internal jugular vein from the jugular foramen and crosses the vein from medially to laterally as the nerve enters the sternocleidomastoid muscle at approximately the junction of the upper and middle third of the muscle. The transverse process of the atlas serves as a useful anatomical landmark. As the muscle has been divided from its cranial insertion into the skin and the mastoid process, and the muscle is retracted caudally, the accessory nerve can be transposed in a craniolateral direction. The dissection plane across the jugular vein lies close to the vessel wall and the vein is cleared and mobilized over a few centimetres. The vein is divided after ligation and transfixed with sutures, e.g. Vicryl 0/0 (Figure 36.9).

Two important structures should be identified before ligating the internal jugular vein: the vagus and hypoglossal nerves. The vagus nerve runs along with the internal and common carotid artery and its position is verified during dissection. The hypoglossal nerve is a very useful landmark during dissection, specifically if the tumour is fixed near or to the carotid bifurcation. The hypoglossal nerve runs across the carotid bifurcation, the lingual and occipital arteries and forms a rather convenient tunnel along which the dissection can be continued. The occipital artery is usually encountered when the internal jugular vein is cleared as the artery crosses the vein and is often the source of bleeding.
Dissection across the carotid bifurcation may cause bradycardia and changes in blood pressure due to triggering of the carotid sinus lying within the bifurcation. Usually, these symptoms disappear when manipulation ceases and if necessary lidocaine can be applied locally.

Once the internal jugular vein has been ligated and dissected at the upper end, the surgical specimen is mobilized by working both from a cranial and a caudal direction. It is useful to remember that usually all branches of the internal jugular vein arise from its anteromedial surface, but of course there are exceptions to this rule, and the branches are ligated. Working from a caudal to cranial direction, the dissection is completed by following the anterior belly of the omohyoid muscle – which is the anterior border of the dissection – to its insertion at the hyoid bone from which it is divided (Box 36.4).

FOURTH AREA OF SPECIAL ATTENTION: THE SUBMANDIBULAR TRIANGLE

It is important to recognize that clearance of level I for oncologic purposes is not synonymous with removal of the submandibular salivary gland. The contents of the triangle, including lymph nodes and fatty tissue must be removed, leaving behind clean muscles that form the boundaries. Dissection of the submandibular triangle (Figure 36.10) is usually begun in the midline, by dividing the fatty tissue on to the dissection plane of the anterior belly of the contralateral digastric muscle. The fatty tissue in the submental triangle between the anterior bellies of digastric muscles is included in the dissection specimen and the dissection continues over the anterior belly of the ipsilateral digastric muscle and the mylohyoid muscle, which are cleared of their covering tissues.

The fascia, including the submandibular gland, is dissected from its attachments across the lower border of the mandible and from its insertion directly behind the digastric muscle to the mandibular angle. The facial artery and vein are encountered and ligated as they cross the corpus of the mandible towards the masseter muscle. It is important to include the tissue in close continuity to the facial artery and vein as this may include a small lymph node regularly found at this site.

By retracting the mylohyoid muscle medially and at the same time retracting the submandibular gland inferolaterally, the floor of the submandibular triangle becomes visible with the lingual and hypoglossal nerve overlying the deep plane formed by the genioglossus and hyoglossus muscles.

Because of the downward traction of the submandibular gland, the lingual nerve is extended slightly. This allows for placement of a ligature around its ganglion – supplying secretomotor innervation – as well as the small accompanying blood vessel which can be the source of bleeding if severed. After dissecting the ganglion and connecting tissues, the lingual nerve retracts upwards to its original position behind the body of the mandible, out of the surgical field.

The hypoglossal nerve is identified on its anterosuperior anatomical trajectory, medial to the anterior belly of the digastric muscle. While keeping the hypoglossal nerve under direct vision, the submandibular duct is ligated or divided according to the surgeon’s preference and the entire gland is

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Box 36.4  Critical steps in radical neck dissection: upper neck

- Divide the upper end of the sternocleidomastoid muscle in the third area
- Retract the posterior belly of the digastric muscle upwards
- Identify and ligate the internal jugular vein
- Identify and preserve the hypoglossal nerve

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Figure 36.10  Anatomy of the submandibular triangle.
mobilized with the specimen. One of the last steps before removing the entire specimen is formed by ligating the facial artery. The facial artery is encountered (again) at the posterior inferior border of the submandibular gland as it rounds the posterior belly of the digastric muscle; it can be ligated at its point of origin (external carotid) or directly near the submandibular gland. The latter preserves a large part of the artery and forms a suitable microvascular anastomosis site for free flaps if the neck dissection is part of major ablative and reconstructive surgery.

Complications of radical neck dissection

An extensive overview of the possible complications of radical neck dissection has been given in Chapter 11, Complications and their management. The most troublesome and crippling long-term complication of radical neck dissection is the shoulder syndrome. It is a direct consequence of the denervation of the shoulder musculature, specifically the trapezius muscle, caused by cutting the spinal accessory nerve and possibly its cervical plexus branches. Due to denervation of the trapezius muscle, several changes within the shoulder girdle and arm movements occur: complete abduction of the arm is impeded at 75°, the shoulder girdle is tilted downwards, rotation is impeded and flexion of the arm can only be performed by the deltoid muscle, resulting in maximal flexion of 45°. Furthermore, the shoulder syndrome is extremely troublesome because of the accompanying long-term pain and it is of the utmost importance that all patients are referred to a physiotherapist postoperatively.

Extended radical neck dissection

In addition to all structures resected during radical neck dissection, it may be necessary to extend the surgical procedure including other adjacent structures due to tumour involvement or lymph node metastasis into additional lymph node groups, such as retropharyngeal lymph nodes or nodes in the parotid gland, and nodes in levels VI (prelaryngeal) or VII. In these cases, the dissection is performed as described for the radical neck dissection procedure with inclusion of the additional levels or structures.

Modified radical neck dissection

SURGICAL BOUNDARIES AND INDICATIONS

The surgical field for an MRND shares the same boundaries as an RND. It is difficult to be certain preoperatively which structures can be spared based on the clinical and radiological findings. In a clinical N1 or N2a, N2b neck in which the accessory nerve is free from the lymph node metastases, it is safe to preserve the nerve. It is often safe to preserve both the nerve and internal jugular vein, specifically if the contralateral neck is also dissected at the same time and in those cases where there is need for a microvascular anastomosis site. Preservation of all three major non-lymphatic structures is specifically advocated for the treatment of cancer of the thyroid gland with lymph node metastases (Box 36.5).

Sparing of the accessory nerve

If the accessory nerve is to be spared, extra care should be taken when the skin flap of the posterior triangle is developed, as the nerve runs at a superficial level and is therefore close to the plane of dissection. It is at this point that the nerve is often damaged during modified radical neck dissection procedures, and it is a safe practice for many surgeons to identify the nerve at an early stage of the dissection, often during the elevation of the skin flaps. Several methods to identify and locate the nerve can be used. These methods are based on the anatomical trajectory of the nerve and on the use of surgical landmarks.

The accessory nerve supplies the innervation of the trapezius muscle and the nerve exits from its trajectory through the sternocleidomastoid muscle, approximately at the junction of the upper third and lower two-thirds of the sternocleidomastoid and runs in a caudolateral direction to the anterior border of the trapezius. The exit point of the nerve from within the sternocleidomastoid muscle can be predicted by the rule of thumb that it is located approximately 1 cm above Erb’s point, the point where the great auricular nerve winds from behind the muscle on its trajectory to supply the skin of the face. Another way, but often thought more difficult, to identify the accessory nerve is to locate it at its entry point into the anterior border of the trapezius muscle a few centimetres above the clavicle. The accessory nerve is then dissected free from its surrounding tissues in its lower course through the neck, from its exit point from within the sternocleidomastoid muscle to its entry point at the trapezius muscle.

It is safe to locate the accessory nerve in its most cranial part as it enters the neck together with the internal jugular vein from within the jugular foramen. Through superior retraction of the posterior belly of the digastic muscle, the accessory nerve and the internal jugular vein can be exposed and the nerve can be identified as it runs along with the internal jugular vein and crosses it medially to laterally across its anterior surface to innervate the sternocleidomastoid muscle. The accessory nerve usually enters the sternocleidomastoid muscle at the junction between the upper and middle third of the muscle, where the transverse process of the atlas serves as a useful landmark. The nerve can safely be dissected from within its trajectory through the

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Box 36.5 Preservation of all three major non-lymphatic structures

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sternocleidomastoid muscle by placing Ellis clamps or clips on the edge of the sternocleidomastoid muscle at either side of the nerve and lifting the muscle up, thus creating a tunnel and the nerve can be followed while dissecting the overlying muscle fibres. During the dissection of the accessory nerve through the sternocleidomastoid, its branch supplying this muscle is cut. The dissection of the nerve involves manipulation as well as devascularization of the nerve possibly leading to unpredictable postoperative loss of function.

**Sparing of the sternocleidomastoid muscle**

Preservation of the sternocleidomastoid muscle requires mobilization of the deep inserting fascia from the anterior border of the sternocleidomastoid muscle and dissection of the muscle from the fascia below allowing for upward retraction of the muscle using loops or retractors. The neck dissection is more difficult to perform if the sternocleidomastoid muscle is preserved and it is often wise for the surgeon to consider the merit of its preservation. The dissection itself is continued under the sternocleidomastoid muscle in the same way as one would proceed as in a radical neck dissection. Sometimes, surgeons opt for division of the sternocleidomastoid muscle in its caudal end, pulling the muscle up during surgery and resuturing it into place at the end of the procedure.

**Sparing of the internal jugular vein**

Preservation of the internal jugular vein requires careful dissection along the surface of the vein over its complete course through the neck. As in radical neck dissection, the vein is located preferably first in the lower neck, after having completed the dissection across the clavicle from trapezius to suprasternal notch. The supraclavicular nerves and vessels (such as the external jugular vein) are divided as well as the sternocleidomastoid muscle. The sternocleidomastoid lies directly over the internal jugular vein and the muscle fibres are divided – if the sternocleidomastoid is to be sacrificed – just above the clavicle. This can be done by using blunt-tipped scissors, isolating the muscle by pushing the scissors under the muscle and then, keeping the scissors in place to protect the underlying vein, the muscle can be cut. After dividing the sternocleidomastoid muscle, the blueness of the internal jugular vein can be seen as the vein lies encompassed within the carotid sheath.

The carotid sheath is opened and the internal jugular vein is exposed. The vein can be easily damaged during dissection, either when dividing the overlying sternocleidomastoid muscle or when the vein itself is manipulated for its dissection. The upper part of the internal jugular vein is also identified by superior retraction of the posterior belly of the digastric muscle and by dissection along the internal jugular vein the vein can be dissected from the surrounding tissues over its entire course through the neck. Of course, all relevant branches of the vein are encountered during dissection, usually branching from the anterior surface of the vein, and ligated.

**Postoperative management and complications of modified radical neck dissection**

The postoperative care of modified radical neck dissection does not differ from the radical neck dissections. Complications have been described in Chapter 11, Complications and their management.

**SELECTIVE NECK DISSECTION**

**Surgical boundaries and indications**

The boundaries of the surgical field are defined by the lymph node levels that are dissected and are thus less extensive than in modified or radical neck dissection.

SND is commonly used for a clinically disease-free neck in which the lymph node levels at the highest risk of containing possible micrometastatic disease are dissected. There is increasing support for the use of SND in N1 neck disease. One should bear in mind that if peroperative positive lymph nodes are found, especially at multiple levels, it may be necessary to convert the dissection to a modified radical neck dissection. However, when postoperative irradiation is planned for favourable N2 disease, SND may still be appropriate in very selected cases. The lymph node levels/group dissected are determined by the patterns of metastatic spread for specific tumour locations.

Based on these patterns of metastatic spread the following indications and corresponding SND can be defined.11, 12, 19, 20, 21

**SELECTIVE NECK DISSECTION FOR ORAL CANCER: SND (I–III) AND SND (I–IV)**

The SND (I–III) is indicated for oral cancer, T1 to T4 with clinical N0 neck, in which levels I–III are the node groups/levels at risk (Figure 36.11). It is also indicated for the contralateral neck in midline lesions of the floor of mouth or ventral tongue. Other indications include extension of parotid surgery in cases of malignancy or facial skin malignancies in a line anterior to the tragus. The SND (I–IV) is indicated for oral cancer of the anterolateral part of the tongue in which lymph node level IV is also considered to be at risk (Figure 36.11).

**SELECTIVE NECK DISSECTION FOR OROPHARYNGEAL, HYPOPHARYNGEAL AND LARYNGEAL CANCER: SND (II–IV) AND SND (II–IV AND VI)**

The SND (II–IV) is indicated in oropharyngeal, hypopharyngeal and laryngeal tumours in which levels II–IV are the most at risk (Figure 36.11). Furthermore, tumours at these sites often cross the midline and thus a bilateral SND (II–IV) is often the case if the neck is managed surgically.

There is good prospective evidence to suggest that dissection of level IIb may be unnecessary for some N0 necks.17 Patients with laryngeal primaries and contralateral N0 necks are ideal scenarios for preservation of sublevel IIb. In laryngeal cancer with subglottic extension, hypopharyngeal
cancer and medullary thyroid cancer level VI is also included in the dissection, as well as in some instances level VII.

SELECTIVE NECK DISSECTION FOR METASTASES OF CUTANEOUS CANCER: SND (II–V, POSTAURICULAR AND SUBOCCIPITAL/PSTEROLATERAL DISSECTION)

Selective neck dissection for lymph node metastases of skin tumours of the scalp and neck (posterior to the tragus) should include the suboccipital and postauricular levels in addition to levels II–V (Figure 36.11).

Operative techniques for selective neck dissection

Positioning, preparation of the surgical field and draping of the patient are largely comparable to radical neck dissection, but in accordance with the levels included in the dissection, variations in position, incision, as well as surgical preference, may occur.

SND (I–III) AND (I–IV)

Once adequate exposure is obtained, the investing fascia of the sternomastoid muscle is mobilized anteriorly and the muscle is retracted laterally. Care should be taken not to injure the greater auricular nerve as most of the sensory branches from the cervical plexus can be preserved for selective neck dissections not involving level V. The investing fascia is then dissected off the undersurface of the sternomastoid muscle to its posterior border, along its entire length. The accessory nerve comes into view when the upper third of the sternomastoid is being mobilized. Mobilizing the muscle laterally will lead the surgeon on to the fat and lymphatic tissue in the posterior triangle. The posterior boundary of the dissected specimen usually corresponds to the posterior border of the sternomastoid and the branches of the cervical
plexus. Dissection should now proceed deeper, cutting though the fatty tissue, leading the surgeon to the pre-vertebral fascia overlying the paraspinal muscles. The specimen is mobilized working from inferior to superior, staying superficial to the cervical plexus branches, which are preserved.

The dissection is taken up to the level of the posterior belly of the digastric muscle where the internal jugular vein is identified along with the accessory nerve as it enters the neck, usually crossing the anterior surface of the IJV to enter the sternomastoid muscle. Here, a decision will need to be made whether to dissect level IIb, which lies posterosuperior to the accessory nerve. If level IIb is to be dissected, the fibrofatty tissue needs to be mobilized off the underlying splenius capitis and levator scapulae and the accessory nerve gently lifted off it, before being passed under the nerve to maintain continuity with the rest of the specimen. Working along the inferior belly of omohyoid muscle that is left in place to form the inferior border of the dissection (levels I–III), the lymph nodal tissue is mobilized further anteriorly in a plane superficial to the prevertebral fascia along a broad front. The IJV is encountered and meticulous sharp dissection helps swing the specimen towards the superior belly of omohyoid. The omohyoid can now be followed to the hyoid, which is skeletonized, and this leads to the contralateral anterior belly of digastric muscle. The fatty contents of the submental and submandibular triangles are cleared as described in earlier sections.

If level IV also has to be dissected, the dissection is extended inferiorly to include this lymph node level. The omohyoid muscle is left in place, but does not constitute the inferior border of the dissection.

**SND (II–IV) AND (VI)**

The dissection of levels II–IV is performed as described above. If level VI is also dissected, as in laryngeal cancer and total thyroidectomy, the pre- and paratracheal nodes in this level are also included. Level VI dissection is discussed in Chapter 23, Surgical management of differentiated thyroid cancer.

**SND (II–V, POSTAURICULAR AND SUBOCCIPITAL/ POSTEROLATERAL DISSECTION)**

This procedure needs greater exposure than required for the other SND types described, with skin flap elevation to ensure the trapezius is identified. The procedure commences with mobilization of the sternomastoid, as discussed above under Operative techniques for selective neck dissection. Following this, the dissection and mobilization of the fatty tissue is started in the posterior triangle, identifying the accessory early in the dissection. Levels Va and Vb are cleared with anterior retraction of the sternomastoid. The dissected fibrofatty tissue in level Va usually will merge with the tissue in level IIb, which will need to be passed under the accessory nerve. This will enable the specimen to be delivered anteriorly under the sternomastoid and the rest of the dissection will proceed as described under SND (II–IV). For cutaneous primaries, this will include clearance of the suboccipital and postauricular lymph node levels. It should be noted that the cervical plexus branches may need to be sacrificed in this type of neck dissection.

**SUPERSELECTIVE NECK DISSECTION AND OTHER UNCLASSIFIED VARIANTS**

These entities are not currently included in the neck dissection classification update published in 2002, but are practised more widely than is recognized. The indications are exclusively in the setting of residual disease following chemoradiation, where appropriate investigations have revealed the absence of active disease in the primary site or at multiple neck levels. It should be noted that these procedures are not yet backed by high level evidence and are best confined to trial settings at present.

The incision is based on the exposure needed, and given the indications for primary chemoradiation in practice today, it is very likely that the lymph node will be in levels II, III or IV. These can be easily accessed through a horizontal incision. The same principles as for the other neck dissections hold, but it must be noted that normal anatomy may be difficult to recognize, with scarred fibrotic tissue making dissection challenging. In most circumstances, the residual lump with adjacent fibrofatty tissue in the same or adjacent level is removed. Sometimes, based on the extent of scarring, the residual node may be adherent to non-lymphatic structures (sternomastoid muscle, accessory nerve or internal jugular vein), making it impossible to safely remove the nidus without their sacrifice. The extent of sternomastoid to be removed in such an instance is only a segment that covers one or two levels as the case may be.

**Haemostasis, closure and postoperative care**

Haemostasis is checked and irrigation of the wound is performed according to the surgeon’s or institutional custom. One or two drains are placed, taking care that they are not placed in proximity to microvascular anastomosis sites and that they do not cross the carotid. Before closing the wound in two layers, subcutis with Vicryl and cutis with staples or Ethilon sutures, a last inspection of the wound is made checking for possible chylous leak and haemostasis.

No dressings are applied to the wound and specific postoperative care is given along individual institutional custom.

**Orientating specimen for pathological examination**

To maximize the yield from pathology services, the authors recommend three important strategies: ensure high quality clinical information about the patient is communicated, identify if any special information is required from the pathological examination and orientate the resection specimen for the pathologist. Broadly, two techniques are used for orientation. The specimen can be pinned on to a cork or polystyrene blocks, with coloured pins used to identify the levels (Figure 36.12). An alternative recommended for SNDs is for the surgeon to separate the node groups, mark the
superior margin of each group with a suture and place each group in a separately labelled container. Surgically important margins may be marked with Indian ink or an appropriate dye. Where feasible, it is desirable to supplement this with a photograph of the specimen.

**Postoperative management and complications of SND**

The postoperative care of selective neck dissections does not differ from radical neck dissections. Complications are described in Chapter 11, Complications and their management.

**Neck dissection as part of a combined surgical procedure: site of desired continuity between the specimens**

A neck dissection is often part of a combined surgical procedure in which the primary tumour is also resected. It is preferable, but not mandatory, that continuity is preserved between the two specimens. Despite the widespread practice of not preserving continuity, there exists no evidence of adverse effect.

- **Oral cancer.** Oral lymphatic drainage is to the submental, submandibular and upper deep cervical lymph nodes of levels I, II and III. Continuity between the dissection specimens can be maintained along the lower border of the mandible, ensuring that the inner layer of periosteum is included.
- **Oropharyngeal cancer.** Oropharyngeal lymphatic drainage is primarily to the upper cervical lymph nodes of levels II, II and IV. Continuity between the dissection specimens can be maintained with the tissue lying medial to the corner of the mandible and oropharynx.
- **Laryngeal cancer.** The neck dissection specimen is left attached to the whole length of the larynx in a total laryngectomy, thus including the superior and inferior laryngeal lymphatic pedicles, and including lymphatic drainage regions of levels II, III, IV and VI. In a supraglottic laryngectomy, the neck dissection specimen is left attached at the thyrohyoid membrane.

**KEY EVIDENCE**

- Neck dissection is a key procedure in the head and neck surgeon’s repertoire, with diagnostic, therapeutic and prognostic roles.
- Neck dissection in its various forms, with or without adjuvant (chemo)radiation continues to be an effective therapeutic procedure to achieve regional disease control.
- The evidence base behind the practice of less extensive neck dissections in the present day, with no reduction in oncologic efficacy, falls into two broad groups: (1) greater understanding of lymphatic drainage pathways and (2) meticulous correlation of the neck levels containing metastatic deposits for various primary sites with anatomical and functional imaging findings.
- Less extensive neck dissections are associated with improved quality of life.
- Surgical expertise should evolve concurrently with the changing evidence base, which behoves the surgeon to keep abreast of the literature and thus ensuring optimal outcomes.

**KEY LEARNING POINTS**

- The neck dissection operation as practised today is vastly different to what was performed even a decade ago. Five level neck dissections, which used to be the standard operation, are now increasingly being replaced by less extensive procedures.
- A thorough knowledge of three-dimensional anatomy is necessary, especially when performing less radical procedures on necks with post-radiation scarring.
- Cross-sectional anatomical and functional imaging prior to neck dissection should enable precise surgical planning.
- Factors that determine the type of neck dissection include primary site, presence of clinical or radiological neck disease, location of neck metastases and the primary treatment modality.
- Careful attention to technique and preservation of non-lymphatic structures where feasible, will minimize complications and maximize functional outcomes.
Neck dissection following chemoradiation, especially performed well after fibrosis has set in, can prove to be a challenging operation.

REFERENCES


INTRODUCTION

Salivary glands are a common source of benign pathology. In contrast, salivary carcinoma is uncommon. However, salivary neoplasms possess some features which make them unlike any other head and neck neoplasm. In the first instance, there is a multiplicity of tumour types, many of which are characterized by a variable and diverse histological appearance. Thus, distinction between tumour types, including the distinction between benign and malignant, may be very difficult on the basis of fine needle aspiration (FNA) or small biopsies. Second, the most common benign tumour (pleomorphic adenoma) has a premalignant potential, which is unique in the head and neck. Third, many salivary malignancies are characterized by an indolent growth pattern, but with a high tendency to recur locally or give rise to distant metastases. Such recurrences may appear after many years of apparent disease-free survival. Thus, a thorough understanding of the nature of salivary neoplasms is essential to the head and neck surgeon.

SURGICAL ANATOMY

Parotid glands

The parotid glands are paired glands situated on either side of the face, between the ear and the ramus of the mandible. Superiortly, the gland extends above the level of the external auditory canal, up to the temporomandibular joint. Anteriorly, it extends superficial to the masseter muscle. In around 20 per cent of individuals, a portion of the gland (the 'accessory' lobe) may be separate from the main gland, over the masseter muscle, in proximity to the parotid duct. The bulk of the gland (the 'tail') extends inferiorly, between the mandible and the upper part of the sternomastoid muscle. There may be an extension of the gland deep to the mandible (the 'pterygoid' process) (Figure 37.1).

The parotid gland is surrounded by a thick capsule derived from the investing layer of deep cervical fascia. Histologically, it is composed of serous secretory units (acini), which drain into intercalated (terminal) ducts. The intercalated ducts converge to form striated (intralobular) ducts, which in turn converge to form secretory (interlobular) ducts, found within connective tissue septae. Secretory ducts empty into the main parotid duct.

The main trunk of the facial nerve enters the posterior surface of the gland and quickly bifurcates into upper and lower divisions. These in turn split into further branches. The pattern of branches is variable. As a general rule, the upper division gives rise to frontal, zygomatic and upper buccal branches; and the lower division gives rise to lower buccal, marginal mandibular and cervical branches. The upper division branches tend to be thicker and more resilient than the lower division branches, and take a more superficial course through the gland before exiting. The lower division branches are thinner and more delicate, and take a deeper course. Neuropraxia after surgical manipulation is seen particularly with the lower division branches. The most
important branches of the facial nerve are the zygomatic and marginal mandibular branches, injury to which leads to considerable functional and cosmetic problems. The facial nerve and its branches arbitrarily define the superficial and deep lobes and of the parotid gland; however, it should be stressed that there is no histological demarcation between these two ‘lobes’ (Figure 37.2).

The facial nerve exits the skull base at the stylomastoid foramen. Several landmarks may help the surgeon identify the nerve at this point, prior to tracing its course through the gland. The posterior belly of the digastric arises from the digastric ridge just below the stylomastoid foramen, and at the same depth, and is probably the most useful landmark. The surgeon can safely deepen the plane of dissection until the level of the digastric muscle is reached, before looking for the nerve just superior to the muscle’s upper border. The tragal pointer is a deep cartilaginous landmark which is 1 cm superior to and 1 cm superficial to the nerve. The tympanomastoid suture line is easily palpable as a hard ridge deep to the cartilaginous portion of the external auditory canal. The facial nerve emerges a few millimeters deep to its outer edge. The styloid process lies deep to the nerve and so should not be used as a landmark. It should be noted that tumours of the parotid gland may displace the facial nerve inwards, outwards, superiorly, or inferiorly, depending on their location (Figure 37.3).

The greater auricular nerve courses superiorly over from the posterior border of the sternomastoid muscle towards the parotid gland. It is usually necessary to sacrifice this nerve when performing parotid surgery, leading to sensory deficit which is most noticeable over the earlobe. The posterior branch of the greater auricular nerve, which supplies the earlobe, may occasionally be preserved.

The tissues superficial to the parotid gland include skin, subcutaneous tissue and the greater auricular nerve. Occasional lymph nodes are also present. Lymph nodes are also found deep to the parotid fascia within the parotid parenchyma.

The retromandibular vein traverses the parotid gland deep to the facial nerve branches. It is frequently encountered in the inferior part of the gland, where, classically, the marginal mandibular and cervical branches cross directly over it. The terminal branches of the external carotid artery are deep to the retromandibular vein and are much less commonly encountered.

The deep lobe of the parotid gland extends medial to the level of the ramus of the mandible. The presence of the mandibular ramus constricts the gland at this point. Deep
The branches of the facial nerve, the submandibular fascia, the supramandibular lymph node. In order to avoid injury to the lower border of the mandible close to the facial artery and gland, also crossing superficial to the facial vein. The marginal mandibular and cervical branches of the facial nerve lie superficial to the submandibular fascia overlying the gland, also crossing superficial to the facial vein. The marginal mandibular nerve curves superiorly and crosses the lower border of the mandible close to the facial artery and the supramandibular lymph node. In order to avoid injury to the branches of the facial nerve, the submandibular fascia should be incised at the lower border of the gland, and dissection should proceed right on the gland, deep to the fascia.

The deep portion of the gland lies on the hyoglossus muscle. The lingual nerve passes anteriorly superior to the gland. The submandibular ganglion is connected to the lingual nerve and is related to the superior surface of the gland. Blood vessels are present between the gland and ganglion which require division during submandibular gland removal. The hypoglossal nerve, which is inferior to the deep portion of the gland, is usually not encountered during simple submandibular gland surgery. The submandibular duct (Wharton’s duct) extends forward from the deep portion of the gland, and courses beneath the floor of the mouth between the sublingual glands laterally, and the genioglossus muscle medially, to open at the submandibular papilla just lateral to the frenulum of the tongue. The sublingual glands are situated just beneath the floor of the mouth, closely related to the submandibular duct. The lingual nerve winds around the submandibular duct, lying first on its lateral, then inferior, then medial surfaces. The lingual nerve supplies somatic sensation to the anterior two-thirds of the tongue. In addition, this nerve supplies secretomotor fibres to the submandibular and sublingual glands, as well as taste sensation from the tongue. The secretomotor and special sensory fibres derive from the facial nerve, and reach the lingual nerve via the chorda tympani nerve.

Minor salivary glands, numbering approximately 600–800 in any individual, are spread throughout the upper aerodigestive tract. The greatest concentration is in the hard palate.

### Submandibular/sublingual glands

The submandibular glands are paired structures situated medial to the posterior part of the body of the mandible. Each gland is composed of a large superficial and small deep part, which are continuous posteriorly around the posterior border of the mylohyoid muscle. The posterior belly of the digastric lies posterior to the gland. At the anterior border of the masseter muscle, it pierces the buccal fat pad and the buccinator muscle. It then courses between the buccinator and buccal mucosa before opening opposite the upper second molar tooth. The intraoral course provides a valve-like mechanism preventing reflux.

Salivary gland tumours present a significant pathological challenge. The reasons for this are as follows: (1) the present classification includes a large number of different types of tumours, with the latest World Health Organization (WHO) classification including over 40 types; (2) many types of salivary tumours are characterized by marked morphological diversity, and thus can have overlapping morphological features, making these tumours very prone to diagnostic confusion; (3) salivary tumours are rare, with some of the subtypes extremely rare, so that most pathologists are likely to have limited experience with the rarer types; (4) rapid changes in nomenclature and classification of the various pathologies have occurred in recent years. Reclassification of tumours according to updated classifications may change the diagnosis in nearly one in three cases.

Approximately 70–90 per cent of salivary tumours are located in the parotid gland. The vast majority (85 per cent) of these are benign. Pleomorphic adenoma comprises 60–80 per cent of parotid neoplasms. Warthin’s tumour (adenolymphoma) is the next most common benign lesion. The most common malignant parotid tumour is mucoepidermoid carcinoma (21–26 per cent), followed by carcinoma ex pleomorphic adenoma (5–18 per cent) and acinic cell...
carcinoma (9–24 per cent), and adenocarcinoma not otherwise specified (NOS) (11–15 per cent).5–7,8 Adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma are rare in the parotid gland. Of note, the parotid gland is a common site for metastases from squamous cell carcinomas and malignant melanomas arising in the skin of the head and neck, particularly from the region of the temple. In Australia, such metastases typically outnumber primary parotid cancers.9

Submandibular gland tumours are much less common than parotid tumours (4–11 per cent of total).1,3,5–7 Roughly half are benign pleomorphic adenomas. Most of the remainder are malignant.1 Adenoid cystic carcinoma is the most common malignancy. Carcinoma ex pleomorphic adenoma, mucoepidermoid carcinoma, non-Hodgkin’s lymphoma and squamous cell carcinoma are also reported.5,9

Just over half (56–58 per cent) of intraoral salivary tumours are benign, most of these being pleomorphic adenomas (59–71 per cent).1,10,11,12,13 Canaliculr adenoma is the next most common benign tumour.10,13 The most common malignant tumours are mucoepidermoid carcinoma (47–52 per cent), followed by adenoid cystic carcinoma (14–23 per cent) and polymorphous low-grade adenocarcinoma (12–19 per cent).14–16 The most common site for intraoral minor salivary tumours is the palate (33 per cent),11,12,13 followed by the upper lip (20 per cent) and buccal mucosa (17 per cent).17 Most neoplasms of the upper lip are benign; in contrast, those on the lower lip, floor of mouth, lower gingiva, retromolar area and tongue are more likely to be malignant.1,10,11,13 Minor salivary tumours are more common in females,10,11,12 except for adenoid cystic carcinoma, which has an equal sex predilection.10,13

Tumours of the sublingual gland are rare. Most are malignant with adenoid cystic carcinoma being the most commonly reported.5,14

**BENIGN TUMOURS**

**Pleomorphic adenoma**

Pleomorphic adenoma is by far the most common salivary tumour. It occurs in patients of all ages, with the highest incidence reported in the fourth to fifth decades. Both sexes are affected equally. Of those arising in the parotid gland, 80 per cent are located in the superficial lobe in the tail of the gland; however they are also seen in the deep lobe, the parotid duct, and anteriorly over the masseter muscle.

Histologically, the tumour is characterized by marked morphological diversity, with glandular areas, myxomatous areas, and solid areas seen. Seifert et al.15 classified these tumours into cellular types (27–35 per cent), myxoid (stroma-rich) type (35–51 per cent) and the classic type (14–37 per cent), where there is a balanced amount of epithelial and myoepithelial cells and stroma component.16,17 A capsule is usually present around the tumour, however, this capsule is usually focally thin or absent, particularly with the myxoid subtype.16,17,18 and with larger tumours.18 In 24–28 per cent of cases, projections of tumour through dehiscences in the capsule are present which are in continuity with the main tumour.16,17,19,20 It is because of these projections that the recurrence rate after enucleation (21–45 per cent over 30 years21,22,23,24,25,26) is so high.20,27 On the other hand, when the tumour removal includes a cuff of surrounding parotid tissue, recurrence rates are typically less than 2 per cent.20,28,29,30 Incomplete capsules with tumour cells immediately next to the mucosa are also reported in intraoral pleomorphic adenomas, suggesting that the overlying mucosa should always be removed during complete excision of these tumours.13

Parotid pleomorphic adenomas usually present as slow-growing, painless tumours. Facial nerve palsy is never seen in benign cases. However, left untreated, up to 5 per cent may become malignant (carcinoma ex pleomorphic adenomas, also known as malignant mixed tumour). For this reason, surgical excision is always to be advised.

**Warthin’s tumour (adenolymphoma)**

Warthin’s tumour (adenolymphoma) is the second most common benign parotid tumour. It occurs almost exclusively in the tail of the parotid gland. Multifocal (20–23 per cent) or bilateral (6–10 per cent) tumours are often seen.31,32 It is far more common in males than females (M:F ratio, 7:1), with an average age at presentation of 70 years. It is reported to be more common in smokers.33

Histologically, it is composed of tall columnar epithelium with glands and papillae with a stroma of abundant lymphoid tissue with germinal centres. Cysts containing mucoid fluid are typically present.

Warthin’s tumours are generally slow-growing, however, the abundant lymphoid tissue in these tumours is susceptible to acute inflammation. Such inflammation may be precipitated by an upper respiratory infection. This may lead to marked swelling, tenderness and even ulceration of the tumour(s). On palpation, they generally have a soft or fluctuant consistency, but may also be firm depending on the extent of previous inflammation. The presence of multilobulated or multifocal tumours on palpation or imaging is suggestive of Warthin’s tumour.

The usual treatment of Warthin’s tumours is simple excision via partial superficial parotidectomy.34 Unlike pleomorphic adenoma, Warthin’s tumours do not have any premalignant potential. Thus, in elderly males with significant medical comorbidities presenting with parotid lumps, with a cytological diagnosis of Warthin’s tumour on fine needle aspiration, observation alone is reasonable management.

**Other benign tumours**

Oncocytomas are benign tumours composed of large eosinophilic cells with mitochondria. They are usually found in the superficial lobe of the parotid gland. Males and females are equally affected with most patients aged over 50 years.

Monomorphic adenoma is a term which was used in the past to lump all apparently benign lesions which were morphologically homogenous, but that did not meet the criteria for pleomorphic adenoma. These lesions are now reclassified into such entities as canalicular adenoma, basal cell adenoma and myoepithelioma.3 The term ‘monomorphic adenoma’ is not used in the most recent WHO classification.
MALIGNANT TUMOURS

Mucoepidermoid carcinoma

Mucoepidermoid carcinoma is the most common salivary malignancy in most series, accounting for roughly 45 per cent of cases. Between 50 and 70 per cent arise in the parotid gland, 15–35 per cent in oral cavity minor salivary glands and 6–11 per cent in the submandibular glands.34 Patients of all ages and both sexes are affected. Mucoepidermoid carcinomas account for the vast majority of salivary carcinomas in children.35, 36

Histologically, the tumour is composed of three cell types: epidermoid cells, mucous cells and intermediate cells. Mucus secreted by the mucous cells accounts for the tumour’s partly cystic structure. On the basis of the histological features, these tumours may be divided into high, intermediate and low grade. This grading is based loosely on the prevalence of cell types and cystic areas, and on features of aggressiveness or cytological atypia, but has mostly been subjective.4, 37 Recently, numerical scoring systems have been devised in an effort to make the grading more objective, however, these schemes are still prone to interobserver error. There is good evidence that grading of mucoepidermoid carcinoma does have prognostic significance. Brandwein et al.38 reported that low-grade tumours never metastasized, and that 100 per cent of patients were disease-free at ten years, compared to 70 per cent of patients with intermediate-grade, and less than 40 per cent of patients with high-grade tumours. Other series have reported metastasis and death to occur in a higher proportion of patients with low-grade tumours;37 it is possible that much of this variance is due to differences in the criteria used to grade the tumours. On the other hand, Spiro et al.39, 40 believed tumour stage to be a much better indicator of prognosis than grade. Other authors also report tumour size and stage to be an important prognostic factor.37, 38, 41 At ten years, over 90 per cent of patients with stage I and II disease are tumour-free, compared to less than 30 per cent with stage III or IV disease.38

Mucoepidermoid carcinoma generally has an indolent natural history, however, high-grade tumours may grow rapidly and give rise to pain and local symptoms. It shows a propensity to metastasize to regional lymph nodes; this occurs in 30–50 per cent of patients with high-grade tumours.

Adenoid cystic carcinoma

Adenoid cystic carcinoma comprises around 30 per cent of salivary malignancies. Most (60 per cent) arise in minor salivary glands. Between 25 and 33 per cent arise in the parotid gland, however, it comprise a small proportion of parotid gland neoplasms.42, 43, 44 Three histological patterns of adenoid cystic carcinoma are recognized: (1) cribriform, or Swiss-cheese pattern, which is the most common; (2) tubular, the next most common; and (3) solid, which occurs in around 21 per cent of cases, and has the worst prognosis. Histological grading of adenoid cystic carcinoma has some prognostic value,45 however, the significance of this has been contested.45, 46 On the other hand, Spiro and others have shown clinical stage to be the most important prognostic factor.43, 46, 47

Adenoid cystic carcinoma generally presents as a slow-growing mass. This tumour has a marked propensity for neural invasion, which occurs in up to 50 per cent of cases.44 Thus, symptoms of pain and facial palsy are common. Skip metastases may be seen along nerves. The presence of facial palsy or perineural invasion of large (named) nerves is a well-established adverse prognostic factor.44, 48, 49, 50 Adenoid cystic carcinoma also has a propensity for spread along Haversian canals of bone, often with little apparent bony erosion. Lymph node metastases are rare.51 Local recurrences are common (30–50 per cent of cases), even after clear surgical margins and many years of disease-free status. Distant metastases occur in around 24–39 per cent of patients within ten years, with the lung being the most common site.43, 44, 49

The usual treatment for adenoid cystic carcinoma is surgery with postoperative radiotherapy. This cancer has a very indolent natural history, and patients may survive with disease for many years, however, they are rarely cured. The five-year survival rate is around 72 per cent, with 15-year survival rate around 34 per cent. Even with pulmonary metastases, patients may live up to five years and even longer.43

Carcinoma ex pleomorphic adenoma (malignant mixed tumour)

Carcinoma ex pleomorphic adenoma, or malignant mixed tumour, is the second most common parotid malignancy. The risk of developing carcinoma ex pleomorphic adenoma is estimated at around 5–6 per cent over 20 years. Patients are typically 10–20 years older than those with benign pleomorphic adenoma.51 Tumours are typically larger and of longer duration than their benign counterparts.51, 52 Pain and facial nerve paresis may also be present.53 It is an aggressive cancer.53 Currently it is generally recognized that there is a progression of benign to malignant change in pleomorphic adenoma, however, to date, no histological features have been identified which are predictive of malignant transformation. The risk of malignant transformation would appear to be higher in tumours of the submandibular gland compared to the parotid gland.51, 52 Three variants are recognized:

1. Carcinoma in pleomorphic adenoma. This is the most common form. The malignant component is usually either a salivary duct carcinoma or adenocarcinoma, and the metastases contain only carcinoma.
2. True malignant mixed tumour (carinosarcoma), in which the malignant components are both carcinoma and sarcoma, and the metastases contain both elements.
3. Metastasizing pleomorphic adenoma. The rarest variety, in which both the primary tumour and metastases consist only of structures typical of benign pleomorphic adenoma.

It has been suggested that the number of carcinoma ex pleomorphic adenomas encountered depends to a large extent on the diligence of the pathologist in searching for areas of residual pleomorphic adenoma in parotid cancers.
By the time of surgical removal, the carcinoma typically makes up more than half of the tumour mass. The malignant component most commonly consists of adenocarcinoma NOS or salivary duct carcinoma. Epithelial-myoepithelial carcinoma, adenoid cystic carcinoma, adenosquamous carcinoma and undifferentiated carcinoma have also been reported. The pathology is usually high grade.

Cervical metastases are common. The depth of invasion beyond the mixed tumour capsule is a valuable guide to prognosis. More invasive tumours have a poor prognosis, even after the diagnosis of distant metastases. Lymph node involvement is common. Intraductal and minimally invasive (<5–8 mm) tumours generally do well. More invasive tumours have a poor prognosis, with high rates of local recurrence, distant metastases and death. Other adverse prognostic factors are large size, local extension, presence of cervical metastases, origin from major (as opposed to minor) salivary gland, high grade and carcinoma making up more than half of the tumour mass.

It has been suggested that pleomorphic adenoma recurrence and the use of postoperative radiotherapy to treat tumour spillage may be factors in malignant transformation, however, there is little evidence to support these notions.

Acinic cell carcinoma

Acinic cell carcinoma is the third most common cancer of the parotid gland. The vast majority arise in the parotid gland. It is a slow-growing tumour, with a propensity for local recurrence and distant metastases, which may occur after many years of apparent disease-free survival. Like adenoid cystic carcinoma, patients may have prolonged survival even after the diagnosis of distant metastases. Lymph node metastases are uncommon. Five- and 15-year survival rates of 76–96 and 50–55 per cent have been reported. Rarely, the tumour may be multifocal or bilateral.

Polymorphous low-grade adenocarcinoma

This is a more recently described entity which is increasingly recognized. Recent reports suggest that in fact it is more common than adenoid cystic carcinoma, and is the third most common salivary neoplasm after pleomorphic adenoma and mucopidermoid carcinoma. It is almost predominantly a tumour of minor salivary glands, with 60 per cent arising on the palate, 20 per cent in the cheek, and 12 per cent in the upper lip. It is rare in the parotid gland.

Histologically, polymorphous low-grade adenocarcinoma shows marked morphological diversity, but a striking cytological uniformity and bland nuclear morphology. It is thus easily confused with pleomorphic adenoma or adenoid cystic carcinoma on small biopsies. Examination of the entire tumour shows the characteristic infiltrative growth pattern. Like adenoid cystic carcinoma, it has a propensity for perineural invasion. Most cases show an indolent natural course.

Although polymorphous low-grade carcinoma has traditionally been considered to be a low-grade tumour, it does not always behave in a low-grade fashion. In fact, this tumour would appear to have a very unpredictable behaviour, with up to 15 per cent of patients reported to develop cervical metastases and 12.5 per cent dying from disease. Local recurrences may develop as late as 15 years after treatment of the primary site with negative pathological margins.

Salivary ductal carcinoma

Salivary ductal carcinoma is an aggressive malignancy which is believed to arise from the excretory duct. It most frequently arises in the parotid gland. Neural invasion and extra-glandular extension are commonly seen. Most patients die within three years.

Epithelial–myoepithelial carcinoma

This a rare tumour composed of both epithelial and myoepithelial cells. It is found predominantly in the parotid (77 per cent) and submandibular (10 per cent) glands. It is generally considered to be a low-grade neoplasm, however, aggressive and lethal cases have been reported.

Basal cell adenocarcinoma

This is a low-grade malignancy which is usually found in the parotid gland. It is generally considered to be low-grade with a good prognosis.

Papillary cystadenocarcinoma

This is a low-grade malignancy which may occur in either major (65 per cent) or minor (35 per cent) salivary glands. It has an indolent behaviour.

Adenocarcinoma NOS

The term ‘adenocarcinoma NOS’ is used to encompass a variety of neoplasms recognized as being of salivary origin, but lacking sufficient histological features to place them into any of the named subcategories. Thus it represents a heterogenous group of tumours. The relative frequency of adenocarcinoma NOS varies between different series. They are generally considered to be aggressive tumours with a propensity for perineural invasion and lymph node metastases.

Squamous cell carcinoma

Most squamous cell carcinomas to the parotid are metastases from skin squamous cell carcinomas. Occasionally, no primary site may be found. It is unknown whether or not such cases represent true primary parotid squamous carcinomas. Concomitant cervical nodal disease and cervical nodal conversion are common, thus surgical therapy should always include a neck dissection, even in clinically N0 necks.

Lymphoma

Non-Hodgkin’s lymphomas may develop in intraparotid lymph nodes. The risk of lymphoma is increased in patients with Sjogren’s syndrome. On fine needle aspiration cytology, parotid lymphomas are frequently confused with Warthin’s
tumour or benign reactive intraparotid lymph nodes. Flow cytometry immunophenotyping may be useful in distinguishing these lesions. In many cases, open or core biopsy is necessary to arrive at the correct diagnosis. Rarely, high-grade lymphomas may masquerade as parotid abscesses. Diagnosis in these cases can be extremely difficult due to the abundance of necrotic tissue and paucity of representative tumour cells.

**STAGING**

The T-staging for parotid carcinomas is given in Table 37.1. The N-staging and stage grouping are identical to that for the larynx.

**HISTORY AND EXAMINATION**

The usual presentation of a parotid tumour is a painless mass within the parotid gland. Tumours in the tail of the parotid may appear quite low in the neck, particularly in older patients, and so may easily be confused with enlarged upper deep cervical lymph nodes. Benign tumours are usually slow-growing and so have a long history, however, rapid enlargement and even ulceration may occur in Warthin’s tumours secondary to acute inflammation of the lymphoid tissue. Pain is unusual in benign tumours and usually indicates an acute inflammatory pathology or a malignant tumour.

Parotid swellings usually have limited mobility because of the dense fascia surrounding the gland, however, tumours low down in the tail of the parotid may be reasonably mobile. On the other hand, marked immobility suggests location in the deep lobe.

The overlying skin should be examined to rule out cellulitis (suggestive of an acute inflammatory process) or skin fixation (suggestive of malignancy). In addition, careful attention should be paid to the remainder of the parotid gland, as well as the contralateral parotid gland to rule out multiple or bilateral lesions. Bilateral parotid swellings most commonly occur in patients with Warthin’s tumours, HIV-related lymphoepithelial cysts, Sjogren’s syndrome or sarcoidosis. The remainder of the neck should be checked for lymphadenopathy. Examination of all five main branches of the facial nerve is an integral part of the examination and should be performed in all cases. In addition, intraoral examination should be performed to check for swelling of the parapharyngeal space (usually manifest by medial deviation of the tonsil or a bulge in the lateral wall of the oropharynx) or any abnormality in the region of Stenson’s duct (situated opposite the upper second molar). Of note, deep lobe parotid tumours may be completely asymptomatic and be an incidental finding on routine head and neck examination or imaging.

There are certain features that are highly suggestive of malignancy and so should be checked for in every patient with a parotid swelling. These are pain, rapid growth, facial palsy, skin fixation and cervical lymphadenopathy.

Occasionally, parotid tumours may present with facial weakness without any noticeable parotid swelling. It should be remembered that facial weakness which is insidious in onset, recurrent, associated with twitching or synkinesis, or isolated to only some branches of the facial nerve, is usually a sign of malignancy, and should prompt imaging of the parotid gland.

**INVESTIGATIONS**

**Imaging**

The use of routine imaging in the investigation of parotid lumps is controversial. In cases of small, mobile, well-circumscribed lumps within the tail of the parotid, it can be argued that imaging is unlikely to add any further information that will influence management. Imaging is obviously more useful in patients with fat necks where examination of the parotid is difficult. Imaging can help confirm that the lump is definitely located within the parotid gland. In addition, by demonstrating the relationship between the lump and the retromandibular vein, it can help determine whether the lump is located in the superficial or deep lobe. Imaging is definitely helpful in large tumours or with suspected malignancy, for better evaluation of the tumour’s third dimension and relationship to the surrounding structures. Imaging may also detect other features suggestive of malignancy (e.g. central necrosis, infiltration of adjacent structures), as well as the presence of suspicious cervical lymphadenopathy. Imaging is also important in cases of deep lobe tumours.

Both computed tomography (CT) and magnetic resonance imaging (MRI) may be used. MRI affords better definition between the tumour and surrounding parotid tissue.

**Fine needle aspiration cytology**

Fine needle aspiration of parotid masses is a commonly performed procedure. It has been shown to be safe and does not cause tumour spread along the needle tract. However, cytological diagnosis of salivary aspirates is far from straightforward. The reasons for this are as follows: (1) There is an enormous number and diversity of salivary tumours. (2) Most salivary tumours are uncommon, thus most pathologists will have limited experience with the rarer types.
(3) Many of the salivary tumours display marked morphological diversity, and many very distinct tumours show overlapping morphological features. (4) Many salivary carcinomas are cytologically bland with little evidence of mitotic activity or cellular pleomorphism. Tumour invasion as a defining feature of malignancy is beyond the recognition of cytology. Because of this, distinguishing between different parotid tumours, including the distinction between benign and malignant, can be very difficult. In particular, such disparate tumours as pleomorphic adenoma, adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma may display such markedly variable and similar features that differentiation in some cases may be near impossible.68

Proponents of fine needle aspiration cytology argue that it has a high accuracy rate (80–98 per cent). However, it should be borne in mind that reports of the accuracy of parotid aspirates may be misleading. This is because most parotid lumps are pleomorphic adenomas; hence, as long as most aspirates are reported as being consistent with this diagnosis, then the specificity and sensitivity for the diagnosis of pleomorphic adenoma is always going to be quite high. On the other hand, fine needle aspiration cytology may fail to diagnose a sizeable proportion of malignancies.69,70 A review of data from the College of American Pathologists Interlaboratory Comparison Program reported 32 per cent of malignant salivary lesions to be falsely reported as benign. The highest false-negative rates were for lymphoma (57 per cent), acinic cell carcinoma (49 per cent), low-grade mucoepidermoid carcinoma (43 per cent) and adenoid cystic carcinoma (33 per cent). For benign lesions, the ‘true negative’ rate (i.e. the proportion of cases correctly diagnosed as benign) was 91 per cent.71

A common scenario in practice is an aspirate being reported as consistent with pleomorphic adenoma, but ‘suspicious’ and/or not able to rule out adenoid cystic carcinoma or other malignancy. In reality, most of these cases will transpire to be pleomorphic adenomas, so this type of report does not necessarily help the surgeon greatly.

A further argument against the use of fine needle aspiration cytology is that, in the vast majority of cases, parotid lumps will require surgical excision, and fine needle aspiration will not change that management. Certainly, surgical excision should be recommended in all cases of malignant parotid tumours, as well as in pleomorphic adenomas, given the risk of carcinoma ex pleomorphic adenoma in untreated cases. However, there are exceptions to the above dictum. In elderly males, who have multiple medical problems and so are not good candidates for general anaesthesia, a cytological diagnosis of Warthin’s tumour may obviate the need for surgery, as this pathology does not have any premalignant potential. Cytology may also obviate the need for surgery in granulomatous disorders. In clinically indeterminate salivary lesions, cytology may help in distinguishing between salivary and non-salivary pathology. Finally, a cytological report which is highly suggestive of malignancy may allow the patient to be counselled preoperatively on the possibility of sacrifice of a branch of the facial nerve.

It is important for the surgeon to be aware of the most commonly confused diagnoses. The confusion between pleomorphic adenoma, adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma is well recognized.71 In addition, Warthin’s tumours, lymphomas and benign or reactive intraparotid lymph nodes are frequently confused because of the abundant lymphoid stroma.71 Inflammatory and cystic conditions like chronic sialadenitis with squamous metaplasia, lymphoepithelial cysts and low-grade mucoepidermoid carcinoma may be difficult to distinguish cytologically. Acinic cell carcinoma, oncocytoma and Warthin’s tumour may be easily confused with normal parotid tissue.71

Open biopsy

As a general rule, open incisional biopsy of parotid lesions should be avoided, due to the risk of causing tumour implantation, particularly if the lesion is a pleomorphic adenoma, which is what the vast majority of parotid tumours will turn out to be. If fine needle aspiration cytology fails to yield a diagnosis, then the surgeon should proceed to superficial parotidectomy with in toto removal of the tumour. On the other hand, open biopsy may be appropriate in very superficial tumours, where fine needle aspiration cytology suggests lymphoma, in order to obtain more tissue to rule out a reactive process, and for classification of the lymphoma type; or in the case of extensive tumours where cytology clearly shows malignancy. In such cases, biopsy may allow the tumour to be categorized, a metastatic process to be ruled out, and definitive treatment to be planned. In cases of diffuse salivary enlargement, incisional biopsy may be appropriate to diagnose Sjögren’s syndrome, sarcoidosis, or other granulomatous disorder, and to rule out lymphoma or other malignant process.

Incisional biopsy is the usual initial diagnostic procedure of choice in minor salivary gland tumours located on the palate. However, the surgeon should be aware that, similar to the case with fine needle aspiration cytology, differentiation between the three most common lesions (pleomorphic adenoma, adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma) can be very difficult on the basis of small biopsies.

Intraoperative frozen section

Intraoperative frozen section for salivary cancers as a diagnostic procedure is prone to the same difficulties as that
encountered in fine needle aspiration cytology, on account of the small sample size submitted to the pathologist. Studies have shown a similar overall accuracy for FNA and frozen section, however, it would appear that sensitivity of frozen section for malignancy (69–77 per cent) is slightly lower than that of FNA, while specificity (96–100 per cent) is higher. Frozen section is useful in determining the extent of tumour spread, including the presence and extent of invasion of the facial nerve, and the assessment of surgical margins. Frozen section as a diagnostic procedure may be useful when preoperative FNA is non-diagnostic, or when the FNA diagnosis is at odds with the clinical and/ or intraoperative findings. The results of frozen section may help in intraoperative decision-making. In cases where frozen section shows high-grade carcinoma, the surgeon may proceed to perform at least a limited neck dissection with the parotidectomy. It may also be helpful in deciding whether or not to proceed with facial nerve sacrifice in case of the unexpected finding of a tumour clinically infiltrating the facial nerve, as well as the extent of resection of other involved structures, e.g. skin or temporomandibular joint.

TREATMENT POLICY

### Pleomorphic adenoma

The vast majority of parotid tumours are pleomorphic adenomas, and the bulk of these are located in the superficial lobe of the gland. Simple enucleation of pleomorphic adenomas is not appropriate treatment as this leads to recurrence in 21–45 per cent of cases. These recurrences occur because of projections of tumour through dehiscences in the tumour capsule which are sheared off and left behind when simple enucleation is performed.

Because of the high recurrence rates for simple enucleation, the traditional treatment for these tumours has been superficial parotidectomy, with removal of all the parotid gland superficial to the facial nerve. More recently, partial superficial parotidectomy, with dissection of less than the full facial nerve, but with removal of a generous cuff all around the tumour, except where the tumour abuts the facial nerve, has become standard of care. Initially, a 2 cm margin was considered the minimum allowable for partial surgery. More recently, a 1 cm margin has been shown to be adequate. With the use of these techniques, when negative pathological margins are obtained, then recurrences should occur in less than 1 per cent of cases.

A common intraoperative finding with pleomorphic adenomas is that the deep surface of the tumour capsule directly abuts the branches of the facial nerve. Thus, in many cases, it is not possible to take a cuff of parotid tissue all around; rather, the surgeon has to dissect right on the tumour capsule in the vicinity of these branches. Thus, focal capsular exposure occurs in the vast majority of parotid operations, regardless of the technique used. However, this practice does not appear to lead to any increased risk of recurrence. Furthermore, in most cases of pleomorphic adenomas located in the deep lobe of the parotid gland, or in the parapharyngeal space, the operation performed to remove them is little better than enucleation. However, again this does not appear to increase the likelihood of recurrence. The reasons for the low recurrence rate despite the high incidences of capsule exposure are unclear. Suggested reasons include: more meticulous surgical technique which prevents separation of pseudopodia and the presence of pseudopodia predominantly on the superficial surface of the parotid gland. In the case of deep lobe tumours, it has been suggested that they have a more complete capsule and less tumour projections through the capsule. Of note, it has been found that although a significant incidence of recurrences is seen when tumour is present histologically at the margin of excision (17.6 per cent), recurrences are rare (<2 per cent) in the case of close (<1 mm) margins. These findings suggest that a margin of a fraction of a millimetre is adequate to prevent recurrence.

Recently, extracapsular dissection (ECD) has been proposed as a surgical treatment for pleomorphic adenoma. In this technique, a small cuff of normal parotid parenchyma just outside the tumour capsule is dissected. Careful attention is paid to the lobulations of the tumour and their relationship to the branches of the facial nerve. This is a technically demanding procedure which requires the tumour to be mobile and large enough to allow digital manipulation. The incidence of capsular exposure and positive margins is reported to be no different between ECD and superficial parotidectomy. Proponents of ECD have claimed reduced complication rates, particularly facial nerve neuropraxia and Frey's syndrome, with no increase in recurrence. On the other hand, others have reported this technique to be associated with an unacceptably high incidence of tumour spillage and tumour recurrence, despite short follow up and the use of postoperative radiotherapy in selected cases.

### Tumour spillage

Capsular rupture and tumour spillage has been associated with a two- to three-fold increased recurrence rate for pleomorphic adenoma; however, other authors have disputed this. In any case, great care should be taken intraoperatively not to penetrate the tumour and cause tumour spillage. Cutting into the tumour should be absolutely avoided. In cases where inadvertent tumour spillage does occur, the most appropriate treatment is probably to remove as much parotid tissue as possible without jeopardizing the branches of the facial nerve. At the conclusion of the case, the wound should be meticulously washed out. The use of postoperative radiotherapy in such cases has been advocated, however, there is no evidence that this is either necessary or beneficial.

### Recurrent pleomorphic adenoma

Recurrent pleomorphic adenoma is a difficult surgical challenge. Most patients (55–100 per cent) present with a multiplicity of nodules in the surgical bed, which are slow growing and often underestimated by palpation. The typical time lag after the initial surgery is between 5 and 12 years, but may be much longer. Facial paresis
may be due to previous surgery or scarring of the nerve, however, the possibility of carcinoma ex pleomorphic adenoma should always be considered in patients with new-onset facial weakness. Carcinoma has been reported in 6–17 per cent of such cases.93, 94

Revision surgery is difficult because of scarring and the multiplicity of nodules, the distorted anatomy, and the more superficial location of the facial nerve branches. In addition, tumour frequently involves the old scar, the facial subcutaneous tissues, the external auditory canal and middle ear, and may encase or involve the nerve.90, 91

In most cases, the treatment of recurrent pleomorphic adenoma is total parotidectomy with scar excision and preservation of the branches of facial nerve. It may be impossible to identify the main trunk of the facial nerve. In such cases, identification of the branches of the facial nerve in the neck and face with retrograde dissection may be necessary. Patients should be counselled regarding the significantly increased risk of transient or permanent facial weakness postoperatively. In cases with facial nerve involvement, frozen sections should be sent to check for carcinoma ex pleomorphic adenoma, and consideration should be given to nerve resection with or without nerve grafting.90, 91

An alternative approach in cases with multifocal recurrence, multiple previous recurrences and where there is little remaining normal parotid tissue is conservative ‘cosmetic’ enucleation, however, this is likely to lead to an increased recurrence rate.90

The incidence of re-recurrence after reoperation for recurrent pleomorphic adenoma varies from 8 to 52 per cent,88, 90, 91, 93, 95 but is much higher (32–52 per cent) in studies with longer periods of follow up.90, 93. The risk of re-recurrence has been suggested to be higher in cases of multinodular recurrence95 and lower in cases where the initial surgery was an enucleation (as opposed to a formal parotidectomy),88, 93 where the revision surgery is a total parotidectomy (as opposed to subtotal parotidectomy)91 and after facial nerve resection.91 The use of postoperative radiotherapy to decrease the probability of further recurrence has been suggested,88, 92, 95 however, there is little strong evidence that this has any major impact on recurrence or the probability of later malignant change. Of note is that even in cases where the facial nerve is successfully preserved, a significant proportion of patients are likely to have long-term weakness.90, 91, 93, 95

Malignancies

The mainstay of treatment for salivary carcinomas is surgical resection with or without postoperative radiotherapy. In the case of parotid malignancies, every effort should be made to preserve the facial nerve, particularly in cases where it is functioning preoperatively. In most cases, it is possible to find a plane of cleavage between the nerve and the tumour.

The goal of surgical treatment is to achieve local control. For early stage cancers, this usually equates to cure. On the other hand, a significant proportion of patients with advanced stage cancers will represent with distant metastases. There may be a lengthy time lag between surgical treatment of the primary site and development of distant metastases. The development of distant metastases is not prevented by either postoperative radiotherapy or by elective neck dissection. It may be that in some patients with advanced tumours, distant metastases are already present at a microscopic level at the time of initial treatment, but, because of the slow-growing nature of the tumour, they do not become clinically evident for many years. Indeed, in the case of adenoid cystic carcinoma, patients with established distant metastases may survive with disease for many years.83

This propensity to develop distant metastases, sometimes many years after apparently successful primary treatment, is a feature characteristic of nearly all salivary carcinomas. Failure in the neck, in contrast, is much less common. A propensity for cervical metastases is seen in some subtypes of salivary carcinoma (mucoepidermoid carcinoma, carcinoma ex pleomorphic adenoma, adenocarcinoma NOS); however, cervical metastases are uncommon with most of the other subtypes. Thus, although the presence of nodal metastases is a well-established adverse prognostic factor in salivary cancers, the benefits of elective treatment of the clinically negative neck are much more contentious.

Overall, most salivary carcinomas are slow growing and have an indolent natural history. However, they show a striking tendency for local recurrence and delayed development of distant metastases. Thus, reports of five-year survival may be misleading; and significant differences between five- and ten-year survival outcomes may be present. Furthermore, it has been suggested that patients with treated salivary cancer should undergo lifelong follow up.

Extent of surgery

The extent of surgery is dependent on the size and site of the tumour. The surgeon should endeavour to take a reasonable margin of normal tissue all around the tumour. In the case of tumours located in the superficial lobe, the deep surgical margin is determined by the plane of the branches of the facial nerve. Thus, most such cases will be treated by superficial parotidectomy with facial nerve preservation. Resecting part of the deep lobe for the sake of it in such cases does not make sense when the closest margin has been determined by the relationship of the tumour to the facial nerve. In addition, parotid malignancies are very rarely multifocal, and are very unlikely to metastasize to the deep lobe. In fact, for tumours less than 4 cm in size, it is likely that partial superficial parotidectomy is adequate treatment, provided that adequate horizontal margins are obtained.96 More extensive surgery is likely to increase the risk of facial nerve paralysis without improving local control.97

It should be noted that in cases where the tumour abuts or is adherent to one or more of the branches of the facial nerve, the final pathology report will typically state that the margin is close or involved. In such cases, the adequacy of surgical clearance is best judged by the surgeon.

Management of the facial nerve

As a general rule, every effort should be made to preserve a nerve which was functioning normally preoperatively. Facial nerve sacrifice should be reserved for cases of preoperative paralysis, cases of recurrent malignancy or of gross
encasement and infiltration of the nerve. Microscopic invasion of the facial nerve is generally not considered an indication for nerve sacrifice. Although this may improve local control, it will not improve survival. Furthermore, it is likely that the addition of postoperative radiotherapy will negate any benefit of nerve sacrifice on local control. An exception to this may be in cases of involvement of a single branch where sacrifice would not lead to unacceptable morbidity.

When facial nerve sacrifice is necessary, then the margins should be checked by frozen section. Immediate repair should be performed using the greater auricular nerve. This nerve is easily accessible, provides adequate length, diameter and arborization. Function may take up to two years to return. A reasonable objective is House-Brackman grade 3. In the case of the zygomatic branch, the optimum rehabilitation may be by means of a gold weight implant, as, unlike nerve repair, this allows for synchronized blinking.

**Neck dissection**

In cases of parotid carcinoma with clinically N+ necks, neck dissection should be performed at the time of parotidectomy. The management of the clinically N0 neck is more controversial. Arguments for performing an elective neck dissection include the following: (1) There is a high rate of occult metastases in high-grade mucoepidermoid carcinoma, carcinoma ex pleomorphic adenoma and adenocarcinoma. (2) Pathological examination of the submitted neck specimen provides prognostic information. (3) The upper neck levels are readily accessible by making a small extension to the standard parotidectomy incision, so that adding a selective neck dissection to the parotidectomy is associated with only a small amount of extra operating time and surgical morbidity.

On the other hand, opponents of elective neck dissection make the following arguments: (1) Cervical metastases are uncommon in adenoid cystic carcinoma, acinic cell carcinoma and many other types of salivary carcinoma. (2) Patients with locally advanced or high-grade cancers will require postoperative radiotherapy regardless, and the pathological information provided by a selective neck dissection will thus not change management, and that this should sterilize any occult disease in the clinically negative neck. (3) Patients with salivary carcinomas usually fail from distant metastases and not from regional disease.

Certain parotid tumours show a high nodal relapse rate in untreated necks. These tumours include T3 + mucoepidermoid carcinoma, carcinoma ex pleomorphic adenoma, adenocarcinoma NOS, squamous cell carcinoma and undifferentiated carcinoma. Thus, if neck dissection is not performed, patients should receive postoperative neck irradiation.

**Radiotherapy and adjunctive treatment**

In general, salivary gland carcinomas are not particularly radiosensitive, although this has been disputed. In a large series of previously untreated patients with salivary carcinoma, all treated with curative intent, those who were treated by radiotherapy alone had a significantly lower ten-year local control rate (42 per cent) compared to those treated by surgery with postoperative radiotherapy (90 per cent). Thus, the role of radiotherapy as primary treatment for salivary carcinomas is limited to unresectable tumours.

On the other hand, adjuvant radiotherapy in the postoperative setting may be useful in improving local control rates. Although there are no randomized data available which assess the efficacy of postoperative radiotherapy, several retrospective series have reported a higher local control rate in patients treated with postoperative radiotherapy compared to patients treated with surgery alone. Other series have not found any significant difference, however, it should be remembered that in most single-institution retrospective series, patients are selected to undergo postoperative radiotherapy on the basis of uncertainty over the completeness of resection, the status of margins, or other poor prognostic factors. Other authors have found improvements in local control for postoperative radiotherapy only in patients with stage III/IV disease (i.e. tumours greater than 4 cm, and/or with extraparenchymal spread and/or with nodal disease).

The effect of postoperative radiotherapy on survival is more controversial. Koul et al. found higher disease-specific survival in patients who received combined treatment. Other authors have failed to find any survival benefit, although a trend towards improved survival in patients with advanced stage tumours has been reported by some. However, given that patients with salivary carcinoma may survive for many years before dying from distant metastases, the addition of postoperative radiotherapy to improve local control may reduce morbidity and increase quality of life.

In general, postoperative radiotherapy is indicated for tumours greater than 4 cm, in the presence of positive surgical margins or in cases where the branches of the facial nerve were preserved despite being adherent to the tumour, and in cases with lymph node metastases. Other factors which may be relative indications for radiotherapy include histological grade, adenoid cystic carcinoma and perineural invasion. The histological grade of the tumour would appear to be less important than tumour stage in determining prognosis and need for postoperative radiotherapy; thus, it is controversial whether radiotherapy is indicated in cases of adenoid cystic carcinoma or high-grade mucoepidermoid carcinoma staged T1/T2, although some authors have claimed a benefit.

In patients with unresectable cancers, the use of neutron radiotherapy has been advocated. This modality has resulted in impressive local control rates. In a trial of 25 patients with unresectable salivary carcinomas randomized to receive either conventional or neutron radiotherapy, neutron radiotherapy was found to have superior ten-year locoregional control (56 versus 17 per cent), but no improvement in survival (15 versus 25 per cent). Most patients treated with neutron radiotherapy developed distant metastases, whereas most patients treated with conventional radiotherapy developed local recurrence. A much higher incidence of severe complications was also seen in the neutron treatment group.

The key to improving long-term survival in patients with salivary cancer would appear to be systemic treatment aimed at reducing the incidence of distant disease. However, to
date, salivary carcinomas have shown poor response rates to combination chemotherapy and molecular therapies.

**Unexpected report of malignancy**

Occasionally, after having performed a superficial parotidectomy where the preoperative diagnosis was pleomorphic adenoma, the pathology is unexpectedly reported as showing parotid carcinoma. This presents the surgeon with a difficult dilemma. The options for the patient at this point are observation alone, referral for postoperative radiotherapy or reoperation with performance of subtotal parotidectomy with or without subsequent postoperative radiation. The correct option will vary from case to case. Factors to be considered include the type of cancer, the size of the cancer, the histological grade, the surgeon’s confidence in having cleared the tumour during the original operation, and the pathological margin status. For tumours which are small, low-grade and where the surgeon feels confident with the clearance, then observation alone may be adequate. On the other hand, large, high-grade tumours will usually warrant a more aggressive approach. Adding to the dilemma is that margins are frequently reported as close or positive on account of having dissected right on the capsule of the tumour in the vicinity of the branches of the facial nerve.

**Recurrent malignancies**

Recurrent salivary cancers usually warrant aggressive surgical therapy, consisting of wide resection of the tumour. More often than not this involves radical parotidectomy with sacrifice of the facial nerve and resection of overlying skin.

**SURGICAL TECHNIQUE**

**Surgical technique of superficial parotidectomy**

**PREPARATION**

Many surgeons use intraoperative facial nerve monitoring. Intraoperative nerve monitoring may be particularly useful for patients with large and/or malignant tumours, patients undergoing revision surgery, cases where retrograde dissection of the facial nerve may be required, and for less experienced surgeons. The facial nerve monitor should be applied and testing prior to prepping and draping the patient.

**INCISION**

An incision should be carefully marked out extending from the preauricular region, around the lobule of the ear towards the mastoid tip, and then curving back down to join a neck crease, well below the angle of the mandible. If a preauricular crease is present, this should be used. Otherwise the incision may be hidden behind the tragus. (Figure 37.5).

Prior to making the incision, it is very useful to make a single crosshatch in the region of the lobule. When making the incision, it is important not to bevel the blade in the postauricular region, as this may compromise the skin in this region.

**FLAPS**

In the face, the anterior skin flap should be raised superficial to the parotid fascia, leaving subcutaneous fat on the flap. It is very easy to buttonhole this flap. If the surgeon sees hair follicles, he is probably getting too superficial. Strong traction and countertraction, with the countertraction being applied as far into the wound as possible, is very helpful in defining the plane. Alternatively, dissecting scissors may be used to open the plane and then cut the intervening fibres.

In the neck, the flap may be raised either superficial or immediately deep to the platysma. A ‘white line’ which defines the plane the surgeon needs to be in is usually apparent between these facial and neck planes.

When raising the flap, it is of utmost importance that the surgeon keeps palpating the tumour and does not inadvertently enter it.

Posteriorly, the neck part of the incision should be deepened to the sternomastoid muscle. The greater auricular nerve can be seen. This is usually sacrificed, leading to some permanent numbness of the ear lobe, although the posterior branch, which supplies the earlobe, may frequently be preserved. The anterior border of the sternomastoid should be defined and followed up to the mastoid tip. The fascia should be raised anteriorly off the sternomastoid muscle. In doing so, the surgeon should stay behind any posterior extension of the parotid gland or the tumour. The surgeon should also be aware of the proximity of the accessory nerve while dissecting on the medial surface of the sternomastoid muscle. The deep cervical fascia should then be incised to display the posterior belly of the digastric muscle, which is an important landmark.

In the region of the ear, the incision should be deepened along the cartilage of the external auditory canal, taking care not to damage this cartilage. As long as the surgeon stays right on the external auditory canal, the incision can be safely deepened all the way to the bony-cartilaginous junction.
The surgeon should look out for the ‘tragal pointer’, which is another useful landmark for the facial nerve.

At this point, the surgeon should divide the tissue anterior to the mastoid process in order to join the dissection in the region of the external auditory canal to that in the region of the sternomastoid muscle. The depth of this should remain superficial to the digastric muscle. There are many blood vessels around the mastoid which will require appropriate control.

**LOCATING THE FACIAL NERVE**

The facial nerve emerges from the stylomastoid foramen just superior to the posterior belly of the digastic muscle, at the same depth as this muscle. The tragal pointer is 1 cm superficial and above this point. The styloid process is medial to the facial nerve so is not a good landmark. The direction of the nerve is anterior, superficial and inferior (Figure 37.3).

Prior to looking for the facial nerve, the posterior belly of the digastic and tragal pointer should be well defined, and the surgeon should have opened a broad plane of dissection, so that he is not working down a narrow ‘hole’. The surgeon should then proceed to look for the nerve using an Adson clamp or artery forceps. This may be opened gently in a direction parallel to the nerve to avoid causing inadvertent damage. Surgeons should thus note that from this standpoint, the nerve is coming towards them. There are usually many fibrous strands in the region of the nerve which will need to be divided in order to find the nerve. In addition, there are usually some blood vessels just superficial to the nerve which, if injured, will cause troublesome bleeding which will make identification of the nerve difficult. It is best to divide these blood vessels after cauterizing them using bipolar diathermy, however, the surgeon must be certain that the facial nerve is not cauterized.

When there is difficulty finding the nerve, the surgeon should look a little more anterior and/or inferior, as often the problem is that the surgeon is too close to the external auditory canal.

Once the facial nerve is found, it should be followed to its bifurcation, prior to division of any parotid tissue.

**FOLLOWING THE BRANCHES**

The branches should be followed in sequence, starting either superiorly or inferiorly. A clamp should be inserted along the nerve, then lifted away from the nerve and opened. The assistant should then divide the parotid tissue between the tines of the clamp (insert – lift – spread – cut). Once inserted and opened, the clamp should not be closed without first withdrawing it. The surgeon should try to divide some tissue with every manoeuvre, otherwise little progress will be made. The surgeon should remember that as the branches are traced distally, they become more superficial, particularly the upper branches.

The dissection should commence over a branch which is clear of the tumour, and then proceed to the successive branches. In so doing, parotid tissue should be divided clear of the tumour. Once two branches have been followed, the intervening tissue at the anterior part of the gland is divided so that the superficial part of the gland containing the tumour can be peeled up or downwards. The surgeon may come towards the tumour both superiorly and inferiorly, so the superficial lobe is well mobilized by the time the tumour is approached.

For tumours located in either the upper or lower pole of the gland, it is not necessary to remove the whole of the superficial lobe. It may be possible to remove the tumour with an adequate cuff while following only either the upper or lower division branches.

Commonly, the deep part of the tumour capsule is applied directly onto the branches of the facial nerve. In this situation, the surgeon should carefully separate the tumour from the nerve, taking great care not to rupture the capsule. If this is done, there is no increased recurrence rate.

**CLOSURE**

Prior to closure, a drain should always be placed, as otherwise the wound will inevitably accumulate saliva and serous fluid. The drain should be ideally left for at least 48 hours. Closure is then performed according to surgeon’s preference.

**Difficult cases**

**DEEP LOBE TUMOURS**

For tumours situated in the deep lobe, the operation begins with a standard superficial parotidectomy, as described above. Having completed this, the branches of the facial nerve overlying the tumour are now easily visible. The branches overlying the tumour are then separated from the tumour and mobilized. The underlying tumour is then mobilized and separated from the deep tissue. This is usually accomplished and, although it usually results in the operation leading to little more than an enucleation, there does not appear to be an increased recurrence rate, similar to that seen if enucleation is performed for superficial lobe tumours. The tumour is then removed between two of the mobilized facial nerve branches. Not uncommonly, particularly in the buccal region, extensive arborization and communicating branches are present. In such cases, it may be necessary to sacrifice some of the minor communicating branches, although this should, if possible, be avoided.

**REVISION CASES**

Revision parotid surgery is one of the most difficult surgeries in head and neck. Usually, it will be necessary to resect the previous scar. Occasionally, skin resection will also be necessary and the surgeon should be prepared to reconstruct the defect. If the previous surgery comprised a formal superficial parotidectomy, then the branches of the facial nerve will be just beneath the skin flap, without any intervening parotid fascia, and so will be vulnerable to injury while raising the skin flap. Extending the previous incision, and identifying the correct plane in virgin tissue, may be a useful manoeuvre. Identification of the main trunk of the facial nerve may be difficult or impossible due to scarring. In such cases, it may be necessary to identify the branches of the facial nerve in the
Complications of parotid surgery

FACIAL NERVE INJURY

Facial nerve injury is usually the biggest concern in parotid surgery. Postoperative weakness may be temporary, if the injury is a neuropraxia, or permanent, due to transection of, or cautery injury to, the main trunk of the facial nerve, or, more commonly, one of the terminal branches. Temporary weakness is much more common and is seen in between 10 and 50 per cent of parotidectomies.28, 77 It occurs more commonly in difficult cases, i.e. large tumours, tumours located in the deep lobe, malignant cases and revision surgery. The precise cause of neuropraxia is not known, but probably results from a combination of trauma while dissecting right on the nerve, traction injury to the nerve, heat injury secondary to the use of cautery, and prolonged operating time. The lower division branches, in particular, the marginal mandibular branch, would appear to be particularly susceptible to neuropraxia. This is probably due to the thinner, more fragile nature of these branches. Neuropraxia usually recovers in a few weeks, but may take many months, particularly in elderly patients. The incidence of permanent facial nerve injury is generally reported as 0–5 per cent. 28, 30, 77

HAEMATOMA

Haematoma is reported to occur in up to 5 per cent of parotidectomies. As a general rule, small haematomas should be evacuated promptly, as their presence leads to compromise of the skin flap with possible necrosis.

SEROMA/SALIVOMA/SALIVARY FISTULA

After superficial parotidectomy, leakage of serous fluid and saliva from the transected parotid tissue is an expected occurrence. This usually lasts for a few days. Thus, a drain should always be placed after parotid surgery and left in place for at least 2–3 days. At this stage, the skin flap should have begun to adhere to the parotid bed, so obliterating the dead space in which fluid can accumulate.

If, after removing the drain, patients develop swelling underneath the wound, this should be aspirated. Seromas usually resolve within a few days of serial aspiration. In the case of salivary collections, drainage of saliva out of the drain site or through the wound when the patient is eating is not uncommon. Any collection should be aspirated. A pressure dressing, similar to the type used after otoplasty, may also be useful to speed resolution.

FREY'S SYNDROME

Frey’s syndrome, or gustatory sweating, is a phenomenon seen after parotid surgery where the patient develops sweating on the side of the face while eating. It is believed to be due to transection of cholinergic secretomotor fibres to the secretory units of the parotid gland, which subsequently sprout new axons and come to innervate sweat glands in the skin flap, which are also responsive to acetylcholine. It is reported that around 10 per cent of patients who undergo parotidectomy will complain of gustatory sweating, but that on questioning, 30–40 per cent will reply that they experience it, while it can be demonstrated objectively in 95 per cent of patients.119 Objective demonstration is possible using Minor’s starch-iodine test. This is performed by covering the affected skin with iodine solution. Once this has dried, it is dusted with starch powder, and the patient given a lemon sweet. As a result of absorption of the wet iodine by starch, the affected area will turn deep blue purple.119

Frey’s syndrome usually develops within weeks or months of surgery, but its onset may be delayed for several years.119, 120 It occurs more commonly with more extensive parotid surgeries. Several techniques for preventing Frey’s syndrome have been described. These include raising a thick skin flap,121 rotation of a superficial temporal artery-based temporoparietal vascular flap,122 rotation of the superficial musculoaponeurotic system (SMAS),123, 124, 125 and rotation of sternomastoid muscle flaps.125, 126 However, there are disadvantages to most of these techniques.119 In established cases, topical anticholinergics may be useful, but have variable efficacy and may lead to anticholinergic side effects.119, 120 For persistent cases, the most effective treatment would appear to be injection of botulinum type A toxin. This inhibits neurotransmitter release and gives long-lasting relief, and may be repeated if recurrent symptoms develop.127, 128

OTHER

Ear numbness is an expected outcome from parotid surgery. It results from transection of the greater auricular nerve. Occasionally, the posterior branch of the nerve can be preserved, which minimizes the sensory deficit. Patients are usually very aware of sensory change immediately after the surgery. Over the course of several months, the area of numbness diminishes, but patients are usually left with an area of persistent numbness around the ear lobe. Patients
who wear earrings will not be able to insert them without looking in a mirror, and should be advised not to wear clasp earrings.

Duskiness of the postauricular skin flap may occur if the flap is too large or the blade of the knife was bevelled while making the skin incision. This usually settles spontaneously. Occasionally, necrosis of the skin tip can occur; this will usually heal by secondary intention.

In patients with bulky parotids, a sizeable ‘hollow’ may be left on the side of the head after surgery, particularly after more extensive resections.

Variations in surgical techniques

STERNOMASTOID MUSCLE FLAP

Techniques involving rotation of sternomastoid muscle into the parotidectomy defect have been described in an effort to reconstruct the ‘hollow’ resulting from the removal of large amounts of parotid tissue. A superiorly based flap may be raised by dividing the sternomastoid around one-third of its thickness halfway down its anterior border and rotating it into the parotid bed in a fan-like manner. Alternatively, an inferiorly based flap may be used by dividing the upper end of the sternomastoid and rotating it into the defect. The rotated muscle may be sutured to the zygomatic arch and masseter muscle. Several authors have reported improved cosmetic appearance and a decreased incidence of Frey’s syndrome.

However, the efficacy of this technique is disputed: several authors have reported no difference in subjective assessment of facial appearance, or incidence of gustatory sweating between patients undergoing and not undergoing sternomastoid flap rotation. On the other hand, patients undergoing sternomastoid flap rotation show decreased return of greater auricular nerve function. There is also a risk of injury to the accessory nerve. In addition, the bulky size of the flap may mask recurrences in the parotid bed.

SUPERFICIAL MUSCULOAPONEUROTIC SYSTEM ADVANCEMENT

Increasingly, techniques involving SMAS advancement are described. The SMAS is the layer situated beneath the skin consisting of the superficial facial muscles (including the platysma) and their fibrous attachments. In these techniques, parotidectomy is performed through a modified face-lift incision. Initially, a skin flap is raised. Following this, the SMAS is incised and raised off the parotid gland. After parotidectomy with dissection of the facial nerve, the SMAS flap is advanced to fill the retromandibular ‘hollow’ resulting from removal of parotid tissue.

The main purpose of using a SMAS flap is to fill the ‘hollow’ which results from removal of parotid tissue, thus improving postoperative cosmetic appearance. It is also reported to lead to decreased incidence of Frey’s syndrome, although others have disputed this. This technique may be combined with a formal bilateral rhytidectomy (facelift) for cosmetic purposes. The SMAS flap has been claimed to offer clear advantages over sternomastoid muscle rotation techniques, both in terms of improving facial contour and preventing Frey’s syndrome.

The disadvantages of techniques involving the SMAS flap are that the facelift incision does not allow access to upper cervical lymph nodes should a neck dissection be necessary, and large tumours may be too close to the SMAS layer to allow it to be raised off the parotid gland intact without leading to an increased risk of recurrence.

Endoscopic techniques

Endoscopic sialoendoscopy is a new technique for the diagnosis and treatment of salivary duct stones or stenosis. The most common usage is for removal of submandibular duct stones. With this technique, the submandibular orifice is first dilated using lacrimal probes, and then incised using a CO2 laser or other means. Following this, a 3.1 mm rigid telescope is inserted into the submandibular duct with normal saline irrigation. Calculi are then identified and removed. Combined with sialadenoscopy, this technique may also be used to dilate strictures.

Recently, endoscope-assisted submandibular sialadenectomy through a 2 cm neck incision has been reported.

PROGNOSIS

Recurrence rates after treatment of benign salivary tumours are generally reported at less than 1–2 per cent. For malignant tumours, outcome is dependent to a large extent on the stage and grade of the tumour. Typical ten-year local control rates are 82–92 per cent for T1/T2 tumours, 74–85 per cent for T3 tumours and 33–37 per cent for T4 tumours. Other factors affecting local control include the presence of facial palsy and the presence of positive surgical margins. Survival is predominantly affected by stage and grade. Renehan et al. reported ten-year disease-specific survival of 96, 61 and 17 per cent for stage I, II and III/IV tumours, while the ten-year survival was 91, 41 and 50 per cent for high, intermediate and low-grade tumours, respectively. T-stage and N-status are the most important prognostic determinants. Survival is also affected by grade, facial nerve palsy, perineural invasion, skin invasion and male sex.

KEY EVIDENCE

- Fine needle aspiration is a highly useful tool in the assessment of salivary masses; however, there are limitations to its accuracy, particularly with respect to its sensitivity for detection of malignancy.
- Surgery should be considered for nearly all salivary masses for definitive histological confirmation.
- The treatment of choice for salivary malignancies is wide surgical excision. However, in the presence of a functional facial nerve, every effort should be made to preserve the nerve, even when it is
postoperative radiotherapy in these cases will give equivalent local control rates as sacrifice of the nerve. However, the impact of radiotherapy on distant metastases and survival is unproven.

**KEY LEARNING POINTS**

- Salivary tumours are rare and are characterized by marked morphological diversity, and are thus highly prone to diagnostic confusion.
- Pleomorphic adenoma is the most common salivary tumour and has a propensity for local recurrence if inadequately excised, and for malignant transformation if left untreated. Thus, these tumours should always be excised using meticulous surgical technique.
- Most salivary malignancies grow slowly, and have a propensity for local recurrence as well as distant metastases. This may occur many years after treatment of the primary tumour, thus long-term follow up is necessary.
- The prognosis of malignant salivary tumours depends primarily on tumour stage. Tumour grade is also an important prognostic indicator.
- Salivary tumours do not respond as well to radiotherapy and chemotherapy as other tumours. Thus surgery is the mainstay of treatment. Radiotherapy may play a role in the adjuvant setting.
- Sacrifice of the facial nerve or its branches should be performed in cases with preoperative paralysis, for recurrent tumours or for tumours grossly encasing and infiltrating the nerve. Microscopic invasion of the nerve is generally not an indication for nerve sacrifice.
- Postoperative radiotherapy is generally given for high-stage or high-grade tumours, cases with positive margins, and cases where the branches of the facial nerve were preserved despite being adherent to the tumour.

**REFERENCES**

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Non-melanoma and melanoma skin cancer

RICHARD CW MARTIN AND JONATHAN CLARK

INTRODUCTION

Skin cancer is the most common malignancy in the world. The highest rates are seen in countries with fair-skinned, Anglo-Celtic populations and high sun exposure. Australia and New Zealand lead the world in this regard, where the annual incidence of basal cell carcinoma (BCC) is 788 per 100,000, squamous cell carcinoma (SCC) is 321 per 100,000 and melanoma is 40 per 100,000 per year. The incidence in other fair-skinned nations such as the United States is considerably lower, where BCC is 146 per 100,000 and SCC is 100 per 100,000.\(^1\) However, the incidence worldwide is increasing at a rate of 2–3 per cent per year, making this a global oncological problem. Cutaneous malignancy is divided into melanoma and non-melanoma skin cancer (NMSC) with BCC and SCC representing the vast majority (Box 38.1). In general, NMSC is a highly curable disease using basic surgical techniques. However, selected cases can challenge the surgical oncologist either due to patient self-neglect, immunosuppression, extensive superficial disease or aggressive variants with the propensity for local invasion and metastases, particularly in the head and neck. Neuroendocrine tumours, such as Merkel cell carcinoma (MCC) and melanoma, represent a completely different spectrum of disease that are characterized by locoregional and distant failure. The search continues, without success, for effective treatment strategies for patients with distant metastatic disease.

Box 38.1 Types of non-melanoma skin cancer

- Basal cell carcinoma
- Squamous cell carcinoma
- Merkel cell carcinoma
- Other rare
  - Sarcoma
    - Fibrous tissue (malignant fibrous histiocytoma, dermatofibrosarcoma)
    - Vascular tissue (angiosarcoma, Kaposi’s sarcoma, hemangiopericytoma)
  - Skin appendage carcinomas (e.g. sebaceous carcinoma)
arms. NMSC is a multifactorial disease and aetiology can be divided into individual, environmental and genetic factors.1

Individual

Individual risk factors include male gender and Anglo-Celtic ancestry. The typical patient has pale complexion, blue or green eyes, fair hair, skin freckles and poor tanning ability. The incidence rises with increasing age and with a history of precancerous (solar keratosis) or cancerous skin conditions.

Immunosuppression is a potent cause of both SCC and BCC and is seen most commonly in transplant patients who have been on long-term immunosuppressive medication such as cyclosporin. This often results in widespread multiple tumours that are locally aggressive and have increased metastatic potential. This can be challenging because of rapidly advancing disease, local recurrence and numerous lesions. The option of cessation of treatment and probably transplant loss needs to be discussed with these patients. This represents an important complication of immunosuppressive treatment. The cumulative incidence at five years in patients with heart transplants was reported at 24 per cent.1 SCC may also occur in chronic inflammatory disorders and arise in scars of skin burns or chronic ulcers (Marjolin’s ulcer).

Environmental

The main environmental risk factor is solar ultra-violet (UV) radiation. UVB is more carcinogenic than UVA. However, there are several other potent risk factors (Table 38.1) such as iatrogenic ionizing radiation and occupational exposure to arsenic and polycyclic hydrocarbons. The important role of viruses in many forms of cancer is emerging and human papilloma virus (HPV) is well established in cervical and tonsillar SCC. HPV is also implicated in cutaneous SCC, however its role is less well defined but appears to be important in the immunosuppressed.

Genetic

The genetic syndromes associated with NMSC (Table 38.2) are rare causes of skin cancer but are important in terms of early identification and genetic counselling. Furthermore, because tumours are usually multiple, minimizing the functional and aesthetic morbidity of surgery and timing of radiotherapy (where indicated) is an additional challenge.

Table 38.1 Risk factors for NMSC.

<table>
<thead>
<tr>
<th>Basal cell carcinoma</th>
<th>Squamous cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solar UV radiation</td>
<td>Solar UV radiation</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td>Arsenic exposure</td>
<td>Tobacco</td>
</tr>
<tr>
<td></td>
<td>HPV (1, 2, 3, 5)</td>
</tr>
<tr>
<td></td>
<td>Polycyclic aromatic hydrocarbons</td>
</tr>
<tr>
<td></td>
<td>Arsenic exposure</td>
</tr>
<tr>
<td></td>
<td>Chronic ulcers/sinus tracts/scars</td>
</tr>
</tbody>
</table>

Xeroderma pigmentosum (SCC, BCC and melanoma) is caused by a defect in DNA repair and synthesis, clinical features include sun sensitivity, ocular involvement and severely damaged skin. Gorlin’s syndrome is characterized by multiple BCCs, palmar pits, jaw cysts, rib abnormalities, calcification of falx cerebri, characteristic facies (frontal bossing, hypoplasic maxilla, broad nasal root, ocular hypertolerism). Bazex’s syndrome (Acrokeratosis paranepolectica) produces BCCs, SCCs, follicular atrophoderma, hypotrichosis and hypohidrosis or hyperhidrosis. Patients with albinism especially develop SCCs. Patients with dyskeratosis congenita have increased skin pigmentation, nail dysplasia and leukoplakia of mucous membranes and are prone to SCCs. Epidermolysis bullosa is characterized by atrophy of blistered areas, severe scarring and nail changes. It presents at birth or in early infancy and BCCs and SCCs develop early.

BASAL CELL CARCINOMA

BCC is the most common malignancy in humans. They typically occur in the head and neck region, most commonly on the nose, but can occur anywhere that is sun exposed. There are five histological subtypes (Box 38.2) which are important to recognize because their clinical behaviour is distinct (see Figures 38.1, 38.2 and 38.3).

Nodular BCC is the most common subtype and has the distinctive features of a small pearly dome-shaped nodule with surface telangiectasia and a raised rolled edge. As these increase in size they may ulcerate and become locally invasive and have been termed a ‘rodent ulcer’. Superficial BCC is also common and the least aggressive subtype. Features include

- Types of BCC
  - Nodular
  - Superficial
  - Basosquamous
  - Pigmented
  - Morpheic

Table 38.2 Genetic syndromes associated with skin cancer.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma pigmentosum</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Gorlin’s syndrome (nevoad basal cell carcinoma syndrome)</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Bazex’s syndrome</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Albinism</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Epidermodysplastic verruciformis</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>Epidermolysis bullosa</td>
<td>Autosomal dominant and recessive</td>
</tr>
</tbody>
</table>

Box 38.2 Histological subtypes of BCC
scaly, dry, erythematous plaques which are round or oval in shape and typically occur on the limbs and trunk. Baso-squamous BCC is a more aggressive tumour, often ulcerated with histologic features of SCC and BCC and has limited but definite metastatic potential. Pigmented BCC is seen in darker skinned individuals. The pigment is due to melanin and easily confused with melanoma. Morphoeic (sclerosing) BCC characteristically appear as an indurated pale plaque with indistinct borders. These are locally aggressive tumours where margin control is particularly difficult and as such have a high propensity for local recurrence. Patients with these tumours need to be counselled in advance that the surgical defect may be much larger than the visible lesion and intraoperative frozen section is recommended to optimize initial disease control.

Most BCCs are low-grade malignant tumours, however massive or deeply infiltrative examples can be problematic in the head and neck, particularly in the peri-ophthalmic region and midface. Regional and distant metastases are very rare and most of these unusual cases will show some degree of squamous differentiation. In contrast with SCC, BCC does not express CD44, a cell adhesion molecule, and this may, in part, explain its low metastatic potential.

**SQUAMOUS CELL CARCINOMA**

SCCs classically occur in elderly males on sun-exposed sites, especially in the head and neck region (Figures 38.4 and 38.5). They may arise from precursor lesions such as actinic keratosis (solar keratosis). The transformation rate is estimated to be between 5 and 20 per cent over 10–25 years with an individual lesion risk of 0.24 per cent. Bowen's disease or SCC-*in situ*, surprisingly has a lower transformation rate of...
up to 5 per cent. Early lesions appear as an enlarging erythematous nodule or scaly plaque. Ulceration (volcano-like) and crusting occur later followed by invasion of deep structures (Figures 38.6 and 38.7).

Regional metastases are uncommon, occurring in 5 per cent overall. However, certain clinicopathological features increase the risk of lymphatic spread (Box 38.3) and these high risk SCCs metastasize in approximately 20 per cent of cases.6–7 The parotid gland represents an important receptacle for regional disease in the head and neck (Figure 38.8).8 Current evidence suggests that between 25 and 50 per cent of patients with parotid node metastases from SCC will have concurrent cervical nodal disease, either clinical or pathological.9 Overall mortality for cutaneous SCC is only 3.4 per cent but increases substantially in patients with regional metastases.10 In a multicentre study of patients with metastatic SCC to the parotid, overall survival was 72 per cent at five years and over 25 per cent of patients had concurrent neck disease.11 Until recently, the AJCC staging system for cutaneous SCC was very limited in its description of nodal disease and several alternative staging systems have

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**Box 38.3 Clinicopathological features of high risk SCC**

- Size > 2 cm
- Invasion into subcutaneous fat (depth > 4–5 mm)
- Poorly differentiated
- Perineural invasion
- Lymphovascular invasion
- Site: ear or lip
- Incomplete excision
- Local recurrence
- Immunosuppression

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**Figure 38.5** Multiple squamous cell carcinoma scalp.

**Figure 38.6** Advanced cutaneous squamous cell carcinoma neck.

**Figure 38.7** Advanced squamous cell carcinoma cheek.

**Figure 38.8** CT scan of metastatic cutaneous squamous cell carcinoma to the parotid gland.
been proposed to better stratify patients with metastatic cutaneous SCC.

**MERKEL CELL CARCINOMA**

MCC is a rare neuroendocrine tumour of skin with approximately 50 per cent of tumours occurring in the head and neck region. The annual incidence is 0.23 per 100 000 and mainly affects elderly males. MCC is thought to arise from mechanoreceptor (Merkel) cells, however the exact aetiology of MCC is unknown. Ultraviolet radiation exposure appears to be an important factor and implicated environmental agents include arsenic, methoxysalen and UVA treatment for psoriasis.

MCC is difficult to identify clinically and is frequently passed over as a benign lesion. It often presents as a solitary cutaneous papule or nodule, and may be purplish or pink in colour (see Figure 38.9). Multiple nodules or satellitosis is relatively common, demonstrating its potential for local recurrence. MCCs are very aggressive malignancies with a high metastatic potential. As such, a common initial presentation is a neck or parotid mass. Of those patients who present with primary disease, 30 per cent have lymph node metastases at diagnosis and 50 per cent develop distant metastases. Sites of distant disease include liver, bone, lung, brain and skin.12

The largest reported series of head and neck MCC reported pathological nodal metastases in 48 of 110 patients.13 MCC is associated with a high mortality and behaves quite differently to cutaneous SCC and is much more akin to melanoma. Important predictors of disease-specific survival include increasing age (hazard ratio 6.19 for patients over 70 years of age) and primary tumour size (hazard ratio 7.55 for tumours greater than 1 cm in size).

**CLINICAL ASSESSMENT AND STAGING**

**Patient examination**

Assessment of cutaneous lesions should be combined with a comprehensive head and neck examination and generalized skin evaluation. Due to the complex anatomy in the head and neck, particular consideration needs to be given to the likely aesthetic and functional consequences of treatment. Areas that are prone to suboptimal surgical therapy include the periorbital region, periauricular region (temporal bone and facial nerve), nose and commissure of the lip. Inexperience or lack of preoperative planning may result in inadequate tissue margins or unacceptable morbidity that could have been avoided. Furthermore, the surgeon needs to consider whether resection alone will constitute comprehensive management or is adjuvant therapy likely to be necessary. Where adjuvant therapy is considered, the patient should be assessed in a multidisciplinary head and neck clinic, particularly as many lesions may be appropriately managed with radiotherapy as a single modality rather than combination therapy.

Cranial nerve examination to assess for perineural invasion should be performed for cutaneous SCC on the face (Figure 38.10). Despite this, many tumours with perineural invasion may not be clinically evident. Motor nerves at risk include peripheral branches of the facial nerve or the nerve trunk division for deeply invasive tumours. Cutaneous nerves at risk are predominantly branches of the trigeminal nerve in the face and less commonly branches of the cervical plexus in the neck, scalp and ear. In particular, the supraorbital and supratrochlear nerves in the forehead and infraorbital nerve in the mid face appear to be most susceptible.

Figure 38.9  Merkel cell carcinoma of the upper lip.

Figure 38.10  Facial paresis from facial nerve (perineural) invasion from metastatic squamous cell carcinoma to the parotid gland.
Examination of regional lymph nodes fields is essential for all head and neck pathology, however the distribution of nodal metastases in cutaneous malignancy has critical differences to mucosal cancer. Lymphoscintigraphy and sentinel node biopsy in melanoma have demonstrated that cutaneous lymphatic drainage is less predictable than expected. Areas peculiar to cutaneous malignancy include the parotid gland (preauricular lymph nodes), postauricular nodes, the external jugular lymph node (Figures 38.11 and 38.12) and sub-occipital lymph nodes.

Biopsy

The majority of NMSC can be managed without biopsy, but if doubt exists histopathology should be obtained. Excision biopsy for suspicious lesions with 3–4 mm margins can be performed routinely for small tumours in non-critical regions without the need for further treatment. Where diagnosis is uncertain and excision is likely to be morbid, an incisional biopsy can be performed.

All patients with enlarged or suspicious lymph nodes should undergo fine needle aspiration biopsy (FNAB) prior to definitive therapy. Ultrasound-guided aspiration and immediate cytological assessment decreases non-diagnostic aspirates and should be performed routinely for lesions that are difficult to palpate.

Imaging

While imaging is not routinely indicated for early stage disease, it is mandatory in advanced lesions and selected recurrent tumours. The technique of choice depends on institutional expertise and the primary concern that has warranted imaging. The standard choice in patients with advanced disease is high resolution multislice computed tomography (CT) scanning with intravenous contrast (see Figure 38.13). This allows assessment of the tumour and surrounding soft tissue structures. Bone windows are used to determine cranial or mandibular invasion. CT examines the parotid and neck for subclinical disease in patients with advanced primaries and extent in patients with palpable nodes. CT of the chest has a low yield for distant disease in cutaneous SCC but is a simple investigation in high risk SCC and MCC.

Magnetic resonance imaging (MRI) can substitute CT in all regards except cortical bone definition. It is the modality of choice for neurotropic cancers and in tumours with intracranial, orbital or parapharyngeal extension (Figures 38.14, 38.15 and 38.16). Cervical node assessment with MRI is equivalent to multislice CT and we reserve MRI for selected patients with nerve deficit or extensive disease. Ultrasound is highly specific and sensitive for cervical node disease in selected series and can be combined with ultrasound-guided fine needle aspiration, but has a limited role in structural definition of primary malignancies.

There are few data examining the role of positron emission tomography (PET) in NMSC. $^{18}$FDG-PET and PET-CT is being used more frequently as a standard investigation in the assessment of regional and distant metastatic disease. Distant metastases are uncommon in cutaneous SCC,
including patients with nodal metastases, and our preference is to perform a chest CT with the head and neck scan. PET is more likely to be positive in patients with MCC where distant disease is common, although because of rarity there are no large series to establish its utility in this setting. Lymphoscintigraphy is also unproven in NMSC but may have a role in high risk SCC and is increasingly used in stage I MCC.

### Staging for NMSC

The seventh American Joint Committee on Cancer (AJCC) TNM staging has seen major modifications in the renamed chapter of ‘Cutaneous squamous cell carcinoma and other cutaneous carcinomas’, and a new separate classification for MCC. As the majority of cutaneous SCCs occur on the head and neck, the staging system has been made congruent with that for mucosal head and neck SCC (Tables 38.3 and 38.4). The 5 cm size cut-off for the T category in the previous edition has been abolished. Two centimetres continues to differentiate between T1 and T2 (<2 and >2 cm, respectively). T3 represents deep invasion into muscle, cartilage and bone, whereas T4 is reserved for involvement of skull base and axial skeleton.

Previously, the TNM staging system was not specific for cutaneous SCC of the head and neck (CSCCHN) and has had minimal clinical applicability and limited prognostic value. Excluding T4 disease, the only variable considered in T classification was horizontal dimension. N status did not discriminate between the number, size and location of the nodes. This has prompted a number of studies aimed at designing a staging system that could be applied in a similar manner to that of mucosal SCC. Fortunately, the latest
The 7th edition of the AJCC staging manual has taken a substantial amount of recent data into consideration.

**O’BRIEN P/N SYSTEM**

O’Brien proposed the P/N staging system to allow for better assessment of the prognostic factors and treatment outcomes. Initially, this system was applied to a cohort of 72 patients finding that increasing P stage, positive margins, and failure to give adjuvant radiotherapy was associated with decreased local control, and advanced neck disease had a negative impact on survival. The P/N system was then applied to 322 patients with metastatic CSCCHN in a multi-institutional international trial, concluding that advanced P stage (P3) and neck disease (N1/2) were independently associated with reduced survival. Although the staging system was a major step forward, the model was complex and did not stratify risk well within P and N groups. However, the discrimination between parotid and neck metastases is still important as it underlies our current treatment philosophies.

**N1S3 SYSTEM**

In an attempt to simplify the O’Brien P/N system and by incorporating the parotid as one of the regional nodal levels, we carried out a further analysis of clinical and pathological information from 215 patients treated with primary surgery for metastatic CSCCHN. N1S3 refers to the number (one or more) and size of nodes (>3 cm), which were found to be significant predictors of survival along with extracapsular spread (ECS). The N1S3 system shown in Table 38.5 is easily applied to both clinical and pathological data.

**ITEM PROGNOSTIC SCORE**

The ITEM prognostic score moves away from traditional models that can be applied clinically to include pathological information only available in the postoperative setting and separates patients into three (low, medium and high) risk groups. It takes into account four variables (immunosuppression, treatment, extranodal spread and margin) that are significantly associated with survival to calculate the ITEM score. In the cohort of patients tested, the five-year risk of dying from disease for patients with high-risk (>3.0), moderate-risk (>2.6–3.0) and low-risk (2.6) ITEM scores was 56, 24 and 6 per cent, respectively. An inherent problem with the ITEM score is that untreated patients cannot be staged and the staging system cannot be used to select patients at low risk of recurrence who may be suitable for less intensive treatment regimens.

**CURRENT TNM STAGING SYSTEM**

The 7th edition of the AJCC staging manual for cutaneous SCC has incorporated current information available to make substantial changes to the T and N staging criteria.
The T stage incorporates size, bone invasion and several pathological high-risk criteria (thickness, perineural invasion, site and differentiation). The N staging criteria is identical to that of mucosal head and neck SCC, thus using extent of disease (nodal size and number), but introduces criteria that have not been validated, such as laterality of nodes.

**MANAGEMENT OF NON–MELANOMA SKIN CANCERS**

**Treatment for early stage NMSC**

Surgery remains the mainstay of treatment after biopsy to confirm diagnosis. The recommended margins for SCC are 4 mm for lesions under 2 cm and 6 mm for greater than 2 cm. BCCs should be excised with a minimum 3 mm margin. Moh’s micrographic surgery or complete resection with comprehensive frozen section analysis of all margins can be utilized in difficult areas where wide excision is impractical. Radiotherapy may be preferred as primary treatment where surgical excision with reconstruction may produce significant cosmetic and/or functional sequelae. Radiation techniques for small cutaneous tumours often differs from mucosal disease. Electrons may be used rather than photons due to their ability to distribute energy superficially without damage to deeper structures. Since regional metastases are unlikely in small NMSC, the fields are generally smaller and both early and late toxicity is less. Cure rates between 60 to 90 per cent are reported for both SCC and BCC. Despite the apparent benefits of this approach, on average 4–6 weeks of daily therapy is necessary which may have a significant socioeconomic impact on patients. Early toxicity usually consists of erythema, desquamation, pain and crusting which resolves within 4 weeks of therapy. However, late radiation sequelae include pigmentation or depigmentation, tissue fibrosis, contracture and atrophy. This may develop over years and is generally irreversible. The theoretical risk of a second radiation-induced malignancy is generally very small when treating small volumes to moderate doses, but does need to be discussed with patients, particularly under the age of 40 years.

There are a number of topical drug therapies including 5 fluorouracil cream for treatment of SCC/BCC in situ and imiquimod 5 per cent for SCC in situ and superficial BCCs. Cryotherapy should be reserved for superficial, non-pigmented lesions only (SCC/BCC in situ, superficial BCCs, actinic keratoses).

**TREATMENT FOR ADVANCED STAGE NMSC**

**Surgery**

Advanced NMSC (T3/T4) require en-bloc resection of tumour incorporating invaded structures (fat, muscle, bone, orbit) (Figures 38.17, 38.18, 38.19, 38.20 and 38.21). These patients should be assessed in a multidisciplinary clinic prior to surgery as many patients will require adjuvant post-operative radiotherapy. Furthermore, the option of definitive radiotherapy with or without concurrent chemotheraphy should be considered in select patients where the morbidity of surgery is excessive. A number of reconstructive options are available for these patients, however direct closure is usually impossible. Skin graft (full thickness or split-skin) may be possible for large superficial lesions, but is unlikely to be a viable option alone for invasive tumours where bone or mucosal surfaces are involved. Generally, local and regional flaps are preferable over free tissue transfer in terms of contour and skin colour match which are important aesthetic factors in the head and neck. However, locoregional flaps are less reliable in terms of wound healing and if adjuvant therapy is planned the most reliable technique of tissue closure should be adopted to minimize time to radiotherapy with the aim of maximizing disease control. In using free tissue for reconstruction, a range of flaps is available and

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease-specific survival at two years (%)</th>
<th>Disease-specific survival at five years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single node ≤ 3 cm</td>
<td>95</td>
</tr>
<tr>
<td>II</td>
<td>Single node &gt; 3 cm or multiple nodes ≤ 3 cm</td>
<td>88</td>
</tr>
<tr>
<td>III</td>
<td>Multiple nodes &gt; 3 cm</td>
<td>66</td>
</tr>
</tbody>
</table>

**Figure 38.17** Magnetic resonance imaging demonstrating extensive perineural invasion of the facial nerve extending to the stylomastoid foramen (sequence T1-weighted image with gadolinium and fat suppression).
depending on ethnicity and patient preference free flap choice should be aimed at achieving the optimal contour and colour match. Specifics regarding local, regional and free flap reconstruction is beyond the scope of this chapter and there are many excellent texts and articles discussing these options.21, 22, 23, 24, 25

Management of subclinical nodal disease in advanced NMSC is controversial and there is little high-level evidence to guide surgeons. In many patients, the choice as to whether a neck dissection is indicated will be predetermined by the method of reconstruction. There is no doubt that patients with clinical disease should undergo neck dissection, however most selective dissections are based upon evidence for mucosal SCC rather than cutaneous SCC. We have adopted a selective technique in the majority of patients with the
anticipation of adjuvant radiotherapy in patients who have pathological neck or parotid disease.

For anterior tumours of the face, nodal groups at risk include the parotid, external jugular nodes and levels 1 (including submental and peri-facial lymph nodes), II, III and IV. For posterior tumours of the scalp, nodal groups at risk include the retroauricular, external jugular, occipital nodes and levels II, III, IV and V. Hence a standard modified radical neck dissection for a patient with a cheek primary will not include some of the high risk groups, in particular the parotid. While location of the primary tumour predicts nodal fields at risk, recent evidence from the melanoma literature suggests a variance in clinically predicted drainage in one-third of patients. Selective lymphadenectomy in melanoma is based on the lymphoscintigram and at risk second tier nodes. One of the most important nodes in head and neck cutaneous malignancy is the external jugular node and this must be removed during lymphadenectomy. Patients with positive nodes in the parotid have approximately a 30 per cent chance of having metastatic disease in the neck. Elective parotidectomy in patients with cervical disease is not generally employed.

Sentinel node biopsy remains a new technique to NMSC but is likely to become more widely applied for high risk SCC and MCC. In addition to providing information regarding the presence of nodal disease, lymphoscintigraphy allows a more selective approach to the removal of at-risk nodal groups.

Surgery following radiotherapy constitutes a particularly complex problem. The tumour margins become less distinct and often recurrence is multifocal. The tissue is indurated and oedematous and clinical judgement can be unreliable. In addition, the pathologist often finds distinguishing islands of tumour within fibrous tissue difficult on frozen (quick) section. Surgery should be preceded by adequate imaging with high resolution CT, MRI and PET-CT. Wide margins should be taken (1–2 cm) where feasible and because of the poor vascularity of surrounding tissue, a low threshold for free tissue reconstruction should be maintained, especially if retreatment with radiotherapy is contemplated.

**Adjuvant therapy**

The standard indications for postoperative radiotherapy for SCC are close or positive margins, perineural invasion, two or more positive nodes, extracapsular spread and nodes greater than 3 cm in size (see **Box 38.4**). Parotid nodal metastases and poorly differentiated tumours are also considered to be high risk groups. Recent data from the TransTasman Oncology Group Post-Operative Skin Trial (POST study) has highlighted parotid metastasis in the high risk group for adjuvant therapy comparing surgery and radiotherapy with surgery and chemoradiotherapy.

Various radiation schedules have been used for regional metastases, however standard fractionation has been advocated as described below. Data from MD Anderson demonstrated that increasing the postoperative dose beyond a biologically effective dose of 60 Gy increased the risk of late complications, with no increased benefit in locoregional control. Where metastases have occurred greater than 12 months following definitive treatment to the primary lesion, consideration should be given to including the primary site and intervening dermal lymphatics in the treatment volume (see **Box 38.5**).

Chemotherapy remains experimental and patients should be entered into appropriate clinical trials. Several studies have now confirmed improved locoregional control and survival with concurrent chemoradiation in the postoperative setting for high risk mucosal cancer. This is at the cost of a substantial increase in both early and late adverse effects. At present there is no compelling data to suggest that the same benefit is present in cutaneous SCC, however this question will be answered by the POST study. Most studies examining mucosal SCC use cisplatin and fluorouracil in conjunction with radiotherapy. More recently, carboplatin has been used to minimize toxicity. This is important for elderly patients who are more likely to present with advanced disease and will not tolerate standard treatment protocols with concurrent cisplatin. For the POST study, carboplatin is given once per week for 6 weeks concurrently with radiotherapy.

BCCs with close or positive margins are best managed with repeat surgery where feasible. However, for advanced tumours with inadequate margins, postoperative radiotherapy should be considered, particularly if there is calvarial or orbital involvement. Most patients with dural or brain invasion will require adjuvant therapy and there should be a low threshold for treating recurrent BCCs with postoperative radiotherapy. Regional therapy is not indicated in BCC unless there is documented nodal disease, which is rare.

**TREATMENT OF MERKEL CELL CARCINOMA**

The treatment of MCC depends on its stage, see **Table 38.6**. There is strong evidence from a large single institutional
series\textsuperscript{31} that small volume primary disease (stage I MCC) can be managed by wide excision alone. Clark et al.\textsuperscript{14} have demonstrated that disease-specific survival for patients with head and neck tumours less than 1 cm in size and no nodal metastases is approximately 95 per cent at five years. The ideal margin of excision is unknown and has not been shown to alter survival. MCC is exquisitely radiosensitive and adjuvant radiotherapy is recommended for patients with large primary tumours or nodal metastases (stage II and III). The dose and volume of radiotherapy is adjusted to the volume of nodal disease, but typically requires 60–70 Gy in 2 Gy daily fractions for clinical disease and 50 Gy for subclinical disease. The target volume should include the draining nodal basin, primary site and also the intervening dermal lymphatics due to the high relapse rate (up to 70 per cent).\textsuperscript{5}

Sentinel node biopsy is increasingly being used in MCC\textsuperscript{32} and is probably of greatest benefit in patients where comprehensive radiotherapy is not planned (stage I). There is no proven benefit for elective neck dissection in MCC.\textsuperscript{5}
The evidence for radiotherapy alone for MCC is increasing\textsuperscript{5} and should be considered in patients who are poor surgical candidates due to either comorbidity or where the morbidity of resection is excessive. Despite aggressive treatment, prognosis remains poor due of the high rate loco-regional failure and also the development of distant metastases. The search for effective chemotherapeutic agents and novel therapies has been disappointing thus far and there is limited evidence to suggest that adjuvant chemotherapy should be regarded as standard treatment.\textsuperscript{5, 34, 35, 36, 37} Despite this, the authors advocate concurrent chemoradation for patients with high risk disease. The most common chemotherapeutic agents used to date are carboplatin, etoposide and anthracyclines.\textsuperscript{37} Patients with distant metastases are generally incurable (stage IV), and radiotherapy should be reserved for symptomatic disease, however chemotherapy may be appropriate as palliative therapy in selected patients.

### Table 38.6 Suggested treatment for Merkel cell carcinoma.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Suggested treatment</th>
</tr>
</thead>
</table>
| I     | Wide excision + SNB  
      | Radiotherapy to primary and neck if SNB positive. (May be definitive treatment in patients with poor performance status) |
| II    | Wide excision + SNB (NO) or neck dissection (N1)  
      | Radiotherapy to primary and neck. (May be definitive treatment in patients with poor performance status) |
| III   | Wide excision + neck dissection  
      | Radiotherapy to primary and neck. (May be definitive treatment in patients with poor performance status)  
      | Consider concurrent chemotherapy in patients with good performance status |
| IV    | Palliative  
      | Consider radiotherapy to primary and neck  
      | Concurrent/adjuvant chemotherapy  
      | Consider clinical trial |

### Table 38.7 Melanoma risk factors.\textsuperscript{41}

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong family history</td>
<td>35–70</td>
</tr>
<tr>
<td>Atypical naevi</td>
<td>11</td>
</tr>
<tr>
<td>Previous melanoma</td>
<td>8.5</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>1.5–3</td>
</tr>
<tr>
<td>Skin type</td>
<td>1.7–2.5</td>
</tr>
</tbody>
</table>

CUTANEOUS MELANOMA OF THE HEAD AND NECK

Melanoma incidence has undergone an exponential increase in the past 30 years. Australia and New Zealand have the highest rates (35–40/100 000), three times greater than that of the USA and Europe.\textsuperscript{38} Ten to 20 per cent of cutaneous melanoma arises in the head and neck\textsuperscript{39} and approximately 20 per cent of patients develop regional metastases.

Melanoma is predominantly a disease of fair-skinned individuals, typically of Celtic background. Sun exposure is the most important risk factor for melanoma, in particular intermittent sunburn during early life.\textsuperscript{40} Other risk factors for melanoma are listed in Table 38.7.\textsuperscript{41} While environmental factors feature strongly, certain genetic defects have been linked with melanoma and a strong family history increases the risk. Mutations of CDKN2A, which is located on chromosome 9, are associated with the development of melanoma in up to 90 per cent of affected individuals by the age of 80.\textsuperscript{42}

#### Diagnosis

The majority of melanomas can be detected by the history of the lesion, and comparison with other pigmented lesions (Figures 38.22 and 38.23). Morphologically, melanomas are classified into six types, as shown in Box 38.6. The most difficult to diagnose and the most commonly missed melanoma is the amelanotic variant.

Early diagnosis is the key to the effective treatment of melanoma. The ABCD system:\textsuperscript{43} Asymmetry, Border irregularity, Colour variation and Diameter greater than 6 mm is a useful tool. Recently ‘E’ was added for elevation or evolution. Surface microscopy with a hand-held dermatoscope is used by some clinicians to improve the clinical diagnosis of skin lesions. The technique uses application of oil to the cutaneous lesion and examination of the pigmented
structures of the epidermis and dermis via magnification and illumination. In expert hands, a sensitivity of 92 per cent and specificity of 71 per cent can be achieved.\textsuperscript{44} Any suspicious lesion should be biopsied with a 2–3 mm margin of normal skin. The pathologist will then produce a synoptic report from which definitive management can be planned (Box 38.7)\textsuperscript{45}.

### Staging of melanoma

The mortality for cutaneous melanoma of the head and neck is high, with overall survival being 66 per cent at ten years. This falls to 34 per cent for patients with proven nodal metastases and further decreases with an increasing number of positive nodes.\textsuperscript{46} Clinicopathological features that predict for nodal disease and mortality are listed in Box 38.8.

A new AJCC staging system for melanoma was released in December 2009.\textsuperscript{48} The new staging system found that in

---

**Box 38.6** Morphological types of melanoma

- Superficial spreading
- Nodular
- Lentigo Maligna
- Acral
- Amelanotic
- Desmoplastic
- Other

**Box 38.7** Synoptic pathological report for primary cutaneous melanoma\textsuperscript{45}

- Site
- Diagnosis
- Histological subtype
- Breslow thickness
- Ulceration
- Dermal mitotic rate (per mm\textsuperscript{2})
- Clark level
- Vertical growth phase
- Vascular or lymphatic invasion
- Neurotropism
- Desmoplasia
- Satellites
- Features of regression
  - Early (TILS)
  - Intermediate
  - Late
- Predominant cell type
- Associated naevus
- Nearest lateral margin to in situ or invasive component
- Distance from tumour to deep margin

TILS, tumour infiltrating lymphocytes.
patients with localized melanoma, tumour thickness, mitotic rate (histologically defined as mitoses/mm²), and ulceration were the most dominant prognostic factors. Mitotic rate replaces Clark’s level of invasion in T1b melanoma. Nodal disease now incorporates immunohistochemically positive nodes and micrometastases less than 0.1 mm in staging (N1). See Table 38.8 for the latest AJCC staging system for melanoma (2009).

The Breslow depth was devised in 1970 and is measured from the granular layer of the epidermis or the base of an ulcer to the deepest contiguous melanoma cell with an ocular micrometer. Clark levels are not as accurate as Breslow depth, but are important in sub-millimetre primaries when deciding on sentinel needle biopsy (SNB) (see Table 38.9).

Management of cutaneous melanoma

MARGINS

Excision margins for melanoma have changed over the years but are still primarily based on Breslow thickness. Numerous retrospective studies and three prospective studies provide evidence for the accepted margins of excision. More recently, the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand have made evidence based recommendations for margins of excision (Table 38.10).

Melanoma in the head and neck region provides more of a challenge because wide excision is often not physically possible or may increase morbidity and disfigurement. A compromise on margins is thus considered acceptable in the region.

SENTINEL NODE BIOPSY

SNB for melanoma was first reported by Morton in the early 1990s (see Figures 38.24 and 38.25). Since then it has been used in numerous other malignancies. Controversy reigns over the use of SNB, however the majority of surgical oncologists perform the procedure for melanomas greater than 1 mm thick. SNB is also offered for melanomas 0.75–1 mm thick that show Clark IV or V, ulceration, high mitotic count or in patients <45 years old. The only randomized control trial to date (Melanoma Sentinel Lymph Trial (MSLT) 1)
shows no overall survival benefit, but a 20 per cent survival benefit was seen on subset analysis for sentinel node positive patients who underwent immediate completion lymphadenectomy versus those on observation who develop clinical lymph node metastases. Patients who are found to be sentinel node positive should undergo completion selective lymphadenectomy as predicted by the lymphoscintogram. The prognostic and staging information gained from SNB is vital for entry into adjuvant treatment trials and for survival prediction (Table 38.11). SNB is a minor surgical procedure with low reported complication rates of 10 per cent (seroma, haematoma, infection, nerve damage).

TECHNIQUE OF SNB

SNB in the head and neck is often technically challenging due to complex anatomy, small nodes, close proximity of primary melanoma and multiple drainage patterns. Pre-operative lymphoscintigraphy is essential to identify which draining lymph node fields contain the sentinel node(s). Technetium-99m antimony sulphur colloid is injected intradermally around the scar, and dynamic and static lymphoscintograms obtained. SNB should be performed within 18 hours of lymphoscintigraphy.

Incisions are marked out with consideration given to therapeutic neck dissection access should nodes be positive. Patent blue dye (1 mL) or isosulfan blue (USA only) is injected into the dermis around the primary scar. This should be performed once the patient is anaesthetized to allow the dye to move to the sentinel nodes (slow transit on the lymphoscintigraphy may require a small delay). Negative pressure on withdrawal of the needle is helpful to prevent inadvertent spraying of the dye (NB always wear gloves and a mask!). The primary site is widely excised first to avoid ‘shine through’ interference of isotope from the primary site. The sentinel nodes are then identified with the use of a gamma probe and blue dye. The blue dye is particularly important in the parotid where high radioactivity is found, making the gamma probe less accurate.

LYMPHADENECTOMY

Elective lymph node dissection has not demonstrated a survival benefit apart from a subgroup of intermediate thickness melanomas of the trunk. However, this study did not use lymphoscintigraphy to predict the draining nodal field which is essential in truncal melanomas to avoid dissecting the wrong nodes. No randomized studies have examined head and neck melanoma. Therapeutic node dissection (TND) is

<table>
<thead>
<tr>
<th>Margin</th>
<th>5 mm</th>
<th>1 cm</th>
<th>1-2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma in situ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 mm Breslow thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1 mm Breslow thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 38.10 Recommended surgical margins for melanoma.

Figure 38.25 Lymphoscintigraphy for melanoma.
considered standard treatment for patients who are sentinel node positive unless they are part of the MSLT II trial, or comorbidity precludes major surgery. Subset analysis of the MSLT I trial showed a 20 per cent survival benefit for sentinel node positive patients who underwent immediate completion lymphadenectomy versus those who develop clinical lymph node metastases.59 The extent of the TND is guided by the lymphoscintogram so that all potential second tier nodes are removed. All patients who are found to be node positive should undergo a whole body staging CT scan or PET/CT scan prior to definitive lymphadenectomy.

Patients presenting with palpable metastatic nodes should undergo a comprehensive neck dissection after confirmation with fine needle aspiration biopsy (Figures 38.26 and 38.27). The recurrence rate is reported at 0 per cent for modified radical neck dissection but 23 per cent when a selective approach is taken.65 However, the routine use of lymphoscintigraphy may enable more accurate prediction of at-risk nodal levels and a more selective approach. As with all cutaneous malignancies, the external jugular node should be removed with the specimen and other nodal groups not incorporated in standard comprehensive dissections may be at risk depending on the primary site (parotid, retro-auricular and occipital).15 Consideration should be also given to adjuvant radiotherapy as discussed below under Adjuvant radiotherapy.

UNKNOWN PRIMARY

In patients who present with cervical melanoma metastases, approximately 10 per cent will not have an identifiable primary site. A thorough head and neck examination should be completed including mucosal membranes and ophthalmoscopy, as well as potential non-head and neck draining sites (upper back/shoulders). Whole body CT should be used to complete staging prior to treatment.

There is little in the literature on the management of the unknown primary.68, 69 A comprehensive neck dissection should be performed based on the site of the metastasis. Prognosis is dependent on the nodal status more than the type of dissection68 and outcome is better than cases with known primaries.

ADJUVANT RADIOThERAPY

Desmoplastic neurotropic melanomas have recurrence rates of up to 50 per cent,70 postoperative adjuvant radiotherapy has been shown to improve local control.71 Other indications for irradiation include microscopically involved or close surgical margins where further resection is impractical, perineural spread or tumour satellites.72

The current indications for postoperative radiotherapy after lymphadenectomy are listed in Table 38.12. To date, no study has shown a significant improvement in regional control with radiotherapy, but an answer should be found with the TROG adjuvant radiotherapy trial.73

ADJUVANT CHEMOTHERAPY/IMMUNOTHERAPY

Dacarbazine, temozolamide and fotemustine are the most commonly used single agents for metastatic melanoma. They have a low toxicity profile and are easily administered, however response rates are only 18–24 per cent with complete response rates less than 5 per cent.41, 74 Vaccines remain experimental and occasional dramatic responses have been reported. Unfortunately, overall, no survival benefit has been shown. Interferon alpha 2B is approved for the treatment of metastatic melanoma, a meta-analysis showed a significant improvement in disease free survival but not overall survival.75

Table 38.12 Indications for postoperative radiotherapy.

<table>
<thead>
<tr>
<th>Palpable nodes</th>
<th>Parotid &gt; 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck &gt; 2</td>
<td></td>
</tr>
<tr>
<td>Extranodal spread</td>
<td>Neck &gt; 3 cm</td>
</tr>
</tbody>
</table>

Figure 38.26 Sentinel node biopsy for melanoma.

Figure 38.27 Comprehensive neck dissection (type III modified radical) and parotidectomy for metastatic melanoma.
Recently, a monoclonal antibody (anti-CTLA-4) called ipilimumab has shown a survival benefit. The median survival was 10 versus 6.4 months, but there are significant side effects including skin rashes, gastrointestinal and hepatic toxicity. Grade III and IV toxicity was seen in 10–15 per cent.76

However, a major advance in melanoma treatment has recently been made with targeted therapy known as BRAF and MEK inhibitors. Only 60 per cent of melanomas have the V600 BRAF mutation required for treatment to work. Dramatic results are seen within days of starting this oral medication. The side effects are minimal but interesting, with 27 per cent of patients in one study developing cutaneous SCCs. This mode of therapy is likely to become available off trial in the near future.77, 78

FOLLOW UP

Patients are followed up for a variety of reasons: to identify recurrence or new primaries (melanoma or NMSC); for education and for psychosocial support plus reassurance. Eighty five per cent of recurrences occur in the first three years following diagnosis, and most are symptomatic or clinically detectable. Routine investigations (imaging and blood tests) are unreliable and not cost effective, except for a chest x-ray and a rising LDH.41 See Table 38.13 for recommended follow up, but this should be tailored to the individual patient and institution.

Table 38.13  Suggested follow-up regime.

<table>
<thead>
<tr>
<th>Type</th>
<th>Follow-up Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma in situ</td>
<td>Every 6 months for life</td>
</tr>
<tr>
<td>Melanoma &lt; 1 mm</td>
<td>Every 4 months for three years</td>
</tr>
<tr>
<td></td>
<td>Every 6 months for life</td>
</tr>
<tr>
<td>Melanoma &gt; 1 mm</td>
<td>Every 3 months for three years</td>
</tr>
<tr>
<td></td>
<td>Every 6 months for life plus CXR ± LDH</td>
</tr>
</tbody>
</table>

Table 38.13: Suggested follow-up regime.

FOLLOW UP

Patients are followed up for a variety of reasons: to identify recurrence or new primaries (melanoma or NMSC); for education and for psychosocial support plus reassurance. Eighty five per cent of recurrences occur in the first three years following diagnosis, and most are symptomatic or clinically detectable. Routine investigations (imaging and blood tests) are unreliable and not cost effective, except for a chest x-ray and a rising LDH.41 See Table 38.13 for recommended follow up, but this should be tailored to the individual patient and institution.

KEY EVIDENCE

- Understanding the differences in biological behaviour and metastatic potential of different cutaneous cancers is key to appropriate management.
- Aggressive and metastatic cutaneous cancers should be managed in a multidisciplinary setting.

KEY LEARNING POINTS

- Basal cell cancers have very limited metastatic potential, but less common subtypes may be difficult to treat on the face due to extensive local invasion and indistinct margins.
- Cutaneous squamous cell carcinoma metastasise in less than 5 per cent of cases, however particular high risk features may increase this risk to 20 per cent. High risk patients should be considered for sentinel nodes biopsy or close observation.
- Most patients with metastatic cutaneous squamous cell carcinoma should be managed with parotidectomy or neck dissection and adjuvant radiotherapy. Early identification of nodal metastases may allow single modality therapy.
- Merkel cell carcinoma is a rare but aggressive cutaneous cancer with high regional and distant metastatic potential. Merkel cell carcinoma is radiosensitive and optimal management depends on tumour size and the presence of nodal metastases.
- Early diagnosis is the key to the effective treatment of melanoma.
- Sentinel node biopsy should be discussed in all patients with melanoma greater than 1 mm.
- Targeted therapy with new oncology drugs is showing great promise in the future management of melanoma, however currently there are few chemotherapeutic agents with demonstrated benefit in any form of cutaneous malignancy. Several trials are underway to further define the role of systemic therapy in melanoma and non-melanoma skin cancer.

REFERENCES


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73. ANZMTG Trial 1-02/TROG 02.01. A randomized clinical trial of surgery versus surgery plus adjuvant radiotherapy for regional control in patients with completely resected macroscopic nodal metastatic melanoma.


INTRODUCTION

Malignant tumours in the nose and paranasal sinuses present some of the most challenging problems in head and neck cancer. First, they are rare, making it difficult for any one person or institution to accrue large numbers and expertise in their management. They represent the area of greatest histological diversity in the body with every tissue type represented. This myriad of individual histologies with individual natural histories renders statistical analysis difficult. Patients initially develop relatively innocuous symptoms which are often ignored by them, their general practitioners and even ENT surgeons. As a consequence, patients more often present with extensive tumours with significant invasion of important adjacent structures, such as the intracranial cavity and orbit.

The combination of these factors means that optimum management can only really be offered in tertiary referral centres where expert imaging and histopathology underpin the medical and surgical oncology.

Surgical anatomy

The complex anatomy of the nose and paranasal sinuses and close proximity of the orbit and skull base can mask early presentation of tumours and compromise oncologic resection (Figure 39.1). The ethmoid bone can be viewed as a cross (perpendicular plate, crista galli and cribiform plate) with the two labyrinths hanging at either side composed of a number of individual cells (3–17). The cells are divided into an anterior and posterior group by the basal lamella of the middle turbinate. Both the lamina papyracea and skull base are intrinsically weak structures, with natural dehiscences where neurovascular structures cross. The roof of the ethmoids is largely composed of hard frontal bone, but the lateral lamella of the cribiform niche offers a route into the anterior cranial fossa as do the anterior and posterior ethmoidal foramina. Similarly, these provide a route into the orbit. The rule of 24-12-6 is well known, representing the average distance in millimetres from the anterior lacrimal crest to the anterior ethmoidal foramen (24), the anterior to posterior ethmoidal foramen (12) and the posterior ethmoid foramen to the optic canal (6), but there is considerable range in these distances and the optic canal can be very close to the posterior ethmoidal artery. Furthermore, the ethmoidal vessels may be multiple or missing. The anterior ethmoidal artery is more vulnerable during endoscopic surgery, running across the anterior skull base posterior to the suprabullar cell and frontal recess, often in a mucosal fold or dehiscent canal.
The posterior ethmoidal artery is usually more protected running within the bone of the roof.

The length and depth of the cribriform niche vary considerably (length 15.5–25.8 mm; depth 0–15.5 mm). Anterior to the crista galli an emissary vein connects to the sagittal sinus, providing a route of spread as do the olfactory fibres passing with their dural prolongation through the cribriform plate. The dura is closely applied in this area and has to be sharply dissected during craniofacial resection.

Behind the cribriform plate lies the jugum of the sphenoid and posterior to this the optic chiasm (mean 21 mm). Tumours invading the medial orbit may run subperiosteally to the apex and thence into the middle cranial fossa. The superior and inferior orbital fissures also offer routes of tumour exit and entry. The inferior fissure communicates with the pterygopalatine fossa medially and the infratemporal fossa laterally while the superior fissure leads to the cavernous sinus.

The sphenoid sinus is variable in size and shape and the optic nerve and internal carotid artery run in the lateral wall. The bone overlying these structures has been estimated to be clinically dehiscent in up to 20 per cent of cases and the opticocarotid recess is variable in depth. The cavernous sinus lies laterally and the foramen rotundum (V2) and pterygoid canal may impinge on the sinus cavity especially if well pneumatized (Figure 39.2). Superiorly sits the pituitary gland. The intersinus septum can be asymmetric and may attach to the lateral wall in the region of the carotid. When posterior ethmoid cells extend superiorly and lateral to the sphenoid (sphenoethmoidal or Onodi cells), the optic nerve and carotid are often exposed in the lateral wall of these cells (Figure 39.3).

The frontal sinus is variable in size and shape. It has asymmetric septations and may be impinged on by anterior ethmoidal cells pneumatizing from below. This makes drainage into the middle meatus more like an hourglass than a 'duct' and is referred to as the frontonasal recess.

The maxillary sinus is a bony box bounded by eye, nose, mouth, cheek, pterygoid space and nasopharynx. The palatine process of the maxilla forms the hard palate and floor of nasal cavity. Natural areas of weakness exist into the nose via the ostium and fontanelles, into the mouth via the premolar and molar teeth roots and into the eye and cheek via the infraorbital canal and foramen. The medial wall has a large opening, the maxillary hiatus, which in life is closed by inferior turbinate, uncinate and bulla of the ethmoid, lacrimal and perpendicular plate of the palatine. Areas without bone lying anterior and posterior to the uncinate are filled by mucosa and fibrous tissue and are referred to as ‘fontanelles’. The lateral wall is thus easily breached by tumours which may arise in the middle meatus.

Attached to the posterior wall of the maxilla are the pterygoid plates, part of the sphenoid. The space between the
plates and the sinus is the pterygomaxillary fissure, through which the maxillary artery runs. This, in turn, connects with the pterygopalatine fossa and the infratemporal fossa. The pterygopalatine fossa is divided into a neural component composed of pterygopalatine ganglion and maxillary nerve and a vascular component containing the terminal part of the maxillary artery and its branches. The infratemporal fossa lies beneath the skull base between the sidewall of the pharynx and ascending ramus of the mandible. It contains the pterygoid muscles, branches of the mandibular nerve, maxillary artery and the pterygoid venous plexus in the lateral pterygoid muscle. Once invaded, the excellent blood supply of these areas facilitate tumour dissemination.

The nasal septum consists of the quadrilateral cartilage, the vomer and perpendicular plate of the ethmoid. Anteriorly it is contiguous with the medial crura of the lower lateral cartilages. Tumours in this area can escape superiorly into the external nasal structures and inferiorly into the upper lip and gingivobuccal sulcus.3

Fortunately, the lymphatic drainage from the sinuses is relatively poor to the retropharyngeal and jugulodigastric nodes, but this is not true of the nasal vestibule, anterior septum and columella from whence bilateral cervical spread can occur to the submandibular region.

**INCIDENCE AND AETIOLOGICAL FACTORS**

Malignant tumours of the nose and sinuses are rare constituting approximately 3 per cent of head and neck malignancy when tumours of the external nasal skin are excluded. In most countries fewer than 1/100,000 individuals per year are affected but other factors, notably occupational, may distort this. A number of occupations have been associated with the development of tumours in this area most notably woodworking (Table 39.1).4 The high incidence of adenocarcinoma of the ethmoids in the furniture industry around High Wycombe was first noted by Acherson and colleagues5 and was subsequently shown to be due to hard wood exposure, such as mahogany. Only those jobs, such as lathing and sanding which create dust particles of greater than 5 μm diameter seem susceptible, increasing the relative risk as compared to the normal population by 70-fold, although it

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Relative risk</th>
<th>Suspected carcinogen</th>
<th>Latent period (year)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodworkers</td>
<td>70</td>
<td>Dust 5 μm diameter</td>
<td>35</td>
<td>Adenocarcinoma (hardwood); squamous (softwood)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aldehydes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aflatoxins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chromium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tannins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leather/shoe manufacturers</td>
<td>87</td>
<td>Dust</td>
<td>55</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aldehydes</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Aflatoxins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tannins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chrome pigment manufacturers</td>
<td>&gt;21</td>
<td>Calcium chromate</td>
<td>–</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Isopropyl alcohol manufacturers</td>
<td>&gt;21</td>
<td>Zinc potassium chromate</td>
<td>&lt;20</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isopropyl oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Textile and clothing</td>
<td>5–8</td>
<td>Wool dust and dyes</td>
<td>–</td>
<td>Malignant melanoma</td>
</tr>
</tbody>
</table>
is not known which component of the dust is responsible. The duration of exposure and interval between exposure and development of the tumour was initially reported as over 20 years in both respects. However, it is clear that there are a number of individuals who develop the tumour with much shorter exposure and lag time.

Other occupations have also been implicated although exposure to cigarette smoke and alcohol appears less damaging in this area than in the rest of the upper aerodigestive tract. 1–6, 7

AGE AND SEX

Malignant tumours in this area can occur at any age though the majority present in the sixth and seventh decades with some tumours, such as malignant melanoma, having a propensity for the elderly. When occupational factors are excluded the male to female ratio is approximately 2:1.

HISTOLOGY

As previously stated, the nose and sinuses have one of the largest ranges of histopathologies in the body (Table 39.2). As a consequence, considerable histological expertise may be required to confirm the diagnosis utilizing a battery of immunohistochemistry.

The distinction between benign and malignant is less clear in this area where individuals may succumb to the local effects of a malignant tumour before manifesting the sine qua non of metastatic disease and, similarly, very large benign tumours may also lead to the demise of their host.

**Squamous cell carcinoma** remains the most common sinonasal malignancy but it can often be difficult to say exactly where the tumour arose as often the nasal cavity and antroethmoid regions are affected. The majority probably arise in the maxillary sinus (Figure 39.4). The degree of differentiation varies and may be getting poorer with time though generally combined surgical and medical oncologic treatment is used. In poorly differentiated or undifferentiated sinonasal carcinomas however, chemoradiation alone may be curative. Rarely the nasal septum or columella are the primary site. These tumours have a particularly poor prognosis in part due to the possibility of bilateral metastatic spread to cervical nodes.

**Adenocarcinoma** is well recognized due to its association with occupation although <30 per cent of patients with this condition are woodworkers. 9 These tumours usually arise in the middle meatus and spread into the ethmoid (Figure 39.5). However, they can spread anteriorly to present with a mass in the glabella or posteriorly into the sphenoid recess and nasopharynx. 9 Differentiation ranges from high to low grade with a commensurate effect on outcome. 10 Adenocarcinoma is generally rather radioresistant but combined therapy is usually offered. 11 Many patients require a craniofacial but in selected cases have been treated successfully by an endoscopic resection. 12–14 The use of topical 5-fluorouracil and surgical debulking has been advocated by some. 15

### Table 39.2  Histology of malignant sinonasal neoplasia.

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial epidermoid</td>
<td>Squamous cell carcinoma (+spindle cell, verrucous, transitional)</td>
</tr>
<tr>
<td>Epithelial non-epidermoid</td>
<td>Adenoid cystic carcinoma</td>
</tr>
<tr>
<td>Neuroectodermal</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Odontogenic tumours</td>
<td>Ameloblastoma</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Vascular</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Cartilaginous</td>
<td>Chondrosarcoma (+mesenchymal)</td>
</tr>
<tr>
<td>Osseous</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Lymphoreticular</td>
<td>Non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Histiocytic/dendritic cell malignancies</td>
</tr>
</tbody>
</table>

**Adenoid cystic carcinoma** is well known for its propensity to spread along perineural lymphatics which compromises attempts at excision. However, it can also embolize along these routes and is known to produce blood-borne metastases, classically to the lung while lymphatic spread is rare. 16 The natural history can be extensive, with good five-year figures, but there is progressive loss with time so that at 20 years survival is quoted at 5 per cent or less. Indeed, it is likely that all patients eventually die from this disease unless some other event intervenes. Treatment is generally combined surgery and radiotherapy though there is no evidence that radiotherapy adds any additional chance of cure, rather it delays recurrence.

**Malignant melanoma** is a rare mucosal neoplasm of neural crest origin usually affecting the elderly. 17 It typically affects the nasal mucosa and presents with nasal blockage and bleeding (Figure 39.6). Satellite lesions and areas of amelanotic tumour can make it difficult to determine tumour extent. However, the tumour exhibits an immunological symbiosis with its host which means that some patients may survive for extended periods with residual disease while...
Consequently, an endoscopic resection is as effective as more radical procedures and craniofacial is contraindicated. The role of radiotherapy is debated but may confer a small advantage. However, this cannot be confirmed statistically, largely due to the poor prognosis and rarity of the condition. In a cohort of 58 patients, five-year actuarial survival was 28 per cent falling to 20 per cent at ten years. Olfactory neuroblastoma or esthesioneuroblastoma classically arises from olfactory epithelium in the upper nasal vault although can originate elsewhere in the nose. Once considered very rare, with improved histologic techniques, it is more frequently diagnosed. Its symptoms of blockage (93 per cent), bleeding (53 per cent) and reduced olfaction are not specific though the presence of a mass in the upper nasal cavity with associated skull base erosion is typical (Figure 39.7). Age ranged from 12 to 70 years (mean 46 years) in a cohort of 42 patients (though 3–90 years has been described with a bimodal peak in the second/third and sixth/seventh decades). As a neuroendocrine tumour, metabolites such as vanillylmandelic acid may be detected. Cervical metastases have been described in up to 23 per cent. The craniofacial resection was designed to deal with this tumour, which can involve the olfactory bulbs and tracts microscopically at an early stage. Consequently, these are routinely resected in craniofacial approaches. Outcome analysis showed a higher rate of recurrence when craniofacial resection was not combined with radiotherapy so
Endoscopic resection is being increasingly offered for this tumour particularly when it arises from the middle and superior turbinates. However, this should always be combined with radiotherapy. Adjuvant chemotherapy is also being offered in many protocols. Late recurrence has been observed up to 14 years after initial treatment, sometimes in the contralateral eye or as disseminated dural plaques at some distance from the original lesion.

**Lymphoma.** No area of histology has been subject to so many changes in classification as lymphoid lesions. In addition to plasmacytoma, extranodal lymphoma, such as sino-nasal B cell and T/NK-cell lymphomas present specific problems. Lymphomas comprise approximately 6 per cent of malignant sino-nasal tumours and less than 1 per cent of lymphomas occur in this area. B-cell tumours present as an infiltrating indurated mass often affecting the external nose and soft tissues. T/NK-cell tumours are associated with Epstein–Barr exposure and are therefore more common in the Far East. They produce aggressive destructive lesions of the midface (Figure 39.8), previously referred to as ‘midline granuloma’ and a host of other pseudonyms. The most important thing is to obtain representative tissue and alert the pathologist about your suspected diagnosis as this can be difficult in the presence of significant inflammation and necrosis. Once diagnosed, a full staging is undertaken and treatment is by established chemoradiotherapy regimes depending on the extent of spread.

**Chondrosarcomas** arise in the nasal cavity, often from the septum or maxillary alveolus, and spread superiorly into the skull base and inferiorly into the palate (Figure 39.9). They may be multifocal and often pursue an indolent course of frequent recurrence over many years. They may be well differentiated resembling normal cartilage, but the term chondroma should not be used as these tumours are associated with a high morbidity as cranial nerves become involved, sometimes bilaterally, and death results from uncontrolled local intracranial disease. The age range includes both young and old and the tumour is generally more aggressive in younger patients. Craniofacial resection usually offers the best
oncologic approach particularly as these tumours are not radiosensitive.12

A particularly aggressive and fortunately rare form, mesenchymal chondrosarcoma, can affect the nose and sinuses. It affects the young, metastasizes to nodes and bone and despite radical medical and surgical oncologic treatment, there are few survivors.

CLASSIFICATION AND STAGING

Although various classification systems have been devised for the nasal cavity and paranasal sinuses, these are of less prognostic use than elsewhere in the head and neck. The diversity of histology and associated natural histories undermines the value of five-year survival rates nor are modern imaging and management options taken into account by these systems.

The TNM classification (Table 39.3) may be of some value but most patients present with advanced local disease whereas lymphatic and haematogenous spread occurs relatively late, if at all, as patients often succumb before this becomes evident.39

There have been a number of attempts to classify according to extent, e.g. Kadish et al.’s staging for olfactory neuroblastoma,40 but these are relatively crude. Histological classification based on degree of differentiation may be of some help in predicting prognosis, e.g. in adenocarcinoma. An interesting study compared the AJCC-UICC 1997, 2002 and their own classification system, perhaps not surprisingly, finding their own to be superior.41

SITE

It can be difficult to determine the exact site of origin in tumours which are often extensive at presentation. However, improvements in imaging and endoscopy have helped enormously in this respect with sometimes apparently extensive tumours having limited origin from the lateral wall of the nose. The different disciplines dealing with these tumours can also give a false impression as maxillofacial surgeons may deal with maxillary tumours leading to a reduction in the numbers seen by ENT colleagues. However, squamous cell carcinoma of the maxilla almost certainly remains the most common tumour in this area even if it is difficult to estimate the percentage of the whole group. Tumours arising in the middle meatus will involve the nasal cavity, ethmoid and antrum at an early stage. From there, disease may spread into the sphenoid and/or frontal sinus whereas primary tumours of these sinuses are extremely rare for reasons that are unclear.

While primary tumours predominate in this area, it should not be forgotten that tumours from adjacent structures, such as the orbit may involve the sinuses, and secondary deposits from other sites, such as kidney, bronchus, breast, thyroid and pancreas have all be described (Figure 39.10). However, these occur with sufficient rarity to render total body screening less than cost-effective except in the presence of a clear cell adenocarcinoma of the ethmoid (often from a hypernephroma of the kidney) or where there are suggestive symptoms and/or a previous history.

MANAGEMENT

Diagnosis

CLINICAL FEATURES

See also Table 39.4 and Figure 39.11.

Nasal cavity

Tumours arising in the nasal cavity present with unilateral nasal obstruction, discharge which may be blood-stained, a reduction in the sense of smell and occasionally facial discomfort. These symptoms do not always arouse suspicion and it is only when the eye or external soft tissues are involved that the problem may be diagnosed. Rarely some tumours, such as malignant melanoma disseminate locally with multiple satellite lesions on the mucosa and may extend into the soft tissues of the midface.

Ethmoid

Ethmoidal tumours readily transgress the lamina papyracea and anterior skull base, but both dura and orbital periosteum are relatively resistant to spread. They produce nasal symptoms as before and may extend across the midline into the contralateral ethmoid to produce bilateral symptoms. Displacement of the eye anteriorly may produce double vision due to a mass effect or latterly by infiltration. The size of tumour required to produce clinical symptoms is greater here than in the posterior ethmoid where infiltration of the

Figure 39.9 A coronal computed tomography scan showing chondrosarcoma of the posterior nasal septum and basisphenoid.
orbital apex may affect vision, movement and the position of the eye at an early stage. The degree of diplopia varies with the speed of tumour growth and rapid displacement can be associated with exposure of the cornea, keratosis and ulceration. Involvement of the nasolacrimal apparatus will result in epiphora, again a relatively common symptom.

From the orbital apex tumour can spread posteriorly either intra- or extraperiosteally to affect the cavernous sinus with its respective cranial nerves, the internal carotid artery and thence reach the middle cranial fossa. Superior extension of the tumour through the lateral lamella of the cribriform plate, along the anterior and posterior neurovascular bundles or directly through the fovea is usually asymptomatic. Cerebrospinal fluid leaks and meningitis are exceptionally rare and even when the dura has been breached and extensive frontal lobe infiltration occurs, any personality changes are usually too subtle to be noticed.

Tumours arising within the anterior ethmoids/middle meatus can spread into the maxillary sinus and/or into the frontal sinus via the frontal recess occasionally producing a mucocele, though this is a rare phenomenon in the presence of a malignant tumour.

<table>
<thead>
<tr>
<th>Table 39.3</th>
<th>TNM classification.39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification Primary tumour (T)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Maxillary sinus</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour limited to the maxillary sinus mucosa with no erosion or destruction of bone</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V2, nasopharynx or clivus</td>
</tr>
<tr>
<td><strong>Nasal cavity and ethmoid sinus</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour restricted to any one subsite, with or without bony invasion</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invading two subsites in a single region within the nasoethmoidal complex, with or without bony invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate or cribriform plate</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades any of the following: anterior orbital contents, skin of the nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx or clivus</td>
</tr>
<tr>
<td><strong>Regional lymph nodes (N)</strong></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>NO</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis as described below:</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node, more than 6 cm in greatest dimension</td>
</tr>
<tr>
<td><strong>Distant metastasis (M)</strong></td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>MO</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Maxillary sinus

In addition to medial spread into the nasal cavity tumours may spread superiorly, particularly through the infraorbital canal. This can produce paraesthesia of the cheek in addition to orbital symptoms. Tumour can also spread directly through bone or infraorbital foramen to produce a mass in the cheek which may ulcerate. Inferior spread produces a mass, loosening of teeth and/or an oroantral fistula. Posterior spread into the pterygoid region and infratemporal fossa is associated with trismus and pain.

Sphenoid and frontal sinuses

It is not known why these sinuses are rarely the site of primary malignant tumours and are generally only involved by local spread or due to involvement of the surrounding bone. A frontal sinus tumour is most likely to present with swelling of the forehead. Sphenoid tumours produce orbital symptoms, in particular visual loss. In certain tumours, such as chondrosarcoma, this can be bilateral.

Orbit

Over 50 per cent of patients with sinonasal tumours present with orbital symptoms, most commonly orbital displacement and periorbital swelling, followed by reduction in visual acuity in up to 20 per cent of patients. Orbital symptoms are most frequently associated with ethmoidal tumours (62 per cent) but occur in just under half of nasal tumours. Orbital invasion occurs in 60–80 per cent of maxillary sinus malignancies. Iannetti et al. have identified three stages of orbital invasion: (1) erosion or destruction of the medial orbital wall; (2) extraconal invasion of periorbital fat; and (3) invasion of the medial rectus muscle, optic nerve, ocular bulb or eyelid skin.

Metastatic spread

The paucity of lymphatic drainage from the sinuses and the propensity for local spread results in a low cited incidence of cervical lymphadenopathy (approximately 10 per cent of epithelial malignancy). However, this varies from tumour to tumour and may occur at any time during the course of the disease. The submandibular, jugulodiagastric, prefacial and postfacial nodes are most commonly involved by tumours from the septum and in particular columellar region which

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**Figure 39.10** A secondary deposit of adenocarcinoma from the lung in the floor of sphenoid sinus.

**Table 39.4** Site of origin and clinical features.

<table>
<thead>
<tr>
<th>Primary</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal cavity</td>
<td>Nasal blockage, bleeding, hyposmia</td>
</tr>
<tr>
<td>Inferiorly into palate</td>
<td>Mass</td>
</tr>
<tr>
<td>Posteriorly into nasopharynx and Eustachian orifice</td>
<td>Middle ear effusion</td>
</tr>
<tr>
<td>Anterosuperiorly into the nasal bone</td>
<td>Glabellar mass</td>
</tr>
<tr>
<td>Externally into skin</td>
<td>Mass/ulceration</td>
</tr>
<tr>
<td>Superiorly into anterior cranial fossa</td>
<td>Minimal, personality change?, headache</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>As above</td>
</tr>
<tr>
<td>Medially into nasal cavity</td>
<td>Mass, ulceration of skin, paraesthesia</td>
</tr>
<tr>
<td>Anteriorly into cheek directly or via infraorbital canal</td>
<td>Trismus and pain</td>
</tr>
<tr>
<td>Posteriorly into pterygoid region and infratemporal fossae</td>
<td>Mass, loosening of teeth, malignant oroantral fistula</td>
</tr>
<tr>
<td>Inferiorly into the palate or alveolar ridge</td>
<td>Proptosis, diplopia</td>
</tr>
<tr>
<td>Superiorly into orbit</td>
<td>As above, can cross to contralateral side</td>
</tr>
<tr>
<td>Ethmoid sinuses</td>
<td>Mucus retention</td>
</tr>
<tr>
<td>Medially into nasal cavity</td>
<td>Proptosis, chemosis, diplopia, visual loss, epiphora</td>
</tr>
<tr>
<td>Inferolaterally into maxilla</td>
<td>Minimal, personality change?</td>
</tr>
<tr>
<td>Medially into orbit</td>
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<td>Superiorly into the anterior cranial fossa</td>
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sometimes spread bilaterally. This is invariably associated with a poor prognosis.

Blood-borne metastases are relatively uncommon but with longer follow up and in the presence of uncontrolled local disease may be relatively common. This is particularly true of olfactory neuroblastoma and malignant melanoma. Adenoid cystic carcinoma is also known to spread along perineural lymphatics either directly or by embolization, often presenting at some distance from the original tumour though patients can survive for some time with disseminated disease.

Thus, although these problems are rare, particularly at presentation, complaints of an unresolving non-productive cough, bone pain or significant fatigue should prompt further investigation.

**IMAGING**

The availability of fine detail and rapidly performed computed tomography (CT) producing images in the coronal, axial and sagittal plane combined with magnetic resonance imaging (MRI) provides an accurate depiction of tumour extent and sometimes an indication of tumour type. The preoperative evaluation protocol developed at the Royal National Throat Nose and Ear Hospital is shown in Table 39.5. Earlier studies suggest that a combination of these modalities produced an accuracy of 98 per cent in predicting extent of tumour, though the assessment of spread through the orbital periosteum and dura still requires macro- and microscopic confirmation. MRI alone is not sufficient as
early erosion of the cribriform plate is still best shown on coronal CT.\textsuperscript{46}

The extent to which imaging beyond the nose and sinuses is undertaken will depend to some extent upon the histology and patient symptoms. For most malignant tumours, it is not routinely undertaken but poorly differentiated tumours, such as sinonasal undifferentiated carcinoma, neuroendocrine carcinoma and lymphomas require more extensive staging. Similarly, adenoid cystic carcinoma which has a propensity to spread to the lung, requires a chest x-ray and/or chest CT.

**BIOPSY**

Although this can sometimes be performed under no or local anaesthesia in the outpatient setting, it is generally more appropriate to perform a biopsy under endoscopic control and general anaesthesia. This is most likely to produce representative tissue, without transgression of normal tissue planes in a controlled setting.

During the surgical procedure, frozen section facilities should be available to confirm complete resection.

**ULTRASOUND AND FINE NEEDLE ASPIRATE**

If ultrasound facilities are available, this is offered to selected patients combined with fine needle aspiration which offers an accurate staging and an important base line for subsequent follow up.\textsuperscript{49}

**ADDITIONAL TESTS**

The accuracy and utility of positron electron transmission (PET) remain to be established in the nose and sinuses but may prove of value, particularly as it becomes more readily available.\textsuperscript{50} In patients in whom bone metastases are suspected, a formal radionucleotide bone scan should be undertaken.

Haematological investigations including bone marrow aspirate may be appropriate in cases of chloroma (leukaemic deposits), lymphoma and in individuals where bone and liver secondaries are suspected.

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### Table 39.5 Protocol for investigation of sinonasal malignancy.\textsuperscript{48}

<table>
<thead>
<tr>
<th>Preoperative: endoscopic examination under anaesthesia</th>
<th>Imaging</th>
<th>CT</th>
<th>Fine detail coronal, axial ± sagittal</th>
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<tr>
<td></td>
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<td>MRI</td>
<td>Contrast enhancement if skull base affected</td>
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<td>Coronal, axial and sagittal T\textsubscript{1} sequences, pre- and post-gadolinium–DTPA</td>
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<td>Axial T\textsubscript{2}-weighted sequences</td>
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<td></td>
<td></td>
<td>± CXR/CT chest\textsuperscript{a}</td>
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<td>± CT abdomen\textsuperscript{a}</td>
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<tr>
<th>Postoperative follow-up protocol: endoscopic examination under anaesthesia</th>
<th>Imaging</th>
<th>MRI\textsuperscript{a}</th>
<th>Coronal, axial and sagittal T\textsubscript{1} sequences, pre- and post-gadolinium–DTPA</th>
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<tr>
<td></td>
<td>MRI\textsuperscript{b}</td>
<td>Axial T\textsubscript{2}-weighted sequences</td>
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\textsuperscript{a}Depending on histology.

\textsuperscript{b}Every four months for first two years, then six-monthly thereafter depending on histology.

CT, computed tomography; CXR, chest x-ray; DTPA, diethylenetriamine penta-acetic acid; MRI, magnetic resonance imaging.

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**ANAESTHESIA**

All the following procedures are performed under general anaesthesia in the reversed Trendelenburg position with 15–20° of head elevation. Nasal mucosal vasoconstriction is achieved by instilling 2–4 mL of Moffat’s solution (10 per cent cocaine, 2 mL, 1:1000 adrenaline 2 mL and 0.9 per cent sodium bicarbonate 1 mL) in the anaesthetic room with the patient head down for approximately 10 minutes. The incision line(s) is infiltrated with 2 per cent xylocaine and adrenaline 1:80 000 and during the procedure ribbon gauzes soaked in 1:1000 adrenaline are applied to the surgical field.

In the case of craniofacial resection, patients are started on phenytoin 200 mg/day 48 hours before surgery. During the surgery, manipulation of the blood pressure and p\textsubscript{CO\textsubscript{2}} are generally sufficient to reduce brain mass without resort to systemic diuretics.\textsuperscript{51}

A broad-spectrum antibiotic, e.g. co-amoxicillin clavulanate or a cephalosporin and metronidazole, is generally administered with induction and continued while any packing is in place.

**SURGERY**

### Craniofacial resection

Since its introduction in the 1970s, craniofacial resection has become the ‘gold standard’ for tumours affecting the anterior skull base.\textsuperscript{52 53 54 55} This approach in its many variations offers a genuine attempt at oncologic resection of the tumour.

**INDICATIONS**

- Malignant tumours which require surgical resection, involving the anterior skull base.

**CONTRAINDICATIONS**

- Extensive frontal lobe and/or middle cranial fossa involvement or bilateral orbital invasion/optic chiasm.
Certain histologies, such as mucosal malignant melanoma where extent of surgery does not influence outcome and those where surgery is not appropriate, such as sinonasal undifferentiated carcinoma, lymphoma, plasmacytoma.

Distant metastasis. However, craniofacial may be considered as a palliative procedure in certain circumstances such as lung metastases in adenoid cystic carcinoma.

INCISION

Following bilateral temporal tarsorrhaphies, an extended lateral rhinotomy is made on the side of maximal tumour involvement (Figure 39.12). Many variations on this theme have been described including a coronal flap combined with a midfacial degloving which is generally employed in young patients\textsuperscript{56} and a subcranial approach.\textsuperscript{57, 56, 59}

TECHNIQUE

The soft tissues of the face are mobilized by subperiostial elevation to expose the nasal bones, frontal processes of the maxilla and frontal bone up to the hairline via an extended lateral rhinotomy.\textsuperscript{12} A self-retaining retractor is then placed superiorly. If a midfacial degloving approach is used, the middle third of the face is elevated as described while the forehead is elevated in the subperiosteal plane via a coronal scalp incision.

Through the lateral rhinotomy, the upper lateral cartilage is separated from the nasal bone to allow complete retraction of the nasal ala, and the incision may be carried on into the vestibule though wherever possible this attachment is preserved.

Usually the tumour is mobilized to define its relationship with the orbit. The orbital periorbitaeum is elevated to expose the lacrimal fossa and the medial orbital wall. The nasolacrimal duct is often transacted obliquely at this point. The trochlea is sharply detached and the anterior and posterior ethmoidal arteries are divided after bipolar coagulation. This allows lateral retraction of the orbital contents. If the lamina

A shield-shaped craniotomy is performed above the level of the supraorbital rim to include the frontal sinus (Figure 39.13). The size and symmetry of the craniotomy will vary depending upon the extent of the tumour but is usually approximately $3 \times 3 \times 3.5$ cm. The bone cuts are made with a rosehead cutting burr or fissure burr until the dura is just visible. Mini-plates are then drilled and attached (Figure 39.14). The bone flap is then removed using straight and curved osteotomes and stored for subsequent reconstruction.

The frontal sinus which has been opened by this manoeuvre is cleared of its mucosa and the posterior wall removed combined with a wide dissection of the dura. It is important to extend this dissection as far laterally to allow the dura to fall back as the brain shrinks with the anaesthesia.

Dissection around the cribriform plate and crista galli is facilitated by the use of the operating microscope. The dural prolongations and olfactory fibres are cut using a No. 11 scalpel blade and the dissection continued using neurosurgical patties and a Freer’s elevator. This dissection continues until the cribriform plate is exposed and continues on to the jugum of the sphenoid. Tumour may be encountered during the dissection and will necessitate adjacent dural

Figure 39.12 Clinical photograph showing extended lateral rhinotomy incision for craniofacial resection.

Figure 39.13 Clinical photograph showing shield-shaped frontal osteotomy.

Figure 39.14 Attachment of miniplates to the frontal osteotomy.
The extent of the dural resection will depend upon the extent of the tumour, but in cases of olfactory neuroblastoma routinely the olfactory bulb and tracts are removed in continuity. The anterior and posterior ethmoidal arteries are coagulated with the bipolar diathermy although care must be exercised as the optic nerve is approached.

Osteotomies are performed around the cribriform plate through the ethmoidal and sphenoid roofs (Figure 39.15). These osteotomies are joined to those around the lamina papyracea and through the perpendicular plate/place of the ethmoid. The posterior osteotomy crosses the planum sphenoidale to include the anterior face of the sphenoid and the nasal septum is separated by quadrilateral cuts (Figure 39.16). The osteotomies may be achieved with a burr and/or curved osteotome. Once the specimen is mobilized this can be removed, haemostasis achieved and the cavity inspected for further resection. This can be done using the operating microscope or endoscope allowing complete exenteration of any residual ethmoidal cells, removal of mucosa of the sphenoid and maxillary antrum if required. It is advisable to fashion a large middle meatal antrostomy to prevent subsequent infection.

Occasionally, the dura has small defects which can be repaired primarily but more often a formal repair is required. Generally, this is undertaken with fascia lata held in place with fibrin glue to which a split-skin graft taken from the thigh is applied inferiorly. A layer of Sofradex soaked gel foam is applied to the skin graft and the cavity is packed with 5 cm ribbon gauze soaked in Whitehead’s varnish (compound iodoform paint; iodoform, benzoin prepared storax, tolu balsam and solvent ether).  

**POSTOPERATIVE CARE**

Patients are kept in a neutral position of approximately 15° for the first 2 or 3 days and then gently elevated, usually getting out of bed on the fifth day. Neurological observations continue for at least 24 hours. Fluid intake is initially restricted to match the inevitable diuresis experienced in the first 24–36 hours. The urinary catheter is removed on the second or third day and facial sutures after 5–7 days. All patients experience some degree of cerebrospinal rhinorrhoea initially so broad-spectrum antibiotics are continued until the nasal packing is removed under a general anaesthetic at 10–12 days. The anticonvulsant is continued for 6 weeks following the operation and patients must douche the nose long term.

**COMPLICATIONS**

Complications using the extended lateral rhinotomy and fascia lata/skin graft repair are few. Duration of the entire operation is a mean of 3.3 hours and the hospital stay 14 days.  

In common with the variations of the incision (subcranial, coronal), a variety of other repair techniques have been described including pericranial flaps and free flaps.

The frontal bone flap is replaced and secured with miniplates. The periosteum and subcutaneous layer is closed with absorbable sutures and the skin closed with clips or fine skin sutures. A pressure dressing is applied to both the head and leg.
Complications are:

- immediate:
  - convulsions
  - haemorrhage
  - air embolism

- intermediate:
  - cerebrovascular accident
  - confusion
  - pulmonary embolism
  - meningitis
  - aerocele

- long term:
  - haemorrhage
  - frontal abscess/encephalitis
  - bone necrosis/fistula
  - cerebrospinal fluid leak
  - epilepsy
  - epiphora
  - diplopia
  - serous otitis media
  - sinusitis/mucocele
  - cellulitis
  - pituitary deficiency.

Midfacial degloving

The degloving approach affords excellent access to the middle third of the face and can be used alone or combined with a coronal scalp incision for craniofacial resection or with an endoscope or even microscope for greater visualization. It was popularized by Casson et al.\textsuperscript{15} in the 1970s and Price\textsuperscript{67} in the 1980s.

INDICATIONS

- Selected malignant tumours affecting the nasal cavity, maxilla, ethmoids, sphenoid, pterygopalatine and infratemporal fossae.\textsuperscript{56} A bilateral maxillectomy can be performed via this approach if required.

CONTRAINDICATIONS

- The limits of resection are posteriorly the posterior wall of the sphenoid, pterygoid plates and muscles, superiorly the skull base and laterally the coronoid process of the mandible.

INCISION

After temporary tarsooraphies, a bilateral sublabial incision is made from maxillary tuberosity to tuberosity down to bone (Figure 39.17). Routine rhinoplasty intercartilaginous incisions are made extending into a transfixion incision along the dorsal and caudal borders of the cartilaginous septum, separating it from the medial crura of the lower lateral cartilages (Figure 39.18). The circumferential incisions are joined across the floor of the nose just anterior to the pyriform aperture (Figure 39.19).

Figure 39.17  Midfacial degloving: a diagram showing a bilateral sublabial incision from maxillary tuberosity to tuberosity down to bone.

Figure 39.18  Rhinoplasty type intercartilaginous incisions, transfixion and complete mobilization.

TECHNIQUE

The soft tissues of the midface are elevated subperiosteally up to the infraorbital nerve on each side to display the pyriform aperture (Figure 39.19). The soft tissues over the nasal bridge are elevated as far as the root of the nose and laterally to
complete the mobilization from below so that the mid-third of the face is completely elevated and can be lifted superiorly over the nasal skeleton (Figure 39.20). Having achieved this, the nasal cavities and maxillary sinuses can be opened using drills, hammers and osteotomes and upcutting bone forceps and thence the maxillary and sphenopalatine arteries accessed and ligated.

Thence the ethmoids, sphenoid, nasopharynx and structures posterior and lateral to the maxillae are reached for further resection. A Whitehead’s varnish pack can be inserted if there is a significant ooze at the end of the procedure.

Closure of the incisions must be done with care to avoid complications, using absorbable suture material. The bridge of the nose may be taped or a rhinoplasty dressing applied for a few days.

Packing is usually removed under a short general anaesthetic and patients advised to use saline douching daily until crusting settles.

**COMPLICATIONS**

These are generally rare and are:

- immediate/early:
  - haemorrhage
  - facial bruising
  - infraorbital paraesthesia
- late:
  - vestibular stenosis
  - oro-antral fistula
  - epiphora
  - septal perforation
  - upward tip rotation.

**Lateral rhinotomy**

This operation has been available since 1848 but is usually ascribed to Moure in 1902. It is rapid and gives excellent access to the nasal cavity through which a medial maxillectomy can be undertaken. It can be extended both superiorly (and inferiorly) if required.

**INDICATIONS**

- Any malignant tumour affecting the nasal septum, lateral wall and extending into ethmoid, sphenoid, maxillary sinuses and up to the anterior skull base.

**CONTRAINDICATIONS**

- Malignant tumours which have spread beyond these areas when an extended procedure is required, i.e. craniofacial, maxillectomy.

**INCISION**

After a temporary tarsoraphy, the incision runs from the level of the medial canthus, midway between the canthus and nasal bridge in the nasomaxillary groove, curving round the lower ala into the nasal cavity (Figure 39.21). The incision is made down to bone and a subperiosteal dissection undertaken over the anterior face of the maxilla. The nasal cavity is opened and the nasal flap lifted and also dissected off the nasal bones and cartilages (Figure 39.22). However, if possible, the incision should stop before the ala to avoid postoperative alar lift.

**TECHNIQUE**

Through this incision, the orbital perioristium can be dissected from the lamina and the nasolacrimal duct mobilized.
The duct can be transected obliquely adjacent to the sac with little risk of stenosis, although sometimes an O’Donoghue stent may be inserted or the sac opened as a formal rhinostomy. The anterior and posterior ethmoidal arteries can be ligated or bipolar diathermied (with care in the posterior ethmoid due to the proximity of the optic nerve). An en bloc or piecemeal removal of the lateral nasal wall can be undertaken including the pyriform aperture, nasal bones, frontal process of the maxilla and anterior maxillary wall, the medial orbital floor and rim, ethmoids, lamina papyracea and lacrimal fossa depending on the extent of the tumour. Then the sphenoid sinus can be opened and if the incision is extended superiorly, the frontal can be accessed. Orbital periosteum can be resected if required and grafted with skin or fascia.

As before, Whitehead’s varnish packing\(^6\) can be used if necessary and the incision closed with absorbable subcutaneous and skin sutures. Considerable care must be exercised at the alar margin to get good approximation and minimize the risk of contracture.

**COMPLICATIONS**

Complications are:

- **early:**
  - haemorrhage
  - orbital oedema
  - cerebrospinal fluid leak/meningitis

- **late:**
  - epiphora
  - diplopia
  - cosmetic – webbing, alar lift, vestibular stenosis
  - facial paraesthesia
  - frontal sinus obstruction, infection, mucocele.

**Maxillectomy**

A traditional total maxillectomy via a Weber-Fergusson or Weber-Dieffenbach incision (Figures 39.23 and 39.24) may still be employed but may be replaced by a midfacial degloving approach particularly in younger patients.

**INDICATIONS**

- Malignant tumours of the maxilla involving the inferior, superior, anterior or posterior walls. Extension through the orbital perisotum superiorly will necessitate orbital clearance. Preoperatively, the patient should consult a prosthetic orthodontist to take an impression of the upper alveolus for future reconstruction.
CONTRAINDICATIONS

- Extension superiorly to the skull base will require an additional craniofacial approach.

INCISION

After temporary tarsoraphy, the classic Weber-Fergusson incision extends 1 cm lateral to the lateral canthus and medially approximately 3 mm below the lower eyelash. The placement is important as if too close to the lashes, ectropion can result, whereas if too low, oedema may occur. At the medial canthus, the incision curves inferiorly into the nasomaxillary groove down to the alar margin. It then continues medially to the midline where it turns at a right angle dividing the upper lip.

The incision then extends round the upper alveolus in the gingivobuccal sulcus as far as the maxillary tuberosity. Medially the incision passes onto the hard palate between the central incisors as far as the junction of the hard and soft palate where it crosses laterally towards the posterior aspect of the maxillary tuberosity (Figure 39.25). The palatal incision in the mucosa should lie approximately 3 mm lateral to the midline so that a mucoperiosteal flap can be formed to cover the raw bony edge.

TECHNIQUE

The entire soft tissues of the cheek are raised subperiosteally off the anterior maxilla from the pyriform aperture to the zygomatic arch including the buccinator. If the anterior wall has been breached, a cuff of soft tissues should be left over the tumour. The orbicularis oculi is left intact around the eye but the orbital periosteum is incised at the bony rim allowing dissection of the orbital contents off the floor of the socket (Figure 39.26). The infraorbital neurovascular bundle is cut at the infraorbital foramen.

To free the maxilla, osteotomies are made (with a drill, oscillating saw, Gigli saw or osteotomes) through the zygoma, beneath the infraorbital rim if the eye is being preserved, across the frontal process of the maxilla, into the pyriform fossa, and inferiorly through the central upper alveolus (Figure 39.27). The lateral nasal wall is divided below the superior turbinate. The hard palate is transected from front to back, just medial to the septum and the mobilization of the maxilla completed by separating the tuberosity from the pterygoid plates with a curved osteotome. Additional soft tissue attachments can be divided with curved Mayo scissors. Once removed, haemorrhage from the maxillary artery can be controlled with ligatures.

Once the maxilla is removed, together with any additional surrounding tissues if involved, a variety of reconstructions are available. At its simplest, a split-skin graft can be applied to the

Figure 39.24 Maxillectomy with orbital clearance employing modified Weber-Dieffenbach incision skirting both lash margins.

Figure 39.25 Palatal incisions during total maxillectomy.

Figure 39.26 Incision of the orbital periosteum at the bony rim allowing dissection of the orbital contents off the floor of the socket.

Figure 39.27 Osteotomies of the maxilla.
cavity walls held in place with quilting incisions, biological glues, a Whitehead’s varnish pack and a temporary gutta percha prosthesis (Figure 39.28). Alternatively, a free flap can be utilized, e.g. rectus abdominis, latissimus dorsi, radial or fibula osteocutaneous flaps with osseointegration. Other methods include vascularized calvarial bone flaps and coronoid-temporalis pedicled rotation flaps. Whatever is used, it is important that the patient can eat and speak in the immediate postoperative period. Closure of the flap can then be effected with absorbable subcutaneous and skin sutures, taking especial care at the vermillion border. A light pressure dressing is usually applied.

Repairing lost orbital support decreases the risk of globe malposition, diplopia and disturbance of extraocular muscle function. Small defects in the floor can be left, larger ones can be repaired using a fascia lata sling secured to the margins of the bony defect. Subtotal or complete defects require some form of rigid reconstruction.

Initial refashioning of an artificial prosthesis is usually undertaken under general anaesthetic and thereafter a permanent prosthesis/denture is made once the cavity has healed complemented by osseointegration.

Extensive spread of the tumour anteriorly into the facial skin may necessitate sacrifice of this with repair using a local pedicled or free microvascular flap. More frequently, extension occurs posteriorly into the pterygoid region which adversely affects prognosis. Limited areas of pterygoid muscle can be removed, but a partial mandibulectomy may be required. Further clearance of the pterygopalatine and infratemporal fossae can be undertaken, bearing in mind the close relationship of the internal carotid artery.

Complications are:
- early:
  - haemorrhage
  - infection
- late:
  - epiphora
  - paraesthesia
  - ectropion or lower lid oedema
  - facial contracture, notching of the lip
  - diplopia.

Endoscopic resection

Since its introduction, endoscopic sinus surgery has been extended to the skull base and orbit. The ability to repair skull base defects and resect orbital periosteum has facilitated the use of this approach alone or in combination with a craniotomy in the management of selected malignant sinonasal tumours. The principle of complete excision of the tumour must be observed and the options discussed with the patient, who should understand that a craniofacial may still be required if there is significant dural invasion and/or infiltration of the superior sagittal sinus. Endoscopic resection should not be employed or regarded as a ‘smaller’ operation but rather an equivalent resection via an endonasal route.

Technique

A complete resection of the tumour is undertaken including a wide field clearance of adjacent mucosa, bone and cartilage. On the skull base, the bone and dural defects can be repaired using combinations of fascia, pinna cartilage and contralateral nasal mucosa dependent on the size of the defect. Ipsilateral septal mucosal flaps are less useful in malignant disease due to the possibility of field-change. Similarly, orbital peristium can be resected and repaired with contralateral mucosa or a split skin graft held with fibrin glue, gelatin sponge and a Whithead’s varnish pack. In practice, a complete fronto-ethmo-sphenoidectomy is generally undertaken (Draf III), combined with removal of the lateral nasal wall (at the least, including a middle meatal antrostomy) and/or septal resection as dictated by the tumour extent.
It is technically possible to undertake an endoscopic craniofacial resection in selected cases. Image guidance is frequently employed. The advent of neuroendoscopic techniques is pushing the boundaries of what can be resected via an endonasal approach, though careful patient selection is paramount to maximize cure and minimize morbidity.

**Total rhinectomy**

**INDICATIONS**

Occasionally, extensive tumours in the nasal cavity will involve the external nose resulting in the need to completely excise the nose. Squamous cell carcinoma of the columella, vestibule and septum and malignant mucosal melanoma are the most common culprits.

**INCISION**

A cut down to bone is made circumferentially around the pyriform aperture remembering that tumour can escape submucosally into the upper lip and premaxilla so a wide margin is recommended.

**TECHNIQUE**

The entire nasal mucosal cuff can be removed together with septum, lateral wall and floor as dictated by the tumour. If it is possible to retain any portion of the nasal bone, this will facilitate subsequent reconstruction and allow placement of osseointegrated implants which will need to be covered by skin. Ideally, the skin edge should be approximated to any residual mucosa and while skin grafts may be applied to exposed bone, this will mucosalize with time.

A Whitehead’s pack60 is placed in the cavity for a few days and can usually be removed under sedation.

Reconstruction may involve a palatal prosthesis if the premaxilla has been resected, often achieved by modifying an existing denture. The superstructure of the nose can be replaced with an artificial prosthesis secured by osseointegration or by a variety of pedicled or free microvascular flaps.

**Management of the orbit**

Involvement of the orbit is an important predictor of recurrence-free, disease-specific and overall survival. As a consequence, in the past if tumour had reached the orbital periosteum the patient was advised to have the eye removed. However, it is increasingly apparent that a more conservative strategy can be adopted without adversely affecting outcome. Therefore, in most instances if tumour has eroded the lamina, is abutting the periosteum but has not penetrated into the orbital fat, the periosteum can be widely resected and repaired with split skin or fascia. The position of the eye can be maintained with a Whitehead’s pack60 while healing takes place and significant enophthalmos avoided. Frozen section is invaluable in making this assessment preoperatively as even the most accurate imaging cannot absolutely predict whether the periosteum has been breached (Figure 39.30).

In the presence of intraperiosteal spread, in cases where cure is possible, the eye should be sacrificed. In most cases, the eyelids can be spared as sinonasal tumours rarely spread pre-septally and there is no lymphatic drainage anteriorly. This constitutes orbital clearance as opposed to orbital exenteration where the lids are also sacrificed. The lids are incised leaving the lash margin on the specimen and the

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Figure 39.29  (a) Postoperative endoscopic view of cavity after endoscopic resection of an adenocarcinoma five years at follow up; (b) coronal magnetic resonance imaging T1 with gadolinium in the same patient.
skin and subcutaneous tissues of the lid are dissected free of the tarsal plates. A circumferential incision is made around the socket, down to bone and the canthal ligaments divided. The periosteum is then elevated using a Freer and ribbon gauze soaked in 1:1000 adrenaline. Care should be taken not to extend out through the fissures. Once the orbital contents are mobilized, the apex is divided with curved Mayo scissors. The anaesthetist should be warned as patients often develop a marked bradycardia as the optic nerve is cut. Significant bleeding is encountered from the ophthalmic artery though this quickly vasoconstricts. It is advisable to put a stay suture through the optic neurovascular bundle, not only for haemostasis but also to close the cerebrospinal fluid space around the nerve.

Primary osseointegrated implants may be placed in the orbital rim but may take up to a year to integrate, especially if radiotherapy is given. The socket is filled with a portion of the Whitehead’s pack and the lids are sutured together using fine absorbable sutures. An orbital prosthesis can be applied once the lids have sunk back to form a skin-lined socket, initially held with adhesives or on a spectacle frame while integration takes place.

After orbital exenteration or if the lids fistularize, the socket may be filled with a temporalis muscle flap to which a split-skin graft can be applied or a variety of free microvascular flaps used.82, 83

**FOLLOW UP**

The lack of specific symptoms and involvement of silent areas combined with a natural history spanning a lifetime, makes careful long-term follow up mandatory. A protocol has been developed which may be modified depending on the histology and patient but involves regular endoscopic examination, initially performed as a formal examination under anaesthesia combined with biopsy and regular MRI (Table 39.5). It is not possible to determine the cost-effectiveness of this approach, suffice to say that patients have been diagnosed with recurrence and salvaged over ten years after their initial presentation.

**Outcome and prognosis**

While lateral rhinotomy, rhinectomy and midfacial degloving still have a role for selected malignancies, craniofacial resection has dramatically improved the outcome for those tumours affecting the anterior skull base. In a cohort of 308 patients undergoing craniofacial resection, the follow up ranged from 6 to 259 months (mean 63 months).12 There were 259 patients with malignant tumours in whom the actuarial disease-free survival was 59 per cent at five years dropping to 40 per cent at ten years and 33 per cent at 15 years. Placing these results in context, the five-year survival figure for olfactory neuroblastoma prior to craniofacial was 35 per cent and is now 74 per cent. In other words, craniofacial resection has doubled the survival for many of these rare tumours. However, late recurrence can be seen in most tumours (Table 39.6) which emphasizes the fallibility of five-year actuarial survival in predicting cure.

Multivariant analysis unsurprisingly identifies brain involvement, type of malignancy and orbital involvement as the three most significant prognostic factors.12, 61, 84, 85 This applies to the nasal cavity86, 87 and maxillary sinus tumours88, 89 as well as those in the ethmoid. However, survival is not affected when invasion is limited to orbital periosteum and this is resected, with orbital preservation.12, 75, 90

By contrast, involvement of the orbital apex significantly reduces survival even if orbital clearance is undertaken.91 In 170 patients with orbital invasion by squamous cell carcinoma, five-year survival and local recurrence were 41 and 20 per cent when the eye was preserved compared to 37 and
36 per cent when the eye was removed.\textsuperscript{44} The impact of orbital invasion on survival can also be related to tumour type. Nishino et al.\textsuperscript{92} reported a five-year overall survival of 74 per cent for squamous cell carcinoma versus 40 per cent for non-squamous tumours where limited orbital invasion was treated with combined therapy but orbital preservation. However, timing of radiotherapy does not seem to affect outcome with no statistical difference demonstrated between those receiving this preoperatively and those treated post-operatively ($p = 0.87$).\textsuperscript{12}

The most frequent recurrence is local and was amenable to treatment with intention to cure in 14 per cent of our series, most of whom underwent surgery in the form of revision craniofacial resection.\textsuperscript{12} This can be repeated, in some cases on numerous occasions, with minimal morbidity and emphasizes the palliative role of the procedure.

Fewer patients have undergone endoscopic resection, with limited follow up to date, so it is not possible to make meaningful comparisons with alternative approaches and statistically robust actuarial survival data are difficult to obtain. Patients are necessarily selected for their limited disease so one would anticipate similar if not better results and this appears to be the case in emerging series.\textsuperscript{13, 14, 31, 32, 93, 94, 95} In addition, there are obvious advantages in terms of morbidity, hospital stay and the ability to start chemoradiation shortly after surgery. However, the principle of oncologic resection must be observed wherever possible and the full menu of surgical approaches available if the excellent results of recent years are to be maintained.

**SPECIAL CONSIDERATIONS IN CHILDREN**

Most malignant sinonasal tumours, albeit rarely, can affect children and should be excluded in any case of unilateral obstruction. Rhabdomyosarcoma is the most common and good results are now obtained using a protocol of chemoradiation with surgery, though this is often reserved for salvage. Embryonal and botryoid subtypes are most common in the young. These represent a better prognosis than alveolar and undifferentiated types.\textsuperscript{96}

If radical surgery is required, it may be undertaken without significant deleterious effects on facial development as long as the cartilaginous septum, upper lateral cartilages and palate are preserved.\textsuperscript{97}

**CONCLUSION**

There have been tremendous strides in the management of malignant tumours in the sinonasal region, both in diagnosis and treatment with improvement in outcome while minimizing morbidity.\textsuperscript{95–98} The task is to identify patients at the earliest opportunity in order to give them the best chance of survival from these rare and distressing conditions.

**KEY EVIDENCE**

- Epidemiological studies confirm an association between adenocarcinoma of the ethmoids and the woodworking industry.\textsuperscript{5}
- Prognosis in the anterior skull base relates to the spread into brain, orbit and the type of malignancy.\textsuperscript{12}
- Craniofacial remains the gold standard by which other treatment strategies must be measured, but prospective data on endoscopic resection is increasing.\textsuperscript{12, 95}

**KEY LEARNING POINTS**

- Malignant tumours of the nose and sinuses are rare and present late due to initially innocuous symptoms.
- These tumours have the greatest histological diversity with individual natural histories.
- Their management requires expertise in histopathology imaging, as well as surgical and medical oncology.
- Rehabilitation may require prostheses and a range of reconstructive techniques, as well psychological support for the patient.
- Survival has doubled for a number of tumours since the introduction of craniofacial resection.
• In selected patients, an endoscopic approach may be employed to perform surgical exenteration of the tumour.
• All patients require long-term follow up including endoscopic examination and imaging.

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In this chapter, we will discuss temporal bone resections for primary malignant tumours of the temporal bone and malignant tumours extending to the temporal bone. The remaining aspects of lateral skull base surgery will be reviewed elsewhere in the text.

In the 1980s, reports on improved survival appeared. Goodwin and Jesse, in a report on 136 patients, demonstrated a 58 per cent overall five-year survival rate for squamous cell carcinoma of the temporal bone. This is, to our knowledge, the largest reported series on temporal bone resections. Importantly, it was demonstrated that deep temporal bone involvement resulted in a poor outcome due to difficulty in obtaining clear margins. This landmark study also demonstrated that postoperative radiotherapy was of no benefit when clear margins could not be achieved. A benefit in local control was observed when radiotherapy was used as an adjuvant in those patients with clear margins. No benefit on survival was observed. This study is the basis for modern practice in the management of temporal bone malignancies. Also in the 1980s, there were various reports on temporal bone resections with carotid artery resections without significant impact on survival.

A thorough understanding of the temporal bone anatomy is paramount during oncolgic surgery of the temporal bone. The temporal bone anatomy is quite complex and an in-depth description is beyond the aims of this chapter. Briefly, the temporal bone has four components. The squamosa constitutes a vertical plate whose medial surface forms part of the middle cranial fossa. On the lateral surface, the zygomatic process projects from it, and the mandibular fossa is located...
Figure 40.1  T₁-weighted magnetic resonance image with axial cuts demonstrating a tumour involving the anterior wall of the external auditory canal and the temporomandibular joint.

below its root. The mastoid process, which projects from the squamous and petrous parts, articulates with the occipital and parietal bones. The petrous bone is a pyramidal projection from the mastoid portion, the apex of which inserts in the angle between the occipital and sphenoid bones. It divides the middle and posterior cranial fossae. The tympanic bone is a ring opened superiorly which forms the anterior and inferior walls, as well as part of the posterior wall of the external auditory canal (EAC). The temporal bone occupies the inferolateral skull base. Although osseous, it also houses the epithelialized ear canal, mastoid and middle ear. In addition, cranial nerves VII–XI, the carotid artery, and the sigmoid sinus all traverse the temporal bone.

Several tissue types, from cartilaginous to glandular, can be found within the temporal bone. Any of these structures can potentially give rise to a malignancy. However, as already mentioned, most temporal bone cancers arise from the EAC, and of these, squamous cell carcinomas (SCC) is the most common. These tumours can spread (1) anteriorly, into the parotid gland, infratemporal fossa, glenoid fossa (Figure 40.1) or facial skin; (2) posteriorly, into the bony EAC, mastoid air cells and posterior fossa; (3) inferiorly, into the neck soft tissue, jugular foramen, foramen magnum or cervical spine, and (4) superiorly into the epitympanum, tegmen tympani and middle fossa. Tumour spread may dictate the need for additional procedures (i.e. parotidectomy, neck dissection, and mandibular condylectomy).⁹

Lymphatic drainage from the EAC is into the parotid and pre-auricular lymph nodes anteriorly; inferiorly, into the upper deep cervical and deep internal jugular nodes; and posteriorly into the post-auricular nodes. The middle ear and mastoid lymphatics drain into the Eustachian tube area and then into the deep upper jugular and retropharyngeal nodes.⁹

PATHOLOGY AND EPIDEMIOLOGY

Malignant tumours of the temporal bone are rare and therefore it is difficult to establish treatment protocols that are universally applicable. Primary tumours of the temporal bone are usually SCC of the external auditory canal or middle ear. SCC of the pinna is considered a cutaneous malignancy, with a different staging and prognosis. The prevalence of temporal bone carcinomas is approximately six cases per million in the general population.¹⁰ The main risk factor is a long, often two or more decade history of chronic suppurative otitis media.¹¹ Other potential inciting factors include chronic dermatitis,¹² cholesteatoma¹³ and history of previous radiation.¹⁴, ¹⁵ Less commonly, adenocarcinomas and adenoïd cystic carcinomas may be observed. In addition, the temporal bone may be affected by direct extension of parotid malignancies. Less commonly metastatic spread from the breast, prostate, lung or kidney to the marrow containing petrous apex can occur.¹⁶, ¹⁷, ¹⁸, ¹⁹ In our practice, perineural spread through the facial nerve from skin SCC is a frequent indication for some form of temporal bone resection along with direct spread of cutaneous malignancy to the temporal bone.

CLINICAL EVALUATION AND STAGING

Otorrhoea, often blood stained, an external auditory canal mass and pain are usually the initial signs and symptoms. As the disease progresses, the pain becomes severe or excruciating. Facial and vagal palsies are late signs.²⁰, ²¹, ²² A high index of suspicion is necessary as the initial presentation may mimic more common otologic conditions. An ear examination under magnification, a complete head, neck and cranial nerve examination, and audiometry should be performed.

Because SCC of the temporal bone routinely invades bone and soft tissues, most patients should ideally undergo fine-cut computed tomography (CT) of the temporal bone with bone windows and magnetic resonance imaging (MRI) of the head and neck. We obtain a fine-cut high resolution CT scan to identify the tumour extent and degree of bone erosion. An MRI is performed on all cases unless the tumour is localized to the external auditory canal and there is no bone erosion on CT. If the carotid artery is suspected to be involved (rare with poor prognosis), angiography with trial ipsilateral balloon occlusion should be performed, followed by xenon diffusion test to assess the adequacy of cerebral blood flow from the contralateral carotid artery. Special attention is also given to the venous outflow phase to determine the adequacy of the torcular and contralateral drainage pathway, in case the surgery requires sacrifice of the sigmoid sinus or internal jugular vein. In a cadaveric study, up to 25 per cent of specimens did not have a patent torcular.²³ Despite this, in our experience, sacrifice of the sigmoid sinus/jugular bulb is feasible in a significant proportion of cases. Even after careful work up and state-of-the-art imaging, the extent of disease may be underestimated and, thus intraoperative clinical judgement is imperative.

No staging system for temporal bone malignancies is universally accepted. Many authors have proposed staging systems concurrent with a review of patient series from major institutions; however, the small number of patients per group, the disparity of staging criteria, the diversity in management protocols, and the use of non-standardized
surgical nomenclature prohibits meaningful comparison of outcomes. In addition, some patients are reportedly classified into groups with variability in histology types and sites of tumour origin, which further confounds analysis of outcome by stage.

A staging system for squamous cell cancers of the EAC proposed by the University of Pittsburgh has been shown to be useful and has gained support in the literature. This staging system is based on clinical, radiologic and pathologic findings. In general, tumours that are limited to the EAC are defined as early disease, and those that extend beyond the external canal to invade the surrounding soft tissues, the middle ear, the mastoid, or cranial nerves are recognized as advanced disease.

The Pittsburgh staging system was modified by the authors after further review of patients from an extended series. In the modified staging system, facial nerve weakness is considered a criterion for a T4 lesion. The authors observed that facial nerve paresis did not occur in lesions otherwise classified as limited T1, T2 or T3 lesions. Involvement of the facial nerve would be otherwise classified as T4 based on the anatomical area of involvement, including the medial wall of the middle ear (horizontal segment), extensive bony erosion within mastoid (vertical segment), or involvement of stylo-mastoid foramen.

Table 40.1 The University of Pittsburgh staging system for temporal bone squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>T1 N0 M0</td>
</tr>
<tr>
<td>II</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>III</td>
<td>T3 N0 M0, T1 N1 M0</td>
</tr>
<tr>
<td>IV</td>
<td>T4 N0 M0, T2-4 N1 M0, any T N2 M0, any T N3 M0, any T any N M1</td>
</tr>
</tbody>
</table>

EAC, external auditory canal; TMJ, temporomandibular joint.

TEMPORAL BONE RESECTIONS: RATIONALE

With the advent of modern skull base surgery techniques, our ability to remove temporal bone malignancies has been expanded. Nevertheless, the dilemma of defining resectability still persists. Although it is technically feasible to remove structures such as the petrous carotid artery, the morbidity associated with it is significant and surgical cure rates in these scenarios are not significantly improved. The rarity of the problem results in a small collective surgical experience which complicates matters further. Pensak et al. consider that invasion of any of the following structures:

- cavernous sinus,
- carotid artery,
- infratemporal fossa,
- paraspinal musculature

make a patient unresectable. All patients in their series of 46 individuals with SCC of the temporal bone with such invasion died within three years despite surgery and postoperative radiotherapy. The difficulty hinges on the reliability of preoperative staging. This is a subject of significant controversy.

In our practice, a temporal bone resection is performed for malignant tumours involving the temporal bone. We recommend en-bloc resection of the entire specimen by either a complete external auditory canal excision (i.e. lateral temporal bone resection (LTBR)), or a near total temporal bone excision (NTTBR) (Figure 40.2). Any potentially involved adjacent soft tissue is included en bloc with the specimen by means of additional ancillary procedures, commonly a parotidectomy and less so the temporomandibular joint (TMJ) and capsule. We perform a lateral temporal bone resection with preservation of the facial nerve in tumours located lateral to the tympanic membrane.

Tumours medial to the tympanic membrane are best treated with a NTTBR. The assessment of medial spread can

Figure 40.2 Diagram demonstrating the structures that are removed with each of the temporal bone resection types.
be made preoperatively by clinical signs (facial nerve palsy) and radiological assessment. Intraoperative assessment is made by inspection of the middle ear cavity via a posterior tympanotomy. Soft tissue thickening in the middle ear may be due to a mucosal reaction to the tumour or frank tumour invasion. Thus, frozen section verification is recommended.

In essence, three types of temporal bone resections can be performed (i.e. LTBR, NTTBR and TTBR). In addition, sleeve resections of the EAC skin have been described. These are mentioned here briefly mainly to dissuade the reader from using this technique in the management of EAC carcinoma. Sleeve resections are simply stripping of the EAC skin and thus are not an oncologically sound operation, but may be applicable in certain basal cell carcinomas limited to the lateral aspect of the EAC.

**SURGICAL TECHNIQUE**

**Lateral temporal bone resection**

This operation requires complete en bloc removal of the entire osseous and cartilaginous EAC with the intact tympanic membrane. The surgical steps for this operation are outlined below.

1. A postauricular C-shaped incision approximately 1 cm behind the postauricular sulcus is performed. This incision may be extended inferiorly into the neck for a parotidectomy as required (Figure 40.3).

2. The skin flaps are elevated anteriorly above the parotidomasseteric and temporalis fascia. The posterior skin flap is elevated above the temporalis fascia, mastoid bone and sternocleidomastoid fascia. If it is required, the tragus and part of the conchal cartilage may be included in the resection. If the retromandibular area is to be involved in the resection, the depth of the anterior skin flap is extended deep to the temporalis fascia at the root of the zygoma in order to preserve the temporal branch of the facial nerve. It is usual to bring the pinna forward with the wide-based postauricular incision. However, where large amounts of the concha are involved with tumour, then the incision may have to extend in a preauricular fashion with the remnant pinna taken posteriorly to attempt to preserve some vascularity.

3. Blind sac closure of the canal is performed (tragal to conchal skin), if the lateral canal is not involved, after cartilage removal and reinforced medially with an anteriorly based musculoperiosteal flap. This situation is uncommon. If the lateral end of the canal is involved, it is resected and the defect repaired with a local rotation, such as a temporalis rotational flap or free flap.

4. The lateral external auditory canal is sutured closed if tumour spread is a concern.

5. A routine mastoidectomy is performed to expose the bony plate of the sigmoid sinus and the middle cranial fossa dura. A posterior tympanotomy is fashioned and the middle ear is inspected through it.

6. The incudostapedial joint is disarticulated.

7. The mastoidectomy is extended into the root of the zygoma and the epitympanum opened (Figure 40.4).
8. The posterior tympanotomy is extended inferiorly into the hypotympanum, sacrificing the chorda tympani. Care must be taken to dissect the chorda tympani and transect it with a sharp instrument to avoid traction injury to the facial nerve (Figure 40.5).

9. The anterior epitympanic region is drilled extending anteroinferiorly and medially to reach the superior part of the TMJ.

10. The hypotympanic opening is extended anteriorly, lateral to the jugular bulb and internal carotid to reach the inferior part of the TMJ (Figure 40.6). Occasionally, it is necessary to raise the facial nerve from the stylomastoid foramen to the second genu in order to drill the hypotympanic region.

11. The specimen is then removed en bloc by pushing forward on it. Should resistance be present, a 2 mm osteotome may be used via the posterior tympanotomy to liberate the anterior component of the tympanic plate. With a narrow posterior tympanotomy (facial nerve to tympanic annulus), once the temporal bone is fractured forward, the space opens a further couple of millimetres allowing completion of the anterior drilling and clean removal of the specimen (Figures 40.7, 40.8 and 40.9).
12. The Eustachian tube is plugged with muscle and fascia.
13. The defect is filled with temporalis muscle rotated inferiorly. Free abdominal fat grafts are avoided if radiation therapy is planned. Obliteration of the mastoid cavity prevents osteoradionecrosis from developing following radiation therapy. 34
14. The wound is closed in layers and a padded lightly compressive head bandage is then applied.

**TECHNICAL NOTES**

- The vertical portion of the facial nerve may drift lateral to the annulus in the inferior half of the annulus. Care must therefore be taken, in those cases with facial nerve preservation, in extending the posterior tympanotomy inferiorly. As the annulus in this area curves anteriorly, adequate room is present to allow drilling between the nerve and the annulus.
- In extending the posterior tympanotomy into the hypotympanum and forward on to the TMJ, the lateral aspect of the jugular bulb and internal carotid may be encountered.
- The middle cranial fossa descends in the anterior part of the epitympanum. On occasion, it may be necessary to elevate the dura to perform the superior part of the resection.
- The geniculate ganglion sits immediately medial to the medial wall of the anterior epitympanum. Extension of the mastoidectomy into the root of the zygoma and medially into the superoposterior aspect of the TMJ should be performed with care.
- In using the temporalis muscle to obliterate the defect, the anterior half is left in situ to prevent a cosmetic defect in the temporal fossa.

**Near-total temporal bone and total temporal bone resections**

A NTTBR describes en-bloc resection of the medial surfaces of the mesotympanum, leaving the air cells of the petrous apex. This type of resection is indicated for those with malignancies involving the middle ear without extension into the petrous apex. A TTBR involves an en-bloc resection of the entire temporal bone, including the petrous apex and the sigmoid sinus. The petrous internal carotid artery may be included in this resection. There is questionable added benefit of a total temporal bone resection.23, 35 The surgical steps to perform a NTTBR are outlined below.

1. The skin incision must allow access to the middle cranial fossa, mastoid, parotid and retromandibular fossa. It should also allow extension of the incision should a neck dissection be required. A large C-shaped incision from the frontotemporal region 6–8 cm above the auricle, extending up to 4–5 cm behind the retroauricular sulcus, then running 4 cm below the horizontal aspect of the mandible and ending in the submental region may be used. A vertical limb can be made for a neck dissection, ensuring that the three-point junction does not overlie the carotid artery. As much auricle as is required for tumour removal is incorporated with the specimen (Figure 40.10).
2. The superior aspect of the flap is elevated followed by elevation of the temporal muscle (Figure 40.11).
3. A middle-posterior temporal craniotomy is performed. A drill hole is performed at the asterion to find the junction of the lateral and sigmoid sinuses. The craniotomy is commenced here and usually measures 6 × 4 cm extending to the root of the zygoma.
4. The middle cranial fossa dura is dissected from the anterosuperior aspect of the petrous bone and is inspected to ensure the tumour is resectable. If the dura is involved here, it is incised and left as part of the specimen.
5. The sigmoid sinus and jugular bulb regions are exposed using a cutting burr initially, followed by a diamond burr which is useful for haemostasis. The dura in front of the sigmoid is then sufficiently exposed so that it is possible to dissect the dura over the posterior aspect of the petrous bone toward the area of the internal auditory meatus and pars nervosa of the jugular foramen. The dura in this region is also inspected for tumour.
6. A total parotidectomy and, if necessary, a neck dissection are performed. Any resection required of tissue anterior to the external auditory canal may also be performed at this stage. If dural involvement and therefore resectability is not a concern, this step is performed prior to the craniotomy.
7. The sigmoid is opened and packed with haemostatic packing proximally and distally down towards the jugular bulb region. The jugular bulb is then opened and the inferior petrosal sinus...
openings are gently packed. A preoperative magnetic resonance venogram should be performed to assess the adequacy of the torcula.

8. A diamond drill is used to make a cut along the superomedial aspect of the jugular bulb into the hypotympanum and up to the posterior wall of the carotid canal.

9. The middle cranial fossa dura is dissected free to the posterior part of the foramen ovale coagulating and cutting the middle meningeal artery in the process. It is then continued to the connective tissue of the posterolateral margin of the foramen lacerum and along the petrous ridge. The roof and lateral wall of the internal carotid canal are removed using a diamond drill all the way to the level of the cochlea.

10. A diamond drill is used to create an osteotomy via the middle cranial fossa across the petrous bone just lateral to the porus acusticus to reach the carotid canal anteriorly and the posteromedial part of the preserved wall of the jugular fossa inferiorly. Care must be taken in performing this step so as to prevent injury to the lower cranial nerves.

11. The final cut is made medial to lateral joining the area of the glenoid fossa or root of the zygoma, across the floor of the middle cranial fossa, to run immediately behind the foramen ovale to the carotid canal.

Figure 40.10 Incision options when performing a near total temporal bone excision. (a) A large C-shaped incision from the frontotemporal area, extending post-auricular and the running below the body of the mandible. (b) A Y-shaped incision.

Figure 40.11 Schematic representation of the anatomy following flap elevation during a near total temporal bone excision.
12. The specimen is then cracked free by pushing anteroinferiorly from the posterior surface of the petrous bone using a rocking motion. There are usually some soft tissue attachments preventing liberation of the specimen, including the nerves of the internal auditory canal (IAC), which need to be cut. Bleeding from the inferior petrosal sinus is managed with haemostatic packing (Figures 40.12, 40.13 and 40.14).

13. Haemostasis is achieved and any dural defect is repaired. This may require primary closure with, or a fascial graft for, larger defects. We favour a 5-0 non-absorbable monofilament suture for dural suturing.

14. The facial nerve rehabilitated either by a crossface cable graft or by a split XII–VII neurorraphy. Experience at the Cleveland Clinic has been favourable with XII–VII anastomosis. The split XII–VII neurorraphy can also be used as a babysitter graft in patients in whom a crossface anastomosis is performed to maintain the viability of the motor end plates. Our practice is to perform static reanimation with facial slings and gold weight concurrently with cable grafting.

Our preference is to repair the defect with a free flap graft (Figure 40.14). We feel that free flaps are better at preventing leakage of cerebrospinal fluid and at protecting the carotid artery in large resections which is important because these patients will routinely receive post-operative radiotherapy or have already failed radiotherapy.

**TECHNICAL NOTES**

- Drilling anterior to the sigmoid to allow elevation of the dura is generally safe as this region is rarely involved with tumour. On the occasions where tumour is seen anterior to the sigmoid sinus or if the sinus is very anterior, drilling is commenced retrosigmoid and the sigmoid opened and packed from behind.
Care must be taken in packing the inferior petrosal openings into the jugular bulb as excessive pressure may cause a palsy of the glossopharyngeal and possibly the vagal nerves.

Exposure of the carotid via the middle cranial fossa should be adequate for the insertion of a small dissector to free the carotid artery from the wall of the carotid canal.

In freeing the carotid from its canal, it may be necessary to bipolar coagulate the carotico tympanic or periosteal branches.

The framework of the medial porus acousticus is preserved if possible to allow packing with bone wax and prevent a cerebrospinal fluid leak.

A total resection of the petrous bone is almost never necessary; if it is required, closure is more difficult.

In our experience, facial nerve grafting when followed with postoperative radiotherapy has lead to poor outcomes. We always perform static facial reanimation with a gold eyelid weight and static fascial slings concurrently with cable grafting.

Ancillary procedures

As mentioned above under Clinical evaluation and staging, p. 780, tumours of the temporal bone can extend outside the temporal bone necessitating ancillary procedures. More commonly, parotid tumours will extend to the temporal bone. In either case, the procedure planned should encompass a complete tumour resection. Thus, ancillary procedures commonly performed with a temporal bone resection include parotidectomy with or without facial nerve sacrifice, condyle/temporomandibular joint resection, auriculotomy and a neck dissection. A superficial parotidectomy is generally performed to obtain clear margins in tumours extending to the gland or in close contact with it. The decision to perform a total parotidectomy and/or facial nerve sacrifice is based on the extension of the tumour within the gland and the pre-operative nerve function. In addition, a neck dissection can be performed if there is evidence of neck lymphadenopathy. This is preferably removed en bloc with the temporal bone specimen. A routine neck dissection is not performed due to the low incidence (10–15 per cent) of occult involvement of the cervical lymphatics and the routine use of post-operative radiation therapy which includes treatment of the neck.

A unique circumstance in our practice is perineural spread from skin SCC. In these cases, we advocate for a radical resection of the disease. Thus, if the magnetic resonance neurography study demonstrates perineural spread up to the stylomastoid foramen, a cortical mastoidectomy with dissection of the facial nerve should be performed and the nerve is sacrificed at the second genu with intraoperative frozen section control. If the margins are positive at this stage, or if pre-operative magnetic resonance neurography suggested that the disease extends further, a NTTBR should be performed to achieve clear neural margins. If there is further extension, resection of the facial nerve up to the brainstem may be required. With gross involvement of the facial nerve, it is common for the third branch of the trigeminal nerve to be involved as well. If the MRI suggests that the disease is resectable, the temporal bone is resected en bloc with a radical parotidectomy, ascending mandible and infratemporal fossa contents up to the Gasserian ganglion.

RADIOThERAPY

Radiotherapy as the sole modality for the treatment of temporal bone malignancies has a very limited role and is mostly historical. Before the development of modern skull base, surgery techniques radiotherapy was used because of the dismal surgical results. Birzgalis et al. reported on 53 patients with radical radiotherapy. An overall 32 per cent five-year survival rate was noted. Unfortunately, an unspecified number of these patients also had radical mastoidectomy. Early (T1) cancers had excellent control, with eight of ten cases being alive at five years, but, as mentioned above, the contribution from surgery was unclear. Zhang et al. had a 29 per cent survival rate for radiotherapy alone, and a rate of 60 per cent for combined surgery and radiation. These and other authors have recommended combined therapy for advanced disease. 25, 39, 40 Similarly, Hahn et al. noted that survival rates improved from 14 per cent with surgery alone to 50 per cent with surgery and radiotherapy, Importantly, none of three patients with advanced disease who received radiotherapy alone were alive at five years. The authors concluded that surgery or radiotherapy alone is not sufficient for most of the cases of carcinoma of the middle ear because of late presentation. Only isolated reports of stereotactic radiotherapy are available. At this juncture, we can recommend radiotherapy has an adjuvant to surgical clearance of disease.

TREATMENT OUTCOMES

Fortunately, improved survivals have been observed over the last 50 years from a five-year survival rate of 25 per cent to a current rate of 50 per cent. The survival rates of T1 and T2 carcinomas are 80–100 per cent. The main controversy is whether a larger operation gives better results for advanced disease (T3 and T4 lesions). As with smaller lesions, there are advocates of a limited surgical procedure coupled with postoperative radiation for advanced disease. Used a radical mastoidectomy and postoperative radiation in a series of 47 patients, 29 of whom had cancer originating in the middle ear with an overall survival rate of 53 per cent. With a similar approach, Zhang et al. reported a 69 per cent survival rate in stage III patients and a 20 per cent survival rate in stage IV patients, whereas Liu et al. had a 54 per cent survival rate with combined radiation and radical mastoidectomy.

On the other hand, Moffat et al. reported on 15 patients with recurrent, extensive squamous cell carcinomas of the temporal bone. The primary site of origin in nine patients was the middle ear and mastoid, and all patients had undergone previous partial temporal bone resection, usually followed by radiotherapy. Five patients had T3 tumours, and ten patients had T4 tumours. The five-year survival rate in
this group of patients, who normally would be believed to have a dismal prognosis, was 47 per cent (7 of 15). Of the seven survivors, brain involvement was present in two patients, and dural involvement in three patients. The authors concluded that TTBR gave a chance of survival to patients previously believed to have inoperable extensions of tumour and suggested that radical surgery combined with radiotherapy as primary therapy could give better five-year survival figures than limited surgery followed by radiotherapy.26 In a subsequent study from the same group, 37 patients were treated with curative intent. Two patients had T2N0 tumours, three patients had T3N1 tumours, 23 had T4N0 tumours and six had T4N1 tumours. In this study, patients with N-positive disease or carotid involvement had dismal prognosis. Importantly, two of seven patients with brain involvement had long-term survival. This study also supported a beneficial effect of postoperative radiation on survival.44

A large meta-analysis by Prasad and Janecka45 that included 26 publications containing information on 144 patients found that there was no significant difference in five-year survival rates between mastoidectomy (five of ten, 50 per cent), LTBR (17 of 35, 48.6 per cent) and NTTBR (one of two, 50 per cent) on lesions confined to the external auditory canal. For middle ear extension, the five-year survival rate for NTTBR was 41.7 per cent (5 of 12), for LTBR was 28.7 per cent (two of seven), and for mastoidectomy was 17.1 per cent (6 of 35).45 Although these figures did not reach statistical significance, there was the obvious decreasing survival rate with less extensive operations for advanced disease. Basal cell carcinomas of the external auditory canal, middle ear and mastoid are much rarer than squamous cell carcinoma. The evaluation and treatment options are the same as for squamous cell carcinoma. In general, survival results are better. In the Pensak et al. series, 7 of 46 (15 per cent) temporal bone cancers were basal cell carcinomas, most with extratemporal spread. None of the patients with basal cell carcinoma died of their disease.21 Goodwin and Jesse6 had an 81 per cent survival rate for basal cell carcinoma compared with a 58 per cent survival rate for squamous cell carcinoma. Although encouraging, other authors have reported less encouraging outcomes.29

PROGNOSTIC FACTORS

Several factors are associated with decreased survival rates, including extent of disease, facial nerve paralysis, positive margins, dural involvement and lymph node involvement. Several reports have documented decreased survival rates with facial nerve paralysis. Birzgalis et al.38 reported a decrease in survival from 46 to 24 per cent, Liu et al.43 reported a decrease from 56 to 10 per cent and Manolidis et al.29 reported a decrease from 66 to 29 per cent. Facial nerve involvement with paralysis constitutes a T4 lesion because it implies erosion of the medial wall of the middle ear or mastoid Fallopian canal or >0.5 cm soft tissue extension at the stylomastoid foramen.22 The facial canal can also act as a conduit for tumour spread.29

Goodwin and Jesse6 felt that incomplete resection was the primary cause of failure and that postoperative radiation was of no benefit if the cancer could not be resected completely. In their series, 13 patients with advanced cancer had incomplete resections, and all patients were treatment failures despite postoperative radiation. In the study by Arriaga et al.,24–46 patients with clear pathologic margins had a 63 per cent survival rate compared with a 25 per cent survival rate for patients with positive margins. One of the margins involved can be the dura. These investigators found that only one of six patients with documented dural extension was free of disease on follow up. This patient had an isolated erosion through the tegmen to the middle fossa dura. Other authors have found similar results with dural involvement.27, 40, 45 Other factors indicating poor prognosis include multiple cranial nerve involvement and moderate-to-severe pain on presentation.20, 29, 38

Regional lymph node involvement is an ominous sign, but is unusual (5–15 per cent of cases).6, 20, 21, 26, 41, 44 In their staging system, Arriaga et al.24 automatically considered any nodal involvement as advanced disease (e.g. a T1N1 patient is considered stage III, and a T2N1 patient is considered stage IV). In their 1989 report, the overall two-year determinant survival rate was 46 per cent, but fell to 29 per cent if nodes were involved.46 Other authors have found a similar trend.20, 25, 30, 36, 47 Despite the poorer prognosis with nodal disease, a neck dissection does not seem to affect survival rates.6, 20, 27, 46 These figures highlight that the major cause of death is local recurrence rather than regional or metastatic disease.6, 24, 25, 45, 47 Of 54 patients who died of disease and had site-of-failure data, Prasad and Janecka45 reported the site of recurrences as 45 local, five local and regional, three regional, and only one local and metastatic. Recurrences usually occur in the first two to three years postoperatively.29, 46

KEY EVIDENCE

- Temporal bone carcinoma is rare.
- Treatment remains controversial. En bloc versus radical mastoidectomy have similar outcomes on lesions confined to the external auditory canal, but en-bloc surgery offers better outcomes on middle-ear extensions. Dura and temporal lobe invasion are poor prognostic indicators.
- The main predictor of poor outcome is positive margins.
- Surgery followed by radiotherapy has the best outcomes.
- Radiotherapy alone has only a palliative role.

KEY LEARNING POINTS

- Surgical approaches to the temporal bone are difficult and can carry significant morbidity.
- The major arteries and veins supplying the brain, intracranial structures and all the cranial
nerves either exit through or are contiguous with the temporal bone.

- Improvements in techniques and an increased involvement of a multidisciplinary team in the management of temporal bone tumours have led to a decrease in the morbidity and mortality associated with temporal bone resections.
- Modern reconstructive techniques have allowed for improved cosmetic outcomes.
- The need for a considerable knowledge of temporal bone anatomy and temporal bone-drilling laboratory experience cannot be overemphasized.
- A thorough understanding of the tumour biology and meticulous preoperative planning are necessary for a successful outcome.

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Rare cancers of the head and neck

ANDREW K CHAN, ANDREW HARTLEY, ROBERT J GRIMER, RABIN PRATAP SINGH AND PREM MAHENDRA

If you do not expect the unexpected, you will not find it; for it is hard to be sought out, and difficult
Heraclitus (c.535–475BC)

NEUROECTODERMAL MALIGNANCIES OF THE HEAD AND NECK

Introduction
Sinonasal undifferentiated carcinoma (SNUC), olfactory neuroblastoma (ONB) and neuroendocrine carcinoma (NEC) form a spectrum of rare malignancies of neuroectodermal origin. The rarity of these tumours precludes any prospective trials and reports in the literature of management have been limited to retrospective single institution series. These tumours are therefore best managed in specialized centres with treatment options largely dictated by local expertise and patient choice. SNUC and NEC are aggressive tumours which require a multimodality approach with surgery, radiotherapy and chemotherapy, whereas early stage ONB may be treated with local therapy.

Sinonasal undifferentiated carcinoma

Sinonasal undifferentiated carcinoma was first described by Frierson et al. \(^1\) in 1986 as a clinicopathological entity arising from the Schneiderian epithelium or from the nasal ectoderm of the paranasal sinuses. Reports in the literature are emerging since its recognition as a distinct entity; however, the true incidence is not known with fewer than 100 reported cases.\(^2\) The majority arise from the nasal cavity with the remaining cases originating from the maxillary and ethmoid sinuses. The age range is broad with a bimodal distribution affecting young adults and the elderly. A median age of presentation of 50 years (range 20–77 years) has been reported.\(^1\,3\,4\,5\,6\,7\)

CLINICAL FEATURES

SNUC commonly presents with locally advanced features with its propensity to aggressively invade local structures, such as the orbit, cranial cavity, nasopharynx, and sphenoid and frontal sinuses. Symptoms and signs characteristically develop over a short period of weeks to a few months in keeping with its locally aggressive behaviour. These include nasal obstruction, epistaxis, proptosis, periorbital discomfort with swelling, diplopia, and other cranial nerve palsies.\(^1\) Locoregional nodal involvement and distant metastases, particularly to the lung and bone, can also occur in up to 30 per cent.\(^8\)

PATHOLOGY

Light microscopy can differentiate most cases of SNUC from other undifferentiated tumours but immunohistochemistry and electron microscopy can be helpful to confirm the diagnosis. Features seen on light microscopy include small to medium-sized undifferentiated cells showing significant pleomorphism, a high nuclear–cytoplasmic ratio and moderate eosinophilic cytoplasm. These cells are classically arranged in nests, trabeculae or sheets. Large ovoid nuclei with numerous mitotic figures, extensive vascular invasion
and necrosis can also be prominent features. SNUC stains positive for keratin and epithelial membrane antigen. Some cases show neuroendocrine differentiation. Neuron-specific enolase and CD99 are often expressed, but chromogranin, synaptophysin, S-100 and vimentin markers are usually negative. SNUCs are typically negative for Epstein–Barr virus on immunohistochemistry.

DIFFERENTIAL DIAGNOSIS

Given the lack of differentiation seen with SNUC, the differential diagnosis can be very broad and includes ONB, lymphoma, embryonal rhabdomyosarcoma, melanoma, nasopharyngeal carcinoma (lymphoepithelioma) and small cell carcinoma. It is crucial to differentiate SNUC from ONB because natural history, treatment and prognosis differ greatly. SNUC is characteristically locally aggressive associated with a poor prognosis, whereas ONB generally has a slower natural history.

INVESTIGATIONS

Initial assessment of a sinonasal mass routinely includes nasoendoscopy, examination under anaesthesia and biopsy. Initial imaging is often with a computed tomography (CT) scan which commonly shows a non-calcified mass arising either from the nasal cavity or paranasal sinuses with local bone destruction and invasion of adjacent structures, such as the orbit, anterior cranial cavity or nasopharynx. A magnetic resonance (MR) scan with gadolinium contrast is also frequently undertaken to complement the CT scan and complete local staging. It characteristically shows heterogenous gadolinium-enhancement of the tumour with a superior soft tissue resolution compared with a CT scan which, in contrast, provides superior bone delineation.

MANAGEMENT

SNUC is a locally destructive tumour and therefore is often found to be unresectable at presentation. A radical approach to treatment involves the combined modalities of surgery (craniofacial resection), radiotherapy and chemotherapy. Craniofacial resection entails an en bloc resection of the tumour, the cribiform plate and any intracranial extension. However, the aims of treatment are realistically to control disease. Other approaches have been to give neoadjuvant radiotherapy followed by surgery, or concurrent chemoradiotherapy in those that are not resectable. The role of adjuvant chemotherapy is unclear. In view of its rarity, the optimal sequence of treatment has yet to be established.

Chen et al. recently reported one of the largest series of SNUC (21 patients) treated in a single institution. The majority of patients had T4 disease. Seventeen patients were treated with surgery followed by postoperative radiotherapy with or without adjuvant chemotherapy. Two patients received neoadjuvant chemoradiotherapy followed by surgery and two patients received definitive chemoradiotherapy alone. Five-year overall survival was 43 per cent and two-year local control rate was 60 per cent. No difference in local control was seen between the treatment approaches but it was observed, among the patients who underwent surgery, that local control was significantly better in those who had gross tumour resection compared to those with a subtotal resection (two-year local control 74 versus 24 per cent, respectively, p = 0.001). However, in view of the small study size, this did not translate to a survival difference between the groups. The median dose of radiotherapy given was 60 Gy in those treated with definitive chemoradiotherapy and 57 Gy in those given postoperative radiotherapy. Chemotherapy regimes used varied: cyclophosphamide, doxorubicin and vincristine given in five patients; cisplatin and etoposide in four patients; cisplatin and 5-fluorouracil in two patients; carboplatin and etoposide in one patient; and cisplatin alone in one patient. The investigators concluded that gross tumour resection was the only factor which demonstrated a significant benefit in local control and therefore aggressive surgical resection either up front or after neoadjuvant therapy, in those with initially unresectable tumours, should be the main objective of treating non-metastatic SNUC.

A further recent series reported that surgery combined with radiotherapy, either given preoperatively or postoperatively, demonstrated the highest locoregional control. Of the 15 patients, nine were treated with surgery and radiotherapy (two patients received preoperative radiotherapy with concurrent cisplatin, seven patients received postoperative radiotherapy) demonstrating a three-year locoregional control rate of 78 per cent.

It has also been advocated that, in view of the poor prognosis associated with most cases of SNUC, induction chemotherapy followed by concurrent chemoradiation should be considered primary treatment. A series of seven patients treated with three cycles of platinum and 5-fluorouracil followed by radiotherapy with concurrent platinum showed a two-year overall survival of 64 per cent.

Olfactory neuroblastoma

Olfactory neuroblastoma is a tumour of neural crest origin arising from the olfactory neuroepithelium of the roof of the nasal cavity and paranasal sinuses. It was first described by Berger et al. in 1924 and has also been known as esthesioneuroblastoma, esthesioneuroepithelioma, esthesioneurocytoma and neuroendocrine carcinoma. ONB represents 5–10 per cent of sinonasal malignancy and has no sex predilection. It has a bimodal age distribution peaking at 15 years and 50 years of age.

CLINICAL FEATURES

The symptoms of ONB include nasal obstruction, rhinorrhea, epistaxis, anosmia, facial pain and diplopia. However, patients often present with non-specific symptoms resembling chronic sinusitis and therefore many cases are diagnosed late with advanced disease. It has been reported that up to 70 per cent of patients present at a locally advanced stage. Nasoendoscopy usually confirms an exophytic polypoid or sessile mass arising from the superior portion of the nasal cavity. The risk of cervical lymph node involvement is approximately 8–25 per cent and tends to occur late in the
A CT scan will assess local invasion into the adjacent bony structures, particularly the cribriform plate, and a MR scan will assess the extent of soft tissue invasion, particularly involvement into the anterior cranial cavity and orbit. A small unilateral mass in the nasal cavity with or without bony involvement is seen in the early stages. More advanced stages present with extensive bone destruction, involvement of the paranasal sinuses, and orbital and intracranial involvement (Figure 41.1).

**PATHOLOGY**

The hallmark of ONB is the formation of tumour cells into rosettes, pseudorosettes, or sheets and clusters separated by a fibrovascular stroma. Tumour cells characteristically have round nuclei containing dense chromatin which are surrounded by pale eosinophilic cytoplasm with indistinct borders. Necrosis is infrequent and is generally associated with high mitotic rates. However, most ONBs have a low mitotic rate with mild to moderate nuclear pleomorphism. Homer Wright pseudorosettes are seen in a half of ONBs. These are composed of tumour cells surrounding a central pink fibrillar material. True rosettes (known as Flexner type), which are uncommon, are formed by tumour cells surrounding a central lumen.

Electron microscopy and immunohistochemical studies are frequently needed to establish the diagnosis. ONB stains strongly positive for a variety of neuroendocrine markers, such as neuron-specific enolase, chromogranin and synaptophysin. The rosettes may be surrounded by several spindle or stellate cells which stain positive for S-100.

It is well established that the degree of histopathological differentiation is strongly correlated with the biological behaviour and prognosis. Hyams et al. introduced four grades of differentiation based on growth, architecture, mitotic activity, necrosis, nuclear pleomorphism, rosette formation and fibrillary stroma. A higher grade in the Hyams classification is associated with a poorer prognosis.

**HYAMS HISTOLOGICAL GRADING SYSTEM**

The grading system is as follows:

- **Grade I** tumours have a prominent fibrillary matrix, tumours cells which have uniform nuclei and lack nuclear pleomorphism, mitotic activity and necrosis.
- **Grade II** tumours have some fibrillary matrix, moderate nuclear pleomorphism and some mitotic activity. No necrosis is present.
- **Grade III** tumours are characterized by minimal fibrillary matrix and Flexner-type rosettes are seen. Prominent mitotic activity, nuclear pleomorphism and some necrosis may be present.
- **Grade IV** tumours have no fibrillary matrix or rosettes. Marked nuclear pleomorphism and increased mitotic activity with frequent mitoses are seen.

**STAGING**

Despite three staging classifications being devised over the past three decades to help predict prognosis and tailor treatment strategies, there is no established consensus on the staging system for ONB. Kadish et al. first introduced a three-tier classification in 1976 based on local disease extent with Morita et al. later adding a stage D in 1993 (Table 41.1).

A further staging system devised by Dulguerov et al. was introduced in 1992 based on the TNM system (Table 41.2).

Some centres have found the TNM classification to be more accurate in correlating prognosis and in guiding treatment compared with the original Kadish system. The TNM classification takes into consideration involvement of the cribriform plate and intracranial extension without dural invasion. Tumours arising below and not involving the cribriform plate can potentially be managed with a more conservative approach rather than extensive surgery. Similarly, intracranial involvement which is extradural carries a better prognosis.

**Table 41.1** Kadish stages of olfactory neuroblastoma, modified by Morita.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Disease confined to the nasal cavity</td>
</tr>
<tr>
<td>B</td>
<td>Disease confined to the nasal cavity and paranasal sinuses</td>
</tr>
<tr>
<td>C</td>
<td>Disease beyond the nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of skull, orbit or intracranial cavity</td>
</tr>
<tr>
<td>D</td>
<td>With metastasis to cervical lymph nodes or distant metastases</td>
</tr>
</tbody>
</table>
prognosis than true invasion of the cerebral parenchyma and this is recognized in the TNM staging.

### MANAGEMENT

There is no universally accepted optimal treatment for ONB in view of its rarity and the lack of randomized trials. Small tumours confined to the nasal or paranasal sinuses may be considered for an endoscopic resection providing appropriate expertise is available. However, a combined treatment modality approach with surgery and radiotherapy is needed for more advanced stage disease.30, 31, 32, 33, 34, 35

Endoscopic endonasal resection has been receiving attention recently in order to minimize surgical morbidity, such as cerebrospinal fluid leakage, intracranial haemorrhage and infection, as well as to reduce cosmetic complications associated with craniofacial resection (Figure 41.2). Tumours confined to the nasal or paranasal sinuses (Kadish A and B) and highly selected cases of Kadish C without deep infiltration of the orbit and pterygopalatine fossa or gross intracranial extension can be considered for this endoscopic approach. A few institutions have recently reported their experience showing good outcomes.36, 37, 38

Craniopharyngeal resection is the standard surgical approach for most cases enabling en bloc resection with the cribriform plate. This has been shown to improve overall survival as well as disease-free survival.22, 32, 33, 39, 40 Five-year survival has been shown to improve from 37.5 to 82 per cent with craniopharyngeal resection.33 However, despite macroscopic clearance, there is a relatively high risk of locoregional recurrence of 10–30 per cent with craniopharyngeal resection.33

Craniofacial resection is the standard surgical approach for most cases enabling en bloc resection with the cribriform plate. This has been shown to improve overall survival as well as disease-free survival.22, 32, 33, 39, 40 Five-year survival has been shown to improve from 37.5 to 82 per cent with craniopharyngeal resection.33 However, despite macroscopic clearance, there is a relatively high risk of locoregional recurrence of 10–30 per cent with craniopharyngeal resection.33 However, despite macroscopic clearance, there is a relatively high risk of locoregional recurrence of 10–30 per cent with craniopharyngeal resection.33 However, despite macroscopic clearance, there is a relatively high risk of locoregional recurrence of 10–30 per cent with craniopharyngeal resection.33 However, despite macroscopic clearance, there is a relatively high risk of locoregional recurrence of 10–30 per cent with craniopharyngeal resection.33 However, despite macroscopic clearance, there is a relatively high risk of locoregional recurrence of 10–30 per cent with craniopharyngeal resection.33

A review of 390 cases published between 1990 and 2000 supports the addition of radiotherapy to surgery demonstrating a five-year survival of 65 per cent for those treated with surgery and radiotherapy compared with 48 per cent for surgery alone.43 This is consistent with a recent analysis from the Surveillance, Epidemiology, and End Results (SEER) database reporting a five-year survival of 66 per cent with surgery and radiotherapy compared to 51 per cent with surgery alone.44

Similar to SNUC, the timing of radiotherapy around surgery varies in practice. Some centres prefer using preoperative radiotherapy with concurrent chemotherapy,35, 45, 46 whereas others prefer using postoperative radiotherapy.21, 30, 47 Patients with tumours which are unlikely to be resectable with clear margins may be offered definitive chemoradiotherapy. Levine et al.33 reported their experience with surgery followed by postoperative radiotherapy demonstrating a five-year survival rate of close to 100 per cent for Kadish stage A and 75 per cent for Kadish stage B tumours. Kadish stage C tumours were associated with a relatively high incidence of local recurrence and distant metastases (10–20 per cent), and therefore adjuvant chemotherapy can be considered in this group.

Cisplatin-based chemotherapy has generally been used in the adjuvant or palliative setting. The Mayo Clinic reported a case series of ten Kadish stage C patients with recurrent disease who were treated with platinum chemotherapy.42 The investigators concluded that cisplatin has activity in advanced ONB and that the Hyams grading is important at predicting response to chemotherapy with high-grade tumours having the most tumour regression. Non-platinum chemotherapy, such as irinotecan and docetaxel, have also been shown to have activity in advanced ONB.48

Locoregional recurrence can be salvaged with a radical neck dissection or radiotherapy depending on the site of recurrence and the original treatment modality. Kim et al.49 reported their experience of salvage treatment in six patients. Nodal recurrence was generally managed with a radical neck dissection or a radical course of radiotherapy. Distant metastases, commonly to the central nervous system or bone, were associated with a dismal prognosis despite palliative

### Table 41.2 TNM staging of olfactory neuroblastoma.30

<table>
<thead>
<tr>
<th>T/N/M Characteristics</th>
<th>T/N/M Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumour (T)</td>
<td>Regional lymph nodes (N)</td>
</tr>
<tr>
<td>T1 Tumour involving the nasal cavity and/or paranasal sinuses (excluding sphenoid), sparing the most superior ethmoidal cells</td>
<td>N0 No cervical lymph node metastasis</td>
</tr>
<tr>
<td>T2 Tumour involving the nasal cavity and/or paranasal sinuses (including the sphenoid), with extension to or erosion of the cribriform plate</td>
<td>N1 Any form of cervical lymph node metastasis</td>
</tr>
<tr>
<td>T3 Tumour extending into the orbit or protruding into the anterior cranial fossa, without dural invasion</td>
<td>Tumour involving the brain</td>
</tr>
<tr>
<td>T4 Tumour involving the brain</td>
<td>Distant metastasis (M1)</td>
</tr>
<tr>
<td>M0 No metastasis</td>
<td>M0 No metastasis</td>
</tr>
<tr>
<td>M1 Distant metastasis</td>
<td>M1 Distant metastasis</td>
</tr>
</tbody>
</table>

Figure 41.2 Transnasal endoscopic resection of an olfactory neuroblastoma (courtesy of Gerald McGarry).
chemotherapy with agents such as cisplatin, etoposide and ifosfamide.

The Hyams grading system is helpful for planning treatment. Surgical resection alone can be considered for small, low-grade tumours providing an R0 resection has been carried out. For high-grade tumours, which have a high risk of both local and distant recurrence, postoperative radiotherapy with or without chemotherapy is usually recommended.17,34

Small cell undifferentiated (neuroendocrine) carcinoma

Neuroendocrine carcinomas can occur in any site of the head and neck region with a predilection to the larynx. They have been traditionally classified into three groups: carcinoid tumour, atypical carcinoid and small cell carcinoma. Those involving the sinonasal tract are usually small cell undifferentiated carcinoma; however, it is the least prevalent type of sinonasal carcinoma of neuroectodermal origin. It is believed to originate from the glandular epithelium of the exocrine glands of the olfactory mucosa.30 The development and behaviour of NECs are distinct from those of ONB. NEC tends to arise more inferiorly in the nasal cavity, infrequently presents with regional nodal involvement, and has more potential for distant spread than ONB. It more frequently affects the elderly and has a poorer prognosis than ONB. In contrast, ONB can usually affect a younger age group, develops in the superior nasal cavity with a higher risk of regional nodal disease.

PATHOLOGY

Neuroendocrine carcinoma of the paranasal sinuses is microscopically indistinguishable from those of the bronchogenic origin. Light microscopy characteristically shows nests of poorly differentiated cells separated by thin branches of connective tissue. Nucleoli are often not prominent with nuclear chromatin having a fine granular appearance and the cytoplasm is scanty to moderate. NEC stains positive for the neuroendocrine markers (chromogranin, neuron-specific enolase, synaptophysin) and usually for cytokeratins.51

CLINICAL FEATURES

The presentation of NEC of the paranasal sinuses is similar to SNUC with nasal obstruction and epistaxis as common early symptoms, and cranial nerve palsies as more locally advanced features. Direct extension into the brain and multiple local recurrences are common. Distant metastases to the lungs, liver and bone are often relatively late events when compared to NEC arising from other anatomic sites. Furthermore, NEC may metastasize to the paranasal sinuses, and therefore a primary NEC of another site, such as the lungs, should always be sought and excluded.

MANAGEMENT

There is no recommended standard treatment for NEC of the nasal cavity or paranasal sinuses as a result of its rarity, and evidence to tailor treatment is extrapolated from data from small cell lung carcinoma. In view of its propensity to metastasize and its sensitivity to chemo-/radiotherapy, surgery is often considered not appropriate. The role of surgery is limited to very early stage disease which is uncommon. If surgery is used as primary treatment, craniofacial resection may not be necessary providing the cribriform plate, dura or brain are not involved. Locally advanced cases of NEC can be treated with induction chemotherapy, with regimens including a platinum, followed by a radical course of radiotherapy with consideration of concurrent chemotherapy in those who have responded and who are fit to receive this form of treatment. Metastatic NEC can be treated with chemotherapy, using a platinum plus etoposide, with consideration of radiotherapy to the primary or metastatic sites for palliation of local symptoms.

Outcome

SNUC and NEC are aggressive tumours with a high risk of locoregional and distant recurrence. Despite a radical treatment approach for SNUC, prognosis still remains very poor with median survival ranging from 10 to 18 months.3, 5 NEC shares the same poor clinical outcome as SNUC with a reported median survival of 14.5 months.52 Although prognosis of ONB is largely determined by the extent of disease at presentation, it can vary widely despite the Kadish staging and Hyams grading. ONB can show an indolent natural history with survival of more than 20 years in some cases. However, more aggressive cases of ONB which metastasize rapidly have survival often limited to a few months. Five-year survival rates have been reported as 57–88 per cent for Kadish stage A, 58–60 per cent for stage B and 0–50 per cent for stage C.30, 53

Follow up

Clinical follow up is determined by the aggressiveness of the tumour. However, this is often balanced by the potential for any salvageable treatment options which is largely influenced by the previous treatment and the patient’s fitness. Follow up is usually a minimum of five years with a general ENT examination with locoregional nodal assessment and nasoendoscopy every two months for the first two years, then every six months for the third to fifth years, then annually as guided by local practice. ONB may need to be followed up for ten years or more as late recurrences can occur with indolent cases. Repeat imaging can be undertaken with either a CT or MR scan after six months, and then annually. Thyroid and pituitary function should both be monitored following radiotherapy.

BONE AND SOFT TISSUE SARCOMAS

Introduction

Both bone and soft tissue sarcomas are rare in the head and neck, but when encountered, treatment will follow the principles of management of these tumours at their more usual sites, but modified to suit the anatomical constraints of the head and neck. Advice and shared care with a sarcoma
specialist team will ensure appropriate diagnosis and treatment is achieved.54-55

Bone sarcomas

Primary malignant bone sarcomas are very rare. There are approximately 400 each year in the UK (population 50 million) so the incidence is about 8/million population per year. The most common bone sarcoma is osteosarcoma, followed by Ewing’s sarcoma and chondrosarcoma, while there are a smaller number of other primary malignant bone sarcomas which do not have typical features of any of the above three and are known as spindle cell sarcomas, including such diagnoses as a fibrosarcoma, leiomyosarcoma or MFH (malignant fibrous histiocytoma). The most common site for bone sarcomas to develop is in the long bones of the skeleton and about two-thirds of all primary bone sarcomas will arise around the knee. Less than 10 per cent of all bone sarcomas arise in the axial skeleton and of these only a few will arise in the head and neck.

This chapter gives details about the current management of primary malignant bone sarcomas, so that a head and neck surgeon encountering one of these will have an idea of their current management and outcome and can discuss the case with the appropriate bone sarcoma experts for advice on management.

OSTEOSARCOMA

Osteosarcoma is principally a disease of adolescents with the most common age being 15 years and is slightly more common in males than females. Most osteosarcomas are high-grade malignant tumours presenting with a short history of pain followed by swelling. In the peripheral skeleton, the classic radiological features include sunray spiculations and periosteal elevation known as Codman’s triangle. These classical features may not be present in other sites and any patient presenting with an x-ray exhibiting any of the four following characteristics should be considered to have a potential bone tumour until proved otherwise:

- periosteal elevation;
- soft tissue swelling;
- bone destruction;
- new bone formation.

There are, however, a variety of other types of osteosarcoma:

- Parosteal osteosarcoma. This is a relatively low-grade variant of surface osteosarcoma typically arising at the back of the knee. It is densely calcified.56 57
- Periosteal osteosarcoma. This arises within the periosteum and usually presents relatively early. It has a better prognosis than conventional osteosarcoma, but is treated similarly.58-59
- Low-grade central osteosarcoma. This is a slowly progressive and difficult to diagnose condition. Histologically, it looks remarkably similar to fibrous dysplasia and there can be significant delays in diagnosis because of this. Treatment is surgical.60

- Paget’s osteosarcoma. This is a highly malignant and rapidly progressive tumour arising in patients with pre-existing Paget’s disease.61-62
- Radiation-induced osteosarcoma. This is an osteosarcoma developing in bone which has previously been exposed to radiation, usually following treatment for a previous malignancy lying adjacent to the bone (e.g. thyroid cancer, orbital cancer). The sarcoma typically develops from five to 30 years later and should be treated like a conventional high-grade osteosarcoma.63-64

A few patients with osteosarcoma will have the Li–Fraumeni syndrome (a familial cancer clustering of breast cancer, brain tumours, leukaemia and sarcomas). There is an increased incidence of osteosarcoma in patients with previous retinoblastoma because of the RB1 gene. The risk is related to age of diagnosis and treatment of the retinoblastoma with a 25 per cent incidence for those treated prior to 12 months of age and 3 per cent for those treated after that age.65

In the head and neck region, osteosarcoma usually arises in young males who present with pain and swelling of the face. Radiological investigations will reveal abnormalities either involving the maxilla or mandible. The tumours are often relatively low grade, but careful histological analysis by a sarcoma expert is recommended in all cases to confirm the diagnosis and guide treatment.

Any patient with a bone sarcoma requires staging, which is the assessment of the extent of the disease, both locally and distantly.66 Sarcomas spread by the bloodstream and metastases nearly always arise in the lungs, but occasionally another bone will be involved. Staging will thus consist of imaging of the chest (a computed tomography (CT) scan), a bone scan, and magnetic resonance imaging (MRI) or CT of the primary site.

The outcome for patients with osteosarcoma has been dramatically changed by the use of chemotherapy. For patients with high-grade osteosarcoma, survival rates of 65 per cent or greater would now be expected. Treatment consists of a combination of chemotherapy and surgical excision of the primary site with reconstruction if required. A raised alkaline phosphatase at diagnosis and the presence of metastases are both poor prognostic indicators, as are a poor response of the tumour to chemotherapy, axial site (including head and neck), large size of the tumour, as well as older age of the patient.67, 68

Chemotherapy is based on regimes using cisplatin, doxorubicin, methotrexate and ifosfamide. Most chemotherapy for osteosarcoma will be given in specialist centres where there is expertise in using these regimes. It is standard practice to give approximately ten weeks of chemotherapy before proceeding to surgery. Following resection of the tumour, the removed specimen is analysed to assess the amount of necrosis caused by the chemotherapy. If more than 90 per cent of the tumour is found to be necrotic, this is a very good prognostic indicator. For those patients with poor necrosis however, there is no evidence that changing the chemotherapy improves survival, although this is currently the subject of an international trial.69-70

Surgical resection of the tumour remains essential for both local control and cure. The principle is to excise the tumour with a ‘wide’ margin of normal tissue around the
tumour itself. Effective chemotherapy will help improve the margins of excision.

In the head and neck, obtaining wide margins will be extremely difficult, but every attempt must be made to achieve them. The narrower the margin of excision and the worse the response to chemotherapy, the greater the risk of local recurrence. There is a natural tendency to consider the use of radiotherapy in cases where a wide margin cannot be achieved, but there is at the moment little evidence that this improves local control. Radiotherapy can be used for palliation in cases of extensive recurrence.

There have been no large studies of osteosarcoma of the head and neck, but there are a number of case series. All these comment on the necessity for a multidisciplinary approach and the need for clear margins of excision to maximize local control.

Patients with low-grade central osteosarcoma or low-grade parosteal osteosarcoma do not require chemotherapy and can be managed purely surgically.

The techniques of reconstruction used in the head and neck will be very similar to those used for other tumour types arising in similar sites and will not be documented further.

CHONDROSARCOMA

Chondrosarcoma is the second most common type of bone tumour and is more common in older people from about 40 years onwards. It is slightly more common in males than females and on the whole it is a low-grade, slow-growing type of sarcoma. It frequently presents as a painless mass arising either within the bone (central) or on the surface (periosteal). Chondrosarcoma is graded from one to three based on the histological appearance and most will be grade one or two. Grade 3 chondrosarcoma is a highly malignant tumour with a poor prognosis. Rarely, a chondrosarcoma will differentiate to a high-grade spindle cell sarcoma and again the prognosis is poor.

Chondrosarcomas do not respond to chemotherapy or radiotherapy and treatment is by surgical excision and reconstruction if necessary. Clear margins of excision are absolutely essential for local control.

Chondrosarcoma of the head and neck is rare but a review by the National Cancer database in the United States identified 400 cases of head and neck chondrosarcoma in a ten-year period. The authors reported a disease-specific survival of 87 per cent at five years dropping to 70 per cent at ten years. Complete surgical excision led to the best chance of local control and survival.

EWING’S SARCOMA

Ewing’s sarcoma of bone arises in children and young adults and although common in the axial skeleton (25 per cent of cases arise in the pelvis), it is rare in the head and neck. The cell of origin remains uncertain, but the tumours are small blue round cell tumours characteristically demonstrating a t(11;22) translocation. The histological diagnosis can be extremely difficult, in particular differentiating these tumours from rhabdomyosarcoma or synovial sarcoma and the use of molecular genetic studies is essential to confirm the diagnosis prior to treatment starting.

Ewing’s sarcoma usually responds very well to chemotherapy using ifosfamide, doxorubicin, vincristine and etoposide. The tumour is also usually very sensitive to radiotherapy. In the past, treatment with chemotherapy and radiotherapy resulted in a high rate of local recurrence (20 per cent or more) and so now attempts are made in most cases to surgically remove the tumour once it has been downstaged by preoperative chemotherapy. Postoperative radiotherapy will still be used if there is a poor response of the tumour to chemotherapy or if the margins are not wide. If the surgical excision would not achieve clear margins or there would be a major functional deficit following the surgery, then consideration should still be given to definitive radiotherapy despite the increased risk of local recurrence. The overall prognosis for patients with Ewing’s sarcoma is dependent upon the presence or absence of metastases at the time of diagnosis, the age of the patient and the size of the initial tumour, as well as the response to chemotherapy. Overall, survival rates of approximately 70 per cent at five years are to be expected.

SPINDLE CELL SARCOMAS

Spindle cell sarcomas of bone are treated in a very similar manner to osteosarcoma with chemotherapy and surgical excision and reconstruction. Because these patients tend to be older, it is often more difficult to give them a full course of chemotherapy and beyond the age of 60 years, chemotherapy proves very toxic and it may not be possible to use this. Survival rates are slightly better than for osteosarcoma in a similar age group.

There are a variety of other bone tumours which may affect the head and neck region, the most important of which is in giant cell tumour of bone (osteoclastoma). This is a benign but locally aggressive tumour where the bone is simply eaten away. The aetiology is unknown and treatment is usually curettage of the giant cell tumour. The site and size of the tumour will depend on whether any form of reconstruction is needed. A bone graft or bone cement can both be used to fill the defect. Although some people use adjuvants, such as liquid nitrogen or phenol, to clean out the cavity, local recurrence rates vary between 10 and 25 per cent. In cases of very aggressive or recurrent tumours, complete surgical excision may be required for local control and radiotherapy can also be used if essential. The main differential diagnosis of a giant cell tumour both radiologically and histologically is a brown tumour of hyperparathyroidism and it is mandatory to check the serum calcium of any patient with a suspected giant cell tumour of bone.

CHORDOMAS

Chordomas are tumours arising from the primitive notochord. The most common site is in the sacrococcygeal area, but about 25 per cent will arise in the cervical spine or base of skull. They are slow growing, but locally aggressive malignant tumours with a low rate of metastasis. Surgical excision with clear margins is the treatment, but can be very difficult to achieve. Conventional radiotherapy seems to have little role in controlling progression of the tumour, but in very selective cases heavy particle proton beam radiotherapy may have a role.
FOLLOW UP

Any patient who has been diagnosed and treated for a sarcoma should be regularly followed up to try and identify locally recurrent disease at a stage when it is still treatable. The other purpose of follow up is to identify early metastatic disease because surgical resection of metastases (usually in the lungs) can be worthwhile, providing long-term cure in up to 30 per cent of cases. It is usually recommended that patients should be seen clinically every three months for the first two years, six monthly the next three years and annually thereafter. They should have a routine x-ray of the primary site and a chest x-ray on each occasion. At the present time, there is no proof that regular follow up with either CT or MRI is beneficial or cost-effective.

Soft tissue sarcomas

Soft tissue sarcomas are malignant tumours originating from various soft components of the mesenchymal tissue anywhere in the body. They are rare in the head and neck accounting for less than 10 per cent of all soft tissue sarcomas and approximately 1 per cent of all head and neck tumours.91, 92, 93, 94, 95

There is a variable male predominance with median age between 50 to 55 years.92-95 In children, head and neck soft tissue sarcomas are much more common comprising 35–40 per cent of all soft tissue sarcomas.96-97

A variety of histological entities, some clearly defined, others more ambiguous, with varied biological behaviour are observed (Box 41.1). This heterogeneity makes individual subtypes of the disease even more rare, although the more commonly reported subtypes are fibrosarcoma, liposarcoma and malignant fibrous histiocytoma, each accounting for about 20 per cent in most studies.93-98 Rhabdomyosarcoma is rare in adults, but is the principal paediatric type.98 It has a distinct natural history and is managed differently to other soft tissue sarcomas, and is thus discussed separately.

Box 41.1 Histological subtypes of soft tissue sarcomas

- Malignant fibrous histiocytoma
- Liposarcoma
- Fibrosarcoma
- Malignant peripheral nerve sheath tumour (MPNST)
- Spindle cell sarcoma
- Ewing’s sarcoma
- Synovial sarcoma
- Dermatofibrosarcoma protuberans
- Leiomyosarcoma
- Myxoid chondrosarcoma
- Sclerosing epithelioid fibrosarcoma
- Angiosarcoma
- Epithelioid sarcoma
- Rhabdomyosarcoma
- Lymphangiosarcoma
- Unclassified sarcoma

The rarity of soft tissue sarcomas suggests that they are best treated at multidisciplinary specialist sarcoma units where the opportunity is available to gather knowledge and skills, and develop expertise.98

AETIOLOGY

The majority of patients do not have any obvious risk factors, however a number of genetic and environmental exposures have been associated with an increased risk of soft tissue sarcomas. The Li–Fraumeni syndrome is an autosomal dominant disorder involving a mutation of p53 tumour-suppressor gene and is associated with soft tissue sarcomas, as well as multiple other malignancies.99 Neurofibromatosis type 1 is associated with rhabdomyosarcoma, liposarcoma and fibrosarcoma in children and MPNST (malignant peripheral nerve sheath tumor) in adults.99,100 Other conditions which have been implicated in the increased risk for soft tissue sarcomas include hereditary retinoblastoma and Gardner’s syndrome.97-99 Previous radiotherapy to treat other conditions, especially breast cancer has been associated with increased risk of late development of soft tissue sarcomas in the head and neck.93, 101, 102, 103-104

CLINICAL FEATURES

Soft tissue sarcomas may occur in any part of the head and neck, although the most commonly reported primary sites include scalp, face and neck.93, 97 The clinical presentation is mostly related to the anatomical site of the lesion and presence or absence of compression of the surrounding structures by the lesion. The most common presenting feature of head and neck sarcomas is a painless mass which is reported in 80 per cent of cases.105 A wide spectrum of other symptoms have been reported which include nasal blockage, epistaxis, proptosis, diplopia, otalgia, deafness, tinnitus, vertigo, dental pain, tooth mobility, dysphagia, alteration in voice quality and facial palsy. Most tumours are nonmetastic at presentation. Occasionally, the patients may present with an enlarged neck node due to regional spread. It is extremely unlikely for the patients to present with symptoms related to spread to distant sites.

It is common to discover soft tissue sarcomas incidentally following excision of a lump, without prior suspicion of a sarcoma. The clinical signs are mostly nonspecific, however a submucosal or subcutaneous mass may be expected.97 Angiosarcoma typically presents as a macule or plaque resembling dermatological entities on the forehead and scalp of elderly white males.106, 107

Current guidance issued by National Institute for Health and Clinical Excellence (NICE) recommends that a lump with any of the following features should be investigated for potential malignancy:

- larger than 5 cm;
- increasing in size;
- deep to the fascia;
- painful.

Similar guidance published about early diagnosis of head and neck cancer recommends urgent referral for any unexplained lump in the neck, of recent onset, or a previously
undiagnosed lump that has changed over a period of 3–6 weeks.108

There should be clearcut pathways for referring patients in either of the above categories either to a head and neck or a sarcoma rapid diagnosis unit.

INVESTIGATIONS

Delay in diagnosis for soft tissue sarcomas is common as often the patients and clinicians do not perceive the symptoms and signs as sinister. The initial role of the head and neck surgeon includes assessment of the primary tumour and clinical investigations including nasendoscopy, examination under general anaesthesia and biopsy. Because soft tissue sarcomas are so rare, it is unlikely that the diagnosis will be initially considered, but it is important not to jeopardise subsequent management of a potential sarcoma by hasty treatment.

Any patient with a suspicious lump should undergo appropriate investigation, which, in the head and neck will usually follow the pathway recommended for the site of the lesion. While imaging to assess the anatomical location of the mass is essential, biopsy is mandatory in confirming the diagnosis of soft tissue sarcoma.

Very few pathologists, even in specialist centres, will be happy to diagnose a soft tissue sarcoma on a fine needle aspiration (FNA) cytology sample, although this is frequently the first procedure carried out in head and neck clinics. A needle core biopsy will however be diagnostic in most cases and should be the next step in investigation if FNA is not helpful.93, 101 An incisional transmucosal biopsy is appropriate for lesions in the aerodigestive and sinonasal tracts. Complete resection of the tumour in the parotid, neck and parapharyngeal space is preferable to incisional biopsy to prevent iatrogenic seeding of tumour cells into a possible future operative site. An incisional biopsy on these sites may only be considered if unacceptable level of cosmetic or functional morbidity is expected if complete resection was undertaken.97

The patients should undergo imaging studies, such as MRI and/or CT, to enable accurate assessment of the lesion and to ascertain regional node status although the risk of regional spread is low.93–97 The most common site for distant metastases is the lungs and therefore the patients should have a CT scan of the chest before treatment to rule out the possibility of metastatic disease, especially in cases of high-grade tumours. In the absence of lung metastases, other distant metastases are highly unlikely and therefore further investigations are not essential.93, 97

PATHOLOGY

Most soft tissue sarcomas are high grade and are located deep to the superficial fascia.93 Establishing accurate histological subtype of the tumour is unfortunately not straightforward as it requires complex immunohistochemical and cytogenetic studies by specialist pathologists, and all cases of suspected sarcoma should be referred to a specialist sarcoma pathologist for confirmation of diagnosis prior to treatment.95–97, 109 An accurate histological diagnosis will provide helpful information on the likely prognosis for the patients. Malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, synovial sarcoma, alveolar soft part sarcoma and Ewing’s sarcoma are generally high-grade tumours with poorer prognosis, whereas dermatofibrosarcoma protuberans and desmoid tumours are low-grade tumours with better prognosis.91, 97, 105, 110, 111, 112

There is currently no universally accepted staging system for soft-tissue sarcomas. Several staging systems are used, of which the most commonly used are the TNM (tumour, node, metastasis) system developed by the American Joint Committee on Cancer and the Enneking system.96, 113 Both of these staging systems take histological grade into account, as well as size and spread of the tumour.

MANAGEMENT

Soft tissue sarcomas are best managed by a multidisciplinary team which may include a sarcoma specialist, a site-specific head and neck surgeon and an oncologist, as well as the sarcoma pathologist and appropriate radiologists. The important features that determine management of soft tissue sarcomas are site, size and grade of the tumour, and presence or absence of nodal or distant metastases.93–97

Complete surgical resection is the treatment of choice for all soft tissue sarcomas. Surgical excision with a wide margin of normal tissue around the lesion should be attempted in all cases unless contraindicated by the possibility of an unacceptable level of functional or cosmetic morbidity or in those tumours in close proximity to vital anatomical structures. Contemporary surgical advances, such as free tissue transfer with microvascular reconstruction, have made it possible for larger tumours to be resected and this may require a multidisciplinary surgical team consisting of a sarcoma surgeon, head and neck surgeon, and a maxillofacial or plastic surgeon. Locoregional lymph node dissection is rarely necessary for sarcomas, however it may be considered in certain tumours with a predilection for lymph node metastases (e.g. epithelioid sarcoma, clear cell sarcoma and occasionally synovial sarcoma).

Adjuvant radiotherapy is indicated for all high- or intermediate-grade tumours and also for marginally or incompletely resected low-grade tumours. Radiotherapy alone may be used in cases of unresectable tumours and may provide temporary local control in some patients.93

Chemotherapy is not usually used for soft tissue sarcomas as it has not been shown to produce an overall survival benefit. It does however have a role in the treatment of specific soft tissue sarcomas, such as Ewing’s tumour, and soft tissue sarcomas in children.73, 114 A meta-analysis published in the Lancet revealed a 10 per cent benefit of chemotherapy on recurrence-free survival which may support a case for considering adjuvant chemotherapy for patients with large, high-grade deep soft tissue sarcomas in an attempt to improve relapse-free survival (Figure 41.3).114 The treatment is essentially palliative if metastatic disease is present.

OUTCOME

The most significant prognostic factors for overall survival of soft tissue sarcomas are grade, size and depth, while margin status of the excised tumours is the most important prognostic factor for local control.115 High grade, tumour size
larger than 5 cm in diameter, tumours incompletely excised and location deep to the superficial fascia are all associated with poorer survival.95, 97, 106, 110, 112, 116, 117, 118

Head and neck soft tissue sarcomas are recognized to have a worse prognosis than similar sarcomas elsewhere in the body. The five-year overall survival and local control rates for soft tissue sarcomas of the head and neck ranges from 60 to 70 per cent.93 This is much lower compared with local control rates of up to 90 per cent for sarcomas of the extremities.93, 119 This is most likely related to the difficulty of obtaining wide surgical margins in many cases in the head and neck. Unlike limb soft tissue sarcomas, there is no option of undertaking an amputation if local recurrence occurs.

The local recurrence rates for high-grade soft tissue sarcomas after surgical excision is as high as 50 per cent and the risk is increased with intralesional or marginal surgical margins.92, 93, 119, 120 It is therefore extremely important that every effort is made to maximize the margins at the time of the first surgical procedure. If the margins prove positive at the first attempt, performing a further and wider excision should always be considered. Patients who present after inadvertent excision of a lump which turns out to be a sarcoma should always be considered for a further wide excision as residual tumour cells will be found in up to 70 per cent of cases.121 The risk of developing distant metastases is between 10 and 30 per cent and the risk is higher for large, intermediate or high-grade and deep lesions.93 The majority of patients who develop metastatic disease do so within two to three years of receiving the treatment.93, 122, 123

A nomogram to predict survival of patients following excision of soft tissue sarcomas is available online (www.mskcc.org/mskcc/html/6181.cfm).124

**FOLLOW UP**

Following definitive treatment, patients should be followed up routinely in order to detect treatable local recurrence or metastatic disease at a stage when it can be dealt with. A minimum period of up to five years is recommended as it is uncommon for local recurrence to occur after this period and prolonged follow up may result in unnecessary distress to the patients and inappropriate use of resources. Clinical assessment and chest radiograph should be considered at each clinic visit. These would usually be four times a year for two years following diagnosis then twice a year for the next three years. Surgical excision of local recurrence or metastatic disease should be considered if possible. Palliative chemotherapy or radiotherapy may have a role.
Rhabdomyosarcoma

Rhabdomyosarcoma is a distinct clinicopathological entity and its management is significantly different from other types of soft tissue sarcomas. It accounts for about one-fourth of all head and neck sarcomas and 4–8 per cent of all paediatric cancers. Other than in the head and neck, it may arise in genitourinary organs, limbs and may also rarely occur elsewhere.

There are four different histological types of rhabdomyosarcoma—embryonic, alveolar (Figure 41.4), botryoidal and pleomorphic, of which the embryonic types are the most common and the alveolar tumours have the worst prognosis. Rhabdomyosarcoma arises in three main head and neck primary sites with different prognostic significance—orbit, parameningeal sites (nasopharynx, nasal fossa, paranasal sinuses, infratemporal fossa, pterygoid fossa, middle ear and mastoid) and non-parameningeal sites (scalp, face, parotid, oral cavity, oropharynx, larynx and neck). Those arising at parameningeal sites have an affinity to invade the cranial cavity via basal skull foramina and are consequently associated with the worst prognosis.

Rhabdomyosarcoma has a propensity to metastasize early to regional lymph nodes and therefore radiological investigation of the neck with MRI should be undertaken routinely. In cases of parameningeal rhabdomyosarcoma, a MRI of the brain and cytological examination of cerebrospinal fluid (CSF) may be needed.

The specific site of origin of rhabdomyosarcoma is incorporated into the TNM staging system as it correlates well with the outcome. The Children’s Oncology Group (COG) based in the United States and European Paediatric Soft Tissue Sarcoma Study Group (EPSTSSG) conduct studies and produce protocols for management of soft tissue sarcomas in children. They have used surgicopathologic criteria including local extension, regional and distant metastases, and amount of residual tumour after surgical resection of the tumour, to stage rhabdomyosarcoma.

Complete surgical excision remains a critical component of treatment for rhabdomyosarcoma, however radical surgery is frequently not possible due to close proximity of the tumours to vital structures and also due to the possibility of significant postoperative cosmetic and functional morbidity.

Combination chemotherapy with or without adjuvant surgery and/or radiotherapy is commonly used as primary treatment for rhabdomyosarcoma.

The five-year overall survival for rhabdomyosarcoma in children ranges from 74 to 77 per cent, while the five-year disease-free survival ranges from 38 to 74 per cent. The outcome in adults is unclear due to lack of studies, however may be significantly worse.

HEAD AND NECK LYMPHOMAS

Introduction

Lymphomas involving the head and neck broadly fall into four main categories:

1. Primary central nervous system lymphoma (PCNSL) is rare and accounts for 1–2 per cent of all lymphomas. It is defined as a non-Hodgkin’s lymphoma (NHL) that is confined to the craniospinal axis without systemic involvement. Patients present with symptoms due to either ocular or involvement of the brain (in 50 per cent of cases the frontal lobes are involved). Patients with either congenital or acquired immunodeficiency (e.g. due to human immunodeficiency virus or immunosuppression secondary to solid organ transplantation) have a significantly greater risk of developing PCNSL. Patients with PCNSL usually present to neurologists, neurosurgeons or ophthalmologists and hence further information about this rare but complex lymphoma is not included in this chapter.

2. Primary extranodal lymphomas are defined as lymphomas occurring in tissue other than lymph nodes, spleen or bone marrow. Approximately 25 per cent of NHL occur in extranodal sites. Lymphoma involving Waldeyer’s ring (tonsil, nasopharynx and base of tongue) accounts for approximately 10–15 per cent of extranodal lymphomas. NHL involving the sinuses accounts for approximately 4 per cent of all extranodal lymphomas. Thyroid lymphomas account for 5 per cent of thyroid cancers and 5 per cent of extranodal lymphomas.

3. Nasal T/NK-cell lymphoma is now considered to be a distinctive pathological entity and typically is a destructive tumour which affects the midline facial structure. It has an unusual epidemiological pattern and is seen predominantly in the Far East (China, Hong Kong, Japan, Malaysia and Korea), as well as Central and South America (Mexico and Peru). Sporadic cases in other parts of the world are only rarely seen. It is an exceedingly rare lymphoma and even in places where it is observed more frequently, such as the Far East, it accounts for only 5 per cent of all lymphomas.

4. Hodgkin’s lymphoma is relatively rare and in the UK there are approximately 1500 new cases/year. The disease has a bimodal age distribution with one peak between 15 and 35 years, and a second peak in patients older than 50 years. Cure rates for patients...
with Hodgkin’s lymphoma are generally better than for NHL and are usually in excess of 50 per cent.

Primary extranodal lymphomas involving the head and neck

LYMPHATICS OF THE HEAD AND NECK

The lymphatics of the head and neck are arranged in deep and superficial chains. The deep jugular chain extends from the skull base to the clavicle and is formed into superior, middle and inferior groups of lymph nodes.

The superior deep jugular nodes receive primary drainage from the soft palate, tonsils, palatoglossal and palatopharyngeal arches, posterior and base of tongue, pyriform sinus and larynx above the vocal folds. The middle deep jugular nodes receive primary drainage from the larynx above the vocal folds, lower pyriform sinus and posterior cricoid. The inferior deep jugular nodes receive primary drainage from the thyroid, trachea and cervical oesophagus (see Figure 41.5a,b). The retropharyngeal and paratracheal nodes receive drainage from deep structures in the midline of the head, including the nasopharynx, posterior nasal cavity, paranasal sinuses and posterior oropharynx.

The superficial nodes are the submental, superficial cervical, submandibular, spinal accessory and anterior scalene. The submental nodes drain the chin, tip of the tongue, anterior mouth and middle of the lower lip. The submandibular nodes drain the upper lip, lateral lower lip, lower nasal cavity, anterior mouth and the skin of the cheek. The superficial cervical nodes receive drainage from around the parotid gland, behind the ear, parotid and occipital nodes. The nodes in the posterior triangle lie around the spinal accessory nerve and drain the parietal and occipital regions of the scalp. The anterior scalene (Virchow’s) nodes are located at the junction of the thoracic duct and the left subclavian vein and receive drainage form the thoracic duct. They are usually the site for metastases from the stomach. The supraclavicular nodes receive drainage from the spinal accessory nodes and infraclavicular sources (see Figure 41.6).

All the lymphatics from the head and neck region eventually drain into the venous system either through the thoracic duct on the left or the right lymphatic duct.

Clinical presentation

Patients with head and neck lymphomas generally present with airway obstruction, difficulty in swallowing, mass lesion, blockage of the Eustachian tube or neck nodes. Frequently, the mass may be palpable. However, a flexible direct endoscopy is recommended in all patients since such an assessment may reveal multiple sites of involvement. Fine needle aspiration/cytology is inadequate to make a detailed pathological diagnosis and hence a tissue biopsy or excision biopsy is required in all patients. To allow for full molecular, cytogenetic and immunohistochemical analysis, the sample should be sent fresh to the pathology laboratory as a matter of urgency. Although surgery may debulk the tumour, surgical resection alone is not curative and hence full staging is required on all patients.

Staging investigations

The following investigations are recommended at diagnosis:

- Computed tomography (CT) or magnetic resonance imaging (MRI) scan of the head and neck
- Whole body CT/positron emission tomography (PET) scan or if not available, CT scan of the chest, abdomen and pelvis
- Bone marrow aspirate and trephine biopsy
- Full blood count
- Biochemistry profile, including lactate dehydrogenase (LDH)
- For patients presenting with lymphoma involving Waldeyer’s ring, investigation of the gastrointestinal (GI) tract with either endoscopy or contrast imaging is required.
Approximately 30 per cent of patients with tonsillar lymphoma have systemic disease. There is an association between Waldeyer’s ring lymphoma and the GI tract. In a large randomized trial,132 approximately a third of patients with relapsed Waldeyer’s ring lymphoma, relapsed in the GI tract.

Diffuse large B-cell lymphoma (a type of high-grade or aggressive B-cell NHL) accounts for 60–80 per cent of non-Hodgkin’s lymphoma occurring in the head and neck region, other histological types include follicular (14 per cent), mantle cell (12 per cent) and mucosa-associated lymphoid tissue (MALT)-lymphoma (9 per cent). Sixty per cent of patients present with localized disease.

**Treatment**

**Limited stage**

Surgical resection is rarely curative and treatment of patients with localized head and neck lymphomas generally consists of a combination of chemotherapy and radiotherapy. The chemotherapy schedule that is almost universally used for patients with high-grade B-cell NHL is R-CHOP.133 This consists of a cocktail of five drugs: rituximab (a monoclonal antibody against CD20), cyclophosphamide, doxorubicin, vincristine and prednisolone. The chemotherapy schedule is given on a 3-weekly basis. For patients with limited stage disease, treatment generally consists of three cycles of chemotherapy followed by radiotherapy. A randomized trial of 316 patients with stage I Waldeyer’s ring high-grade lymphoma showed a higher relapse rate for patients treated with CHOP or irradiation alone compared with combined modality treatment.132 Twenty-three per cent of patients treated with chemotherapy alone relapsed compared to 5 per cent treated with a combination of chemotherapy plus radiotherapy. In a retrospective review of 130 adult patients with stage I and II NHL affecting the Waldeyer’s ring, Ezzat et al.134 found that 84 per cent had diffuse large B-cell NHL, 58 per cent had primary tonsillar, 35 per cent nasopharyngeal and 7 per cent base of the tongue lymphoma. Fifty-eight per cent received chemotherapy alone, 20 per cent received radiotherapy and 35 per cent were managed with a combination of chemotherapy and radiotherapy. The complete remission rate of approximately 80 per cent was no different between the three treatment modalities. Most distant relapses were seen in non-gastrointestinal sites. Patients treated with combined modality treatment had a better event-free survival; this study did not show a difference in overall survival for the combined modality treatment when compared with single modality treatment. However, a further study from Italy135 in 107 patients with localized extranodal head and neck lymphoma treated with either radiotherapy alone (n = 59) or chemotherapy plus radiotherapy (n = 48) showed a significant improvement in five-year overall survival for combined modality treatment; 63 versus 38 per cent for radiotherapy alone. In multivariate analysis, the only significant prognostic factor was age <60 years. Eighty per cent of the relapses occurred systemically and only 7.5 per cent of patients relapsed in-field.

Contrary to diffuse large B-cell or aggressive NHL, patients with indolent, localized lymphoma of the Waldeyer’s ring can achieve long-term disease control with radiotherapy alone.

**Advanced stage disease**

Patients with stage III/IV diffuse large B-cell NHL, those with B-symptoms or bulky disease (>10 cm) should be treated with between six and eight cycles of R-CHOP chemotherapy, followed by radiotherapy to any residual sites of disease. Residual disease is best assessed by a PET scan.

Patients with extensive low-grade lymphoma can be treated with single agent (e.g. chlorambucil or fludarabine) or combination (R-CVP, rituximab in combination with cyclophosphamide, vincristine and prednisolone) chemotherapy.

### Nasal T/NK–cell lymphoma

**SINUS LYMPHOMA**

Approximately 3 per cent of extranodal lymphomas involve the sinuses. The sinuses most commonly involved include the ethmoid, frontal, maxillary and sphenoid.

**Presenting symptoms**

Patients usually present with:

- Local pain and/or facial swelling.
- Nasal or airway obstruction.
- Rhinorrhoea.
- Epistaxis.
- If the tumour involves the periorbital area, patients may present with proptosis, loss of vision or diplopia.

In British Columbia, a retrospective survey was carried out of 44 patients with primary paranasal lymphoma presenting between 1980 and 1999.135 Eighty-four per cent of patients had diffuse large B-cell lymphoma, 8 per cent had T/NK nasal type and 8 per cent had T-cell/not classified. Median age at presentation was 66 years (range, 27–97 years). All patients were treated with chemotherapy plus radiotherapy. In addition, from 1985, they received intrathecal chemotherapy. The addition of intrathecal chemotherapy reduced the risk of central nervous system (CNS) relapse and also improved...
overall and disease-free survival (from 20 to 51 per cent and 40 to 65 per cent, respectively).

Sinus lymphoma usually follows an aggressive course and has a tendency to cause bony destruction, break down natural anatomic barriers and systemically disseminate. Once the diagnosis is confirmed, patients should be commenced on chemotherapy (which will be R-CHOP in the majority of cases). Patients usually receive between six and eight cycles of chemotherapy followed by involved field radiotherapy. Given the anatomical proximity of the sinuses to the central nervous system, it is not surprising that this type of lymphoma has a tendency to spread to the central nervous system. The risk of spread has been estimated to be as high as between 20 and 40 per cent. Administering prophylactic intrathecal chemotherapy may reduce the risk of CNS relapse to less than 10 per cent.

**THYROID LYMPHOMA**

Primary thyroid lymphoma is a lymphoma that arises from the thyroid. It is relatively rare and accounts for 5 per cent of all thyroid malignancies. It is more common in women and the median age of presentation is 60 years. Lymphomas affecting the thyroid are usually non-Hodgkin’s lymphomas. The incidence of thyroid lymphoma in patients with Hashimoto thyroiditis is markedly increased and the incidence of pre-existing autoimmune thyroiditis in patients with thyroid lymphoma ranges from 27 to 100 per cent. The risk of developing thyroid lymphoma in a patient with Hashimoto’s thyroiditis is 40–80 times greater than that of the general population.

**Presenting symptoms**

Patients most commonly present with:

- Patients with diffuse large B-cell NHL present with a rapidly enlarging thyroid mass. Patients with mucosa-associated lymphoid tissue (MALT-lymphoma) have an indolent histology and can present with a slowly growing mass which has been present for months or sometimes years.
- Hoarseness.
- Respiratory difficulty.
- Cough.

**Diagnosis**

Fine needle aspiration (FNA) is insufficient for diagnosis and for histological diagnosis to be made, an incisional biopsy is required. Over 80 per cent of thyroid lymphomas are diffuse large cell B-cell lymphoma (DLBCL) and most (80 per cent) present with stage I or II disease. The second most common histological variety is the indolent B-cell marginal cell lymphoma (also known as MALT-oma).

**Staging**

Before commencing treatment, the following are required to fully stage a patient:

- CT scan of neck, chest, abdomen and pelvis or CT/PET scan;
- bone marrow aspirate, immunophenotyping and trephine biopsy;
- serum LDH.

**Treatment**

**Diffuse large B-cell lymphoma**

All patients with DLBCL of the thyroid are treated with R-CHOP chemotherapy. For patients with stage I/II disease, three cycles of chemotherapy followed by involved field radiotherapy is usually given. For patients with stage III/IV disease, B symptoms or bulky disease more than 10 cm, more prolonged chemotherapy with between six and eight cycles of R-CHOP chemotherapy is indicated.

**MALT-lymphoma of thyroid**

Patients with localized MALT-lymphoma are treated with involved field radiotherapy and this can result in five-year survivals of 90 per cent. For more extensive disease, chemotherapy is indicated. Agents commonly used include chlorambucil, cyclophosphamide, rituximab and fludarabine. Combination regimens such as R-CVP may also be used.

Patients with treated thyroid lymphoma (especially those treated with radiotherapy) are usually rendered hypothyroid and hence lifelong monitoring of thyroid function tests is required.

**Nasal T/NK cell lymphoma**

Nasal natural killer cell/T-cell cell lymphoma typically affects the midline facial structures and has distinctive pathological and immunophenotypic characteristics.

It has a strong association with Epstein–Barr virus and is the most common extranodal lymphoma in Taiwan. It is seen predominantly in the Far East (China, Japan, Korea and Malaysia) and less commonly in Central and South America. Median age of onset is 50 years and there is a slight male preponderance. Measurement of EBV DNA load by PCR (polymerase chain reaction) is used as a surrogate marker of tumour load.

Patients usually present with a nasal mass causing obstruction and bleeding. The tumour usually causes bony destruction to the maxillary sinuses and nasal passages. It frequently has an aggressive course with a poor outcome.

Treatment usually consists of a combination of chemotherapy and radiotherapy. CHOP chemotherapy is generally ineffective and hence regimens such as the SMILE (steroid = dexamethasone, methotrexate, ifosphamide, l-asparaginase and etoposide) are more commonly used. There is some evidence to suggest that radiotherapy doses ≥50 Gy may result in more favourable local control.

**Hodgkin’s lymphoma**

The vast majority of patients with Hodgkin’s lymphoma present with lymphadenopathy. In about 75 per cent, the lymph nodes are enlarged in the neck. The enlarged nodes may wax and wane over time. About a third of patients with Hodgkin’s lymphoma present with B-symptoms (fevers, sweats or weight loss >10 per cent). Alcohol-induced pain/
pruritus is rare, but is typically associated with Hodgkin’s lymphoma. Histologically, the disease is characterized by the presence of Reed–Sternberg cells. The aetiology of Hodgkin’s lymphoma is unknown, but there is an association with Epstein–Barr virus. Similar to non-Hodgkin’s lymphoma, there is a higher incidence in patients who are HIV positive.

As with other lymphomas, diagnosis requires an incisional biopsy (FNA is inadequate). Once the diagnosis is confirmed, full staging as with a newly diagnosed patient with non-Hodgkin’s lymphoma is required.

**Treatment**

Most patients will require combination chemotherapy. The most common regimen used is ABVD (adriamycin, bleomycin, vinblastine and dacarbazine). Patients usually require between six and eight cycles of treatment. Patients with bulky disease at presentation or those with residual masses post-chemotherapy may benefit from adjuvant radiotherapy. Patients presenting with limited early stage disease (stage I/IIA) may be treated by two to four cycles of ABVD followed by radiotherapy. CT/PET scanning is particularly useful in assessing response to treatment.

**Key evidence**

- The rarity of neuroectodermal malignancies of the head and neck precludes any randomized trials and evidence is from a collection of institutional experiences.
- Gross tumour resection either up front or after neoadjuvant therapy is the main aim of treating non-metastatic SNUC to maximize on local control. Adjuvant radiotherapy is associated with improved locoregional control.
- A combined treatment modality approach with surgery and radiotherapy has been associated with improved survival compared with surgery alone for ONB.

**Key learning points**

**Neuroectodermal malignancies of the head and neck**

- In view of the rarity, these tumours are best managed in specialized centres with the appropriate histopathological, radiological, surgical and oncological expertise.
- The biological behaviour of sinonasal malignancies of neuroectodermal origin can be broadly divided into two main groups: ONB or non-ONB.
- ONB can be associated with a very good prognosis following local therapy, typically surgery and postoperative radiotherapy. Late locoregional recurrences can be seen with ONB.
- Non-ONB (such as SNUC and NEC) have high rates of locoregional and systemic failure, and therefore combined treatment modality approaches are necessary for disease control. However, prognosis of non-ONB generally remains poor and more effective therapies are needed for the future.

**Bone sarcomas**

- Bone sarcomas are difficult to diagnose and manage, and the opinion of a specialist sarcoma team should be considered in every case.
- Chemotherapy has dramatically improved survival for osteosarcoma and Ewing’s sarcoma.

**Soft tissue sarcomas**

- Soft tissue sarcomas are rare in the head and neck.
- Diagnosis is frequently delayed.
- Wide surgical excision is the mainstay of treatment unless contraindicated.
- The overall five-year survival after treatment ranges from 60 to 70 per cent.
- There is high incidence of local recurrence and metastatic disease.
- Lungs are the most common distant site.
- They are best treated at specialist sarcoma units.

**Rhabdomyosarcoma**

- Rhabdomyosarcoma is a significant disease of children comprising 4–8 per cent of all paediatric cancers.
- The head and neck sites include orbit, parameningeal and nonparameningeal region.
- They are usually treated with combination chemotherapy and adjuvant radiotherapy, and/or surgery.
- Five-year survival for children after treatment is around 75 per cent.

**Head and neck lymphomas**

For patients being investigated/diagnosed as having a head and neck lymphoma:

- Flexible direct endoscopy is recommended for all patients.
- Fine needle aspiration is insufficient to make a tissue diagnosis and all patients require an incisional biopsy.
- Lymph node biopsies need to be sent ‘fresh’ (i.e. not in formalin) as a matter of urgency to a designated lymphoma pathologist.
- Surgical resection is never curative and full staging is required in all patients.
- The most common histological type is diffuse large B-cell non-Hodgkin’s lymphoma.
- Patients with diffuse large B-cell NHL will require chemotherapy with R-CHOP ± radiotherapy.
- Patients with sinus lymphoma benefit from administration of prophylactic intrathecal chemotherapy.
- Assessing response to treatment is best done by combined CT/PET scanning.

REFERENCES


FURTHER READING


Non-surgical treatments

Section editor: Nick Slevin

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Principles of radiotherapy

NICK ROWELL

INTRODUCTION

Radiotherapy is the application of radiation for the purpose of therapeutic gain. Most commonly, this is by means of external beam radiotherapy (sometimes known as teletherapy) where a radiation beam is directed from a machine placed outside the patient to a treatment volume located within. Alternatively, radioactive material can be introduced directly to within a tumour or tumour-bearing area (brachytherapy). Recent decades have seen considerable progress in technology, with more effective means of immobilizing patients, of defining the treatment volume and of limiting dose to normal tissues. With this, our understanding of tumour and normal tissue biology has steadily evolved as has our understanding of fractionation and, more recently, the consequences of adding chemotherapy (either sequentially, concurrently or both). There remain significant areas of uncertainty and many areas where further research is needed. The balance between delivering treatment of sufficient intensity to cure the highest proportion of patients and minimizing the risk of serious sequelae remains a challenge for oncologists, just as it remains a challenge for surgeons in the surgical arena.

RADIOTherAPY EQUIPMENT AND PHYSICS

Treatment with photons (x-rays and gamma rays)

Historically, external beam radiotherapy began with low energy x-ray beams generated by modified diagnostic tubes. Beams with peak energies between 50 and 300 kV (known as orthovoltage) are still used in the treatment of superficial tumours, principally skin cancer. The van de Graff generator bridged the gap between orthovoltage and megavoltage (beams of ≥1 MV) but was quickly overtaken by the advent of the cobalt unit. This contained a cobalt-60 source within the head of the machine which would traverse from a shielded ‘safe’ position within the head of the machine to the treatment position for a specified time. Gamma rays (which arise from radioactive decay) have the same biological and physical properties as x-rays (which are produced artificially). The rate of decay of cobalt sources necessitated replacement approximately every five years. A small amount of radiation would still leak through the head of the machine so that treatment staff on cobalt units received greater radiation exposure than those on other units. Concerns about misuse of radioactive sources around the world has led to most cobalt units being replaced with linear accelerators, the standard megavoltage treatment unit in use today. A beam from a cobalt unit (1.1 MeV photons arising from the natural decay of cobalt-60) has similar tissue penetration properties as a 3 MV beam from a linear accelerator.

In a linear accelerator, a stream of electrons produced from a filament in an electrically charged field is accelerated through a series of wave guides in conjunction with a
radiofrequency pulse to within a fraction of the speed of light. This electron beam can itself be used for treatment or can impact on a target to produce a photon beam of maximum energy between 4 and 20 MV according to the design and calibration of the machine. Beams of 10 MV or greater are mostly used in the treatment of abdominal or pelvic tumours, while beams of 4–6 MV are most appropriate for the treatment of head and neck cancer (Figure 42.1).

All photons interact with matter by producing secondary electrons, which have a finite range according to the amount of energy imparted to them, which in turn is determined by the energy of the photon beam. Secondary electrons cause a number of ionization events along their path and it is these events, together with oxygen, which are responsible for free radical formation and consequent tissue damage. This also means that it takes a finite depth in tissue (defined by the maximum path length of the secondary electrons) before the dose builds up to a maximum (the build-up depth). This accounts for the relative skin sparing of megavoltage photon beams – the maximum absorbed dose from a 6 MV photon beam is 1.5 cm beneath the skin surface. Mostly this is an advantage in reducing the severe skin reactions associated with earlier forms of irradiation.

Electron beams can treat to depths of up to 5 cm or so according to the beam energy used; a 4–6 MV beam would be mostly used to treat skin tumours and a beam of approximately 12 MeV to treat neck nodes (Figure 42.1).

**Brachytherapy**

Radium needles were the first to be used for this purpose and resulted in significant radiation dose for the operator. Iridium (Ir-192) wire is the source of choice for modern head and neck brachytherapy. Radio-opaque hollow needles or tubes (applicators) can be inserted under general anaesthetic and then following return of the patient to a radiation-protected side-room, the sources are introduced (afterloaded). Nowadays, a remote afterloading device houses the sources within a lead chamber in the treatment room and is connected to each applicator within the implant. This then automatically loads each applicator with a predetermined length of active iridium wire when treatment and nursing staff have left the room, thereby minimizing radiation exposure to staff. In most cases, the volume at risk is implanted with either one or two planes of radioactive sources, where individual sources and planes of sources lie parallel to each other and evenly spaced (generally about 1 cm apart). The implant is imaged prior to afterloading to allow precise calculation of radiation dose, which is delivered over 2–5 days depending on the specific activity of the iridium wire and the dose to be delivered.

The advantage of brachytherapy is that it provides a means of delivering a high dose to a small area and as the radiation dose falls off rapidly outside the treatment volume, the dose to adjacent normal tissues can be kept within acceptable limits. On the other hand, a major limitation is the need for adequate radiation protection and that the technique is not appropriate where wider field irradiation is required, for example to cover adjacent nodal areas. Brachytherapy, both as primary and postoperative treatment for oral cancer, has largely been replaced by resection and repair with free flaps, but is still sometimes used for recurrent disease in the neck or nasopharynx.

**Immobilization**

Accuracy of delivery of external beam radiotherapy is dependent on maintaining a stable target volume. Individually moulded thermoplastic shells covering the head and neck area are used to immobilize patients (Figure 42.2). These are located onto a fixed frame on the treatment couch. Reference marks are placed on the outside of the shell, avoiding the need for any skin marks or tattoos. Standard techniques allow treatment accuracy to within approximately 3 mm. More rigid frames providing accuracy closer to 1–2 mm have been developed for stereotactic radiotherapy (sometimes referred to as radiosurgery) and intensity modulated radiotherapy (IMRT) where movement can be more critical to dose delivery.

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![Figure 42.1](image1.png)

*Figure 42.1* Comparison of depth dose characteristics of a 6 MV photon beam and a 12 MeV electron beam from a linear accelerator and a 150 MeV proton beam from a cyclotron. The photon beam shows a degree of skin sparing with the maximum dose apparent at 1.5 cm. The proton beam shows an initial plateau then a peak (the Bragg peak) followed by a rapid decline.

![Figure 42.2](image2.png)

*Figure 42.2* Individually moulded thermoplastic shell covering the head and neck area used for patient immobilization. Field centres and field borders are marked on the outside of the shell. The areas around the eyes and mouth are cut out for patient comfort and the part of the lower neck field to reduce the surface dose.
Target definition and coverage

The vast majority of radiotherapy planning is now done using computed tomography (CT) images obtained within the immobilization shell. According to the clinical situation, the gross tumour volume (GTV) and/or clinical target volume (CTV)\textsuperscript{2,3} is outlined on screen. This allows for inclusion of areas at risk, such as nodal areas, or potential routes of spread. A number of radiotherapy treatment plans include two consecutive phases of treatment, the first covering areas of known involvement together with areas at risk and the second solely the areas of known involvement. In this case, a phase 1 CTV and a phase 2 CTV are outlined separately. These volumes are 'grown' three-dimensionally to derive the planning target volume (PTV) for each phase by adding an additional margin. This margin allows for patient movement and normal set-up variation. In most cases, this margin is 1 cm although tighter margins may be used in circumstances where there is a need to minimize dose to adjacent normal tissues. Organs at risk, such as spinal cord, parotid and submandibular glands are also outlined (Figure 42.3). Radiotherapy planning technicians and physicists then devise a treatment plan which defines the positioning and weighting of two or more photon beams to provide adequate coverage of the PTV while not exceeding agreed maximum doses to adjacent normal tissues (see below under Treatment morbidity). Current convention\textsuperscript{2} stipulates that the stated dose is the dose to the centre of the treatment volume and that all of the PTV receives at least 95 per cent of this dose and that there is no point which receives greater than 107 per cent.

All megavoltage units (i.e. cobalt units and linear accelerators) vary the size of the irradiated field by moving large lead blocks within the head of the machine (collimators) in and out of the beam thus generating square or rectangular fields of any size. Individual beams are shaped either by the introduction of custom-made lead or alloy blocks mounted onto a perspex plate and positioned just below the head of the machine or by multileaf collimators. Rather than using single large blocks, the collimators of modern linear accelerators are constructed with individual leaves of approximately 0.5 cm width. These multileaf collimators can be programmed to produce any shape of field allowing the 95 per cent isodose to conform closely to the PTV in three dimensions (Figure 42.4).

Figure 42.3 Treatment plan for irradiation of a T\textsubscript{2}N\textsubscript{0} tonsillar carcinoma showing outlining of the contralateral parotid (a) and submandibular gland (b). Anterior and posterior oblique fields are used to cover the planning target volume (PTV, pale blue shading). The PTV is surrounded by the 95 per cent isodose (red line). The parotid and submandibular glands lie between the exit beams of the two fields thus ensuring minimal disruption to saliva production.

BIological effects of radiation: DNA damage and repair

Photon beams interact with matter by producing secondary electrons. Ionization events along the path of secondary electrons result in very localized tissue damage. Although many events will occur in non-critical parts of the cell, some will occur within DNA. A wide range of types of damage are described and there is now a good understanding of repair mechanisms in response to each. While ionization events resulting in single strand breaks within DNA are generally repairable, double strand breaks frequently cannot be repaired faithfully so that cell death will occur within the next few cell divisions. Sublethal damage refers to DNA damage that can be repaired given the right cellular conditions and sufficient time. It is known that sublethal damage repair is less efficient in tumour cells than in normal cells and in areas of hypoxia or low pH. Proportionately more DNA damage is repairable with smaller radiation doses (fractions). Half-time for sublethal damage repair is in the order of hours with about 95 per cent being complete within 6 hours.
TUMOUR CELL KINETICS AND RESPONSE TO RADIOTHERAPY

Cell proliferation and loss

Rates of cellular proliferation of most tumours exceed that of most normal tissues. The ultimate and measurable increase in tumour size is a result of the balance between proliferation and cell loss from necrosis, desquamation and apoptosis. Potential doubling times (Tpot) calculated from incorporation of \(^{3}\)H-thymidine are therefore substantially less than actual doubling times. In a series of head and neck squamous cancers, values of Tpot range from 2 to 67 days (median 6.4 days).\(^4\) In a study investigating the effects of treatment delays, actual doubling times ranged from 15 to greater than 234 days (median 99 days).\(^5\) More rapidly proliferating tumours may be those that are less well differentiated or have other adverse histological features. Only the fate of tumour cells with clonogenic potential (between 1 and 10 per cent of all tumour cells) will determine the response to treatment. At any one time, not all cells with clonogenic potential will be actively proliferating – with a lower proportion in hypoxic areas.

As tumour cells proliferate, stromal cells also proliferate in response to growth factors produced by tumour and stromal cells. Proliferation of vascular endothelium, in response to vascular endothelial growth factor (VEGF), is crucial to the continuing growth of tumour cells and the balance between rate of expanse of the tumour and its supporting vascular network will influence the development of hypoxia and necrosis.\(^6\)

Intrinsic radiosensitivity

Accurate prediction of response to radiotherapy would be valuable in advising patients about treatment options. Conventional histological features correlate poorly with response to radiotherapy and assays which measure the fraction of cultured tumour cells surviving a 2 Gy dose of radiotherapy (SF\(_2\)) are not routinely available. Such assays may take several weeks and not all attempts to culture tumour cells are successful. Cell cultures effectively exclude the additional problem of hypoxia present in vivo. In a study of 84 head and neck tumours treated with radiotherapy, local failure was seen in 9 per cent with an SF\(_2\) less than 0.40 (the median value) and in 26 per cent with an SF\(_2\) greater than 0.40.\(^7\) The ultimate response to a 35-fraction course of radiotherapy is SF\(_2\) to the power of 35 so that even small changes in SF\(_2\) can result in significant differences in outcome. Intrinsic radiosensitivity is likely to account for the largest differences between tumours in response to radiotherapy.

Hypoxia

Thomlinson and Gray\(^8\) were the first to demonstrate that tumour cells greater than 100–150 \(\mu\)m from the nearest capillary suffered increasing hypoxia with necrosis present at greater distances. At that time, it was also demonstrated that anoxic cells were 2.5–3.0 times less sensitive to the effects of radiation.\(^9\)

Substantial areas of hypoxia can be identified by the insertion of oxygen electrodes into primary tumour and neck nodes\(^10\) or by imaging with a \(^{18}\)F-labelled nitroimidazole.\(^11,12\) Greater degrees of hypoxia are associated with worse outcome following radiotherapy.\(^12,13\)

Human papillomavirus infection and response to radiotherapy

It has recently been recognized that evidence of past human papillomavirus (HPV) infection, determined by HPV-16 DNA \(in\ situ\) hybridization, is more common in patients with oropharyngeal cancers and especially in those who have never smoked.\(^14\) Furthermore, in patients with oropharyngeal cancers treated with radiotherapy (with or without chemotherapy), the outcome is significantly better in those with evidence of HPV infection compared to those without.\(^14,15,16,17\) The reasons for greater sensitivity to treatment are as yet unknown, but likely to be more than just younger age and the absence of smoking-related comorbidity.

Changes in cell kinetics and oxygenation during a course of radiotherapy

As tumour cells do not die immediately after irradiation, visible consequences are slow to appear. As cells die, oxygen penetrates progressively further into hypoxic areas stimulating hypoxic cells to proliferate. Oxygenation may improve as treatment progresses, as assessed by oxygen electrodes\(^10\) or by imaging with \(^{18}\)F-labelled misonidazole.\(^11\) In normal tissues,
resting cells enter the cell cycle, the cell cycle time shortens and the rate of proliferation increases. This accelerated proliferation accounts for the rapid healing of acutely responding normal tissues, such as mucosa and skin, after an initial latent period. Accelerated proliferation within tumours probably starts within the third week of treatment.\textsuperscript{18}

**Assessing response to radiotherapy**

Generally, it takes up to 4–6 weeks after the end of a course of radiotherapy for maximum tumour response to become evident. Assessment prior to this can be misleading, so a minimum of 8 weeks is preferable before reimaging with CT or carrying out further biopsies. Post-treatment magnetic resonance imaging (MRI) is best left until 12 weeks to allow the general increase in signal in the irradiated area to subside. A systematic review of 27 post-treatment fluorodeoxy-glucose-positron emission tomography (PET) studies showed a positive predictive value of 75 per cent and a negative predictive value of 95 per cent with greater sensitivity of scans performed 10 or more weeks after treatment.\textsuperscript{19}

**TREATMENT MORBIDITY**

The extent of acute and late normal tissue morbidity will depend on the area being treated and the dose received. Modern planning systems permit very accurate dose calculations within normal tissues. This aids shielding (where possible) and better prediction of the consequences of treatment.

**Acute toxicity: development**

Tiredness is a side effect experienced by most patients. This can date from the very start of treatment and may build up as treatment continues. Chemotherapy adds to tiredness generally. Recovery of pretreatment levels of energy following more intensive courses of chemoradiotherapy can take up to six months. The biological basis of tiredness is poorly understood.

Dryness of the mouth (xerostomia) can develop during the first week of treatment – rather earlier than would be expected from direct tumour cell kill. It is likely that selective radiation damage to the plasma membrane of secretory granules is responsible.\textsuperscript{20} Parotid and submandibular salivary flow rates fall rapidly to less than 20 per cent of pretreatment values by the end of the second week.\textsuperscript{21} As watery and mucous components of saliva are not affected equally, the initial general dryness gives way to increasing thick sticky saliva beyond the fourth week. Certain foods, particularly bread, become more difficult to swallow. Even when the contralateral salivary glands are spared, the sticky saliva from the irradiated side can predominate in the latter part of treatment and the few weeks following. The effects of dryness may be greater in patients who have lost a submandibular gland as part of a neck dissection. In the past, there has been undue attention to the parotid gland, ignoring the submandibular gland, in standard radiotherapy planning texts. The contribution of the submandibular gland to resting salivary function is now better understood and the need to spare the submandibular glands increasingly emphasized. Dose–response relationships are now established for both. For the parotid gland, the mean dose for 50 per cent loss of salivary excretion at seven months was 22.5 Gy\textsuperscript{22} and for 75 per cent loss at six months, 40 Gy.\textsuperscript{23} Recovery can be expected up to 12 months after completion of treatment.\textsuperscript{23} Doses to the submandibular glands in excess of 39 Gy were not associated with recovery but at doses < 39 Gy, recovery of salivary flow took place at 3 per cent per month up to 24 months.\textsuperscript{24} Where possible, beam arrangements should ensure that dose received by the parotid and submandibular glands should be as low as possible.

Loss of taste accompanies most head and neck radiotherapy and is exacerbated by dryness of the mouth. Loss of taste compounds the problems of maintaining an adequate nutritional intake.

Mucositis develops from the third week of treatment onwards and increases in severity according to the volume irradiated and total dose. The visible reaction progresses from erythema to patchy mucositis (characterized by white patches of fibrinous exudate on an erythematous base) to confluent mucositis (where the exudative patches coalesce). In severe cases, contact bleeding may occur. Confluent mucositis, common toxicity criteria (CTC) grade 3,\textsuperscript{25} is seen in 40–80 per cent of patients receiving more than 60 Gy (or equivalent), more frequently in those receiving concurrent chemotherapy or accelerated radiotherapy.\textsuperscript{26–27} Painful swallowing increases progressively and is further aggravated by difficulty clearing thick saliva.

Skin erythema also increases from the third week onwards. Progression is from faint erythema to bright erythema to moist desquamation.

**Acute toxicity: management**

A systematic review of interventions used for the prophylaxis of mucositis in patients receiving radiotherapy for head and neck cancer identified only antibacterial pastilles as having any objective benefit in reducing the incidence of more severe mucositis.\textsuperscript{28} However, these are not widely used because of general concerns about antibiotic resistance.

To relieve symptoms of mucositis, a combination of good mouth care, an antiseptic mouthwash and narcotic analgesics is recommended.\textsuperscript{29} Alcohol-based mouthwashes should be avoided as these can sting and may have a drying effect in an already dry mouth; a water-based mouthwash (e.g. Biotene) is preferred. Candidal infection is common during radiotherapy, particularly if chemotherapy is also used, so there should be a low threshold for prescribing antifungals. Fluconazole is preferred as this has been shown to be more effective than oral amphotericin or nystatin in the treatment of oral candidiasis\textsuperscript{30–31} and, as it is absorbed systemically, can treat other sites at risk (e.g. gastrostomy site).

Analgesics in increasing strength are essential, moving from soluble aspirin or paracetamol to soluble cocodamol 30/500 to morphine sulphate solution (Oramorph) in increasing doses. Analgesia given 4-hourly 20–30 minutes before meals can relieve the worst of the pain and help maintain nutrition. Patients requiring higher doses of opiates may benefit from...
fentanyl transdermal patches and/or switching to oxycodone liquid (also given 4-hourly before meals).

Dietetic support is essential and oncology teams should have the benefit of a dedicated dietitian working alongside. The aim is to ensure sufficient dietary modification and supplementation to maintain a steady weight during the course of treatment and in the weeks following. Quite often, dietetic support and analgesics alone are insufficient.

Feeding via a percutaneous endoscopic gastrostomy (PEG) should be considered for all patients at risk of severe and prolonged mucositis. Nasoantral tubes are unreliable and less well tolerated by patients. It has been our practice for some years to recommend PEG insertion prior to all courses of radiotherapy to the larynx, pharynx or oral cavity lasting 6 weeks or more, particularly when given with concurrent chemotherapy. This allows patients to become familiar with care and use of the PEG allowing a smooth transition to PEG supplementation and then total PEG feeding as treatment progresses. All medication can then be administered via the PEG. Leaving PEG insertion until when it is absolutely required usually results in a week or two of very poor nutrition and a degree of dehydration. A recently reported randomized trial demonstrated improvement in post-treatment quality of life in those undergoing prophylactic gastrostomy compared to those in whom gastrostomy was only required usually results in a week or two of very poor nutrition and a degree of dehydration. It is unclear whether poor nutrition in itself compromises treatment outcome, but poorly nourished patients are at greater risk of treatment interruptions and possibly intercurrent illness and do take substantially longer to recover from the effects of treatment.

Other strategies, such as sucralfate, are ineffective. Anti-inflammatory mouthwashes (such as benzylamine hydrochloride, Difflam) can be helpful although alcohol-based mouthwashes should be used with caution. Topical steroids (e.g. as hydrocortisone pellets) have been used in the past but are of uncertain benefit and are not currently recommended. Early reports favour zinc supplementation as a means of reducing mucositis. Trials are continuing, in particular to establish that there is no protective effect on tumours.

Saliva substitutes can relieve dryness and help break up the thick saliva which aids clearance. Mucin-based products, such as Saliva Orthana, are preferred to those which are cellulose based. Oral Balance Saliva Replacement gel is an alternative and may give more prolonged relief at night. Despite the promise of early trials with pilocarpine tablets or mouthwash given during radiotherapy to stimulate salivary glands, more recent randomized trials have not shown a benefit in reduction of xerostomia. Trials of submandibular gland transfer have shown some reduction in xerostomia by swinging the contralateral submandibular gland on its pedicle and relocating it to a more anterior position. The procedure is not without its own risks and side effects, possibly leading to delays in commencing radiotherapy, and limited to situations where interference in the neck poses no risk to subsequent tumour relapse and treatment.

The radioprotectant drug amifostine has been investigated as a means of reducing the incidence of xerostomia and mucositis. Amifostine needs to be given intravenously daily prior to radiotherapy and can cause nausea and hypotension. In one study, 21 per cent of patients withdrew from the amifostine treatment, principally due to adverse events. Subcutaneous administration was no more effective in a randomized trial. A meta-analysis of five randomized trials in head and neck cancer treated with radiotherapy alone and published prior to 2005, demonstrated a decrease in xerostomia and mucositis with amifostine. However, these studies comprised only 439 patients between them and were not sufficiently powered to exclude tumour protection so concerns about safety remain. In a single randomized trial of patients undergoing chemoradiotherapy, amifostine did not reduce either mucositis or xerostomia.

Skin care is essential; aqueous cream (or equivalent) relieves dryness and itch. Geliperm can relieve soreness of intact skin. Moist desquamation requires a strategy that maintains skin hydration, either with hydrocolloid dressings or copious aqueous cream. Secondary infection, generally uncommon, requires systemic antibiotics.

### Acute toxicity: recovery

Rates of recovery of acute side effects of radiotherapy are shown in Table 42.1. Recovery of salivary function decreases rapidly with increasing salivary gland dose beyond 30 Gy.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Time to recover after completion of treatment</th>
<th>Degree of recovery expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema of skin</td>
<td>7–10 days</td>
<td>Complete, though dry and more sensitive to the sun for the year following</td>
</tr>
<tr>
<td>Mucositis: mild</td>
<td>10–14 days</td>
<td>Mostly complete, though mucosa can remain more sensitive; ≤5% patients may remain PEG dependent</td>
</tr>
<tr>
<td>Mucositis: severe</td>
<td>Recovery may not begin until 2–3 weeks after treatment completion then take up to 4–8 weeks to regain normal swallowing</td>
<td>Total in most cases</td>
</tr>
<tr>
<td>Taste</td>
<td>6–8 weeks</td>
<td>If salivary gland irradiation unilateral, recovery to within 80–90%; if salivary gland irradiation bilateral, recovery limited, particularly with doses &gt;30 Gy</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Sticky saliva resolves within 2–3 weeks; recovery of dry mouth from 3–24 months</td>
<td>Complete</td>
</tr>
<tr>
<td>Lethargy</td>
<td>6 months</td>
<td>Complete</td>
</tr>
</tbody>
</table>
In addition, large areas of oral mucosa, if irradiated, can remain dry and very sensitive.

Patients at greater risk of remaining PEG dependent include those with more advanced tongue base tumours where the effects of the tumour and treatment both contribute to impairment of the swallowing mechanism. Evidence suggests that continuing swallowing problems are most closely related to the dose received by the middle pharyngeal constrictor.41

Late toxicity

Late toxicity is dose related and, to some extent, predictable. Modern radiotherapy planning systems give much clearer indications of the dose received by organs at risk. Normal tissue shielding can be more effectively utilized than previously or, when sufficient shielding is not possible, a more accurate estimate of dose permits a clearer assessment of potential future problems.

Because most late effects result from damage to tissues with a slow rate of cellular turnover, these consequences do not become apparent for months or years after completion of treatment. The latency varies according to the proliferation characteristics of the tissues at risk. In many cases, the damage to small blood vessels results in endarteritis obliterans and consequent local ischaemic damage. Those who continue to smoke are at greater risk of late effects.42

Table 42.2 lists the potential late effects of radiotherapy for head and neck tumours, as detailed in the sections below.

### Table 42.2 Summary of late effects with incidence and latency (see also text).

<table>
<thead>
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<th>Late effect</th>
<th>Latency</th>
<th>Incidence</th>
<th>Relationship to radiation dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoradionecrosis: mandible43, 44, 45</td>
<td>Mostly 1–3 years</td>
<td>2–14%</td>
<td>More frequent in the anterior mandible with higher dose per fraction; generally ≤5% with 66 Gy in 33 fractions over 6.5 weeks to the anterior mandible</td>
</tr>
<tr>
<td>Osteoradionecrosis: maxilla43</td>
<td>Mostly 1–3 years</td>
<td>&lt; 5%</td>
<td>Loss of enamel from direct irradiation; aggravated by loss of saliva; worse if teeth in poor condition prior to treatment</td>
</tr>
<tr>
<td>Loss of teeth46</td>
<td>1–5 years</td>
<td>Variable</td>
<td>Generally mild but severity related to presence of trismus prior to treatment and to dose to masseter and pterygoid muscles</td>
</tr>
<tr>
<td>Trismus47, 48</td>
<td>6–12 months</td>
<td>Up to 50%</td>
<td>Greater risk in the presence of cartilage invasion</td>
</tr>
<tr>
<td>Larynx necrosis49</td>
<td>6–18 months</td>
<td>&lt; 2%</td>
<td>Greater risk in the presence of cartilage invasion (i.e. T4 cancers) or local infection; higher risk (up to 15%) with courses of radiotherapy that use doses per fraction ≥4 Gy or orthovoltage</td>
</tr>
<tr>
<td>Cartilage necrosis (nose and pinna)50, 51</td>
<td>6–18 months</td>
<td>&lt; 5%</td>
<td>Dose to more than one-quarter of retina; greater risk in those with diabetes or hypertension; lower risk with hyperfractionation</td>
</tr>
<tr>
<td>Spinal cord damage52</td>
<td>6 months to 5 years</td>
<td>45 Gy: 0.03%; 50 Gy: 0.2%; 60 Gy: 5%</td>
<td>Spinal cord dose limited to 45 Gy in most treatment plans Lhermitte’s sign not a sign of spinal cord damage53 (see text)</td>
</tr>
<tr>
<td>Optic nerve damage54, 55</td>
<td>6 months to 5 years</td>
<td>50 Gy: 0%; &lt; 63 Gy: 4%; ≥ 63 Gy: 18%</td>
<td>Optic chiasm and optic nerve dose limited where possible to 45 Gy; optic chiasm probably more sensitive than optic nerve</td>
</tr>
<tr>
<td>Retinal damage46</td>
<td>1–5 years</td>
<td>&lt; 50 Gy: 4%; 50–60 Gy: 15%; 60–70 Gy: 39%</td>
<td>Risk increases with doses to lens above 10 Gy</td>
</tr>
<tr>
<td>Cataract57</td>
<td>1–5 years</td>
<td>Variable</td>
<td>Risk increases with doses to lens above 10 Gy</td>
</tr>
<tr>
<td>Deafness58, 59</td>
<td>6 months to 5 years</td>
<td>Variable</td>
<td>Risk increases with doses to the inner ear &gt;40 Gy; risk further increased by use of concurrent cisplatin chemotherapy</td>
</tr>
<tr>
<td>Carotid artery stenosis60, 61, 62</td>
<td>&gt; 5 years</td>
<td>Up to 15% at 15 years</td>
<td>Higher risk in smokers or those with hypertension</td>
</tr>
<tr>
<td>Hypothyroidism63, 64</td>
<td>6 months onwards</td>
<td>Up to 50%</td>
<td>According to volume of thyroid tissue irradiated</td>
</tr>
</tbody>
</table>

### MANDIBLE AND DENTITION

The majority of patients receiving radiotherapy to the pharynx or oral cavity suffer from a degree of long-term dryness. For those with teeth, close dental follow up is essential to minimize the loss of teeth from dental decay. Fluoride mouthwashes may be beneficial. Loss of enamel from direct irradiation may be more difficult to avoid. Individual episodes of osteoradionecrosis may be associated with dental extractions, which are therefore best avoided where possible.43, 44, 45 The risk of osteoradionecrosis is mostly closely related to those undergoing mandibular surgery and those receiving higher doses of radiotherapy.43 The risk is reduced in those without teeth.
TRISMUS

Difficulty with mouth opening at diagnosis is related to disease extent. Following radiotherapy, the incidence of trismus is related to the dose of radiotherapy received by the masseter and pterygoid muscles. Treatment for trismus should be begun early. Clinical experience suggests that earlier treatment results in a better functional outcome.

SPINAL CORD AND OPTIC PATHWAYS

Damage to spinal cord and optic pathways is predictable and it is a normal part of the radiotherapy planning process to minimize dose to these areas. However, where tumour extends very close to a sensitive structure, for example a sinus tumour invading the orbit, a degree of compromise is required. Limiting the dose in that area to 45 Gy would compromise tumour control substantially, but giving the full dose to the optic nerve would be associated with a risk of late damage. This has to be weighed against the consequences of failed local control where the risk of subsequent invasion of the optic nerve could be as high as 100 per cent. In practice, doses in the region of 60 Gy are often used to localized areas provided the dose to the contralateral optic pathway can be kept within safe limits. This optimizes tumour control and limits the worst consequence to unilateral blindness. This must always be discussed in principle with the patient prior to radiotherapy planning and again in detail once the exact dose calculations are available. Patients with CT or MRI evidence of optic nerve involvement require ophthalmological assessment prior to treatment and subsequently. Eye clinic follow up should be offered to all those considered at significant risk of damage to the optic pathway.

Patients receiving radiotherapy to a length of spinal cord may experience Lhermitte’s sign 6 weeks to six months after completing radiotherapy. Patients may experience tingling or electric shock sensations down the spine and sometimes into the backs of the legs and aggravated by neck flexion. This is due to transient demyelination as a result of temporary loss of oligodendroglia. It recovers spontaneously after a period of months and neither predicts subsequent spinal cord damage nor is itself a sign of spinal cord damage. Patients require reassurance; further investigation is not required.

CAROTID ARTERY STENOSIS

The risk of carotid artery stenosis has only relatively recently been recognized as a consequence of radiotherapy. In a series of 367 patients under 60 years of age at the time of radiotherapy, the incidence of stroke was 12 per cent at 15 years. In another study which included 240 patients of all ages, there was evidence of carotid artery stenosis in 10 per cent at a mean interval of six years after irradiation. This equates to a relative risk of stroke of 2.1 at five years and 10.1 at 10 years. Up to 40 per cent of patients with greater than 50 per cent stenosis will have experienced transient ischaemic attack or stroke. The risk is greater in those with a history of hypertension and smoking. With increasing use and increasing effectiveness of chemoradiotherapy for oropharyngeal cancer in younger people (even though mostly non-smokers), this is likely to become of increasing significance in the future. Consideration should be given to screening programmes for these patients so that appropriate intervention may be considered before serious sequelae develop. This risk has contributed significantly to the decline in use of radiotherapy for benign parotid tumours.

HYPOTHYROIDISM

Hypothyroidism was recorded in 21 and 48 per cent of patients three and five years, respectively, after receiving radiotherapy to the thyroid gland. Incidence is related to dose received by the thyroid gland and therefore seen more commonly after irradiation of cancers of the larynx, hypopharynx or cervical oesophagus. Hypothyroidism occurs more commonly in women. In patients considered at risk, thyroid function tests should be recorded prior to or during treatment, then six months following treatment and at annual intervals thereafter.

RADIOThERAPY FRACTIONATION

The radiobiological equivalence of different radiotherapy fractionation schemes is based on mathematical relationships derived from observations of tumour control and normal tissue reactions. Optimum total dose is a balance between tumour cell kill and the impact of early and late side effects. As the relative effectiveness of different treatment strategies will be considered in Chapter 43, Head and neck squamous cell carcinomas: radical radiotherapy, Chapter 44, Postoperative radiotherapy in head and neck cancer and Chapter 45, Chemoradiation in head and neck cancer according to their clinical indication, only the principles will be considered here.

Definitions and rationale

CONVENTIONAL FRACTIONATION

The term conventional fractionation refers to the use of individual treatments (fractions) of 1.8–2 Gy each given daily for 5 days per week. Curative doses are generally in the range 66–70 Gy delivered in 33–35 fractions over 6.5–7 weeks. Historically, postoperative doses have been 10 per cent lower, in the range of 60–64 Gy delivered in 30–32 fractions over 6–6.5 weeks. This lower dose is on the basis of lower doses being sufficient to control microscopic (as opposed to bulk) disease and on the lower tolerance of patients to radiotherapy when given postoperatively.

HYPOFRACTIONATION

There are a number of fractionation schemes with roughly equivalent doses, in common usage around the world and particularly in the UK, based on one fraction per day five times per week. Resource limitations over many decades have
been the driver towards shorter regimens, which means fewer fractions and larger dose per fraction. Though shorter courses limit the opportunity for tumour repopulation, proportionately less DNA damage is repaired after larger fractions thereby increasing the risk of late damage. Table 42.3 lists a number of regimens in common use showing the approximate equivalence between them. Strictly speaking, courses of treatment using larger fraction sizes than 2 Gy are classed as hypofractionated.

### HYPERFRACTIONATION

Hyperfractionation involves use of smaller fractions (i.e. less than 1.8 Gy). The use of smaller fractions may reduce the risk of late damage for a given total dose, but the increase in the overall treatment time tends to reduce the effectiveness of treatment. Regimes delivering 50–60 fractions (e.g. 81.6 Gy in 68 fractions over 7 weeks as used in the RTOG 9003 trial) place a large burden on treatment units.

### ACCELERATED FRACTIONATION

Accelerated regimes are those where the overall treatment time has been shortened. This can be done by hypofractionation, a greater benefit can theoretically be obtained from combining acceleration with hyperfractionation and treating two or three times each day. This combines the reduced risk of normal tissue damage with the benefits of completing treatment in a shorter overall time. Sufficient time between fractions must be allowed for repair of sublethal damage. Some schemes in the past have used a 4-hour gap but it is now believed that a minimum 6-hour interval between fractions is preferable.

A good example is the CHART regime (continuous hyperfractionated accelerated radiotherapy) in which radiotherapy at 1.5 Gy per fraction is given three times daily and continuously for 12 days to a total dose of 54 Gy (i.e. without a weekend break).

### Relative effectiveness of altered fractionation

Within the UK, a number of different schemes of once daily fractionation that have evolved appear broadly equivalent although there has been a lack of head-to-head comparisons between them. A randomized trial of CHART versus conventionally fractionated radiotherapy to 66 Gy in patients with locally advanced cancers of the larynx and pharynx demonstrated approximate equivalence of the two regimes although subgroup analysis did show a possible benefit in patients with more advanced larynx cancers. A randomized trial of CHARTWEL (CHART weekendless, similar to CHART but treating Monday to Friday only for 2.5 weeks) versus conventionally fractionated radiotherapy to a dose of 64 Gy as postoperative treatment for head and neck cancer has recently been completed within the UK.

In a meta-analysis of different fractionation schedules, there was a significant advantage of altered fractionation over conventional fractionation, amounting to a 6.5 per cent improvement in five-year survival. Benefit appeared greater in the subgroup employing hyperfractionation compared to the accelerated subgroups. Hyperfractionation has been used most in the US with greater European interest in acceleration, such as investigated in the DAHANCA 6&7 trial in which patients were treated six times per week (either on 6 days or twice on one of the 5 days) to a dose of 68 Gy in 34 fractions in an overall time of just under 6 weeks. This was found to be more effective than conventional five times weekly radiotherapy to 70 Gy with greatest improvements in control at the primary site. Larynx preservation was seen in 80 per cent of those treated six times weekly compared to 63 per cent of those treated conventionally.

However, attempts to deliver radiotherapy on all 7 days of the week have been limited by increased toxicity, demonstrating the extent to which unrepaired damage can accumulate during the week and that a day of rest is essential to maintain normal tissue tolerance.

### Comparative side effects of altered fractionation

Late damage can appear more frequently with hypofractionated regimens. Osteoradionecrosis was observed in 14 per cent of patients receiving 3-week courses of radiotherapy. Conversely, the use of a larger number of smaller fractions reduces the risk of late damage as seen in the CHART trial, where the incidence of osteoradionecrosis was 0.4 per cent in the CHART arm compared to 1.4 per cent in the conventional arm, although only a proportion of patients received the full dose to the mandible. In contrast, in a series of 200 patients treated very effectively for early (T1) carcinoma of the larynx with 50–52.5 Gy in 16 fractions (of 3.12–3.28 Gy) over 3 weeks (a regime in widespread use across the UK), only one case of larynx necrosis was observed, demonstrating the safety of hypofractionated regimes where the treatment volume is small.

Shorter schemes can result in a more brisk mucositis. The CHART trial demonstrated very clearly that not only was the severity of acute mucositis increased in the CHART arm but the peak severity occurred sooner and mucositis resolved more rapidly.

### Table 42.3 Radiobiological equivalence of different radiotherapy schedules; radiotherapy given once daily, five times per week.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Radiotherapy as primary treatment</th>
<th>Radiotherapy as postoperative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5–7 weeks</td>
<td>66–70 Gy in 33–35 fractions</td>
<td>60–64 Gy in 30–32 fractions</td>
</tr>
<tr>
<td>5 weeks</td>
<td>60 Gy in 25 fractions</td>
<td>55 Gy in 25 fractions</td>
</tr>
<tr>
<td>4 weeks</td>
<td>55 Gy in 20 fractions</td>
<td>50–52 Gy in 20 fractions</td>
</tr>
<tr>
<td>3 weeks</td>
<td>50–52.5 Gy in 15–16 fractions</td>
<td>45–50 Gy in 15–16 fractions</td>
</tr>
</tbody>
</table>
Limitations of altered fractionation

Straightforward comparisons of radiotherapy regimes are no longer as informative as previously because for more advanced cancers of the head and neck, radiotherapy is no longer given in isolation.

Mathematical extrapolations to determine the most effective regime are limited as these do not take into account the potential additive effect of concurrent chemotherapy or biological agents as the benefit of these may also be related to treatment duration.

Radical versus palliative radiotherapy

In situations where the emphasis is on control of symptoms and quality of life rather than long-term control or cure, lower doses of radiotherapy may be sufficient (equivalent to 30–40 Gy in 15–20 fractions over 3–4 weeks). With a lower total dose, there is more flexibility around fractionation so that, in general, it is preferable to give fewer larger fractions. Examples include 20 Gy in five daily fractions over 1 week, 30 Gy in ten daily fractions over 2 weeks or a single fraction of 10–12 Gy. This reduces the number of patient attendances, especially important where performance status or mobility are reduced or where the patient lives some distance from the oncology centre. Where disease is relatively localized and there is a lower potential for acute side effects, slightly higher doses may be given (e.g. 21 Gy in three daily fractions, 25 Gy in five daily fractions over 1 week or 35 Gy in ten daily fractions over 2 weeks, although these doses do exceed spinal cord tolerance).

Radiotherapy techniques differ for palliative radiotherapy. As total dose is lower, and in many cases within spinal cord tolerance, simpler or varied field arrangements may be used. The aim should be to minimize acute side effects, particularly mucositis. An example would be the use of a direct field angled posteriorly to treat a parapharyngeal mass – irradiation of the pharynx is minimized and spinal cord dose is within tolerance (Figure 42.5).

In the AIIMS study, 20 Gy given in five daily fractions over 1 week improved symptoms in approximately 50 per cent of patients. Other studies using rather different schemes, the Hypo trial (30 Gy in five fractions given twice weekly over 2.5 weeks) and QUAD SHOT trial (14 Gy in four fractions over 2 days) showed similar degrees of symptomatic benefit.

As durable relief of symptoms can be related to dose sometimes to the point where a radical course of treatment may be considered to provide the best palliation, the option of giving radical treatment with tight margins and a 4-week schedule (rather than longer) should be considered for those with borderline performance status or comorbidity.

FACTORS INFLUENCING THE EFFECTIVENESS OF RADIOTHERAPY

These factors are summarized in Table 42.4.

<table>
<thead>
<tr>
<th>Factor</th>
<th>% Increase in local control</th>
<th>% Decrease in local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent chemotherapy or cetuximab</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>70 Gy rather than 66 Gy</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Delays in starting radiotherapy</td>
<td>15% per month</td>
<td></td>
</tr>
<tr>
<td>Treatment interruptions</td>
<td>1.4% per extra day</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>10–15%</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>10–15%</td>
<td></td>
</tr>
</tbody>
</table>

Total dose

A review of the effectiveness of ten different fractionation schedules used in the treatment of T3N0 carcinoma of the larynx demonstrates a clear dose–response relationship. On this basis, just increasing the dose from 66 to 70 Gy would be expected to improve local control by 5 per cent. Analysis of
the RTOG 9003 trial of accelerated and hyperfractionated regimes indicated an increase in locoregional control of 1 per cent for each 1 Gy increase in effective total dose.\textsuperscript{78} The relative merits of different schemes of altered fractionation are considered above and in Chapter 041, Head and neck squamous cell carcinomas: radical radiotherapy, Chapter 42, Postoperative radiotherapy in head and neck cancer and Chapter 043, Chemoradiation in head and neck cancer.

**Concurrent treatment with chemotherapy or biological agents**

The MACH-NC meta-analysis\textsuperscript{79} demonstrated an 8 per cent improvement in local control at five years with concurrent platinum-based chemotherapy. Concurrent treatment with cetuximab produces a benefit of similar magnitude.\textsuperscript{80} These strategies are discussed in detail in Chapter 45, Chemoradiation in head and neck cancer and Chapter 46, Biologically targeted agents, but are mentioned here so that their benefits can be considered alongside other factors which impact the effectiveness of radiotherapy.

**Delays in starting treatment**

Many oncology centres around the world have limited capacity which historically has resulted in significant delays in starting radiotherapy. The current UK standard is that treatment with radical radiotherapy should commence within 4 weeks of the decision to treat and palliative radiotherapy within 2 weeks. Provided there is adequate capacity, this is generally achievable even for patients who require PEG insertion and dental treatment prior to radiotherapy.

A systematic review has shown that delays in commencing radiotherapy significantly reduce locoregional control.\textsuperscript{81} This meta-analysis demonstrates a relative risk of locoregional recurrence of 1.15 per month of delay for radiotherapy as primary treatment and 1.28 for postoperative treatment. A similar impact on survival was also seen. Two CT-based studies comparing tumour volumes at diagnosis and at the time of radiotherapy planning showed a mean increase in volume of 46 per cent over a median waiting time of 28 days\textsuperscript{82} and a 70 per cent increase over a median interval of 56 days.\textsuperscript{82}

In the latter study, this equated to an estimated reduction in probability of tumour control of 18 per cent.

**Treatment interruptions**

Where a course of radiotherapy is prolonged beyond the prescribed duration, local control falls by 1.4 per cent per extra day.\textsuperscript{83} Oncology centres routinely move patients between treatment machines to avoid interruptions due to machine servicing, quality assurance or breakdowns. Interruptions due to public holidays, transport failure or intercurrent illness are compensated for by planning a treatment session on a public holiday or at the weekend, by hyperfractionation (treating twice in 1 day with a minimum 6-hour gap) or by refractionation.\textsuperscript{84} Refractionation involves adjusting the remaining dose and number of fractions to deliver an equivalent dose in the remaining prescribed time or increasing the total dose (equivalent to 0.9 Gy per day of interruptions) and giving additional fractions. Refractionation is the least preferred option as increases in total dose or dose per fraction may increase the risk of late normal tissue damage.

**Anaemia**

There is clear evidence that locoregional control and survival are reduced in patients who are anaemic at the time of radiotherapy.\textsuperscript{85, 86} From earlier studies it was unclear whether this was related to true radioresistance or due to the milieu in which the tumour had developed or to an interaction between tumour and host. However, in multivariate analysis disease-free survival was more clearly related to the haemoglobin concentration at the end of radiotherapy than to pretreatment haemoglobin.\textsuperscript{87} In a study of postoperative radiotherapy, it was the fall in haemoglobin between surgery and radiotherapy, rather than the absolute values, that had the greatest impact on outcome.\textsuperscript{88} This detriment with falling haemoglobin is equivalent to a loss of local control of approximately 10–15 per cent for a 2 g/dL fall in haemoglobin.\textsuperscript{87, 88} The relationship with haemoglobin at the end of treatment suggests that efforts to maintain haemoglobin to a level $\geq 12.0$ g/dL are worthwhile. Blood transfusion is the principal means of maintaining haemoglobin. Erythropoietin analogues cannot at present be recommended for routine use because of concerns that these may stimulate erythropoietin receptors present on some tumour cells.\textsuperscript{89} However, in a study using epoetin alpha to counter anaemia during chemoradiation, the detrimental effect of low pretreatment haemoglobin seen in historical controls was abolished by use of epoetin alpha to maintain haemoglobin in the anaemic subgroup.\textsuperscript{90} This appears contrary to the results of randomized trials in which epoetin did not improve outcomes in patients treated with radiotherapy alone.\textsuperscript{91}

**Smoking**

Smoking during radiotherapy reduces treatment effectiveness, probably by inhaled carbon monoxide displacing oxygen from haemoglobin. In a study of 973 patients undergoing radiotherapy, local control at five years was significantly worse in active smokers compared to former smokers (80 versus 67 per cent).\textsuperscript{92} In two older studies, smoking was a significant adverse factor in univariate but not in multivariate analysis.\textsuperscript{93, 94} It would seem prudent, therefore, to encourage patients to stop smoking prior to radiotherapy. Use of a carbon monoxide monitor (of exhaled air) in clinic is a valuable adjunct to other strategies aimed at patients stopping smoking.

**NEW DEVELOPMENTS**

**Intensity-modulated radiotherapy**

Although conventional three-dimensional conformal radiotherapy remains a significant step forward compared to
planning techniques of 20–30 years ago, doses to critical normal tissues remain a limiting factor. Using only two or three fields means a significant dose is received by tissues between the skin surface where the beam enters and the target volume, and between the target volume and the distant skin surface where the beam exits. If more fields are used the relative contribution of each field diminishes, and therefore the absolute dose in front of and behind the target volume for each beam is reduced. The dose outside the target volume is therefore more dispersed and in this way can be kept below accepted thresholds for specified normal tissues. Furthermore, if the relative intensity of individual parts of each beam can be varied during the treatment itself by the use of rapidly moving multileaf collimators, this can further optimize dose homogeneity within the target volume and reduce dose to critical normal tissues. This effectively constitutes IMRT. Hardware options include adaptations of existing linear accelerators (and delivering treatment by means of between seven and nine static fields) or newer modified linear accelerators which deliver radiation continuously as they move around the patient for one or two circular or helical revolutions.

The use of IMRT to treat carcinomas of the nasopharynx and oropharynx effectively reduces parotid dose resulting in reduced long-term dryness of the mouth.\(^{95-96}\) Submandibular gland dose and subsequent symptoms may similarly be reduced with IMRT.\(^{97}\) While on the whole, tumour control can be improved by providing more even coverage of the target volume, and therefore avoiding underdosing areas adjacent to critical normal tissues, there are reports of marginal misses which might have been avoided by wider field conventional radiotherapy.\(^{98,99}\) Where there are very tight margins around critical normal tissues, there is a steep dose gradient in that the dose can move from 95 to 10 per cent over a matter of millimetres. Tumour shrinkage or general weight loss during a course of radiotherapy results in the immobilization shell fitting less well and there being excessive movement within. Significant day-to-day variation in positioning has been recorded in these situations and recompilation of dose indicates that the sharp cut-off of dose is lost and the dose actually delivered to normal tissues may exceed what was planned.\(^{100}\) Efforts to minimize movement during treatment are therefore critical to achieving the potential of IMRT. This is addressed by the next development in this area, image-guided radiotherapy (IGRT).

**Image-guided radiotherapy**

Part of conventional radiotherapy includes regular portal imaging. In previous decades this was done with film but now images of each beam can be obtained, stored and reviewed electronically. These are used to confirm that set up is within tolerance (3 mm for head and neck cancer and up to 5 mm in the pelvis) and that there are no unacceptable deviations from the original treatment plan. IGRT involves both fitting the linear accelerator with CT capability so that the patient position may be confirmed prior to treatment and programming the linear accelerator to carry out any necessary shifts in treatment position.\(^{101}\)

While image guidance can be used in conjunction with conventional radiotherapy (probably of greater value in the pelvis and chest), for head and neck cancer the major advance is with newer generations of machine (e.g. tomotherapy or types of Rapid Arc) which combine IMRT and IGRT. While the future of head and neck radiotherapy most definitely lies in this direction, the extent to which these developments will improve treatment outcomes remains uncertain. Randomized trials are necessary to show that the benefits of IMRT in minimizing normal tissue morbidity are not at the expense of marginal misses and greater risk of second primary tumours.

Resource implications of IMRT and IGRT are considerable. At present, substantial development time is required to integrate these systems with existing planning software or to install separate planning software. Planning times for individual patients are currently much longer both for planning technicians and physicists and for clinicians. Individual treatment times are also longer.

**PET-based radiotherapy planning**

There are situations where tumours are poorly defined on CT or MRI or where there are sites of active disease in areas which appear anatomically normal. Radiotherapy planning based on fused PET/CT images has the potential to improve accuracy of target definition. If, in addition, PET images were also obtained using a hypoxia marker, this would offer the possibility of delivering a greater dose to hypoxic areas in order to overcome their relative radioresistance.\(^{102}\)

**Heavy particles**

For several decades, there has been interest in the therapeutic potential of neutrons, proton and heavy ions produced in cyclotrons.

Neutron beams are more densely ionizing than photons and there is less to be gained by fractionation. On the other hand, hypoxic cells are relatively less resistant. A number of early trials showed little overall benefit but significantly increased normal tissue morbidity and even mortality.\(^{103,104}\) Early neutron beams had poor penetrating power — essentially that of orthovoltage photons. Although higher energy neutrons may penetrate deeper tissues better, the problem with greater normal tissue morbidity remains.

Protons, also produced in a cyclotron, have similar radiobiological properties to photons but are very different to photons in the deposition of dose at depth. After an initial plateau, there is a peak (the Bragg peak) followed by a rapid decline (Figure 42.1). Higher energies of proton beams have greater penetration so that an energy can be chosen appropriate to the depth of the tumour. An additional advantage of proton beams is the very tight edge to the beam so that with adequate immobilization, adjacent normal tissues only millimetres away receive very little dose. Chordomas within the clivus are a good indication for proton beam irradiation whereby a high dose can be delivered to the tumour with relative sparing of the brainstem. Research is continuing with both proton and heavy ion beams (e.g. helium or carbon ions).\(^{106}\)
REIRRADIATION

In most cases, courses of radical radiotherapy deliver doses very close to normal tissue tolerance so that repeating a course of radiotherapy even some years later carries a greater risk of normal tissue damage. However, as time goes by, some tolerance does return although this is difficult to quantify. A short time interval since initial irradiation may imply persistent radioresistant tumour unless this can be shown to have been due to a geographical miss or a second separate primary in the irradiated area. Reirradiation has to be weighed against other treatment options and against the risk and consequences of normal tissue damage. For example, in the case of a new laryngeal cancer arising in a larynx irradiated ten years previously, and where treatment options lie between further radiotherapy or total laryngectomy, the risk of irradiation is justifiable provided the spinal cord is not reirradiated. There is a higher risk of larynx necrosis for which, at worst, laryngectomy would be required. In the case of nasopharyngeal cancers, long-term control can be achieved in more than 50 per cent by reirradiation but in a proportion of cases this is at the expense of optic nerve damage (and blindness), temporal lobe necrosis, osteoradionecrosis, trismus or cranial nerve palsies. The general rule in reirradiation is to minimize dose to critical normal tissues, especially spinal cord and, where possible, optic tracts. This may involve using a different beam arrangement or IMRT. Addition of chemotherapy increases the effectiveness of reirradiation without increasing late morbidity.

KEY EVIDENCE

- An increase in total dose of 1 Gy improves locoregional control by 1 per cent.
- Shortening of duration of radiotherapy improves locoregional control by 1 per cent per day.
- Prolongation of radiotherapy reduces locoregional control by 1.4 per cent per day.
- Smoking during radiotherapy reduces locoregional control by 10–15 per cent.

KEY LEARNING POINTS

- Radiotherapy potentially causes greater morbidity and is less effective than surgery for cancers of the oral cavity.
- Radiotherapy has fewer functional consequences and is at least as effective as surgery for cancers of the larynx and pharynx.
- Postoperative radiotherapy or chemoradiotherapy is indicated for cancers of the oral cavity and high-risk features.
- As primary treatment, chemoradiotherapy is more effective than radiotherapy alone for cancers of the larynx and pharynx.
- Factors which increase the effectiveness of radiotherapy as primary treatment include:
  - higher biological doses of radiotherapy;
  - concurrent chemotherapy;
  - neoadjuvant taxane-based chemotherapy for locally advanced cancers.
- Factors which reduce the effectiveness of radiotherapy include:
  - delays during treatment;
  - delays in commencing treatment;
  - smoking during a course of radiotherapy;
  - anaemia.
- Late effects of radiotherapy within the first three years include:
  - trismus;
  - pharyngeal stenosis;
  - osteoradionecrosis;
  - larynx necrosis.
- Late effects of radiotherapy after the first three years include:
  - hypothyroidism;
  - carotid artery stenosis;
  - hypopituitarism.

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Head and neck squamous cell carcinomas: radical radiotherapy

PETRA J JANKOWSKA AND CHRIS M NUTTING

INTRODUCTION

For many early-stage head and neck squamous cell carcinomas (HNSCC) surgical excision or radiotherapy (RT) alone have similar cure rates, but have different adverse effect profiles. Radical radiation alone is indicated in the treatment of several early-stage tumours, particularly when organ preservation and/or cosmesis are important. Patient preference should also be taken into account when decisions between surgery and radiation are taken.

RT is frequently employed in the treatment of early cancers of the larynx, oropharynx and hypopharynx, so that natural speech and swallowing, respectively, may be preserved. Equally, radiation may preserve cosmesis and function in patients with cancers of the nasal cavity, columella, paranasal sinuses and ear.

Early oral cancer including superficial (<5 mm thickness), T1 and T2 lesions should be considered for brachytherapy.

Many patients with more locally advanced disease will be treated with a combination of surgery plus postoperative radiotherapy (PORT) or chemoradiotherapy. However, a significant proportion will be unsuitable for radical surgery or combined chemoradiation due to comorbid conditions and this cohort may be offered radical radiotherapy in order to maximize local control, even though long-term cure is only achieved in 30–40 per cent of patients. In the small proportion of patients presenting with metastatic disease, moderate-dose short-course RT may be used to ameliorate local symptoms.

GENERAL PRINCIPLES OF TREATMENT VOLUME AND DEFINITION

Patients with head and neck cancer should be seen in a multidisciplinary setting by a team comprising specialist surgeons, oncologists, pathologists, radiologists and palliative care doctors, together with dietitians, speech and language therapists and clinical nurse specialists. At the initial visit, a full history and examination, including nasendoscopy if relevant, will be carried out. Further pretreatment assessment should include examination under anaesthesia (EUA) and tumour biopsy, imaging in the form of computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck, chest x-ray or CT thorax, full blood count, urea and electrolytes, liver function tests, dietitian assessment, and assessment by a speech and language therapist. In particular, patients with poor dietary intake and a low body mass index should be identified and considered for elective percutaneous gastrostomy or nasogastric feeding. Dental assessment is also essential for any patient in whom the radiation field is likely to include either mandibular or maxillary alveolus, since dental extraction subsequent to a radical dose incurs a greater risk of chronic non-healing ulceration or osteoradionecrosis. Written informed consent,
detailing both the acute and late toxicities of radiation, should be obtained prior to embarking on a course of radical treatment. Smoking cessation should be advised since smoking is known to both increase radiation-induced toxicity and reduce cure rates.\(^3,4\) Alcohol cessation should also be advised at least for the duration of the radiation since, again, toxicity is likely to be increased.

Most patients with early tumours will usually be treated in a single-phase radiation plan, although the field arrangements will vary for each site.

However, tumour sites such as tongue base and hypopharynx, which are associated with a higher risk of occult nodal micrometastasis, are more likely to receive their radiation in two phases. Phase 1 is typically a larger volume encompassing the primary tumour, involved lymph nodes and potential areas of microscopic nodal spread while in phase 2, a smaller volume including the primary tumour and involved lymph nodes alone is treated. Elective irradiation of lymph nodes is indicated when the risk of microscopic lymphatic spread exceeds 15–20 per cent. Table 43.1, categorizes the risk of occult micrometastases to lymph nodes, which have been documented from surgicopathological series.\(^5,6,7\) Lymph node levels are defined as: level Ia, submental; level Ib, submandibular; level II, upper deep cervical; level III, mid-deep cervical; level IV, lower deep cervical; level V, posterior triangle (Figure 43.1). Recommendations for specific node groups to be included in the field of treatment are meant as a guide (Table 43.2). The responsible clinician must make the final decision based on the details of the individual case.

A similar two-phase technique is employed if proceeding with total mucosal irradiation and in patients being treated for locally advanced inoperable disease.

**Table 43.1** The risk of nodal metastases based on tumour site and location.

| High risk (>60%) | Nasopharynx | Oropharynx | Hypopharynx | Supraglottis |
| Moderate risk (20–60%) | Oral cavity | Advanced larynx | Salivary gland (parotid, submandibular, etc.) |
| Low risk (<20%) | Early glottic | Nasal cavity | Paranasal sinuses | Skin |
| Predominantly unilateral risk | Early tonsil | Well-lateralized oral cavity | Parotid |
| Bilateral risk | Tongue base | Hypopharynx (pyriform sinus) | Advanced larynx | Nasopharynx |

**Table 43.2** Recommendations for elective lymph node irradiation in patients undergoing definitive radiotherapy for head and neck cancer.

| Larynx |
| T1/T2 N0 glottic | No elective nodal irradiation |
| T3/T4 N0 glottic | Levels Ib to IV bilaterally |
| T1/T2 N0 supraglottic | Levels Ib to III bilaterally |
| All other stages | Levels Ib to V bilaterally |

| Oropharynx |
| T1 N0 tonsil | Levels Ib, II ipsilateral |
| T2 N0 tonsil (lateralized) | Levels Ib to IV ipsilateral |
| T1/T2 N1 tonsil (lateralized) | Levels Ib to V ipsilateral |
| T2 N0 tonsil (approaching midline) + other sites | Levels Ib to V bilaterally |
| All other stages | Levels Ib to V bilaterally |

| Hypopharynx |
| All stages and subsites | Levels Ib to V bilaterally |

| Nasal cavity |
| Any T, N0 | No elective nodal irradiation |
| Any T, N+ | Levels Ib to V bilaterally |

| Paranasal sinuses |
| Any T, N0 | Lateral pharyngeal/retropharyngeal lymph node |
| Any T, N+ | |

| Oral cavity |
| T1/T2 N0 (lateralized primary) | Levels I, II ipsilateral |
| T2 N1 (lateralized primary) | Levels I to V ipsilateral |
| T2 N0 (primary approaching midline) | Levels I to IV bilateral |
| All other stages | Levels I to V bilateral |
Palliative radiation fields aim to employ the simplest beam arrangement to cover macroscopic disease while limiting acute toxicity.

**PLANNING TECHNIQUE**

**Patient position and immobilization**

The anatomy of the head and neck region is very complex, with bony structures, soft tissues and air cavities all present within a relatively small volume. In addition to the tumour, many critical structures are frequently in close proximity, such as the spinal cord, brainstem, optic apparatus, mucosa and salivary glands. These structures are defined as organs at risk (OAR). Although OAR may lie close to the tumour volume, internal organ motion is relatively limited. Therefore, immobilization of the head and neck region using a custom-made cabulite or thermoplastic shell should ensure reproducible patient set up to within 3 mm. The mechanical stability of these shells is such that large areas may be cut out to maximize skin sparing during treatment. Thermoplastic shells are more convenient but have been associated with less stability in the past, and so were reserved for the palliative setting. However, the repositioning accuracy of the newer thermoplastic shells is comparable to that of cabulite, particularly when more locating points are used. The addition of a tattoo on the body may also help with this. The main disadvantage of the cabulite shells, apart from the time factor, is that by virtue of their method of attachment to the treatment couch, necessary limitations are imposed on the radiation beam directionality. This has implications for the delivery of intensity-modulated radiotherapy (IMRT). In contrast, newer carbon fibre head and neck boards are available for use with the thermoplastic shells, and are likely to become standard in the future. In the meantime, before adopting any changes, it is recommended that departments assess their own system, comparing it to any new proposed system, because of differences in attachment to bed, number of locating points used and head rest used. This enables the estimation of both set-up systematic and random errors that one might expect, prior to the introduction of new systems.

Prior to the manufacture of an immobilization shell, the head and neck position, shell extent, requirements for mouth bite and full planning details should be specified.

For most sites, patients are immobilized in the head neutral position with the spinal cord straight. This enables matching between photon and electron fields along a straight line in front of the spinal cord, if necessary, during the second phase of treatment. However, patients being treated with IMRT are likely to be immobilized in the neck extended position in order to limit the volume of oral cavity irradiated.

Any patient with palpable lymphadenopathy should have this marked with wire and a simulator image taken to facilitate planning at subsequent visits. This step may be omitted, however, if virtual simulation using a CT scan is planned, where tumour definition is more easily apparent.

Mouth bites are used primarily in tumours of the oral cavity, nasal cavity and maxillary sinus. The action of the mouth bite is to open the jaw and depress the tongue. Thus it may be possible to exclude either the upper or lower half of the mouth from the treatment field, thereby reducing the acute toxicity of the treatment. Caution is required in the immobilization of patients with early tongue tumours with a mouth bite, however, since the mouth bite may push the mobile tongue posteriorly and superiorly out of the radiation field.

**Volume definition**

The International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 contain recommendations on how to report a treatment in external beam radiotherapy. In particular, they specify the concepts of the volumes needing to be treated. The gross tumour volume (GTV) and clinical target volume (CTV) are pure oncological concepts. The GTV is defined as the macroscopically identifiable tumour, while the CTV allows a margin around the GTV to account for the potential spread of subclinical disease. The margin used for CTV requires knowledge of the natural history of the tumour as well as any relevant risk factors in a given patient. The planning target volume (PTV), a concept which was refined in the ICRU 62 report, takes into account two components of movement. The internal margin (IM) takes into account variations in size, shape and position of the CTV in relation to anatomical reference points, while the set-up margin (SM) accounts for uncertainties in patient–beam positioning and relates to technical factors such as accuracy of set up and immobilization of the patient.

Delivery of dose to the PTV depends on the tumour type, the need for radical as opposed to elective radiation, and the nearby organs at risk. OAR (e.g. spinal cord, parotid gland) have defined tolerance doses which have been summarized in Table 43.3.

With regard to the elective irradiation of a nodal target volume, consensus guidelines were recently published in order to define a reproducible standard applicable internationally.

**Volume localization**

Conventional radiotherapy planning employs the use of a radiotherapy simulator to define the fields and has been

<table>
<thead>
<tr>
<th>Organ</th>
<th>Normal tissue tolerance (2 Gy/fraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens</td>
<td>6 Gy</td>
</tr>
<tr>
<td>Cornea</td>
<td>40 Gy</td>
</tr>
<tr>
<td>Retina</td>
<td>50 Gy</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>50 Gy</td>
</tr>
<tr>
<td>Optic chiasm</td>
<td>50–55 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>44–48 Gy</td>
</tr>
<tr>
<td>Brainstem</td>
<td>48–54 Gy</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>30 Gy</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>30 Gy</td>
</tr>
</tbody>
</table>
standard practice in most treatment centres for many years. Typically, field borders are defined in relation to standard bony anatomical landmarks which represent the extent of a given tumour subsite. These field borders may then be modified in individual patients. This planning method does not use the GTV, CTV and PTV definitions outlined in the ICRU 50 and 62 reports. Instead, the field borders represent the PTV plus a physical margin for penumbra. Most commonly, lateral parallel opposed fields are used to treat the target volume. For more complex plans, such as a wedged pair beam arrangement, the PTV is marked on a patient outline taken through an appropriate level, often the central slice, with the PTV then being manually reconstructed from orthogonal simulator films. The clinical results, as well as the toxicities, from such treatments are well described and expected.

Computed tomography planning is, however, increasingly used for head and neck cancer patients. The ICRU 50 and 62 recommendations should be followed and the responsible clinician should define the GTV, CTV, PTV and OAR. The outlining of these structures should be done with the aid of diagnostic imaging, including CT and MRI, as well as clinical examination, flexible nasendoscopy, and notes from all EUA and relevant operations. This enables accurate definition of both the GTV for the primary as well as the nodal GTV and CTV.

A planning CT scan with intravenous contrast is recommended, since this gives better definition of the primary and nodal GTV. CT planning also results in more accurate dosimetry, as well as being essential for inverse planning and IMRT.

Early tumours of the head and neck are frequently best assessed clinically or endoscopically, since cross-sectional imaging such as CT or MRI may not easily identify small lesions of the larynx, oral cavity and oropharynx. However, CT and MRI are useful in the assessment of tumours where the signal intensity of the tumour compared to the adjacent normal tissue is more contrasting, such as nasal cavity or paranasal sinus tumours.

CTV definition for radical radiotherapy is controversial. The magnitude of the margin required to ‘grow’ the GTV to the CTV is taken to be between 1 and 2 cm, and accounts for the estimated subclinical spread of disease. It therefore necessitates sound knowledge of the natural history of the disease and patterns of local tumour extension. However, where a tumour is known to exhibit significant submucosal spread, e.g. pyriform sinus cancer, this margin may be increased. Equally, where there is an anatomical barrier to spread, e.g. bone and air cavities, this margin may be reduced.

The recent publication of consensus guidelines for both the elective irradiation of lymph nodes and nodal irradiation in the involved or postoperative setting has been a valuable contribution for nodal CTV localization. The carotid arteries are important structures in the definition of the deep cervical lymph nodes. Therefore, as previously stated, the use of intravenous contrast with CT scan is recommended. Where lymph node metastases are present in addition to the primary tumour, they each require localization as a separate GTV, with a 1–2 cm margin added for CTV as for the primary. Again, this margin may be reduced where there is an anatomical barrier to spread.

A final margin accounting for both internal organ motion and set-up error is added to the CTV to derive the final PTV. In the head and neck region, most internal organ motion is minimal and therefore the magnitude of this margin is largely dependent on the immobilization technique and accuracy of set up. A margin of 3–5 mm, based on the accuracy of immobilization, is sufficient for most primary sites, although for tumours of the hypopharynx and larynx, where movement occurs on swallowing and breathing, a margin of at least 5 mm may be preferable.

Outlining of OAR is essential in CT planning, since these are usually the dose-limiting structures. The OAR relevant to head and neck tumour outlining include the brain, brainstem, spinal cord, optic apparatus (lens, eye, retinae, optic nerves and chiasm), parotid glands, mandible and thyroid gland. Their tolerance doses have previously been summarized (Table 43.3). All OAR in close proximity to the PTV, or falling within the likely path of one of the radiation fields, should be outlined in their entirety. This enables accurate cumulative dose–volume histograms (DVHs) to be derived. Such DVHs can be derived for both photon and electron fields, and give a mathematical estimation of the maximum point dose to an OAR, as well as the mean and minimum dose to other volumes, such as the PTV. An example of a DVH for PTV, spinal cord and brainstem is demonstrated in Figure 43.2.

IMRT is a new technology in three-dimensional conformal radiotherapy (3D CRT), where by virtue of the beam intensity varying across the treatment field, radiation can be delivered to the PTV with greater sparing of the surrounding normal tissues. While 3D CRT uses radiation beams of uniform intensity, in IMRT, the tumour is treated with multiple small beams of variable intensity, which are achieved by use of a static or dynamic multileaf collimator. Highly conformal dose distributions can therefore be produced, including concave shapes, such as that seen where a tumour is wrapped around an OAR, e.g. parotid gland or spinal cord. IMRT is currently being used both in protocols for the reduction of treatment-related toxicity and also in dose escalation trials, in order to improve local tumour control. IMRT planning is dependent on the inverse planning algorithm. In addition to outlining the target volume and OAR, the clinician must generate constraints in the form of dose volume points. The computer algorithm, using the ‘inverse method’ is then capable of generating significant dose gradients between the target volume and the adjacent structures. For the target volume, the constraints are usually the prescription dose ± 5 per cent, and for OAR the tolerance dose to a small volume of that organ.

Online real-time image guidance (IG) protocols for tumour volume localization are also currently under assessment, including for patients with head and neck cancer. This requires the implementation of kilovoltage cone-beam CT on board a linear accelerator and will become increasingly available in the clinical, as well as the research, setting. Preliminary studies have shown that residual set-up errors reduce with increasing frequency of IG during the course of external beam radiotherapy for head and neck cancer patients. Tomotherapy is a helical system of RT delivery which offers both IMRT and IGRT advances for HNSCC patients.
Dose prescription

Every dose prescription should specify the total dose, the number of fractions or treatments, the schedule of treatment delivery (daily, twice daily, etc.), the prescription point and the photon or electron beam energy. Plans should be normalized to the ICRU reference point. The plan should subsequently be checked to ensure adequate PTV coverage, dose homogeneity, and also that the doses to OAR are within tolerance. Cumulative DVHs are helpful for this purpose.

For radical treatment courses for squamous cancers of the head and neck, tumour tissue and OAR will usually be treated close to tolerance, in order to optimize the probability of local control and cure. Conventional radiotherapy involves daily radiation, Monday to Friday, with a dose of 1.8–2 Gy per fraction to a total dose of 66–70 Gy. Some centres, however, use a hypofractionated regime, delivering 55 Gy in 20 fractions daily, Monday to Friday over 4 weeks (2.75 Gy per fraction).

For large volume disease, where surgery has been deemed inappropriate or not possible, there will usually be a target volume for macroscopic disease, which includes the primary tumour and involved lymph nodes, as well as an elective target volume. In this setting, the former, high-dose volume is frequently overlying the spinal cord, in the lateral projection of the field. This necessitates the use of a two-phase technique in order to maintain the dose to the spinal cord within tolerance. Macroscopic disease should receive 66–70 Gy in 1.8–2 Gy per fraction. Microscopic disease in the elective target volume should receive 44–50 Gy in 1.8–2 Gy per fraction.

Conventionally, 50 Gy is the dose considered to be required to sterilize microscopic disease. Data from both the CHART (continuous hyperfractionated accelerated radiotherapy) trials and Europe demonstrated no significant excess of level 5 neck recurrences with elective doses of 44–46 Gy. However,

Figure 43.2 Cumulative DVH for PTV, spinal cord and brainstem.
this is a comparatively low-risk site for recurrence in most cases.

For locally advanced disease, the outcome with radical radiation may be improved by using altered fractionation regimes (Table 43.4)37, 38, 44, 45 or through the addition of concomitant platinum-based chemotherapy (see Chapter 45, Chemoradiation in head and neck cancer).46 There are also data to suggest that unplanned prolongation of the overall time of treatment detrimentally affects local control rates, and, thereby, tumour cure rates.47 This is important to consider at the outset of a patient’s treatment, since there are many predictable and unpredictable interruptions possible.

For radical radiation, the prescription point is defined as the ICRU reference point, or intersection point. However, for IMRT plans, where the isocentre of each treatment segment may not be located within the target, the dose is specified to the median.

### Table 43.4 An outcome-based comparison of various fractionation schedules.

<table>
<thead>
<tr>
<th>Fractionation</th>
<th>Tumour growth rate indication</th>
<th>Radiobiological principles</th>
<th>Data for tumour response</th>
<th>Data on complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional Accelerated</td>
<td>Average</td>
<td>Reduced overall treatment time prevents tumour cell repopulation</td>
<td>5-year LRC, 66 vs 57% (p = 0.01); 5-year DFS, 72 vs 65% (p = 0.04); no difference OS</td>
<td>More acute mucositis, no difference in late complication rate</td>
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<tr>
<td>fractionation</td>
<td>Rapid</td>
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<td>DAHANCA 6 &amp; 7 trial</td>
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<td>total dose reduction)</td>
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<td>GORTEC 94-02 (accelerated #</td>
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<td>with total dose reduction)</td>
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<td>RTOG 90-03 (accelerated #</td>
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<td>with concomitant boost)</td>
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<tr>
<td>Hyperfractionation</td>
<td>Slow</td>
<td>Greater number of fractions, usually of smaller dose per fraction, allows reoxygenation,</td>
<td>Higher LRC (p = 0.045); trend to improved DFS (p = 0.067); no difference in OS</td>
<td>More acute mucositis, no difference in late effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>allows stem cell repopulation and spares late damage</td>
<td></td>
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<tr>
<td>RTOG 90-03</td>
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<td>with higher total dose)</td>
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</table>

DFS, disease-free survival; LRC, locoregional control; OS, overall survival.

### Field arrangement and beam modification

Lateral parallel opposed fields and a wedged pair field arrangement are the most commonly employed, although more complex beam arrangements are sometimes necessary. These are discussed below under Site-specific treatment planning.

The most common methods of beam modification used in radical radiotherapy are the use of wedges and shielding.

A radiation beam may be modified by the introduction of a wedge which alters the dose distribution, due to greater absorption of radiation through the thicker end of the wedge (Figure 43.3). In head and neck radiation, wedges are used primarily to improve dose homogeneity of unilateral wedged pair fields (Figure 43.4), although they may also be employed to compensate for the natural curvature of skin surfaces, or for a sloping target volume.
Shielding is the method of shaping the radiation beam for conformal treatments. Most centres achieve this through the use of multileaf collimators. Typically there are 20–80 leaves arranged in opposing pairs which can be positioned under computer control to create an irregular field which conforms to the tumour shape. However, some still use customized alloy blocks which must manually be placed on a template prior to irradiation.

**Implementation of treatment**

Radiographers, who are responsible for the day-to-day implementation of treatments, must check for shell loosening during the course of therapy. This is particularly relevant in patients who experience significant weight loss. Here, the effect of shell loosening results in inaccuracies of target volume, and importantly, OAR localization, and it is advisable to make a new shell, and replan the volume.

For most treatments, the shell can be cut out, to reduce dose to skin, unless the tumour extends close to the skin, such as laryngeal cancer involving the anterior commissure.

**Verification**

Prior to treatment, the treatment isocentre, radiation fields and beam shaping are verified against the treatment plan. This may be achieved either using fluoroscopy in a simulator or immediately prior to treatment using electronic portal imaging (EPI). Tolerance of ±3 mm is usually acceptable (unless critical OAR are very close to the PTV when tolerance levels may be more stringent). During the initial 3 days of radiotherapy, EPI should be used to verify RT field position and confirm set-up reproducibility which continues to be monitored throughout the remainder of the treatment course.

**Toxicity of radiation and care during treatment**

Patients will have given written informed consent prior to commencement of treatment. Toxicity of RT may be categorized as acute and late. Acute effects occur during the RT, and would usually be expected to have largely resolved within 4–6 weeks of a radical treatment course. By contrast, late effects begin to occur from months after treatment, and some may not develop until years afterwards.

Expected acute toxicities vary according to the primary site irradiated. Skin erythema and tenderness may occur. For doses exceeding 60 Gy, or for larger fraction sizes, skin breakdown or desquamation may occur, which may either be dry or moist. A mucositis commonly occurs from the second to third week. This may be accompanied by dysphagia, odynophagia and ulceration. A dry mouth secondary to salivary, particularly parotid gland irradiation, is usual from the third week onwards. Hoarseness is usual with irradiation of the larynx, and patients should be monitored closely for the development of stridor, particularly in the setting of T3/ T4 tumours or subglottic disease at diagnosis. Hair loss in the irradiated areas is expected, but is usually reversible, depending on the fraction size. Irradiation of the mucous membranes of the nasal cavity also results in dryness and crustng, as well as transient bleeding. If the entrance of the nasolacrimal duct is in the radiation field, patients may experience epiphoria.
The late effects of radiation depend on the area treated and the dose per fraction, as well as total dose, delivered during treatment. Salivary gland irradiation in excess of 26–30 Gy will usually result in permanent xerostomia. This, in combination with the severe mucositis often seen in treatments to the oral cavity and oropharynx, may result in long-term swallowing difficulties and percutaneous endoscopic gastrostomy dependence, and appears to be related to the radiation dose, the concomitant use of chemotherapy, advancing age, and the presence of neck disease at diagnosis. Irradiation of the mandibular or maxillary alveolus puts the patient at risk of osteoradionecrosis in the event of future dental work required. Irradiation of the pterygoid muscles may result in trismus, which is ideally identified before interference with nutrition. The risk of second malignancy resulting from conventional irradiation is reported to be approximately 1 per cent per ten years following RT, although this figure may increase with the widespread adoption of IMRT, where a greater volume of normal tissue is exposed to lower doses of radiation. In contrast, the background risk of developing a second smoking- or alcohol-related malignancy is about 20 per cent.

It is therefore good practice for all head and neck patients undergoing a course of radical radiotherapy to be seen in a weekly review clinic by a clinical oncologist, a head and neck clinical nurse specialist (CNS), a dietician, and a speech and language therapist (SALT). Following completion of treatment, and as part of ongoing follow up in a joint head and neck clinic, continued review by a dietician, SALT and head and neck CNS may be advisable.

SITE-SPECIFIC TREATMENT PLANNING

Larynx

The larynx is divided into three regions: the supraglottis (laryngeal epiglottis, false vocal cords, ventricles, aryepiglottic folds and arytenoids), the glottis (true vocal cords, anterior and posterior commissures) and the subglottis (10 mm below the free edge of the vocal cords to the inferior border of the cricoid cartilage). Each has its own natural history and pattern of spread, which dictates treatment recommendations.

Immobilization for all larynx cancer patients should be in the supine position with the cervical spine straight.

GLOTTIC TUMOURS

Most stage T1/T2, N0 glottic tumours are treated with radical radiotherapy, with surgery reserved for salvage after radiotherapy failure. The local control rate with definitive radiotherapy for T1 lesions is approximately 90 per cent and for T2 lesions, 70–80 per cent. Controversy remains about which modality gives the best voice quality, though irradiation is generally preferred as it preserves natural voice and avoids a tracheostomy.

Typically, a lateral parallel opposed field arrangement is used, with 5 cm (T1) or 6 cm (T2) square fields centred on the vocal cord (1 cm below thyroid promontory and anterior to the lower border of C5 cervical vertebra).

For T1 lesions, the radiotherapy portal extends from the lower border of the hyoid bone superiorly, to the lower border of the cricoid cartilage inferiorly. Anteriorly, the field border should be in air at the field centre, and posteriorly through the anterior part of the vertebral body. Irradiation of the mandibular or maxillary alveolus puts the patient at risk of osteoradionecrosis in the event of future dental work required. Irradiation of the pterygoid muscles may result in trismus, which is ideally identified before interference with nutrition. The risk of second malignancy resulting from conventional irradiation is reported to be approximately 1 per cent per ten years following RT, although this figure may increase with the widespread adoption of IMRT, where a greater volume of normal tissue is exposed to lower doses of radiation. In contrast, the background risk of developing a second smoking- or alcohol-related malignancy is about 20 per cent.

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For T2 tumours, the field size is extended based on the supraglottic and/or subglottic disease extension. In cases of extensive subglottic extension, it is recommended that the paraoesophageal and paratracheal lymph nodes are included.

Where glottic tumours extend to the anterior commissure, tumour underdosage is a risk due to the skin-sparing effects of the megavoltage beam. In such cases, the immobilization shell should not be cut out, and it may even be necessary to increase the dose to the skin by the addition of bolus to the shell anteriorly. If the calculated dose is still low, a further improvement in the dose may be seen by reducing or removing the wedge from each lateral field.

In some patients, it will not be possible to deliver lateral fields to the larynx due to high shoulder position or short neck. In this situation, an anterior oblique wedged pair field arrangement is more appropriate. For conventional planning, this requires an outline to be taken through the field centre, or alternatively, a PTV can be localized by CT planning.
Dose prescription

The dose prescription, dependent on field size, is as follows:

- $< 36 \text{ cm}^2$, 50 Gy in 16 fractions treating daily, five fractions a week;
- $36-42 \text{ cm}^2$, 55 Gy in 20 fractions treating daily, five fractions a week;
- $> 42 \text{ cm}^2$, 64–66 Gy in 2 Gy per fraction, treating daily, five fractions a week.

SUPRAGLOTTIC TUMOURS

Radical radiation is indicated for most early (T1/T2, N0) supraglottic tumours. However, in contrast to glottic disease, the supraglottic region has richer lymphatics and, consequently, a higher incidence of occult lymph node metastases in levels II and III. All patients, therefore, require elective nodal irradiation of these levels. This is achieved through the use of a two-phase technique (Figure 43.7). Phase I includes the primary tumour, the whole larynx, the pre-epiglottic space and the cervical lymph nodes bilaterally in levels Ib, II and III anterior to the spinal cord. Phase II includes the primary tumour and larynx only. Parallel opposed wedged fields are used for both phases.

Dose prescription

The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to microscopic disease; for example, phase I: 50 Gy/25#/5 weeks; phase II: 20 Gy/10#/2 weeks.

SUBGLOTTIC TUMOURS

Subglottic tumours are rare, and usually present with locally advanced disease requiring surgery followed by adjuvant radiotherapy. However, for patients with early-stage disease, definitive radiation is a recognized larynx preservation approach. Although the incidence of cervical lymph node metastases is rare, the involvement of paratracheal nodes is estimated at 50 per cent, and therefore these nodes should be treated electively. The radiation portal should extend from the top of the thyroid cartilage superiorly to the mid-trachea inferiorly. This requires the use of either an anterior oblique beam arrangement or a coronal technique (Figure 43.8), in order that good coverage of the inferior-most area is achieved.

Figure 43.6 Anterior oblique wedged pair field arrangement for early larynx cancer irradiation in a patient with short neck or high shoulder position.

Figure 43.7 Radiotherapy technique for node negative supraglottic carcinoma.
Dose prescription

Dose prescription is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week.

LOCALLY ADVANCED DISEASE OF THE LARYNX

Increasingly, stage III/IV tumours of the glottis, supraglottis and subglottis are treated with primary chemoradiation as an alternative to surgery and PORT. This maximizes organ preservation rates, maintaining natural speech and swallowing. However, where patients are not fit for surgery or chemoradiation due to pre-existing comorbid conditions, they may also be considered for radical radiotherapy, as an option to optimize local control, ahead of first-line palliation.

The target volume will include the larynx, pre-epiglottic space, involved lymph nodes and all lymph node areas at risk of involvement with occult metastases, namely, levels Ib, II, III, IV and V in all patients bilaterally. This is achieved with a two- or three-phase technique, depending on the anatomical site(s) of involved lymph nodes, and a combination of megavoltage photon fields and matched electron fields. Phase I will include the primary tumour, the entire larynx, pre-epiglottic space and bilateral cervical lymph node levels Ib–V with radiation delivered using a combination of lateral opposed photon beams and a matched lower anterior neck photon field. This neck field is matched below the level of the cricoid cartilage and therefore allows midline shielding of the spinal cord. Laterally, some shielding of the lungs below the clavicles is also possible. In phase II, the posterior border of the lateral portals is brought anterior to the spinal cord, and matched electron fields, used because their rapid dose reduction at depth limits the dose to this critical OAR, are applied bilaterally to the posterior level II and level V lymph nodes. In cases where the involved lymph nodes are at or below the level of the larynx, a further superior field border reduction is possible in phase III. One should note that where IMRT has been introduced into routine practice, there is no need for electron fields.

Figure 43.8 Coronal technique for treatment of laryngeal bed and tracheostomy site.

Dose prescription

Dose prescription is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week.

Oropharynx

The oropharynx is divided into four main subsites: the tonsil, tongue base, soft palate and posterior pharyngeal wall. Treatment recommendations are guided by natural history as well as the laterality of the tumour, with the long-term outcome for patients treated with radical RT being equivalent to primary surgery. All lesions of the oropharynx have a relatively high risk of nodal metastasis. Where a lesion is well lateralized, e.g. tumour confined to tonsillar fossa, the risk of contralateral nodal metastasis is low (15 per cent) and a unilateral irradiation technique may be employed. This results in sparing of the contralateral normal tissues, especially the contralateral parotid gland. By contrast, midline tumours, such as tongue base and soft palate, may metastasize to either side of the neck, necessitating bilateral neck irradiation, which inevitably causes xerostomia. Conventional beam arrangement with irradiation of both parotid glands results in xerostomia in 475 per cent of cases. IMRT should therefore be considered wherever possible for such patients otherwise planned for parallel opposed radiation portals.

TONSIL

Small (T1/T2, N0) well-lateralized tumours of the tonsil are amenable to treatment with irradiation alone. Immobilization is in the supine position with the cervical spine straight. The target volume for the macroscopic dose includes the tonsillar fossa while the ipsilateral cervical lymph nodes, levels Ib–IV, are treated to a microscopic dose. This is achieved by using a wedged pair field technique to treat the tonsil, with anterior and posterior oblique radiation portals, extending from the hard palate superiorly to the lower border of the hyoid bone inferiorly. A modest wedge of approximately 30–45° is required for each of the fields to improve dose homogeneity. This field arrangement encompasses the upper cervical lymph nodes levels Ib–II. At the level of the hyoid bone, a matched ipsilateral anterior neck radiation portal is used to treat the cervical lymph node levels II–IV.

Dose prescription

The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to microscopic disease; for example, phase I: 50 Gy/25#/5 weeks; phase II: 20 Gy/10#/2 weeks.

Figure 43.9 Wedged pair treatment portals including the tonsillar fossa and posterior pharyngeal wall.
TONGUE BASE

Most tongue base tumours present with locally advanced and/or node positive disease, which are best treated with radical chemoradiation, since resection is usually associated with poor swallow and speech function. However, small tongue base tumours (T1/T2) presenting early (N0), particularly exophytic tumours without fixity, may be offered radical radiotherapy, with locoregional control rates of approximately 70 per cent. However, either side of the neck may harbour occult lymph node metastases, so bilateral neck irradiation to levels Ib–V is mandatory.

Immobilization is in the supine position with the cervical spine straight. The radiation technique employs the use of lateral parallel opposed fields to the primary tumour and upper echelon lymph nodes, with the field extending from the hard palate superiorly to the lower border of the hyoid bone inferiorly. Anteriorly, the CTV extends to include the level Ib lymph nodes or 1 cm anterior to the tumour, whichever is the more anterior. Posteriorly, the CTV includes the posterior level II and level V lymph nodes. After 40–44 Gy, the posterior border is reduced to come off the spinal cord and the primary tumour continues to the radical dose. The posterior upper neck is treated with applied electron fields to complete the dose for microscopic disease (Figure 43.10). The lymph nodes below the level of the hyoid bone are treated with a bilateral anterior neck field with midline spinal cord and infraclavicular shielding.

Dose prescription

The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to

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Figure 43.9 (a) Radiotherapy technique for locally advanced laryngeal carcinoma. Field borders for phase I and II will be coincident and are depicted as smaller for illustrative purposes only. (b) Radiotherapy technique for anterior neck field matching at cricoid level, with midline spinal cord and infraclavicular shielding.
microscopic disease; for example, phase I: 50 Gy/25#/5 weeks; phase II: 20 Gy/10#/2 weeks.

**SOFT PALATE**

Immobilization is in the supine position with the cervical spine straight.

For early (T1/T2) node-negative tumours, elective nodal irradiation is not necessary. The target volume is therefore the GTV with a 2 cm margin, and can be irradiated with small lateral opposed radiation portals to the radical dose.

**Dose prescription**
The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week.

**LOCALLY ADVANCED OROPHARYNGEAL CARCINOMA**

Patients with locally advanced or node positive disease who are not fit for chemoradiotherapy or for consideration of surgery and adjuvant radiation, may be considered for definitive radiation alone, to maximize their chances of long-term palliation. The radiation technique is similar to that for tongue base tumours, where bilateral neck irradiation is undertaken. However, it is important to note that all involved lymph node areas must receive a macroscopic tumour dose, including those in the posterior neck, which may be treated with electrons in the second phase of treatment.

**Dose prescription**
The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to microscopic disease; for example, phase I: 50 Gy/25#/5 weeks; phase II: 20 Gy/10#/2 weeks.

**Hypopharynx**

The hypopharynx has three recognized subsites: the pyriform fossa, the postcricoid region and the posterior pharyngeal wall. All are characterized by a high incidence of nodal metastases as well as submucosal spread. Therefore, even in the case of early primary tumours, elective nodal irradiation is necessary. As tumours of the hypopharynx have a tendency to present with locally advanced disease, the majority will be treated with radical chemoradiation, if an organ preservation approach is desired. Dose escalation approaches, such as with IMRT, should also be considered where possible. Nevertheless, for patients unable to tolerate concomitant platinum-based chemotherapy, and for whom surgery is not feasible, radical radiation is an option.

**PYRIFORM FOSSA**

Immobilization is in the supine position with the cervical spine straight. The target volume includes the primary tumour and levels Ib–V lymph nodes bilaterally. The radiation technique usually involves the use of lateral opposed beams to treat the primary disease, involved nodes and upper cervical lymph nodes in phase I, with a small matched lower anterior split neck field to treat the lower echelon lymph nodes. The lateral radiation portals extend superiorly from the skull base to the lower border of the cricoid cartilage inferiorly. Then, as for treatment of the tongue base, the posterior border is reduced to come off the spinal cord at 40–44 Gy with the phase II lateral photon fields, while the posterior cervical nodes are boosted to the appropriate dose using matched electron fields. Where patients have a short neck or high shoulder position, sometimes it may not be possible to achieve adequate coverage of the most inferior aspects of the disease, and the coronal technique may be necessary (see Figure 43.8). Since it is technically difficult to match an electron field posteriorly to an anterior coronal
field, in such cases, the phase I coronal plan, encompassing the posterior lymph nodes, should receive 44 Gy in 22 fractions, before coming off spinal cord for phase II of the plan. This ensures that the posterior lymph nodes are treated to the highest possible elective dose.

Dose prescription
The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to microscopic disease; for example, phase I: 50 Gy/25#/5 weeks; phase II: 20 Gy/10#/2 weeks.

POSTERIOR PHARYNGEAL WALL AND POSTCRICOID REGION
Immobilization is in the supine position with the cervical spine and upper thoracic spine as straight as possible. This may require imaging in the simulator to define the optimal patient position prior to making the shell. For both posterior pharyngeal wall and postcricoid tumours, an inherent radiation planning difficulty is the ability to adequately cover the inferior-most extent of disease once a margin has been added for CTV and PTV. The CTV includes the primary tumour with a 2 cm (posterior pharyngeal wall) or 5 cm (post-cricoid) margin craniocaudally and levels Ib–V lymph nodes bilaterally. It is therefore usually necessary to use the coronal technique described above, although even this may not achieve an adequate dose distribution in the superior mediastinum. In this instance, a low-weighted anterior field with a superior to inferior wedge may increase the dose in this region, although often at the expense of spinal cord dose. Where there are overt lymph node metastases at presentation, radiation may have to be palliative, as the full dose cannot be delivered to all the PTV without compromising the OAR, in particular the spinal cord.

Dose prescription
The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to potential microscopic disease.

Nasal cavity and paranasal sinuses
The main sites are the maxillary sinus, ethmoid sinus and nasal cavity. Most patients are best treated with a combination of surgery with radiation and/or chemotherapy, since most lesions present when they are locally advanced, frequently invade several adjacent sinuses, may invade the orbit and not infrequently invade the anterior and/or middle cranial fossa.\(^{75}\) Definitive radiation is possible, however, for the occasional early tumour.\(^{76}\) It may also be offered for advanced unresectable disease, although five-year survival rates for the latter do not usually exceed 10 per cent. In the case of advanced lesions where chemotherapy is not possible, one should consider optimizing the results of radical radiation by using an altered fractionation regime.\(^{78}\)

MAXILLARY SINUS
Immobilization is in the supine position with the cervical spine straight and a mouth bite in place to exclude the tongue and lower part of the oral cavity from the radiation field. CT planning is recommended due to the close proximity of many critical OAR. The majority of tumours are node negative, even if locally quite advanced, and tend to exhibit submucosal spread. The CTV is therefore the maxillary sinus, the ethmoid sinus, the nasal cavity, pterygoid fossa and the lateral pharyngeal node. This is usually achieved using a heavily weighted anterior field in combination with one or two lateral fields (Figure 43.11). The ipsilateral eye should be shielded if possible from the anterior field, although in cases of frank orbital invasion this may have to be limited to shielding of the ipsilateral lacrimal gland, to avoid xerophthalmia. The anterior border of the lateral fields should be non-divergent to avoid exit through the contralateral lens. This may be achieved either through angling of the lateral field posteriorly by 5–10° or by half-beam blocking. The area at greatest risk of underdose is the posteromedial part of the PTV. It may be necessary to consider a further ‘in-field’ IMRT boost to this area (‘field within a field’) to improve PTV coverage and dose homogeneity, although care must be taken with the dose to the optic chiasm and brainstem. It may be necessary to introduce shielding to these structures thus compromising PTV coverage, if their tolerance is exceeded. Under these circumstances, patients must be clear that radiation is unlikely to effect long-term cure, rather high-dose palliation of symptoms.

Dose prescription
The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week.

ETHMOID SINUS
Immobilization is again in the supine position with the cervical spine straight and a mouth bite in place, with CT planning recommended due to the close proximity of the optic apparatus. Where available, a planning MRI scan may be performed, and co-registered with the planning CT, as this further aids identification of the OAR and helps with target volume definition. The CTV should include both ethmoid sinuses, the nasal cavity, the medial half of the maxilla on the ipsilateral side and the pterygoid fossa. A three-field plan, using a heavily weighted anterior field and two lateral fields, similar to the arrangement in maxillary sinus tumours, usually achieves the best dose homogeneity. Again, lymph node metastases are rare, so there is no need for elective lymph node irradiation to be undertaken. Occasionally, patients present with very small (T1) tumours, such that the radiation portals can be confined to covering the ethmoid sinuses and nasal cavity alone using superior and inferior anterior oblique fields (Figure 43.12).

Dose prescription
The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week.
For tumours of the nasal cavity being treated with radical radiation, rather than surgery, immobilization and CT planning are recommended. Again, the probability of lymph node metastases is extremely low, such that the CTV includes the primary lesion and a 1 cm margin. The field arrangement may be either an anterior wedged pair of photon fields, or in more advanced disease, a three-field technique similar to maxilla/ethmoid sinus plans, where the entire nasal cavity is included in the CTV.

**Dose prescription**

The total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week.

**NASAL COLUMELLA/VESTIBULE**

Radiation is often undertaken in the first instance to avoid deformity. Patient immobilization is undertaken as previously. The natural history of nasal columella tumours is such that tumours with seemingly localized presentation may infiltrate quite deeply submucosally along the nasal septum. By contrast, vestibule tumours tend to be more locally confined. The local control rate for vestibule tumours treated with radiation is in the order of 80–90 per cent at five years. Vestibule tumours and small lesions of the nasal columella, without evidence of extension up the nasal cavity and/or septum, may be treated with appositional electrons, with the CTV including the primary tumour with a 2 cm margin. In order to produce a homogeneous tissue density for deposition of dose, the nose may be ‘built up’ using a wax block externally and wax nostril plugs internally. This is usually a relatively small volume, and may therefore be treated with the hypofractionated regime given below.

With more locally advanced lesions, CT planning is recommended, with the CTV including the primary tumour with a 1 cm margin and the entire nasal septum. An anterior oblique wedged pair field arrangement usually achieves good dose homogeneity, although occasionally a three-field technique as for nasal cavity irradiation may be necessary. In cases where tumour is in the build-up region of the radiation...
beam, the immobilization shell should not be cut out over this area, and the additional application of wax bolus may be necessary to increase the dose to the PTV at the skin surface.

**Dose prescription**

The dose prescription for small lesions confined to the columella or vestibule is 55 Gy in 20 fractions, treating daily, five times a week and that for more advanced lesions, with extension up the nasal septum/cavity is 66–70 Gy in 2 Gy per fraction, treating daily, five times a week.

**Oral cavity**

The oral cavity is divided into several subsites: the oral tongue, floor of mouth, buccal mucosa, alveolus and hard palate. Published data suggest that most oral cavity tumours are best treated with surgery, followed by adjuvant radiation with or without chemotherapy, depending on the presence of intermediate or high risk pathological features. However, small (T1/T2), superficial (<5 mm thickness) lesions of the oral tongue and floor of mouth should be considered for interstitial brachytherapy. It is also possible to offer definitive radiation to patients with early lesions when surgery is not possible for comorbid reasons.

In lesions being considered for interstitial brachytherapy (brachy = Greek, short distance), an anaesthetic assessment is required in addition to the other preparatory measures for radiation described previously. Interstitial brachytherapy consists of surgically implanting small radioactive sources directly into the target tissues. It is therefore helpful to conduct this procedure with the assistance of the surgical oncologist. Most head and neck brachytherapy treatments use low dose rate (LDR) temporary iridium-192, with an activity of approximately 50 cGy per hour, or 10 Gy per day. All interstitial implants rely on classic systems which define rules governing the distribution of the radioactive sources, the dose specification and also to aid dose calculation. These systems enable advance planning of interstitial implants and the one most frequently used in head and neck brachytherapy is the Paris system. The Paris system is a simple system, founded on empirical clinical practice and mathematical calculations, and is adaptable to many clinical situations, since it is applicable to both single- and multi-plane implants. Paris rules specify that implants should be parallel, uncrossed and straight. Wire spacing should be equidistant from 5 to 20 mm, with wire separation determined by target volume thickness and wire length being approximately 1.5 times the target volume length. These are the features which the clinician must aim for when implanting the volume, and which the physicist will use to determine the precise duration of implantation in order to deliver the prescribed dose.

**FLOOR OF MOUTH**

Again, small, superficial lesions may be treated with interstitial brachytherapy as above.

If EBRT is considered, the mouth should be held open during immobilization with a mouth bite, to limit the dose to the upper oral cavity, in particular the hard palate. Tumours of the floor of mouth are frequently in the midline, such that EBRT requires the use of lateral parallel opposed radiation portals to cover the target volume, which includes the primary tumour and locoregional lymph nodes.

**Dose prescription**

The dose prescription for interstitial brachytherapy is 60 Gy over 6 days with iridium-192 LDR. For EBRT, the total dose is 66–70 Gy in 2 Gy per fraction, treating daily, five fractions a week, to macroscopic disease and 44–50 Gy in 2 Gy per fraction, treating daily, five fractions a week, to microscopic disease.

**BUCCAL MUCOSA, ALVEOLUS AND SMALL HARD PALATE TUMOURS**

These sites are almost invariably treated in the postoperative setting.

**Reirradiation**

Patients with recurrent disease largely fall into four categories: (1) the patient who has disease recurring in a previously operated but not irradiated site; (2) disease in a previously irradiated site and amenable to surgical salvage; (3) disease in a previously irradiated site, not amenable to further surgery where reirradiation may be considered; (4) recurrent disease associated with other distant metastases, or other comorbidities, such that a further radical dose of radiation would be inappropriate. Within these broad categories, the cause of recurrence can be attributed to radiation resistance, anatomical miss, or the development of a second primary HNSCC (for review, see Creak et al.). Tumours occurring due to geographical miss, and arising in the
penumbra region of the previous RT field, or in the low-dose region, and second primary tumours, often occurring after a tumour-free interval of several years, should be considered for reirradiation.

RATIONAL FOR REIRRADIATION

Only one-third of HNSCC recurrences are amenable to salvage surgery, with a median survival of approximately nine months.86 Palliative chemotherapy with a cisplatin-based regimen, while associated with response rates of 20–40 per cent and median survival of between five and nine months, is often associated with significant morbidity, and is only usually recommended for patients with WHO performance status 0–1.87

As a comparison, for carefully selected patients the locoregional control (LRC) rate with reirradiation ranges from 20 to 60 per cent, with a recognized cohort of patients surviving beyond five years (five-year survival, 10–93 per cent).88, 89

The clinical judgement lies between proceeding with palliative chemotherapy or whether to risk irradiation to a site where there will inevitably be overlap of past and current fields. The clinician must be guided by features such as the time elapsed since previous irradiation, the total dose previously received as well as the dose fractionation, the critical structures previously in proximity to the target volume and whether they were irradiated short of tolerance, as well as the patient’s performance status and personal wishes. It should be possible to determine the maximum dose to OAR given previously, and factor in a degree of ‘recovery’ depending on time elapsed since treatment.90, 91 Nevertheless, the reirradiation dose is almost always limited by the dose to OAR. The risks of normal tissue toxicity are greater, so the patient must take an informed decision. However, there may be more durable palliation and disease control with this modality than with chemotherapy.

The planning technique is as above, with cautious consideration of CTV definition, based on CT planning scans performed with intravenous contrast.

Table 43.5 details the patient and treatment factors to be considered when planning reirradiation.

REIRRADIATION WITH BRACHYTHERAPY

For T1/T2 locally recurrent disease of the oropharynx or nasopharynx, without evidence of regional lymph node metastasis, LDR iridium-192 implant brachytherapy may be considered, employing the afterloading technique. When a mean dose of 60 Gy is achieved, five-year local control rates as high as 80 per cent for rT1 and 67 per cent for rT2 may be seen, although the overall survival at five years is lower at 30 per cent, due to the high incidence of other alcohol- and smoking-related comorbid disease.92–94

REIRRADIATION WITH EXTERNAL BEAM RADIOTHERAPY ALONE

This approach has been most successful in rT1/rT2 disease of the larynx. Again, the optimum dose is 60 Gy or greater, with either conventional or altered fractionation, giving five-year actuarial local control and survival rates of approximately 60 and 90 per cent. Notably, the majority of local failures went on to have salvage total laryngectomy.98

REIRRADIATION WITH CONCOMITANT CHEMOTHERAPY

The addition of concomitant chemotherapy to reirradiation is associated with considerable toxicity. However, for carefully selected patients, where optimal debulking has been possible, with only microscopic residual disease, this is an approach again associated with some long-term survivors.95

REIRRADIATION WITH IMRT

Some patients develop recurrence within, or at the periphery of a previous radiation portal, but at a site not suited to surgical salvage, such as the skull base or infratemporal fossa.

Table 43.5 Patient and treatment factors to consider for reirradiation.

<table>
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<tr>
<th>Anatomical site</th>
<th>Nasopharynx and larynx recurrence associated with a more favourable outcome than other sites</th>
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<td>Patient factors</td>
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<td>Treatment-free interval</td>
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<td>Treatment factors</td>
<td>Surgery</td>
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<td>Radiation dose</td>
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RT, radiotherapy.
Reirradiation with IMRT is an attractive option in this setting since this technique affords the advantage over conventional RT of a greater normal tissue-sparing effect while delivering highly conformal RT to the tumour.\textsuperscript{97, 98} In series reported to date, the LRC has been excellent, with acceptable acute toxicity. Longer follow up is needed to evaluate late toxicity.\textsuperscript{97, 98}

**KEY EVIDENCE**

- Radiotherapy is a key modality in the treatment of head and neck cancer, providing high rates of tumour control and organ preservation in early stage tumours.
- For patients with advanced stage tumours, radiotherapy is usually combined either with chemotherapy or used in the postoperative setting.
- Appropriate use of advanced radiotherapy technologies can reduce side effects and improve outcomes for head and neck patients.

**KEY LEARNING POINTS**

- An important consideration in radiotherapy planning is patient positioning and immobilization to ensure reproducibility of treatments.
- ICRU Reports 50 and 62, as well as the consensus guidelines, should dictate the delineation of GTV, CTV, PTV, nodal target volume and the organs at risk.
- Early tumours, particularly those with low risk of lymph node disease, are often treated in a single phase, with conventionally planned volumes and simple radiation fields.
- Some early, superficial tumours, particularly those sited in the oral cavity, may be suitable for treatment with interstitial brachytherapy.
- More locally advanced tumours, and those with a higher risk of lymph node disease, are often treated in two or more phases, using CT-planned volumes and more complex radiation fields.
- For conventionally fractionated treatments (1.8–2 Gy per fraction) the dose needed to adequately treat macroscopic disease is 66–70 Gy, while 44–50 Gy is needed to sterilize microscopic disease.
- For locally advanced disease, the results of definitive radiation may be improved by using an altered fractionation regime or by the addition of chemotherapy.
- Recurrent disease should be carefully considered for optimal surgical debulking and reirradiation.

**REFERENCES**


65. Mendenhall WM, Amdur RJ, Stringer SP et al. Radiation therapy for squamous cell carcinoma of the tonsillar


INTRODUCTION

The role of postoperative radiotherapy is important in the treatment of head and neck cancer. The delivery involves close collaboration between head and neck surgeons and oncologists. Patient selection, dosage of postoperative radiotherapy and optimum treatment starting and completion time have yet to be fully determined. This chapter will briefly cover some historical aspects of the development of postoperative radiotherapy in head and neck cancer and the current usual practice.

EVIDENCE FOR THE USE OF POSTOPERATIVE RADIOTHERAPY IN SQUAMOUS CELL CARCINOMA

Any consideration of the role of postoperative radiotherapy in squamous cell carcinoma of the head and neck is hindered by a lack of prospective randomized trials. This dearth of quality data has resulted from difficulties in performing studies which randomize patients to no radiotherapy when the results from surgery alone for advanced clinical stages have historically been poor. For example, in a series of 71 patients with either extracapsular lymph nodal extension and/or positive resection margins the three-year local control rate for patients with both these factors was 0 per cent.¹

It is therefore difficult to estimate the benefit of postoperative radiotherapy in a given stage and site of tumour let alone assess the therapeutic ratio of tumour control over side effects in a patient with their individual comorbidity and performance status. Retrospective data or other studies with methodological flaws have to be relied upon to give clinicians some idea of the likely benefit of such treatment. In one series, 140 patients with stage 3 and stage 4 buccal mucosal cancer were ‘randomized’ to surgery or surgery followed by 58–65 Gy postoperative radiotherapy. Disease-free survival at three years was 38 per cent in the surgery alone arm and 68 per cent in the postoperative radiotherapy arm ($p < 0.005$). The preference of surgeons in the study to assign patients to the postoperative radiotherapy group if they were node positive regardless of the randomization resulted in an excess of node positive patients in this arm (70 versus 6 per cent, $p = 0.05$). This imbalance together with the heterogeneity of the radiotherapy dose and small sample size allow few conclusions on the precise effect of postoperative radiotherapy to be drawn. However, it is reasonable to conclude some likelihood of a beneficial effect given the superior disease-free survival despite higher nodal stage.²

In a small study, 51 patients with completely resected head and neck cancer were randomized to no further treatment or 50 Gy in 25 fractions postoperatively. Again, despite randomization, there was an excess of histologically node positive disease in the postoperative radiotherapy arm (63 versus 84 per cent). There was also a non-significant decrease in all recurrences (distant and local considered together) (56 versus 37 per cent). This difference was felt to be largely due to
relapse in the non-operated contralateral neck (15 per cent), and the authors concluded no significant benefit from postoperative radiotherapy as such relapses may often be surgically salvaged.\(^3\)

In a non-randomized series \((n = 125)\) prior to the advent of single multidisciplinary teams within major hospitals, patients with head and neck cancer seen by general surgeons were not routinely sent for postoperative radiotherapy whereas those cases seen by specialist head and neck surgeons were considered. The three-year local control rate for patients with extracapsular spread was higher with postoperative radiotherapy \((31\% \text{ versus } 66\% \text{ per cent}; p = 0.03)\) than it was for patients irradiated with positive margins \((41\% \text{ versus } 49\% \text{ per cent}; p = 0.04)\), with the most significant difference in local control occurring in patients with both these factors \((0 \text{ versus } 68\% \text{ per cent}; p = 0.001)\). Disease-free survival was also increased with postoperative radiotherapy in this series \((25 \text{ versus } 45 \text{ per cent}; p = 0.0001)\).\(^1\)

While none of these studies reaches currently acceptable standards of evidence, it is reasonable to assume some effect of postoperative radiotherapy on reducing recurrence. However, given the likely hypoxic environment in the postoperative surgical bed might radiotherapy given preoperatively be more efficacious? Two randomized prospective studies have examined this question. Forty-nine patients with hypopharyngeal cancer were randomized to 50 Gy completed 2 weeks prior to a laryngopharyngectomy and neck dissection, or the same surgery followed within 4 weeks by 55 Gy. The preoperative arm fared generally worse than the postoperative with more carotid haemorrhage \((5 \text{ versus } 1)\), less patients undergoing surgery \((17/25 \text{ versus } 24/24)\), more cancer deaths \((11 \text{ versus } 6)\) and five-year survival was 20 versus 56 per cent.\(^4\) In a larger study of 277 patients, there was significantly higher locoregional control \((LRC)\) with postoperative radiotherapy of 60 Gy when compared with 50 Gy preoperative radiotherapy \((p = 0.04)\). There was no difference in overall survival due to distant metastases and second primary tumours in the postoperative arm.\(^5\) These studies suggest that if combined modality treatment is to be employed in resectable head and neck cancer radiotherapy should be employed postoperatively.

**INDICATIONS FOR POSTOPERATIVE RADIOTHERAPY**

Several groups have identified pathological factors based on the available literature which enable classification of patients postoperatively into high, medium and low risk disease. As above, the presence of nodal disease with extracapsular spread is considered in all systems as a marker of high risk disease where postoperative radiotherapy is mandatory.\(^1\), \(^6\), \(^7\) In addition, the CHARTWEL group at Mount Vernon randomizing patients to conventional or accelerated postoperative radiotherapy considered as high risk the presence of an involved surgical margin or four of the following factors: excision margins less than 5 mm, stage T3/T4, perineural or vascular invasion, poor differentiation, oral cavity primary, multicentre primary, more than four nodes positive, soft tissue invasion and dysplasia or carcinoma *in situ* at the resection margin.\(^6\) Patients with two of these factors were assessed at intermediate risk with all other patients judged at low risk and not considered for postoperative radiotherapy.

The MD Anderson group considered patients with either extracapsular spread or two of the following factors at high risk: oral cavity primary, involved surgical margins, perineural invasion, more than one node involved, more than one nodal group involved, largest node greater than 3 cm, and an interval between surgery and radiotherapy greater than 6 weeks.\(^7\), \(^8\) Patients with one of these factors were considered at intermediate risk. These classifications have been used to assign patients to varying dose levels and fractionation schedules in the prospective trials described below.

Following laryngectomy in addition to the factors described above, the presence of transglottic disease, a preoperative tracheostomy and lymph node involvement in level 6 are additional risk factors.

**EVIDENCE FOR DOSE ESCALATION AND ACCELERATION OF POSTOPERATIVE RADIOTHERAPY**

The main body of evidence with regard to the appropriate postoperative dose of radiotherapy for a given risk disease is derived from a study of 302 patients performed at the MD Anderson Cancer Center between 1983 and 1991.\(^7\) Using a point system dependent on adverse pathological variables, patients were assigned to a low risk or high risk group. The low, medium and high risk groups described above were subsequently formulated based on the results from this study. Patients assigned as low risk were initially randomized to postoperative doses of either 52–54 Gy in 29–30 fractions or 63 Gy in 35 fractions. An interim analysis after only two years showed a higher rate of recurrence in the lower dose arm and so for the rest of the study the dose in this arm was increased to 57.6 Gy in 32 fractions. In the high risk group, patients were randomized between 63 Gy in 35 fractions and 68.4 Gy in 38 fractions. After the initial dose adjustment in the low risk arm, and in the high risk arm throughout the whole study, there was no significant advantage in the use of a higher dose of radiotherapy when analysing the study as originally planned. However, the primary tumour local control for patients receiving 63 Gy in 35 fractions was identical at 89 per cent for patients in both the low and high risk groups suggesting that the initial pathological scoring system was flawed, prompting the subsequent analysis of pathological features leading to the system described above. Subgroup analysis of patients with extracapsular nodal involvement identified a significant increase in local control between the 35.6 and 63 Gy arms \((52 \text{ versus } 74 \text{ per cent}; p = 0.03)\).

The conclusions from this study are that a dose less than 57.6 Gy in 32 fractions is suboptimal for postoperative radiotherapy and that patients with extracapsular spread should receive at least 63 Gy in 35 fractions. The lack of a dose response above 57.6 Gy in all patients led the same group to examine the possibility that accelerated repopulation might nullify any additional dose due to prolongation of overall treatment time.
In a second study at MD Anderson between 1991 and 1995, 213 patients were assigned to the low, medium and high risk groups as per the system derived from the above study. Low risk patients without any adverse risk factors did not receive radiotherapy and had similar five-year local control to patients with one risk factor (other than extracapsular spread) who received 57.6 Gy in 32 fractions (90 versus 94 per cent). There were similar rates of distant metastases between these two groups (3 versus 4 per cent) and a non-significant difference in five-year survival (83 versus 66 per cent). The high risk group with either extracapsular extension alone or two risk factors had a significantly lower rate of local control and overall survival (68 per cent, \( p = 0.003 \) and 42 per cent, \( p = 0.0001 \)) together with a higher rate of distant metastases (33 per cent). This group of 151 patients was randomized to 63 Gy in 35 fractions delivered in 1.8 Gy fractions either once daily over 7 weeks or once daily for the first 3 weeks and then twice a day with a 6-hour interval for the last 2 weeks with an overall treatment time of 5 weeks. This accelerated arm resulted in a trend towards improved local control \( (p = 0.11) \) and a trend towards improved overall survival \( (p = 0.08) \).

**EFFECT OF DELAY BETWEEN SURGERY AND POSTOPERATIVE RADIOTHERAPY**

The optimal timing of postoperative radiotherapy has yet to be determined although overall treatment time (OTT) is a known important factor in treatment of head and neck cancer treated with radiotherapy alone. The potential doubling time of squamous cell carcinomas in head and neck cancers can be as few as 5 days, hence higher total dose may be required to maintain tumour control if treatment duration is prolonged. Relapsed tumours were found to have shorter doubling time than those that did not as found in a flow cytometry study of 70 patients although it did not reach statistical significance \((5.3 \text{ versus } 6.1 \text{ days, } p = \text{NS})\).

Another radiobiology factor is the concept of accelerated repopulation whereby the tumours grow even more quickly after surgery and may be related to increase in tumour growth factors and inflammatory response in the areas of wound healing.

With combined modality of treatment of surgery and postoperative radiotherapy, radiobiological considerations of potential doubling time and accelerated repopulation suggest that delays in commencing postoperative radiotherapy may be detrimental to the outcomes. However, no randomized control trial has addressed the optimal timing of postoperative radiotherapy specifically.

A series from Memorial Sloan-Kettering Cancer Center with more than 100 patients with stages 3 and 4 squamous cell carcinoma of head and neck had a higher incidence of regional failure when radiotherapy was delayed by more than 6 weeks after surgery. However, the results could be confounded by suboptimal radiation doses as the majority of patients who failed received less than 56 Gy. When patients who had treatment delays of more than 6 weeks were analysed into groups of patients receiving less than 56 Gy versus at least 60 Gy, the latter had better LRC suggesting a compensatory effect by a higher radiotherapy dose. Moreover, the relapse incidence of the latter group was similar to another group receiving at least 60 Gy and who started treatment within the first 6 weeks after surgery. The authors concluded that a delay in postoperative radiotherapy may not have a negative impact provided the radiation dose is more than 60 Gy.

A retrospective study in France of 420 patients did not find delays in starting postoperative radiotherapy to be a statistically significant factor for locoregional relapse or survival. The patients were treated with doses of 45–55 Gy if margins were >5 mm or node negative, 56–65 Gy if margins were <5 mm or node positive, and 66–74 Gy if margins were microscopically positive or if there was extracapsular nodal spread. The patients were divided into starting treatment \( \leq 30 \) or \( >30 \) days. Of the patients, 19.5 per cent had radiotherapy starting \( >30 \) days after surgery.

The authors offered several explanations for the negative results. First, the rate of locoregional relapse at 18.3 per cent was possibly too low to be influenced by the delays in radiotherapy. They postulated the low incidence of relapse was affected by the increased incidence of metastasis, second primaries and unrelated deaths. Second, the inclusion criterion of complete macroscopic resection might mean the impact of radiotherapy delays was limited as residual cancer cells might be minimal. Third, tissue hypoxia following surgery might make residual cancer cells more resistant to the effects of radiotherapy. Therefore, they concluded that delay in starting postoperative radiotherapy might not be such an important factor as suggested by radiobiological considerations.

Amdu et al. reported an older series of 134 patients of whom 96 per cent were stage 3 and 4, who achieved macroscopic clearance following surgery and who were treated with continuous course radiotherapy. They did not find the interval between surgery and starting radiotherapy (ranging from 1 to 10 weeks) was a significant factor based on multivariate analysis.

However, a few studies found the delay in starting postoperative radiotherapy and the OTT of combined modality treatment might influence outcomes.\(^8,14,15,16,17\)

An MD Anderson prospective randomized trial of 213 patients addressed the issue of postoperative radiotherapy or no further treatment after surgery. They found that high risk patients who received conventional fractionated radiotherapy over 7 weeks had a lower LRC \( (p = 0.03) \) and lower survival rates \( (p = 0.01) \) if there was >6 weeks delay between surgery and radiotherapy.\(^8\) There was no significant effect in high risk patients who received accelerated radiotherapy over 5 weeks, even if there was a delay in starting postoperative radiotherapy.

When they looked into OTT, which takes into account the time of surgery until the time of completing radiotherapy, the LRC and survival were lower in the groups who had prolonged OTT. The five-year actuarial LRC for OTT \(<11 \text{ weeks were } 76 \text{ per cent compared with } 62 \text{ per cent for } 11–13 \text{ weeks and } 38 \text{ per cent for } >13 \text{ weeks } (p = 0.002)\); and the corresponding survival rates were 48, 27 and 25 per cent \((p = 0.03)\). Hence, the authors suggested that OTT should be taken into account and the treatment of surgery and postoperative radiotherapy should be considered as a package that needs to be delivered in a coordinated fashion. However,
logistics required to complete the combined modality treatment in <11 weeks might not be achievable given the nature of the advanced disease requiring major surgery, the possibility of delayed wound healing and radiotherapy capacity.

A retrospective series from the University of Florida with 226 patients with squamous cell carcinoma of the oral cavity was reported by Hinerman et al. The group that was deemed to have higher risk of recurrence (defined as ≥3 indications for postoperative radiotherapy) tended to have a lower LRC if the interval between surgery and radiotherapy exceeded 51 days or the OTT was >101 days.

Another retrospective review of 208 patients treated from 1992 to 1997 with a dose of radiotherapy ≥55 Gy with stratification of OTT into ‘short’ (≤100 days) or ‘long’ (>100 days) found that the ‘short’ OTT was associated with improved tumour control and survival on multivariate analysis (p = 0.022 and 0.035, respectively).

In addition, two smaller series reported that time interval from surgery to postoperative radiotherapy was potentially important. Kajanti et al. reported 63 patients with squamous cell carcinoma of the tongue with stages 1 to 4 treated with surgery and split-course postoperative radiotherapy with a total dose of 66 Gy. They stratified patients into time intervals of surgery to radiotherapy of <6 weeks, 6–8 weeks and >8 weeks. They found that grade of tumour and time to radiotherapy were the most important factors in influencing LRC. However, they acknowledged that the time to radiotherapy could be influenced by other prognostic factors, such as surgical complications, infections or poor general conditions, which might reflect a more advanced stage disease. When these factors were taken into account, the effect of delay in starting radiotherapy had almost disappeared.

Ampil et al. reported a retrospective study of 70 patients of stage 3 and 4 where the LRC was lower when postoperative radiotherapy was delayed but, surprisingly, no advantage when the total dose was increased.

A system review in 2003 by Huang et al. of seven studies of postoperative radiotherapy in head and neck cancers involving 851 patients found that the pooled probability of local control was lower if the patients started radiotherapy more than 6 weeks after surgery. The pooled odds ratio (OR) was 2.89 (95 per cent CI 1.60 to 5.21). However, there was a considerable amount of heterogeneity in the studies and when three studies of low quality data were excluded, the OR was reduced to 2.29 (95 per cent CI 1.15 to 4.59). There were two studies where survival data were obtained. In one study, delay in radiotherapy was associated with a survival decrease but was not in the other.

In summary, the interval between surgery and postoperative radiotherapy and the OTT may be significant in the outcomes of LRC and possibly survival but these factors are confounded by the diverse radiotherapy doses, fractionations and techniques, patient and tumour factors. Moreover, the delay in starting postoperative radiotherapy may also be related to the poor wound healing which, in turn, may reflect a poorer prognostic group which, in turn, will give a worse outcome. It would appear sensible to aim for the postoperative radiotherapy to start as soon as feasible with advance preparations for the radiotherapy, such as dental extractions, supplementary feeding and booking of radiotherapy, made ahead.

### KEY EVIDENCE

- Patients who are classified as high or intermediate risk of relapse benefit the most from the addition of postoperative radiotherapy.
- Overall treatment time is an important factor in treatment of head and neck cancer and delays in starting postoperative radiotherapy may compromise locoregional control.

### KEY LEARNING POINTS

- A few retrospective studies suggest potential benefits of postoperative radiotherapy.
- Higher overall doses of postoperative radiotherapy may potentially increase locoregional control, but will be limited by toxicities and organ tolerance.
- Classification of risk depends on multiple factors. Presence of extracapsular spread, involved surgical margins, higher T stage, perineural invasion, number, size and multiple levels of lymph node involvement and oral cavity primary indicate likely higher risk of relapse.
- Early recognition of which patients may benefit and the subsequent preparatory work with any necessary dental extractions, supplementary feeding, booking, preparation, e.g. beam direction shell and planning of postoperative radiotherapy will be helpful to facilitate an early start and timely completion of radiotherapy.
- Any delays in starting and completing postoperative radiotherapy may compromise outcomes of locoregional control and overall survival.
- Concepts of doubling time and accelerated repopulation are important considerations in head and neck cancer.

### REFERENCES


Chemoradiation in head and neck cancer

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Mater artium necessitas.
William Horman, 1519

INTRODUCTION

Head and neck cancer is best managed in a multidisciplinary setting. Approximately two-thirds of patients present with locally advanced disease; half of these develop locally recurrent or metastatic disease within two years of primary definitive treatment. The aim of treatment is to maximize tumour control while preserving function and quality of life. Surgery, radiotherapy, chemotherapy and, more recently, 'targeted' therapies are utilized in various combinations in attempts to effect cure.

Radiotherapy, with or without concomitant platinum-based chemotherapy, has overtaken surgery as the primary treatment modality for many head and neck cancers, largely in the setting of organ-conservation approaches to treatment. It is also used in the adjuvant setting with or without platinum-based chemotherapy to enhance locoregional control following primary surgical management. The last two decades have witnessed significant developments in radiation treatment. An improved understanding of the underlying radiobiological principles has been the catalyst for optimizing radiation dose fractionation. Technological advances have improved radiation delivery capabilities from two-dimensional (2D) radiographic simulation using bony landmarks to the utilization of complex computer driven machines delivering radiation with high accuracy, to the potential of integrating functional imaging for enhancing target volume definition. The role of systemic therapies in head and neck cancer is attracting considerable interest with ongoing research into the role of induction chemotherapy and hypoxic cell sensitizers in the treatment of locally advanced head and neck cancer. The integration of targeted therapies fuelled by an ever-expanding elucidation of the molecular basis of cancer shows some promise but their role needs to be better defined. These innovations, unless otherwise specified, have been supported by high quality level I data from multiple large randomized controlled trials and individual patient data meta-analyses and form the basis of the ensuing discussion.

While the future remains particularly exciting for the non-surgical head and neck oncologist, this has to be tempered with due vigilance and an awareness of the potential long-term impact of our endeavours upon patients with this group of diseases. The ultimate goal is to enhance the therapeutic ratio in the treatment of head and neck cancers through collaboration in a multidisciplinary setting in order to improve cure rates while decreasing treatment-related morbidity and maintaining the patient’s quality of life.

RADIOOTHERAPY DOSE FRACTIONATION

Radiation therapy has historically evolved as an empirical art rather than as an exact science. Conventional practice involves once daily treatment for five fractions a week over 6–7 weeks using 1.8–2 Gy per fraction. In the UK, resource limitations have led to a selective adaptation of shorter dose fractionation schedules with duration of treatment varying between 3 and 7 weeks. The efficacy of these shorter...
Modified radiation dose fractionation.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Examples in head and neck radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Normal tissue toxicity expressed within weeks or months after exposure</td>
</tr>
<tr>
<td>Late</td>
<td>Normal tissue toxicity expressed months to years after exposure</td>
</tr>
<tr>
<td>Consequential</td>
<td>Chronic toxicity as a consequence of severe early effects</td>
</tr>
</tbody>
</table>

Table 45.2 Modified radiation dose fractionation.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Hypofractionation</td>
<td>The use of doses &gt; 2 Gy per fraction</td>
</tr>
<tr>
<td>Hyperfractionation</td>
<td>The use of doses &lt; 1.8 Gy per fraction</td>
</tr>
<tr>
<td>Acceleration</td>
<td>Reducing overall treatment time by using a dose rate &gt; 10 Gy per week used in conventional treatment</td>
</tr>
</tbody>
</table>

Hyperfractionated radiotherapy utilizes doses less than 1.8 Gy per fraction to deliver radiation treatment. A larger number of fractions are delivered over the same period of time as a conventional schedule by delivering multiple fractions per day. Smaller doses per fraction reduce the probability of late effects; however, an interfraction gap of a minimum of 6 hours is recommended to allow for normal tissue healing, although tissue such as the central nervous system may require a longer period for repair.13, 14 Hyperfractionation allows a higher overall dose to be delivered with the objective of improving tumour control.

Normal tissue responses to ionizing radiation are broadly divided into early and late effects (see Table 45.3). Early effects typically occur during a course of fractionated radiotherapy as a consequence of mitotic arrest of rapidly dividing cells. These are typically transient with resolution of symptoms usually occurring 4–6 weeks following treatment completion unless excessively high doses of radiation have been administered over a short time period, following which, consequential damage may occur as a result of excessive normal epithelial stem cell depletion. The severity of early reactions is influenced by the duration of treatment with shorter overall treatment times leading to increased normal tissue toxicity. Late effects are conventionally defined as normal tissue responses manifesting beyond 90 days from commencing radiotherapy. Late effects may progress over many years and are manifest by tissue fibrosis or, in extreme cases, by radionecrosis. In contrast to early effects, dose per fraction has more influence on the incidence and severity of late effects and late-responding tissues are relatively more sensitive to larger doses per fraction and to high linear energy radiation, for example with neutrons.
while reducing the risk of incurring excessive late damage as exemplified by the EORTC 22791 trial comparing a hyperfractionated schedule of 80.5 Gy given in 70 fractions (1.5 Gy per fraction, two fractions per day) over 7 weeks to a conventional dose of 70 Gy using 35–40 daily fractions in 356 patients with oropharyngeal cancer.15 Five-year local control was increased from 40 to 59 per cent (p = 0.02) with a trend towards increased survival without incurring a higher risk of late tissue damage. The benefit of hyperfractionated radiotherapy over conventional schedules has further been shown by an individual patient meta-analysis of 15 trials involving 6515 patients; this showed a significant survival benefit for altered fractionation schedules, with the benefit being greatest for hyperfractionated radiotherapy.16 Despite promising results hyperfractionated radiotherapy has failed to gain widespread acceptance because of resource constraints and the considerable demands upon patients’ psychological and physical tolerance for undergoing 70 fractions of radiotherapy.

### Accelerated radiotherapy

By delivering more than five fractions per week accelerated radiotherapy reduces the overall treatment time while maintaining the same total dose and number of fractions compared to a conventional treatment schedule with the object of counteracting the negative impact of tumour cell repopulation. A trial of accelerated radiotherapy giving multiple fractions a day was abandoned early due to high rates of grade 4 acute mucosal toxicity,17 while dose reduction in the accelerated arm reduced acute toxicity but failed to demonstrate improved disease-free or disease-specific survival or locoregional control.18

The Danish DAHANCA 68/7 randomized trials involving 1476 patients randomized patients to five or six fractions a week. Acceleration was achieved by treating on the weekend or by delivering two fractions on 1 day with an interfraction gap of at least 6 hours, thus reducing the overall treatment time by 1–2 weeks. There was a statistically significant improvement in locoregional control and disease-specific survival in favour of accelerated radiotherapy, but no overall survival benefit was demonstrated.19 Another study of similar design involving 350 patients failed to demonstrate a significant improvement in local control for accelerated fractionation, however the smaller number of patients in the study may explain the negative results.20 When the next logical step was taken to avoid all weekend breaks by using a 7-day per week treatment schedule, the result was an unacceptable 22 per cent rate of consequential damage. Five-year local tumour control rates were 33 versus 75 per cent and there was a statistically significant overall survival benefit in favour of accelerated radiotherapy.21 Reducing dose per fraction from 2.0 to 1.8 Gy eliminated the phenomenon of consequential damage. Perhaps one of the most important messages from this trial is the demonstration of the criticality of seemingly small changes in radiation dose fractionation.

### Accelerated hyperfractionation

The radiobiological rationale for combining both approaches is two-fold: to overcome the effect of tumour clonogen repopulation and to reduce late tissue damage. A four-arm randomized trial comparing hyperfractionation versus accelerated fractionation with concomitant boost versus acceleration with 2-week rest during treatment versus conventional fractionation demonstrated that both hyperfractionation (81.6 Gy in 68 fractions over 7 weeks) and acceleration with concomitant boost (72 Gy in 42 fractions over 6 weeks) were associated with improved local control rates but overall survival was similar in all arms.22 All three altered fractionation schedules resulted in significantly greater acute but not late side effects. In the EORTC 22851 randomized trial, 512 patients with advanced head and neck cancer were randomized to an accelerated hyperfractionated schedule (72 Gy in 45 fractions over 5 weeks) or to a conventional schedule (70 Gy in 35 fractions over 7 weeks). Hyperfractionated accelerated radiotherapy improved locoregional control by 13 per cent but at the expense of a 14 per cent risk of severe late tissue damage including two cases of radiation myelitis, another example of unacceptable damage resulting from relatively small changes in dose and fractionation.23 Perhaps the most radical approach is exemplified by the CHART (continuous, hyperfractionated, accelerated radiotherapy) trial which, to date, is one of the largest head and neck radiotherapy fractionation trials. Nine hundred and eighteen patients were randomized to either a conventional fractionation (66 Gy in 33 fractions over 6.5 weeks) or a highly accelerated and hyperfractionated schedule (54 Gy in 36 fractions over 12 days). There was no significant difference in control or survival parameters between the control and experimental of the trial,24 however late effects appear to be less for CHART25 suggesting that the overall radiation dose reduction was perhaps greater than necessary. A similar accelerated and hyperfractionated schedule was investigated in the adjuvant setting whereby 70 patients were randomized to receive 46.2 Gy over 12 days: three fractions per day of 1.4 Gy with a 6-hour interfraction interval for 6 days per week or a conventional dose of 60 Gy for 5 days per week over 6 weeks. Improved three-year locoregional control rates (88 versus 57 per cent; p = 0.01) were achieved with the experimental arm but this did not translate into a statistically significant survival benefit (60 versus 46 per cent; p = 0.29).26 Furthermore, both early and late reactions were increased in the experimental arm with the latter considered to have resulted from a higher incidence of consequential damage. The study indicated that optimal results are achieved if the interval between surgery and radiotherapy does not exceed 6 weeks and if the overall treatment time is kept to within 10 weeks.

### Hypofractionation

This refers to the utilization of doses <2.0 Gy per fraction. The total radiation dose is reduced to deliver an equivalent biologically equivalent dose to reduce the risk of late morbidity from radiation treatment. An example of hypofractionated radiotherapy used in the treatment of laryngeal cancers is to deliver 55 Gy in 20 fractions over 4 weeks. Radiobiologically this has the advantage of being able to complete treatment before accelerated tumour clonogen repopulation can occur. Additional benefits include more efficient use of scarce resources and reduced physical and psychological burden placed on patients by reducing the total number of fractions.27 There are currently very few trials addressing the role...
of hypofractionated radiotherapy alone in the management of head and neck cancers.

**Meta-analysis of modified radiation fractionation**

An individual patient data meta-analysis of 15 randomized controlled trials including 6515 patients has demonstrated a statistically significant overall survival benefit of 3.4 per cent at five years in favour of altered fractionation radiation. Median follow up is six years with cancers of the larynx and oropharynx accounting for the most commonly studied tumour sites, of which 74 per cent had stage II–IV disease. The benefit was significantly higher for fractionated radiotherapy (8 per cent at five years) compared to accelerated radiotherapy which offers a 2 per cent gain, but less if the total dose is reduced. The main benefit appears to result from enhanced local tumour control with a smaller effect upon nodal disease.\(^{16}\)

**SYSTEMIC THERAPIES IN THE TREATMENT OF HEAD AND NECK CANCERS**

Concurrent platinum-based chemoradiation remains the standard of care for the non-surgical management of locally advanced head and neck cancers. Platinum-based chemotherapy is also used with radiotherapy for the adjuvant treatment of patients with head and neck cancers where pathological features suggest a high risk of local recurrence. As locoregional control has improved, distant metastasis as the first site of failure has becoming an increasing problem, leading to a renewed interest for the role of neoadjuvant chemotherapy as a strategy for reducing the incidence of distant metastasis and also as a strategy to downstage locally advanced tumours prior to definitive (chemo-)radiation. Targeted therapies, specifically with cetuximab, in combination with radiotherapy in patients where platinum-based concurrent chemoradiation is contraindicated has shown an improvement in overall survival compared to radiotherapy alone. Finally, there is ongoing research into the role of hypoxic cell sensitizers to improve the therapeutic index from radiation treatment of head and neck cancers.

**Hypoxic cell sensitization**

*Cellular hypoxia* decreases the concentration of intracellular oxygen-free radicals and increases resistance of tumour clonogens to radiation therapy.\(^{28}\) It has been shown to be of importance in controlling several cancers, including head and neck cancers. While treatment with hyperbaric oxygen to overcome cellular hypoxia showed initial promise, there has been little subsequent interest in this technique as over half the patients are considered medically unfit for this procedure, which is also complex, time-consuming and costly.

As an alternative, a group of bioreductive nitroimidazole drugs, which mimic oxygen but have greater tissue perfusion characteristics, have been investigated in several prospective randomized trials. Misonidazole and etanidazole both failed to demonstrate overall benefit compared with radiotherapy alone in several phase III randomized trials with any benefit being limited to subset analyses.\(^{29, 30, 31, 32, 33}\) Neurotoxicity was the dose-limiting toxicity for both agents, restricting the dose of the agents that could safely be given, which may account for the negative results in these studies.

Nimorazole is another agent belonging to the same class of drugs but is associated with reduced rates of neurotoxicity and can therefore be given at higher doses despite having a lower sensitizing effect (sensitizer enhancement ratio). It has been shown to significantly improve local control rates when used in combination with radiotherapy in a placebo-controlled phase III randomized study, with an apparent additive effect on haemoglobin concentration.\(^{34}\) While these results show some promise, further investigations are required to confirm their validity. Tiparamazine is a bioreductive agent which undergoes selective electron reduction in hypoxic conditions, forming free radicals which enhance cell death. It has been shown to potentiate the cytotoxic effect of ionizing radiation and of several chemotherapeutic agents including the platinum compounds and taxanes.\(^{35}\) Another approach in an attempt to modify tissue hypoxia has used nicotinamide, which causes vasodilation with the objective of reducing transient or acute hypoxia caused by intermittent vasoconstriction of tumour feeding vessels, and the breathing of carbogen in order to overcome chronic hypoxia, which occurs in cells more distant from feeding arterioles than the oxygen perfusion distance. These agents are well tolerated although nicotinamide can cause impairment of renal function and concomitant administration with nephrotoxic drugs should be avoided. While preliminary results are promising\(^ {36}\) this approach for overcoming tumour hypoxia requires confirmation in large randomized trials.

Anaemia is correlated with reduced local control and overall survival in head and neck cancers.\(^ {37, 38, 39}\) and the effect appears to be independent of the stage of disease. However, the underlying mechanism by which anaemia reduces survival rates remains uncertain and may not be simply related to tissue hypoxia as the same effect has been observed in surgically treated patients and may be an epiphenomenon related to patient performance status. In the absence of a clear explanation for this phenomenon, it is recommended that anaemia should be corrected in any patient undergoing radical radiotherapy for head and neck cancer.

**Concurrent chemoradiation as primary treatment for head and neck cancers**

There is a radiobiological rationale for the synergistic use of chemotheraphy and radiotherapy in the treatment of locally advanced head and neck cancers. Chemotherapy can sensitize tumours to radiation by inhibiting sublethal DNA repair and thus reduce tumour clonogen repopulation, preferentially kill radiosensitive hypoxic cells, sterilize micrometastatic disease outside the radiation field, and reduce tumour bulk which leads to improved tumour reoxygenation. Fractionated radiotherapy can sensitize tumours to chemotherapy by inhibiting repair of drug-induced DNA damage, and decrease tumour mass leading to improved blood supply hence enhanced drug delivery to the target.
While there is a lack of phase III randomized trials comparing concurrent chemoradiation as a sole treatment modality versus surgery, several randomized trials have investigated concurrent chemoradiation versus radiotherapy alone in the treatment of locally advanced squamous cell carcinoma of the head and neck cancer, as well as in nasopharyngeal carcinoma. A summary of these seminal trials is presented in Table 45.4. While associated with increased acute toxicity, concurrent chemoradiation has been demonstrated in these trials to be superior to radiotherapy alone or to induction chemotherapy followed by radiotherapy in terms of improving local control rates. However, not all the trials have shown a survival benefit in favour of concurrent chemoradiation over the alternative approaches. Nonetheless, on the basis of these seminal studies, concurrent chemoradiation remains the standard of care for the management of patients with locally advanced, non-metastatic head and neck cancer. Alternative methods of delivering chemotherapy, for example using a weekly schedule of cisplatin chemotherapy instead of the 3-weekly schedule used currently, have been investigated to alleviate the acute toxicity associated with concurrent platinum-based chemoradiation. Amifostine is a cytoprotective agent which has been investigated in randomized trials to reduce mucositis and xerostomia commonly associated with concurrent chemoradiation.

### Altered fractionation and concurrent chemotherapy

As discussed above, altered fractionation radiotherapy has been shown to be superior to standard fractionation radiotherapy in a meta-analysis of 15 trials. Results of this meta-analysis in concert with the positive results in favour of concurrent chemoradiation over radiotherapy alone led to the development of several randomized trials investigating altered fractionation schedules with concurrent chemotherapy to further improve local control and overall survival. Brizel et al. randomized 116 patients with locally advanced head and neck cancer to hyperfractionated radiotherapy alone (75 Gy in 1.25 Gy twice daily fractions) or the same schedule with two cycles of concurrent cisplatin-based chemotherapy. Patients treated with concurrent chemotherapy had a statistically significant improvement in local control and overall survival. Budach et al. randomized 384 patients with locally advanced head and neck cancer to hyperfractionated radiotherapy alone (75 Gy in 1.25 Gy twice daily fractions) or the same schedule with two cycles of concurrent cisplatin-based chemotherapy. Patients treated with concurrent chemotherapy had a statistically significant improvement in local control and overall survival.

### Table 45.4 Randomized phase III trials of definitive chemoradiation versus radiation in advanced head and neck cancer.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Trial arms</th>
<th>Local control rates</th>
<th>Overall survival rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelstein et al.</td>
<td>Unresectable HNC (n = 271)</td>
<td>RT (arm A) vs CRT (arm B) vs split-course CRT (arm C)</td>
<td>NR</td>
<td>3-year projected: 23% (arm A) vs 37% (arm B) vs 27% (arm C) (NS)</td>
</tr>
<tr>
<td>Forastiere et al.</td>
<td>Stage III/IV laryngeal carcinoma (n = 518)</td>
<td>RT (arm A) vs CRT (arm B) vs C-RT (arm C)</td>
<td>5-year rates: 51% (arm A) vs 68.8% (arm B) vs 54.9% (arm C) (p = 0.002 A vs C) (p = 0.001 B vs C) (p = NS B vs C)</td>
<td>5-year rates: 55% in all three arms (NS)</td>
</tr>
<tr>
<td>Denis et al.</td>
<td>Stage III/IV oropharynx carcinoma (n = 226)</td>
<td>RT (arm A) vs CRT (arm B)</td>
<td>5-year rates: 24.7% (arm A) vs 47.6% (arm B) (p = 0.002)</td>
<td>5.5-year rates: 15.8% (arm A) vs 22.4% (arm B) (p = 0.05)</td>
</tr>
<tr>
<td>Brizel et al.</td>
<td>Advanced HNC (n = 116)</td>
<td>RT (arm A) vs CRT (arm B)</td>
<td>3-year rates: 44% (arm A) vs 70% (arm B) (p = 0.01)</td>
<td>3-year rates: 34% (arm A) vs 55% (arm B) (p = 0.07)</td>
</tr>
<tr>
<td>Budach et al.</td>
<td>Advanced HNC (n = 384)</td>
<td>RT (arm A) vs CRT (arm B)</td>
<td>5-year rates: 37.4% (arm A) vs 49.9% (arm B) (p = 0.001)</td>
<td>5-year rates: 23.7% (arm A) vs 28.6% (arm B) (p = 0.023)</td>
</tr>
<tr>
<td>Al-Sarraf et al.</td>
<td>NPC (n = 147)</td>
<td>RT (arm A) vs CRT (arm B)</td>
<td>Crude rates: 74% (arm A) vs 90% (arm B)</td>
<td>3-year rates: 47% (arm A) vs 78% (arm B) (p = 0.005)</td>
</tr>
<tr>
<td>Wee et al.</td>
<td>NPC (n = 221)</td>
<td>RT (arm A) vs CRT (arm B)</td>
<td>Crude rates: 91% (arm A) vs 92% (arm B)</td>
<td>3-year rates: 65% (arm A) vs 80% (arm B) (p = 0.006)</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>NPC (n = 350)</td>
<td>RT (arm A) vs CRT (arm B)</td>
<td>4-year rates: 68% (arm A) vs 80% (arm B) (p = 0.051)</td>
<td>5-year rates: 58.6% (arm A) vs 70.3% (arm B) (p = 0.049)</td>
</tr>
</tbody>
</table>

CRT, chemoradiation; C-RT, induction chemotherapy followed by radiotherapy; HNC, head and neck cancer; NPC, nasopharyngeal carcinoma; NR, not reported; NS, not significant; RT, radiotherapy alone.
fractionation radiotherapy alone versus altered fractionation radiotherapy with concurrent mitomycin C-based chemotherapy.\textsuperscript{46} Patients randomized to the radiotherapy alone arm in this study received a total radiation dose of 77.6 Gy compared to 70.6 Gy for patients randomized to the concurrent chemotherapy arm. Nonetheless, patients randomized to the concurrent chemotherapy arm also had a statistically significant improvement in local control and progression-free survival. Several other randomized trials have also reported positive results in favour of concurrent altered fractionation chemoradiation\textsuperscript{52, 53, 54} with the exception being a study by Staar \textit{et al.}\textsuperscript{55} in which patients underwent a second randomization to either receive or not receive granulocyte colony-stimulating factor (G-CSF). G-CSF was given to reduce the risk of treatment-related mucositis, and it has been hypothesized that administration of G-CSF may have inadvertently led to stimulation of tumour clonogens. A meta-analysis of 32 trials of altered fractionation radiotherapy with or without concurrent chemotherapy concluded that concurrent chemotherapy was associated with a significant improvement in overall survival regardless of the radiation fractionation schedule used.\textsuperscript{56}

The question as to whether concurrent modified fractionation chemoradiation is superior to conventional fractionation concurrent chemoradiation remains unanswered.\textsuperscript{57} This key issue is being addressed in two large randomized controlled trials in Europe and the United States, the results of which are awaited with great anticipation. The US RTOG 01-29 study is comparing standard fractionation concurrent chemoradiation versus altered fractionation chemoradiation and the European-based GORTEC study is a three-arm study comparing concurrent altered fractionation chemoradiation versus ‘very accelerated’ radiotherapy alone versus standard chemoradiation.

**Adjuvant concurrent chemoradiation for head and neck cancer**

Following surgery for head and neck cancer, the presence of inadequate resection margins, multiple lymph node involvement or extranodal spread predicts for a high risk of local recurrence. Adjuvant radiotherapy has been shown to reduce the risk of local recurrence compared to preoperative radiotherapy.\textsuperscript{58} Results of previously published randomized trials demonstrated superiority of concurrent chemoradiation over radiotherapy alone in the adjuvant setting.\textsuperscript{59, 60} Results of these smaller trials have been confirmed by two landmark trials published simultaneously in 2004. The European-based EORTC trial by Bernier \textit{et al.} randomized 334 patients to adjuvant radiotherapy or cisplatin-based concurrent chemoradiation.\textsuperscript{61} The addition of chemotherapy to radiotherapy resulted in a statistically significant improvement in local control rates, progression-free survival and overall survival. In the US-based RTOG trial reported by Cooper \textit{et al.}, the addition of cisplatin chemotherapy to adjuvant radiotherapy significantly improved local control rates and disease-free survival but not overall survival when compared to radiotherapy alone.\textsuperscript{62} An ‘entente cordiale’ pooling of their results published in 2005 demonstrated a significant survival benefit for adjuvant concurrent chemoradiation in patients with positive margins or lymph node involvement with extracapsular spread.\textsuperscript{63} There was a trend in favour of chemoradiation in patients with stage III–IV disease, presence of perineural infiltration, and lymphovascular invasion.

**Meta-analysis of concurrent chemoradiation in head and neck cancer**

A large number of randomized trials designed to investigate chemotherapy given as neoadjuvant (induction), concurrent (concomitant, synchronous, simultaneous) and, less frequently, adjuvant (following definitive treatment) have now been reported with many of the earlier studies drawing conflicting conclusions, possibly because of small sample sizes and because of the use of less effective chemotherapy agents. Meta-analyses have greatly improved our understanding of the benefit and limitations of these techniques. Results of neoadjuvant and adjuvant chemotherapy are discussed below under Neoadjuvant chemotherapy in head and neck cancer.

The first meta-analysis reported by Stell and Rawson was based upon a review of 23 randomized trials of adjuvant chemotherapy in squamous carcinoma of the head and neck,\textsuperscript{64} none of which were individually large enough to detect the anticipated survival improvement of the order of 5 per cent. Only synchronous and or maintenance trials appeared to confer benefit. Perhaps unexpectedly, cisplatin containing regimens offered no benefit and patients treated with the commonly used vinblasticine, bleomycin and methotrexate regimen fared worse. While the incidence of locoregional recurrence was reduced in the chemotherapy arms, the distant metastasis rate was unchanged. Toxicity was poorly reported in these trials; however, the average mortality rate in nine series was an alarming 6.5 per cent, an unacceptable figure by current standards. A larger meta-analysis of 54 randomized trials published by Munro reiterated Stell’s findings with cisplatin containing regimens once again failing to confer a survival advantage.\textsuperscript{65} However, single agent simultaneous chemotherapy increased survival by 12.1 per cent with a corresponding confidence interval of 5–19 per cent.

Over the last 15 years, many more trials have reached maturity. In 2000 the Meta-analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) collaborative published its first meta-analysis based upon individual patient data, which included almost 11 000 patients from 63 randomized trials.\textsuperscript{66} The same group published, in 2009, an updated meta-analysis involving 17 346 patients from 93 randomized trials.\textsuperscript{67} The addition of chemotherapy to radiotherapy was shown to give an absolute benefit of 4.5 per cent at five years in improving overall survival from head and neck cancer. The same group have performed a meta-analysis of 11 randomized trials in nasopharyngeal carcinoma, and concluded that chemotherapy confers an absolute benefit of 6 per cent at five years in improving survival from nasopharyngeal carcinoma.\textsuperscript{68}

**Concomitant epidermal growth factor receptor inhibition and radical radiotherapy in head and neck cancer**

The epidermal growth factor receptor (EGFR) is a member of the ErbB/HER family of receptor tyrosine kinases.
It possesses an extracellular N-terminal ligand-binding domain, a transmembrane region and a C-terminal intracellular domain which includes the kinase domain and multiple phosphorylation sites.69 The great majority of squamous cell carcinomas of the head and neck express EGFR.70 Activation of EGFR activates intracellular signal transduction pathways which are potent oncogenic regulators of tumour cell growth, invasion, angiogenesis and metastasis.69 High EGFR levels in tumours are associated with adverse outcome and exposure of tumour cells to ionizing radiation increases the level of EGFR expression, the blockade of which increases cell sensitivity to radiation.71,72

Cetuximab is a human–murine chimeric immunoglobulin-G monoclonal antibody that competitively binds to the extracellular domain of EGFR. Phase I and II studies indicated safety and efficacy in head and neck squamous carcinoma and were shown to reverse platinum resistance.73 Bonner et al. undertook a multicentre, randomised controlled trial in which 424 patients with advanced head and neck squamous cell carcinoma were randomized to radiotherapy alone versus radiotherapy with concomitant cetuximab.74 Cetuximab was given initially as a loading dose of 400 mg/m² a week prior to commencing radiotherapy then weekly throughout at a dose of 250 mg/m². Radiotherapy was defined as high dose although the schedules varied according to the trial centre. Daily fractionation to the US of 70 Gy in 35 fractions over 7 weeks was commonly employed as was hyperfractionated and concomitant boost accelerated irradiation. There was a statistically significant overall survival benefit in favour of the cetuximab treatment arm (36.4 versus 45.6 per cent, \( p = 0.018 \)).75 Patients receiving cetuximab experienced more infusion reactions and acneiform skin reactions; patients experiencing at least a grade 2 acneiform skin reaction had a statistically better survival compared to those experiencing a grade 1 reaction. A major criticism of this study remains that the standard arm in the trial was not concurrent chemoradiation which is now accepted as the standard of care in locally advanced head and neck cancer, hence despite clear benefits the use of cetuximab concomitant with radiotherapy cannot be accepted as the new standard of care. It seems unlikely that such a trial will be performed in the future. In practice, cetuximab concomitant with radiotherapy is often reserved for patients with locally advanced head and neck cancer considered not to be fit enough to withstand the rigors of platinum-based concurrent chemoradiation. The RTOG 0522 randomized trial comparing the addition of cetuximab to cisplatin-based concurrent accelerated chemoradiation may provide further useful data for the role of cetuximab in locally advanced head and neck cancer.

Neoadjuvant chemotherapy in head and neck cancer

The rationale for chemotherapy in head and neck cancer was founded upon high response rates observed with a variety of chemotherapy agents including methotrexate, vinblastine, bleomycin, 5-fluorouracil, cisplatin, carboplatin and the taxanes, either alone or in combination. In early studies, chemotherapy was mostly used in an attempt to downstage disease prior to definitive local therapies and to reduce the incidence of distant metastases. These neoadjuvant chemotherapy schedules were initially investigated in non-randomized trials using historical or case-matched controls, which suggested a major advance in overall survival. However, such encouraging results were not subsequently borne out by randomized controlled trials, at least, not until very recently. The issue of using neoadjuvant chemotherapy for ‘organ preservation’ is worthy of note, an approach which was driven by the objective of avoiding ablative surgery in advanced disease. The Veterans Affairs study randomized patients between induction chemotherapy followed by radiotherapy versus surgery followed by postoperative radiotherapy. Those receiving chemotherapy underwent surgery and radiotherapy if a partial response was not achieved. Two-thirds of the patients treated in the conservation arm retained their larynx, although overall survival was the same.76 This trial was heavily criticized for the absence of a radiotherapy alone arm. Consequently, the Intergroup trial R91-11 was initiated, comparing induction chemotherapy and radiotherapy versus concurrent chemoradiation versus radiotherapy alone;77 the addition of chemotherapy reduced the incidence of distant metastases and improved disease-free survival compared to radiotherapy alone; however, there was no difference in overall survival rates between the three arms. Concurrent chemoradiation was significantly superior to induction chemotherapy for organ preservation and local recurrence rates. Similar criticism as for the Veterans Affairs trial can also be levelled at the EORTC trial reported by Lefebvre, which investigated pyriform sinus cancer using a similar strategy resulting in a comparable conclusion albeit with a lower, 35 per cent, rate of pharyngeal preservation.77 These trials are frequently quoted as offering standards of care, but their conclusions should now be reconsidered in the context of the high quality meta-analyses exploring the role of chemotherapy in head and neck cancer.

The latest meta-analysis by the MACH-NC collaborative examined 31 trials of induction chemotherapy involving 5311 patients and a median follow up of 6.1 years.67 Neoadjuvant chemotherapy offers a statistically non-significant absolute benefit of 2.4 per cent at five years (\( p = 0.18 \)). Furthermore, the authors conclude concurrent chemoradiation offers a significantly greater benefit than induction chemotherapy. These results reflect the findings of earlier meta-analyses discussed previously in this chapter.

Reasons for the failure of neoadjuvant chemotherapy in increasing survival from head and neck cancer remain unclear and several hypotheses have been suggested. The concept that tumours treated with chemotherapy may become more aggressive despite apparent down-staging was supported by a study of tumour cell kinetics using flow cytometry in 97 patients with oropharyngeal cancer which demonstrated significantly increased mean labelling indices and shorter potential doubling times following induction chemotherapy compared to pretreatment measurements, particularly in poorly responding tumours.78 Alternatively, the possible benefits of neoadjuvant chemotherapy for responding patients may be offset by the adverse effect of delaying surgery or radiotherapy in non-responding patients. A potential survival advantage may also be eroded by excess mortality associated with the high incidence of intercurrent disease, mainly second tumours and vascular disease, in this group of patients, which may be further offset by toxic related deaths resulting from chemotherapy, which was all
too common in the 1980s. Finally, the chemotherapy schedules used in earlier studies were often devoid of a platinum agent.

As treatment for patients with locally advanced head and neck cancer has improved local control rates, there has been increasing interest in attempts to reduce the rates of distant metastases as a strategy for improving survival from head and neck cancer. While cisplatin with or without 5-fluorouracil has been the mainstay of chemotherapy in head and neck cancer for nearly two decades, the development of newer chemotherapy agents, in particular the taxanes, has offered new scope in the treatment of head and neck squamous carcinoma. This class of chemotherapy agents enhances microtubule formation, thereby suppressing microtubule dynamics required for mitotic function, effectively blocking cell cycle progression resulting in cellular apoptosis. Based on the results of these phase II trials, the TAX 323 and TAX 324 randomized trials investigated the addition of docetaxel to cisplatin and 5-fluorouracil chemotherapy as neoadjuvant treatment in unresectable head and neck cancer. TAX 323 was a European-based trial which randomized 358 patients with stage III–IV squamous cell carcinoma of the head and neck to receive up to four cycles of neoadjuvant chemotherapy with docetaxel, cisplatin, 5-fluorouracil (TPF) (docetaxel 75 mg/m^2, day 1), cisplatin (750 mg/m^2, day 1) and 5-fluorouracil (750 mg/m^2, days 1–5) or cisplatin, 5-fluorouracil (PF) (cisplatin 100 mg/m^2, day 1) and 5-fluorouracil (1000 mg/m^2, days 1–5). Patients with stable or responsive disease then underwent radical radiotherapy. At a median of 51 months, the addition of docetaxel was associated with a statistically significant improvement in response rates to chemotherapy, progression-free survival and overall survival. Surprisingly, quality of life was better in the TPF arm and although there was a higher incidence of grade 3 and 4 neutropenia, thrombocytopenia was less frequent compared to the PF arm.

The TAX 324 was a US-based study and randomized 501 patients to receive up to three cycles of neoadjuvant TPF or PF chemotherapy. While the dose of docetaxel was the same as in TAX 323, patients in TAX 324 received 100 mg/m^2 of cisplatin and 1000 mg/m^2 of 5-fluorouracil in both arms. Following chemotherapy, patients received carboplatin-based concurrent chemoradiation. Once again, the addition of docetaxel resulted in a statistically significant improvement in progression-free and overall survival.

The same combinations of chemotherapy have also been compared in a randomized trial investigating an organ preservation strategy in 213 patients with locoregionally advanced laryngeal and hypopharyngeal cancer. After three cycles, non-responders underwent surgery followed by post-operative radiotherapy while responders underwent radiotherapy. The overall response rates were higher for those treated with TPF, with corresponding laryngeal preservation rates at three years of 70.3 and 57.5 per cent (p = 0.03), respectively, in favour of docetaxel-based chemotherapy.

Hitt et al. reported a randomized phase III trial of 382 patients with locoregionally advanced squamous cancer of the head and neck, randomized to neoadjuvant chemotherapy with cisplatin and 5-fluorouracil or the same regimen with paclitaxel. Following three cycles, patients responding to chemotherapy were treated with cisplatin-based concurrent chemoradiation. The addition of paclitaxel significantly improved response rates and progression-free survival, with a trend towards overall survival.

Results of these trials indicate that both neoadjuvant docetaxel and paclitaxel improve locoregional control and overall survival in patients with locally advanced head and neck cancer. Nevertheless, several unanswered questions remain; how does induction TPF chemotherapy followed by platinum-based concurrent chemoradiation compare to platinum-based concurrent chemoradiation alone? Can taxanes be used safely and effectively concomitant with radiotherapy? What is the optimum management of patients who fail to respond to neoadjuvant TPF chemotherapy? Is there a role for EGFR inhibition in the context of taxane-based neoadjuvant chemotherapy?

### Palliative chemotherapy in locally advanced/metastatic head and neck cancer

Up to two-thirds of patients with head and neck cancer present with locally advanced disease, half of whom relapse within two years of definitive treatment. Ten per cent of patients have de novo metastatic disease. The prognosis for these patients remains dismal with a median survival of seven to eight months. Although the survival benefit of palliative chemotherapy over best supportive care has not been demonstrated in an adequately powered randomized trial, palliative chemotherapy with cisplatin and 5-fluorouracil remains the generally accepted standard of care based on results of several randomized trials. As discussed earlier, there is increasing interest in the role of EGFR inhibition in the treatment of head and neck cancers. While a randomized phase III placebo-controlled trial of 117 patients failed to demonstrate a survival benefit for the addition of cetuximab to cisplatin chemotherapy, a second trial involving 442 patients demonstrated a statistically significant survival benefit for the addition of cetuximab to platinum-based palliative chemotherapy.

### ADVANCES IN RADIATION DELIVERY IN HEAD AND NECK CANCERS

**From two-dimensional planning through conformal radiotherapy to intensity modulated radiotherapy**

The aim of radiotherapy planning is to deliver a homogenous dose to the primary tumour and potential areas of micrometastatic disease while minimizing the dose to the organs at risk. Accurate tumour localization is central to radiotherapy planning and it is important to have the following information to hand: findings of clinical examination including examination under anaesthesia; operation notes and intra-operative findings; relevant histopathology report; results of any radiological investigations including computed tomography (CT), magnetic resonance imaging (MRI) and FDG positron emission tomography (PET) scans.
For more than two decades conventional two-dimensional (2D) planning has utilized standard orthogonal x-ray films taken by a simulator, a diagnostic x-ray machine connected to a television screen which is geometrically identical to the linear accelerator (see Figure 45.1) or cobalt-60 treatment unit. Cross wires mounted in the light beam from the simulator define the size of the area to be treated. As diagnostic x-rays have poor soft tissue resolution the radiotherapist defines the area to be treated on the simulator films using bony landmarks together with clinical and radiological knowledge of the position and extent of the tumour. Resultant volumes are therefore relatively crudely derived from 2D x-ray films with, at best, assumed knowledge of the position of critical soft tissue structures, tumour and organs at risk.

Fast computers introduced in the 1990s permitted the use of CT scanning and other axial slice imaging modalities to allow the radiotherapist to define the tumour and organ at risk using software which permits a three-dimensional (3D) reconstruction of these volumes. The radiation beams should 'conform' as closely as possible to the shape of the tumour, which are by no means simple cuboidal, cylindrical or even spheroidal structures. This is even more exemplified when associated tumour masses coexist in close proximity, for example a primary tumour with locally involved nodes surrounded by normal tissues. The 3D software allows the radiation beams to be shaped by the linear accelerator to achieve this objective hence the term 'conformal radiotherapy' (see Figure 45.2). The software also calculates the dose of radiation delivered to specific volumes of both the tumour bearing target and normal tissue 'organs at risk' and displays these by dose–volume histograms (see Figure 45.3) thus providing the radiotherapist with a tool for determining precise dosimetric information for accuracy of treatment and of risk of damage to normal tissues. While long established in the US and northern Europe, 3D conformal radiotherapy has only recently become available in many UK centres.

3D conformal radiotherapy has undoubtedly been a major step forward. Nevertheless, the radiation beam arrangements are relatively simple and do not permit complex coverage of convex shapes, for example when a high radiation dose curves around an organ at risk such as the spinal cord, brain stem or major salivary glands, as is frequently required in nasopharyngeal irradiation.

The development of intensity modulated radiotherapy (IMRT) is a potential leap ahead. Multiple beams of varying intensities allow the creation of irregular shapes, if necessary with concave contours (Figure 45.4). Most of the data supporting the use of IMRT come from single institution phase II trials; preliminary results have been most encouraging in both squamous cell head and neck cancer and nasopharyngeal carcinoma. The ability to reduce toxicity by avoidance of critical organs at risk, specifically the parotid glands, without compromising tumour coverage and control has been clearly demonstrated. Quality
of life has been shown to be improved when comparing IMRT to 3D conformal radiotherapy by a recent French matched pair analysis cohort study and is the subject of the UK PARSPORT trial. The technology is rapidly gaining a prime position in the treatment of head and neck cancer in the Western world, although disappointingly the UK is once more lagging behind the US and northern Europe. No single imaging modality is entirely accurate and image fusion technology, particularly the use of PET with CT, may improve the ability to define the tumour volume during the process of radiotherapy planning.

Nevertheless, there is a potential downside to IMRT. Since multiple beams are used, often seven or more as compared to two or three with 2D or 3D conformal radiotherapy, a larger volume of normal tissue receives low dose radiation with concerns being raised about the potential of an increased risk of second malignancies.

IMRT is unquestionably a new gold standard, although we must proceed with vigilance. It will undoubtedly be included in future fractionation and combined modality studies with the ultimate aim of achieving even greater enhancement of the therapeutic ratio between tumour destruction and normal tissue tolerance.

**AREAS FOR FUTURE RESEARCH**

Areas for future research are as follows:

- The late effects of recent developments in therapy must be continually monitored and researched.
- Gross tumour target definition requires further investigation and validation of imaging methodologies if we are to use new techniques of more closely targeted radiotherapy (IMRT) safely.
- The efficacy and safety of the combinations and permutations of these new technologies is yet to be confirmed by the following studies:
  - synchronous chemoradiotherapy – 3D conformal radiotherapy versus IMRT (GORTEC 2004-01 trial);
  - synchronous chemoradiotherapy – modified versus conventional fractionation (GORTEC 99-02 and RTOG H029 trials);
  - IMRT or 3D conformal (non-randomized) accelerated radiotherapy + synchronous chemotherapy ± cetuximab (RTOG 0522 trial);
  - role of taxane induction chemotherapy followed by concomitant chemoradiotherapy compared to

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**Figure 45.3** Dose–volume histogram for the plan shown in **Figure 45.2**, demonstrating dose to the target volume and also to the organs at risk.

**Figure 45.4** A radiotherapy plan demonstrating intensity modulated radiotherapy (IMRT) to treat nasopharyngeal carcinoma in a young patient.
concomitant chemoradiotherapy alone (DeCIDE, PARADIGM and GORTEC trials).

- Is there a role for combining EGFR inhibitors such as cetuximab with taxanes and in what sequence?

**KEY EVIDENCE**

The evidence base for most recent developments in non-surgical management of head and neck cancer is of high quality, primarily level I.

**KEY LEARNING POINTS**

- Multidisciplinary team working is essential for ensuring optimum care.
- Commence treatment as soon as possible after diagnosis and staging.
- Avoid treatment interruption.
- Use alimentation support, i.e. percutaneous endoscopic gastrostomy feeding when large areas of mucosa are being irradiated.
- 3D conformal radiotherapy should be a UK standard.
- Modified radiation fractionation confers local control and survival advantage.
- Platinum-based concurrent chemoradiation confers local control and survival advantage.
- Consider use of cetuximab synchronous with radiotherapy in those patients unsuitable for platinum-based concurrent chemoradiation.

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Biologically targeted agents

KEVIN J HARRINGTON

The odds of hitting your target go up dramatically when you aim at it

Mal Pancoast

INTRODUCTION

The non-surgical management of head and neck cancer has undergone a number of significant changes in the last decade. These include: (1) the application of technological advances in radiation delivery as a means of reducing normal tissue toxicity and potentially increasing dose to tumour tissue;1, 2, 3, 4, 5 (2) the clear demonstration of the superiority of concomitant chemoradiotherapy over radiotherapy alone in both definitive6 and adjuvant settings;7, 8 and (3) the identification of some of the molecular biological processes that drive the disease and the development of new therapies that target specifically them.9

Improved understanding of the molecular biology of cancer has fundamentally changed the search for new therapies for malignant disease. Central to this change has been the realization that cancer is a genetic disease that occurs when the information contained in cellular (DNA) is corrupted or decoded aberrantly. These changes are manifest as altered patterns of gene expression which are detected in cancer cells in terms of derangement of normal protein function. In simple terms, the genetic changes that result in the development of cancers can be considered to mediate two general effects: (1) enhancement of the activity of genes that stimulate cell growth, survival and spread and (2) reduction of the actions of genes that repress these processes. As a consequence of these changes, cancer cells acquire the properties that allow them to grow in an uncontrolled fashion, invade adjacent normal tissues, recruit a dedicated blood supply, spread to distant metastatic sites and develop resistance to anticancer therapies.

In this chapter, the key normal cellular processes that are altered in head and neck cancer cells will be described. This essential background information will form the basis of a discussion of the new therapeutic opportunities that are now being assessed in clinical trials and will facilitate an attempt to predict important new targeted treatment combinations for head and neck cancer.

MOLECULAR BIOLOGY OF HEAD AND NECK CANCER

The genetic code

The genetic code is contained in DNA molecules that are packaged in chromosomes in the nucleus of the cell. DNA molecules consist of a sugar-phosphate backbone (deoxyribose sugars joined by phosphate linkages) with each sugar bearing one of four nucleotide bases (the purines adenine (A) and guanine (G) and the pyrimidines thymine (T) and cytosine (C)). Two DNA strands twist around one another to form a double helix with the bases forming hydrogen bonds with specific partners in the opposite strand: A is only able to form pairs with T; C is only able to form pairs with G (Figure 46.1). The helix is wound around nucleosomes, consisting of histone proteins, and is further condensed to form chromatin. The entire genetic code consists of approximately $3.2 \times 10^9$ bases and contains approximately 30,000 genes, which account for only about 1 per cent of the genome. The DNA sequence within a gene comprises so-called exons and introns. The exons represent the protein-coding regions that
are translated at the ribosome, whereas the introns are non-encoding and are edited (spliced) out before translation can occur.

The function of genes is to make proteins and this process occurs in two steps. First, because the DNA code is confined to the nucleus, its information must be carried to the site of protein production by a messenger ribonucleic acid (mRNA) molecule. This process of making a copy of the information in the DNA code is called transcription (Figure 46.2). RNA differs from DNA in two ways: (1) the sugar backbone contains ribose (not deoxyribose) and (2) thymine is replaced by uracil (U). The process by which genetic information is transcribed into mRNA, transported to the ribosome and translated into a cellular protein is complex and subject to multiple levels of control. Regulation of transcription is the key initiating event in the process and is mediated by the interaction between enhancer/promoter elements in the DNA and specific proteins (> 100 individual subunits) that bind to them. At the transcription start site, a DNA-dependent RNA polymerase II is recruited and begins to synthesize an mRNA molecule that is said to be complementary to the coding strand of DNA. This means that the DNA sequence that is being transcribed serves as a template for the production of a specific mRNA molecule, e.g., the DNA sequence CGTATACG becomes GCAUAUGC in the mRNA (note the substitution of U for T in RNA). This mRNA molecule is then subjected to a number of so-called post-transcriptional modifications that include splicing out of introns and processing the ends of the molecule to make it ready for export from the nucleus to the cytoplasm. Many human genes (approximately 60 per cent) can undergo alternate splicing of the mRNA transcripts which means that one gene can give rise to the production of
a number of different protein molecules. Once the mRNA is in the cytoplasm it may be degraded by cellular small interfering RNA molecules (siRNA) before translation occurs. If the mRNA reaches the ribosome, it is decoded into a specific protein molecule through the process of translation, which is based on the fact that groups of three nucleotides represent specific amino acids (e.g. the sequence AUG encodes methionine). It is the protein products of genes that mediate the functional (phenotypic) changes that we recognize as cancer.

Cancer genes

The functions of two classes of genes (oncogenes and tumour suppressor genes) lie at the heart of any understanding of the biology of cancer (reviewed in Ref. 10).

Oncogenes are derived from mutated versions of normal cellular genes (called proto-oncogenes) that encode proteins that control cell proliferation, survival and spread. In normal cells, the expression of proto-oncogenes is very tightly regulated to avoid uncontrolled cell growth. In cancer, abnormalities of proto-oncogenes are responsible for uncontrolled cell division, enhanced survival (even in the face of anticancer treatment) and dissemination. Oncogenes are phenotypically dominant – i.e. a single mutated copy of a proto-oncogene is sufficient to promote cancer – and are almost never responsible for inherited cancer syndromes, with the exception of Ret in hereditary endocrine tumours. Oncogenes can be activated in three ways to cause cancers (see Figure 46.3): (1) gene mutation involves the acquisition of a specific defect in the sequence of a gene such that the gene has enhanced function (e.g. Ras in pancreatic and colorectal cancers); (2) gene amplification occurs when a gene retains its normal sequence – but the gene is multiply repeated in the chromosome (e.g. N-myc in neuroblastoma); (3) gene translocation involves the gene being moved from its normal chromosomal position (locus) to a new position (usually on a different chromosome) where it comes under the influence of a new, more active promoter element (e.g. c-myc in Burkitt lymphoma) or forms a novel fusion protein (e.g. bcr-abl in chronic myeloid leukaemia).

Tumour suppressor genes (TSG) are normal cellular genes whose function involves inhibition of cell proliferation and survival. They are frequently involved in controlling cell cycle progression and apoptosis. TSG are phenotypically recessive – i.e. the function of both copies must be lost in order to promote cancer – and are responsible for inherited cancer syndromes. In familial cancer syndromes, individuals inherit a germ line mutation in one copy (allele) of a TSG such that every cell in the body is affected. It is, therefore, highly likely that at least one cell in the body will suffer complete loss of TSG function because only one copy has to be mutated (so-called loss of heterozygosity). As a result, hereditary cancer syndromes often give rise to multiple cancers at an early age.

The hallmarks of cancer

Hanahan and Weinberg11 described six key changes that occur in cancers and which are largely responsible for driving their malignant behaviour (Box 46.1).

This schema provides a useful way of thinking about the different ways in which cancer can be targeted. However, for individual tumour types, it is becoming clear that some of these processes may represent better targets than others. In the following sections, the individual hallmarks of cancer will

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<th>Box 46.1 The hallmarks of cancer</th>
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<tr>
<td>• Growth factor independence or self-sufficiency</td>
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<td>• Ability to recruit a dedicated blood supply</td>
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<td>• Avoidance of programmed cell death (apoptosis)</td>
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<td>• Insensitivity to anti-growth signals</td>
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<td>• Immortalization by reactivation of telomerase</td>
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<td>• Ability to invade adjacent normal tissues and metastasize to distant sites</td>
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Figure 46.3 Oncogenic activation can occur via three pathways. Normal gene expression leads to formation of normal mRNA and expression of a normal protein in normal amounts. A. Specific mutations in the sequence of the DNA code lead to alterations in the amino acid sequence of the protein, giving it enhanced activity. B. Increased numbers of normal copies of the gene (amplification) result in the formation of increased amounts of normal protein. C. Translocation of part of DNA from one chromosomal location to another can result in the generation of a fusion protein with enhanced biological activity.
be discussed and their potential as targets for therapeutic intervention in head and neck cancer will be reviewed.

**TARGETING GROWTH FACTOR INDEPENDENCE**

A general scheme for the function of growth factor receptors and their ligands in promoting head and neck cancer cell growth (and other effects) is shown in Figure 46.4. In this case, binding of the cognate ligand to the specific ligand-binding domain on the extracellular component of the growth factor receptor (GFR) leads to a change in the shape of the protein that allows it to form a dimer (two protein molecules) with another identical GFR (homodimer) or with other members of the same receptor family (heterodimer). This dimerization process results in the intracytoplasmic domains of the adjacent receptors each adding phosphate groups to tyrosine residues on the other. For this reason, these receptors are known as tyrosine kinase receptors. Phosphorylation of tyrosine residues in the tails of the receptors leads to a cascade of signals via so-called secondary messengers such that the binding of a protein on the cell surface is able to influence the behaviour of the cell. Under normal circumstances, activation of growth factor receptor receptors is very tightly controlled – as is the synthesis and release of the ligands that bind to them. The signalling pathway is normally responsible for regulating physiological cellular processes, such as epithelial tissue development and response to injury.

c-erbB receptor family

One extremely important family of GFR is represented by the c-erbB receptors of the transmembrane type I receptor tyrosine kinase family. This family comprises four members: the epidermal growth factor receptor (EGFR) or c-erbB-1, c-erbB-2/neu/HER-2, c-erbB-3/HER-3 and c-erbB-4/HER-4.12, 13 They consist of a large glycosylated extracellular ligand-binding domain, a hydrophobic transmembrane component and an intracellular domain with tyrosine kinase activity.

Head and neck cancer cells very frequently (> 90 per cent) usurp normal EGFR-mediated signalling pathways.12 By doing so, they are able to gain a growth and survival advantage over neighbouring normal cells. Cancer cells exploit three main strategies for achieving self-sufficiency in growth factors: (1) they manufacture and release growth factors which stimulate their own receptors (autocrine signalling) and those of their immediate neighbours (paracrine signalling); (2) they alter the number, structure or function of the growth factor receptors on their surface such that they are more likely to send a growth signal to the nucleus (even in the absence of the cognate ligand); (3) they deregulate the signalling pathway downstream of the growth factor receptor so that it is permanently turned on (constitutively active).

Squamous cell cancer of the head and neck is probably the most clearly described example of EGFR-driven oncogenesis because this is the dominant signalling pathway responsible for the malignant features of the disease and overexpression has been shown to correlate with poor survival.14, 15 Currently, 12 major ligands with a shared EGF-like motif and affinity for the family of c-erbB receptors are known. The consequences of receptor dimerization and activation and subsequent intracellular signalling provide mechanistic explanations for many of the features that characterize head and neck cancers.16 EGFR is a 170 kDa protein and the founding member of the receptor family.17 In contrast to certain tumour types where EGFR gene amplification or mutation is implicated, overexpression of the receptor, without gene amplification, appears to be the dominant process in squamous cell cancer of the head and neck (SCCHN). Elevated levels of EGFR mRNA and protein and of the ligand transforming growth factor-alpha (TGFα) are present in normal mucosa several centimetres from a malignant lesion. TGFα upregulation is also detectable in pre-invasive lesions and mild dysplasia, consistent with the theory of ‘field cancerization’ due to exposure to environmental chemical carcinogens.18, 19, 20 Upregulation of EGFR is a significant early event in the progression from pre-invasive mucosal dysplasia to invasive head and neck cancer and is most marked in lesions displaying greater dysplasia.20
Several studies have shown links between EGFR overexpression and head and neck cancer oncogenesis and progression. In an experimental xenograft model where highly metastatic sublines were isolated by in vivo selection from nodal metastases, EGFR was one of only 33 differentially expressed genes, showing a two-fold upregulation. A mutated version of EGFR (EGFRvIII) is the most common of seven known variants of EGFR. Deletion of exons 2–7 of the EGFR gene results in a truncated extracellular domain and constitutive activation of the intracellular tyrosine kinase, which continuously triggers multiple downstream phosphorylation cascades. EGFRvIII can associate with and activate wild-type EGFR in the absence of ligand. This particular mutation is common in tumour types such as glioblastoma multiforme and non-small cell lung cancer, and has recently been reported to be present in 42 per cent of head and neck cancers.

The c-erbB-2 receptor is a 185 kDa receptor-like phosphoglycoprotein with no known exogenous ligand. When highly overexpressed it may spontaneously dimerize and autoactivate, but it is more frequently activated by heterodimerization with other erbB receptors. The contribution of c-erbB-2 expression to the pathogenesis of head and neck cancer is less well defined than in other tumour types such as breast and ovarian cancer. However, c-erbB-2:c-erbB-3 heterodimers are potent inducers of the PI3-kinase apoptotic pathway as c-erbB-3 can bind directly to the PI3-kinase p85 subunit. Increasing expression of c-erbB-2 has been shown in parallel with acquisition of a more malignant phenotype in a series of oral carcinomas, which may imply a role in progression.

The distribution of c-erbB-3 protein in tissues is different from that of EGFR and c-erbB-2. It does not have intrinsic tyrosine kinase activity but it can be transphosphorylated by both EGFR and c-erbB2. Its overexpression (but not amplification) has been found in head and neck cancer cell lines and in some cases it has been related to malignant potential. There has been comparatively little investigation of erbB-3 and erbB-4 in clinical samples from head and neck cancers, probably due to the low detection (~10 per cent) in immunohistochemical surveys of clinical specimens. Xia et al. have indicated that expression of all four receptors is associated with shortened survival in patients with oral squamous cell carcinoma, with the combination of EGFR, erbB-2 and erbB-3 (but not erbB-4) giving the greatest prognostic information.

**c-erbB receptor family as a therapeutic target**

c-erbB receptors represent an extremely attractive molecular target in head and neck cancers, because their overexpression in tumour cells offers the prospect of antitumour selectivity (see Figure 46.5). Two classes of drugs have entered clinical trials: (1) monoclonal antibodies (MAB) directed against the extracellular domain of the receptor and (2) small molecules inhibiting receptor tyrosine kinase (TK) activity (so-called TKi). The relative advantages and disadvantages of EGFR blocking agents are detailed in Table 46.1.

**Anti-EGFR monoclonal antibodies**

A number of MAB have been developed for clinical evaluation. They differ from one another in terms of their species of origin (murine, chimeric or fully humanized) and the specific part (epitope) of the target protein that they recognize. Cetuximab (C225, Erbitux) is a human–murine chimeric monoclonal antibody against EGFR which has undergone extensive preclinical and clinical evaluation. In vitro studies have demonstrated antitumour activity against several tumour cell lines through a range of mechanisms including an antiproliferative effect, direct cytotoxicity and the potentiation of the cytotoxic effects of chemotherapy or radiotherapy.

In addition, in vivo experiments have demonstrated anti-angiogenic actions. This agent has been evaluated in early stage clinical trials with favourable indications of efficacy in combination with chemotherapy or radiotherapy. The most significant trial to date reporting on the impact of EGFR inhibition in combination with radiotherapy was conducted using cetuximab in patients with head and neck cancer.

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**Figure 46.5** Vascular endothelial growth factor (VEGF) receptor signalling. VEGF-R can form homo- or heterodimeric complexes that are capable of binding different activating ligands. VEGF-A is the dominant ligand involved in signalling through VEGF-R2 to mediate new blood vessel formation in tumours. Activation of this receptor can be inhibited by binding of the ligand by an anti-VEGF-A antibody (bevacizumab) or by small molecule VEGF-receptor tyrosine kinase inhibitors (VEGF-R TKI).
Table 46.1 Advantages and disadvantages of epidermal growth factor receptor blockade as a therapeutic strategy.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Prevent accelerated repopulation</td>
<td>Stasis in resistant phase of cell cycle</td>
</tr>
<tr>
<td>Enhance apoptotic signalling</td>
<td>Promote tumour hypoxia</td>
</tr>
<tr>
<td>Reduce invasion</td>
<td>Enhance normal tissue toxicity</td>
</tr>
<tr>
<td>Inhibit pro-angiogenic signalling</td>
<td>Off-target systemic toxicity</td>
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<tr>
<td>Inhibit DNA repair</td>
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cancer. Four hundred and twenty-four patients with locally advanced head and neck cancer were randomly allocated to treatment with either radical radiotherapy alone or in combination with weekly cetuximab. The combination treatment arm had significantly improved locoregional control (24.4 months versus 14.9 months; hazard ratio 0.68, \( p = 0.005 \)), improved progression-free survival (hazard ratio 0.70, \( p = 0.006 \)) and improved overall survival (hazard ratio 0.74, \( p = 0.03 \)). Other than a higher incidence of rash and infusion reactions, the grade 3 and greater toxic effects did not differ significantly between the two groups. Further studies are in progress addressing the use of cetuximab in combination with radical chemoradiotherapy in patients with locally advanced head and neck cancer.

Cetuximab has also recently been shown to improve the outcome of palliative chemotherapy in a large randomized phase III study. This is the first new agent to demonstrate an improvement in survival in the setting of relapsed/metastatic head and neck cancer. In this study in 442 eligible patients with untreated recurrent or metastatic SCCHN, cisplatin (100 mg/m\(^2\)) or carboplatin (area under the curve of 5 mg/mL/min) plus 5-fluorouracil (1 g/m\(^2\) per day for 4 days) was administered every 3 weeks for a maximum of six cycles. Two hundred and twenty-two patients received the same chemotherapy plus cetuximab (400 mg/m\(^2\) initially, then 250 mg/m\(^2\) per week) for a maximum of six cycles. Patients with stable disease who received chemotherapy plus cetuximab continued with cetuximab until disease progression or unacceptable toxicity. Adding cetuximab to platinum-based chemotherapy with fluorouracil significantly prolonged the median overall survival from 7.4 months in the chemotherapy alone group to 10.1 months in the group that received chemotherapy plus cetuximab (hazard ratio for death, 0.80; 95 per cent confidence interval, 0.64–0.99; \( p = 0.04 \)). The median progression-free survival time was prolonged from 3.3 to 5.6 months (hazard ratio for progression, 0.54; \( p < 0.001 \)) and the response rate increased from 20 to 36 per cent (\( p < 0.001 \)).

A number of other monoclonal antibodies have entered clinical trials. They include agents such as zalutumumab and panitumumab. These agents differ from cetuximab, which is a chimeric human–murine antibody, in terms of their degree of humanization. Randomized evaluations of these agents in settings that are similar to those in which cetuximab has proven activity are ongoing and are likely to yield interesting and important data in the near future.

Small molecule tyrosine kinase inhibitors

Gefitinib (ZD1839, Iressa\(^5\)) is a low-molecular weight tyrosine kinase inhibitor (TKI) that is highly specific for EGFR. By competing with adenosine triphosphate (ATP) on the intracellular domain of EGFR it has been shown to prevent receptor autophosphorylation, with resultant antiproliferative effects observed in a variety of human xenograft models. Furthermore, combining gefitinib with cytotoxic chemotherapy increases growth inhibition and apoptotic cell death.\(^{45, 46, 47}\)

Four phase I studies have evaluated gefitinib in more than 250 patients, of whom 28 had head and neck cancer.\(^{48, 49, 50, 51}\) Gefitinib was well-tolerated at doses from 150 to 800 mg/m\(^2\), the most frequent grade 1 or 2 toxicities being diarrhoea (47–55 per cent), asthenia (44 per cent) and an acneiform follicular rash (46–64 per cent). Antitumour activity, including both partial responses and cases of prolonged stable disease, was observed at all doses. Clinically meaningful stable disease was achieved in 50 per cent of patients with head and neck cancer, and quality of life ratings also remained stable during treatment, except in one study where they improved significantly over time.\(^52\)

A phase II study has evaluated oral gefitinib (500 mg/day) as first- or second-line monotherapy in 52 patients with recurrent or metastatic head and neck cancer, most of whom had previously received combination chemotherapy or radiotherapy.\(^{53, 54}\) Of these, 47 patients were evaluable for tumour response and an objective partial response rate of 10.6 per cent (one complete response) was demonstrated. Disease control, defined as objective tumour response plus stable disease, was achieved in 53 per cent of patients and was sustained for more than six months in 13 per cent of patients. The response rates and survival times of patients who received gefitinib as first-line therapy were not significantly different to those of patients who had received prior chemotherapy. Overall, the median times to progression and death were 3.4 months and 8.1 months, respectively, with an estimated one-year survival of 29 per cent. These results are more favourable than those achieved with chemotheraphy in this setting, but with the additional benefit of reduced treatment-related toxicity. There was only a single case of grade 4 toxicity (hypercalcaemia), a 4–6 per cent incidence of grade 3 toxicity (anorexia, diarrhoea, nausea and hypercalcaemia), grade 1 or 2 skin rash in 48 per cent and grade 1 or 2 diarrhoea in 50 per cent. A second study using single-agent gefitinib at a dose of 500 mg/day has also been reported.\(^55\) Clinical, symptomatic and radiological response, time to progression, survival and toxicity were recorded. Forty-seven patients were treated and the observed clinical response rate was 8 per cent with a disease control rate (complete response, partial response, stable disease) of 36 per cent. Thirty-four percent of patients experienced a symptomatic improvement. The median time to progression and survival were 2.6 and 4.3 months, respectively. Acneiform folliculitis was the most frequent toxicity observed (76 per cent), but the majority of cases were grade 1 or 2. Only four patients experienced grade 3 toxicity of any type (all cases of folliculitis).

Lapatinib is an oral dual TK inhibitor with action against both EGFR (c-erbB1, HER-1) and c-erbB2 (HER-2).\(^{56, 57}\) It has demonstrated activity both in vitro and in vivo, as well as showing tolerability in phase I clinical trials.\(^57\)
A placebo-controlled randomized phase 0 biomarker study has been performed with this agent in patients with advanced head and neck cancer. A single agent response rate of 17 per cent was reported, with biomarker evidence of significantly reduced proliferation and receptor phosphorylation in the lapatinib-treated group. A phase I dose escalation study of lapatinib administered during radical chemoradiotherapy has been completed in patients with stage III and IV head and neck cancer. Patients were enrolled in cohorts of escalating lapatinib dose: 500 mg, 1000 mg and 1500 mg/day. Patients received 1 week of lapatinib alone followed by 6.5–7 weeks of the same dose of lapatinib plus radiotherapy 66–70 Gy and cisplatin 100 mg/m² on days 1, 22 and 43 of radiotherapy. End points included safety/tolerability and clinical activity. Thirty-one patients were enrolled (seven in each of the 500 mg and 1000 mg cohorts, 17 in the 1500 mg cohort (14 in a safety cohort)). Dose-limiting toxicities (DLT) observed were perforated ulcer in one patient in the 500 mg cohort, and transient elevation of liver enzymes in one patient in the 1000 mg cohort. No DLTs were observed in the 1500 mg cohort. The recommended phase II dose was therefore defined as lapatinib 1500 mg/day with chemoradiation. The most common grade 3–4 adverse events were radiation mucositis, radiation dermatitis, lymphopenia and neutropaenia. No patients experienced drug-related symptomatic cardiotoxicity, and no interstitial pneumonitis was reported. The overall response rate was 81 per cent (65 per cent at the recommended phase II dose). The recommended phase II dose is lapatinib 1500 mg/day with chemoradiation in patients with locally advanced SCCHN, and is associated with an acceptable tolerability profile. Based on these findings, randomized phase II and III studies of lapatinib plus chemoradiation have been initiated. The results of these studies are awaited with interest.

## Targeting Sustained Angiogenesis

In normal tissues, the growth of new blood vessels (angiogenesis) is held very tightly in check by a balance between positive (pro-angiogenic) and negative (anti-angiogenic) signals (see Box 46.2). The growth of cancer deposits is intimately related to their ability to secure a blood supply. A small cluster of cancer cells can grow to 60–100 μm by deriving a supply of oxygen and nutrients by direct diffusion, but beyond this size the fledgling tumour must acquire a dedicated blood supply. Cancers acquire their new blood supply by subverting the balance between pro- and anti-angiogenic factors. Essentially, cancers switch to an ‘angiogenic phenotype’ by upregulating production of pro-angiogenic proteins such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) and/or by downregulating production of anti-angiogenic proteins such as thrombospondin-1, angiostatin and endostatin. Cancer-associated endothelial cells have receptors for both growth promoting and inhibitory factors (Figure 46.5). Binding of cognate ligand to a VEGF receptor on the endothelial cell causes receptor tyrosine kinase activation and downstream signalling to stimulate endothelial cell proliferation, vessel permeability and migration. The net result is formation of new blood vessels. VEGF production in tumour cells is frequently under the control of hypoxia inducible factor (HIF)-1α, which is a transcription factor that is activated by low cellular oxygen tension.

Drugs that target angiogenesis can be classified into two main groups: (1) vascular disrupting agents and (2) anti-angiogenic agents. Vascular disrupting agents cause rapid and selective dysfunction of existing tumour vasculature leading to tumour death. Tubulin-destabilizing agents like combretastatin A4 phosphate and ZD6126 are two such agents. The attraction of these agents is their potential ability to deprive large areas of tumour of a blood supply, with resulting widespread tumour cell death. As such, they are likely to lead to tumour regressions. However, their ability to cause vascular shutdown may also theoretically increase the presence of tumour hypoxia – a factor that is known to be correlated with resistance to standard therapeutics. Anti-angiogenic agents work in a completely different fashion by inhibiting new blood vessel formation, without having an effect on established tumour vasculature. This is achieved by either binding VEGF or inhibiting VEGF-R activation. Bevacizumab (Avastin™) is a humanized monoclonal antibody to the VEGFR ligand VEGF-A. VEGF-R tyrosine TKIs also have anti-angiogenic properties through their ability to inhibit phosphorylation of the tyrosine residues in the cytoplasmic domain of the receptor. A number of small molecule TKIs (SU6668, SU5416 (semaxanib), SU11248 (sunitinib), SU11657, PTK787/ZK222584 (vatalanib) and ZD6474) have shown promise in tumour types other than head and neck cancer. It is highly likely that these agents will be assessed in head and neck cancer in combination with chemotherapy and/or radiotherapy.

As regards the combination of vascular disrupting or anti-angiogenic agents with standard therapeutic agents (radiotherapy, chemotherapy), there are a number of theoretical considerations that might suggest that this approach could be detrimental. For example, depriving a tumour of its blood supply (either acutely by vascular disruption or chronically by reducing angiogenesis) is likely to increase tumour hypoxia – a factor that is known to mediate treatment resistance. However, for the anti-angiogenic agents, Jain and colleagues have suggested that treatment can lead to

### Box 46.2 Pro- and anti-angiogenic factors

<table>
<thead>
<tr>
<th>Pro-angiogenic</th>
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<tbody>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
</tr>
<tr>
<td>Basic fibroblast growth factor (bFGF)</td>
</tr>
<tr>
<td>Acidic fibroblast growth factor (aFGF)</td>
</tr>
<tr>
<td>Transforming growth factors-alpha and -beta (TGF-α, TGF-β)</td>
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<tr>
<td>Platelet-derived growth factor (PDGF)</td>
</tr>
<tr>
<td>Tumour necrosis factor-alpha (TNF-α)</td>
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<table>
<thead>
<tr>
<th>Anti-angiogenic</th>
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</thead>
<tbody>
<tr>
<td>Angiostatin</td>
</tr>
<tr>
<td>Endostatin</td>
</tr>
<tr>
<td>Thrombospondin-1 and -2 (TSP-1, TSP-2)</td>
</tr>
<tr>
<td>Interleukins (IL-1β, IL-12, IL-18)</td>
</tr>
<tr>
<td>Antithrombin III</td>
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</tbody>
</table>

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**Figure 46.5** Binding of cognate ligand to a VEGF receptor on the endothelial cell causes receptor tyrosine kinase activation and downstream signalling to stimulate endothelial cell proliferation, vessel permeability and migration. The net result is formation of new blood vessels. VEGF production in tumour cells is frequently under the control of hypoxia inducible factor (HIF)-1α, which is a transcription factor that is activated by low cellular oxygen tension. **Table 46.2** Pro- and anti-angiogenic factors
normalization of the tumour vasculature – if the dose and duration of treatment lies within certain parameters. The existence of this so-called ‘vascular normalization window’ is supported by experimental data, but not yet by clinical trial findings. In addition, for the vascular disrupting drugs, it is possible that they can be used to trap radiosensitizing compounds or cytotoxic drugs within tumour tissue by collapsing the vascular networks that will serve to wash the drug out of the tissue. In view of both of these rationalizations, there is enormous interest in combining anti-VEGF monoclonal antibodies, VEGF-R TKIs and vascular disrupting agents with radiation and/or chemotherapy.

**TARGETING THE APOPTOTIC PATHWAY**

Normal cells continually audit their viability by assessing the balance of survival (anti-apoptotic) and death (pro-apoptotic) signals that they receive. In normal cells, DNA damage leads to a block in proliferation (cell cycle arrest) while the potential for repair is assessed. If the level of damage exceeds the capacity for repair, the balance of anti- and pro-apoptotic signals tips and the cell undergoes programmed cell death (apoptosis). This prevents maintenance of DNA damage and avoids the risk that mutations will be passed to the progeny of cell division. As such, this mechanism represents a very powerful barrier to the development of cancer.

Loss of normal apoptotic pathway signalling is an extremely common event in cancer. Indeed, two of the best known cancer-associated genes (p53 (TSG) and bcl-2 (oncogene)) are intimately involved in apoptosis. The two main mechanisms of apoptotic signalling (intrinsic and extrinsic pathways) are illustrated in a simplified form in Figure 46.6. Cancer cells are able to evade apoptosis through an ability to ignore signals sent through the extrinsic pathway or by resetting the balance of intracellular pro- and anti-apoptotic molecules in favour of inhibition of apoptosis. By circumventing apoptosis, cancer cells can sustain DNA damage without it causing cell death (unless the damage is to a gene that is absolutely necessary for cell survival). Therefore, cancer cells that have switched off their apoptotic pathway are more likely to be intrinsically resistant to anticancer treatments. In fact, the use of these treatments may promote the accumulation of other mutations that may have a negative influence on the biology of the disease.

Therefore, targeting the apoptotic machinery represents a potentially attractive new therapeutic option in a range of cancers, including head and neck cancer. In general terms, there are two specific strategies that are under investigation: enhancing pro-apoptotic signalling by stimulating the extrinsic pathway and blocking the anti-apoptotic regulators of the intrinsic pathway (Figure 46.6).

The first of these approaches has been assessed preclinically and in early phase clinical trials using both recombinant pro-apoptotic receptor ligands (recombinant human apoptotic ligand 2/tumour necrosis factor-related apoptosis inducing ligand (rhApof2L/TRAIL)) and monoclonal antibodies that can stimulate the DR4 and DR5 death receptors. Agonistic humanized or human monoclonal antibodies against DR4 and DR5 have been tested in phase I and II trials in patients with advanced cancer (other than head and neck cancer). These trials have shown that these antibodies are well tolerated and are capable of producing prolonged stable disease. Clinical studies in which TRAIL-receptor antibodies are being investigated in combination treatment regimens in patients with advanced cancer are ongoing. It is anticipated that the results from a broad spectrum of cancer therapy clinical trials will identify the activity and toxicity profiles of TRAIL death-receptor antibodies as single agents, or in combination with chemotherapy agents or radiotherapy. Studies in patients with head and neck cancer are ongoing and will be reported in the near future.

The second approach to enhancing apoptosis is targeted blockade of anti-apoptotic signalling pathways. This strategy has largely relied on the approach of using antisense oligonucleotides to reduce the expression of proteins such as Bcl-2 in cancer cells. In vitro and in vivo studies in murine models have suggested that targeted reduction of Bcl-2 expression can enhance the therapeutic efficacy of chemotherapy or radiotherapy in head and neck models.
However, this has not yet been tested in patients with head and neck cancer in the clinic. In recent years, another means of blocking anti-apoptotic regulators of the intrinsic pathway has received considerable research attention. This approach is based on blocking the actions of inhibitor of apoptosis proteins. A prime example of this group of proteins is provided by the X-linked inhibitor of apoptosis protein (XIAP) which is a component of the final common pathway that inhibits caspases and suppresses apoptosis. XIAP is overexpressed in many cancer cell lines and cancer tissues and its expression has been correlated with resistance to chemotherapy and radiotherapy and to poor clinical outcome. Inhibition of XIAP can be achieved with either antisense oligonucleotides or small molecule inhibitors. In vitro, XIAP antagonists produce XIAP knockdown and apoptosis which is associated with sensitization of tumour cells to radiotherapy and cytotoxic drugs. In vivo, XIAP antagonists have antitumour effects and sensitize tumours to the effects of chemotherapy. This group of agents is currently undergoing phase I evaluation and may have potential in solid cancers such as head and neck cancer.

TARGETING INSENSITIVITY TO ANTI-GROWTH SIGNALS

There are a number of normal anti-growth signals that counteract the positively acting growth signals described above. Anti-growth signals work either by forcing cells into quiescence (G0 stage of the cell cycle) or by inducing their terminal differentiation such that they are permanently unable to re-enter the cell cycle. Anti-growth signalling is mediated by ligands (e.g. transforming growth factor-beta, TGF-β) that act on cellular receptors (e.g. TGF-β receptor) and send signals to the nucleus via second messengers. These pathways are mainly involved in controlling the cell cycle clock and mediate their effects through proteins that include retinoblastoma protein (Rb), cyclins, cyclin-dependent kinases (CDK) and their inhibitors (CDKi). Abnormalities in anti-growth signalling pathways are extremely common in cancer and play a role in helping cancer cells to progress through the cell cycle. Therefore, loss of Rb and members of the CDKi family and overexpression of certain cyclins and CDK have been shown to occur in a large number of tumour types.

Clinical attempts to target proliferation through cell cycle control are in their very early stages. The cyclin-dependent kinase inhibitor, seliciclib (CYC202; R-roscovitine), has been shown to enhance apoptosis in head and neck cancer cells in preclinical studies. It is the first selective, orally bioavailable inhibitor of cyclin-dependent kinases 1, 2, 7 and 9 to enter the clinic and in a phase I trial in 21 patients at doses of 100, 200 and 800 mg twice daily, it caused dose-limiting toxicities at the 800 mg dose. No objective tumour responses were noted, but disease stabilization was recorded in eight patients. Other similar agents are in development and will enter clinical trials in patients with a range of malignancies, including head and neck cancer, in the coming years.

TARGETING CELLULAR IMMORTALIZATION

Normal somatic cells can only undergo a finite number of cell divisions (Hayflick limit) before they enter a period of permanent growth arrest known as replicative senescence. This process occurs as a result of the cells’ inability to replicate the ends of their chromosomes (the telomeres) fully at each division. Therefore, over time the telomerases get progressively shorter, effectively acting as molecular clocks that count down the cells’ lifespan. In contrast, stem cells and malignant cells have acquired immortality by maintaining the length of their telomeres. In most tumours, this occurs through upregulation of the enzyme telomerase, but in 10–15 per cent of cases a different mechanism, called alternative lengthening of the telomeres, is responsible. Telomerase enzymatic activity involves a large number of proteins, but its two main components are an RNA template (hTR) and a reverse transcriptase enzyme (hTERT); the reverse transcriptase uses the hTR RNA template as a guide in the resynthesis of the DNA sequence of the telomere. Therefore, tumours that have reactivated the expression of telomerase are able to rebuild the parts of their telomeres that they lose with each round of cell division and, so, are able to avoid being sidelined into replicative senescence.

At present, efforts to target the immortalized, stem cell compartment within tumours remains in its infancy. Nonetheless, recognition of the importance of these cells to the overall behaviour of the tumour – in terms of its ability to self-propagate, spread and resist therapeutic intervention – means that active efforts will be made to devise specific targeted therapies against this compartment. Such developments are likely to result in novel approaches to the treatment of a range of tumour types, including head and neck cancer.

TARGETING INVASION AND METASTASIS

Distant metastases cause 90 per cent of cancer deaths. Invasion and metastasis involves careful orchestration of a series of complex biological processes: (1) detachment from immediate neighbours and stroma at the local site; (2) enzymatic digestion of the extracellular matrix followed by specific directional motility; (3) penetration (intravasation) of blood or lymphatic vessels and tumour embolization; (4) survival in the circulation until arrival at the metastatic site that may be chosen on the basis of provision of a favourable supply of appropriate growth factors; (5) it adheres to the endothelium of blood vessels at its destination and extravasates from the vessel; and (6) it begins to proliferate and invade its new location and sets about recruiting a new blood supply.

The development of metastatic disease in locoregional cervical lymph nodes is a hallmark of SCCHN. Such is the predilection of this disease for lymphatic metastasis that patients may present with pathologically involved cervical nodes at any time during the natural history of the disease. The phenomenon of cervical nodal metastasis from an occult primary mucosal site in the head and neck is well recognized. In addition, involved cervical nodes can present synchronously with the primary tumour or metachronously as the first sign of disease relapse. The presence or absence of lymphatic metastasis is the most important prognostic factor for patients with SCCHN. On the basis of this fact, most patients who are diagnosed as having SCCHN will have radiological investigations such as computed tomography (CT) or magnetic resonance imaging (MRI) in an attempt to
identify nodal metastases. Even if these tests suggest that the neck is not involved (clinically node negative or cN0 disease), patients frequently undergo prophylactic treatment of the neck, either by elective neck dissection or radiotherapy, in an attempt to ablate occult micrometastases. Such additional treatment carries a significant morbidity for the patient. For those patients who present with N+ disease, there is a greater risk of systemic metastasis which increases with increasing N stage and involvement of nodes lower in the neck (e.g. level IV compared with level I). Identification of a panel of biomarkers that could predict the likelihood of nodal metastases would represent a useful tool for patient selection for elective or adjuvant treatment of the neck. Alternatively, novel therapies that could reduce the risk of local or systemic metastasis would represent a very significant advance in the treatment of head and neck cancer.

There is evolving evidence that the patterns of metastasis of different cancers to specific organs (e.g. head and neck cancer to cervical lymph nodes; breast cancer to liver, bone and brain; lung cancer to brain and adrenal gland) are not random, but appear to be driven by expression of chemokine receptors by tumour cells that allow them to ‘seek’ a suitable environment in which to establish a colony. Chemokines are small, secreted proteins with characteristic cysteine motifs in their amino acid sequences.77 Most members of the chemokine superfamily have four cysteines and on this basis they have been classified into four groups (CXC or α, CC or β, C or γ and CXC3 or δ) according to the motif displayed by the first two cysteines. Chemokines interact with their cognate receptors which are G-protein coupled, seven-transmembrane receptors.78 Chemokines were initially shown to be involved in controlling the targeted migration of haematopoietic cells, but more recently they have been implicated in a diverse range of physiological and pathological functions including wound healing, the control of angiogenesis and the development of tumour metastases. Indeed, there has been an evolving interest in the role of chemokines and their receptors in the process of tumour metastasis in recent years. A landmark study clearly demonstrated that breast cancer cells that expressed the chemokine receptors CXCR4 and CCR7 were capable of preferentially homing to particular tissues.79

CCR7 is known to be the functional receptor for SLC (secondary lymphoid organ chemokine). It acts by influencing the migration of activated dendritic cells to regional lymph nodes. In a recent study, a strong association was reported between CCR7 expression and synchronous nodal metastasis in patients with tonsillar cancer.80 Only 1 of 11 (9.1 per cent) patients with negative CCR7 immunohistochemistry had nodal involvement at presentation, in contrast to 8 of 13 (61.5 per cent) patients with ‘+’ staining, 24 of 27 (88.9 per cent) patients with ‘+++’ staining and 29 of 33 (87.8 per cent) patients with ‘++++’ staining. Similarly, the degree of CCR7 immunopositivity was directly correlated with the extent of nodal metastasis at diagnosis, such that 43 of 44 (97.7 per cent) patients with N2 or N3 disease had ‘+’ or ‘+++’ immunostaining at diagnosis. CCR7 staining in the primary tumour was also shown to be associated with disease relapse, systemic metastasis and disease-specific and overall survival.

Blockade of CCR7 signalling has been shown to increase the therapeutic efficacy of cisplatin and anti-EGFR therapy in murine models of head and neck cancer.81 Similar effects in a breast cancer model have been reported with blockade of another chemokine receptor (CXCR4).82 Clearly, this is an interesting area for future clinical development, although there have not yet been any clinical trials of targeted anti-chemokine therapeutics.

**CONCLUSIONS**

Despite significant improvements in treatment outcome in patients with SCCHN that have resulted from technological advances in radiation delivery and the use of cytotoxic chemotherapy, there is still a pressing need for novel therapies. In the last two decades, the molecular biology revolution has provided us with a new framework for developing specific targeted therapies. The first major success of this approach was the development of the anti-EGFR monoclonal antibody cetuximab which has been shown to increase control rates in newly diagnosed disease (in combination with radiotherapy) and to prolong survival in relapsed disease (in combination with chemotherapy). This agent is likely to be the frontrunner of a series of new agents that will target specific molecular defects in head and neck cancer. It is likely that the next wave of developments will include active small molecule inhibitors of EGFR (and other members of the c-erbB family of receptors), anti-angiogenic agents and drugs that can increase pro-apoptotic signalling in cancer cells. As with cetuximab, it is most likely that these new agents will first find a niche in the context of combination regimens with standard anticancer therapeutics.

**KEY EVIDENCE**

- The addition of drug treatment (cytotoxic chemotherapy) to radiation therapy has resulted in significant improvements in progression-free and overall survival rates. These data point to the potential benefits of more targeted drugs that can interact with specific hallmarks of cancer to achieve patient benefit.
- Proof-of-principle data for the use of targeted drugs in combination with standard anticancer therapies have been provided by the randomized phase III trial of cetuximab plus radiotherapy. Further studies of agents capable of targeting the hallmarks of cancer are under way.

**KEY LEARNING POINTS**

- The hallmarks of cancer have been described and provide a rational basis for developing novel targeted biological agents for use against head and neck cancers.
- Targeted agents are unlikely to exert significant single-agent activity against head and neck
cancer, but may be active as part of combination regimens with standard anticancer therapies, such as radiation and chemotherapy.

- Studies in which EGFR has been targeted with specific monoclonal antibodies have provided a strong rationale for developing this approach in combination with radiotherapy in patients with locally advanced disease.
- Anti-angiogenic treatments represent attractive potential therapeutics, but their integration alongside standard therapies will require careful evaluation of treatment scheduling in order to avoid the risks of antagonistic interactions.
- Drugs which have the capacity to enhance apoptosis, insensitivity to anti-growth signals and telomerase reactivation all have the potential to increase the activity of radiotherapy and/or chemotherapy.
- Specific drugs capable of targeting the metastatic process are desperately needed as a means of reducing the number of patients who experience systemic disease relapse following successful locoregional treatment.

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INTRODUCTION

Head and neck cancer (HNC) has been portrayed as one of the most devastating cancers. The decision to treat HNC is confounded by the balance of eradicating disease against the cost to the patient's contentment with the consequences of the treatment. Chapter 10, Quality of life, describes the impact of malignancy and the detrimental effects that treatment has on a patient's quality of life. With the commitment to improve survival outcomes for HNC patients, and by aiming to address both the physical and psychosocial concerns following treatment, multidisciplinary team (MDT) working has been the standard for HNC care. MDT working should be an integral part of a health professional's routine in cancer care, and MDT meetings are an essential step for making decisions in the planning of treatment and rehabilitation for HNC patients. Due to this, it is worthwhile familiarizing oneself with the structure, objectives, management and collaboration of the MDT. This chapter focuses on the ‘team’ required for treating HNC, providing an overview of the benefits of MDT working and how the MDT can help reduce patients’ distress using good communication skills. The chapter also expands on the roles of key individuals involved during the different stages of the patient’s journey and, finally, highlights the importance of data collection to provide outcomes which will help future patients.

In the United Kingdom, the Calman–Hine report recommended site-specific MDTs meet regularly to discuss patients and agree on treatment decisions. Multidisciplinary team working ensures the patient receives the benefits and expertise of a range of specialists for their diagnosis and treatment, and that care is given according to recognized guidelines (Box 47.1). Due to HNC being a heterogeneous group of diseases with multifaceted health-related issues, it is recognized that patients may require the involvement of a large team of health professionals from different disciplines (Box 47.2). The MDT gives optimal care for HNC patients by contributing to the decision-making process and addressing a variety of post-treatment issues. Although not all members will be initially involved with the patient and different interventions involving different disciplines may come at different stages during the patient’s pathway, it vital that each member can provide time and expertise for the quality and the continuity of patient care.

For MDT working to be effective, it is important for each member to understand the role of the individuals within the team. This comprehension of the responsibility each member has helps with the cooperation between professionals and ensures that patients receive optimal and timely care. Clarity of the strengths and limitations of the MDT facilitates the communication between specialities and helps create a supportive working environment for the MDT meetings. It can be a difficult balance between working as an independent practitioner and working as a team member with other autonomous professionals. The goal of providing a cure for...
any individual patient may be the common aim of the MDT meeting, but the views on the best way of achieving this may differ. The very nature of HNC means that disagreements about what is in the patient’s best interest will exist between MDT members. Conflicts of judgement should not be seen as negative, since such discussions improve patient care and may highlight the need for further research in a particular area. Teams do not automatically function because a group of professionals have come together. The role of the clinical lead ensures discussion is focused on the patient’s best interest in a composed and respectful atmosphere. The way in which MDT members communicate with the patient can have a direct effect on quality of life. Complicated cases do not always require complex solutions, and the distress experienced by the patient can be managed with good clinical communication skills. Good communication is about the clinician’s and MDT’s adaptable approach to patient care, pre-planning consultation and reflecting on the patient’s and personal experience of the case. Having good communication skills is not something you can read from a script. It can be likened to performing surgery, theoretical knowledge is vital but there is no substitute for practical experience.

Over 30 years of research has shown a key hindrance to a successful consultation is not time, but lack of effective training. Following training focused on eliciting patient concerns, clinicians improve their ability to gather clinical and relevant patient experience data: this leads to more accurate diagnosis, greater doctor–patient concordance, much reduced complaints and an increased likelihood of the patient understanding and following clinical and lifestyle suggestions. In the United Kingdom, 3-day advanced communication skills training workshops approved by the National Cancer Action Team Workshops are open and compulsory to core members of the cancer MDTs. Participants are expected to improve their confidence and skills in advanced communication skills, but also in providing others with constructive and specific feedback on their own communication skills. Good internal communication skills help to achieve a cooperative and effective MDT. Consultations can then be proactively and openly managed.

Patients may not remember all the details about their diagnosis, but they will remember the manner in which the information was conveyed. If the patient feels the consultation is hectic then it may leave an unhelpful and possibly incorrect impression of how their treatment may be. The key is to encourage a therapeutic working relationship with the patient and their loved ones from the first meeting. The aim is to encourage an open, honest and trustworthy rapport.

Box 47.1 Benefits of multidisciplinary team working

- Provides structure to the patient’s pathway
- Formulates consensus about treatment plans
- TMN staging
- Brings together extensive health professional experience
- Improves team communication, coordination and consistency
- Ensures all information and investigations have been completed
- Opportunities for a learning environment
- Reciprocated team support
- Captures data and audits for service improvement
- Highlights research prospect and recruitment to clinical trials

Box 47.2 Members of the head and neck multidisciplinary team (MDT)

- Head and neck consultants
- Consultant oncologists
- Consultant thyroid surgeon
- Radiologist
- Histopathologist
- Clinical nurse specialist
- Palliative care specialist
- Speech and language therapists
- Dietician
- MDT coordinator
- Mental health specialist
- Hospital social worker
- Prosthetic specialist
- Restorative dentist
- Outpatient and ward nursing staff
- Research nurse
- Complementary therapy

CORE CLINICAL COMMUNICATION SKILLS

The way in which MDT members communicate with the patient can have a well-established treatment pathway but the meeting should not simply be a ‘rubber stamp’ exercise. The size of the tumour or the patient’s prognosis does not necessarily determine the level of distress a patient may experience and each case needs to be assessed individually. Sometimes not all the patient’s information is available for the MDT meeting. Logistical problems may occur when obtaining information from satellite centres. Initial investigations may have been inadequate to confirm the stage of the cancer. A decision to treat may be delayed because of concerns about the patient’s capacity to consent for treatment or the ability to cope with the effects of treatment. Further assessment of comorbidities may be necessary before a decision can be reached. Some decisions within the MDT may show that either surgery or radiotherapy may be equally appropriate to offer the patient, and the decision then comes down to informed consent and patient choice. Sometimes the patient may disagree with the MDT’s decision and occasionally ask for a second opinion.
between you and the patient, giving them confidence to share their concerns and feel they have been understood. The purpose of clinical communication is to elicit our patients’ thoughts and feelings and to respond to both with integrity and empathy, providing them with our clinical and human understanding. The goals are to obtain and attend to the patient’s concerns; to agree on their priorities; to tailor our information to their concerns and communication preferences; and to agree with the MDT a joint plan of action. In the process, we can learn how our patients prefer to discuss their condition and try to understand the impact it has on them.

### Before the consultation

Before the consultation it is necessary to:

- Prepare what information might need to be conveyed or obtained, but remember you will be holding back until the patient’s agenda, expectations and concerns are fully elicited.
- Provide a quiet, private space with minimal or preferably no interruptions (no staff coming in halfway through the consultation, no bleeps, mobiles or other calls). A chaotic consultation space will make it impossible for either clinicians or patients to focus on the task in hand. If you are interrupted or the management of your clinic means that intrusion is unavoidable, warn the patient of this before you start. Disruption may tell the patient that you are too busy to listen. This can prevent them raising their concerns. Discuss how you will manage the disruption and when you will continue the consultation.
- Help yourself and your patients by training them to attend your consultations well prepared. Invite them to bring their key issues in writing, as well as a trusted relative or friend, and offer written information about your team and service. Be prepared to reiterate this information in the consultation when necessary.
- Use tools that elicit a wide range of concerns and help them prioritize those for you, such as quality of life measures (see Chapter 10, Quality of life) or the NCCN distress thermometer. Choosing a tool that would be useful to your MDT allows both patients and clinicians to bypass social taboos or blocks, and leads to a more focused discussion of the patient’s key concerns in areas such as family, practical, emotional, spiritual and physical problems.
- Prepare a physical space where you can sit next to the patient, with additional chairs for relatives. Avoid obstacles such as desks. Have writing materials to hand, position them so that both you and the patient can see what you write and use them as a joint planner and record of the consultation. The patient will then be able to see that their concerns are being documented.
- Remember that patients will bring up most of their key concerns in the first 90 seconds of the consultation (the patient monologue), but that we tend to interrupt them after only 17 seconds! Once we have interrupted, we are less likely to elicit their concerns, even if we ask appropriate questions; by then, we have already programmed them not to tell us.

### During the consultation

During the consultation, it is necessary to:

- Welcome your patient and companions in a culturally appropriate manner, inviting them to come in and get comfortable.
- Introduce yourself: name, title, position in the team.
- Find out how they would like to be addressed and who they would like present at the consultation.
- Establish the amount of time available today for your consultation.
- Establish the purpose of the consultation from the patient perspective; clarify the patient’s desired outcome.
- Draw out their concerns and needs prior to the consultation, actively listen to cues about concerns and distress, then explore them tentatively and respectfully: ‘You say you’ve had “terrible pain”. I understand pain itself is very distressing and we will discuss its treatment in a moment. Can I also ask you whether you have concerns about this pain?’ It might be that the pain is made worse by an undisclosed fear of malignancy or recurrences. If that was the case, both the pain and the concern can be addressed.
- Most doctors believe that patients will bring up difficult issues as appropriate, whereas most patients believe they should not bring them up until the doctor has expressed an interest. This leads to most concerns not being discussed. The solution is for the clinician to ask open directive questions that elicit the concerns.
- Once a full history has been taken and the patient’s needs ascertained, summarize your understanding and check it with the patient.
- Align your knowledge to systematically address both their concerns and their information needs.
- Find your balance: patient-centred and respectful but clear and precise as appropriate. Keep your sentences short and clear, your questions even more so.
- Allow pauses for questions, and to check the patient’s and companion’s understanding.
- Timing is everything: as the consultation progresses, new patient concerns will arise; elicit these and the impact on patient and family. Acknowledge them and explore them further as appropriate.
- Signal key transitions in the consultation: i.e. from your information gathering to your delivering, from physical symptoms to key concerns, from impact on the person to that on the family.
- Show your interest in the patient’s understanding by requesting their summary of the discussion so far.
- Find ways of expressing support, or of reinforcing patient coping skills that seem to work for them.
- At appropriate times, check with the patient and family how the communication is going. If it is a difficult consultation, you can acknowledge this and still ask ‘I realize we are talking about a very difficult situation, would it be OK to check how we are progressing?’; ‘Is
there something I am doing that makes this more
difficult?*
• Maintain a culturally appropriate body language
throughout.

### Closing the consultation

When closing the consultation, the following details should
be observed:

• Calmly explore further areas: ‘What issues are important
to you that we have not addressed fully?’, then later:
‘What have we not discussed yet?’ Tone and body
language can convey the difference between genuine
interest, or a rush to finish the consultation.
• It is best to avoid cursory closing questions like: ‘Any
other questions?’, since the negative wording (‘any’) and
the positioning at the end of the consultation are
actually interpreted as cues to end the conversation,
even when we mean to give an opportunity to bring up
further issues.
• Summarize key points, including both clinical and other
worries and concerns. Research using quality of life
measures shows that, if clinicians move beyond the
physical symptoms and discuss patients’ concerns and
quality of life in the consultation, the patients report
being less distressed by their symptoms six months later
(and the consultation lasts the same amount of time).
• List the action points that have been jointly agreed in
the consultation. Identify members of the MDT who
may need to be involved.
• State any actions which are to be taken by you. Identify
any issues you are referring on to colleagues. Also clarify
any action you have agreed the patient or family will
take.
• Set a time to review progress in a future consultation.
• Provide a record of the consultation: written, audio
recording, etc.
• Show your appreciation for your patient’s effort to let
you know about their concerns, whether these are
physical or not.
• If there is no more time but some issues are still
pending, negotiate how they are going to be addressed,
i.e. at a later appointment, with a colleague or other
service.

### After the consultation

After the consultation, the following details should be
attended to:

• When the patient leaves the room, reflect on the
consultation and make a note of issues that were
brought up but not fully addressed so that they can be
attended to next time.
• Get feedback on your strengths and weaknesses from
patients: use questionnaires and patient interviews at
regular intervals.
• Get regular feedback on your strengths and weaknesses
from colleagues, especially after complex consultations:
discuss possible improvements and put them into
practice during your next consultation with that specific
patient, whenever possible.
• Review your own practice by studying video or audio
recordings of successful and unsuccessful consultations.
• Get specialist feedback from professional trainers: this
can be live or through analysis of audio/video
recordings. You can learn which consultations are most
difficult for you and focus on improving them.
• Clinicians need not find the answers to all the patient’s
concerns: most patients will benefit from voicing them
and thinking them through with their clinician. Even
though we are trained to solve problems, it is important
to value the support we can offer our patients to think
through their key concerns. This is likely to lead to an
improved doctor–patient relationship and often guides
the patient to find their own answers.

There are power imbalances in the relationship between the
patient and the MDT that need to be addressed. The patient is
at a disadvantage through the fear and uncertainty that HNC
can create, reducing their confidence, especially at a time when
they are particularly psychologically vulnerable. It is therefore
important that MDT includes a health professional trained in
dealing with the wide range of the mental health issues.

The presence of the clinical nurse specialist at diagnosis is
fundamental to help address the possible disparity between the
information being given by the clinician and the level of
understanding the patient has at this time. The diagnosis and
plan of treatment may need to be discussed at a slow pace,
often with many repetitions, to allow the patient to come
to terms with the situation and give informed consent. The
patient should leave the consultation feeling the discussion
was both compassionate and constructive.

### The role of the clinical nurse specialist

The clinical nurse specialist (CNS) takes a leading role in the
coordination of care for patients coping with a diagnosis of
HNC, any subsequent treatment and supportive care. Many
health professionals are involved in the assessment of each
patient’s clinical, nutritional and psychological state in order
to inform treatment planning and management. The CNS
liaises with them all and also assesses non-medical needs.

At the time of diagnosis and presentation of treatment
options, patients and carers are given a great deal of information
which needs to be presented in an appropriate and
timely way to meet individual needs. This involves informed
discussion between patients and health professionals involved
in their treatment and rehabilitation. The involvement of a
CNS promotes a holistic and organized approach to assessment
and problem solving prior to treatment commencing.
The aim is to help patients and carers gain a realistic
understanding of the treatment involved and the rehabilita-
tion required to achieve an acceptable outcome.

### Support and information giving

It has been suggested that all patients should be offered the
opportunity to see a CNS before final decisions are made
about their disease and its treatment. Many patients are given
Recent research suggests that unmet information needs may contribute significantly to psychological distress. Information should be readily available and be provided by specialist professionals who have good communication skills. The value of good quality written information should not be underestimated. Nurses have an important role in developing and providing this information leading to the potential of improving quality of life. In the early stages, around the time of diagnosis and treatment planning, information is required about the disease, as well as surgery, radiotherapy or chemotherapy. When treatment has been completed, there is a greater need for more supportive information, such as access to practical help and psychological support.

The King's Fund report on HNC care makes clear recommendations regarding information provision as follows:

- People want access to information and advice at all stages of the patient journey: during initial investigations, subsequent diagnosis, throughout treatment and follow up.
- Information should be presented in a timely fashion, with open access a few days after diagnosis in order to have questions answered once the diagnosis has had time to sink in. This illustrates the importance of providing contact details of the specialist support team and arranging a pretreatment appointment for assessment and information giving.
- Information on the impact and side effects of treatment on their lives.
- Information on support services and support groups.

- What to look out for if they suspect a recurrence of their cancer and who to contact.

The CNS assists in many ways during the provision of patient information, from translating medical words and terms into an understandable form to timing the delivery of appropriate written information and suggesting appropriate websites. The CNS will also introduce patient visitors who will talk about their experiences to newly diagnosed patients, and also coordinate patient rehabilitation programmes and support groups.

### Pretreatment assessment

In order to provide information about treatment planning, there needs to be an assessment of each patient’s clinical, nutritional and psychological state. These aspects of care can be considered by the appropriate health professionals in pretreatment assessment clinics. Information gathered can then inform the rest of the MDT when final decisions on treatment planning are made. Key health professionals involved in pretreatment assessment should include a clinical nurse specialist, dietitian, speech and language therapist, specialist/restorative dentist, anaesthetist and an assessment from a mental health specialist.

Following diagnosis, the CNS has a role in coordinating these appointments according to individual needs before the first treatment. A series of meetings is often required to provide timely information and achieve informed consent. When appropriate information is elicited it becomes obvious that many issues require attention and intervention prior to treatment.

### Box 47.3 Areas of assessment

- Presenting symptoms/symptom control requirements
- Comorbidity
- Performance status
- Emotional state
- Psychological state/previous experience
- Existing anxiety and depression
- Alcohol dependence
- Nicotine dependence
- Dentition
- Nutritional status
- Social support network
- Relationships
- Coping skills ability
- Literacy skills
- Financial status/work and professional issues
- Likely equipment requirements
- Previous experience of cancer
- Previous experience of hospitals and treatment
- Anaesthetic assessment
**Referral**

Pretreatment assessment includes communication and liaison with other health professionals both within the hospital and community care setting. This is especially important for patients who will have communication difficulties post-operatively. This may involve the patient being referred to community nursing teams, substance misuse services, smoking cessation services and social and benefit advisors. Social services can be initiated at the pretreatment stage in relation to family care issues or financial problems. Another area of consideration is the provision of medical equipment, such as suction and nebulizer units and communication aids.

**Pretreatment education**

Patients can be helped to cope with a cancer diagnosis and treatment by careful ‘coaching’ from the CNS. The aims of education are to:

- fully inform about all potential treatment options and their anticipated effects;
- facilitate a positive secondary appraisal of a previously perceived threatening situation;
- facilitate pretreatment preparation with information on timing of events and likely outcomes;
- guide the patient and family towards suitable coping strategies.

**Coping ability**

Nursing care should be aimed at developing a therapeutic relationship with the patient and family in order to facilitate the development of coping strategies. Continual contacts with the medical team is necessary to enhance the patient’s feeling of personal control. However, this may be difficult to achieve.

The CNS can act as the front-line point of contact either via the telephone or in the outpatient department to elicit concerns and advise on appropriate interventions, referring on to the medical team if necessary. Essentially, the CNS navigates the patient and family through the system and also assists the patients to cope with the diagnosis, providing quality, individually tailored information to promote understanding of the proposed treatment. Achieving informed consent contributes to long-term coping ability. This process cannot be achieved by a single health professional and requires input from many MDT members.

**Post-treatment considerations**

If patients have been well informed pretreatment, they are likely to recover more quickly. Encouraging self-care promotes a reduction in anxiety. This means that the patient’s perception of control increases and dependence decreases. Research has illustrated that psychosocial problems of head and neck cancer patients change with time following their diagnosis. Medical problems improve with time but psychological problems including anxiety and anger can get worse. Decreased quality of life may reflect patient burnout. This phenomenon may be decreased, if adequate coping skills are acquired.

Patients can also suffer late side effects to treatment which causes further psychological distress. This illustrates the importance of the continued availability of the specialist support team to the patient and carers, so that appropriate interventions can be initiated. It is the role of the CNS to establish a network of health professionals and resources to meet the patient’s needs and requirements at different stages of their disease, treatment and supportive care. Regular outpatient follow up by health professionals, known to the patient, will promote continuity and accurate assessment of changing symptoms.

Pain is a significant problem following surgery for HNC and those who have had both surgery and radiotherapy are more likely to have pain than those treated with radiotherapy alone. On direct questioning, it is evident that a significant number of patients do not use regular pain control medication. With appropriate assessment and advice, nurses can assist patients to manage their pain effectively. Specialist pain teams both within the hospital and community settings should be available if initial pain management interventions have been ineffective.

**Supportive interventions**

After survival itself, patients rate emotional and physical well-being very highly. The use of complementary therapies has grown over recent years, and in many cancer centres forms part of an integrated programme of psychosocial care and support at all stages of the disease.

As previously discussed, for the patient negotiating the stages of investigation, diagnosis and treatment can be an anxious and frustrating time. Once side effects of treatment are subsiding, the threat of recurrence is ever present. The years following cancer treatment can be complicated with physical and psychological difficulties and general well-being can deteriorate. HNC patients find that physical problems can cause significant psychological distress. Indeed, the after-effects, such as dry mouth, taste changes, swallowing difficulties and altered body image have been described as so bad that patients regret ever having had treatment.

The CNS has a role in developing supportive interventions aimed at improving the emotional well-being of the patient, aiming to relieve some of the distress, anxiety, pain and side effects from diagnosis and treatment. If delivered well by appropriately trained and supervised staff complementary therapies, such as reflexology, aromatherapy, acupuncture and massage can be effective in relieving some of the symptoms experienced. It is appropriate to add that complementary therapies provided in a hospital setting are offered to complement medical treatment and not as an alternative.

**THE ROLE OF SPEECH AND LANGUAGE THERAPY**

**Introduction**

Swallowing and communication are two activities that as humans we take for granted. These behaviours are far from...
perfunctory; they are also both highly coordinated and pleasurable. They are ways of being able to express and share enjoyment. For any patient who is limited in their ability to communicate and swallow, social events and, in particular, celebrations have to be coped with in novel and frequently significantly adapted ways. An outsider, or even those familiar with the patient do not easily identify many of the symptoms or feelings associated with the changes that the HNC patient has to tolerate. The patient, in their social environments, should they still choose to try and still be a part of them, may well have to suppress emotions of loss and frustration as family and friends tell them how well they look and how well they are coping.

The assessment and prediction of swallowing and communication abilities for an individual patient is complex. It is part of the team’s responsibility to describe and translate in terms that the patient and their family will understand the current and future effects of the cancer or treatment on the patient’s ability to carry on with their life. Specifically because the anatomical areas that may be most threatened are so involved with swallowing and communication there is a need as part of clinical trials for these functions to be evaluated. Clinicians find it difficult to answer accurately patients’ enquiries as to how they are likely to be affected by the recommended treatment long term.

Members of the MDT are aware how differently HNC patients present with their symptoms. Two patients who may clinically have a similar site and size of tumour can react emotionally and behaviourally very differently to the diagnosis and management of their disease. The results of any assessment may also not truly reflect the patient’s function within their daily life. A patient with little impairment may have poor function and vice versa. Patients’ illness perceptions when diagnosed can explain some of the variance of the quality of life data that are collected. While swallowing and speech are a part of the domains that are measured, there is also an awareness that patients adjust and change with their attitudes over the course of time, so that despite similar function reported by the patient there is a decrease in the perceived difficulty in swallowing a year after treatment.

As members of the team, it is important to remain receptive to these changes and support the patient as they try to maintain what in their terms is an acceptable level of quality of life. The use of disease-specific quality of life assessments has been reviewed. They allow patients at an individual level to score their specific symptoms which must then be acted upon at a clinical level. Such information can help inform and shape the goals of the speech and language therapist (SLT).

Inevitably, as a result of the site and effect of the diagnosed tumours SLTs working with HNC patients are likely to have the opportunity to assess and help patients with their dysphagia and communication needs. The Improving Outcomes Guidelines (2004) produced by the National Institute for Clinical Excellence recommended that as part of the MDT, SLTs should meet and assess patients pretreatment. At whatever stage, the therapist first meets the patient, is important that they are able to assess the communication and swallowing symptoms accurately and have an opinion as to whether there is a way of improving the status of the patient with reference to two fundamental areas of life and function.

### What the research says

As clinicians looking for information with specific reference to swallowing and communication, it soon becomes apparent that there are only a small number of papers that make reference to these functions. Where clinical trials have been conducted and swallowing measured they have been described as crude and non-standardized. The randomized control trial methodology – cause and effect – is difficult to apply to this population. The more complex the topic, the less amenable it is to systematic review because of the multiple comparisons, range of treatments and outcomes that are studied. The heterogeneous nature of the patients and the interaction of some of the effects have been reported. One needs to be mindful that much of the early data did not report on baseline pretreatment information, which means it is difficult to distil what may be a disease effect as opposed to a treatment effect. What is encouraging to note is that the measuring of quality of life and function are being seen as publishable end points alongside mortality statistics. For clinicians the reality is that, as a result of so much variability, informing patients on the likely outcome of their speech and swallow needs to be carried out at an individual level.

### The normal swallow

Swallowing is complex and involves cranial nerves, and the muscles that are innervated by them, transporting a liquid or solid bolus from the oral cavity through the pharynx into the oesophagus to the stomach. The normal process is quick, coordinated, automatic and safe. Tasting and chewing are controlled for the most part by the tongue and the lips, with the oral tongue moving the bolus in a controlled manner around the mouth until it has been manipulated well enough to allow a swallow into the pharynx. There is a need for the build up of pressure in order to move the bolus, and while this is achieved in part by the tongue, the closure of the soft palate, the elevation of the larynx and the adduction of the vocal cords ensure that the bolus whether it is liquid or solid passes, without pooling, or escape into the oesophagus via the criopharyngeus. Elevation and anterior movement of the laryngeal complex allows the criopharyngeal muscle to open, which explains why there can be limited success in performing a criopharyngeal myotomy on the HNC patient. Efficient movement of bolus relies on more than just muscle relaxation.

If one is reminded of the dynamic, precise and strong muscle pattern that is required to swallow safely, and relates the effects of the tumour or the treatment to the process, it is possible to build up predictions as to how the swallow or speech may be affected in general terms which will guide the team in their further assessment.

### The assessment of swallowing

Liaison with members of the nutritional team will allow the MDT to judge whether the patient will be able to maintain adequate calorific intake during their treatment or whether they should be advised to have alternative methods of
feeding. Close liaison with dietetic colleagues allows for the full dysphagic history to be gathered and acted upon.

Assessments fall into two categories:

- Subjective based on observation including bedside assessment and by discussion/case history taking with the patient and their family.
- Objective (flexible endoscopic evaluation of swallowing (FEES) and video fluoroscopy swallowing study (VFSS)) both of which can define the pathophysiology of the swallow and help establish a rehabilitation programme with identifiable goals for the patient.

While Table 47.1, is by no means extensive, from a clinical point of view it highlights the main issues that one will consider when deciding upon which objective measure is best suited to the assessment. The ideal is that both investigations are available and depend on the information which is being sought.

**Swallowing pretreatment**

At pretreatment, HNC patients demonstrate a less efficient swallow. Of the 352 patients assessed using VFSS in this study 59 per cent complained of difficulty swallowing, with those who had oral tumours and smaller tumours less likely to complain of dysphagia. Swallow function was worse for patients with oral and pharyngeal lesions than laryngeal lesions and with increased tumour stage. The conclusions of the study were that the patients, despite their symptoms, had highly functional swallows. In a study that investigated the swallowing function of stage III and IV HNC patients pre-treatment, patients with laryngeal and hypopharyngeal tumours had the most severe dysfunction. This study did not find that swallowing function was correlated with tumour site or overall stage, which would add evidence to the adaption of patients to their dysfunction. In another study of pretreatment speech and swallowing by the use of regression techniques, in a number of patients with tumours of oral tongue and anterior floor of mouth, articulation was significantly reduced. In addition, the percentage of those with oral tongue and tongue base tumours that were also affected also significantly related to swallowing efficiency. While the research does not allow for precise predictions to be made, it underlines the diverse nature of the symptoms and findings that can be identified in patients.

Of course, there is more to swallowing than solely the biomechanical process. Mood (depression, anxiety), change in taste, fatigue, pain on swallowing (odynophagia) and lifestyle will all influence appetite and may mean that a patient is not maintaining their normal weight. It is important for the MDT to bear in mind the different causes of reduced oral intake and to understand these changes within the context of the patient’s normal lifestyle, which may or may not include high consumption of alcohol and tobacco. The pretreatment stage is a valuable opportunity in which there is time to build an informed assessment of a patient’s symptoms and how they might have already adapted to some of the changes caused by the disease process.

**Swallowing disorders after surgery**

If the therapist has seen the patient presurgery, judgements can be made as to how the surgery has impacted upon the patient. The SLT needs to assess the effect of the surgery on the patient’s speech and swallow before the patient starts to

| Table 47.1 Description of flexible endoscopic evaluation of swallow (FEES) and video fluoroscopy swallowing study (VFSS) |
|-----------------|-----------------|-----------------|
| **Assessment**  | **FEES**        | **VFSS**        |
| Description     | View via nasendoscopy swallowing a range of bolus consistencies both liquid and solid | Radiographically image and record swallow of various bolus consistencies mixed with radio opaque material |
| Visualize       | Dynamic view from velum to larynx in colour | Dynamic view of all oral tract structures in black and white from lips through to top of oesophagus. Laterally and anterior/posterior not simultaneously |
| Stage of swallow assessed | Pharyngeal | Pre-oral, oral, pharyngeal and oesophageal |
| Advantages      | Good view of anatomical structures | Able to view temporal nature of swallow |
|                 | Able to check sensation with scope | Good for viewing effect of therapy techniques, repercussions on other stages of swallow |
|                 | Assess pooling of secretions | Silent aspiration evident |
|                 | Good assessment of velopharyngeal wall competence | Objective tool for research |
|                 | Able to view effect of recommended therapy techniques, e.g. good vocal cord closure | No part of the swallow is obscured during the process |
|                 | Repeatable at regular intervals | Well-developed descriptors of swallow |
|                 | Portable | |
| Disadvantages   | Cannot view oral and oesophageal phase | Cannot be taken to the patient |
|                 | If swallow is complete, laryngeal elevation cannot visualize swallow at height of laryngeal elevation 'white out' | Unable to view swallow for long periods, has to be snapshot radiation exposure |
trial oral intake. While in the acute stages of recuperation the need to heal will preclude eating and drinking. The SLT is still able to informally assess the patient’s oral movements and their ability to deal with their saliva. This may include giving the patient an opportunity to try and communicate and give feedback on how they feel about any changes in their communication abilities. It is worth noting that research reports that a tracheostomy tube does not increase the likelihood of aspiration, and that neither the presence of the tube nor decannulation causes a deterioration or improvement in swallowing function. The presence of comorbidities predispose the patient to dysphagia and aspiration rather than the tracheostomy tube per se.53

As a general guide, the larger the resection and the more dynamic the structure resected the more one may expect the speech and swallow to be affected. A study on oral/oral pharyngeal resected patients concluded that the total volume of tongue resected, and percentage of tongue base resected had an impact on postoperative swallowing function.44 In further studies investigating the effect of flaps, patients with comparable site of resection and percentage of oral tongue or tongue base resection had the same or better function if primary closure could be achieved in comparison to those who had a flap reconstruction.45–46

At a laryngeal level, patients requiring a supracricoid laryngectomy are at risk of aspiration, and need the input of SLTs to identify and carry out swallowing and voice rehabilitation in order to prevent repeated aspiration, and to facilitate a return to oral intake and functional voice. Patients need to be carefully selected for the procedure in the knowledge that they are likely to have a period of aspiration after the surgery.47 For patients who undergo a laryngectomy, the presumed outcome has been that they cannot aspirate and therefore have minimal dysphagic symptoms. The incidence of dysphagia for this patient population has been underreported.48 The removal of the larynx results in an increased level of resistance of a bolus to flow through the pharynx into the upper oesophagus. To compensate for this, the patient has to increase the pressure from the tongue to overcome the altered pharynx.49 If there is reduced tongue base pressure, there is prolonged bolus transit times and poor clearance of residue. The effects on the patient’s quality of life and any reduced function are varied, and reduced function does not always lead to reduced quality of life.50 If the disease process is such that there is a need to use a graft or stomach transposition, there may be subsequent dysphagia symptoms for the patient to adjust to.

Swallowing disorders after surgery and radiotherapy

Patients recommended as a result of their pathology to have radiotherapy will experience effects from treatment which may include neuromuscular damage and fibrosis of the irradiated tissues.51 The implications of the treatment are that the oral and pharyngeal stages of swallowing are affected. In a small study of patients who had either had surgery and radiotherapy or surgery, only the latter group were reported to have slower oral transit times, due to xerostomia, greater pharyngeal residue and reduced cricopharyngeal opening due to what is termed a reduction in the pharyngeal bolus driving pressure.52 The same authors further explained the reduction in the pharyngeal bolus driving pressure as a consequence of radiation-induced fibrosis on the soft tissues, and that specifically the affect resulted in reduced tongue base retraction, a decreased bulging of the posterior pharyngeal wall, and a reduced duration of contact of the tongue base to the posterior pharyngeal wall.53

Swallowing disorders from chemotherapy and radiotherapy

Current research now indicates that radiotherapy and chemotherapy can affect the function of patients’ swallow and quality of life issues. The term ‘organ preservation’ seems to have been used because there is not a specific date on which the tumour has been excised. There is plenty of evidence showing both short- and long-term radiotherapy and chemoradiotherapy have an effect on the patient’s ability to return to normal diet.54–56 Based on retrospective analysis of patient data, aspiration is a silent morbidity following chemoradiotherapy, and it is underreported because of the silent nature of the symptom in HNC patients.57 While cure has got to be seen as the main objective of the treatment, it is important for clinicians to discuss with patients that there are going to be some changes in their swallowing abilities. The research remains sparse with information in terms of post one-year treatment, and much of the difficulty in trying to compare the expected effects is that the disease and treatments have many variables. When analysing saliva production post-chemoradiotherapy at 12 months post-treatment, saliva production was found to be significantly decreased which then impacted on the patients’ perceptions of their swallowing ability and therefore their dietary choices.58 In a study that investigated 170 patients who had been treated using both objective and subjective measures, it was the patients three months post-treatment who often had reduced oral intake and had a delayed pharyngeal swallow, incomplete laryngeal vestibule closure, reduced laryngeal elevation and a rating of a non-functional swallow, i.e. demonstrated aspiration, residue within the pharynx and prolonged transit times. Over time at 6 and 12 months, reduced laryngeal elevation and a rating of non-functional swallow remained significant to reduced oral intake, with poor cricopharyngeal opening appearing as a new relationship.59 It is beyond the remit of this chapter to review these data in detail, but the precise nature of the symptoms described would allow a hypothesis-driven treatment plan to remediate or at least minimize some of the symptoms that are being described. In the clinical situation SLTs are moving from merely describing the symptoms to what rehabilitation and compensatory techniques can be used to try and improve the oral intake and communication of the patient.

Speech and language interventions

In a review of swallowing dysfunction and rehabilitation strategies for HNC patients, the behavioural and therapeutic procedures used by SLTs to eliminate aspiration and increase the volume of oral intake are described.60 The
experienced team is aware that there are many variables that will affect a patient’s ability to improve their swallowing and communication. There are essentially two types of rehabilitation that SLTs will use when working with HNC patients, based on the objective and subjective assessments that they have carried out:

- direct compensatory procedures, the aims of which are to reduce or eliminate the risk of aspiration and to control the flow of the bolus.
- indirect therapy exercises to increase the range, strength and stamina of specific muscle groups.

**DIRECT PROCEDURES**

SLTs are recommended to use a hierarchy of techniques so that nutritional quality of intake is not compromised while improving the safety or speed of oral intake. If this can be achieved, the caloric energy spent swallowing is not out-weighing the nutritional benefits of the oral intake. The introduction of a posture-chin tuck, head tilt away from the side of weakness and head rotation to the side of weakness have all been demonstrated to immediately eliminate aspiration in HNC patients. SLTs will discuss with the patient and work closely with dietetic colleagues in order to achieve optimal oral intake using altered dietary consistencies. For some patients having a larger rather than smaller bolus per mouthful can be beneficial, as well as the use of multiple swallows to each mouthful in order to clear the build-up of residue that may occur.

**INDIRECT PROCEDURES**

The use of range of motion and resistance exercises are all therapies designed to improve the strength and control of structure within the oral tract. Swallow manoeuvres (Table 47.2) are an example of teaching and reinforcing to patients that they can have voluntary control over what has hitherto been an automatic function. By altering the timing of a swallow, the neuromuscular sequence for the swallow can be changed. Such techniques do require the patient to have an understanding of their swallowing skills and SLTs are able to describe, explain and reiterate the new behaviours that can allow for successful swallowing or communication.

Swallow manoeuvres have been shown to improve tongue base, posterior motion and pressures generated during swallowing. Part of the SLT’s role is to judge by working with the patient which combination of techniques is going to have the best effect on the patient to enable them to start managing some form of oral intake safely.

**THE ROLE OF PALLIATIVE CARE**

**Introduction**

The World Health Organization (WHO) has redefined palliative care as ‘an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual’. Box 47.4 demonstrates the characteristics of palliative care as described by the WHO. One of the most important points is that palliative care may be as applicable to patients with early cancer as to patients with advanced malignancy, i.e. palliative care is not synonymous with terminal care. Figure 47.1 demonstrates a model of oncological care/palliative care as endorsed by the WHO.

Many of the characteristics of palliative care are also the characteristics of high-quality oncological care. Indeed, the majority of ‘palliative care’ provided by the MDT is provided by the non-specialists within the MDT. However, this provision is not usually viewed as ‘palliative care’, but rather as ‘supportive care’ or ‘holistic care’. The main role of palliative care specialists is to empower the other members of the MDT to provide this type of care: palliative care specialists should

<table>
<thead>
<tr>
<th>Swallow name</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Effortful swallow</td>
<td>Increase the pressure generated by the pharynx and oral musculature during swallow</td>
</tr>
<tr>
<td>Supraglottic swallow</td>
<td>Adduct vocal cords longer to protect airway during swallow</td>
</tr>
<tr>
<td>Super supraglottic</td>
<td>Closes airway entrance before during and after the swallow</td>
</tr>
<tr>
<td>Mendelsohn manoeuvre</td>
<td>Prolongs the opening and increases the diameter of the upper oesophageal sphincter</td>
</tr>
</tbody>
</table>

**Box 47.4 Characteristics of palliative care**

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient’s illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications
provide ongoing education, training and support (physical, emotional) for the other members of the MDT in order that they may provide this type of care. In addition, palliative care specialists should have direct input into the care of patients with complex palliative care problems.

Relevance of palliative care

In the United Kingdom, the incorporation of specialist palliative care services into generic cancer services, and especially into head and neck cancer services, is enshrined within the national cancer framework. Indeed, specialist palliative care professionals are considered to be ‘core’ members of the head and neck cancer MDT. Specialist palliative care professionals may have a role in many aspects of the care of head and neck patients (and their carers). Nevertheless, the major roles involve the management of symptoms, the maintenance of quality of life and supervision of end-of-life care.

SYMPTOM CONTROL

Patients with head and neck cancer may develop a range of different physical problems. Some of these problems are disease specific, while others are not (i.e. present in all groups of patients with cancer). Moreover, patients with head and neck cancer may experience a number of contemporaneous physical problems. These problems may present at any stage of the disease (at diagnosis, during treatment, during remission or during progression) and may even be present following ‘cure’ of the disease. Hence, input from specialist palliative care professionals may be required at any stage of the disease.

The aetiology of physical symptoms includes one or more of the following: a direct or indirect effect of the underlying cancer, as well as the effects of cancer treatment or concomitant disease. Indeed, individual patients may experience a number of different symptoms secondary to a variety of different aetiologies. It is important not to assume that symptoms are always related to the cancer, since this may result in inappropriate treatment of those symptoms. Thus, all physical symptoms should be fully assessed using clinical skills (taking a history, performing an examination) and, where appropriate, relevant investigations.

The management of physical symptoms involves the following: assessment first, then treatment of the underlying cause of the symptom, followed by treatment of the symptom, and then reassessment and (if necessary) secondary referral. Assessment is essential to determine the aetiology of the symptom, and hence the most appropriate form of treatment for the symptom. However, reassessment is also essential to determine the response of the symptom to treatment: the assessment of response should take into account not only the efficacy of the treatment, but also the tolerability of the treatment. If the treatment is not effective, or if the treatment is not tolerated, then an alternative treatment should be initiated. In cases of continued poor efficacy and/or poor tolerability, the patient should be referred for a second opinion, or alternative therapeutic options.

In most cases, the optimal management is treatment of the underlying cause of the symptom. The options for management are influenced by a number of factors, including previous treatment, the patient’s general health/performance status, the patient’s prognosis, and (especially) the patient’s wishes. All reasonable options should be considered, and discussed with the relevant healthcare professionals (e.g. surgeon, oncologist), the patient, and the carers. It should be noted that even at the end-of-life, so-called ‘active’ treatment may be the most effective form of palliation. For example, it may be appropriate to treat patients with bronchopneumonia with antibiotics and physiotherapy in order to improve their symptoms as opposed to trying to prolong their life. A discussion of the management of individual symptoms is beyond the scope of this chapter, and readers are advised to consult the many comprehensive textbooks of supportive and palliative care.

QUALITY OF LIFE

In essence, the aim of palliative care is to provide the best quality of life for the patient. Quality of life is a subjective phenomenon, which encompasses physical, psychological, spiritual and social domains. The importance of these domains varies from patient to patient, and also within an individual patient over time. Thus, it is essential that all of these domains are addressed, and that care is not overly focused on the physical domain.

Calman suggested that quality of life is the relationship between an individual’s expectations and their (perceived) experience in a given situation (Calman’s gap theory). Hence, it is important to communicate honestly with patients about all aspects of their illness, particularly about the likely course of the illness and its prognosis. In advanced disease, the effect of such communication is not to remove hope, but to allow patients to make valued judgements about the best use of their time (i.e. to complete unfinished business, plan for death). The concept of quality of life is discussed in more detail in Chapter 10, Quality of life.

END-OF-LIFE CARE

Overall, the prognosis is relatively poor in this group of patients. The poor prognosis is related both to progression of the malignant disease, as well as to development/progression of associated diseases (e.g. lung cancer, ischaemic heart disease).

Many head and neck patients are hospitalized during the last few months of life, and many remain hospitalized during the terminal phase (see below). For example, a recent study...
from the United Kingdom reported that 53 per cent patients were hospitalized during the last month of life: the reasons for admission included bleeding episodes (17 per cent), pain problems (9 per cent), breathing difficulties (9 per cent), swallowing difficulties (9 per cent), inability to cope (6 per cent) and a fracture (3 per cent).83

In most cases, the terminal phase is relatively straightforward in patients with HNC.79 Thus, it is feasible to consider the option of a home death, particularly as the literature suggests that most cancer patients would prefer to die at home. In such circumstances, it is important that the patient and their families are provided with not only appropriate medical support, but also with adequate practical support (e.g. social services, physical aids). Nevertheless, it appears that most head and neck cancer patients die in hospital, rather than at home or in other care settings.80–82 A recent study from the United Kingdom reported that 62 per cent of patients died in a hospital, 19 per cent died in a hospice, 16 per cent died at home and 3 per cent died in a nursing home.80 There are numerous explanations (but little supportive information) to explain the high rate of hospital deaths (and the low rate of home deaths).82 Nevertheless, a study from Israel reported that patients who died at home tended to be younger and had better symptom control than those who died in a hospital.84

In most instances, head and neck cancer patients die as a result of gradual deterioration in their condition79, 80, 81 Furthermore, as discussed above, the majority of patients have a relatively uneventful terminal phase (i.e. from the health professional viewpoint).79 Nevertheless, in some instances, HNC patients die as a result of an acute complication of their disease (e.g. airway obstruction, haemorrhage), or an acute event not directly related to the disease (e.g. myocardial infarction, pulmonary embolism). Table 47.3 demonstrates the reported cause of death among a cohort of HNC patients admitted to a hospice in the United Kingdom.79

An MDT approach is as valid in the terminal phase of the illness as in the earlier phases of the disease process. This means that while specialist palliative care professionals are experienced in dealing with problems relating to symptom control, they are often less able, for example, to deal with problems relating to tracheostomy tubes or enteral feeding tubes. In addition, the transition from ‘active treatment’ to ‘palliative care’ may be made easier by the ongoing support of familiar healthcare professionals (e.g. CNS in head and neck oncology).

Finally, although the focus of end-of-life care is on the patient, it is important that the needs of the family are not overlooked. Family members often require psychological support during the terminal phase of the illness, but they may also require more practical assistance at this time (e.g. advice on legal matters/financial issues). Furthermore, it is important that ongoing/future problems are identified and that strategies are put in place to combat them. For example, it is possible to identify a person at increased risk of an abnormal bereavement reaction and to arrange appropriate support for such a person following the patient’s death.85

### Table 47.3 Causes of death in head and neck patients receiving palliative care.14

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Number of patients (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive diseasea</td>
<td>17 (47%)</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Massive haemorrhage</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Airway obstruction</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

aCondition gradually deteriorated.

### Quality of Death

Increasingly, the concept of quality of death has been highlighted in the literature. Quality of death, like quality of life, is a subjective phenomenon, which encompasses physical, psychological, spiritual and social domains. Not surprisingly, the concept of a ‘good death’ varies from individual to individual, and may vary within an individual over a period of time. It is influenced by a number of factors including personal circumstances, religion and culture.86 Importantly, there are certain discrepancies between what healthcare professionals and patients and their families consider being a good death.87–89 These discrepancies need to be acknowledged, since they could have implications for the provision of end-of-life care. Steinhauser et al.90 identified factors important for a good death from four groups of people: seriously ill patients, recently bereaved families, doctors and other professionals (e.g. nurses, social workers). The factors that were common to all the groups are shown in Box 47.5. However, a number of other factors were highlighted by the group of seriously ill patients, including being mentally alert, not being a burden, planning funeral arrangements and coming to peace with God.

### Provision of palliative care

In the United Kingdom, the provision of specialist palliative care is relatively comprehensive, although there are significant geographical variations in the type of services available.91 Specialist palliative care services are found in both the primary care setting and also the secondary care setting. For example, in 2006 there were 221 hospice inpatient units, 257 hospice daycare centres, 356 home care teams and 114 ‘hospice at home’ teams in the UK.91 Similarly in 2006, there were 305 hospital support teams.91 It should be noted that the constitution of these services are extremely variable, and the roles adopted by these services are also extremely variable. For example, some hospice inpatient units will provide respite care, while others will only provide admission for symptom control or terminal care.

### Box 47.5 Common factors for a ‘good death’

- Adequate pain/symptom control
- Clear decisions about management
- Being treated as a ‘whole person’
- Making preparations for death
- Achieving a sense of completion
The specialty of palliative care developed as a result of deficiencies in the care of dying cancer patients. The general consensus is that specialist palliative care has improved the end-of-life care of cancer patients, and there is increasing research evidence to back up this impression. However, a significant proportion of cancer patients do not receive specialist palliative care at the end of life. In an attempt to address the latter issue, a number of end-of-life initiatives have been introduced in various countries. In the UK, the Department of Health's End of Life Initiative (www.endoflifecare.nhs.uk) includes support for the Gold Standards Framework in primary care (www.goldstandardsframework.nhs.uk), the Liverpool Care Pathway in secondary care (www.lcp-mariecurie.org.uk) and Preferred Place of Care tools. It should be noted that similar end-of-life strategies have been developed in other countries.

THE ROLE OF DATA COLLECTION

Introduction

The 1995 Calman–Hine Report (a policy framework for commissioning cancer services) identified significant variability in cancer services and care provision in the United Kingdom. These variable outcomes helped shape the National NHS Cancer Plan, and the subsequent National Institute for Health and Clinical Excellence (NICE) report on improving outcomes in head and neck cancers (2004) and more recently 'Improving outcomes: a strategy for cancer'. Recommendations in these documents for improving quality of service provision highlight the importance of clinical data collection and subsequent clinical audit. Audit allows variations in management and outcome to be assessed and helps identify possible contributory factors to these variations, such as inconsistency in standards of clinical practice, variability in resource or differing levels of comorbidity or disease extent. For all head and neck cancer units to be able to contribute to national prospective audit and long-term population-based studies requires the use of a standardized minimum data set.

Evolution of a minimum data set

In April 1999, the British Association of Head and Neck Oncologists (BAHNO) published a National Minimum Data Set to collect the minimum data required utilizing national coding systems, e.g. OPCS4, ICD10 and TNM staging, to allow cross-comparison of care and incorporated the Royal College of Pathologists’ 1998 histopathology minimum data set. The role of data collection

NATIONAL CANCER DATASET

BAHNO actively contributed with other specialist societies to work led by the then NHS Information Authority (now the NHS Information Centre for Health and Social Care (NHISIC)) to deliver the National Cancer Dataset (NCDS).

The NCDS was designed to meet the requirements for:

- local data (research and publication, capacity/demand);
- NHS performance management (ensures national waiting times’ targets are met).

Version 1, published in 2000, included generic data fields applicable to all cancers and was accompanied by a data manual defining all items and codes. The dataset was designed to incorporate events during a patient’s journey, i.e. referral to follow up or death, incorporating diagnostic imaging and procedures, staging and care plan (MDT); surgical and oncology treatments; restorative pathology and included site-specific items relevant to head and neck cancer. A series of updates to the NCDS has been published with a revised version the National Clinical Outcomes dataset to be released in late 2012.

DEVELOPMENT OF NATIONAL CANCER AUDIT

The National Clinical Audit Support Programme (NCASP) originally commissioned by the Healthcare Commission (formerly CHI) was initiated in 2001 to deliver national comparative audit based upon the NCDS subset for head and neck cancer. NCASP also supported professional bodies working in lung cancer (LUCADA), bowel cancer (NBOCAP), oesophagogastric cancer (NOGCA) and mastectomy and reconstruction (NMBRA).

NCASP AND BAHNO

In 2002, agreement was reached for BAHNO together with a multiprofessional Head and Neck Clinical Reference Group to work with NCASP to develop a collaborative approach to national audit, and in 2004 a head and neck national database, DAHNO (Data for Head and Neck Oncology), was deployed in England. Data were received from Wales for the first time in 2006, collected via transfer from the Cancer Network Information System Cymru (GaNISC). The DAHNO project aims for secure centralized data collection, rapid comparative reporting, mortality and data quality tracking, and works towards providing the public and commissioners with access to risk-adjusted comparative clinical audit data, as well as assurance of multiprofessional care provision.

The first phase of DAHNO included all patients with a new diagnosis of squamous cell carcinoma of the oral cavity or larynx. Phase II extended the anatomic sites to include pharynx (naso-, oro- and hypo-) and major salivary gland, and additional data fields relating to specialist nursing, nutrition, swallowing and surgical voice restoration.

The fledgling first annual report published by DAHNO in 2006 showed 1038 cases which compares to 25 per cent of the expected total in England. Subsequent annual reports have shown steady improvements in case ascertainment, and included Welsh data. The sixth (2011) report includes 95 per cent of the expected total for England and Wales, some 6400 cases, with submission from all but two trusts delivering head and neck cancer care. The main findings of the sixth annual report are: improved assurance of delivery of multiprofessional care, increased levels of T and N pretreatment staging and risk factor recording, and improvements were seen in the length of time patients waited for key aspects of care. Delays to radiotherapy remained a challenge.
Key case-mix factors considered in DAHNO are:

- age and sex (patient demographics);
- deprivation (derived from area of residence at time of diagnosis);
- comorbidity using the ACE-27 comorbidity index (presence and level of decompensation from other illnesses);
- performance status using ECOG (ability to perform tasks of daily living);
- stage at presentation using UICC TNM staging at time of treatment decision (to include presenting site, histological type and anatomic extent of disease).

The initial DAHNO reports concentrated on timeliness and delivery of pathway processes and provision of multidisciplinary assessment, but in the sixth report variation in the delivery of care pathways (e.g. early larynx treatment) have been examined. Future reporting will move to look at case-mix adjusted outcomes in order to clearly identify areas of good and poor practice with a view to improving overall patient care. To be able to accurately draw comparative conclusions, it is very important for contributors to include case-mix factors so that ‘like’ can be compared with ‘like’.

THYROID CANCER AND NATIONAL AUDIT

While a National Cancer Dataset has been derived for thyroid cancer, this has not as yet been translated into a national comparative audit. In thyroid cancer, there are significant differences in clinical pathways compared with those of other sites within the head and neck. Thyroid cancer is a much rarer cancer with a better prognosis and, usually, a longer diagnostic pathway and follow-up period. In most cases, the first definitive and curative treatment for thyroid cancer is a diagnostic hemi-thyroidectomy which inevitably means the data have to be collected retrospectively and the patient will not be discussed at MDT until after the first treatment. The British Association of Endocrine and Thyroid Surgeons (BAETS) has maintained a national clinical audit database covering thyroid, parathyroid, adrenal and pancreatic surgery which also encompasses benign thyroid cases. BAETS membership is not mandatory for surgeons who perform endocrine surgery and therefore analysis may not provide a reliable picture of national practice. However, if a surgeon is a member of BAETS, then it is compulsory to participate in the national audit. The third national audit report was published in 2009. Clinical data are entered via a secure web browser-based database and the annually updated data set is informed by current evidence-based clinical practice. The database facilitates anonymised analysis on clinical outcomes and practice, as well as a demographic analysis of disease incidence. The National Cancer Intelligence Network (NCIN) (www.ncin.org.uk) is currently actively engaging clinical groups who manage thyroid cancer to facilitate a process to enable audit in thyroid cancer.

CLINICAL AUDIT AND PEER REVIEW

The National Cancer Peer Review Programme seeks to support quality assurance and enables improvement of services in head and neck cancer. A group of peer reviewers performs assessment of compliance by cancer networks and individual units against a set of detailed measures (standards of service). The outcomes of the peer review programme aim to identify shortcomings in the quality of cancer services where they occur, so that rectification and improvements can be made and confirm that services are of approved quality. The 2011 peer review round has, for the first time, included Clinical Lines of Enquiry (www.cquins.nhs.uk), which take findings from DAHNO, as well as identifying additional local areas for audit. These aim to provide a greater focus within peer review on clinical issues, and to span different professional contributions along the patient pathway.

Cancer waiting times’ targets, December 2005

As from the first quarter of 2006, it became mandatory for all trusts to report waiting times for all their newly diagnosed cancer patients. This was for government monitoring of targets from referral to first definitive treatment for patients with suspected cancer referred urgently by their general practitioner (62 days) and from decision to treat to first definitive treatment for all sources of referral (31 days) (Figure 47.2). This required patient pathways to be streamlined resulting in reduced waiting times for diagnostic tests and changes in the way hospitals work together. An additional benefit is greater focus on cancer data collection, as the only way for hospitals to monitor where patients are on their pathway and how long they have before the targets are breached, is to collect data on each patient.

The continuation of cancer wait times monitoring was affirmed in ‘Improving outcomes: A strategy for cancer’ (2011). 95

Key principles of data collection

BEST PRACTICE

Currently, units use combinations of data collection methods including paper pro formas and expansion of current outpatient notation forms; direct data entry to DAHNO or commercial databases; uploads to DAHNO from a third-party patient clinical information system or custom-made Microsoft Access databases or spreadsheets, and creation of automatic links to existing electronic hospital information systems. Best practice workshops have confirmed that the most successful will be led by one committed individual whose role is to promote and oversee collection, collation,
quality control and analysis of head and neck data. This individual can be a clinician or an administrative data manager, an MDT coordinator or medical secretary. Certainly, multidisciplinary team support and direct involvement of members is crucial as clinical data include everyone involved in the patient’s journey. The dilemma is not only about where and how to collect the data, but who is going to input the data, as every member of the multidisciplinary team will inevitably have a busy workload. Often the person who leads the data process is one who has an avid interest in technology, and has a keen desire to see and act on the results of cancer information and strives to attain the highest standards of patient care by the team.

**TRUST-WIDE STRATEGY**

In an ideal situation, a trust-wide strategy should be developed to use the same software for data collection which will inevitably prevent repetition, inconsistency and misinterpretation of core data. In this way, data can be shared and used for different purposes, such as cancer waiting times’ data measuring and monitoring the 14-, 31- and 62-day waiting times’ targets; national audits; local clinicians’ use for research, audit and management; and audits of local demand and activity, etc. IT departments should be involved in linking the database to existing hospital electronic information systems, such as patient information systems, radiology and pathology systems, oncology tracking systems, etc.

**MULTIDISCIPLINARY TEAM MEETING**

The multidisciplinary team meeting to discuss a patient’s care plan is the central focal point for decision and planning, at which time all professionals involved with each patient should be present. Data on diagnosis, morphology, tumour site and clinical pretreatment staging, comorbidity, performance status, social history and risk factors should be available. This is the ideal time to raise, capture and identify any missing data while the appropriate personnel are all together and any ambiguous data items can be discussed. An individual team member should be responsible for recording and this can be a data manager, MDT coordinator, secretary or clinician. The lead clinician should ensure that all the data required and the care plan are made clear and that there are no missing data at this point, before proceeding to the following patient.

It is imperative to use the NHS number wherever possible as it is this identifier which will be used in national audit. To encourage individuals to input data to a database, rewards in the form of automatically generated correspondence such as discharge letters, GP letters, monitoring reports, MDT meeting lists and minutes, monitoring and tracking reports should be incorporated. Wherever possible, prospective data collection at source should be the ultimate goal, since retrospective data gleaned from hospital notes is time-consuming, may lead to misinterpretation and will be of lesser quality to data collected prospectively. It is essential that any database is networked across the hospital so that any number of individuals can contribute to the database at any time by adding their contribution to the patient record. This will also mean data are secure and backed up.

The clinician should be able to trust the data being collected and this can only be gained by clinical ownership and direct involvement in the process. In reality, not every single item needs to be checked (signed off), but each consultant should be satisfied that the patient record makes clinical sense and the diagnosis, pretreatment staging, clinical status and care plan information are correct, and that subsequent audit submissions are valid. Collection of clinical data must not be viewed solely as an administrative exercise, but as an integral part of the clinician’s role, and for national comparative audit to be successful, clinical audit contribution should be an aspect included within everyone’s appraisal and personal development.

**KEY EVIDENCE**

*The role of speech and language therapy*

- The gold standard of research methodology – the randomized control trial design – is not well suited to the study of HNC patients’ swallowing and communication difficulties. Disease, patient and treatment variables impinge upon the cause and effect paradigm.
- As members of the MDT, SLTs are well placed to assess and review the impact of the disease and treatments on patients both in terms of changes to the oral tract and the impact on quality of life.
- While it is wholly appropriate to review the literature with reference to the impact of disease and treatment on patients’ function, it is also essential that clinical judgement at an individual level is maintained in order to explore the interaction of the patient’s adaptive practices to the symptoms that they present with.

*The role of data collection*

- National comparative head and neck cancer audit is established across the NHS in England and Wales.
- The future agenda in cancer audit has been set out in ‘Improving outcomes: A strategy for cancer’ (2011). Recommendations for improving quality of service provision highlight the importance of clinical data collection and subsequent clinical audit.

**KEY LEARNING POINTS**

*The role of the clinical nurse specialist*

- The clinical nurse specialist (CNS) is a core member of the multidisciplinary team.
- The CNS is key to the coordination of care for the patient and a point of contact for them, the family and carers.
Multidisciplinary team working

The role of speech and language therapy

Swallowing and communication may be affected by either the disease, the treatment directly or the patient’s reaction to the changes that are enforced.

Swallowing is timed and coordinated, and patients show adaptive behaviours prior to treatment. SLTs work as integral members of the MDT and relate closely with many members of the team on a daily basis.

SLTs are well placed to offer ongoing assessment, management and support to the HNC patient which is so much more easily achieved if they are able to meet the patient at the pretreatment stage.

Research needs to be seen in the context of the individual patient because each patient will present with a unique set of variables that the team have to work with.

The larger the resection required and the more dynamic the structure affected, the more dysphagic or communication difficulties are predicted.

Radiotherapy and chemoradiotherapy may impact on the coordination of swallowing and speech in the short or long term as a result of the fibrosing of soft tissues.

Objective and subjective assessments will help devise strategies which include postures, changed consistencies, swallowing manoeuvres and exercises to start or safely maintain oral intake and communication.

The role of palliative care

Palliative care involves the management of the physical, psychological, spiritual and social complications of cancer.

Palliative care is not synonymous with terminal care.

Palliative care may be applicable to patients with early disease.

The role of data collection

Clinician confidence in the data being collected, can only be gained by clinical ownership and direct involvement in the process, and should be seen as an integral part of the clinician’s role.

The multidisciplinary team meeting to discuss a patient’s care plan is the central focal point for decision and planning and is an ideal point at which data can be collected at which time all professionals involved with each patient should be present.

The NHS number should be recorded for all patients as it is the key linkage in assimilating information from different sources.

A trust-wide strategy for cancer information is the preferred route to allow use of the same software for data collection which will inevitably prevent repetition, inconsistency and misinterpretation of core data.

The recent introduction of Clinical Lines of Enquiry aims to provide a greater focus within peer review on clinical issues, and to span different professional contributions along the patient pathway. The national lines of enquiry use information from DAHNO.

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RECONSTRUCTION

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Every act of creation is first an act of destruction.

Pablo Picasso

INTRODUCTION

In head and neck surgery, there are several reconstructive principles. We should aim to replace like with like, there should be movement where movement is needed, we should use thin pliable tissue when mobility is important and bulk where filling is required. Static supports may be needed when tissue ptosis is likely to be predicted and colour matching with excellent tissue handling skills are required to achieve cosmesis, epithelial cover should be robust and we should consider the need for potential future surgery to ensure we keep our options available and not ‘burn any bridges’. Lastly, and perhaps most importantly in the twenty-first century, it behoves the contemporary plastic surgeon to be mindful of the need to keep at the forefront of his mind the need to minimize donor site morbidity. Head and neck reconstruction encompasses plastic surgery of the oral cavity, the oropharynx, the pharynx, the midface and bones, complex aesthetic structures, the head and neck skin and facial reanimation.

HISTORY OF HEAD AND NECK RECONSTRUCTION

Historically, the cheek flap and the forehead flap were probably the first flaps described for head and neck reconstruction. The cheek flap was first described for nasal reconstruction by Sushruta in 600–800 BC, and so plastic surgery as a specialty was born over 2000 years ago in India, as was the specialty of head and neck reconstruction. In his book, the Sushruta Samhita (roughly translated as Sushruta’s Compendium), Sushruta wrote detailed notes on nasal reconstruction. In India at that time, the nose was seen as a symbol of dignity and respect. Prisoners, adulterers and other criminals would have their nose amputated as punishment. Sushruta described the use of a template made from a leaf which was then placed on the cheek from where the flap was raised. The cheek rhinoplasty flap of Sushruta was later modified by using a forehead flap, based probably on the supratrochlear vessels or midline forehead vessels and became known as the traditional method of Indian rhinoplasty. It was when British surgeons working in India saw the results of Indian rhinoplasty on a man called Cowasjee that the procedure was described in the Madras Gazette and the October 1794 issue of the Gentleman’s Magazine of London. The first reported case of an Indian rhinoplasty in the Western world was performed by Joseph Constantine Carpue in 1815 and the procedure gained popularity subsequently within Europe and the USA. Nasal reconstruction also formed the basis of the pedicled medial arm flap, described by Gasparo Tagliacozzi who lived between 1546 and 1599 in Bologna in Italy. He described the procedure in his manuscript De Curtorum Chirurgia Per Insitionem, noting that the skin of the medial arm was thin and had few hairs. He described a multistage technique in which skin of the medial arm was raised as a bipedicled flap, the donor site was left to heal, the flap was then attached to the defect in the nose or lip, with the arm immobilized and the flap pedicle was divided some time later.

Even though the cheek flap was the first described, the forehead flap was used later for nasal reconstruction. It was when British surgeons saw the results of Indian rhinoplasty on a man called Cowasjee that the procedure was described in the Madras Gazette and the October 1794 issue of the Gentleman’s Magazine of London. The first reported case of an Indian rhinoplasty in the Western world was performed by Joseph Constantine Carpue in 1815 and the procedure gained popularity subsequently within Europe and the USA. Nasal reconstruction also formed the basis of the pedicled medial arm flap, described by Gasparo Tagliacozzi who lived between 1546 and 1599 in Bologna in Italy. He described the procedure in his manuscript De Curtorum Chirurgia Per Insitionem, noting that the skin of the medial arm was thin and had few hairs. He described a multistage technique in which skin of the medial arm was raised as a bipedicled flap, the donor site was left to heal, the flap was then attached to the defect in the nose or lip, with the arm immobilized and the flap pedicle was divided some time later.
Although the median forehead flap, based on the supra-
trochlear vessels, was first described for nasal reconstruction,
the other type of forehead flap based on the superficial
temporal artery was used by McGregor in 1963 for intraoral
reconstruction. This workhorse flap in head and neck
reconstruction was followed by descriptions of the delto-
pectoral flap by Bakamjian in 1965 and the pectoralis major
flap in 1979 by Arian. In 1983, after the advent of the
operating microscope for microvascular reconstruction, the
free radial forearm flap was popularized by Soutar for oral
cancer and has remained a popular workhorse flap since.
Now, with the rapid recent advancements in perforator flap
knowledge, we can use almost any area of skin and soft tissue
and thin the area harvested to create a well-contoured, size-
matched flap while simultaneously minimizing donor site
morbidity, and perforator flaps are increasingly being used
and described for head and neck reconstruction.

MUCOSAL RECONSTRUCTION

In mucosal head and neck cancer, the priorities in the
reconstructive principles differ for reconstruction at different
sites in the upper aerodigestive tract. For example, recon-
struction of the floor of mouth has different principles to
reconstruction of the posterior pharynx, and so on. It is also
becoming increasingly clear that functional outcomes are
more dependent on the size of the excision and the structures
involved in the excision, rather than the type of reconstruc-
tion used though, clearly, reconstruction using robust and
reliable techniques with careful attention to the principles of
reconstruction in these areas plays an important role in the
ultimate final outcome.

The principles of reconstruction in the oral cavity fol-
lowing oral cancer excision remain to maximize functional
results. Functions of the oral cavity include the articulation
component of speech, tongue mobility to propel food and
clear the oral cavity of food debris, and mobility of the
tongue tip to prevent pooling of saliva in the sump areas of
the anterior and lateral floor of mouth. The oral cavity
consists of the lips, alveolus, buccal mucosa, hard palate,
anterior two-thirds of the tongue (the mobile tongue),
the floor of mouth and the retromolar trigone. The main pri-
orities of reconstruction are maintenance of tongue mobility,
maintenance of a lingual sulcus, maintenance of mouth
opening, avoidance of bulk where native tissue is thin and
avoidance of convexities at sites of concavity. Tongue mobi-
ity allows a sweeping movement to clear food debris, to
allow food to be propelled to the appropriate regions of the
mouth for chewing and for food to be passed into the oro-
pharynx for further processing. The tongue also shapes much
of the air that is vibrated to produce intelligible speech. To
create speech, we must have air flowing into the mouth; that
air needs to be vibrated to create a sound, and that air needs
to be shaped to create consonants and vowels. The tongue
plays an important role, along with the lips, teeth and oro-
pharynx in shaping air that is already vibrating and also in
creating the vibrations for the sibilant subset of the fricative
sounds (such as sh-, ch- and j-).

Much of the muscle of the tongue can be removed and
function maintained; however, a tongue that is tethered will
not be mobile. Without a mobile tongue, the speech, swal-
lowing and chewing functions of the tongue will be difficult
to maintain. Notably, even a small amount of the oral tongue
may be removed and tethered laterally or anteriorly and this
will lead to poor tongue function in view of the lack of
mobility of the tongue. For example, if a small mobile lateral
tongue tumour is excised and directly closed, if the tongue
defect is sutured to the lateral floor of the mouth, tongue
mobility will be unnecessarily restricted. Similarly, an ante-
rior ventral tongue defect sutured to the anterior floor of
mouth will lead to restriction in tongue protrusion and ele-
vation, again leading to unnecessarily reduced tongue func-
tion. Direct closure of lateral tongue defects should be
considered with a vertically orientated scar to prevent lateral
tethering, and closure of the ventral and tongue tip should be
considered with a longitudinally orientated scar.

Oral sensation is of great importance in maintaining oral
function and many reconstructions are reasonably sensate
when a sensory nerve is used to reinnervate the reconstruc-
tion. When free flaps are used for oral reconstruction, an
appropriate cutaneous nerve may be harvested and a neu-
rorrhaphy performed with a nearby sensory cranial nerve.
Although there are reports of improved function and sensa-
tion following such a nerve repair, the results are in limited
groups of patients studied. Nevertheless, an attempt should
be made to offset some of the sensory changes after ablative
surgery by performing a sensate reconstruction. For total
glossectomy defects, some authors have suggested using
reinnervated muscle flaps for both tongue muscle power and
sensation. However, it is difficult to imagine how a reiner-
vated large muscle would perform the delicate and fine
movements of an organ as sophisticated as the tongue.
The oropharynx consists of the tonsils, the soft palate, part
of the posterior pharyngeal wall, the tonsilolinguine angle
and the posterior one-third of the tongue (the base of the
tongue). Reconstruction of the oropharynx is designed to
prevent nasal escape and hypernasality, thereby maintaining
velopharyngeal competence. Nasal escape occurs when fluid
or food material inadvertently passes from the oropharynx to
the nasopharynx, usually during swallowing. Hypernasality
occurs when air passes inadvertently from the oropharynx
to the nasopharynx, usually during drowsive consonant
production.

The velopharyngeal musculature consists of palatoglossus,
palatopharyngeus, levator veli palatini, tensor veli palatini
and the musculus uvalae muscles. These are innervated by
the trigeminal nerve and vagus nerves and interact during swal-
lowing and speech to maintain normal function. Following
ablative surgery to the posterior oral cavity or oropharynx,
some or all of these muscles will no longer function normally
and the unreconstructed defect will be left with velophar-
yngeal incompetence. Maintaining velopharyngeal compete-
tence therefore forms one of the main reconstructive
principles in oropharyngeal reconstruction and there are
several ways of performing this including providing bulk,
performing a pharyngoplasty and dynamizing the recon-
struction.

If the reconstruction is a bulky flap, the normal concavity
of the soft palate is converted to a convexity. This means that
the normal working and moving muscles do have to move
such a long distance to provide closure of the velopharyngeal
aperture. Bulky flaps include most myocutaneous flaps and
some fascicutaneous flaps, such as the anterolateral thigh flap in people of European origin. Paradoxically, some reconstructive plastic surgeons feel a thin flap in such situations is a better option, as some of the flap is then able to move to assist with closure of the velopharyngeal aperture. Based on this principle, it is also possible to dynamize a thin flap. For example, the radial forearm flap may be taken with a distal strip of palmaris longus tendon as it heads toward the palm. This strip of tendon may be hitched to the normal working muscles on the contralateral side of the velum to the ablative surgery. Although the tendon of palmaris longus does not directly attach to the skin of the forearm, from where the flap has been raised, there is dynamic movement of the flap following such a procedure in the long term, and this can be seen on flexible nasendoscopy of the soft palate postoperatively when the patient is asked to make a plosive consonant. Lastly, a pharyngoplasty performed at the same time as the reconstruction also serves to narrow the velopharyngeal aperture. The pharyngoplasty used is usually a superiorly based flap, but varies according to the extent of ablative surgery. All these methods serve to improve the functional outcome of what can potentially be destructive surgery with noticeable functional impairment. By using one or a combination of these principles very effective rehabilitation can be achieved to allow the patient to speak, swallow and chew well.

In summary, reconstruction of the mucosal surfaces of the upper aerodigestive tract follows some important and fundamental principles. The reconstructive surgeon needs to be aware of the structures excised and the shape of the defect both at rest and during functional activity. By being mindful of these principles, we can make an attempt to maximize functional outcomes.

SKIN RECONSTRUCTION

In external skin and soft tissue reconstruction, the principles of reconstruction differ from those of mucosal reconstruction. The main principles in skin reconstruction are to orientate scar lines in the lines of election, to consider reconstruction of aesthetic subunits, to replace like with like, to be aware of the colour differences in the head and neck skin compared to skin elsewhere and to mimic the contours of the head and neck with the reconstruction used, avoiding bulk where thinness is needed and vice versa. Finally, with large reconstructions on tissues that are likely to drag with time and gravity, the reconstructive surgeon should elevate the tissues and hitch mobile structures to immobile structures. The skin of the head and neck can be considered in terms of the anatomic site, and so reconstructive principles differ at the scalp, the forehead, the upper face, the midface, the lower face, the central face, the lateral face and the neck. All these areas have their own unique characteristics and qualities with differences in reconstruction priorities.

The scalp is where many people have hair-bearing skin that benefits from being replaced following excision. Where hair replacement is required, then the scalp can be reconstructed using a number of options including scalp rotation flaps, scalp interdigitating flaps or rhomboid flaps. By using skin graft on hair-bearing skin, the patient is left with a patch of alopecia; however, this does not seem to concern a large number of our patients who have skin cancers of the scalp. The scalp skin has limited elasticity but can be expanded using tissue expansion. In this two-stage technique, an expandable saline-filled implant with a silicone outer shell is positioned into the layer between the galea and the peristium under the skin requiring growth. Expansion occurs over a period of several weeks until the desired skin size increase has taken place, and a second-stage procedure is performed to remove the expander and reposition the newly formed skin over the defect requiring coverage. In most patients with cancers, the time delay between expander insertion and completion of the expansion process is too long for safe oncologic practice, and for scalp defects this is usually a delayed reconstruction procedure.

The forehead skin is similarly limited in its elasticity, and in those places within the forehead where there is movement it is occasionally undesirable to use this movement for reconstructive local flaps. Tissue expansion can be used in the forehead. For example, around the eyebrow region there is considerable movement but this is needed for facial expression and abnormally positioning a brow is to be avoided. Forehead reconstruction is often possible with skin grafts and local flaps. When a forehead flap is used as a donor flap, then some authors argue for letting part of the donor site heal by secondary intention. There is little wound contracture because of the bony base of the defect and much wound healing takes place by epithelial growth as opposed to wound contraction. Although wound healing by secondary intention at the forehead takes place over a protracted period, the ultimate aesthetic result is often better than if resurfaced with a split skin graft.

The midface consists of the area between the lower eyelids and angle of the mouth and has central and lateral components. The midface is a very prominent part of the facial anatomy and is highly visible. Light usually falls from above onto the midface and the human eye and brain is used to seeing contour differences and contrast differences. Accordingly, central midface reconstruction should ensure that contours are maintained, a suitable colour match is achieved and scars are placed in lines of election and run as close to possible as parallel to these. Useful local flaps for midface reconstruction include V-Y flaps, W-plasties or Z-plasties for cheek scar revisions, cheek rotation flaps, cervicofacial flaps and MACS (minimal access cranial suspension) facelift-type reconstructions with excision of Burrow’s triangles in the postauricular region for reconstruction of defects anterior to the root of the helix in the sideburn region. Local flaps such as rhomboid flaps on the cheek can sometimes lead to prominent scars that run perpendicular to lines of election and are often a second choice for reconstruction. Regional flaps for reconstruction of the cheek, such as the deltopectoral flap and the forehead flap based on the superficial temporal vessels, often provide excellent colour-matched results, but have the disadvantage of being two-stage procedures and the donor site often needs a skin graft in places. When reconstructing the midface, it is important to avoid tension on the lower eyelid at the end of the procedure. Additionally, because of gravity and inflammatory oedema, tissue ptosis takes place over the course of time and can lead to late development eyelid malposition or ectropion. Tension on the lower eyelid at the end of the procedure, pulling the lid down, should not be the case and never improves with watchful waiting. To avoid tissue ptosis in the
midface, one or two carefully placed deep sutures are occa-
sionally needed to hitch the mobile structures of the midface
to immobile structures. The most immobile structure in the
midface is the facial skeleton and the use of anchors or bony
tunnels occasionally helps in securing the mobile to immobile
sutures to prevent cheek ptosis dragging down the lower
eyelid. Although the lower eyelid does form part of the mid-
face, reconstruction of the lower eyelid itself is included below
under Eyelid reconstruction.

The lower face is far more forgiving, but reconstruction
here must prevent lateral ptosis of the angle of the mouth. A
ptotic angle of mouth leads to oral incompetence and dental
show at rest, both of which are undesirable outcomes fol-
lowing lower facial reconstruction. Oral competence is also
an integral part of lip reconstruction which is discussed below
under Lip reconstruction. Neck skin reconstruction involving
large areas often requires local or free flaps. The radial
forearm flap was first used as a means of neck reconstruction
in head and neck surgery following burn contractures, and
the qualities of the flap reflect the principles of reconstruc-
tion. The neck skin needs to be thin, pliable, needs to permit
movement in many vectors and there should be a good col-
our and contour match with the surrounding skin. Examples
of local flaps used for neck reconstruction include delto-
pectoral flaps, pectoralis major muscle flaps with skin grafts,
supraclavicular artery perforator flaps and local neck skin
random pattern flaps. Whenever neck skin is incised for use
as a local flap, the incisions must be placed in a manner
which will permit subsequent incisions for a neck dissection
without compromising skin flap vascularity.

Clearly, the larger the skin defect in any area of the head
and neck, the more likely the need for free flap reconstruc-
tion. The choices for free flaps are many, and include muscle
flaps with overlying skin grafts (which seem to give excellent
colour and contour matching to the surrounding skin, in
the author’s experience), fasciocutaneous flaps, cutaneous flaps
and musculocutaneous flaps.

BONY RECONSTRUCTION

The bones commonly requiring reconstruction in the head
and neck are the mandible and the maxilla. The history of
head and neck bony reconstruction dates back to ancient
Egypt and China with prosthetics. Towards the end of the
nineteenth century, bone grafts were first performed, and
microsurgical reconstruction was described from the late
1970s onwards. Nowadays, our principles of reconstruction
are to provide cosmesis, speech, swallowing, chewing and
dental occlusion and restoration, either with dentures or with
dental implants. Our decision-making in bony reconstruction
of the mid and lower face depends on the extent of the defect,
the need for postoperative radiotherapy, the presence of
radionecrosis, the state of the potential donor vessels in the
region, the fitness of the patient, the height of the native
mandible requiring reconstruction, the presence of teeth and
the availability of donor sites.

Mandibular reconstruction

Mandibular reconstruction may be performed with no
reconstruction, plate reconstruction, bone graft reconstruction,
and vascularized bone either on a pedicled or free flap. When
no reconstruction is performed of an anterior mandible defect,
the patient is left with a so-called ‘Andy Gump deformity’. Andy
Gump was a cartoon character in an American comic book
between 1917 and 1959 who had no chin whatsoever. No
reconstruction of an excised mandible will lead to severe ret-
rognathia with loss of anterior tongue support, oral incom-
petence with severe difficulties of speech, swallowing and
chewing. The soft tissues collapse around the dead space cre-
ated by the loss of anterior mandible leading to the deformity.
This type of defect is rarely seen nowadays and even in the
most unfit of patients we have an option of using a plate-only
reconstruction. Mandibular reconstruction plates nowadays are
usually malleable locking 2.0 or 2.4 mm plates. Commonly
used are the low profile plates with threaded plate holes for
screws with threaded heads, providing an internal or external
fixation device for increased bony stability. These titanium
plates are one of the means of maintaining dental occlusion
prior to mandibular excision, and they can be resterilized
following tumour excision. Additionally, the plates can be pre-
bent using stereolithographic models for greater accuracy. At
least three screws should be used in the native mandible at
either end of the reconstruction plate for stability.

In addition to using a plate-only reconstruction, a plate
can be used as a template for bony reconstruction which can
be vascularized or non-vascularized. Vascularized bone is
preferred in mandibular reconstruction because of the large
forces generated by normal jaw movements and vascularized
bone is more robust. Of all the vascularized bone flaps that
are available the commonly used ones for the mandible are
the fibular flap, the vascularized iliac crest flap (more com-
monly referred to as the deep circumflex iliac artery flap or
DCIA flap), the scapular flap and the radial forearm osteo-
cutaneous flap. There are advantages and disadvantages to
each flap.

The fibular flap provides a long straight segment of vas-
cularized bone, based on the peroneal artery. The flap can
contain skin and muscle depending on how it is raised.
Harvesting the flap is performed under tourniquet control
and allows a two-team approach in the operating theatre –
one team can perform the head and neck surgery and the
other team can perform the flap surgery. The flap is raised
and subsequent osteotomies are performed on the harvested
bone, and these can be either closing wedge osteotomies
where a triangular wedge-shaped portion of bone is removed
and the two remaining bony segments are plated. Alter-
natively, open wedge osteotomies may be performed in which
the bone is fractured and fixed to a reconstruction plate
which forms a framework for the bony shape required. The
peroneal artery is a good size match for many of the branches
of the external carotid artery and the peroneal veins tend to
be large, thin-walled vessels with multiple valves. The fibula
can provide enough length to reconstruct a mandible from
angle to angle, but neomandibular height is limited with this
reconstruction.

The deep circumflex iliac artery provides vascularized
bone from the iliac crest. The flap may incorporate the
internal oblique muscle, supplied by the ascending branch of
the deep circumflex iliac artery, and skin overlying the iliac
crest, supplied by perforating branches of the artery, for a
composite flap for reconstruction of all the layers of the lower
face. The iliac crest can be taken for a considerable height
allowing for adequate neomandibular height reconstruction. Use of the internal oblique muscle provides excellent lining tissue after it mucosalizes and recreates the normal situation of a tightly bound mucosa to the underlying mandible. Long-term orthopantomograms of patients at our institution have shown neomandibular remodelling almost indistinguishable from the native mandible. Donor site morbidity is a significant consideration for this flap and has been reduced by utilizing only the inner plate of the iliac crest.

The scapular provides a robust segment of bone when incorporated in the scapular flap. The flap is based on the cutaneous branch of the circumflex scapular artery and the vascular pedicle passes through the triangular space above teres major, the long head of triceps and the subscapularis. A segment of the lateral border of the scapula may be harvested along with a cuff of surrounding muscle and significant muscle dissection is required to harvest the bony segment. The patient needs to be turned during the procedure so that the reconstructive surgeon may gain access to the flap following the head and neck surgery.

The radial forearm flap provides up to 10 cm of bone when raised as an osteocutaneous free flap. The vessels supplying the bone pierce through flexor pollicis longus, arising on the deep aspect of the radial artery, and a cuff of this muscle is harvested when raising the flap as an osteocutaneous flap. Bone between the attachments of pronator teres and brachioradialis may be raised and in an average adult this provides approximately 10 cm of bone. A boat-shaped segment of bone taking less than one-third of the circumference of the radius should be taken, to avoid weakening radius, reducing the risk of subsequent fracture. Only one osteotomy may be made in the bone thereby reducing the length to 5 cm of a double segment of bone. Osseointegration cannot be performed in the reconstructed mandible and donor site morbidity is potentially considerable. The radius is weakened, and options to increase the strength of the radius after harvesting the flap include the use of a 2.4 mm straight fixation plate between the two ends of the bone and the use of cancellous bone graft from the iliac crest to replace the bone removed. An above elbow cast is used for 6 weeks post-operatively when a plate is not used for radial reconstruction.

In summary, mandibular reconstruction may be performed using a variety of techniques, and the choice of the surgeon depends on mandibular height (which is particularly relevant in dentate patients), the length of bone needed, the number of osteotomies planned, future osseointegration, flap familiarity (though it could be argued that the reconstructive surgeon should be familiar with most flaps), donor site availability and morbidity, the position of donor vessels and flap composition.

Maxillary reconstruction

Maxillectomy defects are most commonly created following excision of carcinomas, but other bony and sinus diseases can lead to the need for maxillary reconstruction. In general, narrow and superficial defects are more likely to need obturators. The wider and taller the defect, the greater the need to use vascularized tissue. When reconstructing, a maxillectomy defect, consideration needs to be given to oronasal closure, velopharyngeal competence, the position of the globe of the eye, the height of the cheeks, dental rehabilitation with either implants or dentures. These are the principles of maxillary reconstruction.

Obturator reconstruction is a very effective and surgically simple method of oronasal closure. However, in larger and wider defects, vascularized reconstruction is generally used. Options include the DCIA flap and non-vascularized iliac crest supported by vascularized muscle. Since the maxilla has less force acting on it than the mandible, the latter option is mechanically sound. There are advantages and disadvantages to each method of reconstruction.

Obturator closure is a relatively simple procedure for the patient to tolerate (and for the surgeon to perform). Usually, at the end of the procedure, the defect is filled with a malleable material which subsequently hardens. This allows an obturator to be made by the prosthetician which the patient can insert and remove as required. An obturator is ideal for smaller defects.

Ideally, larger defects require flap reconstruction. The two options that seem to have found favour amongst reconstructive surgeons are the DCIA flap and vascularized muscle with non-vascularized bone graft. The DCIA flap provides well-vascularized composite tissue in the form of bone, muscle and skin if required and fills the maxillectomy defect very effectively. The main disadvantages of the procedure are donor site morbidity and the pedicle length which necessitates either anastomosing the flap vessels to the facial vessels in the face or to vessels in the neck but with the additional use of vein grafts. However, there is only one donor site and harvesting can be performed at the same time as resection. Muscle flaps with bone grafts include the rectus muscle or latissimus dorsi muscle, which have long pedicles and muscles that can be tailored in their size and shape to match the defect. The bone graft from the iliac crest is inset with mini-plates and the muscle is sutured into the defect. Some surgeons use skin grafts to reline the nasal pasageways with a nasopharyngeal tube left in situ for a few weeks to prevent blockage of the nasal airway. A dental plate is usually secured with small screws to help compress the muscle into the correct shape for the first couple of weeks in the post-operative period.

Reconstruction of Complex Aesthetic Units

The face is a complex structure and defects often involve complex aesthetic units either in the central face or in the lateral face. The central face complex units include lips, nose, eyebrows and eyelids. The lateral complex units include the external ear.

Lip reconstruction

The principles of lip reconstruction are to maintain oral competence, to maintain labial sensation, to maintain a lower sulcus and to maintain aperture size. Oral competence is maintained with correct alignment of the orbicularis oris muscle, along with careful suturing of full-thickness defects in multiple layers. Aperture size is maximized using tissue
laxity from neighbouring areas though there is an inevitable degree of microstomia with many reconstructions. To avoid embarrassment, the edentulous patient wearing dentures should remove the dentures prior to lip surgery in case they are unable to remove them postoperatively. Lip reconstruction can be considered in terms of the upper lips and the lower lips, and because of lip switch procedures, often the reconstructive surgeon will reconstruct the upper lip with the lower lip and reconstruct the lower lid defect with a flap.

There has been a wealth of reconstructions described for lip reconstruction, including direct closure, step advancement flaps, large rotation flaps, flaps based on excisions elsewhere using the principles of Burrow's triangles and lip switch flaps. For small lower lid defects, direct closure can be used, and as the defect becomes larger, a flap needs to be used for closure. Common flaps used by the author include: the Johansen stair-step advancement flap for central defects; bilateral Karapandzic flaps for larger central defects, with a contralateral unilateral Karapandzic flap used for laterally based defects that do not cross the oral commissure; and Estlander cross lip flaps for defects in the commissure. For extensive cancers, radiotherapy should be considered or total reconstruction using a radial forearm flap with a sling of tendon to maintain oral height, but oral competence is inevitably lost with loss of sensation in the area, even with sensate flap reconstructions of the lower lip. For upper lip defects, the author prefers to use a lip switch flap from the lower lip and reconstructs the lower lip defect using one of the aforementioned techniques. Using these methods, it is possible in most cases to preserve labial function as best as possible and to minimize the potential aesthetic effects of such excisions.

**Eyelid reconstruction**

As with lip reconstruction, eyelid reconstruction can be considered in terms of lower lid or upper lid reconstruction. The eyelid is a trilaminar structure and all three layers need to be reconstructed. Lower lid reconstruction can be considered in a stepwise manner, with increasing complexity of reconstruction as the defect enlarges. Traditionally, the stepwise approach for the lower eyelid has been, as the defect enlarges, direct closure, lateral canthotomy, small local flaps such as the McGregor flap in combination with lateral canthotomy, and large local flaps such as the Mustarde cheek rotation flap either in combination with a lateral canthotomy to allow for conjunctival closure or in combination with a graft for inner lining, such as a chondromucosal nasal septal graft or hard palate graft.

In elderly patients, there is usually laxity of the lower lid skin and tarsus and this is reflected in the ability to close relatively larger defects directly. A careful preoperative examination of the lids usually reveals any pre-existing tarsal laxity, a positive snap test, negativity or positivity of the orbital vector, presence of scleral show and the presence of skin laxity.

Complex, near total, lower lid reconstruction requires reconstitution of all three layers. The inner conjunctival layer in the lower lid may be reconstructed with one of several methods. These include techniques such as a hard palate graft, Hughes tarsoconjunctival flap and mucosal grafts with supporting underlying cartilage from the nasal septum. Reconstruction of the skin and muscle component may be with a flap from the temporal region, or from the upper eyelid as a unipedicled or bipedicled Tripier flap if there is enough skin and muscle laxity in the upper lid. Reconstruction of the upper lid also requires careful examination of the eyelid to note the presence of blepharoptosis, lid retraction, lagophthalmos and skin laxity. Since the upper lid is more of a dynamic structure with more important lid retractors, reconstruction of the upper lid is often performed with a lower lid switch and the lower lid is subsequently reconstructed using an appropriate full-thickness flap reconstruction technique.

**Nasal reconstruction**

For nasal reconstruction, we need to consider the skin, the skeletal support and the lining. The lining is in part skin and in part mucosa, but can be reconstructed with skin. Where lining remains, the skin only needs to be reconstructed either with a local flap or a full-thickness skin graft, but where lining is in need of replacement a more complex reconstruction occurs. Common skin flaps used for nasal reconstruction include local bilobed flaps, flaps from the forehead (including but not limited to the classical forehead flap), nasolabial flaps (though a superiorly based nasolabial flap should never cross the alar crease), glabellar flaps and sliding advancement flaps.

For full-thickness and total or near total defects, the principles of reconstruction involve recreating the lining, skeletal support and skin. Local flaps can be combined with grafts, including auricular cartilage or costal cartilage grafts when cartilage is required. Bony skeletal reconstruction is often performed using calvarial bone or rib grafts. By using a combination of a skin flap or graft for lining, a skin flap for external cover and skeletal grafts, total nasal defects can be performed. As with all complex aesthetic unit reconstructions, it is important to appreciate aesthetic subunits, and in the nose these have been well described by Millard and modified by Burget. These units are the tip, dorsum, lateral sidewall, soft triangle and alar. Reconstruction of each unit gives a better final aesthetic result, in general.

**Ear reconstruction**

Ear reconstruction following tumour excision requires either partial auricular reconstruction or total pinna reconstruction, and can be autologous or prosthetic. The external ear consists of the helical rim, the root of the helix, the lobule, the tragus and antitragus, the intertragal notch, the triangular fossa, the conchal fossa, the cymba concha, the scaphoid fossa and the antehelical fold which has a superior and inferior crus. A number of local flaps are available to use for skin-only reconstruction but, equally, full-thickness grafts at select locations can yield excellent aesthetic results when skin-only reconstruction is required. For total pinna reconstruction, multistage autologous reconstruction often involves the use of costal cartilage grafts wrapped in a temporoparietal fascial flap with overlying skin grafting. More extensive tumour infiltration around this area often means lateral skull base
reconstruction with its attendant considerations of cranial nerve function, dural repair and major vessel presence.

CONCLUSION

In summary, head and neck cancer reconstruction is arguably the most challenging area of reconstruction for the reconstructive surgeon. We need to consider functional and aesthetic considerations as well as some of the unique characteristics of the structures in the region.

KEY EVIDENCE

- Evidence relating to reconstruction of the head and neck is limited and there are no good studies comparing different methods of reconstruction of any of the subsites within the head and neck.
- Evidence is, therefore, needed to improve outcomes. Outcomes include cosmesis and function and data relating to functional aspects of head and neck cancer reconstruction are now being collated in large head and neck centres.

REFERENCES

INTRODUCTION

This chapter discusses wound closure in the head and neck using grafts and local flaps; these are most commonly used to deal with defects following skin cancer excision, but can also be applied to various other defects around the face and to facilitate wound closure following resections in the aerodigestive tract. Primary closure is always the first option to be considered when closing surgical wounds, however if this cannot be achieved then the use of skin grafts and local flaps are of use. A graft is a piece of tissue that has no blood supply of its own and is dependent upon the blood supply of the recipient site to survive, whereas a flap is a piece of tissue with its own blood supply and its survival is not dependent upon the recipient site. The basic principles of wound closure, skin grafts and local flaps are discussed and their use in reconstruction of different regions of the head and neck are then illustrated.

WOUND CLOSURE

Following ablative cancer surgery in the head and neck many defects can be directly closed if they are small and enough tissue is available locally. For larger defects, closure of the wound can only be achieved through the use of grafts, local flaps, pedicled flaps, free flaps or a combination of these techniques. Areas of the face, head and neck facilitate direct closure because of the availability of lax skin; this is particularly true in the elderly as the skin loses its elasticity with age. The concept of relaxed skin tension lines are useful when considering where to place skin incisions (Figure 49.1). These lines are parallel to the natural skin wrinkles and tend to be perpendicular to the underlying muscle fibres. Ideally, surgical incisions should be placed parallel to these lines and,
in particular, the scar from a direct closure of a defect should be in a relaxed skin tension line. This is because it will be under the least tension as skin contraction is at its greatest when a scar is perpendicular to the relaxed skin tension lines.

Elliptical excision

Classically, a defect is designed as an ellipse three times as long as it is wide. This is the best dimension to take account of skin stretch and elasticity to approximate the wound edges with the least tension. If an ellipse is too short then excess skin (dog ears) can form an unsightly appearance (Figure 49.2). If there is uncertainty about the direction of the relaxed skin tension line then the lesion can be excised as a circle with the correct margins to obtain clearance. The skin edges of the wound can then be pulled together in various directions to assess in which axis there is the least tension. The circle can then be extended as an ellipse perpendicular to this axis and then closed.

Wedge excision

An alternative to excising lesions as an ellipse is to excise them as a wedge. Lesions located at the free edge of tissue such as the eyelid, lips of helical rim of the ear can be excised in this fashion and then closed directly (Figure 49.3). It should be remembered that these free edges are not just skin but composite tissue and should be closed in layers to obtain optimal function and appearance. In the case of lips these layers are mucosa, orbicularis oris and skin; in the ear, cartilage and skin on both the anterior and posterior surface; and in eyelids, conjunctiva, tarsal plate, orbicularis oculi and skin.

Suture materials

Many suture materials and techniques have been used to primarily close defects in the head and neck. These can be permanent or absorbable sutures which can be placed through the skin or buried within it; recently, skin adhesives and tapes have been developed which can be used instead of sutures. Each has their own advantages and disadvantages and these are summarized in Table 49.1. There are no correct or incorrect techniques and due consideration should be given to the method of wound closure on a case by case basis.

SKIN GRAFTS

Grafting of skin originated in India over 3000 years ago, where surgeons from the tile-making caste took skin grafts.
from the gluteal region to repair traumatic defects of the face. The first report in the English language was in 1817 when Sir Astley Cooper grafted a full-thickness piece of skin from a man’s amputated thumb onto the stump for coverage. Lawson reported successful elective full-thickness skin grafting in 1871, which was followed by Ollier, a French surgeon, describing a split-thickness skin graft in 1872. Thiersch, from Germany, was the first to recognize the importance of recipient site for graft survival, and in 1875 Wolfe used a full-thickness skin graft taken from the patient’s forearm to treat a traumatic ectropion of the lower lid following a gunpowder explosion. Full-thickness skin grafting of the eyelids is now a procedure with which Wolfe’s name has become synonymous.

In 1929 Brown and Blair differentiated between full-thickness and split-thickness skin grafts; they identified the advantages and disadvantages of each and using their techniques consistent, acceptable results were achieved. Medawar studied the underlying biology of healing skin grafts in the 1940s. His work described the cellular changes in both the epidermis and dermis giving the technique of skin grafting a scientific basis and laying the foundation of modern transplant immunology.

Skin grafts can be split-thickness, full-thickness or composite. Split-thickness skin grafts (STSG) contain epidermis and a variable amount of dermis whereas full-thickness skin grafts (FTSG) contain epidermis and all of the dermis. In practice, there is a spectrum of depth of skin grafts from thin to thick as shown in Figure 49.4. Composite grafts consist of two different tissue types, such as skin and cartilage or septal mucosa and cartilage. The part of the body from which the skin is taken is the donor site and the area onto which the skin is transplanted is the recipient site or bed. An autograft is a graft taken from one part of an individual’s body and transferred to a different part of that same individual. An isograft is a graft between genetically identical individuals, such as identical twins. An allograft is taken from another individual of the same species. A xenograft is when the donor is of a different species to the recipient. The terminology used in skin grafting is summarized in Table 49.2.

Table 49.1 Methods of wound closure.

<table>
<thead>
<tr>
<th>Material</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutures</td>
<td>Simple and effective</td>
<td>Wound dehiscence if removed too early</td>
</tr>
<tr>
<td></td>
<td>Non-absorbable cutaneous</td>
<td>Scarring if left too long</td>
</tr>
<tr>
<td>Absorbable cutaneous</td>
<td>No need for removal</td>
<td>Scar caused by stitch marks</td>
</tr>
<tr>
<td>Non-absorbable subcuticular</td>
<td>Minimal scar</td>
<td>Need for removal</td>
</tr>
<tr>
<td>Absorbable subcuticular</td>
<td>No need for removal</td>
<td>Risk of wound dehiscence</td>
</tr>
<tr>
<td>Fasteners</td>
<td>Can effectively approximate wound edges</td>
<td>Retention of foreign body</td>
</tr>
<tr>
<td>Skin tapes</td>
<td>Easy to apply and remove</td>
<td>Need to be kept dry</td>
</tr>
<tr>
<td>Skin staples</td>
<td>Fast wound closure in long incisions</td>
<td>Need removal which can be painful</td>
</tr>
<tr>
<td>Skin adhesives</td>
<td>Evert wound edges well</td>
<td>May need deeper sutures to prevent wound dehiscence</td>
</tr>
</tbody>
</table>

Alternatives

Secondary intention Useful for small superficial wounds May take some time until fully healed Risk of an unsightly scar

Table 49.2

<table>
<thead>
<tr>
<th>Material</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

Alternatives

Secondary intention Useful for small superficial wounds May take some time until fully healed Risk of an unsightly scar

Figure 49.4 Differing depths of skin grafts.
Skin graft terminology.

<table>
<thead>
<tr>
<th>Composition</th>
<th>Graft origin</th>
<th>Table 49.2 Skin graft terminology.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split-thickness</td>
<td>Autograft</td>
<td>Same person</td>
</tr>
<tr>
<td>Full-thickness</td>
<td>Isograft</td>
<td>Identical twin</td>
</tr>
<tr>
<td>Composite</td>
<td>Allograft</td>
<td>Same species</td>
</tr>
<tr>
<td></td>
<td>Xenograft</td>
<td>Different species</td>
</tr>
<tr>
<td></td>
<td>Alloplastic</td>
<td>Synthetic</td>
</tr>
</tbody>
</table>

Graft survival

Once a skin graft has been harvested, it has been detached from its blood supply and is, temporarily, not viable. In order to survive permanently, it has to become reattached and obtain a new blood supply from its recipient site; this process is known as ‘take’. Successful take of a skin graft is dependent upon the extent and speed at which vascular perfusion is returned to the graft. This is determined by the characteristics of the graft itself, the characteristics of the bed on which the graft is laid and the conditions under which the graft is applied to the bed.

Under comparable conditions, two properties of a graft determine its take. These are the blood supply of the skin from which the graft was harvested, as a graft taken from a highly vascular donor area will heal better than a graft from a poorly perfused area, and the metabolic activity of the skin graft at the time of its application to the recipient bed. This metabolic activity will direct how the graft responds to the period of ischaemia before it undergoes successful revascularization.

The recipient wound bed must have an adequate blood supply to support the skin graft. Muscle and fascia act readily as recipient beds whereas fat is less suitable. Bone covered with periosteum will take a graft but exposed bone will not, however burring bone and allowing it to granulate (such as the outer table of the skull) will facilitate graft take. Healthy granulation tissue covering a pre-existing wound on the head and neck will also take a graft but any necrotic tissue has to be debrided first.

To obtain successful graft take, the conditions have to be optimized. These conditions can be either specific to graft location or systemic. The graft has to be immobile and in direct contact with the bed. Numerous methods of attachment of grafts, such as tie-over dressings, have been described and shearing forces which make the graft move from side to side have to be avoided. The most frequent cause of graft loss is the presence of a haematoma which separates a graft from its bed. Scrupulous haemostasis and either meshing or fenestrating the graft may help to prevent this. Infection is another common cause of graft loss and if suspected should be treated with systemic and/or topical antibiotic agents. Common pathogens include *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and mexitillin-resistant *Staphylococcus aureus* which can all destroy fibrin and prevent graft adherence. In addition to these local conditions, systemic conditions of the patient can also influence skin graft take.

These include diabetes mellitus, smoking, previous radiotherapy and chemotherapy, as well as nutritional status.

Graft adhesion and revascularization

Two processes allow the skin graft to adhere to the recipient site. The first is fibrin adherence which takes place in the first 2–3 days; during this time the graft is held to the recipient bed by a thin layer of fibrin from both the wound bed and undersurface of the graft. Within 48 hours, this fibrin starts to break down and adhesion to the bed is maintained by the proliferation of fibroblasts and the deposition of collagen.

Once the graft is adherent, two separate processes keep the skin graft alive. The first of these is called serum imbition. Immediately after a graft is inset it absorbs plasma that is leaking from the recipient bed. This provides temporary nourishment for the graft and is demonstrated by the graft gaining weight and swelling. The process keeps the graft alive for the first 48 hours, after which vascular flow through the graft begins to be re-established. The second process is collectively known as graft revascularization. This is a combination of cut vessels from the host bed lining up with the cut ends of the vessels of the graft to form anastomoses (inosculation) and the ingrowth of new capillary buds from the host into the graft. Ingrowth of vessels into the graft produces new vascular channels (true revascularization) or, alternatively, by the endothelium of the old vessels degenerating but the basement membrane remaining and this acting as a conduit for the capillary buds to travel down (neovascularization). All these processes restore blood flow and continue for approximately a month until revascularization is complete.

Full-thickness or split-thickness skin graft?

The amount of dermis included with the graft determines both the likelihood of survival and the degree of contraction. STSGs can tolerate less vascularity but have a greater amount of contraction. Full-thickness grafts require a better vascular bed for survival but undergo less contracture. Owing to this, split-thickness skin grafts have the best take and can be used under conditions that may cause the failure of FTSGs. However, STSGs tend to contract, have abnormal pigmentation and are susceptible to trauma once healed. In contrast, FTSGs do not contract as much, resists trauma better and has a better colour match. Sensory recovery of the full-thickness graft is superior to that of the split-thickness graft due to more sensory organs being retained in the transferred tissue, but the innervation takes longer to recover as there is more tissue for new nerves to grow through. These differences are summarized in Table 49.3.

Skin graft donor sites

After a STSG is harvested, the donor site heals by re-epithelialization from adenexal structures, such as hair follicles.
and sweat glands, in the remaining dermis. Resurfacing occurs by the migration of keratinocytes from these structures to cover the wound. As there is no remaining epithelium in full-thickness graft donor sites, the wound needs to be closed directly; this limits the amount of skin that can be harvested and the size of the defect that can be reconstructed using a FTSG. Split-thickness skin grafts can be taken from anywhere on the body. Commonly used areas include the thigh, trunk and buttocks as shown in Figure 49.5.

The graft is harvested with either an air or battery powered dermatome or a hand knife such as a Watson knife. The standard thickness which is preset on a dermatome is 0.3–0.4 mm or 10–12/1000 of an inch. The skin can then be either meshed or fenestrated by hand. The donor site is dressed with a non-adherent dressing and left undisturbed for approximately 14 days. Most STSG donor sites are healed by 21 days with minimal scarring but may be discoloured and susceptible to sunburn for two years afterwards.

The thickness and colour of skin varies greatly from different parts of the body and this affects the choice of FTSG donor site. Commonly used sites are pre- and postauricular, the supravacular fossa, the antecubital fossa and the groin as shown in Figure 49.6. The FTSG is harvested with a scalpel and is closed directly with sutures to leave a linear scar. The amount of skin that can be taken is limited by the need to obtain a tension-free closure of the donor site. Examples of the use of skin grafts in the head and neck are given in Figures 49.7 and 49.8.

### Table 49.3 Advantages and disadvantages of split-thickness and full-thickness skin grafts.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Split-thickness skin graft</th>
<th>Full-thickness skin graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of dermis harvested</td>
<td>Variable amount of dermis</td>
<td>All of the dermis</td>
</tr>
<tr>
<td>Chance of successful graft take</td>
<td>More likely to 'take'</td>
<td>Higher risk of graft loss</td>
</tr>
<tr>
<td>Graft contraction</td>
<td>Contracts more</td>
<td>Contracts less</td>
</tr>
<tr>
<td>Final graft colour once healed</td>
<td>Pigment abnormal</td>
<td>Better colour match</td>
</tr>
<tr>
<td>Robustness of healed graft</td>
<td>Susceptible to trauma once healed</td>
<td>More robust once healed</td>
</tr>
<tr>
<td>Return of sensation</td>
<td>Limited sensory recovery</td>
<td>Better sensory recovery</td>
</tr>
<tr>
<td>Donor site healing</td>
<td>Slow donor site healing by re-epithelialization</td>
<td>Fast donor site healing by primary intention</td>
</tr>
<tr>
<td>Size of skin graft which can be harvested</td>
<td>Potentially large volumes of donor skin</td>
<td>Limited availability of donor skin</td>
</tr>
<tr>
<td>Graft characteristics</td>
<td>Can be meshed to increase surface area</td>
<td>Primary contraction decreases surface area</td>
</tr>
</tbody>
</table>

PRINCIPLES OF LOCAL FLAPS

Local cutaneous flaps of the head and neck can be classified according to their circulation, composition, contiguity and contour. The circulation of flaps may be random or axial, which means that they are based on an anatomically recognized artery. Flaps can be composed of different tissue types, such as skin, fascia and skin (fasciocutaneous), muscle or muscle and the overlying skin paddle (myocutaneous). The contiguity of a flap means its source. A local flap is composed of tissue adjacent to the defect. A pedicled flap is from a
distant part of the body to which it remains attached. A free flap is completely detached from the body and anastomosed to recipient vessels close to the defect. The contour of the flap depends on the method in which it is transferred into the defect. It can either be advanced or moved about a pivot point. A flap is inset into a primary defect. The secondary defect is the site from which the flap is raised. This is usually closed directly but can be grafted or closed by another flap.

When designing a local flap in the head and neck the two most important considerations are appreciation of the cosmetic units and the relaxed skin tension lines. The face can be subdivided into separate units (Figure 49.9). It is preferable to use one flap to reconstruct one cosmetic unit and it may be necessary to excise an entire cosmetic unit, beyond the boundary of the original cancer resection, to obtain an optimal result. Conversely, if the resection involves two cosmetic units then two flaps, one for each unit, may be necessary. The donor area from the flap should be from the same cosmetic unit or one adjacent and should not transgress multiple units. Relaxed skin tension lines have already been discussed above under Wound closure, p. 914. Ideally, the scar from a direct closure of a secondary defect should be in a relaxed skin tension line as it will be under the most tension of any part of the flap.

In order to accurately plan a flap, reverse planning can be used where a template of the primary defect can be reflected onto surrounding skin to help assess where the flap can be raised from to give minimal donor site morbidity. When skin flap is designed randomly, its blood supply is from the base of the flap. Normally the breadth of the base should be no more than the length of the flap to prevent necrosis of the flap (a ratio of 1:1). In the head and neck, the blood supply is good so this can be extended to a ratio of base breadth to flap length of 1:1.5. In an axial flap based on a known artery system, the ratio of base breadth to flap length can be much greater.

### Advancement flaps

Advancement flaps may be simple or modified. A simple advancement flap just relies on the skin’s elasticity to cover the primary defect. They can also be modified in a number of ways to aid advancement; one example of this is to include Burow triangles at the base of the flap. These are triangles of skin that are excised either side of the base of the flap. This is demonstrated by a Rintalla flap being used to cover a defect of the nasal tip (Figure 49.10). A V-Y flap is another modified advancement flap. The flap itself is triangular (or ‘V’ shaped), the flap is advanced and the secondary defect is closed directly to leave a ‘Y’-shaped scar. The nasolabial V-Y advancement flap, shown in Figure 49.11, is an axial flap which can be based on either the superior labial artery or the angular artery, both of which are branches of the facial artery. A bipedicled flap receives a blood supply from both ends as it has two bases. It is less prone to necrosis than flaps of similar dimensions which are attached at only one end. An example of this is the Tripier flap for lower eye lid reconstruction (Figure 49.12). Skin from the upper lid based on both a medial and a lateral attachment is swung down, like a bucket handle, to provide cover for a defect in the lower lid. To increase the viability of this flap, a strip of the orbicularis oculi muscle can be included making it a musculocutaneous flap.

### Pivot flaps

A pivot flap moves about a fixed pivot point and can either be a transposition flap where the flap moves laterally across the pivot point or a rotation flap where the flap is rotated around the pivot point (Figure 49.13). When a flap is transposed to cover the primary defect, the secondary defect is normally skin grafted. This secondary defect can be closed directly when a rotation flap is used.

### RHOMBOID FLAPS

A rhomboid flap is a type of transposition flap where the donor defect is closed directly. The defect is designed as a rhomboid; each of the limbs of the defect and the flap being raised need to be of equal length and the angles of the
rhomboid need to be $120^\circ$ and $60^\circ$, respectively. The flap needs to be designed so that the scar from the donor site sits parallel to the relaxed skin tension lines. This is demonstrated in Figure 49.14. A variation of the rhomboid flap is the Dufourmentel flap,\textsuperscript{24} which has equal lengths of the limbs but the angles are $150^\circ$ and $30^\circ$. Other variations of the geometry of the rhomboid flap have been described.\textsuperscript{25} One of these is the ‘square peg in the round hole’ where the primary defect is circular (as is the case in most clinical situations) and the rhomboid flap is stretched to fill the defect.\textsuperscript{26} This reduces the need to excise extra skin in cosmetically sensitive areas such as the face.

Figure 49.7 (a) Defect resulting from wide local excision of a melanoma from the scalp. (b) Split-thickness skin graft being harvested from thigh. (c) Skin graft inset on scalp. (d) Foam dressing held with surgical clips.
FLAG OR BANNER FLAPS

A number of small transposition flaps can be used around the face and generally the donor site is closed directly. These are termed flag flaps as the piece of tissue moved resembles a flag or banner. These are normally random pattern flaps but can be based on a known artery in some parts of the head or neck. A glabellar flap is an axial transposition ‘flag’ flap based

Figure 49.8  (a) Defect resulting from excision of a basal cell carcinoma from the forehead. (b) Full-thickness skin graft being harvested from left supraclavicular fossa. (c) Skin graft inset on forehead. (d) Proflavin wool and paraffin gauze tie-over dressing.
on the supratrochlear artery, a branch of the ophthalmic artery. This allows the flap length to be three times the base breadth and in Figure 49.15, is shown covering a defect of the medial canthus. It is transposed to cover the primary defect and the donor site is closed directly.

**BILOBED FLAP**

A bilobed flap consists of two transposition flaps. The first flap is transposed into the primary defect, the second flap is transposed into the secondary defect (the original site of the first flap) and the tertiary defect (the original site of the second flap) is closed directly. Again, the flap should be designed so that the directly closed tertiary defect is parallel to the relaxed skin tension lines (Figure 49.16). Theoretically, the bilobed flap uses less tissue than any other method of wound closure and because of this minimizes tension at the primary defect. The ideal use of a bilobed flap is where there is tissue available locally and where it is important to avoid producing tissue stretch. The bilobed flap is most commonly used to deal with defects at the tip of the nose. Although there is some spare tissue around this area, the nasal tip can become displaced if skin is imported to cover defects here as a local flap.

**Rotation flaps**

Rotation flaps are large flaps that rotate into the primary defect. The volume of tissue raised in the flap is high when compared to the defect being closed. Normally the flap is a semicircle and the primary defect is designed as a triangle, like a slice of cake. The flap circumference should be at least eight times the width of the defect. Unlike transposition flaps, where the secondary defect is closed with a skin graft or primarily using skin adjacent to the flap donor site, it is tissue redistribution and skin elasticity of the flap itself that usually permits direct closure of the donor site in the case of rotation flaps. Occasionally, the use of a Burrow's triangle or a back cut may be needed. A back cut releases a rotation flap that is too tight by decreasing the tension at the base of the flap and thus the tension of closure at the site of the primary defect. This however does have the risk of devascularizing the flap by decreasing the width of its base. These flaps are useful for dealing with defects of the scalp or cheek (Figure 49.17).

**RECONSTRUCTION OF SPECIFIC REGIONS OF THE HEAD AND NECK**

**Scalp**

**ANATOMY**

The scalp has five distinct anatomical layers; from superficial to deep, these are the skin, subcutaneous connecitive tissue, muscle or aponeurosis (galea), loose areolar tissue and pericranium. The skin of the scalp is the thickest on the human body, ranging from 3 to 8 mm. Beneath the skin, the subcutaneous tissue contains the vessels and nerves supplying the scalp. Deep to this is the muscular-aponeurotic layer consisting of the frontalis muscle anteriorly and the
Figure 49.10  (a) Rintala advancement flap to cover a defect on the dorsum of the nose. (b) Note the Burow triangles at the base of the advancement flap that have been closed directly. (c) The final result.
Figure 49.11  (a) A V-Y advancement flap to close a defect on the right alar base. (b) The V-shaped piece of tissue is advanced to cover the defect. (c) The flap is inset and the donor site is closed directly to leave a Y-shaped scar.
occipitalis muscle posteriorly. These muscles are connected by an aponeurosis (the galea aponeurotica). Laterally, this aponeurosis is connected to the subcutaneous musculoaponeurotic system (SMAS) of the face. The layer of loose areolar tissue deep to this, also known as the inominate fascia, is an avascular plane. Owing to this, most local flaps of the scalp are raised at this level because it is easy to dissect and relatively bloodless, thus making scalp flaps fasciocutaneous rather than cutaneous. The deepest layer is the pericranium (the periosteum of the skull) which is firmly adherent to the underlying bone. However it can be raised and turned over on itself to form a pericranial flap. This is viable tissue that can cover exposed bone and is capable of taking a skin graft. Laterally, the pericranium is continuous with the deep temporal fascia overlying the temporalis muscle.

**BLOOD SUPPLY**

The scalp has a rich blood supply from tributaries of both the external and internal carotid arteries (Figure 49.18). The paired superficial temporal, posterior auricular and occipital...
arteries are all branches of the external carotid, whereas the paired supratrochlear and supraorbital arteries are branches of the ophthalmic artery. There are anastomoses between all these arteries and the entire scalp can survive on any single one of these vessels. However, when planning reconstructions of the scalp using local flaps, it is convenient to think of three

Figure 49.13  (a) A rotation flap is rotated around a pivot point to close a scalp defect. (b) The rotation flap donor site is closed directly. (c) A transposition flap is moved laterally across a pivot point to close a similar scalp defect. (d) The transposition flap donor site is closed with a split-thickness skin graft.
separate axes of blood supply: an anterior axis (supratrochlear and supraorbital), a lateral axis (superficial temporal and posterior auricular) and a posterior axis (occipital). Scalp flaps should contain one of these axes at the base of the flap to provide a reliable vascularity. The venous drainage of the scalp runs parallel to the arterial supply; in addition, venous blood also drains through the diploe of the skull via emissary veins to the dural sinuses.

SCALP FLAPS

Small defects of the scalp can be closed directly. If there is too much skin tension, then the use of a split-thickness skin graft is to be considered. To have a successful take of a skin graft, a healthy recipient bed is needed. This normally means healthy pericranium following the excision of a cutaneous malignancy, most commonly a squamous cell carcinoma. When the excision defect following ablative surgery includes the pericranium and the outer table of the skull is exposed there are two options. The first is burring the outer table to obtain a healthy vascular bed which will take a skin graft or performing a pericranial turnover flap to provide a graftable bed. However, if adjuvant radiotherapy is to be used, then this may influence the decision to skin graft a scalp defect which is down to bone as there is an increased risk of breakdown of the recipient site. If this is the case, then a scalp flap should be considered.

Larger defects of the scalp are best treated with a local flap. These can be either rotation or transposition flaps. If a rotation flap is to be used, it has to be designed big enough to cover the primary defect and allow direct closure of the donor site. This normally means that a scalp rotation flap is at least half the area of the patient’s scalp. In addition to the size of the scalp flap, back cuts can be useful as well as scoring the undersurface of the flap (the galea) to enable it to stretch adequately. The alternative to a rotation flap is a transposition flap. This does not need to be designed as large as a rotation flap, but the donor defect needs to be covered with a split-thickness skin graft. This leaves a ‘bald spot’ on the patient’s head but, considering the majority of patients are elderly and being treated for a cutaneous malignancy secondary to sun exposure, this is not as cosmetically disfiguring as might be supposed. Other techniques have been described to increase the amount of tissue available for scalp flaps. These include the use of tissue expansion to provide a greater volume of tissue which can be used to provide a larger flap. Alternatively, multiple interdigitating flaps can be used as described by Orticochea. For very large defects, the use of microvascular free tissue transfer needs to be considered, however that is beyond the scope of this chapter.

Figure 49.14  (a) The design of a rhomboid flap. (b) An area of lentigo maligna in the neck which is to be excised and closed with a rhomboid flap. (c) The flap raised and transposed into the defect.
Figure 49.15  (a) A basal cell carcinoma of the right medial canthus. (b) The excision defect and the glabellar transposition flap drawn. (c) The flap transposed with the donor site directly closed. (d) The flap inset into the defect.
Figure 49.16  (a) Geometrical principle of the bilobed flap. (b) Basal cell carcinoma on the tip of the nose with a bilobed flap drawn. (c) The flap raised and transferred.
TEMPOROPARIETAL FASCIA FLAPS

When discussing scalp flaps it is useful to consider tissue from the scalp that can be used to reconstruct defects around the head and neck. The fascia in the temporal region can be used for this purpose. This fascia has several well-described layers. The superficial temporal fascia (temporoparietal fascia) lies immediately deep to the hair follicles and is in

**Figure 49.17** (a) Squamous cell carcinoma of the cheek with a cheek rotation flap drawn. (b) Closure of the defect with the rotation flap. (c) Diagram of the technique.
Forehead

The forehead is bounded by the anterior hairline superiorly and the eyebrows inferiorly. The lateral limits are the temporal hairline. Underlying the skin is the frontalis muscle and deep to that the frontal bone. The skin can appear very smooth in younger patients, but in the older population transverse furrows appear, which are more obvious on frowning (contraction of the frontalis muscle). Small defects of the forehead should be directly closed. The forehead is very visible to observers and so care should be taken to place incisions to give minimal scarring. This is done by placing scars horizontally or along the hair line and eyebrow; defects as large as 6 cm can be closed in this way. Distortion of these hair-bearing surfaces can be cosmetically unsightly so for some larger defects where direct closure may cause malposition of the hairline or brow a flap should be used to cover defects within their arc of rotation. They are particularly useful in covering exposed bone around the skull base and related structures such as the ear and the orbit. This is shown in Figure 49.19 where a temporoparietal fascia flap is used to cover the exposed temporal bone following total resection of the external ear and extended neck dissection for a T4N1M0 squamous cell carcinoma.

Figure 49.18 The blood supply of the scalp.

continuity with the galea superiorly and the SMAS inferiorly. Deep to this is an avascular layer, known as the innominate fascia, which is in continuity with the loose areolar tissue of the scalp. The deep temporal fascia (or temporalis fascia) is the deepest layer and this is in continuity with the pericranium superiorly. Each of these layers may be used as a local flap to cover defects within their arc of rotation. They are particularly useful in covering exposed bone around the skull base and related structures such as the ear and the orbit. This is shown in Figure 49.19 where a temporoparietal fascia flap is used to cover the exposed temporal bone following total resection of the external ear and extended neck dissection for a T4N1M0 squamous cell carcinoma.

Eyelid

ANATOMY

The anatomy of the periorbital region is complex and without a good understanding of the structure and function of the eyelids periorbital excisions and reconstructions should not be undertaken. The upper eyelid and the lower eyelid differ in their roles. The upper eyelid both elevates due to contraction of the levator palpebrae muscle, which is innervated by the oculomotor (3rd cranial) nerve and constricts due to contraction of the orbicularis oculi muscle which is innervated by the facial (7th cranial) nerve. The lower lid is only able to constrict and relax due to the action of orbicularis oculi. This means that the upper lid has a far greater excursion (movement) than the lower lid. Both the upper and lower eyelids are divided into anterior and posterior lamellae. The anterior lamella consists of the skin and the orbicularis oculi muscle, whereas the posterior lamella consists of the conjunctiva and the tarsal plate. The skin of the eyelid is the thinnest in the body (1 mm) and is loosely attached to the orbicularis oculi muscle. This is arranged in a concentric ring around the orbit and upon contracture acts as a sphincter closing the orbital aperture. It can be divided into three parts: an outer orbital part covering bone, and inner preseptal and pretarsal components. Dividing the anterior and posterior lamellae is a septum. This is continuous with the pericranium at the orbital rims and extends to the margin of the eyelid. The tarsal plate forms the skeleton of the eyelid and is a dense sheet of fibrous tissue. The deepest structure of the eyelid is its lining, the conjunctiva, which contains many mucus secreting cells.

EYELID RECONSTRUCTION

Defects in the eyelid can be partial thickness, with either the anterior or posterior lamella having been excised or full thickness. Partial thickness defects of the anterior lamella are best either closed directly if small or covered with a full thickness skin graft. The posterior lamella can be closed with a graft of buccal or hard palate mucosa or a chondromucosal graft from the nasal septum consisting of nasal mucosa and septal cartilage. Full-thickness defects of up to one-quarter of the lid length can be closed directly and this increases to one-third in the elderly population with lax skin. When reconstructing a larger full-thickness defect, it is important to remember that both the anterior and posterior lamellae need to be replaced. This can be done by either using a single flap to reconstruct both layers or by using a flap to reconstruct the anterior lamella and a graft for the posterior lamella. At least one of the two layers must have its own blood supply as a graft placed on another graft will fail.
When closing a defect directly, two additional techniques may be used to bring in adjacent lateral tissue to enable a tension-free closure. The first of these is a lateral cantholysis. A horizontal incision is made from the lateral canthus to the orbital rim. The lateral canthal tendon is identified and divided. The lateral part of the lid can then be mobilized medially to close the wound. A second method is to place a z-plasty over the lateral canthus. A z-plasty consists of two interdigitating flaps of equal size and can be used to move tissue from one area to another. To reconstruct larger defects either a rotation or a transposition flap may be used. To reconstruct the lower eyelid a cheek rotation flap may be utilized, whereas a glabellar transposition flap is useful for the upper eyelid (Figure 49.15). These can both be combined with a composite graft from the nasal septum to reconstruct both anterior and posterior lamellae separately (Figure 49.20).

**Nose**

It is difficult to close primary defects in the nose directly without distortion, due to a relative lack of skin laxity. The use of full-thickness skin grafts gives very good cosmetic results and these remain the mainstay of nasal reconstruction for superficial defects. The skin grafts will take on recipient beds of subcutaneous tissue or perichondrium. However, if the deep margin has included the perichondrium, the nasal cartilages or is full thickness and has included excision of nasal mucosa then a different approach needs to be used. When constructing a full-thickness defect of the nose, three distinct layers need to be considered and reconstructed: these are nasal lining, nasal support and overlying skin (inside, scaffold and outside). A composite graft taken from the ear is an option when a small nasal rim defect is being reconstructed. This involves taking a full-thickness piece of the ear including both anterior and posterior skin. When the defect is medium sized, then a local flap needs to be used. The undersurface of such a flap can then be skin grafted to replace the nasal lining. Normally this can be a split-thickness skin graft but when support is needed to keep the nasal aperture open then a composite graft from the ear containing just anterior skin and cartilage is used. The cartilage is used as a non-anatomical strut (i.e. not in the normal anatomical position of the alar or lateral cartilages). The local flap options used to cover nasal defects are varied and can include...
Figure 49.20  (a) A squamous cell carcinoma of the left lower eyelid was excised leaving a full thickness defect. (b) The posterior lamella was reconstructed with a chondromucosal graft. (c) The anterior lamella was repaired with a cheek rotation flap. (d) The final result.
advancement flaps such as the Rintalla flap\textsuperscript{21} (Figure 49.10), transposition flaps such as a superiorly based axial nasolabial flap (Figure 49.21) or a bilobed flap (Figure 49.16). In addition to these techniques, microvascular free tissue transfer of a chondrocutaneous flap from the ear has been described.\textsuperscript{43}

Larger full-thickness defects of the nose following partial or total rhinectomy are more difficult to manage. A local flap can be used to reconstruct both the lining and skin cover of the nose by folding the flap in two. The most commonly used flaps for this are superiorly based nasolabial flaps. Bilateral flaps can be raised to import a large volume of tissue.\textsuperscript{44} An alternative to folding a flap is to use one flap for the lining and another for the cover. The nasolabial flap can be used for the lining as can a random hinge flap where adjacent tissue is raised and flipped over to fill the defect.\textsuperscript{45} This technique is more commonly used when the defect has been excised previously and the old wound margins have healed. The flaps used as lining can then be covered with either a skin graft or another flap such as a forehead flap (see below). It has to be remembered that when dealing with a total rhinectomy defect very good results can be obtained using a prosthesis. With the advent of osseointegration a prosthetic nose is both cosmetically acceptable and convenient for the patient.\textsuperscript{46} This is a viable alternative to surgical reconstruction.

Figure 49.21 (a) Defect following previous excision of large infiltrating squamous cell carcinoma of the nose with bilateral nasolabial and forehead flap marked. (b) Nasolabial flaps raised. (c) Nasolabial flaps inset to provide internal lining of nose. (d) Nasal support provided with auricular cartilage grafts. (e) Forehead flap raised. (f) Forehead flap inset to provide external cover. (g) The final result.
Figure 49.21  Continued
FOREHEAD FLAP

The forehead flap is a local cutaneous axial flap based on the supratrochlear artery. It is one of the oldest flaps in use and the earliest available description is from 600 BC by Susruta in India.47 A large flap of skin from the forehead can be raised on this vessel which can then be used to cover defects around the orbit and the nose. The donor site can be the vertical height of the forehead or the flap can be planned obliquely to maximize the length, and therefore the reach, of the flap. An obliquely placed donor site also reduces the arc of rotation. The donor site can be closed directly if the width of the flap is kept small (less than 2.5 cm) and this leaves minimal scarring. If a wider flap is required then the defect needs to be skin grafted; an alternative to this is to leave the defect to heal by secondary intention which can give a very acceptable cosmetic outcome.48 The transfer is normally carried out in two stages: the flap is raised and the tip of the flap inset into the primary defect. The remainder of the flap is then tubed to form a pedicle. After 3 weeks, the tip of the flap will have undergone some revascularization from the recipient site and the pedicle is then divided and reinset into the secondary defect (Figure 49.11). Alternatively, when reconstructing nasal defects, a third stage can be included.49 The flap is raised 2 weeks after it is inset, thinned and then reinset. The pedicle is then divided after a further 2 weeks. This prevents having a bulbous nasal tip, giving an overall better cosmetic result.

Cheek

The cheeks are the largest region of the face. They consist of skin which covers muscle groups which are either attached to the underlying maxilla and mandible or are lined on their inner surface by buccal mucosa. Various important structures transverse the cheeks including the parotid duct and the branches of the facial nerves. The cheek has been subdivided into three separate zones: a suborbital, a preauricular and a buccal mandibular area.50 When reconstructing defects in the cheeks, it needs to be considered that they are a three-dimensional structure with natural contours, shadows and hair lines. The majority of defects will be following ablative surgery for cutaneous malignancies. These normally present in the elderly population and even quite large defects can be closed directly, due to pre-existing skin laxity in this age group. Skin grafts on the cheek are very noticeable as they tend to transgress the different regions of the cheek and alter contour and colour, giving a poor cosmetic result. This means that primary defects of the cheeks should be closed directly or by using local flaps. As well as the relaxed skin tension lines, there are other noticeable lines in the cheek in which scars can be hidden. These are the nasolabial fold, infraorbital rim, alar crease, hairline and jawline. Due to the large surface area of the cheek a full range of flaps can be utilized; however, the most commonly used are rotation flaps (Figure 49.17) or V-Y advancement flaps (Figure 49.11).

Lips

The lips are complex structures involved in articulation, swallowing and facial expression. The lips are three-dimensional structures with an outer layer of skin and an inner layer of mucosa separated by muscle. The junction between the skin and mucosa is a specialized area as the skin blends into white roll, then vermillion and then into mucosa. A 1 mm discrepancy at this junction is noticeable at a distance of one metre. The orbicularis oris muscle contained within the lips is a complex muscle containing fibres in different orientations which can close the mouth, approximate the lips to the maxilla and mandible or purse the lips. Addition muscle fibres blend into the orbicularis oris from the levator labii superioris and other elevators of the lip superiorly, from buccinator laterally and from depressor labii inferioris and the other lip depressors inferiorly. The options for donor tissue for lip reconstruction are the remaining lip, the adjacent cheek, the opposite lip or from distant sites. It should be remembered that the goal of lip reconstruction is to restore oral continence; that is the role of the mouth as a sphincter, without causing microstomia (a tight or small mouth).51 The upper and lower lips should be considered separately as different techniques are needed to reconstruct similar defects in either the upper or lower lip.

LOWER LIP

Defects up to one-third of the length of the lower lip can be excised as a wedge (or a pentagon) and closed directly. Larger, superficial defects of the lip can be resurfaced with a split-thickness skin graft (the entire lower lip can be resurfaced in this way) or by a tongue flap. A flap is raised from the undersurface of the tongue and inset in the defect in the lower lip. The flap is based anteriorly and the donor site is not closed at the time the flap is raised. After ten days, the flap is divided and inset. At this point the donor site is closed directly. For defects of three-quarters of the lower lip the Karapandzic flap can be used.52 This is a combined axial advancement/rotation flap based on the facial artery. A transverse incision from the base of the defect to both nasolabial folds is made and the nasolabial folds are then incised in a cephalic direction. Laterally, the vessels and nerves are identified and preserved. The flap is mobilized by spread, not dividing, the fibres of the orbicularis oris. The bilateral flaps are then advanced and rotated and the defect closed in layers. Total reconstruction of both the upper and lower lip has been described using microvascular free tissue transfer.53

UPPER LIP

Defects up to one-quarter of the size of the upper lip can be closed directly. The orbicularis oris needs to be dissected free of the skin and the mucosa and repaired separately before the overlying tissues are closed. For larger defects, a reverse Karapandzic flap can be used where the nasolabial folds are incised along with the nasal sill and the skin kept intact in the submental area. The Abbe flap is a full-thickness flap taken from the lower lip and inset into the upper lip. The layers of mucosa, muscle and skin need to be accurately inset. The flap is then left attached to the lower lip for 1 week before division of the pedicle from the lower lip.54 The Abbe flap should be taken from the lower lip to reconstruct the upper lip and not from the upper lip to the lower lip. A variation of the Abbe
flap is the Abbe-Estlander flap which is used to reconstruct defects of the oral commissure. It can be taken from either the upper or lower lip and is a single stage operation as the pedicle of the flap becomes the new commissure.

KEY EVIDENCE

The use of local flaps is as much an art as it is a science and as such there is a scarcity of strong evidence (level 3/4).

KEY LEARNING POINTS

- Grafts are reliant on the blood supply of the recipient site while flaps take their own blood supply with them.
- Flaps can be random or axial; advanced, transposed or rotated.
- When using local flaps in the head and neck, the preoperative planning of the flap is of prime importance.
- There is no one correct flap for a particular part of the face or size or shape of defect to be closed.
- The reconstructive surgeon needs to be comfortable with a range of techniques as every patient is different and a one operation fits all approach will give unsatisfactory results.

ACKNOWLEDGEMENTS

In addition to photographs of the authors’ cases, we would like to thank Mr S Srivastava (Consultant Plastic Surgeon, University Hospital, Coventry) for supplying some of the images used in this chapter. The artwork in this chapter was drawn by Dr James Chan MA, MB Chir.

REFERENCES


Specific local and distant axial and myocutaneous flaps

RALPH W GILBERT AND JOHN C WATKINSON

INTRODUCTION

Reconstruction of the oncologic defects of the head and neck requires an advanced understanding of all the available options for reconstruction. The reconstructive ladder is applied to planning of all defect reconstructions progressing from closure by secondary intention to the use of free tissue transfer. This chapter will address the use of the major local axial pattern flaps and myocutaneous flaps used for reconstruction of mucosal defects of the head and neck and extensive cutaneous defects.

Distant axial and myocutaneous pedicled flaps are less frequently used in head and neck reconstruction following the introduction of free tissue transfer. This chapter will address the use of the major local axial pattern flaps and myocutaneous flaps used for reconstruction of mucosal defects of the head and neck and extensive cutaneous defects.

Forehead flaps

Table 50.1 Advantages and disadvantages of pedicled flap transfer.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Relatively straightforward to raise</td>
<td>Bulky</td>
</tr>
<tr>
<td>Reliable</td>
<td>Cannot be tubed</td>
</tr>
<tr>
<td>Adequate blood supply</td>
<td>Maybe associated with significant donor site morbidity</td>
</tr>
<tr>
<td>Can be used as 'life boats' for salvage surgery</td>
<td>May represent a compromise balancing the ideal reconstruction and the surgeon's skill set</td>
</tr>
<tr>
<td>Useful in the presence of infection</td>
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The forehead flap is an axial flap, which provides large areas of skin, and subcutaneous tissue, which may be used to

 Thou shalt provide thyself with a lifeboat.

Sir Harold Gillies¹

AXIAL FLAPS

An axial flap is based on a named arterial pedicle that runs within the skin superficial to the underlying muscle layer, parallel to the overlying skin (Figure 50.1). Axial flaps have an extremely good blood supply, which is determined not only by their length and breadth ratio, but also by the vascular territory of the vessels that supply them. Because of this, they can generally be raised to a much greater length than random flaps and can therefore be used to move skin over a greater distance. The use of these flaps in the 1960s was the first major step in head and neck reconstruction. Musculocutaneous and free tissue transfer have largely superseded their routine use, but the deltopectoral flap still has a role in head and neck surgery.
reconstruct defects below the level of the eyes. In its original form, as described by McGregor and McGregor, the axial forehead flap based on the anterior branch of the temporal artery was one of the first flaps used for intraoral reconstruction. Its major drawbacks are the donor site defect on the forehead and its reliability in oral reconstruction. Currently, it is most frequently used as a salvage flap following failure of a free tissue transfer or regional myocutaneous flap. When used for oral cavity reconstruction the flap is passed into the oral cavity medial to the zygomatic arch. The temporalis muscle tendon must be divided from the coronoid process to facilitate access.

The most commonly raised forehead flap is the cutaneous axial median forehead flap, based on the supratrochlear artery. It can be raised and transposed to reconstruct areas in the upper medial cheek region and any defect of the external nose (Figure 50.2). The donor site will often close primarily and the cosmetic result is excellent. Where larger areas of tissue are required, for example in complete nasal resurfacing, larger forehead flaps may be designed (e.g. Millard flying seagull flap), which may be facilitated by prior tissue expansion to ease donor site closure. Controversy exists regarding the use of tissue expansion to achieve primary closure. Some authors believe that the expanded forehead flap contracts excessively when used for nasal reconstruction, compromising the ultimate reconstructive result. In addition, the defect on the scalp when left to close with secondary intention often produces an excellent aesthetic result with normal contour and skin colour. These techniques are best suited in patients with high foreheads with some lax tissue to facilitate primary closure.

**Nasolabial flap**

The nasolabial flap was first documented in the Indian Sushruta of 600 BCE and has been a workhorse for reconstruction of defects around the face and the anterior oral cavity. The flap is based on distal branches of the facial artery and its venae comitantes. The flap is usually designed with an inferior base, but can be based superiorly with a more random vascular supply. The design usually places the most medial limit of the flap in the nasolabial fold with the superior limit approximating the medial canthus of the eye. The medial to lateral dimension of the flap is determined by the defect to be reconstructed and the ability to primarily close the donor site. Flap elevation is usually initiated distally with a retrograde dissection above the plane of the facial musculature. In the intraoral application a tunnel is placed traversing the facial muscles and buccinator allowing the inferiorly based flap to enter the oral cavity (Figure 50.3). This flap is extremely reliable when based inferiorly, with a relatively inconspicuous donor site particularly when bilateral flaps are used. Its greatest application intraorally is for the anterior floor of mouth and gingiva and it is simple and effective. The flap does usually require a secondary stage for division of the pedicle running through the face from the facial artery pedicle. The donor site for this flap is best tolerated in elderly patients with rhytids, which mask the donor site.

**Submental island flap**

This flap first described by Martin et al. in 1983 has great utility as an axial pattern flap or a free flap for reconstruction of the facial skin or intraoral lining. The flap is supplied by a branch or branches of the facial artery which either pass over or through the submandibular gland traversing medially on the mylohyoid muscle and then deep to the anterior belly of the digastric muscle to provide a perforator-based arterial supply and venous drainage to the submental skin. The flap has a variable venous drainage via the facial vein. There can be occasional problems with venous congestion particularly in the reverse flow design because of valves in the facial vein. The flap is usually designed in the midline just below the margin of the mandible with the superior/inferior dimension determined by the ability to close the submental skin (Figure 50.4). Dissection is usually initiated on the contralateral side to the planned vessel pedicle. Skin and subcutaneous tissues
are incised down to the level of the investing fascia of the digastric muscle with the plane of dissection carried in the submental triangle at the level of the mylohyoid muscle. The ipsilateral anterior belly is usually divided distally and proximally to preserve the blood supply to the flap and the dissection proceeds in a retrograde fashion to the facial artery and vein. The flap can be tunnelled under the mandible and through the submandibular and submental space for oral reconstruction or can be rotated or transposed onto the face for soft tissue coverage. The unique advantage of the flap is its colour match with facial skin and the relative inconspicuous nature of the donor site scar. There have been reports of problems with venous congestion particularly when tunnelled through the submandibular space.

### Facial artery myomucosal flap

The facial artery myomucosal flap (FAMM) was first described by Pribaz et al. in 1992. This flap is composed of oral mucosal and buccinator muscle and is based on branches of the facial artery. The anatomy of this flap is based on the buccinator muscle and its relationship to the facial artery. The buccinator is covered medially by the submucosa and

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**Figure 50.2** Use of a midline forehead flap to repair a defect in the left lower aspect of the nose and cheek. (a, b) A patient with a T4 basal cell carcinoma of the lower aspect of the nose and medial part of the cheek. (c) Wide excision was achieved, repair of the lateral side of the nose was with an infolded delayed forehead flap and the cheek repaired using V to Y advancement. (d) The forehead flap was divided 3 weeks later. (e) The final result.
mucosa and laterally by the external lamina of the muscles of facial expression, the masseter, the buccal fat pad, and the facial artery and vein.

The facial artery, a branch of the external carotid artery, enters the face by curving around the lower border of the mandible at the anterior edge of the masseter muscle. It then follows a tortuous course, passing superiorly and anteriorly to a position just lateral to the commissure of the mouth. At this point it lies deep to the risorius, zygomaticus major muscle and the superficial lamina of the orbicularis oris muscle. It lies superficial to the buccinator muscle and the lateral edge of the deep lamina of the orbicularis oris muscle. At this point in its course it gives off multiple perforating vessels to the cheek and the superior labial artery. It continues superiorly to the angular artery, which reaches the medial canthus. It has communicating branches with the buccal and infraorbital branches.

The FAMM flap is an axial pattern flap based on the facial artery. The flap may be harvested as an inferiorly based flap based on antegrade flow or a superiorly based flap with retrograde flow. The basic harvest technique is to Doppler out the facial artery through the buccal mucosa and map the course of the vessel. For the inferiorly based flap, dissection begins anterosuperiorly to identify the arterial supply to the upper lip with division of the facial artery at this point and then retrograde dissection which includes the mucosa, buccinator, facial artery and the tissue and venous plexus that lies between the artery and the muscle. In the superiorly based flap, the dissection begins inferiorly with visualization and ligation of the facial artery and then a retrograde dissection of the tissues including the buccinator muscle. A flap of 7–8 cm can be harvested with a thickness of 8–10 mm.

The FAMM flap is ideally suited for reconstruction of small mucosal defects in the oral cavity and, in particular, the mucosa of the lip. The flap can also be rotated across the alveolus to close small defects of the floor of mouth or tongue as well as the palate.

**Temporoparietal fascial flap**

The temporoparietal flap is a versatile local rotation or free fascial flap for reconstruction of the head and neck or extremities. Golovine first described the flap in the nineteenth century for orbit reconstruction. More recently it has been popularized by Brent and Byrd, and others for microtia repair and auricular reconstruction. Its unique characteristics are a remarkably robust vascular supply with a very thin and pliable flap with minimal donor site morbidity.

The arterial supply of the temporoparietal flap is the superficial temporal artery, a terminal branch of the external carotid artery. The vessel classically has a number of branches above the zygoma with most patients having a prominent frontal branch and dominant branch, which ascends towards the vertex of the skull. The venous drainage is via the superficial temporal vein running with the artery. There is some variation in venous anatomy with a small percentage of patients having venous drainage through the post-auricular vein or occipital veins. The temporoparietal fascia (TPF) lies just under the subcutaneous tissue of the lateral scalp (Figure 50.5). The fascia has an inner and an outer layer with the
artery and vein entering between the inner and outer layers and then coursing vertically in the outer layer of the fascia. The outer layer of the TPF extends as the superficial muscular aponeurotic system (SMAS) below the zygoma. A thin muscular layer (the superficial auricular muscle) separates two parts of the outer layer of the fascia below the temporal line. The inner layer of the TPF contains a dense vascular network, which originates from the outer layer. Two nerves have an anatomic relation to the flap. The auriculotemporal nerve, a branch of V3, lies within the superficial layer of the TPF and theoretically could provide for a sensate flap. The frontal branch of the facial nerve traverses over the zygoma in the same plane as the frontal branch of the superficial temporal artery and can be injured if the dissection is carried too far forward in the plane of this vessel.

For flap harvest, the patient is usually positioned in the supine position, with the drape line along the vertex of the scalp leaving the post-auricular area exposed.

The important landmarks for this flap are the arch of the zygoma, the pinna and the usual landmarks of the facial nerve. The artery usually lies just in front of the pinna and is easily palpated or detected with the Doppler in this location. The artery ascends vertically to the apex with a frontal branch coming off 1–3 cm above the zygomatic arch. The flap is harvested as an elliptical or teardrop shape, above the level of the zygoma. The incision is placed just posterior to the

Figure 50.3  (a) Design of the nasolabial flap placed in the nasolabial fold; (b) elevation of bilateral nasolabial flaps inferiorly based; (c) Inset and donor site closure flaps tunnelled through the buccal mucosa across the gingiva.
position of the vertical branch and can be either a straight or curvilinear incision into the scalp or can be ‘Y’ shaped for larger teardrop-shaped flaps. The inferior limit of the incision is usually the tragus, but inferior extensions can be used for extended rotations or if the surgeon wishes to visualize the facial nerve. The initial incision is started just above the zygoma extending into the scalp. The surgeon harvesting this flap for the first time must take great care not to incise too deeply as the pedicle can easily be divided during the incision. The plane of dissection is initiated by defining the level of the superficial temporal fascia just below the subcutaneous fat layer in the scalp. A good landmark is to look for the hair follicles; if they are being transected, the surgeon is elevating the flap too superficially. Once fully mobilized from the overlying skin the flap is incised around its periphery and elevated in the plane just above the temporal fascia. Dissection is carried down to about 2 cm below the arch of the zygoma to ensure an appropriate arc of rotation (Figure 50.6).

Clinical applications for this flap include orbital reconstruction including the extenteration cavity, upper and lower eyelids and the eyebrow as a fasciocutaneous hair-bearing flap. The flap has been widely used for auricular reconstruction including microtia and traumatic or oncologic deformities, as well as palate reconstruction and buccal mucosal reconstruction.

DISTANT AXIAL FLAPS

Deltopectoral flap

This flap was described by Bakamjian and Littlewood in 1964 and is an axial pattern flap designed on the anterior chest wall between the line of the clavicle and the level of the anterior axillary fold. Its vascular supply arises from the upper three or four perforating branches of the internal...
mammary artery, which emerge through the medial end of the intercostal spaces (Figure 50.7). Its boundaries are the clavicle superiorly, the acromion laterally and a line running through the anterior axillary fold to above the nipple inferiorly. The flap will extend to any site in the neck and is extremely useful for neck resurfacing. The territory of the perforator vascular system has been shown to extend as far as the groove separating the deltoid from the pectoralis major (deltopectoral groove). Any extension of the flap beyond this should not be regarded as a random component.

The flap is marked out using the landmarks described above and then elevation begins laterally. The pectoral fascia is left on the flap, leaving the muscle fibres below absolutely bare. Any branches of the acromiothoracic axis that are encountered should be ligated.

**PLANNING THE TRANSFER**

The deltopectoral flap has an anomalous pivot point. There is considerable laxity of the skin on the anterior axillary fold when the arm is abducted. This means that the lower border of the flap is considerably longer than the upper part. The pivot point on the flap is thus at the medial end of the upper limb and not the lower limb. This needs to be taken into account when planning the flap. The donor site is usually covered with a split skin graft.

The uses of a deltopectoral flap are:

- a one-stage reconstruction of the anterior neck skin;
- a two-stage reconstruction as the flap may be passed over existing neck structures to resurface distant sites.

**OTHER DISTAL AXIAL CUTANEOUS FLAPS**

These include cervical skin flaps and occipitomastoid-based flaps.

Cervical-facial skin flaps of varying shape, size, site and direction may be designed to make good use of lax neck skin for reconstructive purposes. In general, they make use of the side of the neck. They are most frequently used as a primary or salvage procedure for external skin defects of the lower face and cheek. This flap has the unique advantage of providing excellent if not identical colour match for external defects. The nape of neck (Mütter) or posterior scalp flap is a random pattern skin flap, which exploits the neck skin over the trapezius muscle and can be raised on the occipital vessels and extended downwards to the spine of the scapula. It may be swung on its upper pedicle to reconstruct areas in the lower face and submandibular region.

**MYOCUTANEOUS AND MUSCLE ONLY AXIAL DISTANT FLAPS**

One of the most important discoveries in the last 20 years is that the skin over most parts of the body receives its blood supply from small musculocutaneous arteries (perforating vessels) that enter it from the underlying muscle (Figure 50.8). It subsequently became apparent that an obvious way...
to move a large area of skin for reconstructive purposes was to transpose the skin with its underlying muscle vascularized by its dominant blood supply. Box 50.1 lists the myocutaneous and muscle only axial distant flaps.

The pectoralis major and the latissimus dorsi flaps represent the workhorses for many head and neck reconstructive surgeons and a detailed understanding of the anatomy and harvest techniques will be a significant asset to the head and neck surgeon.

The muscles are supplied ultimately by segmental vessels, which run deep within the muscle and give off perforators that enter the muscles and provide communication between the segmental vessels and the musculocutaneous vessels in the skin. There may be several arterial pedicles. The artery is usually accompanied by two venae comitantes that unite after leaving the muscle to drain into a major regional vein. Five types of muscular arterial supply have been described (Table 50.2).

The blood supply to the muscles may also be segmental or axial in pattern (see Box 50.2). Most of the round muscles, for example the sternomastoid, have a segmental supply; perforators penetrate the muscle along its course and immediately break up into small branches. The flatter muscles such as pectoralis major and latissimus dorsi have an axial supply: the major arterial supply runs a portion of the length of the deep surface of the muscle, ultimately penetrating the muscles and dividing into intramuscular branches which provide perforators to the overlying skin.

**Pectoralis major flap**

This flap was first described by Ariyan in the late 1970s. The muscle’s origins are the clavicle, the sternum and slips from the upper seven ribs. There is also a variable origin from the aponeurosis of the external oblique that is variable in size. It inserts into the bicipital groove of the humerus. The muscle has three major segmental subunits: clavicular, sternocostal and an external segment (the most lateral part of the muscle), which originates from the ribs.

The main arterial supply, which provides the vascular basis for this flap, comes from the pectoral branch of the acromiothoracic artery that arises from the first part of the axillary artery (Figure 50.9). The pectoral branch of the acromiothoracic axis emerges from the clavipectoral fascia, along with the lateral pectoral nerve, medial to the insertion of pectoralis minor on the coracoid process, a bony prominence that can be felt below the clavicle near the junction of its middle and outer thirds. The point, 2–3 cm medial to the coracoid process, represents the surface marking of the vascular hilum of the muscle. The vessels do not enter the

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**Box 50.1 Myocutaneous and muscle only axial distant flaps**

- Pectoralis major
- Latissimus dorsi
- Sternocostal
- Trapezius
- Platysma

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**Table 50.2 Patterns of vascular anatomy.**

<table>
<thead>
<tr>
<th>Vascular pedicle</th>
<th>Examples used in head and neck surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: One pedicle</td>
<td>None</td>
</tr>
<tr>
<td>II: Dominant pedicle and minor pedicles</td>
<td>Sternocleidomastoid</td>
</tr>
<tr>
<td>III: Two dominant pedicles</td>
<td>Trapezius, Platysma</td>
</tr>
<tr>
<td>IV: Segmental pedicles</td>
<td>Temporalis</td>
</tr>
<tr>
<td>V: One dominant pedicle plus secondary segmental pedicles</td>
<td>Pectoralis major, Latissimus dorsi</td>
</tr>
</tbody>
</table>

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**Box 50.2 Essential surgical points**

- With the axial muscular flaps, although the blood supply to the muscle is axial, the blood supply of the skin upon the muscle is random based on the presence of perforating vessels.
- There is a minimum size of skin paddle that should be taken to ensure that one incorporates enough perforators to supply the skin flap. For pectoralis major and latissimus dorsi flaps, this usually means a skin paddle measuring 5 × 3 cm (the size of the palm of an adult’s hand).
- Smaller skin paddles may not incorporate perforators and may not survive.
muscle belly immediately, but run on its deep surface in a downward and medial direction giving off its branches. The acromiothoracic artery gives off a superior (clavicular) branch to the clavicular segment of the muscle and a main pectoral branch which then gives off an inferior thoracoacromial branch to the sternal segment and a lateral thoracic trunk to the external segment.

The major advantages of this flap are that it has a large skin territory (the whole of the skin overlying the muscle may be raised), it has a rich vascular supply and it can be transferred without prior delay. It has a large arc of rotation and can be transferred up to the upper aspect of the ear utilizing a skin paddle extension from the abdomen. It can be harvested in the supine position, and can be transferred as a muscle-only flap or a skin and muscle paddle. Primary donor site closure is easily achieved. However, it is a large bulky muscle, which is relatively immobile and, therefore, is suited best to providing well-vascularized tissue to fill large defects where mobility is not of paramount importance, as in the repair of fistulae. It violates the breast in the female and can be particularly bulky in women with large breasts. Incision design in the inframammary fold is critical to avoid a significant breast deformity. In females where the pectoralis flap is not appropriate the latissimus dorsi flap provides an appropriate alternative.

**TECHNIQUE**

With the patient in the supine position, the surface markings of the acromiothoracic artery are outlined. A dotted line is marked from the acromion to the xiphoid process representing the approximate location of the vascular pedicle (Figure 50.10). A skin island of the appropriate size and shape may be drawn over the distal part of the muscle, to facilitate a suitable arc of rotation. The borders of the skin paddle should lie between the lateral edge of the sternum medially and the nipple laterally. The incision for access should be extended into the axilla. The technique described by McGregor, i.e. designing the skin incision to allow a secondary deltopectoral flap from the same side, should be considered in both males and females. This technique allows for an easier wound closure and provides a salvage flap for neck resurfacing.

Unless the arc of rotation needs to be increased, it is advisable not to extend the lower part of the skin paddle beyond the inferior edge of the muscle. This part of the flap is random and, although the survival of this segment can be increased by taking part of the rectus sheath, this is not wholly reliable and should not be done unless absolutely necessary.

Elevating the pectoralis major flap is described in Box 50.3.

Hemostasis is maintained throughout the elevation of the flap by carefully cauterizing the intercostal perforators as well as the perforators supplying the medial portion of the muscle from the internal mammary vessels.

Modifications of the flap include harvesting of muscle alone when, for example, closing large lower neck wounds which require bulk with no skin paddle. A subsequent skin graft can be applied to the raw muscle surface. Access is achieved along the lateral border of the muscle and primary closure easily achieved. The incorporation of vascularized bone has been described where part of either the fifth rib or the sternum can be transferred with the flap to provide composite soft tissue and bony reconstruction. The vascular supply to these bony segments is at best precarious and in the majority of instances non-existent. Newer and more effective techniques for composite soft tissue and bony reconstruction are available obviating the need for the myo-osseous pectoralis major flap. Where the excessive bulk of the pectoralis major is a problem, harvesting over the thinner, parasternal area has been described, e.g. to tube the flap for reconstruction in the hypopharynx. Although this sounds attractive, practical experience has shown that it is virtually
impossible to tube a pectoralis major myocutaneous flap. This should be considered as a salvage technique only as better free tissue transfer techniques are available.

When the above guidelines are followed, there are very few potential pitfalls with this flap. It is highly reliable and even when the skin paddle fails, the underlying muscle will usually survive and can be allowed to granulate and heal by secondary intention, or covered subsequently with a skin graft. It is always worth checking for congenital absence of the pectoral head as part of Poland’s syndrome.

When a conventional flap is used, the skin paddle is designed medial to the nipple, at about the level of the sixth rib. In this area, the skin overlying the muscle is usually relatively thin in males. To achieve similar thickness in females, a design placing the skin island in the inframammary fold oriented transversely or slightly angled superiorly in its medial extent allows for the thinnest flaps. The surgeon considering this flap in females should consider the inframammary incision as the preferred approach.

**Latissimus dorsi flap**

This flap represents the first myocutaneous flap described in the medical literature.\(^1\) It was repopularized by Olivari\(^2\) in 1976 for the repair of local defects. Further work by Quillen\(^3\) in 1978 described its use for head and neck reconstruction, and it remains a reliable and versatile fundamental component of the surgeon’s repertoire.

The muscle is large and triangular in shape and arises from the sacrum and lumbar vertebrae, thoracolumbar fascia, the posterior iliac crest and the lower six thoracic vertebrae. In addition, some slips arise from the lower three ribs and the muscle converges to have a narrow insertion into the intertubercular groove of the humerus. Hence, it forms the posterior wall of the axilla. It is a type V muscle that receives a significant but smaller blood supply from the perforating vessels through the lumbosacral fascia, and a pedicled flap can be based on this to repair defects in the buttock region.

Its major vascular supply arises from the thoracodorsal vessels, which have their origin in the subscapular artery (Figure 50.11). This latter artery arises from the axillary artery, gives rise to the circumflex scapular artery about 4 cm from its origin and then continues as a thoracodorsal artery to enter the latissimus dorsi about 10 cm from its humeral insertion. Just before its insertion, it gives off a branch, which accompanies branches from the thoracic artery (which also arises from the subscapular artery) and carries on to supply the serratus anterior. Within the latissimus dorsi muscle, the thoracodorsal vessels divide into superior and lateral branches, which allow the muscle to be split into two. Either two flaps can then be taken or just one flap, thereby leaving some muscle behind.

Venous drainage is by the venae comitantes, which accompany the thoracodorsal artery and drain into the axillary vein. The nerve supply is via the thoracodorsal nerve, which is a branch of the posterior cord of the brachial plexus.

Large amounts of tissue are made available using this flap. Flaps measuring 10 × 8 cm are easily harvested and subsequent primary closure is easily achieved. Even larger amounts of tissue may be taken as a musculocutaneous flap measuring 40 × 20 cm but this requires skin grafting of the donor defect and may lead to problems with healing on the back.

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**Box 50.3 Elevating the pectoralis major flap**

- Incise the skin down to the underlying muscle.
- Define the inferior and lateral borders of the pectoralis major muscle.
- Mobilize the lateral border of the pectoralis major muscle dissecting the subpectoral plane which is relatively avascular.
- Visualize the pedicle on the deep surface of the muscle running medial to lateral.
- Divide the inferior muscle attachments from the ribs or rectus sheath.
- Mobilize in an upward direction.
- If the skin paddle is thick or excessively mobile place sutures from the dermis of the skin island to the muscle surface to prevent shearing and flap loss.
- Combine mobilization in an upward direction first laterally and then medially.
- Identify the lateral border of the external segment of the muscle.
- Divide the sternal insertion of the muscle at the level of the anterior axillary line and remember to continue in an vertical direction.
- Divide the insertion of the muscle usually with a monopolar cautery to avoid bleeding from the lateral perforators of the pectoral artery.
- The muscle will be now rotated and the vascular pedicle will be clearly identified.

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**Figure 50.11** Blood supply to the latissimus dorsi flap. The thoracodorsal artery is a continuation of the subscapular artery which comes directly off the axillary artery.
A latissimus dorsi flap may not only be raised as a myocutaneous pedicled flap but also used for free tissue transfer. It is reliable, with a long pedicle of 10 cm, which can be further lengthened by dividing the circumflex scapular artery. The diameter of the subscapular artery at this point is at least 3 mm and the veins are of similar size.

By designing the flap low down on the back, the arc of rotation allows transfer into the head and neck region up to the zygomatic arch and flaps can be made to reach the top of the head (particularly if only muscle is used). The other advantages of this flap are that it does not violate the breast and because it is a large flat muscle, it is possible in extreme circumstances to tube it for total pharyngeal reconstruction. In addition, the subscapular artery offers a variety of flaps, which may be used either singularly or in combination.

Therefore, a scapular flap along with a latissimus dorsi flap and serratus anterior flap may all be raised on the same pedicle (Box 50.4).

Despite the advantages, it still remains a musculocutaneous flap with thick skin and is therefore more bulky than, for example, a radial free forearm flap. Its use tends to be in resurfacing large defects of the external neck skin and for secondary repair of wound complications such as salivary fistulae. It has an excellent application in reconstructing the total glossectomy defect as the volume of the flap makes it ideal for filling the mucosal defect and the dead space below the resection site. Serious donor site problems are rare but dehiscence and late wound seroma can be a problem.

Congenital absence of the muscle should be checked for prior to surgery, and in athletes and those who do manual work the flap should be raised from the non-dominant side.

Raising the flap usually involves a variable amount of turning of the patient. Some authors advocate the lateral decubitis position that often requires a repositioning manoeuvre following the ablative procedure (see Box 50.5). Most surgeons experienced with this flap will harvest it with the patient turned 15 to 30° which obviates the need for the repositioning manoeuvre and allows two team procedures.

**RAISING THE FLAP**

Small flaps may be raised with the patient supine, but larger flaps require the patient in a rotated position with the arm freely draped so that it may be moved during the flap harvest.

Skin may be raised over the whole area of the muscle, although the vascular supply from the thoracodorsal artery decreases as one approaches the lumbosacral fascia. The posterior axillary fold is marked out and this represents the anterior edge of the muscle. The posterior iliac crest is also marked, together with the tip of the scapula. The skin flap is designed to the appropriate size and shape, with particular...
behind the bra strap.

An acceptable scar in young women since it can be hidden
harvested in a horizontal direction, which gives a more
or vertical design, but if a free flap is required the flap may be
pedicled myocutaneous flap, it will usually mean an oblique
required to facilitate transfer to the head and neck via a
reference to the length of pedicle. If an arc of rotation is
required to transfer to the head and neck via a pedicled myocutaneous flap, it will usually mean an oblique or vertical design, but if a free flap is required the flap may be harvested in a horizontal direction, which gives a more acceptable scar in young women since it can be hidden behind the bra strap.

Elevation of the latissimus dorsi is shown in Box 50.6.

When using the flap as a myocutaneous rotation flap, consideration should be given to not dividing the insertion of the muscle. When the muscle is left intact the insertion prevents twisting of the vascular pedicle and reduces the risk of kinking and venous congestion. If an extended pedicle is required then the tendon must be divided to get additional length.

Delivery of the latissimus dorsi flap is shown in Box 50.7.

The donor site is closed primarily in two layers using two large drains, one of which should be left for up to a week to avoid a seroma, which can occur following such a large dissection. This can be avoided by suturing the muscle remnants to the chest wall prior to closure. With a pedicled flap, the muscle should be denervated by dividing the nerve. If a free flap is being used, the thoracodorsal nerve may be preserved and used for reinnervation procedures such as anastomosis to a cross-facial nerve graft for facial reanimation, or following total glossectomy where the maintenance of muscle bulk has been noted following anastomosis to the hypoglossal nerve.

**Sternomastoid flap**

The sternocleidomastoid muscle, unlike the previously described muscles, does not have a localized vascular hilum. It is supplied segmentally by vessels, which enter the muscle at intervals along its length. There are two principal vessels in its upper half, which consist of two branches of the occipital artery, and in its lower half, a branch from the superior thyroid artery. Further minor arterial branches enter in between. Its use has been described as a myocutaneous flap raised as a composite skin muscle flap, as a myocutaneous skin island flap taking a skin island based over the lower aspect of the muscle (Figure 50.14) or as a composite muscle–bone flap used for mandibular reconstruction taking

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**Box 50.6 Elevation of latissimus dorsi**

- Outline the flap.
- The initial incision exposes the anterior edge of the latissimus dorsi muscle.
- Identify the serratus anterior.
- Do not go deep to serratus anterior here: this places the pedicle in jeopardy.
- Identify the branches to serratus and follow them in a retrograde direction to visualize the pedicle to the latissimus dorsi.
- Divide latissimus dorsi inferiorly.
- The muscle flap may be extended beyond the skin island in a lateral to medial and supero-inferior direction to provide additional muscle to resurface external defects or provide additional volume to fill defects. Remember at this point that if one is low and on top of the latissimus dorsi, the pedicle is not in jeopardy.
- Elevate the flap in the submuscular plane.
- Identify the pedicle running down the muscle, usually in its central portion. The key to easy identification and protection of the pedicle to latissimus dorsi is to identify the branches to the serratus and follow them superiority to the take-off from the thoracodorsal. Occasionally, patients will have a separate pedicle to serratus but this is very infrequent. Once the thoracodorsal pedicle is identified divide the vessels to serratus anterior and continue dissecting superiority.
- Continue the dissection up towards the tip of the scapula.
- The junction of the thoracodorsal vessels with the circumflex scapular vessels to form the subscapular artery can be clearly seen at the upper anterior end of the muscle in the axilla.
- If a longer pedicle is required (as is usual), ligate the circumflex scapular vessels.
- Follow the subscapular vessels into the axilla.

**Box 50.7 Delivery of the latissimus dorsi flap**

- Ligate the circumflex scapular artery and vein.
- Follow the subscapular vessels into the axilla.
- If a pedicled transfer is to be completed, the flap must be tunnelled into the neck. There are essentially two options, sub- or suprapectoral, with the subpectoral route being the favoured approach. The border of the pectoralis major is identified and dissection deep to the muscle establishes the space between pectoralis major and pectoralis minor. A tunnel may be developed with blunt or sharp dissection making sure that the pedicle to the pectoralis major is kept medially. The surgeon then develops the superior dissection if exposing the clavicle and the clavipectoral fascia has not already performed it. Splitting the pectoralis major then develops a tunnel. The tunnel needs to be wide enough to allow the passage of the muscle without compression, usually the breadth of one's hand.
- Use blunt finger dissection going on top of the pedicle.
- Remember to go ‘over pectoralis minor – under pectoralis major’.
- Dissect from above through the clavipectoral fascia, dividing some of the lateral fibres of pectoralis major.
- Open and widen the tunnel.
- Deliver the flap without twisting or rotating the muscle.
a segment of clavicle. Its routine use is not recommended as it has a number of distinct disadvantages (Box 50.8).

The sternomastoid flap is therefore rarely used but it may still have a role to play in two situations. First, it can be particularly useful as a muscle-only flap pedicled superiorly to fill small defects in the pharynx and oral cavity, and second, when split along its length and rotated anteriorly, it may be used to cover vessels in the compromised neck.

**Trapezius flap**

Three basic myocutaneous flaps have been described which make use of trapezius: the upper trapezius, the lateral trapezius and the lower trapezius flaps. These may be pedicled into the head and neck area and, in addition, descriptions of the upper and lateral trapezius flaps to include transfer of the spine of the scapula have been described for mandibular reconstruction. The vascular supply of these flaps is complex and varied depending on the design.

The superiorly based trapezius flap incorporates the upper third of the trapezius muscle and the overlying skin. The flap is supplied predominantly by the occipital artery and its venae comitantes. This flap has a limited use but can be applied for defects of the temporal bone, lateral face or upper neck. The flap is harvested by designing a skin island over the pars descendens of the trapezius muscle with dissection carried out in a retrograde direction along the deep surface of the muscle.

The pars horizontalis (middle) and pars ascendens (lower) of the trapezius muscle form the basis of the lateral and lower trapezius flaps (Figure 50.15). The middle parts of the muscle are supplied mainly by the superficial cervical artery (superficial branch of the transverse cervical artery) and the lower part is supplied by the dorsal scapular artery (deep branch of the transverse scapular artery) and segmental intercostal perforators. The origins of the arteries supplying the trapezius muscle are highly variable and the aforementioned vessels may arise from different trunks.

A recently published anatomic study has demonstrated that the superficial cervical artery always runs lateral to the levator scapulae and rhomboid muscles dividing into a short superior branch and long inferior branch which courses inferiorly with the accessory nerve to the level of the scapular spine. The dorsal scapular artery, the dominant supply to the lower third of the muscle, runs deep to the levator scapulae and minor rhomboid muscles.

The flap with the most utility for head and neck reconstruction is the pedicled lower trapezius myocutaneous flap. This version of the flap has an arc of rotation appropriate for resurfacing of the neck and face, and has great utility as a salvage option when a free tissue transfer has failed or there are no recipient vessels available for anastomosis of a free tissue transfer. The patient is positioned in the lateral

### Box 50.8 Disadvantages of the sternomastoid flap

- The upper sternomastoid composite skin muscle flap is poorly vascularized and not reliable.
- The blood supply to the skin paddle based over the lower third of the muscle is similarly unreliable.
- The upper and lower ends of the muscle are areas of oncological significance.
- The inclusion of clavicle for mandibular reconstruction is usually no longer required as superior reconstructive options are available.
Box 50.9   Disadvantages of the platysma flap

- Blood supply can be unreliable.
- There may have been previous surgery which has violated the neck and therefore precludes its use.
- When based on the submental branch of the facial artery, this requires preservation of musculature in an area of oncological significance which may have to be addressed in the resection.
- By and large, the neck should be avoided as a source of reconstruction for the oral cavity.
- Removal of the platysma interferes with the blood supply to the overlying skin, which can have disastrous results.

decubitus position with the arm draped freely for repositioning of the scapula during dissection. The muscle margins, the medial border of the scapula and the thoracic spines down to the 12th vertebra are marked. The skin island is usually designed with the majority of the flap overlying the lower trapezius. Dissection begins medially identifying the superior and lateral borders of the latissimus dorsi muscle and the lateral border of the trapezius. Dissection continues under the trapezius muscle where the dorsal scapular artery is identified. Retrograde dissection continues following the vascular pedicle of the flap, the descending branch of the dorsal scapular artery (running deep to the rhomboids) must be divided to allow rotation and complete elevation of the flap. Dissection can be carried up to the levator scapulae with occasional division of the minor rhomboids to improve the arc of rotation. The flap can then be tunnelled subcutaneously into the neck.

Although these flaps are reasonably reliable and may play a role particularly in the repair of the posterior aspect of the head and neck, such areas are easily reached with a pedicled latissimus dorsi flap. The patient positioning issues and anatomic variability related to the trapezius flap mean that it has a limited role to play in current head and neck reconstructive practice. Its role is principally to salvage, e.g. as a lifeboat when other flaps have been exhausted.

Platysma flap

The platysma flap was first described in 1978. It is really one half of the myocutaneous apron flap and the skin transferred can either be at the level of the hyoid or in the supraclavicular region, after which the donor site is closed primarily. The blood supply to the upper part of the flap comes from the submental branch of the facial artery and to the lower part from a branch of the transverse cervical artery. Although initially attractive as a simple way of providing a method of intraoral reconstruction, this flap has a number of distinct disadvantages and is rarely used today (Box 50.9).

CONCLUSION

While the majority of complex defects are reconstructed with free tissue transfers, pedicled local or regional flaps have a major role to play in head and neck reconstruction. A clear understanding of the principles of use of local flaps and a comprehensive understanding of the anatomy of these flaps provides the head and neck surgeon with a plethora of local and regional options for primary and secondary reconstruction.

KEY EVIDENCE

- Myocutaneous and local flaps remain a major option in the management of head and neck defects. Their current role is largely limited to cutaneous defects and secondary reconstructions of failed free tissue transfer or primary reconstruction in centres where free tissue is not available.

KEY LEARNING POINTS

- Pedicled flaps are usually straightforward to both use and harvest
- They are generally reliable, but may be bulky and poorly pliable
- Can be useful for salvage, particularly in the presence of infection
- May be associated with significant donor site problems
- Should be in the surgical repertoire of every head and neck surgeon

REFERENCES


Defect-based reconstruction: mandible and oral cavity

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INTRODUCTION

Mandibular reconstruction is one of the most difficult challenges that a head and neck surgeon may face. The field has evolved dramatically over the last 20 years and continues to do so.

The mandible is important functionally and cosmetically. It is a major determinant of facial appearance (in particular chin projection and lip support), mastication, speech and swallowing. It also provides support for the tongue and is crucial in maintenance of the airway.

Mandibular resections can be segmental (whole height of the mandible) leading to mandibular discontinuity, or marginal where only the alveolar bone is resected (Figure 51.1). Marginal defects are usually reconstructed to improve dental rehabilitation and the placement of dental implants. Segmental defects are reconstructed to provide mandibular continuity. Segmental mandibulectomy has been associated with a poor quality of life (HRQOL). Loss of mandibular continuity laterally (i.e. posterior to the mental foramen) results in deviation of the mandible towards the resected side due to the unopposed pull of the remaining muscles of mastication, soft tissue contracture and scar formation. Thus although the cosmetic deformity in lateral mandibular defects may not be great, the dental occlusion will be affected.

If the patient is edentulous the ability to wear a lower denture will be compromised.

Loss of mandibular continuity anteriorly (i.e. anterior to the mental foramen) will result in not only functional problems but gross facial disfigurement (Andy Gump deformity) (Figure 51.2).

The aims of mandibular reconstruction must be to restore the facial dimensions (facial height, width and projection). For optimal results, the skeletal buttresses and the soft tissue (internal and external) must be reconstructed around which dental rehabilitation can be planned. Many reconstructive techniques restore the mandibular continuity and provide a good cosmetic result, but fail to achieve an adequate functional result.

The most appropriate mode of reconstruction for each patient is determined by the size and position of the defect, the quality of the remaining bone, the size and position of any associated soft tissue defect and the vascularity of the tissues adjacent to the defect. A thorough assessment of the patient’s biological age and comorbidity is required. The relevant surgical and supportive expertise must be available in the hospital.

ANATOMICAL CONSIDERATIONS

The mandible is a membranous bone. It has a horseshoe-shaped body and a pair of rami. The body of the mandible meets the ramus on each side at the angle of the mandible (Figure 51.3).
The upper part of the mandible from the midline to the angles is the alveolar process. This bone carries the teeth. The ramus is vertically placed and forms the coronoid process and the mandibular condyle. The condyle articulates with the skull base at the mandibular fossa to form the temporomandibular joint. This is a synovial joint.

Figure 51.1 (a) A segmental defect of the mandible where mandibular continuity is lost. (b) A planned marginal (rim) resection where mandibular continuity is retained.

The effects of not reconstructing the anterior mandible (Andy Gump deformity).

Figure 51.2

Figure 51.3 A mandible with the body, ramus and condyle and alveolar process labelled.
Various muscles (the elevators and depressors of the mandible) are attached to the mandible at a variety of sites. They are responsible for the complex movements required of the mandible in mastication, swallowing and speech. As the mandible projects anteriorly from its articulation with the skull base, a cantilever system with a fulcrum at the temporomandibular joint is created. This requires the mandible to sustain significant forces particularly in mastication. Tensio-nal forces are created at the upper border and compressional forces at the lower border. Whatever mode of reconstruction is used, it must be able to withstand these considerable forces.

ANATOMICAL CONSIDERATIONS AND RECONSTRUCTION

The cosmetic deformity and functional loss that occur after mandibular resection depends on the size and location of the segmental defect.

The more anterior the defect, the greater the deformity and loss of function. Posterior defects are much better tolerated but a malocclusion may result in a dentate patient.

CLASSIFICATION OF THE MANDIBULAR DEFECT

Not only the size and location of the mandibular defect should be assessed, but also the associated soft tissue deficit. The size and location of the soft tissue deficiency, the vascularity of the remaining soft tissues, the presence of infection and whether the tissues have been irradiated will determine the best mode of reconstruction. Only a thorough understanding of the defect allows optimal reconstruction.

In 1991, Urken et al. described a classification scheme not only taking into consideration the mandibular defect but also the soft tissue defect.

The mandibular defect can be classified as H, C, L:

- H – lateral defects of any length including the condyle
- C – entire central segment from lower canine to canine

The soft tissue defect can be classified as none, skin, mucosal and through and through.

Boyd et al.’s classification uses three upper case and three lower case letters.

For a bony defect, it is similar to the above classification. A combination of letters is possible, for example a defect from angle to angle of the mandible is LCL.

For a soft tissue defect:

- o – neither skin or mucosa affected
- s – skin
- m – mucosa.

A through and through defect will thus be sm.

The mandibular reconstructive ladder is shown in Box 51.1.

NO BONY RECONSTRUCTION

Advancements in soft tissue reconstruction and thus improving the recipient soft tissue bed has allowed the reconsideration of alloplastic materials to reconstruct the mandible. Improving the soft tissue vascularity around the mandible with free tissue transfer or pedicled flaps reduces previous problems seen with using alloplastic materials in reconstructing the mandible. Kiyokawa et al. reconstructed the oro-mandibular complex using a petoralis major flap with a metal plate in seven patients with no complications.

The ideal alloplastic material must be biocompatible and able to withstand the forces sustained by the mandible in mastication.

Materials that have been used include medical polymers, ceramics and a variety of metals. The initial metal alloys used were vitallium and stainless steel in the form of a plate. However, these were susceptible to screw loosening and fracture. The titanium reconstruction plates and the THORP (titanium hollow osseointegrated reconstruction plate) plate are able to withstand masticatory forces and plate fracture is much rarer. However, plate exposure through the external skin or into the mouth is still a major problem.

Bhathena and Kavarana used a sialastic mandibular implant for mandibular reconstruction in 69 patients. Only 30 per cent of the implants were retained for greater than one year. Chemoradiotherapy was one of the major determinants for extrusion.

Okura et al. in a series of 100 patients reconstructed mandibular defects with bridging plates. The plate survival at five years was 62 per cent. Anterior defects and radiotherapy were major determinants for survival.

Anterior mandibular defects are much more likely to fail than posterior ones. Ninety-two per cent of reconstruction with plates is successful in lateral defects but only 30 per cent with anterior ones. It is also argued that patients who require mandibular reconstruction for advanced cancers will die of their disease within two years and so the use of alloplastic materials is recommended. Shiptzer et al. showed good results of mandibular reconstruction with just plates. There was no plate exposure, extrusion or fracture in 83 per cent of their sample one year and 72 per cent at two years.
As the risk of initial complications with alloplastic reconstructions is less than that with more complex reconstructions, delays in starting adjuvant chemoradiotherapy are less. There is also no evidence that alloplastic metals are responsible for radiation shielding in patients.

Lindquist et al.\textsuperscript{11} concluded that functional and aesthetic results were excellent in their series of 34 patients when reconstruction plates were used.

Blackwell et al.\textsuperscript{12} in a series of 17 patients abandoned using soft tissue flaps with THORP plates even for lateral defects as the risk of reconstructive failure in their series was as high as 40 per cent.

Kim et al.\textsuperscript{13} presented 41 cases reconstructed with AO plates. Twenty-two per cent of patients required plate removal but the incidence varied as to the location of the defect – 52 per cent of anterior, 12 per cent of lateral and 8 per cent of condylar and ramus defects.

Wei et al.\textsuperscript{14} looked at 80 patients reconstructed with a reconstruction plate and a soft tissue flap. Thirty-one per cent of surviving patients had required secondary surgery for plate exposure, soft tissue deficiency, intraoral contracture, trismus and lack of gingivolabial sulcus.

Ryu et al.\textsuperscript{15} showed that significantly more mandibular plates were lost when the patient had received radiotherapy in the postoperative period.

The patient’s quality of life and oral rehabilitation does not appear to be related to the quantity of mandible resected but on the amount of associated tongue resection.

Although some success has been achieved with alloplastic materials, the general consensus among reconstructive surgeons is that the potential problems outweigh any benefits and so this technique is reserved for patients with medical comorbidities.

**Technique**

The reconstruction plate must be accurately contoured to the shape of the mandible. This can be facilitated by the construction of a three-dimensional model on which the plate is pre-bent. The plate can then be sterilized and placed \textit{in situ} prior to the resection. The cost of the three-dimensional models is countered by improved reconstructive results and a reduction in operative time. It is imperative that the condyles remain in the correct position after reconstruction. If the condylar position is not replicated, the occlusion or mouth opening may be affected. If the tumour has breached the buccal cortex of the mandible (\textbf{Figure 51.4}) then it may not be possible to pre-bend a plate intraoperatively. Alternative means of ensuring the condyles remain in their pre-morbid situation are used. Methods include intermaxillary wire fixation if the patient is dentate or external fixators or the use of three-dimensional models.

In our practice, a 2.0 mm locking plate is used for most cases. This reduces the risk of plate exposure, facilitates placement of dental implants and is easier to bend. In our series of 85 patients over the last five years, we have had no plate fractures. However, if the plate is also carrying a prosthetic mandibular condyle, we use a 2.4 mm locking plate due to the plate being load bearing and increased forces (\textbf{Figure 51.5}). The plate must be positioned to allow optimal placement of the bone to ensure good aesthetics and subsequent implant placement.

The overlying soft tissue closure must be watertight to reduce the risk of infection and fistula formation.

**NON-VASCULARIZED BONE WITH OR WITHOUT SOFT TISSUE FLAP**

**Free bone grafts**

Free bone grafts may be in the form of block grafts or particulate cancellous bone in metallic trays.
Free bone grafts were first carried out by Bardenheuer in 1881. Defects smaller than 5 cm in length in healthy surrounding soft tissue and not to be treated with postoperative radiotherapy or in the medically compromised are ideal for reconstruction with non-vascularized bone grafts. In longer defects, or patients with poor surrounding soft tissues that has been irradiated or may be irradiated, reconstruction with a bony free flap is recommended.

The types of non-vascularized bone grafts are:

- autologous
- allogenic
- xenografts.

Owing to the risk of infection, allogenic and xenografts are rarely used. Autologous grafts have osteogenic potential while the rest provide a scaffolding over which the patient's cells can induce bone formation.

When using non-vascularized bone grafts, it is critical to avoid oral contamination and if the oral mucosa is perforated then a watertight closure must be achieved to avoid infection of the graft. The use of trays packed with cancellous bone was popularized in the 1960s. However, they were associated with very high failure rates due to infection and graft extrusion. Failure rates of up to 50 per cent are described when grafts are placed in irradiated tissue, or contamination of the graft with oral microbials occurs.

Lawson et al. in 1982 found a 46 per cent overall success rate with primary reconstruction using bone grafts. Most failures were attributed to salivary leak. They also reported a 90 per cent success if the definite reconstruction was delayed from the primary surgery. This was thought to be due to the decrease in orocutaneous fistulae.

The greatest site for harvest of autologous bone in terms of quality and quantity is the anterior or posterior iliac crests.

The main advantages of non-vascularized bony reconstruction are:

- quick and easy technique
- no viable neck vessels required
- no risk of microvascular failure.

The main disadvantages are:

- a healthy bed of surrounding tissue required
- high risk of bone resorption
- high risk of infection
- increased complications with radiotherapy
- inability to carry out composite reconstructions.

**SURGICAL TECHNIQUE**

The patient is placed in a supine position with a jelly pad under the hip from which the bone is to be harvested. The anterior superior iliac spine and the iliac crest is marked. An incision is made over the anterior iliac crest, retracting the abdominal skin medially to ensure that the scar is as lateral as possible. The incision (length determined by how much bone is required) extends through the skin, subcutaneous tissue and Scarpa's fascia. The incision then is deepened on to the iliac crest in the relatively avascular plane between the tensor fascia laterally and the abdominal muscles medially. The periosteum is then cut and lifted to expose the bone.

Costochondral rib grafts

The main role of costochondral rib grafts in mandibular reconstruction is in the reconstruction of the temporomandibular joint. This is particularly so in the paediatric patient. The costochondral graft is similar in size to the native condyle and the cartilaginous covering allows continued growth and the prevention of ankylosis at the skull base.

The main aims in condylar reconstruction are to restore the ramus length and thus the vertical face height, restore the occlusion and ensure the new TMJ movements allow normal mastication and speech but also growth in children.

**TECHNIQUE**

Usually the sixth or seventh rib is harvested. If cartilage is not required for continued mandibular growth, an incision is made over the relevant rib in a cosmetic location, the periosteum is reflected and the appropriate length of rib removed protecting the neurovascular bundle.

If a cartilage cap is required, the dissection must extend medially to the costochondral junction leaving some periosteum and perichondrium over the rib. Only 2–3 mm of cartilage is required.

The rib graft is then carefully secured to the mandible. Closure of the chest is completed only after a potential breach of the parietal pleura is excluded.
The serratus muscle/rib myo-osseous flap has also been described as providing vascularized muscle, bone and cartilage. Conley raised a segment of the fifth rib with the overlying pectoralis major muscle. However, anatomical studies have shown that the blood supply to the bone in these pedicled flaps is tenuous and long-term bone survival is disappointing.

Although the costochondral grafts do have the potential for continued growth, this is unpredictable and can lead to mandibular asymmetry and occlusal disturbance over time.

VASCULIZED BONY RECONSTRUCTION OF THE MANDIBLE

Vascularized bone may be transferred as:

- pedicled osseous flaps
- microvascular bone transfer.

Pedicled osseous flaps have been described as relatively easy technically, with minimal donor site morbidity and reliable. The use of the serratus muscle/rib myo-osseous flap and the pectoralis major with rib have been briefly mentioned above. However, the vascularity and quality of bone is poor and the flexibility to position the bone and muscle in the appropriate position is not good.

The advent of microvascular surgery allows the reconstruction of complex head and neck defects in one stage. It also allows larger resections to be contemplated as this improved mode of reconstruction allows better rehabilitation in mastication and speech, and improved aesthetics.

The main advantages of free flaps over pedicled flaps is the improved quality of the associated soft tissues (thinner and more pliable), the more reliable blood supply to the bone, the improved bone quality and quantity, and the independence to place the bone and muscle in the appropriate position.

The main advantages of using the fibula are:

- length of bone available – in an average adult up to 26 cm of bone being available for transfer. It is the only single flap that can be used for total mandibular reconstruction;
- good bone quality and reasonable quantity;
- pedicle length;
- consistent anatomy;
- good skin quality that is reliably transferred;
- two team operating possible.

The main disadvantages are:

- the high incidence of atherosclerosis in lower limb vessels;
- the lack of height of bone. (Nocini et al. have tackled the problem of lack of vertical height by distracting the fibula vertically and thus correcting the vertical discrepancy between the native mandible and fibula). We counter the problem of lack of bony height in the fibula by placing it higher than the lower border (Figure 51.7).

Fibula flap

The first microvascular transfer of a fibula was carried out by Taylor et al. for a defect in the tibia. Chen and Yan were the first to describe the osseocutaneous fibula flap. Hidalgo was the first to use the composite fibula flap for mandibular reconstruction. Hidalgo and Rekwo reconstructed 60 patients with mandibular defects using a composite fibula flap. Of the flaps, 59 of 60 were successful and 90 per cent of skin paddles were viable.

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Figure 51.7 X-ray of a fibula plated in situ. The fibula is placed a bit higher than lower border to allow easier implant rehabilitation.
PREOPERATIVE ASSESSMENT

The leg and foot must be assessed for symptoms and signs of vascular compromise. Any history of intermittent claudication, hyperaesthesia and cold intolerance must be ascertained. The foot pulses and skin quality are also noted.

Doppler or angiography is essential to ensure that there is three-vessel flow to the foot.

CONSENT

The patient must be warned of flap failure (5 per cent), ankle stiffness, mild ankle instability, foot drop due to peroneal nerve weakness, sensory loss, infection and deep vein thrombosis.30

TECHNIQUE

The patient is placed in a supine position with the hip and knee in flexion and internal rotation. A tourniquet is routinely placed but it is the author’s preference to raise the flap without it being inflated.

The head of the fibula and the lateral malleolus are marked and with a straight line connecting the two. This line marks the position of the posterior crural septum separating the lateral and posterior compartments of the lower limb. The common peroneal nerve is marked, usually about 2 cm below the fibula head.

The highest density of skin perforators are usually found at the junction between the middle and lower thirds of the lower leg. They can usually be localized with a hand-held Doppler to ensure the skin paddle is located to capture the highest number of perforators (Figure 51.8).

The incision is commenced 6 cm below the fibula head and extended to the lateral malleolus over the previously marked line. The incision leaves this line to traverse the anterior aspect of the skin paddle. The incision is deepened through the skin, subcutaneous tissue and through the fascia overlying the peroneus muscles. The dissection then proceeds in a subfascial plane towards the posterior edge of the peroneus longus muscle.

The peroneus longus muscle is then retracted anteriorly and the lateral aspect of the fibula is approached through the intermuscular septum between the lateral and posterior compartments. Care must be taken to protect the fragile septocutaneous and musculocutaneous perforators. Once the lateral aspect of the fibula is reached care must be taken to preserve the periostium with a thin cuff of muscle over the fibula. The anterior crural septum is divided and the anterior tibial vessels may become visible in the anterior compartment. Dissection then proceeds anteromedially until the interosseous septum is reached. The interosseus septum is divided over its full length and the fibula is divided 6 cm below the fibula head and 6 cm above the lateral malleolus. Removal of a 1 cm segment of fibula may facilitate visualization of the pedicle at its lower end. Rotation of the fibula and modest distraction laterally aid dissection of the peroneal vessels which are located under the tibialis posterior muscle. The dissection of the pedicle is carried out until the bifurcation of the peroneal tibial trunk.

If a skin paddle is being raised with the fibula and there are no obvious septocutaneous perforators, a cuff of flexor hallucis is required to protect the musculocutaneous perforators. Yoshimara et al.31 described the perfusion to the fibula skin and classified three patterns: (1) musculocutaneous via soleus and flexor hallucis longus; (2) musculocutaneous via flexor hallucis longus; and (3) septocutaneous (Figure 51.9).

After thorough haemostasis, the leg is closed with a drain in situ with vicryl and clips. If a skin paddle was taken then

Figure 51.8 Illustration of the surface markings to raise the fibula. The fibula head and lateral malleolus are marked out and the common peroneal nerve. The perforators to the skin are also illustrated.

Figure 51.9 Fibula raised with a skin paddle.
tension-free closure may be difficult and forced closure may result in a pseudo-compartment syndrome. A split skin graft can be placed over the defect with an overlying pressure dressing and a plaster of Paris back slab to allow optimum conditions for graft uptake.

The fibula is a straight bone and usually requires careful osteotomies to reconstitute the shape of the mandible. The diffuse segmental periosteal supply to the fibula bone allows multiple osteomies as long as they are performed with care. The minimum amount of periosteum should be stripped (Figure 51.10). Wei et al.33 reported a 100 per cent success rate with the skin paddle in 80 per cent of cases.

POSTOPERATIVELY

The leg should remain elevated for a few days with careful monitoring for any signs of ischaemia.

Deep circumflex iliac artery flap

Taylor et al.,34 and Sanders and Mayou35 were the first to describe the transfer of the iliac crest based on the DCIA. Ramaasstry et al.,36 in 1984 identified the ascending branch of the DCIA as the dominant axial pattern blood supply to the internal oblique muscle.

The DCIA was initially described in extremity reconstruction and Urken et al.37 was the first to use it for oromandibular reconstruction in 1989.

The main advantages of using a DCIA flap are:

- the best quality and quantity of bone, making it ideal for dental implants and rehabilitation;
- the shape of the pelvis can resemble the lateral mandible thus reducing the osteotomies required;
- predictable anatomy;
- two team operating possible;
- the internal oblique muscle when raised as part of the flap epithelializes to produce an intraoral lining that mimicks oral mucosa.

Disadvantages of the flap are:

- the poor pedicle length;
- high risk of hernia formation;
- skin quality and manoeuvrability are so poor that the author never raises the skin in a DCIA flap.

PREOPERATIVE ASSESSMENT

Obesity is a relative contraindication to using this flap as the dissection is much more difficult. Scars on the abdomen must be assessed carefully as damage to the DCIA vessels or the ascending branch may have occurred.

CONSENT

There is a substantial risk of hernia formation (9.7 per cent),38 marked hip pain and numbness on the lateral upper thigh.

ANATOMY

The blood supply to the flap is from the deep circumflex artery which is a branch of the external iliac artery and travels laterally towards the anterior superior iliac spine. This gives off the ascending branch usually before it reaches the anterior superior iliac spine that travels on the undersurface of the internal oblique muscle and supplies this muscle. The ascending branch may arise as an independent branch of the external iliac artery in approximately 5 per cent of patients. In this situation, two sets of anastomosis are required if the internal oblique muscle has been raised. Rarely, duplication of the DCIA may occur. The DCIA vessels continue laterally to travel on the inner aspect of the crest in a fibro-osseous tunnel between the iliacus muscle and the transversus muscle. The overlying skin is supplied by perforating branches that travel directly from the DCIA vessels.

TECHNIQUE

The patient is placed in a supine position with the hip being operated on elevated. The external iliac vessels, the anterior superior iliac spine and the iliac crest are marked. The incision extends from over the external iliac vessels and runs laterally about 2 cm above the iliac crest towards the lateral subcostal area (Figure 51.11). The incision is deepened through skin, subcutaneous tissue, and through the external oblique muscle. The internal oblique muscle is outlined if it is required for lining. The internal oblique muscle is then raised carefully off the transversus muscle looking out for the ascending branch that supplies the muscle and is a branch of the DCIA. (In a small percentage of cases there is no separate ascending branch.) The ascending branch is followed medially until its junction with the DCIA. The DCIA vessels are then chased to the external iliac vessels. The iliacus is cut below the DCIA pedicle as it travels on the inner iliac crest. The muscles on the outer aspect of the iliac crest are reflected subperiosteally. The bony cuts are made through the iliac crest protecting the pedicle on the inner surface. The bone is taken as laterally as possible to increase the length of the pedicle, reduce postoperative pain and decrease the risk of hernia formation (Figure 51.11). Haemostasis is ensured and
Closure of the abdominal wall must be meticulous. The transversus muscle is closed to the iliacus. As the iliacus is quite thin, this may be aided by making drill holes in the ilium to which the transversus is attached. The defect in the internal oblique is closed with prolene mesh. The external oblique muscle is closed. A superficial and deep drain are left in situ with an epidural catheter for pain relief. The skin is closed with clips (Figure 51.12).

Composite scapula flap

Saijo in 1978 was the first to investigate the vascular anatomy subscapular system. The first scapula flap was a soft tissue only flap. The parascapular flap was described by Nassif in 1982 based on the descending branch of the circumflex scapula artery. As the vascular pedicle for the scapula and parascapula flaps originate from the same artery as that for the latissimus dorsi flap, both flaps can be raised to be supplied by only one artery. Teot et al. were the first to demonstrate the lateral border of the scapula could be harvested on the circumflex scapula artery.

The main advantages are:

- good donor scar
- minimal donor site morbidity
- reasonable quality skin that is hairless and thin
- peripheral vascular disease is rare in these vessels
- reasonable bone quality and quantity
- skin paddle or paddles (multiple independent paddles can be raised) are entirely independent of the bone and so the best flap for complex defects.

The disadvantages are:

- two team operating is not possible as the patient needs to be turned, increasing operating time
- bone quality and quantity not as good as the fibula or DCIA flaps.

PREOPERATIVE ASSESSMENT

The patient must be assessed for previous surgery and scars around the intended operative site. Some surgeons prefer to mark out the circumflex scapula artery as it leaves the triangular space with a hand-held Doppler. The author has found this to be unnecessary.

CONSENT

The patient must be warned about the risk of shoulder stiffness.

ANATOMY

The circumflex scapula artery (CSA) is a branch of the subscapular artery. The CSA leaves the axilla via the triangular space formed by the teres major, teres minor and the long head of triceps muscles. The CSA via perforating
branches supplies the lateral edge of the scapula and carries on to divide into the transverse branch (supplying the scapula flap) and the descending branch (supplying the parascapular flap). The tip of the scapula is separately supplied by the angular artery, a branch of the thoracodorsal artery. The tip of the scapula can however survive without the angular branch from perforators from the CSA.

The scapula skin paddle should be 2 cm lateral to the midline, 2 cm below the spine and 2 cm above the tip of the scapula.

The pedicle length may be increased by dividing the thoracodorsal artery (if a latissimus dorsi or serratus anterior flap is not being raised) and chasing the subscapular artery into the axilla.

**TECHNIQUE**

Appropriate patient positioning is crucial or access into the axilla will be impaired.

The patient is placed in a lateral decubitus position. The circumflex scapula artery may be identified in the triangular space with a hand-held Doppler (Figure 51.13).

The skin paddle is marked and its lateral edge should be over the triangular space. The skin paddle is raised from medial to lateral in a suprafascial plane. The CSA is identified in the triangular space. Once identified, the lateral aspect of the skin paddle is raised. The teres major muscle is cut to allow the CSA and subscapular arteries to be chased into the axilla, dividing the thoracodorsal en route.

The infraspinatus muscle is cut vertically parallel to the lateral edge of the scapula about 3 cm from the lateral edge. A horizontal bony cut is made 2 cm below the glenohumeral joint and then vertically to the inferior aspect of the scapula to include the tip. The subscapularis muscle is divided and the flap is ready for delivery.

The skin is closed in layers with two drains in situ (Figure 51.14).

**Composite radial flap**

The fasciocutaneous radial forearm flap was first described by Yang *et al.* in 1981. Soutar and McGregor* popularized the use of the radial fasciocutaneous flap for intraoral reconstruction. Soutar and Widdowson* reported the use of the composite flap.

In Thoma *et al.*'s series of 60 cases of composite radial flaps,* the flap success rate was 98 per cent and the radial fracture rate 15 per cent.

Villaret and Futran* reported the use of the radial composite flap for seven anterior maxillary defects and 27 lateral

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Figure 51.13  Landmarks for the scapula flap showing the planned skin paddle and the vascular pedicle.

Figure 51.14  Myo-osseous scapula flap with a scapula and parascapula skin paddle. Courtesy of N Grew.
mandibular defects. They had no flap failures or fractures of the radius. They concluded that with rigid fixation, fractures of the radius are rare.

Edmonds et al.\(^47\) in cadaveric studies reported that a radial composite flap decreases the strength of the radius by 82 per cent but by plating the radius the strength is increased by 75 per cent.

The main advantages are:

- thin pliable skin
- consistent anatomy
- good pedicle length
- two team operating possible.

The disadvantages are:

- poor bone quality and quantity
- poor healing over tendons may lead to tendon exposure
- poor cosmetic result
- risk of fracture of the residual radius
- altered sensation to the thumb due to injury to superficial branches of the radial nerve
- decreased function of the hand.\(^48\)

PREOPERATIVE ASSESSMENT

The patency of the ulnar artery must be ensured by carrying out the Allen test – both the ulnar and radial arteries are compressed with finger pressure, with the wrist in flexion and the hand closed. The hand is then opened and the wrist returned to neutral and the hand is seen to be pale. The ulnar artery is then released and the time taken for the hand to return to normal colour is noted.

CONSENT

The patient must be warned about the risk of fracture of the residual radius, parasthesia of the thumb and the poor wound healing.

ANATOMY

The brachial artery gives off two main branches, the radial and ulnar arteries. The hand is supplied by a communication between these arteries via the superficial and deep palmar arches (Figure 51.15). As long as the arches are intact, the radial artery can be sacrificed without impairing the vascularity of the hand. Venous drainage can be via the deep venous system (the two venae comitantes accompanying the radial artery) or via the superficial system (based around the cephalic vein). Nearly all the flexor aspect of the forearm skin can be taken for the flap.

**TECHNIQUE**

The arm is exsanguinated and the flap is raised under tourniquet control. The right-sized and -shaped skin paddle is marked over the flexor aspect of the forearm over the radial artery. The more distal that this is positioned, the longer the pedicle. The radial, ulnar and brachial arteries are marked.

The skin is incised at the ulnar aspect of the paddle and the skin is raised laterally in a subfascial plane. Care must be taken not to injure the ulnar vessels and the paratenon must be kept over the flexor tendons. Dissection proceeds laterally until the lateral aspect of the flexor carpi radialis is reached. The distal aspect of the skin paddle is incised and the radial artery and its two accompanying venae comitantes are seen and ligated. The incision is then extended laterally, taking care not to damage the cephalic vein or the radial cutaneous nerve, and the skin is elevated medially until the brachioradialis is reached.

The flexor carpi radialis tendon is retracted medially to expose the flexor pollicis muscle and the tiny perforators that travel to the radius through it. An incision is made through the flexor pollicis at the ulnar aspect. Care must be taken to leave as much flexor pollicis attached to the radius as possible. Unicortical cuts are then made through the flexor aspect of the radius leaving 70 per cent of the radius in situ. The arm is then rotated and the brachioradialis is retracted laterally. The bone cuts are made through the lateral aspect of the radius, again just unicortically, and leaving 70 per cent of the radius in situ, but join the flexor cuts proximally and distally (Figure 51.16).

By this technique only the exact predicted amount of radius is removed reducing the risk of fracture. Only 30 per cent of the radius should be removed.\(^49\)

The risk of fracture is reduced even further by using a locking 2.4 mm plate with bicortical screws to strengthen the residual radius (Figure 51.17). The skin of the forearm is replaced with a full-thickness skin graft from the abdomen. The arm is then immobilized in a plaster of Paris back slab.
COMPLICATIONS

The main morbidity from this flap is the high risk of fracture of the radius. However, this can be reduced by not removing greater than a third of the radius and plating it prophylactically. Healing over the flexor tendons may also be poor. There is a high probability of sensory impairment over the thumb.

The flap is reserved for defects that do not require bicortical bone to re-establish structural integrity and, in particular, where the soft tissue needs are more critical than the bony ones. There are also situations where it may not be possible to raise any other bony flap.

Although early studies advocated using the osseocutaneous radial forearm flap for mandibular reconstruction, other superior donor sites have relegated it to a minor role.

Comparison of bony flaps

When bony flaps are compared, the bone quality and quantity (Table 51.1), skin quality (Table 51.2) and other factors (Table 51.3) must be taken into consideration. The tables are the author’s personal preferences for each flap.

Wilson et al.50 compared patients who had undergone hemimandibulectomy and were either reconstructed with bone or just soft tissue. They concluded that restoration of mandibular continuity led to improved function and a superior quality of life.

Chen et al.51 concluded that in their experience the absolute indications for free vascularized bone transfer are:

1. osteoradionecrosis of the mandible or an irradiated tissue bed
2. hemimandibular reconstruction with the free end in the glenoid fossa
3. long segmental defects
4. inadequate skin or mucosa to reconstruct soft tissue defects
5. failure of reconstruction by other modes
6. near total mandibular reconstruction.

Success of composite reconstructions are now approaching 95 per cent.52

DISTRACTION OSTEOGENESIS

Distraction osteogenesis is the technique of growing new bone by distraction (stretching) of pre-existing bone. Ilizarov33 applied the principles of distraction osteogenesis to treat thousands of patients with limb defects. There are four main stages:

1. Osteotomy – cuts through the bony cortex.
2. Latency – (time between osteotomy and the start of distraction. It allows formation of a primitive callus).
3. Distraction – The callus is stretched at a rate of 1 mm per day. If the rate is less than 0.5 mm per day, there is a risk of early fusion. If the rate is greater than 1.5 mm per day, there is a risk of fibrous union. The optimum rate of 1.0 mm per day is ideally divided into four movements of 0.25 mm per day.
4. Consolidation – the new bone is stabilized for up to 4 weeks.

The initial bone formed is non-lamellar and gradually gets replaced by lamellar bone.

Kuriakose et al.34 treated four patients with distraction with defects between 3.5 and 6.5 cm. Mandibular distraction devices used to be extraoral, but intraoral devices are now available. Extraoral devices leave unsightly facial scars.

The efficacy of distraction in previously irradiated mandible has been shown by Gantous et al.35 in a canine model.
Rubio-Bueno\textsuperscript{56} distracted five patients with intraoral distractors for segmental defects of 35–80 mm. They were successful in three of the five patients. In one patient there was intraoral exposure of the distractor and one patient died. Distraction is likely to be better for dental prosthesis and implants in view of the better bone quality, quantity and the ability to produce normal mucosa. However, it is time-consuming with occlusal disturbance likely as it is difficult to get all the vectors of movement right. Although distraction has been shown to be possible in the irradiated canine model, its use in patients who have received radiotherapy is still in question.

### DENTAL IMPLANTS

For the complete rehabilitation of a patient after mandibular resection, mandibular continuity needs to be restored and the dentoalveolar structures reconstructed.

Any patient who has undergone resection of the mandible with or without soft tissue resection has disturbed internal anatomy and altered sensation despite reconstruction. The alveolar bone height is reduced with poor lingual and labial sulci and the tongue anatomy and mobility may also be reduced. Cancer sufferers may also have received radiotherapy and be suffering from a dry mouth. All these factors make conventional dentures difficult to wear.

Osseointegration is the incorporation of metal into living bone. There is no fibrous connective tissue intervening between the implant and bone. The bone is able to remodel under loading of the implant.

The soft tissue around which the implant exits the bone has to be keratinized and attached mucosa otherwise chronic inflammation may result.

The implants are coated with titanium oxide and contamination must be avoided at the time of placement. Care must also be taken to ensure that the bone is not overheated and damaged during placement of the implant.

Although implants may be loaded immediately, integration rates are more predictable if loading is delayed.

The use of hyperbaric oxygen in irradiated patients may increase implant survival rates.

### TEMPEROMANDIBULAR RECONSTRUCTION

If at all possible, the mandibular condyle should be preserved but tumour resection should never be compromised. If the condyle is preserved, the new bone must be fixed to it. Every

---

**Table 51.1** Bone quality.

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th></th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contour</td>
<td>Iliac</td>
<td>Fibula</td>
<td>Scapula</td>
</tr>
<tr>
<td>Implants</td>
<td>Iliac</td>
<td>Fibula</td>
<td>Scapula</td>
</tr>
<tr>
<td>Bone quality</td>
<td>Iliac</td>
<td>Fibula</td>
<td>Scapula</td>
</tr>
<tr>
<td>Bone length</td>
<td>Fibula</td>
<td>Iliac</td>
<td>Scapula</td>
</tr>
<tr>
<td>Anterior dentate</td>
<td>Iliac</td>
<td>Scapula</td>
<td>Fibula</td>
</tr>
<tr>
<td>Posterior dentate</td>
<td>Iliac</td>
<td>Fibula</td>
<td>Scapula</td>
</tr>
<tr>
<td>Anterior edentulous</td>
<td>Fibula</td>
<td>Iliac</td>
<td>Scapula</td>
</tr>
<tr>
<td>Posterior edentulous</td>
<td>Fibula</td>
<td>Iliac</td>
<td>Scapula</td>
</tr>
</tbody>
</table>

**Table 51.2** Skin quality.

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th></th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reliability of skin</td>
<td>Radial</td>
<td>Scapula</td>
<td>Fibula</td>
</tr>
<tr>
<td>Ease of placement</td>
<td>Scapula</td>
<td>Fibula</td>
<td>Radial</td>
</tr>
<tr>
<td>Thickness</td>
<td>Radial</td>
<td>Fibula</td>
<td>Scapula</td>
</tr>
<tr>
<td>Extensive soft tissue resection</td>
<td>Scapula</td>
<td>Fibula</td>
<td>Iliac</td>
</tr>
</tbody>
</table>

**Table 51.3** Other factors.

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th></th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of harvest</td>
<td>Fibula</td>
<td>Radial</td>
<td>Scapula</td>
</tr>
<tr>
<td>Pedicle length</td>
<td>Fibula</td>
<td>Radial</td>
<td>Scapula</td>
</tr>
<tr>
<td>Pedicle size</td>
<td>Fibula</td>
<td>Scapula</td>
<td>Radial</td>
</tr>
<tr>
<td>Two team operating</td>
<td>Fibula</td>
<td>Iliac</td>
<td>Radial</td>
</tr>
<tr>
<td>Donor site</td>
<td>Scapula</td>
<td>Fibula</td>
<td>Iliac</td>
</tr>
</tbody>
</table>

966 Defect-based reconstruction: mandible and oral cavity
effort must be made to position the condyle in the glenoid fossa at its preoperative position.

Where the condylar head needs to be sacrificed for tumour resection, the bony flap can be placed directly into the glenoid fossa. The shape and size of the fibula make it the ideal bony flap for temperomandibular reconstruction. However, if the patient is dentate, a prosthetic condylar head used within a bony flap provides a more predictable occlusion (Figure 51.18).

CONCLUSION

The aims of mandibular reconstruction are to restore form and function, cover any defects causing minimal morbidity, and maximizing quality of life. This requires thorough defect analysis, assessment of all donor sites, knowledge of all the modes of reconstruction and working in a multidisciplinary environment.

It is important that every unit treating patients with mandibular tumours possesses the full repertoire of reconstruction so the most suitable modality is chosen for each patient. Free tissue transfer is now the gold standard in reconstruction of the mandible. It is an extremely reliable method of reconstruction, particularly in a hostile recipient bed. However, it requires specialized teams and significantly longer operating times. Postoperative morbidity and possible loss of form and function at the donor site are important considerations.

KEY EVIDENCE

- Use of reconstruction plates for segmental defects of the mandible is much more likely to fail in anterior than posterior defects.9
- Significantly more mandibular plates are lost when the patient has postoperative radiotherapy.15
- Patients who have undergone hemimandibulectomy and then had mandibular continuity restored have improved function and a superior quality of life.50

KEY LEARNING POINTS

- Mandibular reconstruction is challenging.
- Lateral mandibular defects are better tolerated functionally and cosmetically than anterior ones.
- Use of reconstruction plates without bony reconstruction is likely to fail, particularly in patients who have radiotherapy.
- It is important to assess the mandibular defect carefully and choose the most appropriate bony flap for reconstruction as each flap had different characteristics.

REFERENCES


INTRODUCTION

The technical aspects of pharyngeal reconstruction advanced tremendously over the twentieth century and, in particular, over the last three decades. This has enabled important improvements in functional outcomes, reliability, reduced morbidity and length of hospital stay. Despite these steps forward, the basic concepts of pharyngeal reconstruction have not changed significantly. In the majority of pharyngeal defects, the reconstructive surgeon only aims to achieve a patent and well-sealed tube that permits the passive passage of food and air. Reconstructing laryngopharyngeal defects with an intact larynx is a more complex process. Ingenious techniques have permitted laryngeal preservation in select cases, but speech and swallowing remains unpredictable. While the three-dimensional structure of the laryngopharyngeal unit can be closely replicated, the problems of aspiration due to insensate, adynamic tissue highlight the remarkable complexity of combining deglutition with voice production in a single orifice.

This chapter discusses the history of pharyngeal reconstruction, detailing the major technical advances, and then focuses on current reconstructive methods and their relative merits. Pharyngeal defects can be divided into partial and total (circumferential), depending as to whether the full circumference of the larynx and pharynx has been removed. Partial pharyngeal defects are further subdivided into simple and complex, depending on whether the larynx has been extirpated. Complex defects are those where the larynx is preserved, either in part (partial laryngectomy and pharyngectomy) or in its entirety (pharyngectomy without laryngectomy). These defects are termed ‘complex’ because reconstructive techniques need to focus not only on creating a patent conduit but on minimizing disabling aspiration and facilitating functional speech.

The morbidity, major and minor, associated with pharyngeal reconstruction is substantial and methods of minimizing this are continually being sought. The repercussions of the present chemoradiation era are now being felt by ablative and reconstructive surgeons alike, particularly in the area of pharyngolaryngectomy. Novel approaches to minimize pharyngocutaneous fistula by the use of highly vascularized free or regional tissue have limited success and the effect of chemoradiation on the residual native tissue impairs coordinated deglutition. As a result, patients may require long-term feeding tubes despite a patent reconstruction. Although organ preservation protocols have enabled functional larynx preservation in many patients with advanced larynx and hypopharyngeal tumours, more sophisticated techniques need to be developed to determine which patients will perform poorly with these protocols.

Functional outcomes are poorly documented in the present literature and objective evidence to support one reconstruction over another is remarkably scant. Putting this aside, one should consider the dramatic improvements in functional outcomes that have been achieved through regional and free flap reconstruction. The common problem of three permanent cervical stomas is, in the majority, now a complication of the past. Despite these advances, survival following total laryngopharyngectomy remains unfavourable and this needs to be considered in the reconstructive
algorithm. Minimizing perioperative morbidity is important so that patients can enjoy quality time out of the hospital environment with early and reliable return to functional speech, swallowing and social interaction.

GOALS OF RECONSTRUCTION

The goals of reconstruction of pharyngeal defects, in particular following surgical resection of hypopharyngeal and laryngeal cancers are primarily to restore a patent pharyngeal conduit that permits acceptable speech and swallowing. Secondary goals are to prevent complications, in particular pharyngocutaneous fistula and pharyngeal stricture, but also to minimize systemic and donor site morbidity. The optimal reconstructive technique depends upon a number of factors including the nature of the defect, prior treatment, patient comorbidity, disease-related outcomes (survival) and the reconstructive surgeon’s experience. Minimizing operative morbidity for patients with advanced malignancy is particularly important. The reconstruction should facilitate early discharge so that patients can enjoy quality time out of the hospital environment. Prolonged, complex multistage reconstructions may be inappropriate for patients with a limited life expectancy if simple and reliable alternatives are available. Table 52.1, summarizes the components of an ideal reconstruction based on those described by Couch. Currently, no method fulfills all of these criteria.

HISTORY OF LARYNGOPHARYNGEAL RECONSTRUCTION

The history and evolution of pharyngo-oesophageal reconstruction illustrates the complex issues regarding functional restoration for patients undergoing circumferential resections. The introduction of free tissue transfer has increased the complexity but substantially reduced the morbidity of many forms of head and neck reconstruction. Currently, free flap reconstruction is preferred for most cases except where there is significant cervical oesophageal involvement or substantial patient comorbidity. The increasing application of chemoradiation organ preservation protocols has challenged the reliability of standard reconstructive techniques. This has led surgeons to apply new methods to minimize complications, in particular pharyngocutaneous fistula, skin flap necrosis, major vessel rupture and late stricture.

Cervical skin flaps for staged reconstruction

The first methods of laryngopharyngeal reconstruction preceded the anatomical description of axial and regional flap reconstruction and were based on random pattern skin flaps. Czerny reported local skin flap reconstruction as early as 1877, only a few years following the initial description of total laryngectomy by Billroth in 1874. The early literature is dominated by European surgeons such as Mikulicz (1886) and Trotter (1913), who both described similar techniques to Czerny. These early techniques were multistage and highly unreliable and did not gain general acceptance. Modifications by Wookey in 1942 resulted in a more reliable two-stage reconstruction which was more widely applied (Figure 52.1). Despite the improved technique there are inherent problems with cervical skin flaps and complications occurred in over 90 per cent of patients. Multiple stages necessitate a prolonged period where the patient endured a separate pharyngostome (oropharynx) and oesophagostome, resulting in aspiration of saliva into the open tracheostome.

Radiotherapy was standard treatment for laryngeal cancer in many parts of the Western world in the early twentieth century. Table 52.1  Ideal pharyngeal reconstruction.

<table>
<thead>
<tr>
<th>Surgical</th>
<th>Morbidity</th>
<th>Functional and quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilitate resection with adequate surgical margins</td>
<td>Highly reliable flap</td>
<td>Single-stage procedure with short hospital stay</td>
</tr>
<tr>
<td>Allow two team approach to reduce operative time</td>
<td>Low complication rate, in particular fistula and stricture</td>
<td>Short time to swallowing and normal diet</td>
</tr>
<tr>
<td>Simple technique that is reproducible</td>
<td>Prevention of life-threatening complications, in particular vascular rupture and mediastinitis</td>
<td>Quality voice with normal intelligibility</td>
</tr>
<tr>
<td></td>
<td>Low donor site morbidity</td>
<td>Functional tissue, in particular sensation and dynamic reconstruction for patients where the larynx is preserved</td>
</tr>
<tr>
<td></td>
<td>Flap vascularity to withstand adjuvant therapy and promote neovascularization in radiated tissue</td>
<td></td>
</tr>
</tbody>
</table>
century. Using cervical skin within the radiation field often resulted in partial flap necrosis, wound breakdown and pharyngocutaneous fistula, particularly as radiotherapy was poorly regulated in terms of dose and fields. Life-threatening complications, such as mediastinitis and major vessel rupture, were likely sequelae and long-term complications were also problematic, in particular pharyngeal stricture for ‘successful’ reconstructions. These techniques were not suitable where a substantial length of oesophagus was resected. The next stage in skin flap reconstruction did not evolve until Bakamjian described the deltopectoral flap more than two decades later. Alternative techniques included skin grafts placed over temporary or permanent synthetic implants, however results were at best unreliable.

Transposed viscera for pharyngo-oesophageal reconstruction

Early descriptions of using pedicled viscera to reconstruct the oesophagus extend back to the turn of the century when Willstein (1904) described the use of pedicled jejunum, Kelling (1911) described colonic transfer and Jianu (1912) described the gastric tube. At a similar time Denk (1913) described the technique of blunt oesophagectomy in the animal model and cadaver. However, over a half century transpired before these techniques were to be applied to pharyngo-oesophageal reconstruction.

The gastric tube was well established in Europe following Kirschner’s (1920) work. Additional length was achieved through modifications by Mes (1948), who used an antiperistaltic tube based on the right gastroepiploic vessels, and Gavriliu and Georgescu (1955) with an antiperistaltic tube relying on the left gastroepiploic arcade; however, these were designed for thoracic oesophageal reconstruction. Heimlich (1961) popularized the reversed gastric tube in the United States, and further modifications allowed extension of the reconstruction to reach the oropharynx where this was applied to the total laryngopharyngectomy–oesophagectomy defect for cervical oesophageal cancer before 1970. Prior to both of these publications Goligher and Robin (1954) used pedicled colon to reconstruct the pharyngo-oesophagus, utilizing both right and left colon.

Both the reverse gastric tube and pedicled colon continued to be used with relative frequency into the early 1980s, predominantly with extra-anatomic placement of the conduit in a subcutaneous or subternal position. While these reconstructions were prone to the cardiopulmonary complications of thoracoabdominal surgery, generally they were reliable when performed as a two-stage reconstruction. The primary limitation of oesophagocoloplasty is the functional delay of food passage from oropharynx to stomach, which is a marked problem in nearly 50 per cent of patients. This technique still has a role in patients unsuitable for alternative techniques, in particular following gastric necrosis complicating gastric transposition where the oesophagus has already been removed.

Gastric transposition

The introduction of single-stage anatomic reconstruction of the pharynx and oesophagus is generally credited to Ong and Lee who described three cases of gastric transposition in 1960. However, Shefts and Fischer reported a one-stage procedure in 1949 for cervical oesophageal cancer. Ong and Lee argued that laryngopharyngectomy was essentially a palliative procedure and that effective palliation could not be achieved by multistage operations. The initial descriptions involved three body cavities; however, the morbidity of gastric transposition was minimized by performing a closed chest (blunt) transhiatal oesophagectomy and pull-up as reported by LeQuenes and Ranger in 1966. This concept was not original, being based on work by Denk (1913) and Turner (1933) half a century earlier. Gastric transposition effectively replaced reversed gastric tube, oesophagocoloplasty and other techniques for pharyngo-oesophageal reconstruction. Its popularity increased such that some surgeons advocated its use for all patients requiring pharyngolaryngectomy (Figure 52.2).

Functional results of gastric ‘pull-up’, in terms of stricture and swallowing were superior compared to prior techniques. Rapid restoration of swallowing and early discharge from hospital represented a major advance, especially when compared to multistage techniques. Unfortunately, the major morbidity and mortality following gastric transposition has been formidable. Wei et al. reviewed the literature on 978 patients undergoing gastric transposition after pharyngolaryngectomy and demonstrated a 16 per cent mortality and 37 per cent major morbidity. Institutions performing this technique regularly have been able to reduce mortality over time. Wei et al. reported that mortality in their institution prior to 1980 was 31 per cent but declined to 9 per cent after 1985. Anastomotic leak similarly decreased from 23 to 9 per cent. Despite this improvement, others have argued that a 10 per cent mortality rate remains excessive and that a body cavity should not be entered unless necessary. Since microvascular reconstruction has become routine, gastric transposition is increasingly reserved for tumours with significant cervical oesophageal extension. While there are no strict limitations on how high the stomach can reach, it is recognized that pedicled enteric flaps become less reliable approaching the skull base. In these cases, it is advisable to ‘supercharge’ the stomach with a cervical microvascular anastomosis. Recent advances have focused on laparoscopic transposition to neck.
and thoracoscopic dissection to further minimize morbidity; however, this technique is in its infancy.\textsuperscript{31}

**Pedicle and axial flap reconstruction**

The deltopectoral flap represented a major advance in non-enteric reconstruction of the pharynx.\textsuperscript{8} This was a superior technique compared to local skin flaps because it used tissue outside the irradiated field and had the advantage of an axial blood supply for most of its length. Furthermore, it provides thin and pliable tissue. It has remained an essential part of the head and neck reconstructive surgeon’s armamentarium and has recently been revived in the guise of the internal mammary artery perforator (IMAP) flap (Figure 52.3).\textsuperscript{32, 33} The deltopectoral flap was highly reliable and effectively replaced Wookey-type skin flap reconstructions. However, it represented a two-stage reconstruction with a controlled distal pharyngostome (Figure 52.4). Consequences of this were a prolonged time to oral intake, multiple hospital admissions and long-term stricture. Fredrickson et al.\textsuperscript{34} demonstrated that the average time to swallowing was 90 days over seven admissions compared to 12 days for gastric transposition. In patients with a limited life expectancy from advanced hypopharyngeal cancer this represented an unacceptable delay. As a result, the deltopectoral flap’s main niche was reconstructing the substantial number of patients not likely to tolerate the significant cardiopulmonary insult imposed by gastric transposition.

Ariyan is best known for his description of the ‘work-horse’ flap that revolutionized head and neck reconstruction in 1979, the pectoralis major pedicled myocutaneous flap.\textsuperscript{35} However, prior to this, he had already used the trapezius and sternomastoid muscle flaps for pharyngeal reconstruction.\textsuperscript{36} The pectoralis major flap was used frequently for non-circumferential pharyngeal defects and the first reports of ‘tubing’ the flap for circumferential reconstruction were by Withers et al.\textsuperscript{37} Owing to its bulk many surgeons found this difficult to perform\textsuperscript{38, 39} particularly in females. Fabian\textsuperscript{40} described partial tubulation of the flap combined with skin graft of the prevertebral fascia as an alternative method for circumferential defects.

Few flaps have been used as extensively as the pectoralis major and total flap failure is very unusual. The technique is excellent for selected patients with non-circumferential defects as shown in Figure 52.5. However, problems with partial flap necrosis are not rare, particularly when attempting to thin or fold the flap, place it under tension or use tissue at the limits of its vascular territory. As a result pharyngocutaneous fistula is reported in 13–63 per cent of pharyngeal reconstructions.\textsuperscript{29, 40–42, 43, 44} Inappropriate application of bulky flaps may result in pharyngeal obstruction, poor quality TEP voice\textsuperscript{45} and long-term stricture, particularly where adjuvant radiotherapy is used. These restrictions have limited its widespread application for circumferential defects despite its ease of harvest.\textsuperscript{1} Other limitations include patients with low oesophageal resections and long or complex defects. The development of reliable microvascular reconstruction has called into question the blanket application of the pectoralis major flap, particularly for reconstruction of the circumferential laryngopharyngeal defect. Despite this, we still consider regional musculocutaneous flaps, such as the pectoralis major and latissimus dorsi, as the first choice for salvaging complicated scenarios in a

![Figure 52.3](image1.png)  
**Figure 52.3** Vertical internal mammary perforator (IMAP) flap raised in preparation for inset to partial pharyngectomy defect.

![Figure 52.4](image2.png)  
**Figure 52.4** Deltopectoral flap.
hostile neck following flap necrosis, pharyngocutaneous fistula and major vessel rupture. 46

Enteric free flap reconstruction

It is surprising that the first successful free tissue transfer in a human preceded the description of both gastric transposition and the deltopectoral flap. The natural appeal of jejunum to replace the laryngopharynx and oesophagus led Seidenberg 47 to use this for pharyngeal reconstruction in 1959. The availability of the operating microscope, modern instrumentation and suture material has made this commonplace. Series of free jejunal autotransplantation were first reported using the canine model, 48 and following this, human series emerged in the 1970s.

Free jejunal transfer is by far the most widely reported flap for circumferential pharyngeal reconstruction. A literature review 49 of 595 circumferential reconstructions is summarized in Table 52.2, alongside the authors’ own experience. Accurately determining the complication rate associated with free jejunal transfer is difficult because morbidity varies so widely in the literature even from centres with extensive experience. 49, 50, 51, 52, 53, 54, 55, 56 For example, Triboulet 59 published a single institutional French series comparing free jejunal transfer (n = 77) with gastric transposition (n = 127). They found a substantially higher fistula rate in the jejunal group (32.5 versus 15.7 per cent), whereas other authors have found the reverse. As expected, cardiopulmonary complications were greater in the gastric transposition group (22.1 versus 6.5 per cent). This supports the concept that institutional experience has considerable bearing on morbidity and other treatment-related outcomes.

The popularity of the free jejunum relates in part to the aesthetic similarity to oesophagus, ease of harvest and that only two mucosal anastomoses are required in the neck, that is, there is no vertical suture line. Jejunum is very versatile and any length can be provided to allow superior extension to the skull base or inferiorly to the abdomen for total oesophageal replacement. 55 It is also amenable to techniques designed to allow better calibre match to the oropharynx, such as ‘double barrelling,’ 41, 50, 57 which also prevent problems associated with uncoordinated peristalsis. 58 Sarukawa et al. 59 reported a large Japanese series with 269 patients undergoing free jejunal transfer over a 12-year period. They emphasize the importance of standardization to facilitate a replicable technique which minimizes morbidity and improves functional outcomes. One critical aspect is keeping the jejunum under tension, as redundancy has a marked adverse effect on swallowing and vocal rehabilitation. This series also demonstrates that outcomes improve over time in experienced units. Pharyngocutaneous fistula reduced from 18 to 5 per cent, stricture from 18 to 3 per cent and average hospital stay from 32 to 24 days. Flap failure, however, was unchanged at approximately 2 per cent, although early revision surgery decreased from 12 to 4 per cent.

Disa et al. 60 reported a large North American series with 90 consecutive patients undergoing free jejunal transfer. Flap failure was 2 per cent, the fistula rate was 10 per cent, mortality occurred in one patient and late stricture in 8 per cent. One of the major limitations of jejunum is dysphagia due to uncoordinated peristalsis. This is reflected by the fact that while 88 per cent maintained oral nutrition, less than 65 per cent had an unrestricted diet. Peristaltic action decreases with time and is also diminished by postoperative radiotherapy. High rates of tracheo-oesophageal speech (60 per cent) have been reported using jejunum; 51, 62 however, this is unusual and few reports have critically and objectively appraised the quality of that speech. Peristalsis, again, is unhelpful, with the typical ‘wet’ quality being interrupted by contractions. Radiotherapy also aids tracheo-oesophageal speech by reducing secretions and intrinsic muscle activity. 53

Free jejunal transfer has been used extensively at our institution, but we now avoid its use for the reasons described above. In addition, many patients are nutritionally deplete with major cardiopulmonary comorbidity. This makes laparotomy a high-risk procedure which should be avoided where there are suitable alternatives. Where laparotomy is indicated, we favour the gastro-omental free flap as the enteric reconstruction of choice. 64 Further advances in free jejunal transfer have been achieved by reducing the donor site morbidity through laparoscopic harvest. Only small series have been published to date, 65, 66, 67 but nonetheless demonstrating that it is a viable option.

Compared to jejunum, the gastro-omental flap has had limited application in pharyngeal reconstruction. Despite this, it is not a newcomer to the reconstructive arena, with free transfer of gastric antrum reported by Hiebert and

Table 52.2 Circumferential reconstructions.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Shanghold et al. 49 (%)</th>
<th>Clark et al. 64 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Flap failure</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal complications</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Fistula</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Stricture</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Oral diet</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
<td>TEP speech</td>
<td>14</td>
<td>33</td>
</tr>
</tbody>
</table>
Cummings\textsuperscript{68} in 1961 and omental transfer in 1972.\textsuperscript{69} The combined use of both stomach and omentum to reconstruct the pharynx was subsequently described in 1979 by Baudet.\textsuperscript{70} Recently, this flap has undergone revival as a result of the ‘organ preservation era’ where fistula rates for salvage surgery exceed 30 per cent and wound complications approach 50 per cent in recent post-chemoradiation series.\textsuperscript{21,72}

Genden et al.\textsuperscript{73} described the suitability of this flap in a series of high-risk patients. Similarly, we have used it almost exclusively for salvage after either high-dose accelerated radiotherapy or concurrent chemoradiation.\textsuperscript{74} This composite flap is unique because the omentum can be draped over the pharyngeal anastomoses, exposed vasculature and microvascular anastomosis as demonstrated in Figures 52.6 and 52.7. Hence, if a leak occurs it is rapidly walled off, preventing major sequelae such as high volume fistulae, neck sepsis, mediastinitis and vascular rupture. Early experience has documented radiological fistula rates between 0 and 16 per cent in an extremely high-risk group of patients.\textsuperscript{63, 73, 74, 75} While the stomach has intrinsic muscular activity, the gastric tube does not develop significant persistalsis and tracheoesophageal speech does not have the typical wet character of jejunum despite secretory mucosa. The flap is versatile in terms of length and width, and pedicle length is good and easily harvested. Donor complications are similar to jejunum with a risk of respiratory compromise, bowel obstruction, enteric leak and hernia, and in addition the prepyloric (antrum) region needs to be avoided to prevent pyloric stenosis. Laparoscopic harvest has not been reported, but is likely to be feasible.\textsuperscript{1}

Free colon transfer has not become a popular technique for laryngopharyngeal reconstruction but continues to be used for laryngopharyngectomy with oesophagectomy, mainly as a pedicled flap, in certain institutions. The unique anatomy of the ileocaecal valve and appendix has been used by some authors to full advantage.\textsuperscript{65, 73, 74, 75} While these innovative techniques hold some promise, there are no comparative data to show whether they are useful in the mainstream. In general, the patulous nature of colon results in poor quality tracheoesophageal speech.\textsuperscript{1}

Figure 52.6 Exposed right internal carotid artery and subclavian artery during circumferential pharyngolaryngectomy. This patient is at high risk of a vascular rupture in the event of a salivary fistula.

**Fasciocutaneous free flaps reconstruction**

The forearm flap was first described in the Chinese literature\textsuperscript{26} in the late 1970s and then reported in the English literature by Song et al. in 1982.\textsuperscript{79} It has become the most common flap for head and neck reconstruction because of its ease of harvest, long pedicle, versatility and reliability. Harii and Ebihara\textsuperscript{80} popularized it as a tubed flap for pharyngeal reconstruction in 1985, initially reporting its use in 12 circumferential defects (Figure 52.8). At a similar time, Hayden\textsuperscript{81} was using the lateral thigh flap as an alternative tubed fasciocutaneous flap after it was first reported in 1983.\textsuperscript{82} The lateral thigh flap had the distinct advantage of being able to harvest a large area of tissue with primary closure of the donor site; however, its harvest is relatively complex when compared to the anterolateral thigh flap, which otherwise has similar properties.

Early experience with tubed fasciocutaneous free flap reconstruction of the hypopharynx was plagued by an unacceptably high stricture rate, predominantly at the distal pharyngeal anastomosis. A variety of methods have been reported to overcome this problem. The most popular techniques have been either to break up the suture line using a V- or Z-plasty\textsuperscript{83, 84} or by stenting the anastomosis with a salivary bypass tube.\textsuperscript{65, 86} Deschler\textsuperscript{87} reviewed the English literature and compared 919 free jejunal autografts with 179 fasciocutaneous free flaps (mainly radial forearm). Overall flap failure was higher in the jejunal group (7.5 versus 1.8 per cent), but other complications such as fistula (17 versus 23 per cent) and stricture (9.1 versus 16 per cent) were similar or lower.

Recently, the anterolateral thigh (ALT) flap has all but replaced the lateral thigh flap, mainly because it has all of the advantages of the lateral thigh flap but is comparatively easy to harvest. This flap was described by Song\textsuperscript{88} and then popularized by Wei following some large Taiwanese series. It is particularly suited to the Asian population, who generally have minimal subcutaneous fat in the thigh, and in selected centres this is now considered the fasciocutaneous flap of choice.\textsuperscript{89, 90} In other ethnic groups, the thigh may be thicker making it difficult to tube,\textsuperscript{91} not unlike the pectoralis major flap. The ALT flap can be thinned to provide an ‘ultra-thin’ flap, however this reduces the vascular territory to approximately 80 per cent of what is usual and may reduce flap reliability either due to trauma to the small perforators or disruption of the subdermal plexus.\textsuperscript{92}

We have reported our experience with the ALT for both general head and neck reconstruction\textsuperscript{93} and specifically for pharyngeal reconstruction\textsuperscript{86} (Figure 52.9). Recent data suggest that the ALT is replacing the radial forearm for fasciocutaneous hypopharyngeal reconstruction, mainly due to donor site morbidity, but also the fistula rate may be lower than that of the radial forearm.\textsuperscript{84} We perform a subfascial dissection and use the dense layer of fascia lata as a second layer to bolster the pharyngeal anastomoses, and in a series of 14 circumferential reconstructions only one patient developed a radiological leak and there were no clinical fistulas.\textsuperscript{86} The stricture rate was 14 per cent where a salivary bypass tube was used to stent the anastomosis compared to 20 per cent for jejunum.\textsuperscript{64} The salivary tube is sutured to a feeding tube which is then fixed to the nasal septum to prevent migration and can be removed in the outpatient clinic without sedation.
There is increasing evidence to suggest that fasciocutaneous flaps are superior to jejunal flaps with regards to tracheo-oesophageal speech and deglutition while avoiding the morbidity of laparotomy. Anthony et al. demonstrated that objective parameters of tracheo-oesophageal speech were similar following radial forearm reconstruction and primary mucosal closure after total laryngectomy. More recently, Yu et al. compared patients undergoing ALT flap reconstruction with jejunal reconstruction and found that the ALT was superior in terms of achieving a complete oral diet.

Figure 52.7 Gastro-omental free flap showing inset stomach and omentum wrapped around all tissue to contain any potential salivary leaks.

Figure 52.8 Tubed radial forearm free flap used to reconstruct circumferential pharyngeal defect over a salivary bypass tube.

Figure 52.9 Anterolateral thigh (ALT) free flap rolled to create a tube over a salivary bypass tube. The ALT flap can be harvested with the fascia lata of the leg and used as a second layer of closure to prevent fistulas.
(95 versus 65 per cent) and fluent speech (89 versus 22 per cent) with no significant difference in fistula or long-term stricture rates.

**RECONSTRUCTION OF PARTIAL LARYNGOPHARYNGEAL DEFECTS**

**Partial defects: simple**

Partial defects are those where the full circumference of the laryngopharyngeal complex is not removed. These are subdivided into simple partial defects where the larynx has been removed and complex defects where the larynx is retained, in part or in entirety. Simple defects are termed such because the aim of reconstruction is essentially to provide enough tissue to allow closure of the defect without narrowing or fistula. In fact, classical total laryngectomy presents us with a simple defect where minimal piriform fossa mucosa is resected and the defect can, in fact, be closed primarily. In general, native mucosa is the optimal tissue for reconstruction where possible, although following high-dose radiotherapy or chemoradiation there may be a role for covering this anastomosis with well-vascularized tissue to prevent or minimize the high likelihood of fistulization.

Several options are available for reconstruction of simple partial defects of the laryngopharynx. Conceptually, these are divided into defects where external skin is required and those where it is not. The authors do not consider that the tissue used is critical to functional outcomes as it does not need to be tubed or folded, which necessitates a thin pliable flap. As a result, most of the issues of flap selection revolve around donor site morbidity, cosmesis and reliability.

**PARTIAL DEFECTS: SIMPLE WITH EXTERNAL SKIN**

In patients where an external skin defect requires replacement the simplest option is a pectoralis major pedicled flap and skin graft on the muscle. This is a good option where simplicity, time and reliability are crucial. Regional muscle flaps are particularly suitable in the context of active pharyngocutaneous fistula or flap necrosis where the neck is hostile and free flap reconstruction is high risk. The latissimus dorsi flap can act as a substitute for the pectoralis major flap for partial pharyngeal reconstruction, but requires some rotation of the torso for harvest.

Alternatively, an internal mammary-based flap may be used to create external lining. This may be the classical deltopectoral flap or the more recently IMAP flap. The internal mammary flaps are good options for peristomal cover where a skin graft and its dressing can be problematic, and has the advantage of providing thin, pliable material with good colour match, depending on prior therapy, ethnicity and sun exposure. The IMAP flap has some advantages over the traditional deltopectoral flap. These include the ability to close the donor site primarily, although this is not likely to be possible where a pectoralis major flap has been taken from the same hemi-thorax. The IMAP can also be used to close the mucosal defect without a controlled fistula and two flaps can be used to reconstruct both internal and external lining simultaneously. Unfortunately, being a perforator flap the IMAP flap is less robust and anecdotal experience suggests that it is less reliable than the deltopectoral flap. While a pectoralis major flap can be used for external lining, its bulk makes it suboptimal around the tracheostomal and not used in our reconstructive algorithm.

The chest donor site is problematic from an aesthetic point of view, particularly in females where the combination of a pectoralis major flap primarily closed and deltopectoral flap skin grafted is a highly disfiguring combination. There appears to be considerable variance in psychosocial impact based on ethnicity, age, personal preference and donor site. In the current era, where free flap reconstruction is commonplace and highly reliable, we believe that donor sites need to be carefully chosen taking all factors into consideration.

Possibly the most suitable reconstruction of simple partial defects requiring external skin cover is the double paddle...
anterolateral thigh free flap. The anterolateral thigh flap is unique in that most patients have multiple long perforators arising from the descending branch of the lateral circumflex femoral vessels. This can be assessed preoperatively by Doppler mapping and allows the flap to be divided into separate islands that can be used to reconstruct both the internal and external defects without a de-epithelialized segment (Figure 52.13). Colour match is variable depending on sun exposure and ethnicity. Certainly any fasciocutaneous flap can be used with a de-epithelialized segment to create internal and external lining, however orientation becomes critical in this setting and if a leak occurs this segment will re-epithelialize and form a chronic fistula.

PARTIAL DEFECTS: SIMPLE WITH INTACT EXTERNAL SKIN

Reconstruction of these defects is relatively simple. Either regional or free tissue flaps can be used with similar outcomes. The pectoralis major flap has been extensively used for this purpose and appears to be well suited as long as there is not excessive subcutaneous fat. Other regional flaps are also reasonable options for closing these defects. In centres with microvascular expertise a fasciocutaneous free flap (such as the radial forearm or ALT) avoids the donor site concerns in the chest and is arguably more reliable. Numerous other flaps have been used for these defects, such as jejunum opened on the antimesenteric border, and optimal choice also depends on institutional expertise as much as flap selection.

TRACHEO-ÖESOPHAGEAL PUNCTURE

The choice of flap does not appear to significantly impact on voice outcomes for these simple partial reconstructions, although there are minimal data to verify this. Bulky flaps may interfere with speech in the short term, however after two to three months atrophy is sufficient to overcome this problem for musculocutaneous flaps. This may not be the case if there is excessive subcutaneous fat. Timing of tracheo-öesophageal puncture is controversial and based on theoretical concerns rather than evidence. Due to the thickness of the pectoralis major flap, early placement of a tracheo-öesophageal puncture valve is difficult if it has to be placed through the flap itself and will need to be resized numerous times. In this situation, secondary puncture is preferred after the muscle has atrophied. Free fasciocutaneous and enteric flaps do not atrophy to the same degree, however all flaps undergo some remodelling and placing a primary puncture though the flap may concern the reconstructive surgeon.

Often enough native mucosa is retained that the puncture passes through the öesophagus rather than the flap. In this case, personal preference and resources will dictate timing of puncture. Our preference is to avoid primary placement outside the setting of a standard total laryngectomy and primary closure because of complexity and the risk of fistula, particularly in the context of chemoradiation. Patient and institutional factors need to be taken into consideration, in particular cognition, motivation, visual acuity and manual dexterity are more important in ultimate tracheo-öesophageal speech success than flap selection. If there is any doubt, we favour secondary puncture since care of the laryngostoma is more difficult with a tracheo-öesophageal fistula in place in the early postoperative period (Figure 52.14).

Partial defects: complex

Small defects confined to the lateral pyriform sinus or posterior pharyngeal wall with larynx preservation can be closed primarily while larger defects require reconstruction with a regional or free flap. Preference should be given to thin pliable flaps, such as the forearm or thigh flaps, depending on body habitus. Free jejunum has also been used as a mucosal patch to reconstruct partial defects or bypass postcricoid stricture. Our practice has been to combine flap reconstruction with a silastic salivary stent for 6 weeks when stricture is likely. Most patients require a tracheotomy until swelling subsides and the stent is removed.

Complex pharyngolaryngeal resections are not new concepts, being pioneered in the mid-twentieth century, and represent extensions of partial laryngeal surgery with
important contributions by Alonso, Ogura, Biller, Pearson, Laccourreye, Bocca and others (see Table 52.3). The advent of free tissue reconstruction held much promise in allowing patients to undergo increasingly more radical larynx preserving procedures. While numerous techniques have been described, reconstructive surgery has not proved to be the panacea for the triad of dysphonia, dysphagia and aspiration that plagues laryngeal reconstruction. The success of these techniques can be unpredictable and depends on patient, tumour and treatment factors.

Reconstruction of the hypopharynx usually results in some initial aspiration and is more severe if part of the larynx is resected concurrently. Patient compliance and motivation are important factors and elderly patients or those with significant cardiopulmonary disease are unlikely to tolerate this. The chances of successful reconstruction, defined as return to normal nutrition without a gastrostomy tube and functional speech, are further diminished in patients who have previously been treated with radiotherapy or chemoradiation for numerous reasons. Partial laryngeal surgery has demonstrated that the minimal functional apparatus is preservation of a single cricoarytenoid unit. Without this, there are currently no reconstructive techniques that allow speech and swallowing without a tracheostoma. In patients undergoing concurrent hypopharyngectomy, there are multiple factors which may interfere with deglutition, described below.

Prior radiotherapy causes problems related to fibrosis, oedema and xerostomia. Elevation of the laryngeal apparatus is restricted, food is poorly lubricated, sensation is altered and normal coordinated pharyngeal contraction is impaired. When partially replaced with insensitive, non-contractile and structurally aberrant tissue such as a free flap the result is laryngeal penetration and without adequate laryngeal reflexes, aspiration follows. The ultimate outcome then depends on severity of aspiration, pulmonary reserve and the individual’s ability to compensate through dietary modification, physical manoeuvres and cough.

Numerous methods of resection and reconstruction of complex partial defects have been described. Many are extensions of horizontal or partial laryngectomy and very few have been tested in large series outside of a single institution in the modern era. Examples of the basic defects and references are described in Table 52.3. The authors believe that in appropriately selected patients these are reasonable options with the aim of functional organ preservation.

CIRCUMFERENTIAL DEFECTS

Figure 52.15 summarizes the authors’ current reconstructive algorithm for circumferential defects of the laryngopharynx. Most patients are reconstructed using free vascularized tissue which has increased the complexity but substantially reduced the morbidity of pharyngeal reconstruction. Free tissue is preferred except in situations where there is significant cervical oesophageal involvement.

Cervical oesophageal involvement

For tumours extending to the cervical oesophagus that require a laryngo-pharyngo-oesophagectomy, we favour gastric transposition. Alternative methods include pedicled or free jejunal flaps and colonic transfer depending on institutional expertise. There is no clearly defined cut-off at which the extent of oesophageal involvement necessitates total oesophagectomy either from an oncologic or reconstructive perspective, although a 2 cm margin on the distal extent of the tumour is preferable. We use free tissue reconstruction for all patients where a hand-sewn anastomosis can be performed to the proximal oesophagus safely. This depends on patient body habitus; however, in general, if the tumour extends below the thoracic inlet (first rib) it will be difficult to inset a free flap and gastric transposition is preferred. Circular stapled anastomoses have been described and facilitate anastomosis in the mid to upper thorax but anastomotic leak in this location is potentially disastrous. Functional problems include regurgitation, dumping syndrome and poor tracheo-oesophageal speech due to the patulous nature of the vibratory segment of stomach wall.

Gastric 'pull-up’ has been used widely, however there are multiple technical aspects that necessitate an experienced thoracoabdominal surgeon to deliver the stomach into the neck; in particular, adequate Kocherisation of the duodenum, atraumatic handling of the right gastroepiploic vasculature, tubing to lengthen the stomach, minimal blind dissection of the thoracic oesophagus and, above all, tension-free anastomosis in the neck. Transhiatal thoracoscopy has been used to minimize bind dissection and subsequent haemorrhage. In patients where a high anastomosis is required, supercharging the stomach by microvascular anastomosis of the left gastric or gastroepiploic vessels may decrease distal necrosis and subsequent fistula. Given that gastric necrosis is not infrequently associated with mortality, we suggest that this procedure should only be performed by surgeons with considerable expertise or training in this technique. Figure 52.16 demonstrates the disastrous complication of gastric necrosis following transposition.
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
<th>Reconstruction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended supraglottic laryngectomy or supraglottic hemilaryngopharyngectomy</td>
<td>Resection of supraglottis with epilaryngeal or medial piriform sinus</td>
<td>Primary closure, with musculoperichondrial flap</td>
<td>Alonso,⁹⁸ Ogura et al.,⁹⁹ Bocca et al.,¹⁰⁰ Chevalier et al.,¹⁰¹ Makeieff et al.,¹⁰²</td>
</tr>
<tr>
<td>Partial laryngopharyngectomy or extended vertical hemilaryngectomy or supraaortic hemilaryngopharyngectomy or partial laryngopharyngectomy with hemicricoid resection</td>
<td>Resection of tissue above or including cricoid, vocal cord, paraglottic space, laryngeal cartilage, pre-epiglottic space, epiglottis and preservation of one cricoarytenoid unit. Incorporating medial piriform</td>
<td>Primary closure with mucoperichondrial flap or ricohyoidopexy or reconstruction with radial forearm free flap</td>
<td>Ogura et al.,¹⁰³ Pearson et al.,¹⁰⁴,¹⁰⁵ Laccourreye et al.,¹⁰⁶ Laccourreye et al.,¹⁰⁷ Chantrain et al.,¹⁰⁸ Urken et al.,¹⁰⁹</td>
</tr>
<tr>
<td>Lateral pharyngectomy without laryngectomy</td>
<td>Resection of lateral piriform sinus or posterior pharyngeal wall</td>
<td>Primary closure or radial forearm free flap</td>
<td>Ogura et al.,¹¹⁰ Delaere et al.,¹¹¹ Urken et al.,¹¹²</td>
</tr>
</tbody>
</table>
As discussed earlier (see above under Gastric transposition) gastric transposition has been extensively reported in the literature and is associated with a high morbidity and excessive mortality rate in some series. Wei et al. reviewed 20 published series between 1966 and 1995 and found that the average major complication and mortality rates were 37 and 16 per cent, respectively. This was confirmed by reviews at our own institution in 1989 and 2005 as shown in Table 52.4.

### Table 52.4 Gastric transposition.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Goldberg et al. (1989)</th>
<th>Clark et al. (2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>Major morbidity</td>
<td>46%</td>
<td>66%</td>
</tr>
<tr>
<td>Fistula</td>
<td>22%</td>
<td>48%</td>
</tr>
<tr>
<td>Stricture</td>
<td>n.a.</td>
<td>29%</td>
</tr>
<tr>
<td>Mean length of stay</td>
<td>31 days</td>
<td>34 days</td>
</tr>
</tbody>
</table>

n.a., Not available.

As discussed earlier (see above under Gastric transposition) gastric transposition has been extensively reported in the literature and is associated with a high morbidity and excessive mortality rate in some series. Wei et al. reviewed 20 published series between 1966 and 1995 and found that the average major complication and mortality rates were 37 and 16 per cent, respectively. This was confirmed by reviews at our own institution in 1989 and 2005 as shown in Table 52.4.

### Primary surgery

Selected patients are not appropriate for organ preservation protocols and while jejunum has been used most widely to reconstruct these defects, there is considerable movement towards tubed fasciocutaneous free flap reconstruction of these defects. There are numerous reasons for this trend including a desire to avoid the inherent risk associated with laparotomy and superior functional outcomes. Jejunal voice tends to have a ‘wet’ quality and patients often suffer intermittent dysphagia from uncoordinated peristalsis during deglutition.115, 116, 117
The forearm and ALT flaps are the most commonly used fasciocutaneous flaps for reconstruction of circumferential defects. The tubed anterolateral thigh flap is ideally suited for reconstruction of these long pharyngeal defects as 8–10 cm width and 15–20 cm length can generally be harvested easily with primary closure of the thigh. The flap is difficult to tube in patients with a ‘female distribution’ of body fat, particularly in the Western population where obesity is common, even in patients with head and neck cancer. The flap can be thinned, however we prefer to use the fascia lata as an additional layer to bolster the oropharyngeal and oesophageal anastomosis. In patients unsuitable for an ALT flap, we prefer to use a radial forearm free flap, which provides ultra-thin tissue that can readily be tubed. Unfortunately, the donor site after harvest of 15×8 cm of forearm skin is particularly noticeable. Stricture has been a problem with all tubed fasciocutaneous flaps and we have adopted the policy of using a silastic salivary bypass tube as a stent in the postoperative period for approximately 6 weeks.\(^\text{\textsuperscript{86}}\)

**Salvage surgery**

Salvage surgery should be considered whenever recurrent disease is resectable, the patient is free of distant metastatic disease and medically fit for surgery. Only a limited number of patients are suitable to undergo surgical salvage and in those selected patients undergoing salvage five-year survival ranges from 18 to 35 per cent.\(^\text{\textsuperscript{118-119, 120-121}}\) The literature is inconclusive regarding the effect of standard radiotherapy on fistula and other complications following salvage laryngectomy or laryngopharyngectomy. This probably represents variability in dosing, timing and individual tissue response. Since the advent of chemoradiation and high-dose accelerated radiotherapy, the effect on tissue healing and subsequent wound complications has become even more apparent. Grouping patients who received 50–60 Gy of standard fractionated radiotherapy with those receiving ≥70 Gy combined with concurrent cisplatin is inappropriate. Furthermore, timing of salvage surgery may also play a role in the complication rate. Hence our approach has been to select the reconstruction based on prior therapy and individual patient factors.

Where salvage follows standard single daily radiotherapy to a moderate dose (<70 Gy) and the patient has had the usual tissue response to this therapy the risk of fistula is not substantially increased. In these patients, we use a thin fasciocutaneous free flap reconstruction. The preferred flap is the ALT tubed over a size 14 Fr silastic salivary bypass tube. In patients with a thick thigh, tubing and insetting the flap to

| Table 52.5 Complications following laryngopharyngectomy and reconstruction. |
|---------------------------------|-----------------|-----------------|
| **Immediate**                  | **Wound**       | Haematoma       |
| **Flap**                        | **Microvascular occlusion** |
| **Gastric transposition**       | **Tracheal tear** |
| **Thoracic haemorrhage**        |                 |
| **Early**                       | **Wound**       | Infection       |
| **Fistula**                     | **Dehiscence**  |
| **Seroma**                      |                 |
| **Flap**                        | **Radiological** |
| **Clinical pharyngocutaneous fistula** |
| **Necrosis**: partial; total flap failure |                 |
| **Vascular**                    | **Cardiac ischaemia** |
| **Cardiopulmonary**             | **Atelectasis/pneumonia** |
| **Pulmonary embolism**          | **Mediastinitis** |
| **Endocrine/metabolic**         | **Hyopoparathyroidism** |
| **Gastric dumping**             |                 |
| **Late**                        | **Donor site**  | Small bowel construction |
| **Abdominal hernia**            | **Limb weakness** |
| **Limb dysesthesia**            |                 |
| **Stricture/stenosis**          | **Pharyngo-oesophageal** |
| **Tracheostomal**               |                 |
| **Endocrine**                   | **Hypothyroidism** |
| **Dysphagia**                   | **G-tube dependence** |
| **Poor speech rehabilitation**  | **Neck and shoulder stiffness/pain** |
the oesophagus is difficult and in this instance a forearm flap is preferred. Each suture needs to be placed under vision and often this is best achieved by parachuting the flap into position for the posterior wall, passing the salivary tube into the oesophagus and then suturing the anterior wall under vision. The posterior vertical suture line created by tubing the flap is placed against the prevertebral fascia to minimize leak. The salivary bypass tube is sutured to a nasogastric feeding tube and this is sutured to the nasal septum to prevent migration of the stent into the stomach. At 6 weeks postsurgery, the nasal sutures are divided and the nasogastric tube is pulled through the mouth and used to remove the stent without sedation. This has substantially reduced the incidence of long-term stricture that was observed using fasciocutaneous flaps.

In patients who have undergone chemoradiation, high-dose accelerated hyperfractionated radiotherapy, or where a severe tissue response to radiotherapy is observed, the risk of pharyngocutaneous fistula and wound breakdown is increased. Our preference in these patients is to perform a gastro-omental free flap reconstruction (Figure 52.15). The primary advantage of this flap is the abundant vascularized omentum which can be draped over the mucosal anastomoses and exposed vasculature. This is very effective in minimizing major complications of pharyngocutaneous fistula and vascular rupture and also has the unexpected advantage of softening the neck skin and subcutaneous tissue which can be a disabling problem. Before planning this reconstruction, an assessment of patient performance status is essential. We believe that in patients with significant cardiopulmonary comorbidity, severe nutritional depletion or prior major abdominal surgery laparotomy is best avoided and these patients should undergo fasciocutaneous free flap reconstruction, as discussed above under Primary surgery. The addition of a regional myogenous flap to cover the anastomosis should be considered at the initial surgery.

### COMPLICATIONS

Morbidity following laryngopharyngectomy and reconstruction is difficult to classify because there are many potential complications that may occur. A standard approach is to classify these as immediate, early and late, as shown in Table 52.5. Certain sequelae can be directly attributed to the reconstruction or the ablation, however many, such as pharyngocutaneous fistula and stricture, are functions of both. Current data suggest that some form of complication will occur in the majority of patients, especially if minor or anticipated complications, such as hypocalcaemia, are included. Table 52.6 provides the relative frequencies of early and late morbidity from the University of Toronto. The effect of radiotherapy on fistula and wound complications is inconsistent in the literature. Our experience demonstrated that salvage patients had a 40 per cent radiological pharyngocutaneous fistula rate following radiotherapy compared to 27 per cent in the primary setting. The lack of agreement

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound</td>
<td>109</td>
<td>71</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Infection</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haematoma</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Major vessel rupture</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Fistula</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>Flap</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Necrosis</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Free flap failure</td>
<td>3</td>
<td>4.7a</td>
</tr>
<tr>
<td>Donor site</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Stent migration</td>
<td>4</td>
<td>36b</td>
</tr>
<tr>
<td>Cardiopulmonary</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>69</td>
<td>45</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Late total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stricture</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>Stomal stenosis</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>5</td>
<td>9c</td>
</tr>
<tr>
<td>Permanent feeding tube</td>
<td>25</td>
<td>16</td>
</tr>
</tbody>
</table>

aPercentage of patients undergoing free tissue transfer.
bPercentage of patients where salivary stent was used.
cPercentage of patients undergoing laparotomy.
regarding effect of radiotherapy reflects the heterogeneity in radiation treatment approaches. In this series, an accelerated hyperfractionated accelerated radiotherapy regimen was routinely used and evidence suggests that high-dose, accelerated and concurrent chemoradiation is certainly a predictor of increased and more severe wound complications. Much effort needs to be invested in minimizing the morbidity associated with these complex procedures.

**KEY EVIDENCE**

- Common complications after pharyngeal reconstruction are fistula and stricture.
- Hospital length of stay has reduced dramatically with the introduction of gastric transposition and free flap reconstruction of circumferential pharyngeal defects.
- There is little evidence to guide flap selection in pharyngeal reconstruction, however, fasciocutaneous flaps probably provide better quality tracheo-esophageal voice than enteric flaps, but are associated with a higher stricture rate.

**KEY LEARNING POINTS**

- Pharyngeal defects may be partial or circumferential, simple or complex, depending on whether the larynx has been preserved.
- Common options for pharyngeal reconstruction include pedicled flaps, such as pectoralis major flap or free tissue flaps, which may be fasciocutaneous or enteric.
- The choice of reconstruction depends on patient comorbidity, prior treatment and institutional expertise.

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87. Deschler DG. Pharyngoesophageal reconstruction: state of the art. AAO-HNSF Committee Presentation Tape Recording, September 1999.


There’s no art to find the mind’s construction in the face.


**INTRODUCTION**

The option to reconstruct the maxilla or the midface must be taken with a full understanding of what prosthetic rehabilitation can provide. There is no doubt that the use of an obturator can provide a simple and complete option for a standard hemimaxillectomy, which provides a separation of the oral and nasal cavities and a functioning dentition from the outset. It is often claimed that the advantage of being able to inspect the resection site by removing the obturator is an advantage in disease control, but no survival advantage has been confirmed in the literature. Reconstructive options include the usual array of local, pedicled and free flaps, and the aim of this chapter is to discuss these options in relation to the type of maxillary resection that has been carried out. The main part of the discussion will relate to the use of free tissue transfer techniques.

**ANATOMICAL CONSIDERATIONS**

**Maxillary bone**

The maxilla is the central bone of the midface which articulates with the zygomatic bone laterally and the nasal bones and ethmoids centrally. It provides part of the main buttresses of the face and forms part of the orbit, the nose and the whole of the upper dental alveolus. It is a bone that provides support to the anterior facial and cheek skin, supports the orbit and provides the dentition. Apart from the covering of skin, the bone is lined with nasal epithelium in the nasal airway, attached mucoperiosteum in the oral cavity and antral ciliated epithelium in the maxillary sinus. The need to ablate the tumour will often result in the ablation of related bones and soft tissue. Posterior to the maxilla are the palatine bone and the medial pterygoid plate, which often require resection in tumour ablation.

**Paranasal air sinuses**

These are paired asymmetrical spaces lined by mucoperiosteum with a ciliated epithelium, which is less glandular and therefore thinner than the nasal mucosa. The frontal sinus extends into the frontal bone and drains into the ethmoid sinuses. The ethmoids lie on either side of the medial orbital walls and the bone forms the crista galli and cribiform plate of the anterior skull base. The sphenoid sinus lies immediately posterior to the ethmoid sinuses and occupies the body of the sphenoid bone. The important relations of this sinus are the pituitary fossa, the internal carotid artery that grooves the lateral wall and the ridge formed by the optic nerve superiorly. The maxillary sinus is a three-sided hollow pyramid with the base forming the lateral wall of the nose and the three sides making up the orbital floor, the face and the infratemporal fossa.
ANATOMIC CONSIDERATIONS AND RECONSTRUCTION

Although the midface skeletal structure is complex in shape, the need to faithfully reconstruct these bones is often not necessary. The region of the paranasal sinuses with the exception of the medial orbital wall does not require reconstruction or obturation as long as there is no oronasal fistula. Resecting the maxilla, however, may result in the loss of support for the orbit, the facial skin and the dentition, and it is in these areas that adequate obturation or reconstruction are essential to avoid facial collapse, ectropion and/or enophthalmos, and the loss of the dentition. It is also essential to reconstruct the nasal bones to avoid nasal collapse although they are generally spared following maxillectomy.

CLASSIFICATION

There have been many attempts to provide a simple and descriptive classification of the maxillectomy defect, which can relate to the method of treatment. The classification proposed by the author is the first to attempt to combine both the surgical (Box 53.1) and dental (Box 53.2) factors related to maxillectomy and so predict the effect of the defect on the quality of life of the patient as well as the likely requirement in terms of reconstruction.

In simple terms, there is a vertical or surgical defect, which relates to the extent of the resection in the vertical plane from the dentition to the skull base. This defect results in a mainly aesthetic defect as there is initially loss of support of the cheek, then support for the orbit and then loss of the orbit itself. As a result, patients who wear an obturator or undergo reconstruction still have at least half of the functioning dentition, and although they lose binocular vision with the loss of the eye, the vision is still maintained through the orbit that is left. A letter (a, b or c) is added depending on how much of the upper alveolus is removed which is considered as the horizontal or dental component of the defect (see Figure 53.1).

Box 53.1 Surgical component (vertical)

- **Class 1**: The removal of alveolar bone not resulting in an oronasal or oroantral fistula. Resections of the ethmoid and frontal sinus cavity defects, or removal of the lateral nasal wall would fit into this part of the classification. Included in this group is the removal of only palatal bone, which will inevitably result in an oronasal fistula but leaves the dental bearing part of the maxilla intact.
- **Class 2**: Partial maxillectomy including the alveolus and antral walls, but not including the orbital rim or the maxillary buttress.
- **Class 3**: Partial maxillectomy including the floor of the orbit with or without periorbital ± skull base resection.
- **Class 4**: Partial maxillectomy with orbital exenteration ± anterior skull base resection.

Box 53.2 Dental component (horizontal)

- **a**: Unilateral alveolar maxilla and hard palate resected. Less than or equal to half the alveolar and hard palate resection not involving the nasal septum or crossing the midline.
- **b**: Bilateral alveolar maxilla and hard palate resected. Includes a smaller resection that crosses the midline of the alveolar bone including the nasal septum.
- **c**: The removal of the entire alveolar maxilla and hard palate.

The principle of this classification is that it is simple to remember and relates to the likely need for reconstruction of the higher class of defect, such as class 3 and 4. There was clear evidence that this was the case with the experience in the unit in Liverpool (Table 53.1). There was also a correlation with the quality of life outcome, which was less likely to be favourable as the defect became larger whatever the method of facial and oral rehabilitation.

A MULTIDISCIPLINARY APPROACH TO REHABILITATION OF THE MAXILLECTOMY PATIENT

In the management of the maxillary defect, it is not only the method of treatment for the disease that requires the rigours of a multidisciplinary decision-making process but also the method of rehabilitation. At present, there is very little information on patient outcomes in terms of survival and quality of life treated with either prosthetic rehabilitation alone or reconstruction with subsequent dental and facial prostheses. As with many aspects of head and neck cancer management, the evidence base is weak because of the small number of cases, the variety of the pathology, and the publication of case series that represent a single method of management with no comparative analysis. In the Regional Maxillofacial Unit in Liverpool, we have now prospectively entered more than 1600 patients onto the database. There are 153 (Table 53.1) patients with the site of the tumour in the palate, maxillary alveolus or paranasal sinuses who have undergone a maxillectomy and 38 have been rehabilitated with obturation and 115 reconstructed with a variety of techniques. Even though there are now between 350 and 400 new patients discussed at the multidisciplinary team meeting (MDT), relatively few of them have tumours requiring maxillectomy.

There are very few data on the comparison of obturation and reconstruction in terms of function and quality of life. A group from Japan found little difference in speech intelligibility between reconstructed (rectus abdominis) and non-reconstructed cases but there were only four patients in each group. We compared a group of 28 patients who underwent either obturation or reconstruction, and completed a series of questionnaires that examined their denture satisfaction as well as their function and quality of life. Table 53.2 represents the results of the study, which indicate that overall the patients who underwent reconstruction probably fared
Table 53.1  Midface rehabilitation and reconstruction in Liverpool (1992–2006).

<table>
<thead>
<tr>
<th>Method of rehabilitation/reconstruction</th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obturate</td>
<td>6</td>
<td>28</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Radial (fasciocutaneous)</td>
<td>8</td>
<td>29</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Radial (osteocutaneous)</td>
<td>–</td>
<td>14</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Iliac crest with internal oblique</td>
<td>–</td>
<td>19</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Scapula (thoracodorsal)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Fibula (osteocutaneous)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Latissimus dorsi</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Rectus abdominis</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 53.2  Comparison of obturation and reconstruction.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Obturation</th>
<th>Reconstruction</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3a/b</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4a/b</td>
<td>–</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>10% (1/10)</td>
<td>19% (3/18)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

University of Washington Questionnaire (cumulative score)

| Cumulative score | 74 | 75 | 0.68 |

EORTC head and neck (35% with problem during the last week)

| Pain in your mouth | 60 | 22 | 0.04 |
| Soreness in your mouth | 80 | 33 | 0.05 |
| Problems opening mouth wide | 30 | 39 | 0.98 |
| Gained weight       | 20 | 61 | 0.06 |

Oral symptom check list (% item present)

| Aware upper teeth | 90 | 40 | 0.06 |
| Self-conscious    | 50 | 9  | 0.06 |

Denture satisfaction (% satisfied (NB. 8 patients in reconstructed group))

| Satisfied with upper denture | 50 | 100 | 0.07 |
| Satisfied with function      | 40 | 100 | 0.03 |
slightly better. The comparison of these groups is not uniform in that more of the reconstructed group had larger defects and radiotherapy. Even with that difference, most of the comparisons seemed to be in favour of reconstruction as an option (Table 53.2).

The most important factors that have to be considered by the surgical and prosthetic team can be listed as follows:

1. The medical health of the patient.
2. Patient’s expectations and choice which includes age.
3. Extent of the predicted defect.
4. Expected prognosis.
5. The state of the remaining dentition.

It is important to explain to the patient and family the advantages and disadvantages of each proposed treatment (Table 53.3) so that an informed consent can be obtained.

**RECONSTRUCTION TECHNIQUES**

The main options for reconstruction can be divided into local and pedicled flaps and the use of microvascular free tissue transfer techniques. The main advantage of local and pedicled flaps is their simplicity and rapid transfer, which allows a potentially more reliable operation requiring less expertise and operating time. On the other hand, the type and quality of the transferred tissue is inferior to free tissue transfer techniques and the choice is much reduced especially for the larger defects (class 3 and 4). This chapter concentrates on the option of free flaps in particular but there will be some comment on the most useful local and pedicled flaps listed below.

- Local flaps:
  - palatal
  - buccal fat pad.

  These flaps are used to treat class 1 defects within the hard palate or involving the junction of the hard and soft palate. The size of the flap that can be raised and the limited arc of transfer limit their use. Closure of smaller defects of the palate can, however, be simply achieved with this technique and the use of a dressing plate with an appropriate dental dressing to allow relatively painless healing of the exposed bone from the site of transfer.

- Pedicled flaps:
  - facial artery myomucosal
  - submental island
  - temporalis
  - temporoparietal
  - greater palatine island.

The most widely used of these flaps has been the temporalis flap,7 which when raised with the coronoid process can reach as far as the lower ipsilateral canine. The use of the flap has been described with a titanium implant to give support to the cheek and provide an alveolus.8 This can provide a reasonable option in patients for whom radiotherapy is not required as part of the treatment. The thin temporal bone is generally not recommended for transfer with the temporalis flap, but the coronoid process has been described to reconstruct the orbital floor for class 3 defects.9 Transfer of the parietal bone with the temporoparietal flap will result in a longer arc of transfer for a pedicled flap on the superficial temporal vessels but the outer cortex will provide a relatively thin bone with limited options for bony reconstruction of the maxilla.10

More recently, interest has grown in the use of the pedicled submental island flap in oral and maxillary reconstruction.11 The ability to use reverse flow to extend the arc of rotation means that the flap can be transferred as far as the orbit and thus easily into the maxilla.12 Attempts have been made to include the lower border of the anterior mandible with the transferred tissue but this has resulted in a poor donor site appearance and is generally not practised. The flap can be used reliably for defects in the posterior maxilla in which bone is not required as part of the reconstruction.

The buccal fat pad is a very conveniently placed tissue which can be transferred on its blood supply to cover the ipsilateral palate.13, 14 The tissue is thin if stretched to this extent and obtaining a watertight seal may not be reliable.

---

**Table 53.3** Advantages and disadvantages of obturation and reconstruction.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Obturation</th>
<th>Reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td></td>
<td>Quick procedure</td>
<td>Longer operation</td>
</tr>
<tr>
<td>Donor site</td>
<td>Not required</td>
<td>Donor site morbidity</td>
</tr>
<tr>
<td>Facial restoration</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>Dental restoration</td>
<td>Immediate</td>
<td>Secondary</td>
</tr>
<tr>
<td>Obturator changes under general anaesthesia</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Cavity inspection</td>
<td>Available</td>
<td>Not available</td>
</tr>
<tr>
<td>Retained dentition</td>
<td>Helpful for retention</td>
<td>Simpler second-stage rehabilitation</td>
</tr>
<tr>
<td>Poor fit of obturator</td>
<td>Can be problematic</td>
<td>Avoided</td>
</tr>
<tr>
<td>Oroonasal reflux</td>
<td>Can be problematic</td>
<td>Avoided</td>
</tr>
<tr>
<td>Results for class 3 and 4 defects</td>
<td>Difficult obturator fit and higher risk of failure</td>
<td>Preferred option for larger defects</td>
</tr>
<tr>
<td>Patient preference</td>
<td>Can be a problem in the longer term</td>
<td>Permanent biological solution</td>
</tr>
<tr>
<td>Secondary surgery</td>
<td>Reconstruction remains an option in the longer term</td>
<td>No further major surgery required</td>
</tr>
</tbody>
</table>
The facial artery myomucosal flap has gained in popularity for oral reconstruction in general, but no bone can be harvested with the flap and it is limited by its narrow profile.

**Free tissue transfer**

Many free flaps have been described for the reconstruction of the maxillectomy defect, but any one unit’s experience with a particular technique has been limited. In Table 53.4, there is a brief review of the literature, which shows the number of cases of maxillary reconstructions with each technique. The wide variety of solutions for the maxillary defect emphasizes the lack of consensus as to the best approach. Teaching and guidance as to the best technique, therefore, is based more on clinical opinion rather than clinical evidence.

The variety and complexity of the maxillary defect has already been described and classified, and the rest of the chapter is a discussion on the best reconstructive solutions at present available for each class of defect. Table 53.5, represents the problems and proposed solution, and these basic elements are discussed in detail in the text.

**CLASS 1**

For most class 1 defects of the maxilla, no reconstruction is required as no oroantral or nasal fistula is created. In the situation in which there is an oroantral fistula at the junction of the hard and soft palate, the aim is simply to separate the nasal and oral cavities without causing contraction of the soft palate, which might result in velopharyngeal incompetence.

### Table 53.4 Examples of midface reconstruction reporting on a single free flap technique.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of flap</th>
<th>No. cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashikawa et al.</td>
<td>2006</td>
<td>Radial titanium mesh and obturate</td>
<td>5</td>
</tr>
<tr>
<td>Guelfucci et al.</td>
<td>2001</td>
<td>Radial</td>
<td>23</td>
</tr>
<tr>
<td>Nakayama et al.</td>
<td>2004</td>
<td>Radial and titanium mesh</td>
<td>18</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>2005</td>
<td>Radial (osteocutaneous)</td>
<td>23</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>2002</td>
<td>Iliac crest with internal oblique</td>
<td>24</td>
</tr>
<tr>
<td>Kelly et al.</td>
<td>2004</td>
<td>Inner table of iliac crest</td>
<td>1</td>
</tr>
<tr>
<td>Cordeiro et al.</td>
<td>1998</td>
<td>Rectus with non-vascularized iliac crest</td>
<td>14</td>
</tr>
<tr>
<td>Cordeiro et al.</td>
<td>2000</td>
<td>Rectus abdomen</td>
<td>45</td>
</tr>
<tr>
<td>Davison et al.</td>
<td>2004</td>
<td>Rectus with vascularized rib</td>
<td>6</td>
</tr>
<tr>
<td>Sakuraba et al.</td>
<td>2003</td>
<td>Rectus and obturation</td>
<td>5</td>
</tr>
<tr>
<td>Peng et al.</td>
<td>2005</td>
<td>Fibula</td>
<td>34</td>
</tr>
<tr>
<td>Yazar et al.</td>
<td>2006</td>
<td>Osteomyocutaneous peroneal artery perforator flap</td>
<td>6</td>
</tr>
<tr>
<td>Granick et al.</td>
<td>1990</td>
<td>Scapula (8 osteocutaneous)</td>
<td>11</td>
</tr>
<tr>
<td>Uglesic et al.</td>
<td>2000</td>
<td>Thoracodorsal angular artery with latissimus dorsi and 1 serratus anterior</td>
<td>17</td>
</tr>
<tr>
<td>Yamamoto et al.</td>
<td>1987</td>
<td>Latissimus dorsi</td>
<td>10</td>
</tr>
</tbody>
</table>

### Table 53.5 Summary of the problems and options for reconstruction according to the classification.

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summary of defect</td>
<td>Minimal defect only requiring reconstruction at the junction of the hard and soft palate</td>
<td>Low maxillectomy not involving the orbit</td>
<td>High maxillectomy involving the orbital adnexae</td>
</tr>
<tr>
<td>Aims of treatment</td>
<td>Close oronasal fistula</td>
<td>Close OAF Restore alveolus</td>
<td>Close OAF Restore alveolus Support face and nose Restore orbital floor and rim</td>
</tr>
</tbody>
</table>

IO, internal oblique; OAF, oroantral fistula; TDAA, thoracodorsal angular artery.
In such a situation it may be necessary to use a radial forearm flap (Figure 53.1) for the larger defects but a local palatal flap, buccal fat pad or greater palatine island flap may close the fistula successfully. Ostectomies that involve the lateral nasal wall typically following the excision of an inverted papilloma do not need reconstruction and can be left to epithelialize with no functional or aesthetic deficit.

**CLASS 2 (a–c)**

This is the classic hemimaxillectomy defect in which the orbital floor is left intact although a varying height of the maxillary buttress and anterior wall may be removed. The letters a, b or c represent: a, less than half the upper alveolus; b, more than half the upper alveolus; and c, the whole of the functioning upper alveolus. The success of obturation will decrease as more of the upper alveolus is removed. Not only will there be no chance of retaining any upper teeth in a class c, but it becomes more difficult to supply a functioning prosthesis the more of the palate and upper alveolus is removed.

**Class 2a**

By definition a class 2a involves only half of the upper alveolus and, as such, only a unilateral tuberosity resection is required leaving support of the nose with an intact nasal septum. In this situation there is no chance of nasal collapse and the collapse of the lateral face is unlikely with the retention of the malar arch.

It is not necessary to reconstruct the maxilla posterior to the first molar tooth. It is often necessary to include a resection of the posterior unilateral maxilla for retromolar tumours encroaching on the region of the maxillary tuberosity. In this situation, it is better to carry out a formal posterior maxillectomy including the pterygoid plates in order to obtain a clear margin of resection. These defects will require a flap to reconstruct the cheek, posterior tongue and in some cases the mandible, in which case the choice of reconstruction is decided by the soft tissue or mandibular defect. The soft tissue portion of the flap is all that is required to close the posterior maxillary defect.

For class 2a defects that involve the anterior maxilla, bone will be required if the patient is to be restored to normal dental function. This is an essential part of the planning for the reconstruction considering that an obturator can provide a dental restoration as well as restoration of the facial contour. This is especially true for class 2a defects in which there is a residual functioning alveolus and often sufficient bone to reliably support a prosthesis. The additional advantage of being able to screen the defect by removing the obturator and the simplicity of the surgery may make it difficult to justify a complex reconstruction.

**Reconstructive options**

This defect is too large for local flaps unless used in conjunction with a free tissue transfer or a pedicled flap. The temporalis flap has been used extensively for this defect but the harvest of split calvarial bone is very difficult in the temporal region. Techniques have been described using this flap in combination with titanium mesh and autogenous iliac crest (non-vascularized)\(^{21}\) or a titanium implant fashioned from a stereolithographic model.\(^{17}\) The problem with both techniques is the risk of flap dehiscence, and postoperative radiotherapy introduces a high risk of failure.

All of the composite free tissue transfer options have been described (Table 53.3) and, in my opinion, the best option is probably the fibula flap, mainly on account of the adequate bone for a low maxillectomy and the longer pedicle (Figure 53.2). The tendency for the soft tissue component of this flap to fibrose to the bone is an advantage in the maxilla as it prevents the redundant skin from falling down into the mouth. This makes the pre-implant surgery less difficult and allows a better implant to bone interface. The disadvantage of using skin to line the oral part of the reconstruction is the
need for palatal or mucosal grafting techniques to provide an adequate bone to implant interface. Although the iliac crest with internal oblique provides an ideal implant to bone relationship, the shorter pedicle makes the anastomotic surgery more difficult, which can result in the need for vein grafts and a subsequent higher failure rate. As the fibula can achieve equivalent results, even though the pre-implant surgery will require grafting, the use of the iliac crest and internal oblique, although providing an excellent result, may be considered an overcomplicated solution.

The scapula can also be used for this type of defect, but the skin to bone relationship is less favourable. Although there is much more versatility in the placement of the skin island compared to the fibula, the skin is thicker, complicating the graft preparation site if implants are to be placed. On the other hand, the flap has been described as being raised with the teres major muscle although this is limited in its placement in the oral cavity compared to internal oblique, which is a flatter and longer muscle harvest. It is possible to lengthen the artery of this flap by harvesting the thoracodorsal artery and using that as the anastomoses to the recipient artery. To achieve this, the subscapular artery is tied off and the dissection continued from the circumflex scapula artery in a retrograde manner to the branching of this artery into the latissimus dorsi muscle. Another option is to use the latissimus dorsi muscle and the tip of the scapula on the thoracodorsal angular artery (TDAA). This will provide an excellent soft tissue reconstruction and reasonable bone base for implants. The main disadvantage of using the subscapular system is the need to turn the patient or the difficulty of a two team approach when this site is so close to the head and neck.

The composite radial forearm flap has also been advocated for this defect but the bone is of very poor quality to accept implants essential for a full dental rehabilitation and there are concerns over the donor site, although the use of a bone plate to protect the forearm for postoperative fractures has proved successful.

Class 2b and c

This defect crosses the midline and can involve bone up to the height of the orbit which can include the perinasal bone that supports the alar base, as well as providing the central upper alveolus. If the maxillectomy is low and only involving the height of the alveolus and not including the maxillary buttresses that support the alar base then the fibula flap can provide sufficient height of bone. This flap may be less reliable if the defect includes the anterior maxillary buttresses, in which case some form of midfacial collapse may occur, especially if a large part of the nasal septum has also been resected. This problem has been highlighted in the literature using a horizontally orientated iliac crest with internal oblique which was compared with a similar defect treated with the vertical orientation of the same flap (Figure 53.3). The cases were reported to demonstrate the problem of the loss of central midfacial support in the vertical component, which would be very difficult to restore with a fibula flap that has not been folded over (double-barrelled).

CLASS 3a

This is the most complex of all the midfacial defects because the orbit is retained, but the whole of the anterior maxilla is lost including the upper alveolus. In cases of orbital exenteration, there is a need for an orbital prosthesis, which can disguise some of the failures in restoring the orbital rim or facial contour. If the eye is retained, then the reconstructive aims include avoiding enophthalmos, ectropion, epiphora, hypoglobus and scleral show, while at the same time restoring the orbital floor and medial wall, as well as the anterior maxilla and the upper alveolus so vital to a full dental rehabilitation.

The anatomy of the maxillary bones and relations has been outlined but it is worth emphasizing the nature of this defect in terms of what has been removed before considering the reconstructive options. The maxilla is a bone which is lined by oral mucoperiosteum which is fixed and immobile in the oral cavity. In the nasal region, the bone is also covered with mucoperiosteum and the sinuses include a
ciliated epithelium. In simple terms, this is a large bone covered by mucoperiosteum, which has relatively little vital function apart from the support of the teeth, the facial tissues and the orbit. The most important loss of function is not related to nasal breathing or the sense of smell but the use of the teeth, with its resultant effect on the ability to chew normally and maintain a reasonable appearance. In reconstructive terms, the task is to restore a fixed bone in the midface, which if done with accuracy can completely restore all the potentially lost functions as well as achieve an excellent long-term aesthetic result. The failure to use bone as the main element in the reconstructive option will result in a reasonable short-term result but a poor long-term outcome without a satisfactory oral rehabilitation.

**Reconstructive options**

In the management of the class 3 defect, the surgical and dental rehabilitation team must decide on the complete reconstruction of the defect which includes the orbital floor, facial contour and dental alveolus, or the support of the orbit and obturation of the facial contour and dental alveolus. Obturation alone with a non-vascularized support for the orbital floor will have a high risk of enophthalmos and ectropion with poor function and aesthetics. In basic terms, there are seven main options that have been described in the literature, which can fulfil the necessary requirements:

1. The use of the temporalis flap with either full-thickness cranial bone or the coronoid process to

**Figure 53.4** Class 3a reconstructed with iliac crest and internal oblique. (a) Magnetic resonance image scan showing an extensive ameloblastoma involving the floor and medial wall of the orbit. (b) The surgical specimen emphasizes the point that the resulting defect is a loss of bone and mucoperiosteum, which can be replaced by bone and muscle. (c) The iliac crest can be fashioned to fit with the nasal bones, the anterior alveolus and the zygomatic buttress to ensure a stable graft in the long term. (d) In this case we have used titanium mesh to reconstruct the floor and medial wall of the orbit. Alternatives include bone from the iliac crest or the calvarium. (e) The overall facial result shows the avoidance of enophthalmos and ectropion six months following the completion of the surgery. We plan an implant-retained dental prosthesis and minimal revision of the anterior part of the graft.
4. Reconstruction of the orbital floor with non-vascularized bone or titanium mesh and closure of the fistula with a soft tissue vascularized flap.

5. Reconstruction of the orbital floor, facial contour and dental alveolus with non-vascularized bone or titanium mesh and a soft tissue vascularized flap.

6. Reconstruction of the orbital floor and facial contour and closure of the fistula with an osteocutaneous free flap.

7. Complete reconstruction of the orbital floor, facial contour and the dental alveolus with an osteocutaneous free flap followed by dental rehabilitation with either tissue-borne or implant-retained dental prosthesis (Figure 53.4).

The use of a vascularized pedicle flap, such as the temporalis or the temporoparietal flap in conjunction with obturation, is a good option if the decision is to use obturation as the main support of the facial contour and the provision of a dental appliance. In this situation, the orbital floor is adequately supported and there is sufficient space for the prosthodontist to find undercuts to retain a reasonable functioning obturator. The use of obturation without orbital support risks poor orbital function and appearance due to contraction and fibrosis involving the orbital floor and adnexae. This option allows a simple reconstruction, which can be performed quickly and thus keeps the morbidity of the necessary surgery to a minimum.

I question the use of free tissue transfer when the dental rehabilitation is an obturator.23 This means that there will be skin lining the orbital floor and the side of the nose, which will hinder the retention of the obturator. This option also commits the patient to a prolonged procedure involving microvascular techniques. If the patient is motivated and fit enough to undergo free tissue transfer as part of the reconstructive option then it seems sensible to use an osteocutaneous flap and obviate the need for obturation.

The most important part of the reconstruction is the orbital floor and rim if that has also been resected. If a soft tissue free flap is chosen, then this bone requires reconstruction from one of the main donor sites, which is often split-thickness cranial bone. Cordeiro et al.21 have used the iliac crest as a non-vascularized bone graft for orbital floor and maxillary reconstruction in conjunction with a rectus abdominis flap. This technique requires two donor sites and risks inadequate vascularization of the bony reconstruction. It does fulfil the principle, however, that the bone graft is sealed from the nasal cavity and the air and covered with vascularized tissue on all sides. There is little doubt that non-vascularized bone which is open to the nasal or oral cavity has a high risk of infection and failure.

If the option is to use one of the osteocutaneous flaps then the most important area for bone restoration is the orbital rim and floor to retain the orbit in the correct horizontal plane and avoid ectropion. In this situation, it is difficult to arrange the bone for the fibula or the scapula to fulfil the requirements of orbital and facial support and the provision of adequate bone in the dental alveolus for an implant-retained prosthesis. The fibula will require two osteotomies to provide bone along the orbital rim, vertically down the side of the nose and horizontally along the dental alveolus. The orientation of the skin

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Figure 53.4 Continued.

reconstruct the orbital floor with supporting obturation.

2. The use of a temporoparietal flap with split-thickness calvarial bone to reconstruct the orbital floor with supporting obturation.

3. Reconstruction of the orbital floor with non-vascularized bone or titanium mesh and a soft tissue free flap and obturation.
paddle becomes very difficult in such a situation and the pedicle length is shortened considerably as at least 12 cm of bone is required for this approach. The method still leaves some poor support of the facial skin in the area where no bone has been placed. The scapula bone at least has the necessary height to span the width between the orbital rim and the dental alveolus providing support for the facial skin, but the bone is very thin in the region of the orbit if the lateral rim is used for the alveolus limiting the reconstructive options.

Mark Urken\textsuperscript{30} popularized the use of the internal oblique with the iliac crest raised on the deep circumflex iliac artery and vein. The bulk of the bone harvested allowed immediate mandibular reconstruction with the placement of implants at the same time to reduce the rehabilitation period.\textsuperscript{31} This flap relies on the healing of the internal oblique muscle in the oral cavity as a mucosal reconstruction and, although there is some inevitable contraction, the appearance and feel of this tissue is the most natural reconstruction available. In the maxilla, the contraction, of the tissue is an advantage, both as part of the reconstructed nasal lining and the hard palate. Both these structures are immobile and lined by mucoperiosteum, and the internal oblique becomes epithelialized and forms a structure, which reflects the tissue that has been removed. The anterior iliac crest is the best site for a bone graft except for the posterior crest for which a vascularized option is not available. The combination of an excellent source of bone, both in height and depth as well as the muscle, which can be used to obturate the defect, is the ideal option in the reconstruction of the class 3 defect.

The main alternative to this option is the use of the angle of the scapula raised on the angular artery, which is a branch of the thoracodorsal artery and so allows either angle of the scapula raised on the angular artery, which is a option in the reconstruction of the class 3 defect. The flap except for the posterior crest for which a vascularized tissue free flap has been reported with good results, but vascularized muscle in much the same way that the orbital floor and medial wall is reconstructed for class 3a–c defects.

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short length of the pedicle. While accepting that the pedicle length is short compared to the fibula flap, the osteocutaneous scapula flap also has a short pedicle unless retrograde dissection along the thoracodorsal artery is carried out. This will still leave a relatively short vein, as retrograde flow is not possible due to multiple valves in the thoracodorsal vein.

The evidence for an increased morbidity relating to the iliac crest has not been supported in the literature. In Liverpool, we carried out a study to compare the fibula and iliac crest donor sites and found that the morbidity was equivalent. Similarly, retrospective non-comparative reports have shown a related morbidity, which has been acceptable. In the one main study from Toronto in which the outcome using iliac crest and fibula was compared for mandibular reconstruction, the failure rate was higher for the fibula series. Similarly, Urken et al. has published 137 consecutive iliac crest flaps with and without internal oblique with a failure rate of 4 per cent, which included 27 scapula, 46 fibula and 30 cases with double free flaps. There was no comment relating to a higher failure rate for any particular donor site. He also reported on the morbidity of the donor sites with major complications occurring in one fibula case that required a free latissimus dorsi or tissue loss and poor healing, and one iliac crest donor site that underwent the repair of an abdominal wall hernia. He reported early gait problems in all patients with either a fibula or iliac crest donor site, but only two patients required assisted ambulation with a cane (donor site not specified).

The standard approach in Liverpool for patients requiring a midface reconstruction with a free flap in which the pedicle length may be insufficient to reach the larger vessels in the neck is as follows:

1. The submandibular gland may be removed with preservation of the facial vessels in continuity. If there is a need for a selective neck dissection then, if possible, the facial artery and vein are dissected out and kept in continuity. For modified radical neck dissections a planned vein graft is required but the facial artery may still be useable.

2. The submandibular incision can be extended vertically with dissection and preservation of the mandibular branch of the facial nerve to improve access to carry out the anastomoses.

3. In some cases, an arterial and venous vein graft can be prepared to allow the pedicle to be passed into the neck and in proximity to the larger arteries and veins in the neck. This can also be done with a temporary

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**Box 53.3 Case presentation of class 3 reconstruction with iliac crest and internal oblique**

A 32-year-old man presented with a swelling of the right cheek, which had been increasing in size over the last two months. An oral biopsy was reported as an ameloblastoma. Magnetic resonance imaging (MRI) and computed tomography (CT) showed an extensive tumour filling and perforating the right maxillary sinus and extending to involve the floor of the orbit and the right nasoethmoid sinus.

The planned surgical procedure was a maxillectomy extending to the right ethmoid sinus and including the rim, floor and medial orbital wall. The defect would result in a classical class 3a defect with preservation of the nasal septum and the nasal bones. In this situation, the prognosis is excellent and the patient is looking forward to a normal lifespan with an optimum functional and aesthetic result.

The options of a reconstruction or a prosthetic solution were discussed in detail with the patient and his partner and a decision made to reconstruct the defect. It was decided to place any implants as a secondary procedure.

In this situation, the iliac crest with internal oblique can offer an ideal reconstruction, which faithfully restores the lost bone and mucoperiosteum. In such a situation, there is no need to compromise the patient’s fitness or the length or complexity of the reconstructive surgery.

The ablation was carried out through a Weber-Ferguson incision and an en bloc resection was possible. During the ablative surgery it was possible to raise the iliac crest with internal oblique in a standard manner according to Urken’s description. In this technique, the pedicle is approached from the abdominal side and the inguinal ligament and other attachments to the anterior superior iliac spine can be maintained. Additional pedicle length can be achieved by starting the most proximal bone cut 3–4 cm posterior to the anterior superior iliac spine. A template can be obtained of the maxillary defect, which can help in the modelling process during insetting of the flap.

In order to use the facial artery and vein as end-to-end anastomoses, the submandibular gland is removed to allow easier access to these vessels. If the pedicle is too short to reach the neck, which is often the case, a vertical incision can be made to allow easier access while protecting the mandibular branch of the facial nerve. The flap is inset into the bone, and in this case a titanium mesh sheet was used to reconstruct the floor of the orbit and the medial wall. This was well supported on the iliac crest, which was more than 1 cm thick in this area. The bone is orientated as described previously, with the muscle obturating the oronantral fistula and lining the lateral nasal wall. The muscle also fills the dead space and reduces the risk of infection.

Postoperatively there were no complications that required intervention and the overall result is reasonable. Some points about this case are worth noting in more detail. One of the problems in this case has been the slight ptosis of the facial skin around the right eye, even with bone in place. This could be avoided or at least improved upon by hitching up the orbital tissue with sutures passed through small burr holes in the grafted bone. In such a case, the accuracy of the reconstruction of the orbital floor could be improved by making a mirror image template of the left orbital floor following the construction of a stereolithographic model. We have decided to make no orbital correction as the minimal epiphora is acceptable and the patient is pleased with the result. Further surgery is planned to place implants into the graft and, at the same time, some reduction of the graft on the facial side will be carried out.
shunt using the saphenous vein from the artery to the venous system, which can then be divided, and the anastomoses carried out knowing that at least two of the four anastomoses are working.

4. The methods of lengthening the pedicle for the iliac crest and the scapula have been mentioned, but this is especially useful in the scapula flap where the dissection can follow the thoracodorsal artery rather than into the subscapular system. The thoracodorsal artery is then anastomosed to the recipient artery and the blood flows in a retrograde manner into the circumflex arterial system. Using the angular branch of the thoracodorsal system to the angle of the scapula also lengthens the pedicle, but the bone stock is much less for the larger defects although the latissimus dorsi muscle offers the advantage of a natural looking epithelialized muscle base.

In our experience the main problem has been the poor run-off in the arterial system. In only one case have we required to provide a vein graft in the venous system as a result of the honeycombed septae that were present in the preferred recipient site of the anastomoses. Sometimes it is possible to use the retromandibular vein if sufficient length can be dissected out.

**Box 53.4** illustrates the actions to be taken in the event of an arterial anastomoses that will not perfuse the flap.

<table>
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| • If the run-off from the facial artery looks reasonable, then consider redoing the anastomoses and using a bolus of intravenous heparin (50–80 units/kg) prior to the release of the clamps.  
• If the run-off from the facial artery is poor, then you can consider the following options:  
  – fashion either an arterial (radial donor site) or venous (saphenous or cephalic site) graft and use that to run from the external carotid system once the run-off is adequate (usually the facial artery);  
  – dissect out the external carotid artery up to its bifurcation to the maxillary and superficial temporal arteries and bring that forward for an end-to-end anastomoses to the deep circumflex iliac artery. |

NB. Intravenous heparin must be used with caution in maxillectomy cases due to the increased risk of bleeding, and in my practice this is limited to a single i.v. bolus (50–80 units/kg), as well as routine deep-vein thrombosis prophylaxis. It is routine in our practice to leave other parts of the closure so that the anastomoses and the flap can be finally checked at least 45 minutes after the completion of the microsurgery. We would also advise the use of the Cook-Swartz continuous Doppler readout of the arterial or venous flow when using a muscle flap as these are often difficult to monitor from clinical observation alone.

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**KEY EVIDENCE**

The level of evidence is either a case series (level 4) or expert opinion without explicit critical appraisal based on first principles. The attempts to classify the defects by the author and Cordeiro represent good reviews, and although attempts have been made to compare reconstruction to prosthetic rehabilitation, the evidence is also weak.

**KEY LEARNING POINTS**

- A multidisciplinary approach between ablative and reconstructive surgeons and the expert in oral and facial rehabilitation is essential.
- Muscle provides the best reconstruction of the lateral nasal walls and the oral cavity, which can be supplied by the iliac crest with internal oblique or the thoracodorsal angular artery flap with teres major, latissimus dorsi or serratus anterior.
- It is essential to reconstruct the orbital floor if the eye is retained in high maxillectomies (class 3), for which the iliac crest with internal oblique is probably the best option.
- There is no evidence that midface reconstruction as opposed to obturation compromises the oncological outcome.
- The careful preparation and preservation of the recipient vessels in continuity into the maxillary region will result in better reconstructive options, less need for vein grafting and thus a higher flap success rate.

**REFERENCES**


INTRODUCTION

Since the introduction of craniofacial resection by Smith and Ketcham in the 1950s and 1960s, the treatment of skull base neoplasm has changed dramatically. The treatment of an expanded number of lesions, with significantly decreased morbidity, is indicative of a number of critical advances. The evolution of multidisciplinary teams that specialize in the management of patients with cranial base tumours has been instrumental in the improvement of outcomes. These teams include a head and neck surgeon, neurosurgeon, reconstructive surgeon, as well as nonsurgical specialists, such as radiologists and pathologists. Advances in imaging have provided heightened understanding of anatomy and routes of tumour spread. In the past two decades, devices such as angled endoscopes, image guidance and specialized instrumentation have led to a paradigm shift with respect to the viability of an endoscopic approach to select lesions of the anterior skull base. Perhaps even more integral to the decreased morbidity of skull base surgery have been advances in reconstruction. Adequate and effective reconstruction of the skull base is important because of the location of the defect and the potential morbidity associated with reconstructive failure. Reconstruction after skull base surgery is a broad topic, for which a multitude of specific considerations need to be evaluated before a decision is made regarding the most appropriate intervention.

As in other areas of the head and neck, the critical issues are maintenance of structure, function and aesthetics. Inadequate separation of intracranial contents and the skin or mucosal surfaces leads to extremely high risk of central nervous system complications, including cerebrospinal fluid leak, meningitis and pneumocephalus. Of paramount importance in skull base reconstruction is a watertight dural closure. Furthermore, it is imperative that the reconstruction supports the brain and maintains a safe barrier between the central nervous system and the extracranial cavity. This barrier must eliminate dead space and cover vital structures including the central nervous tissue, as well as the carotid artery. In large resections, soft tissue bulk is required to maintain structure, function and aesthetics. Although not always required, significant resections of the anterior fossa involving the orbital rims or maxilla may

| Table 54.1 Specific factors influencing reconstruction. |
|---------------------------------|---------------------------------|
| Location of skull base defect   | Anterior skull base             |
|                                 | Middle or central skull base    |
|                                 | Posterior skull base            |
| Size of Skull Base Defect       | Bone                            |
| Components of Defect            | Dura                            |
|                                 | Brain                           |
| History of surgery altering     | Prior use of local flap options |
| reconstructive option           | History of radiation or         |
| Factors hindering healing       | chemoradiation                   |
|                                 | Anticipated adjuvant treatment  |
|                                 | Diabetes or other systemic      |
|                                 | factors                         |
|                                 | Contamination or infection      |

(Table 54.2).
require bone reconstruction. Finally, skull base reconstruction may be necessary to provide a framework for the placement of orbital, dental or auricular prostheses.

SKULL BASE ANATOMY

The cranial base forms the floor on which the intracranial contents rest. It may be divided into three regions internally: the anterior, middle and posterior fossae. The extracranial skull base forms the roof of the paranasal sinuses and orbit, nasopharynx and infratemporal fossa (Figure 54.1). The anterior fossa extends from the anterior wall of the frontal sinus to the lesser wings of the sphenoid bone. The anterior fossa includes the cribiform plate of the ethmoid, roof of the ethmoid, crista galli and planum sphenoidale. The lateral aspect of the floor of the anterior cranial fossa provides the roof of the orbit. The middle fossa extends anteriorly from the lesser wings of the sphenoid to the anterior aspect of the petrous bone posteriorly. This encompasses the greater wing and body of the sphenoid sinus, as well as the anterior surface of the temporal pyramid. The extracranial aspect of the middle fossa corresponds with the infratemporal fossa. The posterior fossa involves the clivus, temporal bone pyramid and the entire occipital bone.

As benign and malignant processes can affect multiple regions of the skull base, a number of groups have classified regions based on the surgical approach. Jackson and Hide \(^3\) divided the region into anterior and posterior regions based on the pattern of tumour spread. Jones \(et\ al.\) \(^4\) labelled their surgical regions in concordance with the specific fossa and divided the skull into anterior, middle and posterior regions. Irish \(et\ al.\) \(^5\) divided the skull base into three regions based on the anatomic and tumour correlates. Region I tumours extend from the anterior fossa to the clivus and foramen magnum posteriorly. Region II includes the middle fossa, as well as the infratemporal and pterygopalatine fossa. Region III is composed of the posterior fossa with possible tumour extension to the posterior aspect of the middle fossa. Nomenclature such as ‘anterior skull base’ generally refers to lesions in region I and ‘lateral skull base’ refers to lesions of both regions II and III. Lesions of region I arise from the sinuses or orbit and are accessed via traditional open anterior craniofacial resection or endoscopic techniques. Region II lesions are most frequently accessed through an infra-temporal approach with a hemiconoronal incision, which may be combined with a mandibulotomy or transtemporal approach as needed. Region III lesions are lesions of the ear and temporal bone and are approached with a transtemporal approach.

SPECIFIC OPTIONS FOR RECONSTRUCTION OF THE SKULL BASE

As reconstruction of the cranial vault can involve a number of different grafts and flaps, the most commonly used options will be described first, followed by discussion of the specific considerations of the unique areas of the skull base (Table 54.3).

Grafts

Free grafts are nonvascularized tissues that heal initially via imbition from surrounding tissues until inosulation and angiogenesis commences. Skin grafts were used routinely in the early stages of skull base surgery. These grafts, placed as dural patches or as overlay grafts, have extremely high rates of necrosis with subsequent cerebrospinal fluid (CSF) leak. Ketcham \(et\ al.\) \(^6\) reported a nearly 50 per cent CSF leak rate in the early patient population undergoing craniofacial resection with skin graft reconstruction. While there is no role for primary skin grafting in modern skull base reconstruction,
there is a role for other free grafts. Fascia lata of the lateral thigh, or more locally available tissue such as temporalis fascia, provide material to overlay for dura or to obliterate small, well-contained spaces. Furthermore, fat, most often taken from the periumbilical area, can be used to obliterate dead space, most frequently used in the lateral skull base in the setting of primary interventions for benign disease. Disadvantages of free fat include the inability to heal when infected and the significant reduction of volume with time. Most surgeons would not use grafts if the resection site is in continuity with mucosal surfaces or in the setting of previous radiation impacting on the ability of the graft to heal. Furthermore, anticipation of adjuvant therapy would provide a relative contraindication to the use of free grafts. Free bone grafts, when necessary, can be obtained via split calvarial bone or a portion of a craniectomy. However, most bony defects of the skull base need not be repaired, with the exception of the orbitomaxillary unit.

Local flaps

The use of local flaps in the field of skull base reconstruction was a significant advance in the early era of skull base surgery. Local tissue is mobilized and rotated or advanced, with critical emphasis on maintenance of the vascular supply. The use of local flaps is logical, as these tissues are relatively easy to harvest and have minimal donor site morbidity, usually located within the field of the ablation. Disadvantages of local flaps include the availability of a limited stock of tissue precluding these as an option for large defects. Furthermore, the local tissues of revision cases or cases following radiation often have inadequate vascularity to be used for reliable reconstruction.

The most common local flap used in anterior skull base reconstruction is the galeal/pericranial flap. The pericranial flap, first described by Johns et al. in 1981, is based on the bilateral supratrochlear and supraorbital arteries. The pericranial flap is dissected in a subgaleal plane to the supraorbital rims and then the pericranium is incised and carefully dissected anteriorly, preserving the blood supply. The advantages of this flap include its relative ease of harvest and the fact that the blood supply has been shown to be hearty, even when assessed by Doppler techniques. This flap can provide a layer of separation between the central nervous structures and the paranasal sinuses for anterior skull base defects greater than 3.0 cm. The galeal-pericranial flap includes the pericranium, as well as the galea and frontalis muscle, for a more hearty, well-vascularized option. In addition, a pericranial flap can be used in conjunction with a free bone graft with success in the appropriately selected patient.

Disadvantages of pericranial flaps include the inability to obliterate dead space and tenuous blood supply in the setting of prior surgery or radiation (Figure 54.2).

The scalp and forehead flaps have been used as a local flap for skull base reconstruction. Unfortunately, these options for reconstruction are restricted by the limited tissue available for extension to the posterior aspect of the anterior cranial base. The forehead flap is supplied by the supratrochlear artery and can only be considered in the use of extremely small central defects in the anterior skull base. Furthermore, this flap is difficult to pass through the area of the defect and leaves an aesthetic donor site morbidity. Therefore, these flaps are infrequently used in the modern era of skull base reconstruction.

The temporal flap system is the most common local flap system used for the lateral skull base. The temporal flap system includes the temporoparietal fascia, the deep temporal fascia and the temporalis muscle. The temporoparietal fascia

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<td><strong>Alloplasts</strong></td>
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Figure 54.2 Illustration of a pericranial flap inset below the bone flap to reconstruct the anterior skull base.
is based on the superficial temporal artery and can extend
to and be used for reconstruction of the posterior fossa,
as well as the middle fossa or infratemporal fossa. This
local flap can provide an adequate separation of intracranial
and extracranial contents without the ability to obliterate a
large amount of dead space. Furthermore, temporoparietal
fascia can be used as reconstruction after orbital exenteration.
The temporals muscle blood supply arises from the deep
temporal artery via the maxillary artery and the middle
temporal artery from the superficial temporal artery. Despite
publications illustrating the utility of the temporals muscle
flap in anterior cranial fossa reconstruction, the temporals
local flap has limited applications to most clinicians,
mainly limited to lateral soft tissue reconstruction. The
disadvantages of this flap include limited mobility and
compromise of vascularity with access to the skull base.
Furthermore, use of the temporals muscle flap leads to a
hollowing out of the temporal fossa. Alloplastic implants
are available to obviate this secondary deformity, however
should be used cautiously in patients who are undergoing
adjuvant therapy.

Regional flaps

Regional flaps are frequently used in head and neck recon-
struction. In general, these axial flaps have the advantages of
reliable blood supply, ease of harvest and significant amount
of soft tissue available. Over the past decade, the limitations
of regional flaps for skull base reconstruction have become
evident, as these flaps are often limited in their reach into
various defects. In addition, the distal aspect of these flaps,
the area most critical for safe reconstruction, is the most
sensitive to ischaemia. Therefore, in current practice, the use
of regional flaps is limited, mainly to moderate-sized defects
of the lateral skull base.

The pectoralis major flap is a pedicled myocutaneous flap
based on the pectoral branch of the thoracoacromial artery
that has been used in anterior and lateral skull base
reconstruction. This flap is tunneled under the neck skin,
over the clavicle, to the recipient site. This flap has limited
reach to the paranasal sinuses and cannot extend superior to
the inferior orbital rim; lateral extension of the pectoralis
major flap is limited approximately to the area of the ear. As
in other regional flaps, the distal tip of the pectoralis major
flap is susceptible to necrosis. Furthermore, there can be
unacceptable aesthetic ramifications of the pectoralis major
flap harvest, especially in female patients.

The latissimus dorsi pedicled flap is a myocutaneous flap
based on the thoracodorsal artery which branches off
the subscapular vessels. The latissimus dorsi muscle can
be elevated with or without the overlying skin. This flap has a
large arc of rotation across the axilla. While the pedicled
latissimus dorsi flap can reach most skull base defects
when dissected fully, it is most useful in lateral skull base
defects with large soft tissue components. The lower trapezius
flap has also been used for skull base reconstruction. The
inferiorly based trapezius flap, with blood supply from the
dorsal scapular artery, has a long arc of rotation. The skin
paddle may be fashioned to cover large areas of the lateral
skull base. Care must be taken to preserve the blood supply
to this flap if a neck dissection is being performed at the
same time.

Free tissue transfer

Over the past 20 years, free tissue transfer has been used to
provide vascularized tissue for the most complex skull base
defects. Because free flaps are not limited by a pedicle arc and
there are multiple viable donor sites, there are numerous flap
options. Furthermore, free tissue transfer provides the ability
to recruit multiple tissue types and a variety of bulk
depending on the defect characteristics. Increased complex-
ity, leading to greater operative time is tempered by the
ability to engage two teams. Most high volume centres have
flap transfer success greater than 95 per cent, justifying the
use of free tissue transfer in the reconstruction of skull base
defects. The utility of free tissue transfer has been
supported by the work of numerous authors at high volume
centres. Nelson et al.17 demonstrated significantly decreased
morbidity with free flap reconstruction in comparison with
patients undergoing a pedicled regional flap reconstruction.
In this series from Princess Margaret Hospital, pedicled
reconstructions had a complication rate of 75 per cent,
compared with 34 per cent in the free flap cohort. Interest-
ingly, the complication rate in the locally reconstructed group
was similar to that of the free flap cohort, suggesting that
regional flaps are less appropriate for reconstruction of the
skull base, regardless of the defect. Furthermore, in a series
from Memorial Sloan Kettering Cancer Center, Califano
et al.17 showed that major complication rates for patients
undergoing free tissue transfer were comparable with those
undergoing local or regional reconstruction (31 versus 35 per
cent), despite a significant increase in complexity and extent
of defect. Heth et al.18 confirmed these data showing compar-
able levels of wound complications following local or free
flap reconstructions of the skull base. Data from MD
Anderson Cancer Center revealed an acceptable level of
complications (30–36 per cent) with free tissue transfer for
reconstruction of skull base defects.19, 20

A majority of publications describe microvascular recon-
struction of the anterior and middle cranial base with a
selected group of flaps; these include the radial forearm free
flap, rectus abdominis and latissimus dorsi.21, 22, 23 Lateral
skull base reconstruction is most commonly performed with
anterolateral thigh or scapular system of free flap. The fol-
lowing is a description of the most commonly used free flaps
for skull base reconstruction.

RECTUS ABDOMINUS FLAP

The rectus abdominis free flap is based on the deep inferior
epiproglastic artery and is either a myogenous or myocutaneous
flap. The rectus abdominis was the initial workhorse flap in
skull base reconstruction because of the amount of soft tissue
that can be used for obliteration of a large defect.24, 25 In a
study of 35 patients, of whom most underwent reconstruc-
tion with a rectus abdominis free flap after skull base surgery,
Teknos et al.26 cited an acceptable cerebrospinal fluid leak
rate of 8.6 per cent, with the incidence of meningitis less than
3 per cent. The specific advantages to this flap include long
vascular pedicle, relative ease of harvest and large amount of soft tissue. In addition for cranial procedures, the flap can be harvested with a two team approach and does not require repositioning. The disadvantages of this reconstruction include a flap that can be too bulky for the purposes of skull base reconstruction. Furthermore, the rectus abdominis has the propensity to undergo significant atrophy which can be both an advantage and a disadvantage. The deep inferior epigastric perforator (DIEP) flap can also be used incorporating a smaller island of muscle and fascia with a reduction in donor site morbidity (Figure 54.3).

**FREE FOREARM FLAP**

The radial forearm free flap is a versatile flap that is based on the radial artery. This fasciocutaneous flap has the advantage of a relative ease of dissection and a long vascular pedicle. This flap provides the appropriate bulk for dural coverage and is thus optimal for anterior skull base defects lacking a large dead space. However, this flap lacks adequate soft tissue for use with larger defects and almost all lateral skull base defects. Chepeha et al. have shown acceptable risk of morbidity (35 per cent), in those patients undergoing salvage surgery.

![Figure 54.3](a) Defect post-craniofacial resection including orbital exenteration; (b) Immediate postoperative result with reconstruction of the anterior skull base and dural defect with latissimus dorsi myocutaneous flap; (c) Late postoperative result latissimus dorsi flap, note muscular atrophy and suitability for ocular prosthesis.
anterior skull base resections who are reconstructed with forearm free flaps (Figure 54.4).\textsuperscript{29}

**ANTEROLATERAL THIGH FLAP**

The anterolateral thigh free flap is a fasciocutaneous flap based on the perforators of the descending branch of the lateral circumflex femoral artery. The main advantage of this free flap is the ability to reconstruct larger defects, optimal for use in lateral skull base reconstruction. The pedicle is shorter than that of the radial forearm free flap. Hanasono et al.\textsuperscript{30} have shown the anterolateral thigh free flap to be useful in skull base surgery (mainly lateral defects) with an overall complication rate of 29 per cent.

**SCAPULAR SYSTEM OF FLAPS**

The scapular/parascapular system of free flaps include the parascapular, scapular, as well as latissimus dorsi flaps based on the circumflex scapular and thoracodorsal arteries. The circumflex scapular artery provides nutrient blood supply to the lateral border of the scapula. In addition, the angular artery, most commonly from the thoracodorsal artery, supplies the scapular tip and a distinct osseous flap may be harvested based on this vasculature. This system of flaps can be harvested as cutaneous, myocutaneous or osteomyocutaneous in consistency. The advantages of this system of flaps are the versatility of defects for which it can be utilized. The scapular system can reconstruct large, complex, composite defects of the skull base and orbitomaxillary complex. The bulk of tissue available makes using the latissimus dorsi flap an ideal soft tissue option for large lateral skull base defects. Furthermore, the bony scapula flaps are particularly suited for orbitomaxillary reconstruction; the vascularized bone provides a contour approximating either the palate or the anterior maxillary sinus wall. In addition, free bone obtained from the scapula can be used to the orbital floor. The disadvantages of the scapular system of flaps include the complexity of harvest, unique positioning, as well as a relatively short pedicle when using the circumflex scapular nutrient arteries to the lateral aspect of the scapula. When the angular branch is used for harvest of the scapula tip, there is sufficient pedicle length for skull base reconstruction without the need for vein grafts (Figure 54.5).

**Specific sites of reconstruction**

**ANTERIOR SKULL BASE**

Resection of anterior cranial base tumours often places central nervous system structures in continuity with adjacent mucosa of the nasopharynx or paranasal sinuses. After resection of tumours of the anterior skull base with or without resection of brain parenchyma, the initial most critical aspect of reconstruction is dural closure, with either primary techniques or use of autologous tissues, such as fascia lata. After a watertight seal has been created, it is

![Figure 54.4](image1)

(a) Anterior skull base and exenteration reconstructed with a free forearm flap to create orbital depth for prosthetic reconstruction. (b) Prosthetic result with osseointegrated prosthesis.

![Figure 54.5](image2)

Figure 54.5 Rectus abdominus flap for reconstruction of lateral temporal bone defect (note volume matching).
imperative to place a vascularized soft tissue barrier, such as a pericranial flap, to protect and support the dural reconstruction. In dural defects that are unable to be closed, a large soft tissue barrier may be used to primarily seal and protect the intracranial contents. In addition, in patients who have undergone or will be undergoing radiation therapy, vascularized tissue coverage is critical to prevent wound breakdown and complication.

For most defects, the pericranial flap is the workhorse in the anterior cranial base, as it can provide dural coverage as far posteriorly as the clivus. Furthermore, this layer can be easily tacked to surrounding tissue providing the necessary barrier. In patients with large dural defects including orbital exenteration, our preference is to use a free flap combined with local flaps. Situations favouring free flap reconstruction include tumour factors, patient factors and others. In patients who have had prior pericranial flaps or who have had prior irradiation or will be undergoing radiation, we favour free tissue reconstruction. Interestingly, some authors have shown that patients who receive preoperative radiotherapy have significantly higher rates of complication using the pericranial flaps than those receiving postoperative radiotherapy. In the largest single institution report on skull base reconstruction, Hanasono et al. advocate the use of free tissue transfer for skull base reconstruction in patients who have received preoperative radiation, chemotherapy or who have had previous surgery. Furthermore, surgeons should consider microvascular reconstruction in patients undergoing secondary reconstruction in an infected field with questionable local tissues. In addition, ablations that leave significant adjacent tissue defects require free flap reconstruction. These include resections involving the orbitomaxillary buttresses, orbit, maxilla and nose. Appropriate reconstruction of these areas, which have critical functional and aesthetic ramifications, cannot be understated.

Special consideration should be made for reconstructions that require bone. Defects of the midline anterior skull base do not need to be reconstructed. However, defects of the frontal sinus, orbital rims, maxillae or larger defects of the skull require bony reconstruction. Bone substitutes and different types of mesh are frequently used for repair of flat bones of the skull, however these are inappropriate if the space is in continuity with the paranasal sinuses or in the setting of preoperative radiation or planned adjuvant therapy. Reconstruction of the orbital floor can be performed with autologous bone.

The complexity of the orbit has led Chepeha et al. to advocate for a subgrouping of defects in this region. They divided orbital defects into three groups, the first being orbital exenteration cavity alone, the second being the exenteration cavity with less than 30 per cent of the orbital rim excised, and the third being orbital exenteration cavity with resection of overlying skin, as well as the malar eminence or other bony areas. This group advocated for reconstruction of group 1 defects with a radial forearm free flap, group 2 defects with osseocutaneous forearm free flaps, and group 3 defects with osseocutaneous scalpula free flaps. In a retrospective evaluation of reconstruction of anterior and middle cranial base defects of the orbitomaxillary complex at Memorial Sloan Kettering Cancer Center, Chiu et al. described their approach, which entailed the use of the rectus abdominis in 97 per cent of patients, with the placement of nonvascularized bone in 11 per cent of patients. The incidence of complications was low, with a 0 per cent incidence of flap loss and a 7 per cent incidence of postoperative CSF leak. Interestingly, in patients undergoing maxillectomy with preservation of orbital contents, 52 per cent of these patients had eyelid complications or orbital position anomaly, highlighting the challenges related to adequate orbitomaxillary reconstruction. In all patients undergoing surgery of the orbitomaxillary unit with breach of the lacrimal apparatus, a dacryocystorhinostomy is to be performed to prevent epiphora or the need for a secondary procedure.

Our group favours use of the scapular tip bone flap for complex skull base reconstruction with orbitomaxillary involvement. As stated prior, this vascularized bone flap provides the advantages of similar shape to the palate or anterior maxillary sinus wall with local bone stock appropriate for reconstruction of the inferior orbital rim. The presence of a long pedicle and minimal donor site morbidity make this an optimal option for select anterior skull base defects. We have published on the successful use of this flap in our first 29 patients. There were no flap failures and eight patients (28 per cent) had orbital complications (five patients had ectropion and three had epiphora). All eight patients were treated successfully with minor secondary procedures.

For skull base defects that are small (usually less than 2 cm), created via an endoscopic approach, nasoseptal flaps are appropriate. The Hadad-Bassagasteguy flap, first described in 2006, provides adequate local tissue for local reconstruction of defects created using minimally invasive skull base surgery. The nasoseptal flap is currently the standard of endoscopic reconstructive techniques as it is reliable, available bilaterally, and is easy to harvest in those trained in endoscopic techniques. As with other local flaps, nasoseptal flaps may be taken down and reused for revision cases. In patients without viable tissue for a nasoseptal flap, the inferior turbinate pedicle flap is also an option for small skull base defects. For even larger defects of the skull base after extended endoscopic skull base resections, authors have recently published on novel techniques, such as bilateral nasoseptal flaps, as well as endoscopically harvested pericranial flaps. However, the limitation in endoscopic skull base surgery is inadequate reconstructive techniques for large defects or defects with high flow cerebrospinal fluid leaks.

Middle and central skull base

As in treatment of the anterior cranial base, critical to reconstruction of skull base defects of the middle skull base is watertight closure of the dura with soft tissue separation of the central nervous system and extracranial contents. In contrast to anterior defects, watertight closure of middle fossa defects is difficult, especially in the parasellar area. Therefore, an overlay of vascularized tissue in this area is critical. As in defects of the anterior vault, small defects of the bony skull base without dural disruption can be obliterated with a variety of tissue. Following endoscopic skull base surgery involving the sellar area, free fat or fascia lata can be used to obliterate dead space and create a barrier. However, larger defects are not adequately treated with this option. Certain cases of large dural defects without history of
radiation can be repaired with a pericranial flap. In patients with large defects or with history of radiation, a free tissue transfer is indicated for reconstruction. Free tissue transfer options for the central skull base include myogenous flaps (such as the latissimus dorsi or the rectus abdominis), fasciocutaneous options (such as the radial forearm free flap) or enteric options (such as the gastro-omental flap, which provides a large amount of well-vascularized tissue that is able to fill soft tissue defects). Small bony defects of the middle skull base do not require reconstruction. If the defect extends to involve the orbital rims, zygoma, mandible, maxilla or temporal region, consideration must be given to bony reconstruction.

Lateral skull base reconstruction

Following transtemporal approaches, there is often a lateral skull base defect in which it is not feasible to perform a watertight dural closure. These defects are often as a result of surgical ablation of benign disease and adjuvant therapy is infrequently warranted. In this case, reconstruction involves placement of a soft tissue barrier alone. Some authors have shown good results using synthetic material, such as hydroxyapatite for reconstruction of the selected lateral skull base defect. Care must be exercised on the use of alloplastic materials as they have a risk of extrusion, especially in those undergoing radiation treatment or where there is potential communication with the paranasal sinuses or mastoid cavity.

When vascularized tissue is desired, either a temporoparietal fascia pedicled flap or a temporalis muscle flap may be used. Some authors advocate the use of pectoralis major or trapezius regional flaps for reconstruction of composite lateral skull base defects. When the patient has undergone preoperative radiation or postoperative radiation is anticipated, a free tissue transfer must be considered. The most commonly used options for free flaps in the lateral skull base include the anterolateral thigh, rectus abdominis and scapular system of flaps. In an evaluation of reconstruction after temporal bone resection, Dean et al. cited an acceptable 15 per cent overall complication rate, in their series of 65 patients undergoing a variety of reconstruction (greater than 80 per cent free flaps). Moukarbel et al. demonstrated a low rate of complications, with a 5 per cent flap complication rate using scapular flaps for 60 patients undergoing lateral skull base reconstruction. O’Connell et al., in a study evaluating 65 patients undergoing free flap reconstruction for lateral skull base and scalp reconstruction (68 per cent latissimus dorsi), demonstrated 100 per cent flap success with one patient requiring a re-exploration for venous thrombosis. Using data from two tertiary centres, Rosenthal et al. proposed an algorithm for reconstruction of periauricular and lateral skull base defects; for patients with periauricular defects with preservation of the external auditory canal, the group suggested reconstruction with a radial forearm free flap. For patients with lateral temporal bone resection with auricular preservation, the anterolateral thigh free flap is the preferred reconstruction. Finally, patients undergoing lateral temporal bone resection with total auriculectomy require either the anterolateral thigh free flap or the rectus abdominis flap (Figure 54.6). Bony defects rarely require reconstruction in this area, unless the defect extends anterior to the mandible, orbit or other functionally or aesthetically critical area. Our philosophy is to use the appropriate flap for the defect size, staying focused on matching the volume of the reconstruction and the principles of skull base reconstruction.

Special consideration should be given to the patient undergoing facial nerve sacrifice. If clear margins can be obtained, facial nerve repair should be offered to all patients. As with trauma, if the nerve can be coapted without tension, then primary anastomosis may be performed. In the case that tension is present, primary repair should not be attempted and a nerve graft should be performed. Cable nerve grafts are usually performed using sural nerve, medial antebrachial cutaneous nerve or greater auricular nerve. Hanasono et al. demonstrated evidence of reinnervation at 12 months in 75 per cent of patients undergoing facial nerve repair. Falcioni et al. demonstrated 46 per cent of 56 patients undergoing facial nerve grafting recovered to a grade III on
the House–Brackmann scale. The most important predictor of long-term function was repair prior to 12 months of injury. If a nerve stump cannot be identified proximally, consideration should be made to a hypoglossal nerve or a trigeminal nerve (motor nerve to masseter) to facial nerve graft. Without a viable distal nerve stump, muscle transposition of the masseter or temporalis should be considered. In the delayed setting, there are multiple options for facial nerve rehabilitation in the setting of proximal nerve stump absence: these include cross-facial nerve grafting with or without free muscle transfer or free muscle transfer innervated by the trigeminal nerve (nerve to masseter). When innervated options are not an option, a static sling can provide symmetry at rest. An important concern is the safety of the cornea. In patients with anticipated facial paralysis, a gold weight should be inserted in the upper lid. In the case of anticipated temporary paresis, the clinician should provide aggressive corneal care, including artificial tears, lubrication, and in some cases, tarsorrhaphy to prevent corneal injury.

Patients undergoing auriculectomy during skull base surgery are typically unable to undergo surgical reconstruction of the ear. Local tissue loss and scarring in the setting of treatment for malignant disease requiring adjuvant therapy, render autogenous reconstruction very challenging. Prosthetic reconstruction of the ear can be invaluable and provides outstanding aesthetic results. Auricular prosthesis may be retained with an osseointegrated framework or may be attached to the soft tissue reconstruction with tissue adhesive daily.

COMPLICATIONS OF SKULL BASE RECONSTRUCTION

Relating to the proximity of the skull base to critical structures, complications following reconstruction of this area can be devastating. The reported range of complications after skull base reconstruction is wide, ranging from approximately 10 to 60 per cent, with an international collaborative study citing a rate of 36 per cent. Postoperative mortality was shown to be approximately 5 per cent. The incidence of postoperative complications is likely decreasing secondary to the increased expertise of multidisciplinary teams, improved reconstruction and better postoperative management. A decrease in complication rate may be tempered by expanded indications for surgical intervention, as well as intensification of neoadjuvant and adjuvant treatments.

The most feared complications of skull base reconstruction are those that arise from persistent contiguity of the central nervous system and the extracranial region. This leads to early complications, including unresolving cerebrospinal fluid leaks, predisposing to central nervous system (CNS) infection, such as meningitis, skull base osteomyelitis and abscess. Furthermore, persistent communication may progress to life-threatening tension pneumocephalus. As in all complex reconstruction, there is a risk of wound complication. As stated previously, the use of a regional pedicled flap places patients at higher risk for wound complication, likely related to marginal flap necrosis. Local flaps have a greater risk of wound complication in the patient who has undergone radiation treatment or has comorbidity such as diabetes mellitus. The risk of free tissue transfer failure is relatively low, with most authors publishing approximately 95 per cent success rates with a range of 86–100 per cent. Contributing factors that may lead to these outcomes include lack of bony support in the reconstruction, tissue atrophy or postoperative radiation fibrosis. Secondary procedures are often required to correct late complications of skull base surgery.

CONCLUSION

The ability to reconstruct the skull base following open and minimally invasive procedures is the most important predictor of operative success in oncologic procedures of the skull base. The formation of multidisciplinary skull base teams, advances in imaging and postoperative management, as well as the evolution of ablative and reconstructive techniques have dramatically reduced the morbidity of skull base surgery. Specific patient and tumour factors, including histology, location and size, as well as previous treatment, drive the selection of the appropriate skull base reconstruction. Adhering to the principles of reconstruction including providing a watertight dural seal, obliteration of dead space and maintaining the separation between the intracranial structures and the external skin and mucosal surfaces of the paranasal sinuses will provide the patient with greatest opportunity for a complication-free recovery.

KEY EVIDENCE

- The use of local flaps for small defects and free tissue transfer for large defects have been shown to have a significantly decreased complication rate compared to regional flaps.
- The use of free tissue transfer limits morbidity in patients who have undergone preoperative chemotherapy, radiation or surgery.

KEY LEARNING POINTS

- Management of patients with skull base lesions requires multidisciplinary teams of clinicians experienced in diagnosis, ablation and reconstruction of tumours in this critical area.
- Every patient should have treatment individualized to the specific tumour and patient factors, including previous treatment and plans for adjuvant therapy.
- Critical to skull base reconstruction is the creation of a watertight dural seal, obliteration
of dead space, and separation of intracranial and extracranial contents.
- Using modern techniques, complex defects of the skull base are reconstructed with decreased morbidity using free tissue transfer rather than local or regional flaps.

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Defect-based reconstruction: ear

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INTRODUCTION

The auricle, or pinna, has one of the most complex three-dimensional shapes of any human appendage. By virtue of its position, and because it exists as a paired structure, deformities of the auricle often cause the patient more emotional and psychological distress than might be expected for the size of the defect. Normal aspects of auricular shape and proportion are easily recognized but difficult to recreate without meticulous surgical technique and an in-depth appreciation of the spatial configuration and appearance of the normal ear.

HISTORY

Ancient descriptions of ear reconstruction date back to 600BC, when Sushrutha the ancient Indian surgeon reconstructed ear lobules using local flaps. In 1597, Tagliacozzi used a pedicled arm flap for reconstructing a monk’s ear. The modern era in ear reconstruction evolved with autogenous costal cartilage grafts described by Harold Gillies in the 1920s and Pierce in the 1930s. It was Ranford Tanzer\(^1,2\) in the 1950s who laid the foundations of current ear reconstruction, and his techniques were refined through the works of contemporary surgeons such as Brent\(^3\) and Nagata\(^4\).

ANATOMY

The external ear has a complex three-dimensional topography consisting of skin and cartilage. The cartilage framework is made of fibroelastic cartilage draped by a unique skin which is thinner than the surrounding skin.

The blood supply for the external ear comes from two main sources, the posterior branch of the superficial temporal artery and posterior auricular artery. The venous drainage is to retromandibular, superficial temporal and external jugular veins. The lymphatic drainage is less organized than previously believed but the main draining nodes are parotid, mastoid, superior cervical and infraclavicular nodes. The external ear is supplied by sensory branches from four cranial nerves. The greater auricular nerve supplies the lower half of the ear and a portion of the preauricular area. The anterior surface and the tragus are supplied by the auriculotemporal nerve, whereas the superior and mastoid regions are supplied by the lesser occipital nerve. The external
auditory meatus is supplied by Arnold’s nerve, the auditory branch of the vagus nerve. It is important to have an understanding of the anatomy of the periauricular area since vascularized tissues may need to be recruited from surrounding areas either primarily or in salvage situations.

The postauricular artery is a branch of the external carotid artery. It leaves the external carotid just superior to the occipital artery and courses anterior to the mastoid tip and posterior to the pinna. It supplies the majority of the skin of the auricle and the postauricular skin.

Flaps based on the postauricular artery are useful in auricular reconstruction due to the proximity of the supply artery, and also because postauricular skin provides a good colour match for defects of the ear.

The superficial temporal artery is one of the two terminal branches of the external carotid artery. It crosses over the posterior root of the zygomatic process of the temporal bone; about two inches above this process, it divides into two branches, a frontal and a parietal branch. The branches are sandwiched between two layers of superficial temporal fascia and form the vascular basis for the superficial temporal artery flap. Just above the zygomatic arch, it gives rise to the deep temporal branch which penetrates temporal fascia and anastomoses with the deep temporal branches of the maxillary artery.

The deep temporal branches of the maxillary artery course between the temporalis muscle and the pericranium. They supply the temporalis muscle, and anastomose with the middle temporal artery.

The superficial temporal fascia, deep temporal fascia and temporalis muscle can all be raised as local flaps and are useful in ear reconstruction.

The descriptive terms for various parts of the pinna are illustrated in Figure 55.1. The nomenclature of individual parts is important in understanding the scientific descriptions of various defects and in communication.

The aesthetic aspects of external ear have been described in classical anatomy as early as the time of the Renaissance by artists such as da Vinci. These are important in ear reconstructions, as markers for size, orientation and proportion of the normal components of the ear; they provide a useful guide to the goals for reconstruction in individual patients. More recently, Tolleth has carried out extensive work on aspects of normal ear anatomy (Figure 55.2). The height of the ear is normally subtended by the anatomic landmarks of the lateral aspect of the eyebrow and the alar base. The width of the ear is approximately 55 per cent of the length and it is tilted posteriorly along its long axis by 10–20° to the vertical. The axis of the ear forms an angle of about 15° with that of the bridge of the nose. The rim of the helix is separated from the mastoid by 1–2 cm, the distance increasing caudally.

Figure 55.1 Components of the pinna, standard nomenclature. The components of the pinna are as follows: helix (H), antihelix (AH), cymba concha (Cy), cavum concha (Ca), superior crus (SC), inferior crus (IC), triangular fossa (TF), scaphoid fossa (SF), tragus (T), antitragus (A), intertragic notch (In), earlobe (L).

EMBRYOLOGY

The ear starts to develop from the first and second branchial arches of the developing embryo between the third and sixth weeks of intrauterine life. Six auricular hillocks form around the first branchial cleft; three from the first arch and three from the second. The anterior three hillocks form the helical root, tragus and superior helix. The second arch forms the antihelix, antitragus and lobule. The middle ear cavity begins to form in the first pharyngeal arch by 4 weeks, and the external auditory canal begins to canalize by 28 weeks. The middle ear cavity is fully formed by 30 weeks, but the mastoid air cells pneumatize only after birth.

Abnormalities in the development can form a spectrum of ear anomalies often associated with other facial malformations. Anotia or total absence of the external ear is very rare. Microtia is a more common more condition where there is a rudimentary ear consisting of cartilage remnants in a soft tissue envelope.

AETIOLOGY OF EAR DEFECTS

The causes of ear defects can be congenital or acquired. Most cases of congenital ear defects are idiopathic. Sometimes there can be genetic or environmental causes associated with microtia, such as fetal alcohol syndrome, isotretinoin and thalidomide, or maternal parity of more than four pregnancies.

Owing to the shared embryonic origins of tissues of the face and ear, ear abnormalities may present as part of a syndrome, such as Treacher Collins syndrome, which is
transmitted as autosomal dominant. Craniofacial microsomia is a non-inherited condition characterized by hypoplasia of faciomaxillary mandibular soft tissues and bones which may be associated with microtia. With such intimate facial associations, isolated microtia may certainly be viewed as a mild form of craniofacial microsomia, if only to rule out faciomaxillary mandibular abnormalities.

Among acquired causes of external ear deformities, the most common is trauma, of which, human bites are a common mode of injury. These often result in partial loss of the pinna. Other traumatic defects of the ear include chondritis secondary to burns and ‘cauliflower ear’ which is due to an organized haematoma from a blunt injury. Neoplastic causes include tumours, such as basal cell carcinoma and squamous cell carcinoma, which need surgical resection leaving ear defects.

**CLASSIFICATION OF CONGENITAL EAR ANOMALIES**

Popular classifications of congenital ear anomalies include those of Tanzer⁷ (Box 55.1) and Cosman (Box 55.2).

**MULTIDISCIPLINARY MANAGEMENT OF EAR RECONSTRUCTION**

All ear reconstruction patients should ideally be managed in a multidisciplinary team setting. This ensures that patients receive the best objective advice about treatment decisions, such as autologous versus prosthetic, but also that they have associated problems, such as speech, hearing or craniofacial growth problems, evaluated and treated as necessary. While treatments for different aspects of the patient’s condition may be instituted at different times during the patient’s journey, it is helpful to see the patient with their parents early on so that timely screening for hearing and speech problems can be carried out, as well as allowing the team an opportunity to build rapport and trust with the patient and their family early on.

**GENERAL RECONSTRUCTIVE OPTIONS**

The various options for reconstruction of the external ear are:

- **Stick-on ear prosthesis**: These are prosthetic pieces which are attached using skin adhesives. They are limited by the complex attachment which is time-consuming, may not adhere strongly, and also by skin reactions to the adhesives in some patients.
- **Osseointegrated ear prosthesis**: The ear prostheses are custom-made from pliable silicone which are shape- and colour-matched to the opposite side. Anchorage is by the use of titanium abutments which are held by bone-anchored, osseointegrated titanium implants embedded in the mastoid bone. They have better retention than the stick-on prostheses but require daily cleaning of the

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**Box 55.1 Tanzer’s classification of congenital ear anomalies**

- Anotia
- Complete hypoplasia (microtia)
  - With atresia of external auditory canal
  - Without atresia of external auditory canal
- Hypoplasia of middle third of the auricle
- Hypoplasia of the superior third of the auricle
  - Constricted (cup and lop) ear
  - Cryptotia
  - Hypoplasia of the entire superior third
- Prominent ears

**Box 55.2 Cosman’s classification of congenital ear anomalies**

- Lidding: deficiency of the scapha and sup crus
- Protrusion: deep conchal fossa
- Smaller ear
- Low ear position

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**Figure 55.2** Anatomic site and proportions of the auricle. The pinna sits between the horizontal plane of the lateral eyebrow (EB) and the alar base (AB). It is centred on the Frankfort horizontal plane (FP), which is defined by a line drawn between the inferior orbital foramen and the upper margin of the external auditory meatus. The pinna is situated one ear-height distance posterior to the posterior edge of the lateral eyebrow, and the long axis of the ear is offset from the vertical plane by 20°. This analysis is based on the work of Tolleth.⁷
implant sites and have a higher risk of local tissue inflammation.

- **Use of synthetic auricular frames:** In these techniques a synthetic frame is used to recreate the shape of the ear. The frames are either buried in a subcutaneous pocket or covered with superficial temporal fascia which is then skin grafted. The frames can be made of a variety of materials but the two materials clinically used are silicone and expanded polytetrafluoroethylene (PTFE). Expanded PTFE has the advantage that it has the potential for vascular ingrowth. Both these methods have better success when used in combination with a superficial temporal fascial flap. They have significant risks of infection and extrusion but do not require cartilage harvesting from the chest.

- **Total autologous reconstruction:** Ear frames are made of autologous costal cartilage in these techniques. They are then be buried in a subcutaneous pocket or covered with superficial temporal fascia. There are several technical modifications, of which the two popular methods are those by Brent and Nagata.

**MICROTIA**

Microtia literally means 'small ear', but often what remains of the ear are vestiges of cartilage covered by skin. It is much more common than anotia (total absence of pinna). It has an incidence ranging from 0.76 to 2.35 per 10,000 births. It is more common in Asians and Native Americans. Males are more commonly affected than females (3:1) and the right side is more commonly involved than the left. Although 70 per cent of cases occur as an isolated deformity, it can be part of syndromes such as Treacher Collins syndrome.

Microtia can be associated with several other congenital malformations (Box 55.3). Microtia has been classified by Nagata into five types (Box 55.4).

**Evaluation of patients for microtia reconstruction**

Initial evaluation of congenital ear anomalies includes a detailed history and a thorough physical examination. The medical history should include antenatal history, the possibility of any maternal illnesses or drug intake during pregnancy. The family history gives a clue into syndromic deformities. Examination of the entire face has to be carried out in detail, with special attention for signs of craniofacial microsomia, such as hypoplasia of the mandible, orbit and facial nerve weakness. The ear deformity has to be described accurately making note of the existing components and the missing ones. The presence of a tragus is generally considered an indication of a functioning middle ear.

A complete audiological and radiological evaluation is important to assess the middle and inner ear function. The main hearing loss in microtia is conductive loss (80 per cent) but some patients can have sensorineural hearing loss as well. The middle ear abnormalities can range from complete absence of a cavity to minor disruption of the ossicles. A CT scan will help diagnose the middle ear deformities, whereas an MRI scan is more useful in identifying the course of the facial nerve which can be abnormal in these children.

**Microtia reconstruction**

The aims of reconstruction in microtia include creating an aesthetically pleasing external ear and restoration of hearing.

Children with microtia can have associated hearing problems which sometimes will need middle ear surgery. In the past, hearing loss surgery was not undertaken for unilateral cases of microtia. The mainstay of otological care has been to ensure that hearing in the normal ear is preserved with amplification of hearing in the affected one. However, there is now some evidence that binaural hearing is important in the normal development of a child and patients with unilateral microtia are receiving treatment for hearing loss.

If middle ear surgery is contemplated, it has to be done in consultation with the surgeon undertaking the reconstruction of the external ear. The position of the canal and the location of the flaps have to be considered and it may be wiser to delay middle ear surgery until external ear reconstruction is completed.

**BRENT METHOD OF MICROTIA REPAIR**

Brent operates early between the ages of four and six years. In the Brent technique, the first stage consists of
Figure 55.3  Cartilage frame (Brent). This diagram illustrates a full cartilage frame assembly in the style of Brent. The components include the helix (H), tragus (T) and base plate (BP) segments (left). The superior and inferior crurae are formed by recreating the furrows above and below each crus through a hollowing out of the base plate segment, without using a separate antihelical segment. In the Brent frame, the tragal segment is held to the root of the helix segment with sutures.

Creating a cartilage frame from the contralateral chest wall using a template made from the patient’s normal ear. The template is reversed and made smaller to accommodate for the skin thickness. The contralateral sixth, seventh and eighth cartilage segments are harvested and the synchondrosis between the sixth and the seventh is used to create the base plate which is then carved to create the convolutions of the ear (Figure 55.3). The eighth rib (floating rib) is used to create the helix which is fixed using nylon sutures. Suction drains are used to ensure that the skin drapes snugly over the frame.

In the second stage, lobule transposition is done and is carried out several months after the first stage. The third stage consists of elevating the frame and maintaining the projection by wedging a block of banked cartilage. The postauricular defect is closed with a medium-thickness split skin graft. The fourth stage, the tragus is constructed, the concha is deepened and adjustments for symmetry are carried out. The tragus is made using a composite skin/cartilage graft taken from the contralateral concha through an anterior incision and is inserted into the reconstructed ear using a ‘J’-shaped incision. Conchal deepening is then performed by undermining subcutaneous tissues. Brent later modified his technique to incorporate a tragal strut in the original frame.

NAGATA METHOD OF MICROTIA REPAIR

In the Nagata method, steps one and two of Brent’s technique are combined. The cartilage frame is created using costal cartilage taken from the sixth, seventh, eighth and ninth ipsilateral ribs. The base plate is constructed at the point of, and including, the sixth–seventh costal cartilage synchondrosis. This allows sufficient width to create the transverse dimension of the base plate. The helix is made from the eighth rib and secured to the base plate using stainless steel wire sutures. The antihelix and the crura are created from the ninth rib and secured onto the frame. Further segments are used to create a tragus segment, and two conchal segments (cymba concha, cavum concha) (Figure 55.4). Owing to the increased volume of cartilage required, Nagata suggests operating when patients have reached 10–12 years of age, or when they have a chest circumference of at least 60 cm. Nagata uses a ‘W’ incision on the posterior aspect of the lobule which allows lobule transposition; this incorporates a splitting of the lobular skin which increases the surface area of tissue available to cover the cartilage frame. The cartilage frame is inserted into the subcutaneous pocket and the lobule transposed. Bolster sutures are used to ensure correct skin redraping over the convolutions of the frame.

The second stage is performed six months after the first and the cartilage frame is elevated. Nagata’s second stage is different to Brent’s in that a crescent-shaped piece of cartilage taken from one of the contralateral sixth to eight ribs is carved to and placed in the postauricular space to maintain the projection. In addition, the posterior surface of the pinna and the surface of the mastoid are resurfaced with a combination of a down-turned superficial temporal artery flap and a split-thickness scalp skin graft.

The Nagata technique gives a better aesthetic result and has fewer stages involved, but is technically more demanding, with longer operating times.

A comparison of Brent and Nagata’s techniques is shown in Table 55.1.

RECONSTRUCTION FOR CONGENITAL PARTIAL DEFECTS OF THE EAR

Other common congenital defects of the ear include prominent ears, constricted ear deformities previously known as cup ears and lop ears, cryptotia where the root of the helix is buried and defects of the ear lobule and Stahl’s ear.

Prominent ears are the most common congenital ear anomaly and can range from mild to severe prominence. Many of these cases have a poorly developed antihelical fold,
whereas some others have a well-developed fold but have a deep concha. The aims of surgery in prominent ear correction are to recreate an antihelical fold, reduce the depth of concha where indicated, and to decrease the distance between the helical rim and mastoid which is normally less than 2 cm. These can be achieved using a variety of techniques which include either scoring the cartilage, conchal excision and/or sutures.

Constricted ear anomalies form a spectrum, and in severe cases a total reconstruction using a cartilage frame will be required. Minor deformities can be corrected by altering the skin and cartilage. Cryptotia is corrected by separating the adhesions between the root of the helix and postauricular tissues and advancing it outwards. A V–Y procedure at the root of the helix may sometimes be required. Stahl’s ear is an interesting anomaly in which there is an abnormal third crus which traverses the pinna towards the helical margin and can sometimes give the ear a ‘pixie’-type appearance (Figure 55.5). Correction of Stahl’s ear can be technically challenging and a variety of techniques have been described including wedge excision, reversal of upper pole cartilage and cartilage scoring techniques.

Correction of congenital defects in infancy

Some of the partial congenital defects can be corrected during the neonatal stage using splintage. The splints can be made using dental impression material and secured using tapes. This is based on the fact that neonatal cartilage is mouldable during the first few weeks of life due to high levels of circulating maternal oestrogens and the maternal hormone relaxin. It is especially useful in the correction of prominent ears since 60 per cent are noted soon after birth. There are several studies that have described the benefits of neonatal splintage but it is not clear how long after birth the cartilage remains mouldable.12

**Table 55.1** Comparison of Brent and Nagata techniques.

<table>
<thead>
<tr>
<th>Brent technique</th>
<th>Nagata technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery at 5 years of age</td>
<td>Surgery at around 10–12 years of age</td>
</tr>
<tr>
<td>Four stages</td>
<td>Two stages</td>
</tr>
<tr>
<td>6th, 7th, 8th costal cartilages harvested</td>
<td>6th, 7th, 8th, 9th costal cartilages harvested</td>
</tr>
<tr>
<td>Nylon sutures</td>
<td>Stainless steel sutures</td>
</tr>
<tr>
<td>Auricular projection involves skin graft only</td>
<td>Cartilage wedge and superficial temporal artery flap/scalp skin graft</td>
</tr>
</tbody>
</table>

**ACQUIRED DEFECTS**

The most common aetiology for acquired defects of the ear is trauma. Simple lacerations of the ear require nothing more than an accurate approximation using fine sutures.

Figure 55.5 The Stahl’s ear. This is a congenital abnormality in which there is a third crus which usually extends from the superior crus or the antihelix, to the helical rim. The additional crus can cause a pointed appearance of the pinna giving rise to terms such as ‘pixie ear’ or ‘Spock ear’.

**Table 55.2** Reconstruction of acquired ear defects.

<table>
<thead>
<tr>
<th>Partial defects</th>
<th>Direct closure if possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of local tissues</td>
<td>Prosthetic reconstruction</td>
</tr>
<tr>
<td>Autologous reconstruction</td>
<td></td>
</tr>
<tr>
<td>Total defects</td>
<td>Stick-on prosthesis</td>
</tr>
<tr>
<td>Osseointegrated prosthesis</td>
<td>Synthetic frames covered with autologous tissues</td>
</tr>
<tr>
<td>Cartilage frames covered with autologous tissues</td>
<td></td>
</tr>
<tr>
<td>Skin only defects (perichondrium intact)</td>
<td>Full-thickness skin flaps</td>
</tr>
<tr>
<td>Local flaps from adjacent skin</td>
<td></td>
</tr>
</tbody>
</table>

Partial thickness defects exposing the cartilage can be resurfaced with a full-thickness skin graft taken from the contralateral postauricular sulcus, if the perichondrium is intact (Table 55.2). Full-thickness defects are more challenging and need careful planning for reconstruction. A small segment loss in the middle third can sometimes be closed directly, but a moderate-sized defect may need a local flap. A skin graft is an option in a defect with full thickness loss of cartilage, if the auricular skin on the opposite surface of the pinna is intact and remains vascularized. With a large, full-thickness, segmental loss of pinna, it may be better to close the defect, allow for primary healing with a secondary referral to a specialist centre for reconstruction. Human bites to the ear are frequent in some geographic areas and these wounds need meticulous debridement and cleansing before suturing.
Reconstruction is generally delayed in these cases due to risk of infection.

The other common cause of acquired defects of the pinna is due to oncologic surgery. The common tumors of the ear are squamous cell carcinoma and basal cell carcinoma though melanomas can rarely affect the ear. If the excision involves only the skin a full-thickness skin graft can be used for reconstruction (Figure 55.6). However, in the elderly ear a tumour involving the helical margin is sometimes more easily treated with a wedge excision. Full-thickness excision defects often need local flaps for reconstruction.

Reconstructive options

Individual anatomical areas of the pinna pose specific reconstructive problems (Table 55.3). For the purpose of reconstruction full-thickness defects of the pinna can be classified as follows:

- Upper third defects: Local flaps from the adjacent skin can be used to resurface small defects. Helical advancement using the V–Y technique can be useful to close small to moderate-sized defects. Defects involving the helical rim can be reconstructed using a tubed pedicle flap based on the post-auricular artery (Figure 55.7).
- Middle third defects: As in the upper third, defects of the rim can be reconstructed using post-auricular flaps. If the defect involves the helical and antihelical folds, cartilage support is often needed in the form of costal cartilage grafts. The Antia-Buch reconstruction (Figure 55.8) using advancement of helical rim based on the postauricular skin can be useful for small and moderate sized defects. The Dieffenbach flap is a staged advancement flap that can be used for middle third rim defects (Figure 55.9).
- Lower third defects: The lobule is difficult to simulate using reconstructive techniques. Local flaps are used either as a one- or two-stage procedure and often a non-anatomical cartilage graft can give support for the reconstructed lobule.

<table>
<thead>
<tr>
<th>Site-specific reconstruction of pinna defects.</th>
</tr>
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<tbody>
<tr>
<td>Upper third</td>
</tr>
<tr>
<td>Antia-Buch type advancement with V–Y release</td>
</tr>
<tr>
<td>of helical root</td>
</tr>
<tr>
<td>Partial cartilage frames covered with native skin</td>
</tr>
<tr>
<td>or superficial temporal fascia</td>
</tr>
<tr>
<td>Middle third</td>
</tr>
<tr>
<td>Antia-Buch type advancement</td>
</tr>
<tr>
<td>Tubed pedicle flaps (involves three to four stages and useful for rim defects)</td>
</tr>
<tr>
<td>Postauricular flaps</td>
</tr>
<tr>
<td>Partial cartilage frames covered with native skin</td>
</tr>
<tr>
<td>Lower third</td>
</tr>
<tr>
<td>(lobule)</td>
</tr>
<tr>
<td>Local flaps with non-anatomic cartilage graft</td>
</tr>
<tr>
<td>Concha</td>
</tr>
<tr>
<td>Full-thickness skin grafting</td>
</tr>
<tr>
<td>Swinging door flaps</td>
</tr>
</tbody>
</table>

Figure 55.6 Skin graft of defect. For smaller defects, a skin graft may be used for reconstruction if the bed of the defect is well-vascularized (left). The graft is secured with a tie-over bolster dressing (right).

Figure 55.7 Posterior auricular flap. A flap based on the posterior auricular artery can be created either in a superiorly or inferiorly based fashion. (a) The flap is used for helical rim or marginal reconstructions (b). (c) Flap inset for upper auricular reconstruction.
Defects of the concha: Partial defects of the concha can be resurfaced using full-thickness skin grafts. Trapdoor flaps are ingenious flaps which can be used for conchal defects (Figure 55.10). Defects up to 1.5 cm wide can be excised as a wedge and closed directly in an adult-sized ear. Wedges can be designed as a shield or as a ‘W’ which gives a better appearance. Cartilage can be sutured separately or sutures taken through skin and cartilage together.

**Figure 55.8** The Antia-Buch advancement flap. The Antia-Buch flap is a helical advancement flap which incorporates a chondrocutaneous segment (a). The chondrocutaneous segment can be mobilized to reach defects around the rim (b), but can result in a smaller reconstructed ear (c).

**Figure 55.9** The Dieffenbach flap. Dieffenbach described a staged reconstruction for defects of the mid-auricle. First a flap is raised based on the post-auricular/mastoid skin (a). This provides the anterior layer of skin for the defect (b). When there is sufficient healing and revascularization anteriorly, the posterior pedicle of the flap can be divided at a second stage (c). This tissue can then be advanced and wrapped around the edge of the pinna to reconstruct the posterior layer of skin for the defect (d).

- Defects of the concha: Partial defects of the concha can be resurfaced using full-thickness skin grafts. Trapdoor flaps are ingenious flaps which can be used for conchal defects (Figure 55.10).
- Defects up to 1.5 cm wide can be excised as a wedge and closed directly in an adult-sized ear. Wedges can be designed as a shield or as a ‘W’ which gives a better appearance. Cartilage can be sutured separately or sutures taken through skin and cartilage together.

**Cartilage frames in partial ear defects**

The conventional techniques for repairing partial ear defects use local skin flaps or composite flaps using skin and ear cartilage. The techniques using skin-only flaps may not deliver the best results over time due to the tendency of auricular tissue to develop secondary contracture and deep scarring after surgery. For this reason, bespoke cartilage frames are increasingly being used in reconstruction of ear.
defects. The principles and techniques of making these frames are very similar to those used for microtia reconstruction. Reconstructive examples of upper third (Figure 55.11) and middle third defects (Figure 55.12) are shown.

Amputation of the ear

An amputated ear is not an uncommon scenario in an emergency setting. There are isolated case reports of replantation of ear and successful take of composite grafts where the amputated part has been reapplied surgically.\textsuperscript{15, 16, 17} Composite tissue segments reattached as grafts are unlikely to survive if the grafts are large thus exceeding the capacity for neovascularization to occur ahead of the metabolic requirements of the attached piece. Microsurgical reattachment, or replantation, is dependent upon the quality of available vessels supplying the segment. This includes not only the size of available supply vessels, but also whether or not they have been irreversibly injured during the amputation – this is more likely if the piece was torn/bitten off (avulsion), as compared to cut off with a sharp instrument (classical amputation). The latter scenario provides more likely candidate vessels for replantation. Attempts at ‘banking’ denuded cartilage have been made in the past with the hope that this can be retrieved later for reconstructive purposes. The structural framework of the native ear cartilage is thin, elastic and compliant with the correspondingly thin, overlying auricular skin. The same frame if buried under a skin pocket in the mastoid area will usually collapse under the contractile forces of secondary scarring. The same result usually occurs if contralateral auricular cartilage grafts are used in repair – once the surgeon violates native auricular skin, secondary contractile forces can often overwhelm the strength and elasticity of the auricular cartilage. For this reason, the use of costal cartilage constructs with well-vascularized tissue overlays with or without skin grafts remains the mainstay for reconstructions of an autologous nature. Having considered the options for reattachment after the necessary cleaning and surgical debridement of non-viable tissue, the optimum treatment plan can then be devised. If the situation is unsuitable for primary reattachment, the surgical techniques described so far gives the surgeon the option to discard the amputated part and close the wounds primarily. Patients can subsequently undergo secondary autologous reconstruction of the defect, which in selected cases may provide superior clinical results.

Burns of the ear

Burns involving the ear can cause chondritis which can result in loss of cartilage and loss of ear shape. The mainstay of treatment is keeping the ear free of infection and avoiding pressure to the ear. Topical ointments are applied allowing an eschar to form and separate naturally. If there are areas of exposed cartilage, sometimes local flaps may be necessary to cover them. Reconstruction of an ear lost due to burns can be a challenge since the tissues are scarred and non-pliable, often necessitating the use of superficial temporal artery fascial flaps, as well as prosthetic reconstructions. Microsurgical free tissue transfer may have a role in providing the necessary vascularized soft tissue cover in this situation.

Blunt trauma

Blunt trauma usually results in a subcutaneous haematoma due to rupture of the delicate blood vessels of the pinna. The condition, when related to an organized haematoma, is sometimes referred to as ‘cauliflower ear’. It is a term used to describe an organized haematoma in the external ear from a blunt injury, such as boxing. An organized clot fills the convolutions of the cartilage and destroys the fine architecture of the ear. Treatment is mainly prevention by evacuating the haematoma early before it can get organized and using bolster sutures to prevent it from reaccumulating. Once established it is a difficult problem to treat and it is often necessary to recreate the shape by scoring out the fibrous tissue.

Split ear lobe

Wide ear holes and split ear lobes are due to wearing heavy earrings, which can later pull through due to physical trauma. They can be repaired by excising the edges of the defect and suturing in two layers. In completely split ear lobes, a Z-plasty can be incorporated to break the line of scar. If future piercing is done it is important to pierce away from the scar line and also not to wear heavy earrings.
Figure 55.11  Reconstruction of auricle, upper third. A 28-year-old patient presented with a human bite injury which was previously cleaned, trimmed and sutured in Accident and Emergency. The resultant defect shown in (a) demonstrates a clean, straight cut which, while well healed, is markedly obvious and unnatural. At operation, a cartilage frame is created in layers (b, right) and stabilized using fine stainless-steel wire sutures. This design is based on a three-dimensional prosthetic model which serves as a guide for reconstruction (b, left). Such models can be sterilized and used intraoperatively. An initial attempt at reconstruction using a modified Dieffenbach flap was unsuccessful, necessitating the use of a turndown superficial temporal artery flap surfaced with a partial thickness scalp skin graft for reconstruction of the skin envelope. Early oedema can be seen over the reconstructed cartilage frame. (c) A later evaluation shows the completed first stage reconstruction with resolution of swelling, good contours and excellent colour match of the scalp skin graft. (d) The patient is now ready for the second stage of reconstruction which will require elevation and projection of the frame with reconstruction of the soft tissue of the post-auricular sulcus.
Figure 55.12  Reconstruction of auricle, middle third. A 63-year-old patient presented with a defect resulting from excision of a squamous cell carcinoma of the middle third of the pinna (a). Open dissection demonstrates the combined cartilage and soft tissue defects (b). A bespoke cartilage segment was carved from costal cartilage. In this patient, the costal cartilage was wide and thick enough to allow fabrication of the helical rim, antihelical segment and the base plate in one piece (c, left). A prosthetic model of the proportions of the normal ear was prepared preoperatively and used as a guide (c, right). Part of the lobular tissue was preserved with the skin envelope to maintain blood supply to the envelope at the conclusion of the first stage (d). This was trimmed and inset at the second stage, six months later (e, right). A C-shaped block of cartilage was further harvested and inset to maintain projection (e, left) which was then resurfaced with a superficial temporal artery flap with a scalp skin graft overlay. The final result (f) shows an improved contour, well-defined rim and satisfactory definition of the antihelix, albeit with a small residual scar.
Keloids of the ear

Keloids of the ear typically occur in the ear lobes following piercing. They are much more common in the Asian and Afro-Carribean population and are a difficult problem to treat. The treatment options include intrallesional injection of steroids (triamcinolone/prednisolone), which may be used in sequence or in conjunction with the use of localized pressure (ear clips) or surgery (intrallesional excision). Patients should be cautioned that treatment does not yield uniform results and that recurrence is frequent. In patients with repeated recurrences, surgical options may be restricted.

THE FUTURE OF EAR RECONSTRUCTION

The aim of ear reconstruction is to create an anatomically accurate biological unit of living tissue which is matched to the patient. One of the stated disadvantages of using costal cartilage is that it has to be harvested as a separate procedure, and the full frame construct assembled from constituent cartilages. This results in longer operative times. There is potential pain, discomfort and healing problems with the chest wall harvest site, although with updated methods of nerve blocks and accurate closure these are much reduced compared to previously. A prefabricated, histocompatible tissue-engineered frame would save both surgical and postoperative healing time. Various materials have been trialled to provide the endoskeletons on which cultured chondroblastic and chondrocytic elements can be implanted, but these have so far only reached the cellular viability stage. Although cartilage can be successfully cultured in the laboratory, cultured cartilage is soft and lacks the rigidity and projectile strength of costal cartilage.

Costal cartilage-based auricular framework fabrication with well-vascularized local/regional tissue is the current gold standard for autologous reconstruction, and looks likely to remain so for the immediate future.

KEY LEARNING POINTS

Anatomy

- The pinna is centred on the Frankfort horizontal plane (line drawn from the infraorbital foramen to the upper aspect of the external auditory meatus).
- The upper border of the pinna is level with the lateral aspect of the eyebrow.
- The lower border of the pinna is level with the alar base.
- The pinna is located one ear-length backwards from the lateral canthus.

Multidisciplinary management of ear reconstruction

Ear reconstruction is a multidisciplinary enterprise and should include input from the following specialties:

- otolaryngology
- plastic surgery
- clinical prosthetics
- craniofacial surgery
- audiology
- speech and language therapy
- clinical genetics

General reconstructive options

- A strong cartilage frame is required to resist the forces of secondary scar contracture.
- The height of the reconstruction can be matched to that of the opposite side in unilateral cases.
- A properly constructed autologous reconstruction is permanent, resistant to infection and requires no maintenance.
- If the patient is a child, they should be of an age where they are able to participate in the decisions regarding surgery.

Summary

- Beware of incorporating scar tissue into a repair.
- The liberal use of vascularized tissue is recommended.
- There is as yet no ideal alloplastic implant.
- Scalp skin grafts provide the best texture and colour match.
- Costal cartilage provides the best tissue for framework reconstruction.

KEY EVIDENCE

- A retrospective analysis of 62 patients following ear reconstruction showed that both children and adults reported improvement in social and leisure activities, postoperatively. There were similar improvements for patients undergoing both autologous and alloplastic reconstructions. Patients rated the appearances higher than the surgeons.
- A panel review of the outcomes of 51 microtia reconstructions showed gradual improvement in results over time, and that the learning curve for microtia surgery is a long one.
- A prospective assessment of the psychosocial changes after autologous ear reconstruction in 21 patients, compared to 23 patients who decided not to undergo surgical procedures, demonstrated significant improvements after surgery. More than 80 per cent of the patients would repeat their reconstructions if faced with the same surgical decision again, while 66 per cent reported good integration of the reconstructed ear with their body image.
REFERENCES

INTRODUCTION

Facial nerve paralysis is a distressing and disfiguring condition because of the loss of facial symmetry and expression both at rest and during voluntary movement. Resting tone and coordinated movement of the muscles of facial expression not only convey the aesthetics of the face but facilitate verbal and non-verbal communication. Consequently, these patients have a tendency to avoid social interactions and may retreat from society altogether. In congenital or early-onset facial paralysis the child’s psychosocial development may be severely compromised. In addition, the loss of normal ocular and oral function can result in corneal exposure keratitis, epiphora and difficulty with speech and alimentation. Collapse of the internal nasal valve may create respiratory difficulties and the specialized functions of taste, hearing and lacrimal gland secretion may also be impaired. Facial paralysis therefore results in a combination of functional and aesthetic concerns often associated with profound psychosocial difficulties.

Although there are many aetiologies underlying congenital and acquired facial paralysis, the reconstructive techniques currently practised are relatively few and the management of the patient depends more upon the duration and extent of paralysis than its cause. The management plan is therefore based upon a thorough assessment of the patient’s individual requirements and motivation, their general health and their suitability for operative intervention. The involvement of a multidisciplinary team variably comprising plastic surgeons, neurosurgeons, neurologists, oncologists, otolaryngologists, opthalmologists, psychologists and physiotherapists helps ensure a favourable outcome.

For clarity, the word ‘paralysis’ refers to complete loss of muscle movement, whereas ‘paresis’ is a partial loss or weakness. ‘Palsy’ incorporates both paralysis and paresis. The terms are used interchangeably in this chapter.

HISTORY OF SURGERY FOR FACIAL PALSY

The Scottish surgeon Sir Charles Bell first identified the facial nerve as the motor supply to the muscles of facial expression in 1829. Fifty years later, Drobnick performed the first facial nerve repair by coaptation of the facial and spinal accessory nerves and in 1927, Bunnell attempted the first intratemporal repair of the facial nerve.1

For cases where facial nerve repair was not possible, other reconstructive techniques were sought. In 1971, Thompson reported the first series of non-vascularized muscle transplants for facial paralysis using the palmaris longus and extensor digitorum brevis muscles. He subsequently
advocated microneural coaptation to the contralateral facial nerve.\textsuperscript{3, 5} With the development of refined microsurgical technique and equipment in the 1970s, Scaramella pioneered the use of cross-facial nerve grafting as a technique for the reinnervation of unilateral facial paralysis, heralding the modern era of reanimation surgery.\textsuperscript{4}

Harri et al. described the first successful use of vascularized free muscle transfer for facial reanimation, using the gracilis muscle to reproduce a smile in 1976.\textsuperscript{5} Initially, the gracilis transfer was innervated by the motor branch to the temporalis muscle, but later, the cross-facial nerve graft was used, allowing more spontaneous rehabilitation.\textsuperscript{6} Today, free tissue transfer remains the gold standard of facial reanimation surgery, yielding excellent and reproducible results.\textsuperscript{7, 8, 9}

In 1982, Terzis and Manktelow described the dual innervated pectoralis minor transfer making use of two separate cross-facial nerve grafts to improve independent motor control for eyelid closure and lip elevation\textsuperscript{10} although the technique has proved less useful than first anticipated. Manktelow also described the ‘minitransfer’ of a thinned segment of the gracilis as a means of reducing bulk in the cheek without compromising muscle power or excursion.\textsuperscript{11}

Free muscle transfer with cross-facial nerve grafting is normally a two-stage procedure with at least six months between operations. Recently, interest has again focused on single-stage procedures, making use of a variety of donor muscles with long nerves that obviate the need for cross-facial nerve grafting.\textsuperscript{12, 13, 14, 15, 16}

Although reconstruction of the smile remains one of the greatest challenges in facial paralysis surgery, its other manifestations must also be addressed. A number of adjunctive techniques have been developed to correct brow ptosis and eyelid closure, and a variety of static procedures are designed to achieve facial symmetry at rest for those patients unable or unwilling to undergo free muscle transfer.

**FUNCTIONS OF THE FACIAL NERVE**

The frontalis, orbicularis oris and oculi, zygomaticus major, levator labii superioris and depressor labii inferioris are functionally the most important muscles innervated by the facial nerve. In the upper face, paralysis of the frontalis results in ptosis of the forehead and brow that worsens over time with gravity and the loss of skin elasticity associated with ageing. As a result, the patient may appear to be angry, depressed or unduly serious, the upper visual field may be obstructed and some loss of facial expression is inevitable. Impaired orbicularis oculi contraction prevents normal eyelid closure and may compromise the ability to blink. Globe exposure is further exacerbated by retraction of the upper eyelid due to the unopposed action of the levator palpebrae muscle. Elevation of the upper lid is a function of the oculomotor nerve (CN III) and the sympathetic nervous system and is therefore preserved in pure facial nerve paralysis. Loss of tone in the lower lid due to paralysis of the orbicularis and the effects of gravity, results in ectropion and loss of contact between the globe and the canalicular system, precluding normal tear drainage. These factors, combined with lacrimal gland dysfunction, result in desiccation of the globe, exposure keratitis and epiphora, as well as an expressionless, staring eye.

It is important to appreciate that congenital or neonatal facial palsy rarely produces the same severity of ocular symptoms. The eye appears to tolerate exposure relatively well and the soft tissue elasticity is better. However, as the child grows into adulthood, the same problems may arise.

In the mid and lower face, there are other significant functional and aesthetic consequences of facial paralysis. The perioral retractor muscles normally lift the upper lip, depress the lower lip and move the oral commissures outward while the orbicularis oris allows pursing and protrusion of the lips and assists with labial speech production. Buccinator helps control the food bolus when chewing and prevents food accumulation in the buccal sulcus. Poor oral continence, drooling, cheek biting and poor speech are troublesome symptoms for many patients, and for some the collapse of the nasal valve due to the loss of cheek muscle tone may cause difficulties with nasal breathing. Loss of these functions has predictable results, but the inability to produce a spontaneous and symmetrical smile is perhaps the most devastating of all because patients may be perceived to be emotionally and mentally abnormal on account of their physical appearance.

Each of these symptoms and signs of facial paralysis may be uni- or bilateral, partial or complete. Although unilateral facial paralysis is far more common, the bilateral condition is functionally more severe and leaves the patient totally devoid of facial movement and expression even though the face is relatively symmetrical at rest.

**FACIAL NERVE ANATOMY**

The facial nerve is composed of approximately 10 000 neurons, 70 per cent of which supply the muscles of facial expression together with the stylohyoid, posterior belly of the digastric and the stapedius muscles. The remainder comprises the ‘nervus intermedius’, which carries somatosensory fibres from the anterior two-thirds of the tongue and parasympathetic secretomotor fibres to the parotid, submandibular, sublingual and lacrimal glands. The facial nerve also contains a few general somatic afferent fibres, which join the auricular branch of the vagus nerve to supply sensation to the external auditory meatus, and visceral afferents, which innervate the mucous membranes of the nose, palate and pharynx via the greater palatine nerve. It is an embryological derivative of the second branchial arch.

The anatomy of the facial nerve is described as having a central, intratemporal and extratemporal course (Figure 56.1).\textsuperscript{17, 18}

**Central course**

Motor and sensory neurons originate at the pre- and post-central gyri of the cerebral cortex, passing through the internal capsule and upper midbrain to the pons, where they synapse in the facial nerve nucleus. The tracts supplying the upper face cross back and forth in the pons, whereas those to the lower face cross only once. As a result, the facial
nerve nucleus receives bilateral cortical projections destined for the upper facial muscles, and unilateral projections innervating the lower facial muscles. Clinically, an injury proximal to this level will spare function in the orbicularis oculi and frontalis muscles allowing for eyelid closure and forehead elevation.

The facial nerve nuclei receive afferent input from both the trigeminal nerve and acoustic nuclei, respectively forming a component of the corneal and stapedial reflexes.

Neurons exiting the facial nerve nucleus pass around the abducens nucleus as they emerge from the brainstem. A lesion near the fourth ventricle may therefore involve both these nerves and the superior salivatory nucleus resulting in a dry eye, as well as cranial nerve (CN) VI and VII dysfunction.

The facial nerve's parasympathetic fibres originate in the superior salivatory nucleus and travel with the trigeminal nerve (CN V). The lacrimal nerve travels with V1, the pterygopalatine nerve with V2 and the lingual nerve/chorda tympani with V3.

The facial nerve emerges from the brainstem accompanied by the nervus intermedius, which lies between the facial nerve superiorly and the vestibulocochlear nerve inferiorly. The nervus intermedius conveys taste fibres from the anterior two-thirds of the tongue via the chorda tympani and from the soft palate via the palatine and greater petrosal nerves. In addition, preganglionic parasympathetic innervation of the submandibular, sublingual and lacrimal glands are carried with the nervus intermedius, as is a small sensory component from the skin of the auricle and postauricular area.

The facial nerve, the nervus intermedius and the vestibulocochlear nerve are in close proximity at the cerebellopontine angle and in the internal auditory canal. Consequently, lesions at these levels can result in disturbances of lacrimal function, taste, salivary flow, hearing, balance and facial movement.

Approximately 2 cm after leaving the brainstem, the nerves enter the internal auditory canal.

### Intratemporal course

The facial nerve travels through the narrow petrous temporal bone for a distance of 2.5–3 cm, occupying up to 50 per cent of the canal’s volume. Here, it is vulnerable to inflammatory processes and to traumatic injuries of the bone, such as basal skull fractures. The canal is divided into three segments.

After traversing the short and narrow labyrinthine segment, the facial nerve changes direction at the geniculate ganglion to enter the tympanic segment of the bony canal. Here, the nervus intermedius and the facial nerve form a common trunk. The geniculate ganglion is joined by afferent fibres from the chorda tympani. Three nerves branch from the ganglion: the greater superficial petrosal nerve carrying secretomotor fibres to the lacrimal gland; the lesser petrosal nerve carrying secretory fibres to the parotid gland; and the external petrosal nerve, an inconstant branch carrying sympathetic fibres to the middle meningeal artery.

The distal portion of the facial nerve emerges from the middle ear between the posterior wall of the external auditory canal and the horizontal semicircular canal. Here, the facial nerve reaches the beginning of the mastoid segment. Three branches exit from this segment of the facial nerve: the nerve to the stapedius muscle; the chorda tympani; and the nerve from the auricular branch of the vagus. The facial nerve continues vertically down the anterior wall of the mastoid process to the stylomastoid foramen. At this point, the nerve contains only sensory and motor fibres. A branch exits the nerve just below the stylomastoid foramen and innervates the posterior wall of the external auditory canal and a portion of the tympanic membrane.

### Extradimensional course

Immediately after exiting the stylomastoid foramen, the facial nerve gives off a posterior auricular branch, which innervates the superior and posterior auricular and the occipitalis muscles, as well as providing sensation to an area behind the earlobe. Two separate small branches innervate the stylohyoid muscle and posterior belly of the digastric.

As the facial nerve passes from the stylomastoid foramen to the posterior border of the parotid, it passes anterior to the posterior belly of the digastric, lateral to the stylohyoid muscle and external carotid artery then posterior to the facial vein.

Surgical landmarks to the facial nerve include the tragal pointer and the posterior belly of the digastric. In children, the facial nerve will be found more superficially because of incomplete development of the parotid gland and pneumatization of the mastoid.
As the nerve passes anteriorly from the stylomastoid foramen, it becomes more superficial and therefore more susceptible to injury. On entering the parotid gland, the nerve lies in a plane between the superficial and deep lobes of the gland. It divides early into two major trunks at the pes anserinus: the superiorly directed zygomaticotemporal and the inferiorly directed cervicofacial trunk. Within the parotid substance, five major divisions of the facial nerve exist. These are the temporal (frontal), zygomatic, buccal, marginal mandibular and cervical. In practice, the zygomatic and buccal branches are difficult to distinguish from one another. By the time the divisions exit the anterior margin of the parotid, there are between eight and fifteen branches, which subsequently arborize and interconnect creating some redundancy that is useful in reconstructive surgery. Frequent anastomoses exist between the buccal and zygomatic branches allowing for some preservation of function if one or two branches are injured. The temporal and marginal mandibular branches are, however, without significant connections and are at highest risk during surgical procedures. The facial nerve innervates all of the muscles of facial expression on their deep surface with the exception of the buccinator, levator anguli oris and mentalis muscles, which are innervated on their superficial surfaces.

TEMPORAL BRANCH

The three or four branches of the temporal or frontal division lie along Pitanguy's line, extending from a point 5 mm below the tragus to another 1.5 cm above the lateral aspect of the ipsilateral eyebrow. Having exited the anterosuperior border of the parotid, the nerve crosses the zygomatic arch very superficially within the temporoparietal fascia. The frontal branch then enters the undersurface of the frontalis muscle, which it innervates along with the upper orbicularis oculi and corrugator supercilii muscles.

ZYGOMATIC AND BUCCAL BRANCHES

In the lower face, the five to eight branches of the facial nerve are relatively well protected, running deep to the platysma and superficial musculoaponeurotic system (SMAS) which invests the muscles of facial expression. The SMAS therefore aids the surgeon in identifying the plane of the facial nerve during dissection. The zygomaticus major, minor, levator labii superioris alaeque nasi, depressor septi, compressor and dilator naris muscles are innervated by the zygomatic division, while the buccal branch innervates buccinator and the superior part of the orbicularis oris muscle.

MARGINAL BRANCH

The marginal mandibular division of the facial nerve consists of one to three branches that initially pass below the angle of the mandible, and then arch upwards to cross the body anterior to the facial artery. The nerve courses deep to the platysma, becoming more superficial as it travels medially to supply risorius, depressor labii inferioris, mentalis and the lower parts of the orbicularis oris muscle.

CERVICAL BRANCH

The cervical division innervates the platysma from its deep surface near the junction of the upper and middle thirds of the muscle.

THE PATHOPHYSIOLOGY OF FACIAL PALSY

The aetiology of facial nerve palsy is highly varied and differs somewhat between adults and children. The classification can be congenital or acquired, by site, or by mechanism (Table 56.1). The prognosis depends largely upon the aetiology. Hence, in cases of infectious or idiopathic paralysis, some recovery of function can be anticipated.

Idiopathic/viral

Bell's palsy accounts for more than half of all cases of facial palsy with an incidence of approximately 20 cases per 100 000 per annum and increasing with age. There is an equal male to female ratio, and the left and right sides are equally affected. Less than 1 per cent of cases are bilateral and the recurrence rate is about 10 per cent. Diabetics and pregnant women are known to be at increased risk.

Although originally described in primates with traumatic division of the facial nerve, the term ‘Bell’s palsy’ came to imply a facial paralysis of unknown aetiology and was therefore a diagnosis of exclusion. More recently, an association between idiopathic Bell's palsy and the presence of herpes zoster is thought to account for some of the apparent increase in incidence. Idiopathic Bell's palsy has several features distinguishing it from traumatic palsy, recovery of function is more likely and facial nerve function does not return to normal as well. Some degree of permanent facial nerve weakness is more likely with idiopathic Bell’s palsy.

Table 56.1 Aetiology of facial paralysis.

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Parotid (8-15 branches)</th>
<th>Buccal (2 branches)</th>
<th>Zygomatic (8 branches)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic/viral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Base of skull fractures, facial lacerations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>Opercular syndrome, Millaud-Gubler syndrome, cerebrovascular accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Otitis, mastoiditis, herpes zoster (Ramsay Hunt syndrome), encephalitis, polio, multiple viral and bacterial infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Diabetes mellitus, hyperthyroidism, hypertension, porphyria, vitamin A deficiency and pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Parotid lesions, cholesteatoma, cranial nerve VII tumour, menigoma, sarcoma, carcinoma, neurofibromatosis II, fibrous dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>Carotid artery aneurysm, haemangioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td>Ethylene glycol, alcohol, arsenic, carbon monoxide, mesoprostol, thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Post-immunization, facial or dental surgery including parotid or masseteric surgery, facelift surgery, tumour resection, resection of acoustic neuromas, embolization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Bell’s palsy, Melkerson–Rosenthal syndrome, Charcot-Marie-Tooth, autoimmune disease, temporal arteritis, thrombotic thrombocytopenic purpura, multiple sclerosis, myasthenia gravis and sarcoidosis</td>
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</table>
many cases of Bell’s palsy and herpetic or other viral infections has led to it being considered as a positive diagnosis in the presence of sudden onset unilateral facial palsy associated with a viral prodrome and without evidence of any other aetiological cause. There is an increased incidence of herpes simplex virus antibodies in patients with Bell’s palsy when compared to age-matched controls and the results of animal studies lend weight to the theory of an infectious aetiologic.

Up to 90 per cent of patients recover spontaneously from Bell’s palsy within one month, the remainder not usually showing signs of recovery for three to six months. A minority is left with residual paralysis and may present for reconstruction. Patients with incomplete paralysis from the outset have the best prognosis for recovery.22

Ramsay Hunt described facial paralysis in association with herpetiform vesicular eruptions and vestibulocochlear dysfunction, the third most common cause of facial paralysis. Patients experience more pain than with Bell’s palsy and recovery is less assured or complete. The syndrome is caused by the reactivation of dormant herpes zoster virus in extracranial cranial nerve ganglia. Only about 50 per cent of these patients regain normal facial function.

Melkersson–Rosenthal syndrome is characterized by a triad of relapsing and increasingly severe facial paralysis, facial edema and fissuring of the tongue with onset of these symptoms usually in childhood or early adulthood. The aetiology of this rare condition is unknown but there is a genetic predisposition as well as an association with Crohn’s disease and sarcoidosis.25

**Traumatic**

Trauma is the second most common cause of facial nerve palsy. Temporal bone fracture or gunshot injuries are commonly implicated, but the nerve can also be inadvertently injured during middle ear, mastoid and parotid surgery as well as cosmetic facelift procedures. Occasionally, the nerve is deliberately resected to achieve tumour clearance in cancer surgery but often, inadvertent manipulation of the nerve during tumour resection will result in a temporary paralysis. For example, acoustic neuroma resection is associated with postoperative facial nerve weakness in about 20 per cent of patients.26

**Oncologic**

About 5 per cent of cases of facial nerve paralysis are tumour related. In these patients, paralysis is often of slow onset, intermittent and associated with facial twitching and, occasionally, with other cranial nerve deficits. A palpable neck or parotid mass and lymphadenopathy may be evident. Schwannoma is the most common benign tumour; mucoepidermoid carcinoma and adenoid cystic carcinoma of the parotid gland are the most common malignant tumours.

**Congenital**

Congenital facial palsy is uncommon, with an incidence of approximately 1–2 in every 1000 live births. Birth trauma as a result of complicated or mechanically assisted delivery accounts for over 80 per cent of facial palsy in the newborn. This is due in part to the relatively superficial position of the extracranial facial nerve in infants.

Other causes of congenital facial paralysis include Möbius syndrome, which is characterized by bilateral facial nerve palsy often associated with unilateral or bilateral palsy of the abducens nerve (CN VI). The surgical management of patients with Möbius syndrome is made more complex by the fact that the condition is bilateral.27 Other cranial nerves, particularly III, IX, X and XII, may be involved and skeletal anomalies can occur. Poland’s syndrome and other upper limb abnormalities may be associated with Möbius in up to 25 per cent of cases. Most patients are of normal intelligence. The condition is largely sporadic but can be inherited in an autosomal dominant pattern with incomplete penetrance and variable expression. The pathogenesis is not fully understood but may relate to aplasia or hypoplasia of cranial nerve nuclei, a primary myopathy or disruption of the subclavian artery.

Muscular dystrophy is a steadily progressive familial distal myopathy associated with weakness of the face, jaw and neck. At birth, infants present with facial diplegia. In contrast to Möbius syndrome, however, lateral gaze is intact. Later in childhood, distal progressive myopathy develops.

**HISTORY AND PHYSICAL EXAMINATION**

The patterns of signs and symptoms associated with facial paralysis often point to the likely site and aetiology of the lesion (Table 56.2). A thorough history and clinical examination must therefore be undertaken of each new patient and should elucidate:

- facial nerve pathology;
- clinical course;
- patient’s specific concerns and expectations;
- examination;
- review of options and communication with the patient.

The speed of onset, duration and progression of the paralysis should be noted and may suggest an aetiology and therefore prognosis for recovery. The longer the duration of paralysis, the less likely spontaneous recovery will be. The prospect of spontaneous recovery should be virtually excluded before surgical intervention is contemplated.

Past medical history may be relevant to the aetiology of facial paralysis and should be detailed. This includes previous episodes of facial palsy, trauma or relevant surgery, associated symptoms such as hearing loss, otorrhoea, otalgia, vertigo, headaches, blurred vision and facial parasthesiae. Concurrent medical conditions such as diabetes, pregnancy, autoimmune disorders and cancer should be noted. When evaluating infants with facial paralysis, family history, gestational history and drug consumption are of particular importance. Complicated vaginal deliveries, with or without forceps, facial swelling, bruising over the mastoid or extratemporal course of the nerve, and haemotympanum should also be documented.

Patients must be encouraged to communicate their concerns and expectations. Some patients, particularly men, may be reluctant to focus on their appearance and social function, concentrating instead on functional difficulties, such as eye
discomfort and oral competence. In terms of reconstructive options, some patients are concerned primarily with facial symmetry at rest, while others will seek facial reanimation in order to be able to smile.

The initial evaluation of facial movement and expression can be made during the history taking. Subsequently, the examiner should specifically and systematically identify the functioning muscles and grade their power. Asking the patient to raise their brow, close their eyes, smile, show their teeth and pucker their lips will reveal most deficiencies. Synkinesis, seen most commonly as eye closure with smiling, should be noted (Figure 56.2). The degree of voluntary movement of the facial muscles can be graded or classified, and monitored by systems such as those of House and Brackmann (Table 56.3).28, 29 Digital photography and video can help document the condition and assess future response to treatment.

The head and neck examination should include the ears, eyes, parotid glands and neck as well as a thorough evaluation of the function of all the cranial nerves. Formal audiological and ophthalmologic examination may be appropriate, and radiological, electrophysiological and other special tests arranged.

On examination of the eye, visual acuity and corneal sensation should be assessed. The height of the palpebral aperture should be recorded bilaterally. The palpebral fissure normally narrows with smiling and failure to do so can result in an unsatisfactory aesthetic. The presence of a Bell's reflex should be sought, as this will affect the degree of corneal exposure when the patient attempts to close the eye. Finally, lower eyelid position and tone should also be recorded and compared with the normal side (Figure 56.3).

In children, the physical examination and subsequent radiological and neurophysiological testing are similar to adults but subject to some limitations of cooperation. Physical examination may reveal other cranial nerve palsies or

<table>
<thead>
<tr>
<th>Site of Injury</th>
<th>Effect</th>
<th>Signs and symptoms</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracranial facial nerve injury</td>
<td>Muscles of facial expression</td>
<td>Brow ptosis</td>
<td>Facial movement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inability to close eyes</td>
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<tr>
<td></td>
<td></td>
<td>Lower lid laxity</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Facial asymmetry</td>
<td></td>
</tr>
<tr>
<td>Tympanomastoid</td>
<td>Taste fibres</td>
<td>Loss of taste</td>
<td>Taste test</td>
</tr>
<tr>
<td></td>
<td>Salivary glands</td>
<td>Dry mouth</td>
<td>Salivary test</td>
</tr>
<tr>
<td></td>
<td>Stapedius muscle</td>
<td>Hyperacusis</td>
<td>Stapedial reflex</td>
</tr>
<tr>
<td>Geniculate ganglion</td>
<td>Lacrimal gland</td>
<td>Dry eye</td>
<td>Schirmer's test</td>
</tr>
<tr>
<td></td>
<td>Mucosal glands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal acoustic canal</td>
<td>Cranial nerve VIII</td>
<td>Loss of hearing and balance</td>
<td>Audiology</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td>Sparing of frontalis and orbicularis function</td>
<td>CNS examination</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

Figure 56.2  Synkinesis. Note closure of the eye when the patient attempts to smile.
other congenital anomalies. These should be investigated and managed appropriately.

Thoughtful consideration and assessment of potential nerve and muscle donor sites for reanimation procedures should also be made.

### INVESTIGATIONS FOR FACIAL PALSY

#### Blood tests

Routine preoperative blood tests may be ordered according to the patient’s general health and the proposed operation. Supplementary special investigations may also be necessary to determine the aetiology of facial palsy based upon the history and physical examination. These may include fluorescence in situ hybridization for velocardiofacial syndrome, toxoplasmosis, rubella, cytomegalovirus and herpes simplex screening. When syndromic cases are suspected, chromosomal analysis may be indicated.

#### Imaging studies

Computed tomography (CT) and magnetic resonance imaging (MRI) are useful in the diagnosis of injury to, or tumour around, the intratemporal or intracranial portions of the facial nerve. The path of the facial nerve can be seen, and swelling or disruption noted. Associated abnormalities of the ear, skull base and mandible suggest a developmental aetiology of the paralysis. MRI provides the best definition of the nerve and the surrounding soft tissue and gadolinium can be used to enhance soft tissue resolution. Aplasia or hypoplasia of the nerve strongly suggests a developmental aetiology whereas haematoma and soft tissue swelling point to a traumatic origin.

#### Electrophysiology

Electrophysiological testing can help to determine the site and extent of injury, the potential for recovery and progression. The following tests are performed by percutaneous stimulation of the facial nerve. They are, however, of little value in patients with incomplete paralysis.

The nerve excitability test (NET) is low-cost and practicable, but subjective. A stimulating electrode is placed over the stylomastoid foramen, and the threshold current required to produce a twitch on the paralysed side of the face is compared with the contralateral side. A difference of greater than 3.5 mA indicates a poor prognosis for return of facial function.

The maximum stimulation test (MST) is a modified version of the NET. The difference between the stimulus required to depolarize all facial nerve branches on the paralysed and contralateral sides is compared and graded. An equal or slightly decreased response on the involved side favours complete recovery. An absent or markedly decreased response carries a poor prognosis. Sequential testing allows for assessment of recovery.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>I</td>
<td>Normal</td>
<td>Normal facial function in all areas</td>
</tr>
<tr>
<td>II</td>
<td>Mild dysfunction</td>
<td>Slight weakness or synkinesis</td>
</tr>
<tr>
<td>III</td>
<td>Moderate dysfunction</td>
<td>Obvious asymmetry, but not disfiguring, synkinesis, contracture, or hemifacial spasm; complete eye closure with effort</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately severe dysfunction</td>
<td>Obvious weakness or disfiguring asymmetry; normal symmetry and tone at rest; incomplete eye closure</td>
</tr>
<tr>
<td>V</td>
<td>Severe dysfunction</td>
<td>Only barely perceptible motion; asymmetry at rest</td>
</tr>
<tr>
<td>VI</td>
<td>Total paralysis</td>
<td>No movement</td>
</tr>
</tbody>
</table>
Electroneuronography (ENoG) is an objective, qualitative measurement of neural degeneration. Following facial nerve stimulation, muscle response is recorded. The peak-to-peak amplitude of the evoked compound action potential is proportional to the number of intact axons. The normal and paralysed sides of the face are compared. A reduction in amplitude on the involved side to 10 per cent or less of the normal side indicates a poor prognosis, whereas reduction of less than 90 per cent within 3 weeks of injury suggests a very high likelihood of spontaneous recovery. ENoG studies are useful in determining the timing and the need for surgical intervention.

The NET, MST and ENoG are useful in the degenerative phase but will give normal results during the first 72 hours after injury until nerve degeneration reaches the site of the test stimulus. Furthermore, these tests rely on comparison with a normal contralateral facial nerve, and so, are of no use in bilateral paralysis.

Fibrillation potentials indicating axonal degeneration do not appear until 10–14 days post-onset of facial paralysis. After this time, however, electromyography (EMG) can be used to assess the potential for muscle recovery. Needle electrodes are placed into the muscle and action potentials generated by voluntary and involuntary activity are recorded. Fibrillation potentials indicate degeneration and polyphasic potentials indicate reinnervation. The latter appear between 6 and 12 weeks before clinical return of function is noted.

Newborns who present with a complete facial nerve paralysis should undergo electrophysiological testing within the first 3 days to differentiate congenital and traumatic aetiologies. In traumatic cases, the nerve can be stimulated for up to 5 days post-injury and fibrillation potentials will be seen on EMG at 10–14 days. In congenital cases, neither usually occurs.

Topographical testing

Specific tests can be used to localize the site of injury to the facial nerve and therefore assist in diagnosis and management. If the lesion is distal to a particular branch of the nerve, the function of that branch will be spared. Moving distally from the brainstem, these tests include the stapedial reflex test (stapedial branch), taste testing (chorda tympani), salivary flow rates and pH (chorda tympani):

- Schirmer’s test evaluates lacrimation, a function of the greater superficial petrosal nerve. A strip of filter paper is placed in the lower conjunctival fornix bilaterally. After 3–5 minutes, the length of the strip that is moist is compared to the normal side. A reduction of 25 per cent or a total of less than 25 mm in 5 minutes is abnormal and indicates injury to the greater superficial petrosal nerve or to the facial nerve proximal to the geniculate ganglion. When local anaesthetic is used to avoid reflex tearing, the test is called Schirmer’s 2.
- Stapedial reflex testing evaluates the stapedius branch of the facial nerve. A loud tone is presented to either ear evoking a reflex movement of the stapedius muscle and a change in the tension of the tympanic membrane. This can be recorded and compared with the normal side. In Bell’s palsy, absence of the stapedial reflex during the first 2 weeks is common and is usually of no prognostic significance.
- Taste sensation to the anterior two-thirds of the tongue is carried by the chorda tympani and can be assessed by placing salt, sugar or lemon juice on the tongue. The test is, however, extremely subjective. Tongue biopsy may reveal the absence of taste papillae within 10 days of symptom onset.
- Salivary flow rates can be assessed to evaluate the integrity of the chorda tympani by cannulation of Wharton’s duct, but the test is difficult to perform. A 25 per cent reduction in flow from the involved side is considered abnormal, as is a salivary pH of less than 6.1.

In practical terms, these tests are rarely carried out because interpretation is difficult; a careful history and examination supplemented with CT and MRI provide the most useful information.

**The Treatment of Facial Palsy**

Following accurate diagnosis and thorough physical assessment (see **Figure 56.5**), the probability of spontaneous recovery of nerve function must be estimated and supplemented by appropriate use of electrophysiological testing. Time should be allowed for such recovery to occur spontaneously, and intervention should be limited to conservative therapies or temporary surgical procedures to protect the eye from exposure keratitis.

Further treatment of facial paralysis can be medical or surgical.

**Medical therapy**

The most urgent consideration in facial palsy is protection of the eye. Exposure keratitis is prevalent in facial nerve injury involving the frontal and zygomatic branches lateral to the outer canthus.

Conservative measures aimed at protecting the eye include the use of artificial tears during the daytime and ointment at night. Drops containing hydroxypropyl cellulose, hydroxypropyl methycellulose or polyvinyl alcohol are commonly used by day and may reduce excessive reflex tearing. Thicker ointments containing petrolatum, mineral oil or lanolin are used at night. The eye may be taped closed at night but many patients find this process awkward and prone to failure. Temporary tarsorraphy may be required to protect the eye in anticipation of functional recovery and regular ophthalmologic assessments should be arranged.

In some cases, medication may speed the resolution of facial paralysis. Harris et al. recommended that traumatic facial paralysis in the newborn be managed conservatively with corticosteroids. A recent randomized control trial of steroid and antiviral use in patients over 16 years old supports the use of the former only. No prospective randomized studies are available that evaluate the efficacy of steroid use in the newborn with facial paralysis caused by birth trauma. However, it is reasonable to give steroids during the 3-week observation period before decompression or exploration of the nerve is undertaken. This approach is
similar to treatment of adult acute idiopathic facial paralysis. A combination of steroids and antiviral agents may be used in the treatment of Bell’s palsy and Ramsay Hunt syndrome. Surgery to decompress the nerve is rarely required.

Other medical treatments for facial palsy include the use of botulinum toxin in the management of synkinesis, hyperkinesis and facial asymmetry. Although the effects wear off after only three to four months, the technique yields good results in the control of these sequelae, particularly following facial reinnervation procedures. Botox or local anaesthetic can also be used prior to definitive resection of the depressor anguli oris muscle to address lower lip asymmetry, allowing patients to assess the benefits of surgery without committing to it. In cases of upper eyelid retraction with corneal exposure keratitis where spontaneous recovery is anticipated, Botox can be used to paralyse the levator palpebrae muscle.

Neuromuscular therapy may be employed in patients with partial facial nerve palsy and makes use of specific exercises and biofeedback. In addition, the input of speech therapists and psychologists may be useful.

**Surgical therapy**

**GENERAL PRINCIPLES**

A variety of surgical options are available for the treatment of facial palsy and new techniques are frequently described. It is important to select procedures that will most likely address the needs and expectations of the patient and which fall within the capabilities of the operating surgeon.

A distinction must be made between an acute facial nerve injury in which the function of the paralysed muscles may be restored by timely intervention and a chronic state where depletion of the motor end plates and muscle atrophy preclude successful reinnervation. The cut-off is generally between 12 and 18 months following the onset of paralysis. Beyond this time period, denervated muscle exhibits irreversible degeneration and patients become dependent upon static procedures to improve facial function and symmetry, or upon the transfer of functioning muscle to the face for dynamic reconstruction.

In contrast to developmental cases, early exploration and nerve repair should be considered in all traumatic facial palsies. If a temporal bone fracture is present on CT scanning, surgical exploration of the facial nerve should be undertaken as soon as possible. The nerve must be fully exposed and decompressed and any haematoma within the nerve sheath must be evacuated.

When possible, direct coaptation of the divided nerve produces optimal results. Intraoperative nerve stimulation can be very helpful to assist in locating the distal branches of the nerve only in the first 2 or 3 days following the injury. In cases where the facial nerve is injured medial to the lateral canthus of the eye, the rich anastomotic network may obviate the need for exploration and repair.

Nerve repair should be tension free. Sharp penetrating trauma including inadvertent iatrogenic injury is most amenable to direct repair. Crushing injuries such as those caused by neonatal forceps delivery, result in scarring of longer segments of the facial nerve. This, and resection of the nerve on oncological grounds, necessitates the use of interpositional nerve grafts. Cable grafts may be required, particularly in proximal deficiencies, if the donor nerve is of insufficient calibre. Donor nerves include the sural nerve, which is remote from the zone of injury and, less commonly, the great auricular nerve, which is readily accessible. Sacrifice of these nerves results in reduced sensation to the lateral border of the foot or the lower half of the ear, respectively. Rarely, the hypoglossal nerve, supraclavicular nerve and the medial cutaneous antebrachial nerve are used as graft donors.

Recovery following direct nerve repair or grafting can be satisfactory even though a comparatively small number of axons are regenerated. Muscle tone and movement usually return at around six months postoperatively. Even following technically perfect nerve repairs however, synkinesis, facial spasm and mass movement are frequent complications, particularly in proximal repairs.

![Figure 56.5 An algorithm for the management of facial paralysis.](image-url)
Direct coaptation or nerve grafting may be either impossible or inappropriate. This scenario commonly arises when the facial nerve lesion is within the central nervous system or the temporal bone and no proximal facial nerve stump is available for repair. In long-standing palsies, the motor end plates to the mimetic muscles are permanently lost and nerve repair serves no purpose.

When the proximal facial nerve stump is not available for repair, but the distal branches and motor end plates are still intact, alternative donor nerves may be used. A cross-facial nerve graft (VII to VII) can be used and has the theoretical advantage of providing natural, spontaneous facial muscle control although there is significant loss of axons through the graft, resulting in weak function. Consequently, the cross-facial nerve graft is better suited to powering free muscle transfers and alternative donor nerves are sought to innervate the innate facial muscles when appropriate. These include the glossopharyngeal, spinal accessory, phrenic, trigeminal (masseter) and hypoglossal nerves. Control of facial muscles reinnervated in this way can be unnatural, uncoordinated and prone to synkinesis. The hypoglossal nerve is most commonly used and has been effective in cases of bilateral facial palsy associated with Möbius syndrome. In Möbius syndrome, there is bilateral facial and abducens nerve paralysis often associated with a broad range of other conditions. The absence of the facial nerve on either side compels the use of alternative donor nerves for reanimation procedures. The masseter nerve is proving to be a popular and well tolerated alternative. Tongue atrophy and associated difficulty with mastication, speech and swallowing are known complications of hypoglossal nerve transfer, or, to preserve some of this function, the nerve can be partially divided and coapted end to side to the facial nerve stump with a nerve graft. Finally, direct neurontization of denervated muscle has been reported with variable results. This involves burying a donor nerve directly into the muscle. However, such a technique is only suitable for isolated partial muscle paralysis.

**CHRONIC FACIAL PALSY**

The management of stable, long-standing facial paralysis is governed by the assumption that there will be no further recovery in facial movement and the anticipation of a worsening of facial symmetry as the patient ages. Static procedures are designed to alter the facial posture and symmetry at rest and may improve oral continence and nasal valve collapse. They do not provide voluntary facial movement, but may reduce the distortion produced by muscle activity in the normal half of the face. Brow lifts, blepharoplasties, weighting of the upper eyelid, lower lid canthopexies and sling procedures for support and symmetry of the cheek and mouth are examples of static procedures. They are generally less demanding of the patient and surgeon alike and may therefore be more appropriate in the older, comorbid or less-motivated patient who wants a relatively quick fix and accepts the limitations of these procedures. Although resting facial symmetry is improved, asymmetry is again apparent during animation of the normal contralateral face.

Dynamic procedures, on the other hand, aim to reproduce movement in the paralysed face, improving symmetry both at rest and in motion. Such procedures are appropriate for younger or well-motivated patients as the procedures and rehabilitation are both long and complex. Many patients will require a combination of static and dynamic procedures to address different areas of the face.

The specific procedures available for facial reanimation will be considered by region.

### The brow

Normally, brow ptosis can be compensated in the non-paralysed face by contraction of the frontalis muscle, raising the brow and upper eyelid. In lower motor neuron facial palsies affecting the temporal branch, brow ptosis may eventually contribute to the obstruction of the visual axis, especially in older patients with long-standing paralysis. A ptosis of 3–4 mm is apparent to most people. Loss of forehead movement per se is otherwise not a major concern for most patients but may contribute to the cosmetic deformity.

Static procedures are most appropriate to address brow ptosis. A suprabrow excision of redundant forehead skin and subcutaneous tissue, made along the line of the hair follicles, is often sufficient and the resultant scar is subtle, although some parasthesiae in the supraorbital nerve area may result (Figure 56.6). The outcome can be made more durable if the brow is secured to the peristomeum of the frontal bone. Alternatively, conventional or endoscopic brow lifts may be undertaken. The contralateral brow may also need to be addressed.

### The upper and lower eyelids

Inability to close the eye fully and loss of the blink reflex due to orbicularis muscle paralysis renders the cornea prone to injury, which can be painful and cause blindness. The ectropic lower eyelid exacerbates the problem by interfering with tear transport, resulting in epiphora. An early ophthalmologic assessment and accurate measurements of the degree of ptosis should be made. As with the brow, static procedures are currently more successful in addressing the upper and lower lid deficiencies. The most common corrective procedure involves the placement of a shaped gold weight in the upper eyelid, anterior to and secured to the tarsal plate with permanent sutures. The ideal weight can be estimated preoperatively by taping trial weights to the eyelid skin in clinic. The lightest weight required to bring the lids to within 1–2 mm of closure is preferred; this is generally around 1 g. The operation can be carried out under local or
general anaesthetic, when combined with other procedures (Figure 56.7). Complications include under or over-correction, a visible bulge, infection and extrusion of the implant. Securing the weight with sutures may reduce the exposure rate. Overall though, gold weights permit complete eye closure in 82 per cent of patients. 49

Spring devices are available for lid closure but placement and adjustment of tension can be difficult and complications are more common. Permanent tarsorraphy may be required to aid eye closure when there is little expectation of recovery, but the visual field is compromised and the appearance of the eye can be unsatisfactory.

For dynamic eyelid closure, transfer of a strip of temporalis muscle has been described. A thin strip of this muscle, based inferiorly, is extended with two strips of fascia or tendon, passed through the upper and lower eyelid, and fastened to the medial canthal ligament (Figure 56.8). 50 Because the upper eyelid is responsible for most movement, a static sling may be placed in the lower lid and a temporalis transfer in the upper lid only. Undesirable side effects include a slit-like palpebral aperture with lateral movement and skin wrinkling of the lateral lid region on closure. Frequently there is an obvious muscle bulge over the lateral orbital margin and there will be some synkinetic eyelid movement when chewing, which may assist irrigation of the globe. The procedure can however provide forceful and complete eyelid closure.
Free platysma transfer has also been described for dynamic ocular reanimation. Innervation of this muscle transfer requires a separate cross-facial nerve transfer to which the cervical branch of the facial nerve contained in the platysma transfer is coapted. The vascular pedicle of this transfer is very small, usually about 0.5 mm in diameter which makes the surgery highly technically demanding. The frontal branch of the superficial temporal system is used to revascularize the platysma.

For lower lid ectropion, wedge excision of the lateral lower eyelid and lateral canthopexy can be performed, but are prone to relapse. More definitive lower lid support can be achieved using split tendon slings anchored to the anterior component of the medial canthal ligament and threaded subcutaneously along the subciliary margin of the lower lid to the superolateral orbital margin (Figure 56.9).

Nasal airway

Airway obstruction on the side of the paralysis may occur. The normal side of the face pulls the lower portion of the nose away from the paralysed side and gravity causes drooping of the nasal base on the same side. Correction of airway collapse can be obtained using an intranasal spreader graft or by means of a sling of tendon from the lateral aspect of the alar base up to the orbital margin. However, correction of the lower face and lips will often ease the nasal obstruction.

The smile

The mid-third of the face is the most important area involved in the generation of a smile and is the most challenging region in facial paralysis surgery. In the elderly patient, those in poor health or unwilling to undergo more major surgery, static procedures to improve facial symmetry utilize slings of plantaris, palmaris or second or third toe extensor tendon, fascia lata or, less commonly, Gore-tex or Endotine ribbon, that are anchored between key points in the upper lip and modiolus, and the fascia overlying the zygoma or temporalis (Figure 56.10). 'Thread lifting' has also been successfully employed in some cases to improve facial symmetry with relatively little risk. Careful preoperative measurements of lip position at rest and during attempted smiling improve the accuracy of postoperative symmetry. Overcorrection is frequently required in anticipation of some stretching of the sling and relaxation of the facial tissues postoperatively. Facelift procedures can be combined with static slings to elevate ptotic cheek tissue and excise redundant skin. Children have good facial tone at rest, and generally do not benefit from static procedures.

Dynamic reanimation of the smile is appropriate for well-motivated patients with no contraindications to free muscle transfer. As well as producing a reasonably symmetrical, dynamic smile, the soft tissue defect that may result from prior parotidectomy or facial atrophy may be improved. If the distal facial nerve stump, motor end plates and muscle are still viable, an attempt can be made to bring in alternative nerve supply to power the muscle. If not, local muscle transposition or free muscle transfer will be necessary.

Muscle transposition makes use of local muscle to reanimate the face. Such procedures obviate the need for microvascular procedures, but the results are often less satisfactory and the donor site morbidity more significant. The temporalis or masseter muscles can be used for this transposition technique, but the latter can result in impediment to mastication and speech.

The origin of the temporalis can be detached and rotated distally towards the nasolabial fold and anchored to the orbicularis oris muscle by means of periosteal extensions (the
Rubin transfer), but this technique leaves a temporal hollow and a bulge over the zygoma. Alternatively, the temporalis can be disinserted from the mandible by osteotomy of the coronoid process, which is then secured to the nasolabial fold and the upper lip using tendon or fascia lata graft (the McGlaughlin procedure).

Significantly better results are usually obtained using free muscle transfer. In contrast to muscle transposition, free muscle transfers can be freely positioned to achieve optimum results. Various donor muscles have been described including the gracilis, pectoralis minor, rectus abdominis, latissimus dorsi, extensor carpi radialis brevis, serratus anterior, tensor fascia lata and abductor hallucis. The gracilis muscle is a popular donor, having appropriate excursion and a good neurovascular pedicle length. The muscle can be harvested simultaneously with the exposure in the face and thinned in situ to avoid excessive bulk. The anterior division of the obturator nerve supplies the muscle, and its length can allow for coaptation to a cross-facial nerve graft at the upper lip. Another common donor muscle for free transfer is the pectoralis minor raised on the medial and lateral pectoral nerves. This muscle has the advantage of a strong tendinous insertion, which allows secure anchoring in the face. Donor site morbidity is minimal and, in theory at least, the dual nerve supply allows for single-stage smile and eye closure restoration by splitting of the flap. The muscle transfer is then secured to the area of the insertion of zygomaticus major and levator labii on the upper lip, and to the fascia overlying the zygomatic arch (Figure 56.11). Each muscle has its advocates and the appropriate choice probably depends as much upon surgeon experience as anticipated activity and donor site morbidity.

Of course, muscle transfers require innervation. In the absence of a useable ipsilateral facial nerve, the most desirable donor motor supply for facial reanimation would seem to be the contralateral facial nerve. The obvious advantage of using this nerve is that rehabilitation of facial function will be relatively spontaneous and straightforward. Interconnections between buccal branches of the facial nerve permit the sacrifice of one or two of these branches for facial reanimation without causing significant motor loss at the donor side. Only branches that produce a smile on stimulation should be used and these are identified through intraoperative nerve stimulation. A cross-facial nerve graft is often required to reach the paralysed cheek as part of a two-stage procedure. The sural nerve is the most common donor, providing ample length and appropriate diameter. Partial sensory loss along the lateral border of the foot results following nerve harvest but this is rarely problematic for the patient. Following coaptation to the donor nerve and tunnelling of the graft across the upper lip, axonal regeneration proceeds at a rate of approximately 1–3 mm/day. Clinically, an advancing Tinel’s sign is elucidated but may take several months to reach its destination, during which time the facial muscles may lose their ability to be reinnervated (Figure 56.12). Alternatively, a simpler, single-stage procedure has made effective use of the latissimus dorsi muscle with the thoracodorsal nerve which can be more than 15 cm long. Other single-stage procedures using gracilis, rectus femoris and abductor hallucis have been described, although these may be less effective.

As described above, the hypoglossal nerve can be used as an alternative motor supply to the distal facial nerve stump.
although the patient may experience swallowing and speech difficulties as well as synkinesia. For this reason, the use of the hypoglossal nerve is discouraged in young children whose speech is yet to develop and may be contraindicated in patients with pre-existing difficulties with swallowing. Some studies have shown that these complications can be minimized by transposition of a portion of the hypoglossal nerve only. Alternatively, the hypoglossal nerve can be used to innervate the facial nerve temporarily (babysitting), until a cross-facial graft is prepared.

The motor nerve to the masseter muscle is increasingly used as a donor for free muscle transfer. It has the advantage of proximity to the operative site and so reconstruction can be carried out in a single stage with little donor site morbidity (Figure 56.13). Use of the masseter nerve also appears to result in better excursion of the lip postoperatively relative to the cross-facial nerve graft.58 For this reason, its use may be indicated in patients whose predisposition or occupation requires them to smile frequently, those with a heavy face, and older patients in whom a cross-facial nerve graft is known to be less successful. Initial concern that the masseter nerve would not allow production of a spontaneous smile has not proved true. In a recent study, 80 per cent of patients were able to smile without biting and 60 per cent were able to smile spontaneously with the aid of therapy and biofeedback.7 A dual innervation approach has recently been described where the latissimus dorsi muscle is innervated from both the contralateral facial nerve and the ipsilateral masseter in the hope of gaining the benefits of both.59

The facial or superficial temporal vessels are normally used for microvascular anastomoses to the flap pedicle.

**The lower lip**

The lower lip is animated by the orbicularis, the depressors anguli oris and labii inferioris, mentalis and the platysma. Marginal mandibular nerve palsy causes elevation of the ipsilateral lower lip and drooling. It also affects the symmetry of the smile. Direct neurotization of the depressors can be attempted by cross-facial nerve grafting, but this is infrequently used. Static slings between the lateral orbicularis oris muscle and the zygomatic arch have been used to improve resting posture.60 Alternatively, improved lower lip symmetry can be achieved by resection of the depressor anguli oris muscle on the normal side of the lip, while sparing the branches of the mental nerve.61 A similar effect can be achieved temporarily using Botox, or very briefly with local anaesthetic. This can allow the patient to assess the effect before committing to a more permanent procedure (Figure 56.14).62 Transfer of the anterior belly of the digastric or platysma has also been used successfully but is infrequently undertaken.63, 64 On occasion, a wedge excision of the flaccid lower lip is required.
FOLLOW-UP CARE AND REHABILITATION

In the early postoperative period, free muscle transfers must be closely monitored by clinical assessment of colour and capillary refill if a skin paddle is used. More commonly, however, the muscle flap is entirely buried and flap viability can only be assessed with the help of Doppler, and occasionally, implantable thermocouple devices.

After facial reanimation, return of function takes many months but physical therapy including biofeedback and facial expression exercises making use of a mirror should begin early to achieve optimal results. When a cross-facial nerve graft is used for reanimation, muscle activity may take four to six months to appear but rehabilitation is relatively straightforward. With the masseter nerve as a donor, reinnervation of the muscle takes only two to three months but the rehabilitation is, naturally, more demanding for the patient. Donor site morbidity, including parasthesiae, tongue atrophy in patients with facial nerve–hypoglossal nerve transposition, and difficulty with mastication in patients with masseter or temporalis transfer, should be evaluated. If a nerve other than the contralateral facial has been used as the motor supply, synkinesis and difficulty in controlling the smile can be expected. With the masseter nerve, the patient must at first learn to control the smile by clenching of the teeth. The strength of the smile will be proportionate to the strength of the bite, which the patient can learn to control. In time, the majority of patients can learn to smile without biting and, in some cases, without conscious thought.

COMPLICATIONS

Facial reanimation and static procedures are subject to the same general complications as any surgery including infection, haematoma (3 per cent) and delayed wound healing. In addition, there is a risk of flap failure either in terms of arterial (5 per cent) or venous thrombosis (3 per cent), muscle necrosis (1 per cent) or motor function (3 per cent). Occasional loss of function at the donor site occurs and this may include partial tongue atrophy or contralateral facial weakness. With infants and young children, growth and development should be carefully monitored. The facial nerve is involved with the control of oral competence in the oral phase of swallowing and the ability to suck. Feeding may therefore be impaired. Speech development may also be hampered and therapy is an important adjunct to surgical therapy.

OUTCOME AND PROGNOSIS

More than 90 per cent of adults with Bell’s palsy and children with facial nerve paralysis caused by blunt trauma will recover spontaneously. In other cases, including congenital paralysis, the optimal outcome of facial symmetry at rest, during voluntary movement, and spontaneous emotive movement, is rarely fully achieved without surgical intervention. Bilateral cases, which are most often congenital, suffer from asymmetry even after surgical reanimation, because of the difficulties of obtaining identical muscle placement, innervation and excursion on each side. Under comparable circumstances, however, children often fare better than adults following reanimation procedures.

In adults, an overall improvement can be anticipated in the vast majority of patients following microvascular free tissue transfer. Women and younger patients appear to do better in terms of muscle function and speed of recovery compared with men. Patients with a developmental cause of facial nerve paralysis also appear to do better than those with post-traumatic facial nerve paralysis. This may be because free muscle transfer in developmental palsies generates facial movement where there was none, whereas reanimation of traumatic facial palsies will never achieve preoperative function: patient satisfaction is correspondingly diminished. In terms of donor muscle selection, patients with pectoralis minor muscle transfer may regain function earlier than with gracilis. The best results are obtained by surgeons who commonly manage facial paralysis patients using techniques with which they are highly experienced.

SUMMARY

Facial paralysis engenders many distinct aesthetic and functional problems. A careful individual assessment and management plan are prerequisites for a successful and satisfactory outcome. Paralysis with the prospect of spontaneous resolution must be given time to occur, but interim treatment may be required to protect the exposed cornea and maximize the viability of the motor end plates. In longstanding cases, facial asymmetry and the inability to smile are often the primary indications for reconstruction, but other functional and aesthetic defects are also of great importance. A variety of static and dynamic procedures is available and should be chosen and tailored to the individual needs of the patient. While reconstructive techniques continue to improve, current therapy has its limitations and aims to provide good ocular and oral function, and an acceptable
smile. In the future, tissue engineering, stem cell technology and refined and novel surgical techniques will most likely improve the prognosis in facial paralysis.

**KEY EVIDENCE**

- Single stage facial reanimation procedures are becoming the gold standard and obviate some of the potential for complications and the delay in recovery associated with two-stage procedures.\(^{12}\)
- Bilateral facial paralysis precludes the use of the contralateral facial nerve for reanimation procedures and necessitates a different approach.\(^{38}\)
- In all cases of facial paralysis surgery, the need for multiple primary and revisional procedures can be anticipated to achieve optimal results.\(^{65}\)

**KEY LEARNING POINTS**

- Facial paralysis is aesthetically deforming and functionally disabling.
- The aetiology is varied, but the treatment options for established paralysis are less so.
- The objectives and commitment of the patient are as important as the experience and skill of the surgeon and multidisciplinary team.
- Surgical treatment involves static and dynamic procedures, or a combination of both.
- A sound and consistent approach is necessary for a good outcome.
- Managing such patients is a long-term undertaking and careful follow up is essential.
- The results can be highly rewarding for the patient and surgeon alike.

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Osseointegration ushers in a new era in clinical treatment, one which is safe, predictable and limited only by the imagination of the clinicians who use it.

P-I Brånemark

INTRODUCTION

Osseointegration was originally defined as a direct structural and functional connection between ordered living bone and the surface of a load-carrying implant. It is now said that an implant is regarded as osseointegrated when there is no progressive relative movement between the implant and the bone with which it has direct contact. In practice, this means that in osseointegration there is a means of anchorage whereby non-vital components can be reliably and predictably incorporated into living bone and that this anchorage can persist under all normal conditions of loading.

The scientific basis of this process dates back over half a century. The application has had a fundamental impact on the reconstruction of oral and facial structures. Current research focuses on improving the bone to implant interface, with shorter healing times, improved bone stability and greater success rates. This has resulted in renewed interest in all aspects of osseointegrated implants with a broadening of the scope to include digit, joint and limb replacement.

Much of the early work on osseointegrated implants centred on the replacement of the dentition. Successful reconstruction of the teeth led the way to an expansion of the principles into the head and neck region, with these implants quickly becoming established as the basis of bone anchored hearing aids (BAHA). They can also provide the foundations for prosthetic reconstruction of structures that are difficult or impossible to replace with autogenous tissue.

The prosthetic replacement of the dentition, eyes, nose, ears and composite defects involving two or more of these structures is a craft that dates back many centuries. Retention of these prostheses has always been a challenge. The advent of a direct mechanical link between the patient and their prosthesis via osseointegrated implants has revolutionized what can be achieved. The rehabilitation of patients and the improvement in their quality of life cannot yet be consistently matched by autogenous reconstructive techniques.

As with all techniques, careful case selection is important and osseointegrated implants are not suitable for every patient. Each patient should be considered on an individual basis with prostheses, conventional reconstructive surgery or a combination of both used appropriately.

HISTORY AND BACKGROUND

The replacement of missing anatomical structures has long been a goal of both patients and clinicians, with skeletal fixation providing the basis for retention. A Honduran skull from pre-Columbian times is cited as showing one of the first known dental implants; a mandibular incisor had been replaced with a black stone. This was covered with calculus, confirming a functional prosthetic use. Alabucasim was
probably the first to recommend transplantation of actual teeth around 1100 AD. This was the established standard of care for many centuries until the high failure rate and risks of disease transmission came to be recognized.

Between the sixteenth and twentieth centuries, attempts at replacing the dentition with homologous teeth, gold-wire baskets, iron posts and china pegs were reported, although the results invariably were not. More recently, various implant designs have been developed, all based on an increasing understanding of biocompatibility, tissue healing and functional requirements.

Osseointegration is now well established, and the biological basis for success in both oral and facial rehabilitation is better understood. The number of implants placed increases year on year. Within the dental community it is now considered essential to discuss implants with suitable patients and to offer them as a viable treatment option. Equally, patients with congenital or acquired deformities of the head and neck should have access to multidisciplinary teams with skills that include osseointegrated implants and prostheses, to allow them to benefit from a comprehensive approach to reconstruction.

**IMPLANT DESIGNS**

**Subperiosteal implants**

Subperiosteal implants were devised 70 years ago. They are designed to rest on the bone and under the periosteum, distributing masticatory forces over a wide area. Until recently, these implants required a two-stage surgical approach. At the first operation, the subperiosteal flaps were reflected, and an impression taken of the underlying bone. The implant was produced on the model, cast from this impression and placed into the mouth at a second operation. With computed tomography (CT), and computer-aided design, computer-aided manufacture (CADCAM), the creation of an accurate model of the jaw is now possible. The implant can be produced from this computer-generated model and inserted in a single surgical procedure.

Subperiosteal implants are connected to the bone by fibrous tissue, although some exhibit direct bony contact in places. The transmucosal abutment posts that emerge through the gum and are used to retain a denture are an integral part of the implant.

The facility to coat the implants with hydroxyapatite, as an aid to integration, the refinement of the substructure design and the development of accurate CADCAM-derived models have resulted in renewed interest in this implant type in recent years. Subperiosteal implants remain of value in selected edentulous cases where narrow ridges or deep undercuts and severe angulations preclude endosteal implants. They can be produced quickly and can be specifically designed to avoid anatomical structures or localized defects. Loading is possible immediately after soft tissue healing. The denture is extremely stable as the implant spreads the masticatory load over a wide area of bone. The patient can remove the denture to maintain oral hygiene.

Subperiosteal implants are not appropriate in the very atrophic jaw or in the post-resection patient as the area of available bone on which the implant frame can lie is reduced. Consequently, the load transmitted to the bone during function is increased, causing resorption of bone.

**Endosteal implants**

Endosteal implants are surgically placed into bone (Figure 57.1). This type of implant had been tried for centuries with limited success due to inadequate osseointegration. A variety of materials has been used including platinum-iridium, vitallium, stainless steel, aluminium hydroxide, chrome cobalt and titanium and titanium alloys.

Until recently, few designs had been based on thorough research and development. Swedish and Swiss groups working in the 1950s and 1960s provided the foundation for the current explosion of interest in dental endosseous implants. These implants broadly fall into two groups as detailed in the following subsections.

**ROOT FORM IMPLANTS**

Root form implants are the most commonly used, and many companies produce a number of differing designs. The designs are beginning to converge towards an accepted norm as the benefits of certain features are recognized and developed with successive generations of implants. Most implants are threaded and screw inserted. The threads mechanically lock the implant into the bone and achieve primary stability, i.e. stability at the time of insertion rather than due to later osseointegration.

Early implant designs had surfaces that were machined and relatively rough. The bone to surface contact achieved by these implants was relatively low, and consequently they were long and relied on bicortical engagement of the jaws to achieve the stability that was required for successful osseointegration. These smooth surface implants tend to be longer (up to 20 mm or so in length).

Virtually all systems now rely on roughened surfaces. Some implants have chemically treated surfaces, to improve bone healing. The implants rely on surface roughness and an implant diameter slightly larger than that of the drilled hole to achieve primary stability. The roughened surface enlarges the surface area and promotes increased bone to implant surface contact once integrated. Due to the increased surface area for osseointegration, these implants can be produced in smaller lengths (typically 6–12 mm), and do not require bicortical engagement of the jaws for reliable fixation during healing and subsequent prosthetic reconstruction.

Some implants are coated with hydroxyapatite. In theory, this surface should allow the formation of bony bonds with the bone and provide a greater bone to implant contact. The implants have been advocated for use in the cancellous bone of the maxilla. Some concerns have been expressed over the durability of the coating.

A recent development is that of very long implants (up to 55 mm in length) (Figure 57.2), which can engage areas of good quality bone remote from the defect or area to be reconstructed. These ‘Zygomaticus’ (Nobel Biocare Management, Zurich, Switzerland) implants were originally designed for reconstruction of the edentulous atrophic maxilla,
Figure 57.1 Straumann implant placed into the bone of an extraction socket.

(Figure 57.2) but they are useful in the management of complex composite defects of the face and jaws.

All implants come pre-packaged and pre-sterilized. This avoids potential contamination prior to implant placement, either by metal contamination from non-titanium instruments or organic contamination from tissue contact. These factors have been reported as interfering with success.6

Recent innovations have been aimed at increasing the surface area of the implants; e.g. at the micro level, by experimenting with different textures, and chemically treating the surface to increase the attractiveness of the surface to bone progenitor cells, and at the macro level, by increasing the diameter of the implants.

Wide implants are available in shorter lengths and are primarily designed for use in areas of reduced bone height and where the greater surface area improves their load-carrying abilities, such as the posterior mandible. The shorter implants can be placed to avoid the inferior dental (ID) nerve or the maxillary sinus. They may also be used where primary stability of the normal diameter implants cannot be achieved and there is a need to engage more cortical bone between the buccal and lingual cortices. This can improve primary stability and osseointegration.

Wide diameter implants may have a role in orbital reconstructions where the frontal sinus encroaches on the supraorbital rim, and in auricular reconstructions and BAHA...
placement where the mastoid air cells limit bone depth in the temporal bone.

**METAL SELECTION, SURFACE CHARACTERISTICS AND THE PROCESS OF OSSEOINTEGRATION**

Metals, either as single element materials or alloys, have favourable characteristics for use as implants. They are strong, and easy to machine and manufacture. Metals are often reactive (except for the noble metals such as gold and silver). Most pure metals on contact with air become covered in an oxide layer and it is this oxide layer that is in contact with the host issues.

Leventhal\(^7\) introduced titanium as a suitable biocompatible metal for orthopaedic surgery in 1951. Commercially pure titanium and titanium alloys are the basis for the majority of osseointegrated implants in current use. Millions of titanium implants have been placed over the past 40 years and there are no series reporting allergic reactions or carcinogenicity.

Early investigations into osseointegration established predictable techniques for tooth replacement. A specialized periodontal ligament surrounds a tooth but not an implant. Implants are in contact with either fibrous tissue (fibrous encapsulation) or bone (osseointegration). The latter are more successful and root form, cylindrical implants are now produced with the aim of achieving this.

The concept of osseointegration is based on work undertaken by Dr Per-Ingvar Brånemark in the 1950s and early 1960s. Optical chambers made out of titanium were implanted into rabbit tibias to study *in vivo* bone and marrow function. Once healed, these chambers could not be removed because the bone had grown directly against the titanium frames. Animal models were developed to investigate the potential of these findings.\(^8\) From these results, titanium implants were developed to replace the dentition. Success rates in terms of implant survival and marginal bone loss now exceed those of the original Branemark fixtures which, nevertheless, remain the gold standard against which other systems are compared.

Predictable osseointegration requires the gentle and minimally traumatic placement of a biocompatible implant into bone. The implant should not be mobile at the time of insertion; it should exhibit primary stability. A period of undisturbed healing should follow prior to loading with a prosthesis. Implants can be loaded immediately in certain situations;\(^9\) however, preliminary results suggest that this approach may be associated with a higher failure rate and less predictable soft tissue responses.\(^10\)

**THE IMPLANT AND TISSUE INTERFACE**

The precise mechanism of osseointegration remains under investigation, although the physiology of bone healing, with which it is intimately associated, is well documented.\(^10\) Osseointegration is not restricted to titanium or titanium alloys. Aluminium oxide ceramics, tantalum, stainless steel and cobalt- and nickel-based alloys have all been shown to osseointegrate. Titanium remains the material of choice. It can be easily machined into shapes that are small enough to be placed in the jaws and facial bones and yet strong enough to withstand masticatory loads of up to 500 N. Recent developments with zirconium/titanium alloys have shown that implants made from these alloys are stronger than titanium alone and can be machined as smaller units for easier placement where bone volume is limited.

A thin oxide layer covers the surface of pure titanium after contact with air. This titanium oxide is inert, practically insoluble and very resistant to body fluids. More extensive oxide growth occurs on titanium implants subjected to biological tissues.\(^11\) Macrophages in particular, may contribute to development of the oxide layer by excreting proteolytic enzymes, cytokines, superoxide and hydrogen peroxide.\(^12\) It is hypothesized that the actual interface between the titanium implant and living tissue is a hydrated titanium peroxo matrix.

The formation of such a matrix is unique to titanium. Of fundamental importance is that bone predictably grows on the surface of a titanium implant. Contaminated titanium surfaces have been shown to impede the colonization of human osteoblast cells which only adhere to and cover the surface of clean implants.

Implant placement causes bleeding and an acute inflammatory response in the bone immediately adjacent to the implant. The implant surface becomes coated with the products of acute inflammation. Macrophages remove bone and metallic debris. Undifferentiated mesenchymal cells migrate into the area and produce an extracellular matrix. Within 1 week of implant placement, these cells develop into osteoblasts and produce osteoid. The osteoid gradually organizes into an increasingly dense procallsus, with further mesenchymal cells differentiating into osteoblasts and fibroblasts. The osteoblasts produce fibres that have the potential to calcify. The fibrocartilagenous callus that develops matures into woven bone by the 3rd week. The remodelling of woven bone involves the recruitment of osteoclasts into the area. After 7 weeks, lamellar bone is being laid down. This is more mineralized and further stabilizes the implant. Any bone rendered non-vital by the surgery is gradually replaced by living bone. A very thin layer of proteoglycan exists between the bone and the implant surface of all osseointegrated implants. This layer is up to 500 nm thick. In effect, the body fails to recognize the implant as a foreign body and it becomes incorporated into bone as part of the wound healing process.

The final stages of healing involve maturation of the bone at the implant interface. There is an increase in bone hardness and density that is associated with loading and functional use, and which is ongoing even a year after implant placement. This correlates with Wolff’s law, which states that bone tends to develop the structure best suited to resist forces prevailing upon it.

The soft tissue interface between the skin or mucosa and the implant is equally important. It consists of both epithelium and connective tissue. A rough implant surface has been demonstrated to promote connective tissue attachment. However, as maintenance of good hygiene and the avoidance of plaque accumulation within the mouth, and organic debris from the surrounding skin, is impossible on this roughened surface, endosseous implants are designed to have smooth
components in contact with the soft tissues. This facilitates mechanical cleaning.

The connective tissue fibres run parallel to the implant surface in this situation, forming a tight cuff rather than a direct attachment. A peri-implant sulcus is formed and lined. Non-keratinized epithelium is arguable during the healing periodontium that surrounds tooth roots. As in clinical situations, epithelium does not contact bone, and a layer of connective tissue exists between the marginal bone and the epithelium. Where submerged, two-stage implants are used, the placement of the abutment results in epithelium growing down to the implant abutment junction. If this is at or below the bone level, some resorption occurs as connective tissue always separates the epithelium from the bone. In practice, this apparent shortcoming does not compromise long-term success.

Inflammation and excessive loading can cause bone resorption. Where peri-implant disease develops, the sulcal epithelium desquamates, exposing the underlying connective tissue, which becomes inflamed. This inflammation induces osteoclast activity and chemical mediator release from cells adjacent to the implant surface. As this tissue is less well differentiated than that around teeth where a protective periodontal membrane exists, progressive bone loss can be more rapid. Within the bone, premature loading or overload (as can occur through occlusal trauma, or the non-passive fit of a bar linking implants) causes areas of pressure concentration, osteoclastic activity and angular bone loss at the implant site. This is particularly damaging during the healing phase when osseointegration has not fully developed and the immature bone resorbs easily. Overloading, even after several years, can cause microfractures in the bone that may heal with scar tissue and cause implant mobility to develop.

The combination of inflammation and overload is particularly harmful, but separately or together, the end is the same as osseointegration is progressively lost and the implant fails.

ANATOMICAL CONSIDERATIONS

Bone density varies within the jaws, at different sites in the face, and between individuals. The greater the proportion of cortical bone to cancellous bone, the better the long-term osseointegration results, hence mandibular implants have higher success rates than maxillary implants. Within the facial skeleton, implants at the nasal bridge should be long enough to engage the frontal bone, and those around the orbit are best placed in the upper outer quadrant where bone density is greatest, avoiding the frontal sinus. However, care is required in the preparation of dense bone where the risk of overheating during drilling is greatest.

The presence of adequate bone volume is a prerequisite for the successful placement and subsequent osseointegration of an implant. Patients who most need implants often have the least volume of bone. Congenital deformities, such as severe hemifacial microsomia or Treacher Collins syndrome, are associated with underdevelopment of the temporal bone, limiting sites for implant placement and subsequent BAHA and auricular prostheses. Tooth loss results in acquired patterns of bone resorption which compromise implant placement and have been classified. Specific features of the various facial anatomical sites used for implant placement are considered below.

Maxilla

Maxillary bone is less dense, and the proximity of the nasal floor, maxillary sinuses and the incisive foramen can all have an impact on implant placement. The loss of part of the upper jaw, either due to trauma or after resection, further exacerbates the difficulties.

Tooth loss and subsequent bone resorption concentrates bone stock between the lateral nasal wall and the maxillary sinus. This canine buttress, running up towards the pyriform rim, is the most predictable site for implant placement in the upper jaw. The maxillary tuberosity can also be used. It consists of low density cancellous bone which may compromise osseointegration and is often too posterior for easy use. The perpendicular plate of the palatine bone and the pterygoid plates of the sphenoid bone lie posterior and medial to the tuberosity. Implants can be placed in this region via the tuberosity. However, access can be limited, and the angulation of insertion required to engage the plates can cause difficulties with the prosthetic reconstruction, particularly if trismus exists due to previous surgery or radiotherapy. Implant placement in the maxilla into the zygomatic body via the maxillary sinus is now a well-recognized procedure, and can avoid the need for bone grafting.

Following tooth loss, buccal and vertical bone resorption narrows the maxillary arch width and increases the interarch distance between the jaws. If the dental arches are to occupy the original form, the implants have to be angled away from the sagittal plane, resulting in greater lateral load on the implants. The greater the intermaxillary distance, the greater the prosthetic reconstruction, particularly if trismus exists due to previous surgery or radiotherapy. These factors have to be taken into account when planning the number and size of implants to be used in the reconstruction.

In the atrophic upper jaw, maxillary ridge width and height are reduced. Additional bone augmentation techniques may be required, such as ridge expansion, guided tissue regeneration using membranes and bone grafting of the ridge, sinus floor and nasal floor.

Mandible

Mandibular bone is predominantly cortical around a central cancellous core. The genial undercut should be taken into consideration when assessing the depth of bone available near the mandibular symphysis. The true depth is frequently less than the apparent depth. A lateral cephalogram x-ray will demonstrate this feature and allow accurate measurement of the available bone. Cone beam CT scanning is now readily available. The anatomy of the jaws is easy to appreciate as implant placement can now be predetermined using planning software.
The genial tubercles can lie above the level of the ridge in the very atrophic mandible where they can compromise implant placement. Surgical removal of the prominence may be required.

The mylohyoid ridge creates a lingual undercut in the molar regions. Avoidance of lingual perforation through the cortical plate during implant placement is important as haemorrhage into the floor of the mouth can have life-threatening consequences. In practice, this may preclude using the full height of bone available above the inferior dental nerve. Clinical assessment at the time of patient evaluation can be supplemented with tomograms or coronal CT scans to demonstrate the relevant anatomy.

The ID nerve runs a variable course from the lingula to the mental foramen and influences implant placement. Bicortical engagement is only possible proximal to the mental foramen, unless the implants are inserted either buccal or lingual to the nerve or the nerve itself is transposed laterally at the time of implant placement. A safer alternative is to use short, wide implants and place them above the nerve.

Prior to emergence from the mental foramen, the nerve loops anteriorly to a variable extent. This is often apparent on a panoral tomogram. Care is required when placing an implant immediately in front of the mental foramen, so that this anterior loop is undamaged and lip sensation preserved.

In the very atrophic mandible, the mental foramen may lie on or lingual to the alveolar ridge. To protect the nerve, careful dissection in this area is required during the reflection of a buccal subperiosteal flap.

**Extraoral implant sites**

**TEMPORAL BONE**

The anatomy of the temporal bone is complex and becomes unpredictable in patients with congenital deformity, such as Treacher Collins and hemifacial/craniofacial microsomia. Where practical, the external auditory meatus (EAM) is the landmark for correct implant placement, as the auricular prosthesis will be fitted around this. If the meatus or ear remnants are in the wrong position, then assessment against the other side (if normal) or using anthropometric landmarks, such as the Frankfort plane and alar tragal line, may be required to correctly site implants (Figure 57.3).

The outer table of the temporal bone is usually dense cortex into which implants can be placed easily. The implants should be placed in the posterior, upper quadrant, 18–22 mm from the centre of the EAM, ideally 15 mm apart, and two or three in number. Although the mastoid air cells may underlie the cortex, the cells become progressively smaller away from the mastoid apex and in the normal temporal bone they rarely prevent implant placement. The position of the posterior cranial fossa and the sigmoid and superior petrosal sinuses may vary, but it is usual in children that these structures are encountered or in congenital deformity where the temporal bone is very atrophic or underdeveloped. The shallow depth of bone available mandates the use of short, extraoral implants. If encountered, the dura can be pushed away from the implant during insertion. Should the vascular sinuses be encountered, then the rapid insertion of the implant quickly plugs the hole and haemorrhage is arrested. Cerebrospinal fluid (CSF) leaks are rare.

Implants are generally avoided in children, as osseointegration can impair normal growth of adjacent bone. However, the benefit of a BAHA on hearing, and therefore speech and language development, and the fact that 80 per cent of skull growth has been achieved by the age of two years, means that early implant placement confers significant advantages to this select group of young patients.

**ORBIT**

Orbital prostheses present special problems. The normal eye moves constantly, whereas a prosthesis is static and the eyelids do not move. Careful implant placement is crucial if the prosthesis is to compare well with the normal side. It should sit deep enough within the socket such that symmetry in all three planes is maintained when compared to the normal eye. The proximity of the frontal, ethmoid and maxillary sinuses, and the thin cortical edge to the orbital rim, limits the areas where implants can successfully be placed (Figure 57.4).

In practice, most orbital implants are placed in the upper, outer orbital rim (lateral to the frontal sinus) and into the body of the zygoma. The bone of the medial orbital wall is too thin for implant anchorage. A posteroanterior x-ray or CT scan will show the anatomical landmarks that influence and limit implant placement and, in contrast to auricular implants, imaging is essential when planning orbital implant placement.

Narrow orbital rims should be drilled back until 5 mm width is achieved. Conventional oral implants can be placed directed up into the frontal bone and down into the zygoma. The flange on extraoral implants often ulcerates through the
overlying skin with time and these fixtures are best avoided wherever possible at this site. Correct angulation of the implant ensures that the emergence profile of the implant abutment is within the orbital cavity. In practice, this limits the length of implant that can be used because the hand piece and the implant have to be positioned within the orbit at the time of placement if the correct line of insertion is to be achieved. A surgical template showing the proposed position of the prosthesis in the orbit is a useful guide to correct implant position in all three planes.

NOSE

The prosthetic nose is best produced as a single aesthetic unit. It is therefore sometimes better to undertake excision of the whole nose if an autogenous reconstruction is not going to be attempted. The alae, columella, anterior nasal septum and nasal bone need to be removed so that implants can be placed without interference from surrounding tissues. The best support and retention for the prosthesis relies on placing implants as far apart as possible around the nasal rim. In practice, this confines placement to the pyriform rim inferiorly and the nasal bridge superiorly. Flood and Russell\(^{18}\) describe placing the implants upside down into the nasal floor, so that they emerge under the nostril. However, atrophy of the anterior maxilla in edentulous patients can limit the length of implant that can be placed at this site. Greater bone is available laterally, in the region of the canine buttress, so that oral implants can be angled downwards and backwards into the strut of bone that separates the medial aspect of the maxillary sinus from the lateral nose. The depth available is limited by the height of the palate. In the nasal bridge region, the nasal bones are very thin and frequently fracture or split along the midline suture if an implant is placed at this level. Consequently, resecting the nasal bone back to the nasion allows implant placement in the wider, denser bone of the frontal bone, and again, oral implants can be used to good effect at this site. It is important that the implant is angled so that the emergence profile is behind the line of the nasal bridge (Figure 57.5).

The recent development of the zygomaticus implants has given greater flexibility to nasal reconstruction as these implants can be placed horizontally from the middle of the nasal defect through the maxillary sinus under the eye and engage the cortical bone of the zygoma. They are particularly useful where the anterior maxilla has been lost and pyriform rim implants are not possible (Figure 57.6).

PATIENT ASSESSMENT AND PLANNING

Many implant failures can be traced back to poor pre-operative assessment. The suitability of a patient for implants is based on general and local factors. The following factors should be considered:

- General factors: impaired immune system, smoking, previous radiotherapy; psychological factors: body image/psychiatric disorders, attitudes to complex dentistry, hygiene and aftercare.
- Local factors: available bone, quality of bone, quality of soft tissue, peri-implant infections.

Medical factors

Absolute contraindications to implant treatment are rare, but can include immunosuppression (either by disease or drug therapy) and psychiatric disorders, including those associated with abnormal perceptions of body image. Susceptibility to
infective endocarditis, and patients with prosthetic joint replacements, need consideration, although the risks of implant-related infections are probably very low. In view of the x-rays needed, it is prudent to avoid implant placement during pregnancy.

Diabetes should be well controlled before any elective surgery is considered, so that wound healing is optimized. Osteoporosis, in our experience, is not a problem, although longer healing times with careful loading of the implants is appropriate.

Smoking

Smoking has a detrimental effect on implant osseointegration and long-term survival. Patients should be warned of this during the preoperative assessment. Where it is decided to undertake treatment, consideration should be given to over-engineering the reconstruction, so that an increased risk of failure is built into the treatment plan and sufficient implants will remain to support any superstructure.

Previous radiotherapy

Radiotherapy to the head and neck does not preclude implant placement, but failure rates approaching 50 per cent have been reported. Hyperbaric oxygen (HBO) both before and after implant placement may minimize the onset of osteoradionecrosis and subsequent late implant loss. Twenty dives before and ten dives after surgery, at two atmospheres pressure, are recommended. Failure rates may then be reduced to less than 10 per cent. Trials are ongoing to substantiate this benefit and also the incidence of osteoradionecrosis.

Not all patients are suitable for HBO and it is not universally available. Absolute contraindications include untreated pneumothorax, optic neuritis, existing neoplasia and active infections. Caution is needed in those patients with middle ear disease who will require grommets before HBO. Those with chronic obstructive pulmonary disease whose respiratory drive may be compromised in an oxygen-rich environment and who are more susceptible to a pneumothorax also need careful assessment.

HBO is thought to act by a number of mechanisms:

- Hyperoxygenation of poorly perfused tissues.
- Vasocostriction, without compromising oxygen availability to the tissues.
- It is bactericidal to anaerobes.
- Peroxidase activity in macrophages is promoted, rendering them more effective in killing bacteria.
- Promotes vascular ingrowth to a hypoxic area.
- Bone matrix production and bone mineralization is increased.
- Promotes osteoclast activity and enhances necrotic bone removal.
- Enhances erythrocyte deformation to improve oxygen delivery to damaged tissues.

Local factors

Local factors include poor hygiene, ongoing cutaneous or periodontal disease, and dental neglect. Any physical or mental disability that may prevent meticulous cleaning of the fixtures should give rise to concern over the patient's suitability for implants. The presence of active epithelial or connective tissue disease, such as erosive lichen planus, pemphigus and pemphigoid, is a contraindication. In these conditions, poor wound healing and loss of soft tissue integrity around the implant is likely to compromise the overall outcome.

Counselling

Once a patient has been screened for contraindications to implant placement, it is important to establish that the patient's expectations are realistic at the outset and are balanced against those which are clinically achievable and appropriate. Where more than one clinician is involved in the treatment, it is particularly important that all parties have a clear understanding of each other's role, and a common purpose developed. Many problems (and subsequent litigation) relating to implant cases can be traced back to errors of communication and misunderstandings during the preoperative assessment.

Diagnostic wax-up/models

A diagnostic 'wax-up' is essential for most intraoral and extraoral implant cases. It can be used as a guide for the correct emergence profile of the implants (Figure 57.7). The clinician can use the wax model of the proposed prosthesis to determine the reconstructive options (fixed bridge or
removable denture/obturator, surface area to be covered by the ear, nose, etc.) and the ideal sites for implant placement. The patient can also assess the set up for appearance. Where practical, all parties should agree on this diagnostic stage before continuing with treatment. Skeletal and occlusal influences on intraoral prostheses are dealt with in standard prosthodontic texts.

Once approved, the set up should be retained and duplicated in clear acrylic. Should problems later arise with the construction and appearance of the superstructure then the original set up is still available to refer back to. The clear acrylic set up can be used as an accurate template or stent from which the implant sites and angles of insertion can be transferred from the study casts, directly to the patient's mouth during the operation.

Figure 57.7 Unfavourable implant angulation for a left orbital prosthesis.

Software programs are now available, such as SimPlant8 (Materialise/Columbia Scientific, Leuven, Belgium), which allow CT data to be manipulated so that ideal implant sites can be identified, in terms of the height, width and depth of available bone. Once the appropriate implant sites, angles of insertion and lengths have been determined, the data can be used to produce customized surgical templates. These templates fit directly onto the proposed operative site and guarantee correct implant position and angulation. The correct implant length can be preselected.

Within the mouth, it is much easier and less expensive to achieve acceptable aesthetics with an implant-supported denture than with a fixed prosthesis (bridge). If a fixed prosthesis is used, the teeth are often very long to compensate for the increased interarch distance that occurs in the edentulous jaw. Long teeth can be disguised with pink porcelain or acrylic to mimic a more normal gum margin.

The site of implant placement is determined according to superstructure design, patient factors and radiographic findings. All patients should have a panoral tomogram and periapical x-rays of existing teeth as a minimum if oral implants are planned. Posteroanterior facial views are useful for orbital implants (to show the extent of the frontal and maxillary sinus) and fine cut CT with the facility for 3D reformattting for other sites in the face.

Where a patient has an original denture, it can often be modified or remade to allow for implant placement. It can be converted or copied into an obturator if a maxillectomy is to be undertaken. Acrylic dentures are easily adjusted during the healing phase to avoid loading implants and the operative sites and causing unnecessary pain and implant loss through overload.

Meticulous records should be kept throughout treatment and thereafter to form the basis for prospective studies, audit, appraisal of success or failure, and as defence against litigation. Patients should be well aware of the implications of implant treatment in terms of hygiene and recall appointments. Anything less than meticulous cleaning and regular attendance for review can jeopardise the long-term success of the case. The treatment plan, alternatives, possible complications and cost (where appropriate) should be documented and signed by the patient as part of the consent process before commencing any implant treatment.

Setting up an implant programme needs careful consideration of the workload and costs, including maintenance of the prostheses, for the life of the patient. As the patient cohort increases, so does the cost of replacing prostheses, bars, abutments and the occasional lost implant.

**SURGICAL TECHNIQUES**

**Anaesthesia**

Surgery can be undertaken under local anaesthetic, with or without sedation, or general anaesthetic. Local anaesthetic alone can be advantageous, particularly when placing implants for oral reconstruction. During implant placement, even using a template, difficult interarch and opposing tooth relationships need continuous intraoperative assessment. This is best achieved by maintaining full patient cooperation.

**Prophylactic antibiotics**

Antibiotics are recommended during the surgical phase. A single, 3-g dose of amoxycillin given orally 1 hour
preoperatively (or 600 mg of clindamycin with a second dose 6 hours later, if penicillin allergic) is effective. For routine implant placement, an extended antibiotic course is not necessary. Under general anaesthesia, a single dose of a suitable broad-spectrum intravenous antibiotic is usually all that is required. Where non-vascularized bone grafts are used, oral antibiotics should be continued for 5 days.

**Surgical exposure of the implant site**

The original Branemark protocol advocated the use of an incision remote from the implant site thereby avoiding wound closure directly over an implant. This has been superseded by surgical approaches over or close to the proposed implant position. In most situations, exposure of the bone is improved, soft tissue dissection is reduced and osseointegration is not compromised. With the use of computer-designed guides, flapless surgery is now possible, as the underlying bony anatomy has already been delineated from the CT scan.

The essence of implant surgery is a precise surgical technique with minimal soft and hard tissue trauma. The use of a surgical template has been discussed. Where possible, it should be self-retentive and allow visualization of the operative site from all angles. There should be no interference with the flow of irrigation to cool the bone and wash debris away from the area.

The incision line is planned using the surgical template. This is placed using an appropriate landmark, such as the tragus, eye socket, nasal bridge or adjacent teeth, to locate it. Where possible, the template is retained in position with clasps around teeth, or screwed directly into the underlying bone. The soft tissues are marked at the implant sites and these marks joined up using a scalpel to form the surgical incision line. In the upper jaw, a more palatal approach is recommended, so that keratinized tissue is brought from the palate to the labial/buccal side of the ridge. This can then be recontoured to give the best possible soft tissue cuff around the implant for both functional and aesthetic purposes.

Flaps are raised in the subperiosteal plane and any relieving incisions placed remote from the implant site. The soft tissues can be thinned at this stage if necessary. Flap reflection is limited to allow adequate access and assessment of the bony architecture, for example concavities that may result in fenestration or dehiscence of the implant.

**Irrigation and cooling of bone**

With all implant systems, a series of drills are used to enlarge and deepen the implant hole. Continuous irrigation and cooling of the burs is essential if overheating of the bone is to be avoided. The depth of implant placement is predetermined during the planning stages and checked at the time of surgery with the depth gauges.

Intraoperative radiographs are taken if there are any concerns about adjacent anatomical structures, such as the ID nerve or maxillary sinus, when working within the mouth under local anaesthesia.

**Surgical tapping and threading of bone to increase surface area of contact**

Once prepared to the correct length, the implant site can be irrigated to clear any remaining debris. Where a screw implant is to be used, a thread is tapped into the bone if it is too dense for a self-tapping implant. In less dense bone, implants can be self-tapped (Figure 57.8).

Implants are traditionally submerged under the soft tissues during the healing phase. However, transmucosal and transcutaneous healing is equally successful, and confers some advantages:

- single operative procedure;
- continuous implant assessment during the healing period;
- soft tissue maturation equal to that of the bone;
- easier placement of the abutments under direct vision;
- the junction between the implant and abutment may be above the soft tissues so that cleaning is easier;
- better leverage conditions exist where the abutment/implant junction is closer to the prosthesis.

After implant insertion, the wounds are closed meticulously with a non-irritant suture material that will remain clean, particularly if within the mouth.

The avoidance of direct pressure over the implant site during the healing period is important. This is best achieved with tooth-supported prostheses that prevent loading of the underlying soft tissue and implants. Where practical, dentures or any extraoral prosthesis that rests on the soft tissues or implants during the healing phase should be adjusted or not used. Adhesives may interfere with the wound healing process. Written postoperative should be verbally emphasized.

Healing times vary between 2 weeks and six months depending on the operative site, quality of bone, age of patient and implant system used. Throughout the healing period, meticulous attention to hygiene and a prosthesis that does not impinge on the healing area is essential.

Review appointments are recommended on days 7, 14 and 28 after implant placement, and then monthly thereafter to check on healing. This is particularly important if grafting with a barrier membrane has been undertaken as these have a tendency to become exposed leading to localized inflammation and bone loss.

![Figure 57.8 Self-tapped implant into mandible.](image-url)
Allow time for osseointegration before loading

Once healed, implants that are buried are uncovered and the abutment components placed. Great care is needed to ensure correct alignment of these components. There should be no visible gap between the implant and abutment, either clinically or on x-ray. Soft tissue maturity over a 2-week period after second-stage surgery is usually sufficient to allow prosthetic reconstruction to commence.26

As the bone to implant interface is still relatively immature at this early stage, some authors advocate a period of progressive loading, whereby the forces placed on an implant are gradually increased up to an adequate loading level. Although in theory this seems logical in allowing the bone to remodel, the need for progressive loading is contentious. It would seem prudent in grade 3 and 4 bone to gradually increase the loading exerted on the implant. Physiologically, this meets with Wolff’s law of bone remodelling. In practice, many reconstructions have been placed immediately after osseointegration, without any obvious detriment to the implants.27 An increasing number of implants are being immediately loaded both as intraoral and extraoral reconstructions with very high success rates.

Although the prosthetic reconstruction of implants is a specialist field beyond the scope of this chapter, certain points are worthy of emphasis:

- The prosthesis should determine the position and number of the implants and not the reverse.
- Intraoral prostheses are either removable (denture/obturator) or fixed (bridges). Dentures and bridges replace the teeth and alveolar bone in either jaw. Obturators fulfill the same role but also close off maxillary defects into the midface cavities. Implant-retained overdentures and obturators are easier and significantly cheaper to produce and service than fixed prostheses (bridges).
- Where a fixed prosthesis is used, it should be easily removable so that examination of the local area and the supporting implants can be undertaken.
- Implants are sensitive to load and occlusal loading of the prosthesis needs careful assessment.
- Implant-borne facial prostheses can be retained by magnets, bars and clips that attach to a bar linking two or more of the implants, or individual press stud-type attachments on each implant.
- Where complex defects need to be reconstructed, combinations of the above may be required.

Maintenance

The long-term maintenance of implants is essential for success. Patients should be made aware of their responsibility for implant care as part of the informed consent.28 Regular review appointments to assess soft tissue health and x-ray examination of marginal bone levels are recommended. Cone beam CT can be used to assess facial implants over time. Standardized film techniques are required, with the thread configuration of the implants clearly visible. Recall visits at three months, six months and then annually are recommended.

The patient should be instructed in hygiene methods appropriate to the prosthesis.

ADJUNCTIVE SURGICAL TECHNIQUES

These include:

- ridge expansion
- bone grafts and guided tissue regeneration
- sinus floor augmentation
- distraction techniques
- osteotomies and interpositioned bone grafts
- soft tissue/mucosal grafts.

The patients who benefit most from implants are frequently those with the least bone. They are therefore invariably the most difficult to treat. Bone and soft tissue deficiencies may be localized or generalized. Methods devised to overcome these difficulties range from local manipulation of hard and soft tissues to extensive grafting, distraction osteogenesis facial bone osteotomies and free vascularized tissue transfer.

Trismus is a complicating feature of patients who have undergone maxillary resections and/or radiotherapy. Trismus can be reduced by undertaking an ipsilateral coronoidectomy at the time of maxillary resection and early mobilization with active and passive stretching exercises. Coronoid removal minimizes the effects of temporalis shortening and also removes the tendency for the coronoid to displace an obturator as it moves forwards on mouth opening.

Ridge expanders have been developed to widen maxillary bone without grafting.29 Where possible, intact periosteum should be retained over the expanded bone. This can reduce bone resorption as the expanded fragments retain their periosteal blood supply. In practice, bone grafting is more predictable.

The key element in augmentation of any bony defect is the soft tissue envelope. Tension-free, primary closure over the grafted site is fundamental for success. Consequently, the soft tissues determine the degree to which the area can be enlarged. They can be increased by tissue expansion30 or the introduction of new tissue in the form of skin or mucosal grafts.31

Guided bone regeneration (GBR) (Figure 57.9) involves the use of a barrier membrane to selectively exclude soft tissues from the wound site, thus allowing the migration of bone progenitor cells into the area. This favours bone regeneration when dealing with osseointegrated implants, but was first described around teeth.32, 33

GBR can be used:

- at the time of a tooth extraction;
- after soft tissue healing of an extraction socket, lost implant site or other bony defect;
- at the site of healed bony defects.

Barrier membranes seal off an anatomical site and prevent soft tissue ingress from interfering with osteogenesis. Those currently in use are either (1) resorbable: synthetic, collagen sheets, lamellar bone sheets or (2) nonresorbable: Gore-tex® (ePTFE), titanium mesh.
Membranes can be used to optimize a site for implant placement, or to encourage bone ingrowth to an area of deficiency around an existing implant. This can be either at the time of implant placement or after osseointegration, if evidence of bone loss becomes apparent. The membranes are most effective when protecting a bone graft or bone substitute during the healing period.

The membrane should be larger than the defect to be augmented. It should be kept clear of adjacent structures as flap dehiscence can occur, with detrimental effects on healing. Those defects not isolated were filled with fibrous tissue with very little bony ingrowth.

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Tension-free, soft tissue closure over the implanted membrane is essential if premature exposure of the membrane is to be avoided. Infection can result with loss of any regeneration gained. The membrane should be removed if there is any clinical evidence of inflammation present during the healing phase. Wherever possible, the membrane is left in place for at least six months. This allows adequate time for bony regeneration and maturation. Removal earlier than this leaves an augmented site with soft immature tissue that tends to resorb. Resorbable membranes do not need to be removed, unless infected. Successful long-term osseointegration in membrane-regenerated bone is well established.

Where significant bony deficiencies exist, then the use of barrier techniques alone are not appropriate and bone grafts are needed. The local supply of this is most deficient in those patients who need it most. To overcome this deficiency other sites may be used, such as the iliac crest, tibia or cranium. An alternative is to use bone graft substitutes. Autogenous bone is the material against which other materials are compared.

Various bone graft substitutes have been advocated. The substitutes can be divided into osteoconductive or osteoinductive materials. Osteoconduction implies bone apposition onto and into a framework and occurs from existing bone or bone progenitor cells. Osteoinductive materials convert undifferentiated cells into osteoblast or chondroblasts. Autogenous bone is capable of both of the above as well as osteogenesis, the production of bone in the absence of undifferentiated cells.

Most osteoconductive materials are synthetic alloplasts, usually ceramics. The two main groups of ceramics used in conjunction with implants are tricalcium phosphate (TCP) and hydroxyapatite (HA) derived from a variety of sources. They are biocompatible substances that bond strongly to bone.

TCP is more soluble than HA and is partially resorbable. This occurs at a rate equivalent to the ingrowth of normal bone and is related to the manufacturing process of the TCP. Hydroxyapatite is the major inorganic component of bone. It has good compressive but poor tensile strength. The porous type of particulate HA is most frequently used with osseointegrated implants. Pore sizes of 150 μm facilitate ingrowth of mineralized bone.

Osseinductive materials are mainly allografts derived from screened human donors, such as demineralized freeze-dried bone. The manufacturing process activates bone morphogenetic proteins (BMP) that are present in the bone collagen matrix. These have been purified and isolated as a number of different osseoinductive substances and are predominantly present in cortical bone. The use of synthetically produced BMP in the future may overcome increasing reticence to the use of human-derived bone by both patients and clinicians.

These materials have applications in the management of localized bony defects, frontal and maxillary sinus augmentation and the treatment of peri-implant deficiencies, either at the time of placement or later during salvage surgery.

**Figure 57.9** Resorbable barrier membrane over a bone graft in the anterior maxilla.

Dahlin demonstrated that isolating a bony defect from fibrous tissue invasion using ePTFE allowed bony healing within the defect. Those defects not isolated were filled with fibrous tissue with very little bony ingrowth.

**ADJUNCTIVE IMPLANT TECHNIQUES**

Where local factors adversely affect conventional implant placement, a number of procedures have been developed to modify the local anatomy and aid implant placement.

**Upper jaw**

In the atrophic upper jaw, implant placement may require:

- prior or simultaneous sinus grafting
- placement of implants in the tuberosity or pterygoid plates
- ridge expansion
- nasal floor grafting
- onlay grafting.

There has been a gradual evolution in sinus grafting procedures with current techniques offering predictable success rates. Implant placement into augmented sinuses is associated with at least 80 per cent long-term osseointegration in most series. Where sufficient bone exists to provide primary stability for the implant, the sinus lining can be elevated either with osteotomes or the implant itself, resulting in predictable osseointegration.

Tatum developed a modified Caldwell-Luc procedure, placing bone grafts or a variety of osseointductive and osteoconductive materials under the elevated sinus mucosa, to good effect (Figure 57.10).
The area to be grafted can be approached via an appropriately reflected soft tissue flap. The lateral antral wall can be carefully drilled and intruded on the sinus lining, or the window removed completely. Elevation of the intact antral lining in the subperiosteal plane requires careful dissection through the antrostomy. Septa within the antrum can be seen on preoperative x-rays or scans and avoided or included in the dissection as appropriate. The cavity to be grafted is bounded by the antral lining and bony window above, the medial and lateral sinus walls and the floor of the sinus. Care should be taken not to obstruct the osteum of the sinus with overzealous grafting. While autogenous bone is the ideal, in practice, the volume that can be collected intraorally is limited. The volume can be supplemented with a bone substitute. Good results have been achieved with hydroxyapatite, demineralized freeze-dried bone, glass derivatives and tricalcium phosphate.\(^{36,37}\) In the author’s experience, with informed consent, patients prefer to avoid human-derived bone if possible.

The bony window is replaced or a collagen sheet used to cover the antrostomy and the flaps closed without tension. Antibiotics are continued for 5 days. Nasal decongestants are not routinely used.

Enlarged frontal sinuses can be similarly grafted prior to orbital implant placement. Grafting is usually undertaken prior to implant placement with a healing period of at least six months.

In the atrophic premaxillary region, the nasal floor can be elevated, and grafts placed to allow anterior implant placement.

Where there is considerable maxillary deficiency, onlay grafts can be used to widen and vertically augment the alveolar ridge. Bone can be harvested from the external oblique ridge of the mandible (ramus graft) or from the iliac crest or calvarium if more volume is required (Figure 57.11).

An example is shown (Figure 57.12) where implant placement through onlay grafts was undertaken with osseointegration and subsequent reconstruction of all implants. In this case, the bone grafts were retained with 2 mm mini-screws, and the implants lag screwed through the buccal onlay grafts into the residual bone of the maxilla.

Where the maxilla is very atrophic, the deficiency can be corrected with a Le Fort I osteotomy, advancing the maxilla downwards and forwards, and interpositional bone grafts. However, the Le Fort fragment is fragile and often resorbs. The procedure in many cases has been superseded by conventional grafting.

Distraction osteogenesis techniques and distractors have been adapted for augmentation of the alveolus and closure of defects by bone transport. In selected cases, the techniques...
work well, but demand clinician time and patient compliance. The example shown is of anterior mandibular distraction to reduce the distance between the dental arches (Figure 57.13). Distraction is more challenging in patients who have undergone previous radiotherapy. In practice, bone grafting is often as effective and requires less patient and clinician time.

Placement of an implant into the pterygoid plates has been reported. In practice, this usually results in a prosthetic reconstruction that extends much further back than is required. However, where no other bone stock exists, such as large maxillary defects after ablative surgery, the dense bone of the pterygoid plates and the pyramidal process of the palatine bone provide excellent stability, if sufficient width is available. CT scanning is essential for assessment. The surgical approach requires long instrumentation to overcome the relatively poor access. Oblique insertion of the implant is required if the plates are to be engaged. Non-axial implant loading results, but this does not seem to compromise implant success.

A simpler approach is to use the maxillary tuberosity for implant insertion. The volume of bone is often adequate, but the density is poor. Careful assessment of healing and progressive loading of the implants in this area give predictable results.

Lower jaw

In the atrophic mandible, interferominal implant placement enables reconstruction of the dentition in most cases. Posterior cantilevered prostheses, fixed to anteriorly placed implants, can provide full arch restoration of the lower jaw. However, in some cases, for example where there are sound anterior teeth, implant placement proximal to the mental foramen is indicated. Shorter, wide body, roughened surface implants can be used in this area to good effect. Where insufficient bone is available above the ID nerve, the alveolar ridge can be augmented by bone grafting or distraction techniques. Wherever possible, the avoidance of nerve repositioning is to be recommended as sensory changes in the lower lip after nerve manipulation are almost inevitable and can range from transitory to permanent. Appropriate consent should specifically include changes in nerve function postoperatively.

Severe atrophy of the interfominal zone can be addressed with short, wide body implants, transmandibular implants or onlay grafting. Onlay grafting alone has been associated with rapid resorption and disappointing results. When combined with osseointegrated implants, onlay grafting is more predictable and long-term reconstruction of the atrophic mandible is possible. Onlay grafting allows the placement of longer implants, and reduces the risk of mandibular fracture. The anterior iliac crest is the usual donor site, although calvarial bone also works well and being denser is less prone to resorption.

The graft should be contoured to shape and secured rigidly to the mandible with wires, screws or plates. Implants can be placed at the same time as the bone grafts or after bone healing. The latter requires a second procedure but correct implant placement is easier and complete loss of the graft during healing does not result in loss of the implants too.

Removal of prominent genial tubercles may be required and careful mobilization of the flaps is needed for a tension-free soft tissue closure over graft.

In the atrophic mandible, the keratinized gingiva often shrinks to a thin band overlying the ridge. This is frequently inadequate to give a non-mobile soft tissue margin around the implant. Soft tissue surgery to the local area is required if localized peri-implant inflammation is to be avoided (Figure 57.14). A vestibuloplasty with mucosal graft gives predictable results. Care should be taken to avoid the mental nerves and
retain mentalis attachment. Supraperiosteal dissection, with suturing of the buccal flap to the depth of the newly formed sulcus, ensures a vascularized bed on to which the graft can be laid. The graft can be taken from the buccal mucosa, palate or skin. A stent sutured into place maintains sulcal depth and pressure on the graft but is not strictly necessary.

**IMPLANT SALVAGE**

Peri-implant infections are relatively uncommon and usually develop gradually. Regular reviews enable early assessment of inflammation around an implant. The load on the prosthesis and the abutment to implant junction should always be checked. Most infections are treatable, but the longer they remain, the greater the volume of bone is lost, resulting in eventual loss of the implant. Metronidazole and or Augmentin are appropriate antibiotics for most peri-implant infections. When combined with chlorhexidine topically and irrigation of the peri-implant tissues, using a fine syringe, most acute infections will resolve.

Where bone loss is apparent, surgical salvage may be required. The implant is exposed and the surface mechanically cleaned and disinfected with topical chlorhexidine gel or citric acid. The soft tissues can be recontoured and sutured around the implant or GBR with a membrane and graft attempted. Allografts, xenografts and alloplastic bone substitutes can be used. GBR requires meticulous techniques and careful follow up if the membrane is not to get infected and aggravate the situation.

Where bone loss is extreme, then implant removal is required. The removal of the superstructure allows access to the implant. Various trephines have been devised to enable implant removal with the minimum of surrounding bone loss. Ideally, the defect is then cleaned, allowed to heal and the implant replaced, with bone grafting, if necessary. Where very long implants have failed, consideration should be given to sectioning the implant at the level of the remaining bone. This avoids weakening the basal bone unduly. Fractures of the residual bone have been reported in this situation.

**CONCLUSIONS**

Osseointegrated implants provide the means to reconstruct and rehabilitate. Case selection is important, and indefinite review and maintenance is essential if long-term benefits are to be maintained. With appropriate planning and careful execution implant-borne prostheses may last the lifetime of the patient.

**KEY EVIDENCE**

- Osseointegrated implants can remain in place many decades; they preserve residual bone, aid retention of prostheses and improve quality of life.
- The long-term survival of osseointegrated implants in irradiated bone remains open to question, as does the influence of hyperbolic oxygen. These issues are the subject of ongoing, prospective trials.

**KEY LEARNING POINTS**

- Osseointegrated implants should be available when any reconstructive procedure is considered.
- Implants should be placed in an ideal setting if they are to be used to best effect; this may require pre-implant site preparation, including bone grafting.
- Implants and prostheses require life-long maintenance.
- The influence of hyperbaric oxygen on healing of irradiated bone is under ongoing investigation.

**REFERENCES**


A combined prosthetic and surgical approach to head and neck reconstruction

STEVE WORROLLO AND STEPHEN DOVER

INTRODUCTION

The use of prosthetics has been well documented throughout history. It has allowed a range of artificial replacements from an individual tooth to a complete limb. As a technique, it has had to adapt to improving surgical reconstructive techniques and advances in technology. This has been achieved by changes with the materials available, a greater recognition of the skill of the maxillofacial prosthetist, combined with greater expectations from patients.

The prosthetist has evolved into highly specialized fields within multidisciplined teams. Within the head and neck region, osseointegration has allowed predictable retention of prostheses. However, it is not suitable or desirable for all patients and, on its own, will not guarantee an acceptable aesthetic result. All prosthetic and surgical options need to be evaluated by the team, including the patient, to achieve optimal results.

HISTORICAL PERSPECTIVE

Facial prosthetics is an established art that is well documented as far back as Egyptian times, with artificial eyes found with mummified remains dating from 2000 BC. A variety of materials have been used from precious metals to leather. In the early days, prostheses covered congenital defects, traumatic injuries or infectious diseases, such as leprosy. The medical/dental professions would fashion various appliances and prostheses using craftsmen to fabricate them. Surgery for tumours of the face was rarely undertaken and seldom curative.

Surgeons have practised surgical reconstruction with varying results. Nasal amputation was a common punishment in ancient India. In 600 BC, Sushrula Samhita described nasal reconstruction using cheek flaps. Ambroise Paré (1510–90), a French surgeon with great practical skill, described the technical details of constructing a variety of artificial limbs and prostheses for facial defects. His work in his native language (rather than in Latin, which was normally used at that time by academics) meant that his writing had a wide influence on the public as well as medical professionals. His book *The opera* established him as the father of facial tissue replacement. In Italy, around 1600, Tagliaozzi described surgical reconstruction of the nose using new techniques. However, at this stage, treatment risks associated with the procedure were very high and cosmetic results unpredictable and unsatisfactory.

It was not until the beginning of the nineteenth century that successful nasal reconstruction was reported in India, and only at the end of the nineteenth century did plastic surgery begin to provide an alternative to facial prosthetics. Major advances in plastic surgery evolved during the First World War when large numbers of casualties were treated.
at specialist centres set up for the treatment of facial and jaw injuries; many of those treated had large facial defects. Technical appliances were widely used for jaw fixation and splinting for bony fractures. Prostheses were used for defects which could not be surgically reconstructed, or for patients for whom it was not practical, or when treatment was delayed. These centres were, therefore, important in the development of craniofacial rehabilitation. Teams of surgeons, working together with dentists, helped develop new techniques that radically improved the outcome for patients – an early example of multidisciplinary teams, which are more common in modern practice today.

PATIENT ASSESSMENT

Defects in the craniofacial region can, using carefully planned and unbiased reconstructive regimes, dramatically improve the final outcome for patients with facial disfigurement. Meticulous planning of surgical resections and careful primary handling of the iatrogenic traumatic defects can significantly influence long-term rehabilitation. The decision to provide a patient with a facial prosthesis should always be carefully evaluated and there are many factors to consider.

Prosthetics should be used to complement reconstructive surgery. The decision to use a prosthesis (as opposed to autogenous tissue) should only be made after considering all available options. The aetiology of defects is important in deciding the type of treatment and timing of any reconstructive procedures.

There are differences between the assessment of prosthetic patients for the oral cavity and those with large complex craniofacial defects. Intraoral prosthetics is beyond the scope of this chapter and thus covered only in context with ablative surgery and its immediate use.

Patient assessment will help define what type of prosthesis will meet individual requirements. It is important to consider any other treatment regimes which may be planned, such as radiotherapy or further surgery. Preprosthetic surgery may be required in helping to achieve optimal results.

EXTRAORAL PROSTHESIS TREATMENT PLANNING

The following factors should be considered when planning treatment with extraoral prostheses:

- **Medical factors**: Is further surgery/treatment planned? The patient’s physiological status and general health.
- **Patient factors**: Age, dexterity, hygiene, motivation, compliance.
- **Defect considerations**: Aetiology of defect, use of autogenous tissue, soft tissue cover, skin condition, defect shape allowing for optimum prosthesis positioning, availability of bone for implant placement, support for prostheses, facial movement during function, previous radiotherapy.

AETIOLOGY OF FACIAL DEFECTS

### Congenital defects

Congenital defects include absence of:

- the ear (microtia) (Figure 58.1);
- the nose (arhina);
- the eye and orbits (anoptholima).

In patients with congenital defects, treatment is an elective decision which can only be made by the patient when provided with all the relevant information and the ability to meet and talk to patients previously treated. This gives a balanced, informed view of potential treatment options. It is, of course, possible that the patient may accept the defect, or is unwilling to undergo any possible treatment.

![Figure 58.1 Microtia](image)

### Acquired defects

Acquired traumatic defects include those caused by:

- road traffic accidents (Figure 58.2);
- thermal injuries;
- ballistic injuries;
- accidental injury;
- physical assault.

Acquired surgical defects can result from removal of benign and malignant tumours (Figure 58.3).

Patients with acquired defects have to come to terms with a sudden change of appearance. Cancer patients will also have the psychological worry of dealing with potential life-threatening conditions, for which the treatment can involve
Every effort should be made to use the patient’s own tissue and, if necessary, surgical procedures are undertaken in stages until the optimal result is obtained. If surgery is not possible (or will involve multiple procedures with an unpredictable result), then prostheses can be considered.

For patients with tumours, the defect size is determined by the amount of tissue that has to be removed during ablative resection. How the defect is left is of paramount importance if a prosthesis is to be used as it will determine the final aesthetic result. Ideally, thin skin cover is always preferable as this allows for an optimum interface between defect and prosthesis. Bulky flaps are to be avoided as they restrict contouring and positioning of prostheses and will not allow mirror imaging of existing symmetrical structures, such as eyes.

**Defect reconstruction**

The reconstruction of hard and soft tissues is a combination of art and science. Major defects in the craniofacial region have challenged the skills of the reconstructive surgeon. The use of microvascular free-flap transfer of hard and soft tissue to the mandible, maxilla, cranial and midface regions has greatly improved the outcome for patients. Surgical techniques have advanced using autogenous tissues to replace aesthetically difficult areas, such as the nose and ear. The results of these reconstructions, however, can be highly variable with consistent results difficult to achieve without a very high level of specialization.

It may be that the decision is not to reconstruct immediately as there may be a need to look for evidence of recurrent disease at the defect site, prior to any secondary reconstruction. Alternatively, the defect may be obliterated with a large bulky flap to close a large surgical cavity and perhaps bury residual disease prior to radiotherapy. This can have the advantage of closing communication between oral and nasal components but with limited or unacceptable aesthetics and function.

Craniofacial defects should be reconstructed as soon as the patient’s condition allows. This is an important factor for all patients, including those with a poor prognosis. With the standard of autogenous or prosthetic techniques available it is not acceptable for patients with facial deformity to be precluded from leading as normal a life as possible.

Small soft tissue defects are reconstructed by covering with skin grafts, deeper defects by the use of local flaps (Figure 58.4). Large defects usually require coverage by a free flap. Bony defects may be reconstructed by a non-vascularized bone graft, provided that there is sufficient soft tissue coverage with non-irradiated tissue. For defects of both hard and soft tissue, a composite free flap containing bone and skin is preferred. Skeletal fixation is obtained using internal fixation with plates and screws. Sites of composite free flaps include iliac crest, fibula, scapula and radius. Radial forearm flaps have a large surface area of skin to volume; this makes them thin and suitable for both intraoral and extraoral mucosal or skin defects. However, limited bone volume can be harvested with this flap from the radius. The use of bulky flaps can compromise aesthetics and make prosthetic options impracticable. Smaller, thinner flaps and skin grafting may give coverage without compromising prosthetic possibilities. The two options are compared in Table 58.1.
Defect sites

AURICULAR DEFECTS

The incidence of malformation of the external ear occurs in 1 in 10,000 live births. Auricular defects frequently appear in combination with those of the external auditory canal and middle ear. Unilateral microtia may be associated with facial malformations involving the first and second branchial arch. Unilateral or bilateral microtia can be part of a bilateral condition, such as Treacher Collins syndrome.

Children born with congenital defects can invoke feelings of anxiety and guilt, causing the parents to seek an immediate solution. This should be resisted and reassurance should be given to parents with an explanation of potential treatments available. Delay in treatment will allow sufficient growth to occur for an optimum aesthetic result to be achieved and for the child to understand and be involved in the process. The introduction of families to parents with children of the same condition is very useful in allaying fears that their child is alone in suffering this condition.

Patients are best assessed by a multidisciplinary team, which should include ENT, maxillofacial, prosthetists and plastic surgery colleagues. Depending on the severity of the condition, a variety of treatment options may need to be considered.

The importance of hearing to development should never be overlooked or considered less important than aesthetics and should be a priority. If necessary, a bone anchored hearing aid (BAHA) should precede ear reconstruction.

A realistic age for successful prosthetics in children is 10–12 years and onwards. Our experience is that before this age children are not sufficiently developed physically or psychologically to commit to a long-term treatment regime.

Many patients referred for prosthetics have had disappointing autogenous reconstructions. This should not be used as a reason to preclude further consideration of this, as cooperation between prosthetics and autogenous reconstruction is vital to achieve a balanced and appropriate treatment for the varied range of patients with auricular defects. There have been great improvements in autogenous reconstructive techniques with major contributions by Brent and Nagata. With improved techniques, more consistent aesthetic results can be achieved, but specialization is as important as technique to achieve these standards. The decision to opt for the prosthetic option is easier when an autogenous reconstruction is totally impractical, such as the presence of compromised skin or following tumour resection.

Indications for auricular prostheses include:

- lack of autogenous tissue;
- irradiated area;
- failed autogenous reconstruction;
- cancer resection;
- absence of lower half of pinna;
- microtia;
- patient preference;
- craniofacial anomaly;
- traumatic defect.

Microtia cases can predictably be reconstructed with a prosthesis, but have the disadvantage of long-term follow up. Treatment can compromise any future autogenous
reconstruction by removal of ear remnants or compromise available soft tissue. The amount of ear left (particularly the lower third) or the position and shape of remnants can make autogenous reconstruction a more viable option. There is a role for both autogenous and prosthetic options in auricular reconstruction and both options, working to complement each other, can only benefit patient treatment regimes.

Once treatment is decided upon, careful planning is required to determine the stages and timing of treatment. The prosthetist should be involved in all stages of treatment if prosthetics is the chosen option.

NASAL DEFECTS

Nasal defects are predominantly a result of tumour surgery or traumatic loss; congenital absence is an extremely rare entity. The goal of reconstruction is to construct an aesthetically pleasing and ‘functional’ nose. Autogenous reconstruction must address the underlining bone and cartilage support, skin coverage, and reconstruction of the nasal lining.

Acquired defects produce a variety of midface deformities dependent on the extent of traumatic injury or ablative resection. Smaller defects are easier to reconstruct using autogenous methods. The cosmetic anatomy of the nose is classified in five aesthetic units: dorsum, lateral tip, tip, alar lobule and soft tissue triangle, as described by Burget and Menick.8 The majority of acquired defects are confined to skin. Skin grafts from the postauricular or preauricular area are ideal because of colour and texture match in the proximal two-thirds of the nose. The distal tip requires ‘thicker’ coverage and is usually best reconstructed with a composite flap.

The decision to reconstruct is dependent on the health of the patient, the quality and availability of donor tissue, the presence of any residual disease and patient choice. The defect may also involve orbital and maxillectomy components and this should be considered in treatment planning.

If the lip is to be sacrificed, it is essential to reconstruct the competent boundaries if possible. This can be achieved by using local, regional or free flaps.9 Prosthetic reconstruction is difficult in these cases because of the mobility of the surrounding tissue and the functional seal required for lip competence. Large prostheses can be difficult to stabilize and retain.

The use of osseointegration in the midface region can dramatically improve anchorage and enable complex and dynamic junctions to be accommodated within the prosthesis.10 Placing fixtures at the time of ablative surgery gives great advantages. It significantly reduces the time before prosthetic rehabilitation can commence. In some cases, immediate reconstruction can be started. Fixtures are best placed in bone prior to any radiotherapy, thereby increasing implant osseointegration and survival rate. Implants are ideally placed around the circumference of the defect, in the nasal rim and into the nasal bridge. It is often necessary to trim back thin bone to allow placement into wider bone. Intraoral fixtures should always be used to take advantage of as much depth of bone in the premaxilla and nasal bridge sites as possible. It can be advantageous to utilize zygomatic implants which use good quality bone at distant sites11 while providing stability for prostheses at the defect site. It is important to involve the prosthetist as early as possible so that impressions can be taken of the facial structures prior to ablative surgery. This enables a template to be constructed for use as a starting point in reconstructive planning of the lost tissues (Figure 58.5).

ORBITAL DEFECTS

Any defect that is confined only to the globe is treated with an ‘indwelling prosthesis’, which sits behind the lids. These prostheses, which are self-retaining, are often historically referred to as ‘glass eyes’, although they are now, at least in the UK, made in acrylic. Defects including the loss of orbital contents and the lids are more extensive and an orbital prosthesis will often be the treatment of choice.

The majority of patients requiring orbital prostheses have acquired defects as a result of tumour surgery. These can also include defects extending into the maxilla and or nasal area. The type of surgery for which prosthetics is required is shown in Table 58.2.

Reconstruction in this area is complicated by the presence of neighbouring sinuses. Any extension into the sinuses may produce a chronic discharge. In these cases, the opening can be obliterated or closed over with skin cover or a flap. Where

<table>
<thead>
<tr>
<th>Term</th>
<th>Tissue lost</th>
<th>Solution</th>
</tr>
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<tbody>
<tr>
<td>Evisceration</td>
<td>Cornea</td>
<td>Cosmetic shell</td>
</tr>
<tr>
<td>Enucleation</td>
<td>Eye</td>
<td>Artificial eye</td>
</tr>
<tr>
<td>Exenteration</td>
<td>Eye and orbital contents</td>
<td>Orbital prosthesis</td>
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</table>
there is a congenital deformity, any rudimentary eye, conjunctiva or eyelids and lashes should be removed. This should result in a deep orbital socket and a skin boundary with restricted movement to enhance prosthetic stability.

For patients who are to receive orbital prostheses, it is important that there is sufficient depth within the defect to position the eye unit and achieve symmetry with the normal side. Bulky flaps often preclude this and it is essential that consideration be given to this or further reversionary surgery will be required (Figure 58.6).

Extraoral implant placement can be carried out at the same time as ablative surgery or as a planned secondary procedure.

**ORAL CAVITY**

Intraoral prosthetics are well documented in technical and dental literature. This section will only cover prosthetics in relation to ablative surgery.

The surgical management of oral cancer requires understanding and skills in assessment, access, ablative and reconstruction surgery. Prosthetic input may be required in dealing with complex and difficult defects. Removal of soft and hard tissue has a dramatic effect on function; small defects can be closed by local flaps with free tissue transfer available for larger defects. While surgical reconstruction has improved and it is the treatment of choice, there are occasions where prosthetics is a suitable option, or it can be used if a surgical reconstruction has failed.

The objective of prosthetic rehabilitation in patients with defects of the orofacial region is the restoration of form, function and appearance. In patients with orofacial cancer, a decision should be made as to whether immediate or staged surgical reconstruction is advocated. If possible, a one-stage procedure should be used. Surgery involving the oral cavity will require preoperative dental checks and any necessary treatment should be undertaken prior to surgery. When a maxillary resection requires an intermediate obturator, impressions are required preoperatively to enable design and construction of the plate.

The design needs to consider how the plate is to be retained, the approximate extent of the resection and whether any teeth are to be lost or utilized for retention. The type of dressing/pack is important as the type of pack can affect the design of the plate.

In the maxilla, the bony margins and alveolus should be trimmed such that primary closure of the surrounding tissues can be achieved. The hard palate pterygoid plates and nasal septum should be examined and cut back to provide a smooth, non-sharp surface and, where possible, covered with local mucosa.

Following a maxillectomy, it is important to remove the coronoid process of the mandible as it can dislodge and break the seal of a definitive prosthesis. Retaining the coronoid contributes to postoperative trismus due to temporalis shortening; trismus is further exacerbated by postoperative radiotherapy.

The surgical plate is essential to immediately restore speech and mastication and to provide support for soft tissue. Any prosthesis must be able to be modified at the time of surgery to accommodate any surgical variations that may be necessary.

The obturator is retained by using skeletal wiring, bone screws through the acrylic plate or by clasping to existing teeth. It is possible to use fast setting, expandable, silastic foam as both a dressing medium and to provide retention by a mechanical attachment to the plate. This technique requires the dental plate to be held in place and the foam is poured or syringed into the defect. The foam will expand to fill the defect and sets around the retentive posts that are incorporated into the underside of the plate. The foam can easily be trimmed with scissors to give a flexible and very accurate fitting ‘bung’ which obliterates the defect and provides support and retention to the plate.

Technical requirements for surgical splint construction include:

- dental impressions;
- approximate extent of resection;
- method of retaining plate;
- type of dressing/pack (Figure 58.7a).

Recent surgical developments and the use of digital technology has changed how these patients are managed. With the use of computer-generated models, it is now possible to plan the surgical resection and construct prebent plates that will fit exactly the remaining anatomy and be used as both a template and provide fixation for the free tissue bony flap. When carefully planned, these custom plates can be used for both maxillary and mandibular reconstructions and improve patient outcomes and greatly reduce surgical time.

From a prosthetic perspective, this means that a dental plate is no longer required for the ablative surgical stage as the defect is reconstructed from the patient’s own tissue. Technical input is still required but in the form of planning and in the custom construction of the plates.

Patients can then go forward for conventional or implant-retained prosthetics to restore the dentition (Figure 58.7b–e).
Extraoral prosthesis construction

Once a decision has been taken to provide a patient with a facial prosthesis, a series of technical/clinical procedures is commenced. The retention options for the prosthesis are discussed with the patient. Clinical assessment should be carried out to establish the size and extent of the planned prosthesis and where the prosthetic margins will be finished. Soft tissue examination will help identify any mobile areas that could compromise marginal integrity of the prosthesis. Computed tomography (CT)/magnetic resonance imaging (MRI) and plain x-rays will assess the skeletal structure for potential implant sites. Impressions are taken to provide a working cast of the defect.

If the prosthesis is retained using conventional methods, unless any preprosthetic surgery is required, prosthetic construction can be commenced immediately. In patients selected for implants, it is essential to plan the optimum position for retention without compromising aesthetics. A template is constructed and used during the surgical treatment to identify implant sites for the surgeon.13

It is helpful to use x-ray images to determine bone depth and quality. The use of 3D computer-generated models and implant software programs can be invaluable in complex cases. Surgical guides can be made directly from the CT scan data either resting on the soft tissue or directly onto the underlying bone. However, in many cases, such as the mastoid bone, these are of less value as even in children with thin

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**Figure 58.7** (a) Obturation with dental plate and foam dressing; (b) computer-generated model showing resection and design of plates; (c) resection of maxilla; (d) positioning of plate; (e) fixation of bony flap.
bone, as encountered in early BAHA placement, it is unlikely to change the outcome. If air cells or poor quality bone are encountered in the planned positions, it is only necessary to move from the planned position until sound bone is encountered. The template will keep implant placement within acceptable limits.

In patients having ablative surgery, recent experience has shown that there is a great benefit in placing the fixtures at the time of resection. It is particularly helpful in those who are to receive postoperative radiotherapy, as the osseointegration process is established before the bone is irradiated with improved survival rate compared to fixtures inserted into compromised bone. This also reduces the number of surgical procedures and the time between surgery and the fitting of the prosthesis.

The decision on fixture placement has to be made following tumour clearance and is ideally made by the surgeon and prosthetist based on the availability of bone and the usability of potential sites.

STAGES IN PROSTHETIC CONSTRUCTION

Various technical stages are involved in the fabrication of prostheses (Figure 58.8a):

- impression (Figure 58.8b)
- pattern
- mould
- processing
- fitting.

An impression is taken of the defect to create a master cast on which a wax pattern is sculptured. This can be adjusted and aligned on the patient to achieve the desired contour and orientation.

When completed, a two- or three-part mould is constructed and, using the lost-wax technique, a void is created which is then replaced by the prosthetic material. The materials of choice are silicone elastomers, which are individually coloured to match patient skin shades (Figure 58.8c).

FACIAL PROSTHESIS RETENTION METHODS

The success of facial prostheses depends not just on aesthetics but on the retentive qualities. The prosthesis must be comfortable and give confidence to the wearer. Methods of retention can be categorized as follows:

- adhesive
- anatomical/mechanical
- implant.

With some prosthetic devices, retention can be retained by virtue of the anatomical location, for example an artificial eye held in place by the eyelids. This also disguises any margins. Facial prostheses do not always have this convenient camouflage; therefore, the design must take this into account to minimize any compromise of margin integrity.

Adhesive

Until the advent of implants, adhesives were often the method of choice for extraoral prostheses, providing good aesthetics if used carefully by a compliant patient. The adhesives used are waterproof and, if correctly applied, the prosthesis will remain in position for many hours (Figure 58.9). Most problems are encountered by the continual...
fitting and removal of the prosthesis. This can have a detrimental effect, particularly on the fine edges of the prosthesis. Patients will need a certain amount of dexterity to be able to locate and position the prosthesis. The type and quality of the skin can influence the choice of adhesive and the suitability of this technique. Patients with broken or compromised skin are best treated with other retentive methods. Allergic reactions to the adhesive are well recognized.

**Mechanical/anatomical**

Mechanical retention of facial prostheses is the oldest form of retention. Early retention included spring bands and straps. Spectacle frames are the mainstay of mechanical retention for facial prostheses. Mechanical retention can be incorporated into interlocking intra- and extraoral prosthetic combinations, such as an obturator linked to an orbital prosthesis. Spectacle-retained prostheses are still useful in cases where simplicity and ease of location is of paramount importance. They have a particular application in the elderly and patients who have dexterity problems. The prosthesis is attached to the spectacle frame which means that the patient is not able to remove their glasses without revealing the defect. The adjustment of the glasses is important as it will have a direct bearing on the location and fit of the prosthesis.

Anatomical retention is possible in patients who have favourable undercuts. These are the result of soft tissue contracture, such as in a maxillectomy defect where a soft tissue band contracts to give a ledge over which an obturator rim can be rotated, or in areas where soft silicone flanges may be expanded to create retention via gentle, local, expansive pressure.

Obtaining the correct amount of retentive pressure is difficult and care must be exercised not to ulcerate the tissue as a result of overload. This technique is more suited to intraoral defects. Obturator-retained extraoral prostheses are more likely to be affected by facial movements and can cause the loss of marginal integrity.

**Implant retained**

Implants provide a stable and secure method of retention. The margins of any implant-retained prosthesis can be very thin as they are much less likely to tear than those around adhesive-retained prostheses. Thin margins offer the best possible aesthetics.

Implants were first used in extraoral sites in Sweden in 1977. This is now an established technique that provides predictable results for patients with various craniofacial defects. Implants allow prostheses to be extremely stable and secure. The prosthesis is generally retained in place by a rigid bar with clips or by magnets incorporated into the prosthesis and connecting to magnetic caps on the implant.

The number of implants required for retention of any prosthesis is determined by the size and shape of the defect. Auricular defects that involve only the pinna will usually only require two implants for adequate retention. This is achieved by a bar and clip arrangement. In cases where bone quality is poor or when the tissue has been irradiated, it is advisable to overengineer the reconstruction and place further fixtures as ‘sleepers’ in case of future failures.

Following fixture placement, the size of the abutment that attaches to the implant and which emerges through the skin is determined by the thickness of the tissue and the aesthetic requirements. It may be advisable to initially place healing abutments and then the prosthodontist can select the optimal abutment type and size following the healing phase. These healing abutments can also be used in selected circumstances when the implants are placed in a transcutaneous fashion rather than submerged. The abutments are, in turn, fitted with the appropriate prosthetic components, depending on the retentive elements selected for prosthesis attachment. If necessary, angled abutments can be used to overcome problems with implant placement and to aid prosthesis location. In certain cases, prosthetic components can be connected directly to the fixture.

The bar and clip arrangement has the advantage that the clips are adjustable and the bar design can be modified to keep the retention components low profile and within the margins of the prosthesis. The bar is connected by gold screws into the abutments (Figure 58.10).

Magnets have a role with some patients in auricular cases and retention can be further enhanced by using lip magnets which have increased resistance to lateral dislodgement. Magnets are particularly useful in orbital and midface cases where bar construction is difficult or complex and location of the prosthesis could be difficult for the patient. They also have a role in patients with limited manual dexterity or impaired vision as they are easier to clean and maintain. Ball attachments can also be utilized but are not favoured by the authors. They have been superseded by locator-type attachments which have a greater surface area and are more tolerant of divergent angulations.

The advantages and disadvantages of implant-retained extraoral prostheses are summarized in Table 58.3.
PATIENT FOLLOW-UP MANAGEMENT

The choice of a prosthetic reconstruction results in an ongoing commitment for the prosthetic team and the patient. The patient needs to maintain a significant level of hygiene, particularly if there are skin-penetrating abutments. They have to exercise care in seating and cleaning the prosthesis and commit to long-term follow up.

The success of the reconstruction reflects the ability of the prosthetist to design a functional and well-fitting prosthesis. The prosthetist should give instructions on how to position, apply and remove the prosthesis with details of any instructions regarding wearing. It is important that the prosthesis does not restrict the patient’s activities and lifestyle. Implant-borne prostheses give the most predictable results, but should not be considered the only option.

Dealing with patients with facial disfigurement is very demanding and requires an understanding of patient expectations, tempered with a realization of what is practical or possible. Patient reactions to facial disfigurement vary greatly. Time spent with patients in consultation is important in building a relationship to enable sensible and practical options to be considered.

Quality of life outcomes are now a welcome and vital issue to be considered in patient management. Patients require lifelong follow up for maintenance and adjustment of prostheses, examination of any implants, abutments and the local skin. The commitment to long-term management must be discussed with the patient.

CURRENT DEFICIENCIES AND FUTURE DEVELOPMENTS

There have been many developments in materials used for the production of prostheses. The advent of the percutaneous osseointegrated implant has dramatically improved the potential for retention of any prosthesis. However, many of the construction methods and mould-making techniques have changed little and remain highly skilled and time-consuming. Each prosthesis is individually produced and the use of high technology has been difficult to adapt or, to date, is not cost-effective.

With advances in computer software using CT data, there are programs available that allow 3D simulation of facial reconstructive methods including osteotomy and distraction procedures. Data from medical scanners (CT, MRI) can be used to reproduce physical models of human anatomy via rapid prototyping (RP). Several RP techniques exist, the most common being stereolithography. The basic principle of creating a 3D structure is to build layers using the CT data and an optical scanning system that draws a shape one layer at a time onto the surface of the liquid photosensitive resin until the desired model is completed.

It is possible to have individual implant templates for either soft tissue or direct bone contact to allow exact implant placement. Precise anatomical models (3D) made by RP enable surgeons to view and evaluate their treatment plans. On this physical model, osteotomy lines or drilling holes can be indicated and trial surgery can be undertaken. These models can be used, if necessary, to pre-bend plates ready for surgical procedures. The applications of these models can be advantageous in both facial reconstruction and in the production of obturator prostheses for maxillary defects and designing and planning cranioplasties for skull defects.

Improvements in surgical techniques and the advent of specialization have enabled more accurate and aesthetic reconstructions to be performed. While prosthetic materials continue to be improved and refined, these surgical improvements may render prostheses to be necessary in a more limited format. The necessity of treating tumours by ablative surgery in the future may be reduced by other treatment regimes and therefore the necessity to surgically or prosthetically reconstruct these defects could be reduced.
The use of current technology and digital imaging in processing complex shapes and patterns is now achievable and readily available. In certain circumstances, it can produce moulds and patterns that are difficult to duplicate by conventional methods. It remains to be seen whether the use of this technology is cost-effective in individual cases, or is just another method of obtaining the same result. As with most new techniques, there is a tendency to overuse. Careful evaluation of each individual case should be a balance between the need to obtain the optimal result and the cost-effectiveness of the process. These technological advances are an essential and welcome addition to reconstructive surgical and prosthetic practice.

**KEY LEARNING POINTS**

- Have realistic expectations.
- Follow reconstructive ladder.
- Be able to offer all options to the same standard.
- Keep prosthetics simple and user friendly.
- Spend time with patients to establish a full understanding of procedures.
- Make sure patients have an expected time frame.

**ACKNOWLEDGEMENTS**

The role and practice of medical and surgical disciplines has become increasingly specialized with patients treated in centres with a high concentration of complex cases. These centres with their multidisciplinary teams and expertise can help to provide the comprehensive care necessary to deal with the demands required to deliver a head and neck service. To meet patient prosthetic expectations can be technically, clinically and emotionally challenging, and we would like to acknowledge the work of our colleague Peter Jeynes (MIMPT) for his expertise and support in the prosthetic management of these patients.

**REFERENCES**

APPENDIX: CASE REPORTS

Case report A

This female patient underwent a total rhinectomy for a squamous cell carcinoma of the nose. This was followed by a course of radical radiotherapy of 55 Gy in 20 fractions. Her initial management was with an adhesive-retained nasal prosthesis, but this had limitations in terms of stability and aesthetics. She was then transferred to our unit for her prosthetic management and consideration for extraoral implants to retain her nasal prosthesis. Given her radiotherapy exposure, hyperbaric oxygen therapy was undertaken for 20 sessions pre- and 10 sessions post-implant placement at a pressure of 2.2 ATA with oxygen breathing for 90 minutes. Three implants were placed in the base of the nose 13, 10 and 15 mm in length. The implants were allowed to heal undisturbed for six months before exposure, following which a new prosthesis was made, retained by a bar and clip giving very secure anchorage (Figure 58.11).

As a general rule, we no longer use extraoral implants for the retention of facial prostheses, with the exception of ears. In almost all cases, conventional implants such as those used for intraoral reconstruction are suitable. There are clear advantages to using longer implants in terms of long-term survival and load-carrying ability.

Figure 58.11  Case A, Rinectomy: (a,b) Nasal defect; (c,d) with prostheses.
Case report B

In 1990, a female patient underwent a total rhinectomy and right neck dissection for a squamous cell carcinoma of the nose. Her initial management was with a spectacle-retained nasal prosthesis, but this had limitations in terms of stability and aesthetics. In 1997, she was referred to us and under a general anesthetic had three standard Bränemark fixtures placed, one 10 mm implant in the nasal bridge, extending up into the anterior wall of the frontal sinus and two 13 mm implants placed obliquely downwards into the pyriform rim of the nasal sill (Figure 58.12a). The implants were allowed to heal undisturbed for six months before exposure. Magnets have been used to retain the nasal prosthesis (Figure 58.12b). The patient is now freed from using spectacles and has much greater confidence in the prosthesis, particularly when playing with her grandchildren (Figure 58.12c and 58.12d).

Figure 58.12  Case B, Rinectomy: (a,b) Nasal defect with magnets; (b) with prosthesis; (c) close up; (d) x-ray showing implants.
Case report C

This female patient had a craniofacial resection for an adenoidcystic carcinoma resulting in a right orbital exteration. Extraoral implants were placed for retention for an orbital prosthesis. Initially four implants were placed and three were utilized using magnets for retention; the remaining implant was left as a ‘sleeper’ to be used if required in the future. This patient has now had implants for over 20 years, during which time one was removed because of inherit pain and one lost. Two further implants have been placed and retention is now via a bar and clip arrangement. The patient has consistently used the prosthesis on a daily basis only removing it at night (Figure 58.13).

Figure 58.13  Case C, Orbital exteration: (a) Orbital defect; (b) with prostheses.
Case report D

At the age of 19, this male sustained a gunshot injury to his midface that rendered him blind (Figure 58.14). His mother cared him for until his mid-40s when he was referred to our unit. A large mucocele of the frontal sinus was present and surgically removed, together with debridement of the frontal sinus and bone grafting of the anterior skull base. Once all residual infection had been treated, implants were placed around both orbital rims and a prosthesis constructed to fill the orbital and nasal defects (Figure 58.14b and 58.14c). Although blind, the psychological benefit to this patient and that of his mother can best be expressed by the letter she wrote to the department on completion of treatment.

As a mother and on behalf of my son, I wish to convey to you all my most sincere thanks and admiration for your skills, your care, your unique approach and above all your commitment and professionalism to your work. He has been transformed both visually and spiritually. He enjoys company and has the confidence to meet and make new friends. He wakes in the morning looking forward to another day at last feeling equal and acceptable to everyone. I cannot explain to you how grateful we both are to you all.

Figure 58.14 Case D, Traumatic midface defect: (a) Facial defect; (b) prosthesis; (c) prosthesis in situ.
Case report E

This young girl presented with a lesion on the left ear which was diagnosed as nodular melanoma.

Treatment was a pinnectomy with insertion of two 4 mm extraoral implants for an immediate prosthetic reconstruction. The external abutments were also placed during this procedure. The prosthesis was fitted within three months of the ablative surgery when the skin had fully healed and osseointegration of implants had occurred. Retention was by using a bar and clips method which gives very secure fixation.

Autogenous reconstruction was not considered an option at this stage because of the pathology. Close observation of the defect was considered essential in the initial and intermediate stages. The prosthesis will not prevent any autogenous reconstruction should that be considered in the future (Figure 58.15).

Figure 58.15  Case E, Pinnectomy: (a) Auricular defect; (b) prostheses in situ; (c,d) patient with prostheses.
Case report F

This patient had an infiltrating basal cell carcinoma left pinna extending into the external auditory meatus. Treatment was pinnectomy, coverage with split skin graft and osseointegrated implants.

Two 4 mm fixtures were placed with abutments as a one stage procedure.

Fabrication of the prostheses was commenced following healing of the defect area and integration of the implants. The prosthesis was retained using a bar framework. Patients are given full instruction on the care and fitting of the prostheses.

It is also important to involve them in the process during construction in terms of projection and form, etc. This helps with building confidence and having input to the final appearance (Figure 58.16).

Figure 58.16  Case F, Pinnectomy: (a) Auricular defect; (b) with prostheses.
INTRODUCTION

Despite advances in conservative laryngeal surgery and radiotherapy, laryngectomy still remains the procedure of choice for advanced-stage laryngeal carcinoma and relapse after radiotherapy. However, the procedure results in a lifelong stoma, loss of normal voice, loss of nasal function and lung function changes. Increased cough and mucus and reduced swallowing efficiency are also common.1

Functional rehabilitation of patients has improved in the last two decades as increasing emphasis on primary voice restoration and quality of life have become as important as cure and survival. Concern about loss of natural voice is very often traumatic for the laryngectomee, but with preoperative counselling from speech and language therapists and modern surgical voice restoration, good quality voice results should be the norm.

TYPES OF ALARYNGEAL SPEECH

For normal speech production, a moving column of air from the lungs is exhaled through the adducted vocal cord producing a tone which is modified by the articulators into speech. Following laryngectomy, not only is the vibratory source removed, but the air supply (lungs) is disconnected from the articulators. Attempts to develop voice after laryngectomy have utilized an external sound source (e.g. electrolarynx and Cooper Rand®), or used the pharyngeal mucosa as a vibratory sound source, utilizing the oesophagus rather than the lungs as an air supply (oesophageal speech) or reconnecting the lungs to the pharynx with a surgical shunt (e.g. Staffieri®, Amatsu®) or with a valved prosthesis in a fistula (e.g. Blom Singer®, Groningen®, Provox®).1,2 In the future, possible laryngeal transplantation or artificial laryngeal implantation can be foreseen.

Electrolarynx

There are two types of electrolaryngeal devices, an external type that is placed against the neck (the most common) and an oral type (intraoral placement device). The neck placement type is placed flush to the skin on the side of the neck, under the chin or on the cheek. The sound vibration is transmitted through a metal or plastic head on the device and transmitted through the tissues in the pharynx, hypopharynx and the oral cavity and then articulated normally.1 Most neck placement devices can also be converted into an intraoral device by using an adapter. A small tube is placed in the oral cavity and the generated sound is then articulated. The intraoral feature may be useful in the post-operative period when tenderness can prevent the adequate placement of an electrolarynx on the neck (Figure 59.1).

The main advantages of the electrolarynx are its relatively short learning time, the ability to use it immediately
postoperatively, its relative low cost and its minimal maintenance. The main disadvantages include the mechanical, monotonous and robot-like sound quality, the necessity to use a hand to operate the controls and dependence on batteries.2, 3, 4, 5

**Oesophageal speech**

Oesophageal speech was the mainstay of alaryngeal communication until the early 1980s and had been used as a method of voice restoration for over 100 years. It entails trapping air in the mouth or pharynx and propelling it into the oesophagus.3, 4, 5, 6, 7, 8 The patient can then reflux the air up through the oesophagus, vibrating the pharyngeal mucosa or ‘pharyngo-oesophageal (PE) segment’. This produces a belch-like sound that can be articulated by the tongue, lips and teeth. The vibratory segment is located in the lower cervical region, corresponding to C5 to C7. The cricopharyngeus and thyropharyngeus contribute to the formation of the vibratory segment (Figure 59.2).

The advantages of oesophageal speech are that it requires no batteries and no apparatus need be purchased or maintained, it does not sound mechanical and it does not require additional surgery, and it provides hands-free speech. The major disadvantage of it is that very few laryngectomees are successful users. Success rates for intelligible post-laryngectomy oesophageal speech varies from 14 to 75 per cent and to acquire oesophageal speech requires 30–50 hours of intense speech therapy.4, 5, 6, 7, 8, 9, 10, 11

**Tracheoesophageal voice using voice prosthesis**

Since the introduction of the first useful, reliable voice prosthesis by Singer and Blom in 1980, the success rate of vocal rehabilitation after total laryngectomy has improved considerably.1, 2, 3, 4 Prosthetic voice restoration is presently the method of choice for most medical professionals treating laryngectomized patients, and has transformed the expectation and quality of voice production after total laryngectomy over the past 25 years. The technique involves creating a simple tracheo-oesophageal puncture between the posterior wall of the tracheostome and the upper oesophagus into which a one-way silicone valve is inserted. Occlusion of the stoma allows air during exhalation to be shunted into the pharynx. Sound is then produced by vibrating the mucosa of the pharyngo-oesophageal segment.1, 2 Speech is then produced by articulation of this sound in the oral cavity. The one-way valve prevents salivary and liquid soiling the airway (Figure 59.3).

Initially, the puncture technique was used as a secondary procedure in patients with previous laryngectomy who failed to achieve oesophageal speech, but the consistently good results and superior quality of voice prompted...
Hamaker et al. in 1985 to incorporate the tracheo-oesophageal puncture at the time of laryngectomy as a primary procedure. 12, 13, 14, 15

The advantages of tracheo-oesophageal voice over oesophageal voice are many. It is more quickly and easily attained, it is more intelligible, natural sounding, and has improved intensity and duration of speech, achieving more words with one breath when compared to oesophageal speakers. Although the vibrating PE segment, the resonating vocal tract and the articulators are the same, the major difference between fistula and oesophageal speech is in the volume and capacity of the air reservoir leading to louder and more sustained voice.

Since its air supply is pulmonary, tracheo-oesophageal speech is closer to laryngeal speech than oesophageal speech on a range of voice parameters, such as fundamental frequency, jitter, shimmer, words per minute and maximum phonation time (Table 59.1). 10, 11, 12, 13, 14

For patients undergoing laryngectomy, the gold standard for voice rehabilitation is the rapid restoration of near-normal speech within 2–3 weeks of operation with primary tracheo-oesophageal puncture and voice prosthesis. The contraindications to doing this routinely are few, but careful selection of patients will help to reduce disappointment and failure. In established laryngectomees, careful investigation and selection is more critical for secondary voice restoration in order to achieve success. 1 In all cases, there are a number of anatomical, physiological, psychological and social factors that need to be considered.

**SELECTION CRITERIA FOR PRIMARY SPEECH RESTORATION**

**Primary voice restoration**

Primary voice restoration is now standard practice and patients undergoing laryngectomy should feel confident that they will be able to talk shortly after their operation. There are few contraindications to primary puncture at the time of laryngectomy. 1, 15, 16, 17, 18 Even if there are concerns about dexterity or a patient’s ability to manage their prosthesis, most should be offered this as many will cope well and if there are continuing concerns it is easily reversible by removing the prosthesis. However, if the upper oesophagus is resected and replaced with jejunum or stomach, it is preferable to delay voice restoration for some weeks. Equally, if the trachea is separated from the upper oesophagus, consideration should be given to delaying the formation of the puncture. If circumferential resection and reconstruction is limited to the pharynx, it is quite reasonable to undertake a primary voice restoration provided that the lower anastomosis is well above the proposed puncture site (Table 59.2). 19, 20, 21, 22, 23, 24, 25

**Surgical technique of primary voice restoration**

Certain fundamental principles and modifications have been incorporated into the laryngectomy technique to ensure good predictable voice results with minimal risk of complications.

**SURGICAL TECHNIQUE**

Of prime importance is the need to resect all diseased tissue to provide good oncological results. There are, however, a number of fundamental steps that improve the voice and swallowing results and these should be undertaken if they do not compromise the oncological resection. 1, 3, 15, 16, 17, 18, 26

The laryngectomy is carried out in the usual fashion conserving as much pharyngeal mucosa as possible, particularly over the postcricoid region, the piriform fossae and the valleculae, provided safe clearance from the tumour is obtained. The thyropharyngeus and cricopharyngeus muscles should be dissected off the thyroid laminae on both sides preserving as much muscle as possible. For hypopharyngeal tumours, the mucosa of the uninvolved piriform fossa is carefully preserved to minimize the need for flap reconstruction. Ideally, a transverse mucosal width of at least 6 cm is necessary to enable adequate swallowing and effortless tracheo-oesophageal speech. Augmentation of the pharynx

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*Figure 59.3* Myotomy through full thickness of upper oesophageal muscles.

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**Table 59.1** Comparison between laryngeal, oesophageal and tracheo-oesophageal speech.

<table>
<thead>
<tr>
<th>Physical requirements</th>
<th>Laryngeal speech</th>
<th>Oesophageal speech</th>
<th>Tracheo-oesophageal speech</th>
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</thead>
<tbody>
<tr>
<td>Initiator</td>
<td>Lungs 500 mL</td>
<td>Oesophageal air 40–70 mL</td>
<td>Lungs 500 mL</td>
</tr>
<tr>
<td>Vocoder</td>
<td>Vocal cords</td>
<td>Pharyngo-oesophageal segment</td>
<td>Pharyngo-oesophageal segment</td>
</tr>
<tr>
<td>Articulators</td>
<td>Tongue, teeth, lips, soft palate</td>
<td>Tongue, teeth, lips, soft palate</td>
<td>Tongue, teeth, lips, soft palate</td>
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</table>

Adapted from Rhys-Evans et al. 1
with a flap is preferable if the residual mucosal strip is under 6 cm, otherwise stenosis is likely with significant functional impairment.

**Cricopharyngeal myotomy**

Once the larynx is removed, a myotomy of the upper oesophageal sphincter is carried out. This is important to avoid hypertonicity and spasm of these muscles during attempted phonation and to allow expansion of the upper oesophagus providing an air ‘reservoir’ below the PE segment. Hypertonicity or spasm will interrupt the flow of air to a varying degree, restricting or completely stopping voice production. This spasm appears to be caused by reflex contraction of cricopharyngeal and constrictor muscles when the upper oesophagus is distended with air. It seems to be a cause of tracheo-oesophageal puncture speech failure in 10–12 per cent of patients (Figure 59.3).1, 3, 27

A short posterior midline myotomy is carried out with a scalpel over a distance of 4–5 cm from just below the level of the tracheo-oesophageal puncture site into the fibres of thyropharyngeus. This divides the circular muscle fibres in the upper oesophagus and the cricopharyngeus. It is important that all muscle fibres are cut. It is unclear whether assessment of the upper oesophageal sphincter with a finger can predict the development of spasm and there seems little contraindication to doing a myotomy on all patients, indeed it may also improve swallow. One of the conclusions of the European multicentre audit of speech and swallowing results after laryngectomy was that myotomy improved voice outcomes. A unilateral pharyngeal plexus neurlectomy has been advocated in the past as an alternative method of constrictor relaxation. Three to five branches of the plexus entering the lateral wall of the pharynx are exposed and tested with a nerve stimulator before cautery and division. This is not in widespread use however.

**Tracheo-oesophageal puncture**

The puncture is positioned in the midline about 10–15 mm below the cut end of the posterior tracheal wall. The tip of a pair of curved artery forceps is inserted through the pharyngeal defect and advanced into the upper oesophagus just as far as the puncture site, tenting up the mucosa. A scalpel is used to incise minimally and horizontally through the mucosa and muscle on to the tip of the forceps, which are then advanced into the tracheal lumen and opened to grasp the tip of a 14NG tube or Foley catheter (Figure 59.4).1

The forceps and the catheter are then withdrawn through the fistula tract and the tip of the catheter is passed distally down the oesophagus. The catheter is anchored to the skin above the stoma at the end of the procedure. Absorbable sutures between the oesophageal wall and the posterior aspect of the trachealis on either side of the proposed position of the puncture secure the party wall and avoids inadvertent separation.

**Pharyngeal closure**

A horizontal closure of the pharyngeal defect is preferred using an interrupted or continuous absorbable mucosal suture and then an interrupted muscle layer. This produces a wider pharynx above the PE segment which has been shown to improve resonance for speech. A ‘T’ closure results in a three-point junction which probably increases the risk of leak and fistula. Significant resection of the hypopharynx will necessitate a flap reconstruction. The thyropharyngeus

Table 59.2  Primary versus secondary puncture.

<table>
<thead>
<tr>
<th>Timing of insertion</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>One operation</td>
<td>Initial sensitive stoma</td>
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<tr>
<td></td>
<td>No nasogastric tube</td>
<td>Postoperative radiotherapy may delay speech</td>
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<tr>
<td></td>
<td>Rapid return of voice</td>
<td>lungs powered speech</td>
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<tr>
<td></td>
<td>Lung powered speech</td>
<td>Minimal time off work</td>
</tr>
<tr>
<td></td>
<td>Oesophageal voice usable</td>
<td></td>
</tr>
<tr>
<td>Delayed</td>
<td>Healing stabilized</td>
<td>Two operations</td>
</tr>
<tr>
<td></td>
<td>May have developed oesophageal speech</td>
<td>Considerable time off work</td>
</tr>
</tbody>
</table>

Adapted from Rhys-Evans et al.1
constrictor muscle is then brought together anteriorly with mattress sutures. The purpose is to try to create a suitable, ‘tonic’ PE segment at the optimal site in the pharynx with a good air reservoir below it and a wide resonating pharyngeal segment above (Figure 59.5).

While the upper oesophagus needs to be relaxed so that it does not respond to air being injected through the valve by going into spasm, the neopharynx or PE segment needs to provide an area where the mucosa is in apposition to allow it to vibrate efficiently and produce strong voice. Repairing the thyropharyngeus provides this vibratory segment. Conversely, if the muscles or PE segment wall are hypotonic (e.g. after total pharyngolaryngectomy and reconstruction, or if the thyropharyngeus is not repaired) the voice will be weak because there is minimal or absent muscle in the wall to create a PE segment.

Repair of the suprahyoid muscles
Following repair of the thyropharyngeus, it is important to suture the suprahyoid muscles down to the thyropharyngeus. This strengthens the mucosa above the repair thus avoiding a pseudoepiglottis and anterior pouch which can significantly affect swallow and also reattaches the middle constrictor and other suprahyoid muscles which are important in the swallow reflex (Figure 59.6).

Reinnervation of the pharynx
The cut ends of the superior laryngeal nerves and the recurrent laryngeal nerves may be reimplanted into the muscular wall of the reconstructed pharynx and upper oesophagus respectively in the hope that this may restore some sensory and motor reinnervation. It is felt that this can only have a potentially beneficial effect on neuromuscular coordination of the reconstructed ‘neolarynx’, although obviously it is difficult to measure any effect objectively.

Stoma reconstruction
The size, shape and contour of the stoma and surrounding skin are important to aid digital occlusion of the stoma and help ensure optimal adhesion of the tracheostoma valve housing. In order to avoid unnecessary tracheal retraction, at laryngectomy the trachea should not be transected too low and the margins of the trachea can be sutured to the medial margins of the sternomastoid muscles to secure it near the skin. If the tendons of the sternomastoid muscle are prominent, they could be safely divided to ensure a smooth and circular stomal appearance (Figure 59.7).

SECONDARY VOICE RESTORATION

The technique of tracheo-oesophageal puncture with prosthetic voice restoration was originally developed for those patients who had failed to achieve adequate oesophageal speech. A preliminary videofluoroscopy will determine whether it is necessary to carry out a constrictor myotomy at the same operation and other procedures, such as stoma revision, may also be indicated at the same time. The selection of suitable patients has previously been discussed.
Assessment

Post-laryngectomy, the patient needs a tonic pharyngo-oesophageal segment to provide a satisfactory vibratory source for tracheo-oesophageal (TO) speech. The first step in assessing patients who present for secondary voice restoration after laryngectomy, when they have failed oesophageal speech acquisition, should be an assessment of PE segment tonicity (Tables 59.3 and 59.4).

Tonicity

This is best assessed with videofluoroscopy. Therapeutic options for pharyngo-oesophageal spasm include pharyngeal constrictor myotomy, unilateral pharyngeal plexus neurotomy, and more recently, chemical denervation of the pharyngo-oesophageal segment through the use of Clostridium botulinum toxin. Botulinum toxin is a potent neurotoxin, producing neuromuscular blockade by restricting the release of acetylcholine.

Videofluoroscopy

The most reliable and accurate way of assessing PE segment physiology after a laryngectomy is with videofluoroscopy. This has three important components: a modified barium swallow, an oesophageal insufflation test and attempted phonation (Figure 59.8).

1. Modified barium swallow. The patient is instructed to swallow barium liquid while the pharynx is screened, initially from the front and then in a lateral position. The flow of barium is followed through the pharynx and the PE segment into the oesophagus and any hold up or delay due to spasm or stricture is noted, as well as any fistula or diverticulum.

2. Oesophageal insufflation test. This procedure also called the taub test simulates airflow to the oesophagus at the level of a tracheo-oesophageal puncture. A soft rubber catheter with eyelets at its proximal end is inserted transnasally to the upper oesophagus below the level of the PE segment. Air is passed from an air cylinder through the tube at a slow flow rate (i.e. 0.5 L/min) and the patient is asked to pantomime counting one to ten and/or prolonging a vowel sound. This is simultaneously recorded audiovisually.

<p>| Table 59.3 Videofluoroscopy assessment of pharyngeal constrictor tone. |</p>
<table>
<thead>
<tr>
<th>Pharyngo-oesophageal segment</th>
<th>Ba swallow</th>
<th>Phonation</th>
<th>Assisted phonation (Taub test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic</td>
<td>Passes easily</td>
<td>Good voice</td>
<td>Stronger sustained voice</td>
</tr>
<tr>
<td>Hypotonic</td>
<td>Passes easily</td>
<td>Weak voice</td>
<td>More sustained, stronger with digital pressure</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>Normal or slower passage</td>
<td>Intermittent tight voice</td>
<td>Intermittent tight voice</td>
</tr>
<tr>
<td>Spasm</td>
<td>Some hold up and residue above pharyngo-oesophageal segment</td>
<td>No voice, no air goes into oesophagus</td>
<td>Minimal voice, explosive segment release as pressure increases</td>
</tr>
<tr>
<td>Stricture</td>
<td>Permanent hold up</td>
<td>No voice</td>
<td>No voice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastric distension</td>
</tr>
</tbody>
</table>

<p>| Table 59.4 Management strategy for voice restoration. |</p>
<table>
<thead>
<tr>
<th>Pharyngo-oesophageal tonicity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotonic</td>
<td>Tracheo-oesophageal valve with digital pressure</td>
</tr>
<tr>
<td>Tonic</td>
<td>Tracheo-oesophageal valve</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>Tracheo-oesophageal valve+pharyngeal constrictor myotomy (± botulinum neurotoxin injection)</td>
</tr>
<tr>
<td>Spasm</td>
<td>Tracheo-oesophageal valve+pharyngeal constrictor myotomy (± botulinum neurotoxin injection)</td>
</tr>
<tr>
<td>Stricture</td>
<td>Tracheo-oesophageal valve+pharyngeal flap augmentation</td>
</tr>
</tbody>
</table>
3. Attempted phonation. An alternative method of oesophageal insufflation was described by Blom et al.28, 29, 30, 31, 32, 33 A catheter is inserted transnasally a distance of approximately 25 cm from the nares and connected to an adapter attached with adhesive to the peristomal skin. The patient occludes the adapter and diverts pulmonary air to the oesophagus as he or she attempts to produce sustained voicing (Figure 59.8). Passing is based on the ability to sustain uninterrupted phonation of a vowel for 8 seconds and to count continuously from 1 to 15.

Selection criteria for secondary voice restoration have been summarized in the Table 59.5.

![Figure 59.8](image1)

**Figure 59.8** Videofluoroscopic image of a good tracheo-oesophageal speaker.

**Table 59.5** Selection criteria for secondary voice restoration.

<table>
<thead>
<tr>
<th>Selection criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patient must be motivated</td>
</tr>
<tr>
<td>2. Patient should be mentally stable</td>
</tr>
<tr>
<td>3. Patient must have adequate understanding of post-surgical anatomy and of the tracheo-oesophageal puncture voice prosthesis</td>
</tr>
<tr>
<td>4. Patient should not have an alcohol or other substance dependency</td>
</tr>
<tr>
<td>5. Patient must demonstrate adequate manual dexterity and ability to manage prosthesis</td>
</tr>
<tr>
<td>6. Visual acuity must be sufficient for purposes of managing tracheostoma and prosthesis</td>
</tr>
<tr>
<td>7. Patient should demonstrate positive tonicity results following oesophageal air insufflation test</td>
</tr>
<tr>
<td>8. Patient should not have significant pharyngeal stenosis or stricture</td>
</tr>
<tr>
<td>9. Patient must have adequate pulmonary support for prosthesis use</td>
</tr>
<tr>
<td>10. Patient should have stoma of adequate depth and diameter for prosthesis to avoid airway occlusion</td>
</tr>
<tr>
<td>11. Patient should have an intact tracheo-oesophageal party wall</td>
</tr>
</tbody>
</table>

**PATIENT CRITERIA FOR TRACHEO-oesophageal puncture procedure**

**Surgical technique**

The method described by Singer and Blom in 1980 has provided a reliable technique for restoration of good quality lung-powered speech, but significant problems associated with the rigid endoscopic technique have been described, particularly concerning access down to the stoma level. Similar problems with access using the rigid endoscope prompted the first author to develop an alternative method using a modified pair of curved Lloyd-Davies forceps, which has been used successfully in a series of 94 secondary voice punctures since 1984, with no failed or abandoned procedures.

The forceps are inserted alongside a pharyngeal speculum into the oesophageal opening under direct vision and advanced down to the level of the tracheostome where the tip can be seen and palpated as it tents up the posterior tracheal wall in a similar way to the primary puncture technique.2 An incision is made through the posterior wall of the stoma in the midline on to the tips of the forceps, which are advanced into the trachea. The end of a 14FG catheter is then introduced into the opened tips of the forceps and withdrawn into the pharynx, passed caudally and released. The catheter is sutured to the skin above the tracheostome and, if a Foley catheter is used, the balloon is inflated with 1.5 mL of saline to prevent dislodgement (Figure 59.9).

A normal diet is resumed after the procedure and the stenting catheter remains in place for a period of 2–7 days depending on whether a myotomy has been carried out simultaneously. It is then removed and, after measuring the length of the tract, a suitable Blom-Singer prosthesis is inserted.

**Botulinum toxin injection**

Botulinum toxin is used to provide a chemical neuroectomy and is the treatment of choice for failed tracheo-oesophageal
speech when caused by spasm or hypertonicity. Myotomy is reserved for circumstances where botulinum is ineffective or is required repeatedly (Figure 59.10).33, 34, 35, 36, 37

TYPES OF VOICE PROSTHESES

Two basic types of valve are available from the InHealth Group (High Wycombe, UK): the ‘standard’ valves, including the original ‘duckbill’ valve and the modified ‘low-pressure’ or ‘low-profile’ valves (Figure 59.11).1 The second type is the ‘indwelling’ valve. Each has particular features that may be more appropriate for some patients than others. The ‘duckbill’ valve incorporates a slit aperture over its tip that has a higher airway resistance than the low-pressure valve. The duckbill voice prosthesis is a first-generation device that is economical and durable. Its slit valve design is slightly higher in resistance to airflow through it than the hinged flap valve of the low-pressure style.

The low-pressure style of voice prosthesis is easily and atraumatically inserted using the gel cap insertion system. The 16Fr diameter is routinely used unless a reduction in effort to produce voice is required and can be demonstrated with the larger 20Fr diameter. A simple test for this is to have the user momentarily produce voice through an open puncture. This simulates the effect of a larger opening because there is no prosthesis occupying space. If voice is significantly easier to produce, the larger 20Fr diameter low-pressure prosthesis is indicated.

The indwelling style of low-pressure voice prosthesis has enhanced-retention collar dimensions (i.e. larger and thicker), which secure it without the need for a neck strap and tape. It is ideal for patients who are unable or unwilling to routinely remove, clean and reinsert a regular-style voice prosthesis.

The indwelling voice prosthesis is cleaned in situ without removal and is replaced by a qualified speech-language pathologist or otolaryngologist, usually twice a year. The Provox 2 voice prosthesis is an indwelling style recessed hinged valve supported by a radiopaque, fluoroplastic ring, which is fastened in the shaft of the prosthesis.

Selecting a prosthesis

Careful selection of patients is important for achieving optimal results, but the variety of valves now available has widened the potential population of patients suitable for the prosthesis. Several sizes and styles of tracheo-oesophageal prostheses are available and this issue has been considered in detail below under Troubleshooting tracheo-oesophageal punctures: problems and solution. Selecting a valve should be a conscientious decision and five main issues should be considered:

1. Candidate dexterity. If the patient and his or her spouse appear able and willing to participate in prosthesis management, a valve with no restrictions on placement procedures should be considered. Indwelling devices, although touted for their advanced design, must be inserted by a trained professional. This stipulation creates a situation of patient dependency on the health-care professional. Autonomy offered by devices that can be changed without restriction is appealing to many patients. Conversely, if the patient is unable or unwilling to
change the valve independently, an indwelling style device offers more security from dislodgement.

2. **Phonatory effort.** Before any prosthesis is inserted, phonation should be sampled with a patent puncture tract. The perceptual quality and effort of that sample guides decision-making. For example, if the voice quality is effortless, loud and consistent, then the patient may do well with a higher-resistance device with increased durability. If the voice quality is strained and effortful, a lower-resistance device of greater diameter (20F) may be appropriate. The duckbill valve may be used initially to start prosthetic voice rehabilitation since this is easier to fit and change, as well as being more economical. Once the healing process has stabilized, a more permanent choice of valve can be made. It is also the device of choice for a person who experiences a problem with ‘inhaling’ air through a low-pressure prosthesis during quiet inhalation, resulting in excessive stomach gas.

3. **Thickness of the party wall.** The length of the TO fistula varies from person to person and should be accurately estimated using the measuring device to determine the length of the prosthesis to be used. Every effort must be paid to obtain a snug fit. A too long prosthesis will cause a ‘pistoning effect’ and consequently leakage around the prosthesis, while a too short prosthesis may result in aphonia.

4. **Durability.** Occasionally, the device that provides the least phonatory effort also has a patient-specific tendency to malfunction rapidly. If the device recurrently leaks in less than a couple of months with no treatable cause (e.g. candida infection), a device with higher resistance and durability should be considered.

5. **Cost.** Prices for valves vary widely and cost issues should be considered when devices are comparable in style and performance. Certain health insurance policies do not cover prosthetic supplies. Patients without prosthesis coverage should be provided cost options when selecting a device.

### General steps for fitting a prosthesis

Correct fitting of and appropriate training with the voice prosthesis are critical to success with this method of alaryngeal speech. With both primary and secondary tracheoesophageal voice restoration procedures, the surgeon punctures the tracheoesophageal party wall and places a 16Fr catheter to maintain the hole. About a week after the primary voice restoration procedure, a barium swallow is performed to confirm a patent neopharynx without a leak and the patient can be begun on oral diet. At this time, the catheter is removed and an appropriately sized Blom-Singer voice prosthesis placed. As the amount of neopharyngeal healing necessary to withstand the pressures generated during speech production is greater than that needed for the passage of a good bolus, we generally wait a few more days before voice rehabilitation is begun in non-irradiated patients or about a week in irradiated patients. Following secondary puncture, the prosthesis may be fitted after 2–3 days unless a myotomy has been carried out, in which case fitting is best delayed for a week (**Figures 59.12, 59.13, 59.14, 59.15, 59.16, 59.17 and 59.18**).

The clinician’s task involves removing the catheter, measuring the tracheoesophageal puncture tract length,
determining the type, length and diameter of prosthesis to use, dilating the tract to accept easily either a 16Fr or a 20Fr device, inserting the voice prosthesis, and, finally, confirming safe placement.

A speech–language pathologist is the professional usually responsible for initial and ongoing prosthesis fitting, teaching removal and reinserter, care and maintenance, and tracheo-oesophageal voice restoration rehabilitation. Once the voice prosthesis has been fitted, three equally important tasks must be taught. The first involves facilitating production of the best possible tracheo-oesophageal speech. The second deals with safe and correct voice prosthesis changing, unless an indwelling prosthesis has been selected. The third concerns hygiene of the voice prosthesis and stoma area.

1. Evaluate phonation with a patent puncture tract called ‘open tract’ voice and stoma occlusion to rule out technique/valve problems.
2. Measure the length of the puncture tract.
3. Select and prepare prosthesis.
4. Dilate the puncture tract to slightly wider than the prosthesis.
5. Align the prosthesis with the puncture tract for insertion; alignment is more important than pressure.
6. Ask the patient to drink liquid and watch for any leak through or around the prosthesis.
7. Assess patient phonation with stoma occlusion.

TROUBLESHOOTING TRACHEO-ÖESOPHAGEAL PUNCTURES: PROBLEMS AND SOLUTION

At first glance, the tracheo-oesophageal puncture technique appears to be a straightforward method of alaryngeal voice restoration requiring nothing more than ‘making a hole and sticking in a valve’. However, nothing could be further from the truth, as any experienced clinician can verify. Surgeons and clinicians should recognize that, as with any surgical technique, success is dependent on sufficient knowledge, training and accrued clinical experience. The tracheo-oesophageal puncture technique and the application of its associated prosthetic valves are not always problem free. Although problems and complications occur related to the best efforts for voice restoration for the laryngectomized patient, they are manageable when they are recognized early and a methodical treatment plan is formulated.

Problems related to tracheo-oesophageal punctures and prosthetic devices are mentioned, along with typical causes and corresponding solutions.
Leakage problems

Leakage at the puncture site into the trachea can occur and is usually first noted with fluids, which cause immediate coughing on swallowing. It is important to determine on close examination with good light whether leakage is through or around the valve since the causes and management are quite different.

LEAKAGE THROUGH THE PROSTHESIS

Leakage through the prosthesis may be due to a number of reasons. A faulty or defective valve is usually evident immediately; valve distortion may occur due to excessive compression of the middle part of the prosthesis, for example when the tract has just been dilated up from 16Fr to accommodate a 20Fr valve, which may result in a slightly gaping flap. It is advisable to dilate established tracts slowly by keeping an intermediate-sized catheter in for several hours or preferably overnight before inserting the larger diameter valve. Leakage may also occur if small pieces of debris or undissolved gelatin from the gel cap hold the valve open. The prosthesis should be removed for inspection to make sure it closes completely and then reinserted and checked with a further drink of liquid. Leakage through the prosthesis may be due simply to the natural lifespan of the valve, but this can vary enormously from a few weeks to over a year. Careful cleaning of the delicate valve mechanism either with the prosthesis removed or in situ will prolong its usage. Some patients prefer to remove the prosthesis regularly, perhaps once or twice a week, and replace it with another, alternating the two valves for some considerable time. The spare prosthesis is kept in hydrogen peroxide or other cleaning fluid to prevent accumulation of debris or infecting organisms. Microbial colonization of the prosthesis, predominantly with Candida albicans is the most common cause of leakage through the valve due to distortion of the valve mechanism. Much effort has been devoted to trying to find a prophylactic method of protecting the silicone prosthesis from microbial colonization, but so far without success. Routine use of nystatin suspension (500,000 units twice daily swished around the mouth for 4 minutes) is effective in reducing colonization and almost doubling the lifespan of a valve, but full compliance is often difficult.

Distortion and leakage through the duckbill prosthesis may be due to compression of the protruding valve against the posterior oesophageal wall. This is often relieved by changing to a low profile valve.

LEAKAGE AROUND THE VALVE

A satisfactory seal around the tracheo-oesophageal prosthesis depends on the natural elasticity of the surrounding party wall tissues to provide a ‘snug’ fit around the shaft of the valve. It is also important to have a correct measured length of prosthesis so that the retention collar on the anterior wall of the oesophagus is closely applied to the mucosa to provide a good circumferential seal and to prevent movement or dislodgement. Leakage of liquid around the prosthesis is a difficult problem and may be due to a number of reasons. A prosthesis that is too long acts as a piston and dilates the tracheo-oesophageal tract as the prosthesis moves in and out. It is essential that the length of the tract is correctly measured and the appropriate length prosthesis is selected, particularly during the first six months as the postoperative oedema settles and the thickness of the party wall decreases.

Another important reason is a ‘troubled’ or ‘compromised’ party wall. It is defined as a thin, dilated mobile party wall that is or is in danger of leaking around the prosthesis. This is often seen in cachetic, thin individuals who have received radiotherapy in the past, is less than 6–8 mm in length and wider than 22–24Fr. Attempts at putting in a larger prosthesis may only result in enlargement of the tract and greater leakage. A troubled party wall should be managed with minimal interventional trauma, down-sizing to allow shrinkage and use of a silicon antileakage ring. If this fails, surgical intervention in the form of a submucosal purse-string suture or tissue augmentation with bioplasticque
may be attempted. An effective long-term solution for a chronic thin leaking compromised party wall is closure of the puncture site and reconstruction with a decent layer of muscle, preferably non-irradiated tissue. In some cases, an inferiorly based pedicled sternomastoid muscle flap can be sandwiched between the trachea and the oesophagus using a three-layer closure, with successful repuncture of the tract about three months later. In some instances where there is significant loss of surface mucosa, a pedicled myocutaneous flap may be required to achieve satisfactory closure.

Granulations

Some of the early valves had an inferiorly placed portal that frequently became blocked with granulation tissue and which eventually occluded the valve lumen. This has been resolved by elimination of the inferior opening. Occasionally, granulations arise around the prosthesis on the posterior wall of the trachea due to irritation if the edge of the valve is digging into the mucosa. This may occur if the prosthesis fits too tightly or is positioned at a slight angle. The granulations can be removed easily and cauterized and the position of the valve corrected.

Fibrous ring

When the prosthesis has been used for some period of time, it may gradually become surrounded by an increasingly thick ring of fibrous tissue that forms a 'doughnut' around the tracheal end of the valve. This has the effect of gradually lengthening the tract so that the posterior end of the prosthesis is gradually drawn forwards into the tract. If not recognized, the patient’s voice will slowly deteriorate requiring increasing effort and eventually fail completely as the oesophageal end of the fistula closes off. If the ring is not too prominent, the tract can be resized and a longer valve fitted. Otherwise, excision of the fibrous ring is recommended.

Valve extrusion

The prosthesis may become dislodged during cleaning or coughing, or for other reasons, and if not replaced immediately the tract will close down. A catheter or dilator can be used instead to keep the tract open until the prosthesis can be replaced. Unless the fistula has closed down completely, it is usually possible to dilate it up successfully, and for this purpose a serial set of soft urethral catheters is useful. Alternatively, progressive dilatation of a stenosed puncture tract may be possible with a set of curved metal male urethral dilators, but these should only be used by experienced clinicians. Occasionally, valves may need to be retrieved with bronchoscopy if inhaled.

Aphonia

Aphonia following secondary voice restoration (SVR) using a valve may have a number of reasons. Often this is due to a clogged device either by food debris or undissolved gelatin from the gel cap at the time of insertion. The prosthesis should be removed for inspection to make sure the valve is functional. Another reason could be a duckbill prosthesis that is compressed against the posterior oesophageal wall. This is often relieved by changing to a low profile valve. Other reasons include incomplete insertion that requires resizing and finally repuncture for a puncture closure.

Hypertonicity/spasm

Failure to carry out a myotomy at the time of laryngectomy may lead to voice failure because of hypertonicity or spasm of the pharyngeal constrictors. This can be demonstrated on videofluoroscopy as described earlier in the chapter and corrected with botulinum neurotoxin injection or a long myotomy.

Pseudovallecula

This invariably occurs if the pharynx has been sewn up with a vertical closure at laryngectomy. The anterior pouch at the tongue base and the coronal fibrous web behind it may cause
dysphagia with the patient having to make several swallowing attempts to get food down through the narrowed opening into the hypopharynx. This shows up well on videofluoroscopy. Correction is easily achieved by endoscopic division of the web using a similar technique to excision of the cricopharyngeal bar in the pharyngeal pouch.

**Stenosis**

This may occur if insufficient mucosa/skin has been used for reconstruction of the hypopharynx or at the anastomotic site following total pharyngolaryngectomy. It may also develop slowly after jejunum transposition due to ischaemic contracture if the mesenteric blood supply is compromised. Dilatation may be sufficient if the narrowing is not severe, but reconstruction of the pharynx may be necessary.

**Hypotonic voice**

A reconstructed hypopharynx typically produces a hypotonic voice due to loss or absence of muscular tone, which can be shown on videofluoroscopy. Voice quality may be improved using digital pressure or by wearing an elastic band over the pharynx on the anterior neck. 30, 31, 32

**Excessive flatulence**

Excessive collection of air in the stomach is a disturbing and sometimes painful problem in tracheo-oesophageal voice users and may be due to several different causes. During normal respiration, oesophageal pressure is negative during inspiration; this may cause slight opening of the valve and small amounts of air may be sucked into the oesophagus and swallowed into the stomach. Replacement of the prosthesis with a higher resistance duckbill valve may provide a solution. In a similar way, if the PE segment is hypotonic (Figure 59.23), excessive air ingestion may occur from the mouth during normal inspiration due to the negative oesophageal pressure. In patients with a hypertonic PE segment or stricture, excessive expiratory effort is needed to force air through the vocal tract and some air may be driven in a reverse direction down into the stomach. Problems with tonicity is managed as outlined above under Tonicity.

**Macrostomia**

Occasionally, the tracheostoma opening is too large for the patient to achieve airtight finger or thumb occlusion during speech. Use of a silicone laryngectomy tube may help or the patient may find that a tracheostoma valve housing attached to the peristomal skin will allow better occlusion or preferably use of the hands-free stoma valve. Surgical reduction of the stoma is rarely needed.

**Microstomia**

Until the peristomal scar tissue has stabilized after a few months following laryngectomy, it has a natural tendency to contract and most patients will need to wear a laryngectomy tube or button to prevent stenosis. They may also feel more comfortable and ‘safer’ wearing something, particularly at night. If the stoma size reduces to less than 2 cm, it becomes difficult to manage a prosthesis and under 1 cm breathing becomes difficult. The stoma can usually be dilated with buttons or laryngectomy tubes, but if the stenosis is well established it may be necessary to carry out a stomaplasty. The preferred technique is bilateral Y–V advancements with excision of scar tissue as necessary.

**Excessive stomal mucus**

During the first six months or so following laryngectomy, excessive mucus discharge and coughing can be a problem. Most cases settle with the use of a heat and moisture exchanger system.
HEAT AND MOISTURE EXCHANGE SYSTEMS

Heat and moisture exchange systems (HME systems) have been used for years during anaesthesia and in medical intensive care units (ICU). The working mechanism of a passive heat and moisture exchanger is simple but quite effective. The head and moisture exchanger is placed over the tracheostoma so that all the respired air passed through the device. During expiration, the air passes through the heat and moisture exchanger, where the air loses some of its heat. Because the water vapour content of the air is directly related to the air temperature, water vapour condenses as soon as the temperature and moisture exchanger, which retains water and heat at the same time, is used. The air leaving the heat and moisture exchanger contains less heat and moisture than when no heat and moisture exchange is in use. During inspiration, cool and dry ambient air passes through the heat and moisture exchanger and gains some of the heat and moisture preserved in the device. A heat and moisture exchanger effectively protects the trachea and the lower airway from drying and cooling and considerably reduces the burden of air-conditioning on the lower respiratory tract (Figures 59.24 and 59.25).44, 45, 46, 47, 48

Another function of head and moisture exchangers is the resistance to airflow. Raising airway resistance has a positive effect on tissue oxygen saturation in the laryngectomized patient. Presumably by preventing alveolar collapse, the optimum lung ventilation : perfusion ratio is maintained. The last function of heat and moisture exchanger filters is that they have some particle filtering capability, although the efficiency is not known. Patients should use the HME system for at least two weeks to assess its potential benefit. In addition, all heat and moisture exchanger filters need to be replaced at least every 24 hours. This avoids the risk of heat and moisture preservation decrease, and more importantly, it limits the microbial overgrowth of the filter and the associated risks of airway contamination.

HANDS–FREE TRACHEOSTOMA VALVES

Tracheostoma valves provide two primary functions: hands-free speech and housing for heat and moisture filters. The tracheostoma breathing valve device consists of two parts: an external housing and an adjustable valve. The valve remains open during quiet respiration and automatically closes in response to an increase in expiratory flow to allow speech production (Figures 59.26, 59.27 and 59.28).

There are two types of housing: the first is the standard peristomal housing which is attached to the peristomal skin
with an adhesive disc and a layer of liquid adhesive. The second type of housing is the Barton button, developed by Barton and Associates in 1988, which uses intraluminal rather than peristomal attachment. It is composed of soft, silicone rubber which conforms to the patient’s stoma. An adequate adhesive seal is essential to generate hands-free speech. Without a tight external seal, stomal air escape reduces the amount of airflow available for speech.

CONCLUSION

The great advance of this time is that laryngeal cancer is treatable with voice preservation or restoration, and that patients are no longer condemned to silence while they await the results of their cancer treatments. They can face the challenge of cure of laryngeal cancer with the knowledge that normal quality of life is possible.

Successful voice restoration for alaryngeal speakers can be attained with any of the three speech options. Although, no single method is considered best for every patient, the tracheo-oesophageal puncture has become the preferred method in the past decade. Since the first description of a tracheo-oesophageal voice prosthesis in 1980, many new devices have been developed, and several of the original devices have been modified. In many centres now, voice prostheses have replaced oesophageal speech as the gold standard for voice rehabilitation.

Despite the potential facility of voice production with the tracheo-oesophageal puncture, careful attention must be directed to PE segment integrity, valve selection and troubleshooting. Despite new device designs in recent years, candidal infestation of the prostheses and leakage continues to remain a problem. Successful tracheo-oesophageal voice restoration in laryngectomy patients can be very rewarding, but the cost and other problems associated with maintaining prostheses are often prohibitive, especially in Third World countries.

Finally, remember voice restoration is a process, not a prosthesis!

KEY EVIDENCE

- The advantages of voice prosthesis are numerous and include immediate voice production, relatively low complication rates, reversibility to other forms of rehabilitation and...
Although the last three decades has seen tremendous changes which affect the overall quality of life of the patient, the advantages of surgical voice restoration using voice prosthesis has made this modality the ‘gold standard’ of post-laryngectomy voice rehabilitation.

The last three decades has seen tremendous technical improvements in the valve design, methods of insertion with the introduction of hands-free, low pressure, indwelling and fungal-resistant valves. Despite new device designs in recent years, candidal infestation of the prostheses and leakage continues to remain a problem. Successful tracheo-oesophageal voice restoration in laryngectomy patients can be very rewarding, but the cost and other problems associated with maintaining prostheses can be prohibitive, especially in Third World countries.

Although the end result of acquiring adequate voice rehabilitation is the desired choice, the process of acquiring this requires focused efforts and commitment both from the patient, as well as the clinician.

REFERENCES


DIRECTIONS FOR FUTURE RESEARCH AND DEVELOPMENTS IN HEAD AND NECK CANCER SURGERY
Robotics, laryngeal transplantation, gene therapy, growth factors and facial transplantation

DAVID G GRANT, MICHAEL L HINNI AND MARTIN A BIRCHALL

The future is already here – it’s just not evenly distributed.

William Gibson

INTRODUCTION

Some predictions are better than others (Figure 60.1). We were taught at medical school that ‘half the treatments we employ are useless; it is just that we don’t know which half’. Thus, we entirely expect that much of the vision laid out below will return to haunt us just as much as titles containing ‘modern’, ‘new’ and ‘future’ haunt all authors as the pages yellow with time. Nonetheless, taken with a side portion of healthy scepticism, here is our take on some of the more exciting developments of today and a vision of a possible future for our specialty.

THE FUTURE OF HEAD AND NECK CANCER

Ninety per cent of the head and neck cancer we see and treat today is smoking-related squamous cell disease. Although Sir Richard Doll in Oxford pointed out the clear associations between smoking and cancer in the 1950s,1 governments have only started to embrace the challenge of stopping people smoking in very recent years. World Bank predictions show a depressing picture of escalating tobacco deaths for most of the twenty-first century, due to increased consumption by developing countries and the cohort effect (Figure 60.2).

Meanwhile, life expectancy in Western countries continues to grow (Figure 60.3).2 Since increasing age is the next biggest risk factor for head and neck cancer after smoking, the combined effect is a steady increase in the demand for head and neck cancer treatment for many decades to come. Our generation will not be short of people to treat.

TECHNOLOGY LEADING OR LED?

The past 50 years has seen little change in survival from head and neck cancer: technical changes in reconstruction and rehabilitation have improved the quality of survivorship. The limited, but much vaunted, gains of combined medical therapy have in reality still left ablative surgery at the core of care for over two-thirds of patients.3 Technology, however, is driving change. Like cardiac surgery before us (Figure 60.4), one vision sees head and neck surgery replaced by interventional physicians and technicians and rendered irrelevant by effective molecular therapies. A rump may live on, the slave of technocrats and health ministers.

Alternatively, head and neck surgeons can develop a vision; become the beacon for scientists, physicians and engineers to follow towards a new future, where people who have had head and neck cancer look, talk, eat and drink, and laugh just like everyone else. In this vision, the future head and neck surgeon plays two roles:

1. The pilot of one-stop head and neck offices, where diagnosis, prognosis and treatment selection are all performed in one sitting, using internal and external techniques.
The restorer of normal human interactions, with stem cells, nanotechnology, robotics and transplantation at his or her disposal to restore appearance and function.

Contemplating this vision briefly may allow us to prepare adequately for the future. Whether or not it becomes reality, ploughing the same furrow we have followed for the last 20 years or more might court extinction or relegation. We
propose that head and neck surgeons should engage with the world’s best scientists right now. As the second part of this prescription, we need to embed sufficient scholarship in surgical training to permit the next generation to lead and not be led. Present trends in surgical education should not, therefore, exclude scholarship in the drive to produce pure (and by definition inflexible and soon-to-be-extinct) artisans. In this way, we can future-proof our craft and the central position held by head and neck surgeons in head and neck cancer care for generations to come.

SCHOLARSHIP AND TRAINING

Theodor Billroth (Figure 60.5) had many seminal achievements. His operations, many of them ‘firsts’, such as laryngectomy and gastrectomy, developed in the middle of the nineteenth century are still performed (with modifications) today. Arguably, one of the keys to the longevity of his innovations was the establishment of the world’s first formal surgical training programme. Integral to this programme was scholarship, including research. The drive to streamline surgical training in many countries has tended to lead to a simplified view of what a surgeon is. As surgical curricula developed, it has been difficult to persuade politically driven mandarins to allow time for reflection and research. If we neglect this, however, we will be signing up to a view of surgeons as technicians, taking their place on ‘treatment centre’ assembly lines.

Training in research skills in a world of dizzyingly accelerating technological change can no longer be regarded as optional, however. Only someone who has learnt how to interpret new research (and the best way to learn is by doing) will be able to appraise and assimilate new technologies appropriately and in a timely manner. Furthermore, scientists need people who can place their new work in the context of real human cancer. For all their skills, oncologists do not have the same intimate relationship with and understanding of head and neck cancer and its functional sequelae as head and neck surgeons. Therefore, we need to place future surgeons closer to the science–patient interface than has previously been envisaged.

THE REPLACEMENT OF ABLATIVE SURGERY

We are certainly living in something of an evidence-free zone compared to most other surgical oncology specialties. Randomized controlled trials are very rare indeed, and while there are many barriers and difficulties, oncologists will always hold the whip hand in deciding the direction of services unless surgeons are able to provide level 1 evidence for what they expound. In fact, if we did nothing more than apply all our present knowledge in a thorough, evidence-based way in every country, we would almost certainly make major inroads into morbidity and mortality, even without the development of anything novel.

However, this is to ignore that technology is now the heartbeat of our societies and economies. The company which rests on its laurels and does not embrace technological change rapidly goes out of business. As architects have found,
for example, when building a structure designed to last even 25 years, 'future-proofing' it for all possible technologies that the incumbents may wish to use is already impossible. Once again, the best defence against the future, for the surgeon, as well as the architect, is scholarship, with which comes the flexibility to meet the future head on.

So, let us assume that the promises of gene therapy, antiangiogenesis drugs, immunotherapy and all the other drugs in phase 1 and 2 trials will bear fruit. With injections and tablets, the tumours shrink away before our eyes. What will we be left to do surgically? The answer is reconstruction, regeneration and repair. Even if the magic bullets do not come along, advances in these areas of biomedicine make us beholden to investigate the full potential of their application in postoperative patients. The aim is normal-appearing, normal-talking and normal-swallowing patients throughout.

Here, we present some of the best of today and a little of tomorrow, to set the stage on which our trainees must ultimately walk.

MINIMALLY INVASIVE SURGERY, LASERS AND ROBOTICS

Minimally invasive surgery (MIS) represents an emerging philosophy in head and neck cancer whereby the surgeon gains access to the tumour through the body’s natural oriﬁces, or through small incisions with the assistance of video endoscopy. Indeed, in some cases, the surgeon may no longer directly see or touch the structures that they are operating on. Surgical damage to uninvolved tissues and structures can be avoided as the patient is not disassembled from the outside to gain access to a tumour. Proponents of minimally invasive techniques maintain that patients experience less pain and fewer complications and recover faster, with greater preservation of anatomical and physiological function than compared to open surgery. Numerous authors have described transnasal endoscopic approaches to the anterior cranial base and clivus. Salivary tumours and thyroid cancers are now routinely being removed through incisions as small as 2 cm with the use of specialized instruments and endoscopes.

For head and neck squamous cell carcinomas, MIS has evolved with removal of tumours of the pharynx and larynx through the natural orifice of the mouth using specialized endoscopic instruments, microscopes and lasers leaving wounds to heal by secondary intention. No definitive taxonomy has been decided for such procedures but terms such as natural orifice transluminal endoscopic surgery (NOTES), endoscopic laser surgery (ELS) and transoral laser microsurgery (TLM) have all gained in popularity. Of special mention is TLM. In TLM, the tumour is removed often in a piecemeal fashion, generally using carbon dioxide laser, under an operating microscope (Figure 60.6). This approach, it is argued, permits a more ‘logical’ tumour resection where the tumour is divided and its depth mapped using frozen section. This preserves as much normal tissue as possible and with the smallest volume of normal tissue removed, assures a complete margin in all dimensions. TLM, therefore, has a diagnostic element as it confirms tumour extent and ‘following’ the tumour can prevent undertreatment. Advocates point to the acceptable local control rates when TLM is used and, indeed, there is growing evidence that for select tumours this method is as effective in controlling disease as traditional ablation techniques. It may be that in preserving local microcirculation, TLM can also provide optimal conditions for the effects of adjuvant radiotherapy.

Advantages of MIS and the techniques mentioned above are that patients suffer less morbidity, fewer tracheostomies and reconstructions, shorter hospital stays, and can return to health faster and with improved function compared with traditional surgical and non-surgical techniques. Furthermore, the use of MIS does not preclude any further treatment strategy should the patient experience recurrent or second primary disease. The disadvantages of minimally invasive surgical methods include the abandonment of traditional bias, start-up costs including instrumentation and training, as well as those associated with maintaining both evolving and expensive technologies. Furthermore, there can be technical drawbacks of occasional discomforts associated with limited access and poor line-of-sight visualization.

Lasers

Critical to the development of MIS are new technologies that permit precise tissue instrumentation and visibility through the limiting natural oriﬁces or small incisions. Line-of-sight visibility may at times be impossible, as can be line-of-sight delivery of cutting instruments including lasers. The carbon dioxide laser with its power and absorption characteristics remains the current optimum instrument for use in the aerodigestive tract. The long wavelength (10 600 nm) and physical properties of this laser have, until recently, mandated deploying the beam in a direct path from a mounted mirror manipulator to the end organ. This adds risk to the procedure and limits the workspace of the laser within the patient which can prove particularly problematic as tumour size increases or patient anatomy does not permit line-of-sight delivery. The Omni Guide System (Omni Guide, Cambridge, MA, USA), has been developed to deliver a CO₂ laser via a flexible hollow core fibre. This system allows enhanced delivery of the laser to areas of the head and neck in which the direct visualization required for conventional linear CO₂...
laser systems cannot be acquired. Thus, for the first time, CO\textsubscript{2} energy can be delivered non-line-of-sight and has been surgically used in middle ear surgery, particularly on the stapes footplate, in the nose, sinus and anterior cranial fossa floor, as well as in the upper aerodigestive tract, including the pleural cavity, pleural pharynx, hypopharynx and larynx. This fibre has even been utilized to release gastro-esophageal strictures following minimally invasive bariatric surgery.

Other fibre-based laser technologies are emerging and beginning to find application in the treatment of head and neck cancer. Thulium ion-based continuous wave lasers have similar properties to CO\textsubscript{2} lasers and have demonstrated promise for benign laryngeal and tracheal disease, as well as for cancer. As the wavelength of this laser is only 2013 nm, it can be delivered by a glass fibreoptic fibre, yet retains water as a chromophore. This laser offers smooth vaporization associated with excellent haemostasis similar to that realized with the potassium titanyl phosphate (KTP) laser, but with less risk of deep tissue penetration as it has an absorption length of only 0.180 nm. Arteries 2 mm in size and smaller are reliably sealed with this laser, thus, bleeding during surgery is significantly less than that encountered with CO\textsubscript{2}. In addition, the authors have recently utilized the holmium laser. Similar to the thulium, this fibre-delivered laser energy has excellent tissue interaction properties, less bleeding than CO\textsubscript{2} and less associated margin necrosis than that observed with the thulium-based laser. KTP, Nd YAG and argon may also have utilization in MIS, particularly in treating vascular tumours and malformations. In the future, these wavelengths, as well as other light therapies, will likely become more prevalent in the treatment of both benign and malignant diseases of the head and neck through MIS in both the operating theatre setting, as well as the outpatient setting. As interest, experience and instrumentation for MIS evolve, patients will be able to experience the benefits of MIS for increasingly unfavourable anatomic or tumour characteristics. Furthermore, in conjunction with advances in surgical robotics, the continued progress of light technology will be an integral part of the future ability of minimally invasive surgery.

**Robotics**

Nothing quite seems to capture the imagination more than the possibility of a robot performing surgery on a human being. For many years now, the subject of robotic surgery is one that has fascinated both the public and medical profession alike. Over the last half century, the medical robot has maintained a continuous presence in the literature and media of science fiction writers and perhaps no other aspect of future science receives such enthusiastic prediction than machines taking over the role of doctors.

While the potential benefits of medical robots cannot be denied, what of the wider philosophical questions that arise from the transfer of that most trusted and intimate of relationships from man to machine? Can the surgeon be replaced by a collection of computer chips, sensors and actuators? In this section, we will explore the history and development of contemporary surgical robotics, existing robotic technology, and likely near-term future developments.

Asimov’s three laws of robotics

1. A robot may not injure a human being, or, through inaction, allow a human being to come to harm.
2. A robot must obey the orders given to it by human beings, except where such orders would conflict with the First Law.
3. A robot must protect its own existence, as long as such protection does not conflict with the First or Second Law.

The originator of the term ‘robot’ was Czech painter, poet, and writer Josef Čapek. Josef introduced the term to his brother Karel Čapek, a fellow writer, who used the expression to describe several characters in his stage play ‘R.U.R. (Rossum’s Universal Robots)’ which had its premiere in 1920. Prophetically, the play examines the moral and ethical dilemmas created by the use of ‘artificial people’, called robots, as slave or factory labour. The etymological origins of the word ‘robot’ can be found in the Czech robota meaning ‘compulsory labour’ derived from the Old Church Slavonic rabota or ‘servitude’. More widely known perhaps is the term ‘robotics’ and the famous ‘three laws’ penned by the science-fiction writer Isaac Asimov (Figure 60.7). Despite enthusiasm for the creation of the ‘three laws’, they were in reality a narrative device employed by Asimov in his fiction writing and were never actually meant to function in real life. Apart from the fact that the laws require the robot to have some form of human-like intelligence, which robots still lack, the laws themselves do not actually work very well. Indeed, Asimov repeatedly showed them to be false in his robot novels, showing time and again how these seemingly watertight rules could produce unintended consequences.

While the literary aspects of robotics are easily dealt with, the precise technical definition of what a robot is remains more of a challenge. The International Organization for Standardization (ISO) defines a robot under ISO 8373. A robot is, ‘an automatically controlled, reprogrammable, multipurpose manipulator programmable in three or more axes, which may be either fixed in place or mobile for use in industrial automation applications.’ Some find this definition too simplistic, i.e. a microwave oven could be considered a robot by this standard. Others would say that for a machine to be a robot, it should appear to have intent or agency. ‘Mental’ agency is considered the ability of a robot to make choices, while ‘physical’ agency is a belief that whatever the controlling device of the machine, the robot should possess limbs or limb-like components. In November 2007, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the Minimally Invasive Robotic Association (MIRA) produced a consensus document on robotic surgery. The document examined four areas of robotic surgery: training, clinical applications, risks of surgery/cost–benefit analysis and future research. The authors defined ‘robotic surgery’ as ‘a surgical procedure or technology that
adds a computer technology-enhanced device to the interaction between a surgeon and a patient during a surgical operation and assumes some degree of control heretofore completely reserved for the surgeon.²⁴

The ability of the current generation of surgical robotics is perhaps less alluring than the science fiction. Most readers will now be familiar with the popular da Vinci surgical robotics system (Intuitive Surgical, Sunnyvale, CA, USA). The da Vinci surgical robots are in fact telesurgical instruments and are controlled by a surgeon sitting at a remote console. The surgeon is provided with a stereoscopic visual display that is collocated with control handles that direct movements of the instruments inside the patient’s body (Figure 60.8a). As the surgeon directly controls the motion of instruments in the surgical field, the level of autonomy and mental ‘agency’ in the da Vinci robot is very low. The da Vinci system has been used for a number of types of minimally invasive surgery, including cardiac, abdominal and urology, and, more recently, in head and neck surgery where some authors have reported success in the removal of select tumours through the mouth (Figure 60.8b–d).²⁵, ²⁶, ²⁷ Cadaver experience is also emerging in select centres with the use of robotic transmaxillary approaches to the anterior cranial face.⁵ Proponents of robotic surgery point to minimal invasiveness, decreased pain, faster recovery and lower morbidity when compared to equivalent open surgical procedures. Furthermore, motion scaling increases precision and reduces the larger hand movements required by humans while eliminating tremor. Finally, as one author puts it, the robot ‘suffers no fatigue, does not lose interest or require praise’.²⁸

In contrast to using two hands and perhaps a foot pedal, the robotic surgeon seated at a console with the current S-series da Vinci robot can control four arms. One of these arms holds the three-dimensional video camera, a second when used typically holds a retractor, while the remaining two arms are used to interact with the tissue. These latter two working arms generally include a grasping instrument and a cutting instrument. If a surgeon wishes to change instruments, it is necessary that an assistant remove the robotic arm from the patient or operative field, change the instrument and reinsert it into the surgeon’s line of sight. Seated at the console, the surgeon can then resume the operation with the new or different instrument. The image of the operative field to the surgeon is truly a three-dimensional one. While the surgeon typically controls the working robotic tool on the right of the visual field with the right hand and the tool on the left of the visual field with the left hand, this control can be easily reversed such that the instrument in the surgeon’s right visual field could be controlled by the left hand and vice versa. If one considers that degrees of freedom are measured by the number of joints in the human hand (wrist, metacarpophalangeal and phalangeal), approximately three or four degrees of freedom of motion can be realized. All surgeons have experienced difficulties sewing at one time or another in a cramped operative field. Current robotic tools have a minimum of six degrees of freedom within an inch of the tool’s tip with no radioulnar rotational limitations as

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Figure 60.8 (a) Surgeon console for the da Vinci surgical robot. (b–d) Three robotic arms of the da Vinci are inserted through the patient’s mouth for transoral robotic surgery.
found in the human forearm. These additional degrees of freedom provide vastly superior freedom of movement than that found with traditional open surgery using human hands or laparoscopic instrumentation. While expensive, the enhanced optical visualization with ability to zoom, the enhanced degrees of freedom, the absolute precision with no tremor, and the optical ability to see around corners, afford current robotic surgeons distinct advantages that should not be dismissed out of hand.

The current generation of robots is expensive, bulky and somewhat unwieldy, and may present particular difficulties in the head and neck arena at present. In addition to the current exorbitant expense, some detractors point to the learning curve, the need for better head and neck instrumentations (for example, transoral retractors) and the lack of tactile or haptic feedback from the robot as the system currently exists. While there may be some debate about the place of robotics in the future of head and neck surgery, it is essential that head and neck surgeons be familiar with certain key characteristics and terminology which will be of use in the design and development of the next generation of surgical robots (Table 60.1).

Advancements we can expect to see in robotic surgery in the near future will be in scale and in integration of robotics with fusion of technologies, such as image guidance and computer control. Developments in the area of force feedback will be vital to maintain safety and accuracy as will the development of robotic simulators and patient rehearsal systems. With increasing image and computer control, operators will be able to define ‘no go’ areas or ‘virtual restraints’ which will protect surrounding structures or even facilitate head-up graphic representations. It is already possible for surgeons using a patient’s computed tomography (CT) scans and magnetic resonance imaging (MRI) to practise an operation in advance of the actual one. Such ‘immersion environments’ will represent a total fusion of robotics, imaging and allied technologies, permitting a fully interactive graphic visual and oral environment for the surgeon to work in. Advancements in the technologies of haptics currently permit tools on the International Space Station to sense and detect, and distinguish, different types of metal. Preliminary experiments using sensors to detect on contact benign and malignant diseases are underway and evolutionary intelligence. New evolving robotic technology will bring significant ethical and legal implications for robotic surgeries.

![Table 60.1 Important characteristics of robot design and technology.]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Degrees of freedom</td>
<td>Defines the number of independent motions of which a robot is capable, i.e. the number of ‘knobs’ one can turn to control the tool tip.</td>
</tr>
<tr>
<td>Resolution workspace</td>
<td>The smallest incremental movement the robot can make or measure.</td>
</tr>
<tr>
<td>Inertia</td>
<td>All of the area the end effector can reach, the robots workspace is limited by the length of its links, joint limits and collisions with itself and obstructing anatomy.</td>
</tr>
<tr>
<td>Stiffness</td>
<td>The inertia of a robot is related to its size and material. Higher inertia leads to sluggish movement and a gain in kinetic energy with motion.</td>
</tr>
<tr>
<td>Force dynamic range</td>
<td>The stiffer the robot is and the less spring-like give it has, the easier it will be to maintain control and accuracy.</td>
</tr>
<tr>
<td>Force feedback</td>
<td>The ratio between the highest and lowest forces that the robot can exert is known as the ‘force dynamic range’.</td>
</tr>
<tr>
<td>Bandwidth of motion</td>
<td>Force feedback control allows the operator of a robot to feel the forces that the robot is exerting on its environment. Sometimes referred to as ‘haptics’. As the surgeon’s hand moves quickly, the robot’s bandwith must be higher than the frequency with which the surgeon is moving or it will fall behind the command.</td>
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REPLACEMENT AND REPAIR

Tissue engineering

Regenerative medicine and tissue engineering require two complementary ingredients: cells to replace those lost or damaged, and an ideal milieu in which they can thrive. Great strides are being made in both these areas.

Cells may be obtained as primary cultures from existing, adult, differentiated cells. The big advantage of such an approach over transplantation is that, provided the source of the cells is the recipient patient, there are no questions over rejection and immunosuppression. Primary cells have been used to populate trachea and organ scaffolds as disparate as the bladder and heart. Alternatively, it is possible to use adult mesenchymal stem cells (obtained from bone marrow, fat or other sources) and use culture conditions and growth factors to persuade them to develop into the cell type
required.\textsuperscript{34, 35} Thus, for example, we have taken adult fat-derived stem cells and used them to generate Schwann cells with the aim of supporting cranial nerve regeneration. In practice, bioengineers are already growing up all the requisite building blocks of head and neck organs in most of our major universities: cartilage, nerve, bone, epithelium and even muscle.

Traditional culture methods are two-dimensional. In order to develop new head and neck tissues, differentiating or differentiated cells need to be grown in three-dimensional matrices in order to truly mimic the cell–cell contact and nutrient environments they will encounter when they are implanted. One approach is to use allogeneic, cadaveric human tissues and decellularize them. However, although these form anatomically contoured supports, questions remain over their true allogenicity. Synthetic polymers have been tried.\textsuperscript{36} However, these tend to excite a local immune response, and have high porosity with micrometre-sized fibres, when nanometer dimensions are necessary to truly nest a human cell.\textsuperscript{37} An ideal biological scaffold will be: (1) derived from biological sources; (2) made of basic units which can be ‘designed’ to fit purpose; (3) biodegraded at a controlled rate; (4) non-toxic; (5) supportive of all-round cell–cell interactions; (6) non-inflammatory; (7) cost-effective to produce; (8) transportable; (9) compatible with physiological conditions in man; (10) compatible with other biomaterials. This is a tall order, and one certainly not met by the few matrices presently available,\textsuperscript{38} which are, to be fair, aimed primarily at laboratory work and are really little advance on two-dimensional culture on a simple substrate. However, a number of new approaches have arisen from chemistry with self-assembling peptides at the fore.\textsuperscript{39} These can incorporate the active regions of guidance or growth molecules as well, such as adhesion molecules, to provide a tailored and ‘intelligent’ scaffold for replacement tissue growth.

Tissue engineering, stem cell technology and nanotechnology (see below under Nanotechnology) all offer the possibility of creating ‘off-the-shelf’ tissues and organs. We have already successfully used tissue-engineered patches to reconstruct trachea and bronchi in the clinic,\textsuperscript{40} and have used fat-derived stem cells to generate nerve and Schwann cells for reinnervation, while others have ‘grown’ tissues such as muscle, and ‘organs’ from stem cells.\textsuperscript{41} Combined with implantable, and increasingly small and biocompatible, pacemakers, it is theoretically possible to construct all the component parts of a larynx and make them function as such. However, experience to date with late twentieth century tissue transfer techniques and laryngeal prostheses suggests caution in such predictions.\textsuperscript{42} Success in generating phonation and airway protection usually demands a permanent tracheostomy,\textsuperscript{43} while success in achieving an adequate airway may lead to problems with phonation and aspiration of food.\textsuperscript{44} The human larynx is a unique, three-tiered sphincter supplied by more fine motor control fibres than any other part of the body. It successfully juggles the quite opposing requirements of phonation, deglutition and respiration with ease. Furthermore, it may have an important role in mediating tolerance to inhaled and ingested antigens.\textsuperscript{45} We believe that research into tissue engineering for laryngeal, tracheal and other head and neck organ replacement is absolutely justified.

We believe that tissue engineering techniques will offer a better way for long segment replacement of the tracheal airway than transplantation. Tissue engineering applies the principles of engineering, material science and biology towards the development of biological substitutes that restore, maintain or improve tissue function.\textsuperscript{46} This process of fabricating new, physiologic, functioning tissues may be obtained by (1) guided tissue regeneration with engineered matrices alone, (2) injection of allogenic or xenogenic cells alone or (3) use of cells seeded on or within matrices (cell matrix construct), with the latter two approaches the most common. The use of isolated cell or cell substitutes avoids potential surgical complications and allows cell manipulation before injection, but has the drawback of possible rejection or loss of function.\textsuperscript{41} The use of seeded matrices, the most common method in tissue engineering, is particularly relevant in the present context because these structures are biocompatible, bioabsorbable, non-immunogenic, supportive of cell attachment and growth, and inductive of angiogenesis. They may be created either by isolating the cells from the host’s body with a permeable membrane allowing exchange of nutrients (closed system) or by culturing \textit{in vitro} the isolated cells and seeding them on to a scaffold, either synthetic or natural, that is implanted into the host after a given cultivation time (open system).\textsuperscript{47} Available evidence suggests that single tissue constructs are unlikely to suffice, and that only a composite (mucosa, connective tissue, cartilage) tissue-engineered graft may substitute functionally for the native airway. We are presently working towards this goal.

Transplantation

Laryngotracheal transplantation has been explored experimentally since almost the dawn of organ transplantation itself.\textsuperscript{48, 49} Laryngectomy for irreversible laryngeal disease, usually cancer, is a nineteenth century invention, and leaves recipients with impairment of many of the functions that allow us to interact as human beings. Combined with the recognition that a century of effort has failed to provide autologous or synthetic solutions that can replicate the complex functions of the larynx, the impetus to provide total replacement has been compelling. Despite this need and 40 years of research, however, there has only been one properly documented human total laryngeal transplant.\textsuperscript{50} Replacement of the trachea is theoretically less problematic as it does not perform complex neuromuscular actions, unlike the larynx. Nonetheless, the multiplicity of surgical and prosthetic options, augmented by the promise of tissue engineering as above, makes it unlikely that transplantation has anything to offer for static organs.

The arguments against transplantation are persuasive. They are costly and difficult procedures, with unquantified morbidity and mortality.\textsuperscript{51} They are presently suitable for only a tiny number of patients. As long as we cannot functionally reinnervate, their outcomes will be no better than those having conventional supportive treatments, such as tracheostomy, laser treatment, sleeve resection and reconstruction.\textsuperscript{52} The major target population for transplantation has cancer, and immunosuppression of this group is at best hazardous and at worst unethical.\textsuperscript{53} In due course, scientific advances will cure such cancers anyway, and tissue
engineering and stem cell technology will provide much better forms of reconstruction.\textsuperscript{46} Besides, most people with a laryngectomy have a perfectly acceptable quality of life, so there is no real need for transplantation. These are all cogent arguments which mean that the otolaryngological and thoracic surgical communities are, at best, divided on the future of laryngotraheal transplantation.

There is little doubt that retrieval and implantation of a larynx or trachea represents a major challenge. However, major head and neck cancer operations often take more than 6 hours, and involve a similar number of individual, if different, steps to those required for a transplant, so time alone is not a major consideration. Tracheostomy and gastrostomy are already routine. In our large animal (pig) model, implantation takes a median of 5.5 hours (range, 2.3–9.0).\textsuperscript{24} In the National Health Service (NHS), an all-day head and neck cancer operation, preceded by all the necessary preparation and followed by 3 weeks as an inpatient and associated drug costs currently (2010) comes to around £37 000 (US$40 000: Guy’s Hospital, London tariff). Our estimates suggest an identical figure for laryngeal and tracheal transplantation for the first six months. However, the continuing costs of immunosuppression give an additional monthly cost of between £350 and £500 (US$700–1000) thereafter (extrapolated from human lung transplant modelling).\textsuperscript{55} Our work on tracheal transplantation, also in pigs, suggests a shorter operating time, but similar long-term costs.\textsuperscript{56, 57} We argue that these excess costs, for laryngeal transplantation at least, may not be excessive given the potential returns in quality of life.

A failed historical attempt to graft an unmatched, unvascularized mucosal patch into the skeleton of a larynx from which a cancer had been resected has given rise to much pessimism regarding the potential of airway transplantation.\textsuperscript{51} However, the qualified success of the first complete, revascularized laryngeal transplant has changed the picture considerably. The recipient, whose larynx had been damaged by trauma, has only had two possible acute rejection episodes in the first few months, and subsequently has regained normal swallowing and speech.\textsuperscript{50, 58} On the downside, he retains a tracheostomy and is still on low-dose immunosuppression. Nonetheless, he is essentially well and working as a professional speaker some ten years later (Strome, personal communication). The tolerability of the procedure receives further support from the quality of life rapidly attained by porcine recipients in our own series.

The ideal pool of patients for the first trials would also be those who have irreversible damage due to trauma, as was the case for the 1998 laryngeal transplant. Such patients can generally be managed satisfactorily by conventional techniques,\textsuperscript{52} so the pool of potential recipients for early trials at least is small, perhaps between one and 200 in the United Kingdom. Nonetheless, for the reasons stated above, it is both sensible and ethical to transplant this group before embarking on the major challenge of cancer patients. The argument that was used for the first heart transplants, for example, that there is nothing to lose by trials does not apply to either group as death is far from inevitable, even from advanced laryngeal cancer. The operation is targeted at restoration of quality of life and not quantity.

There are approximately 1000 laryngectomies carried out per annum in the UK for cancer.\textsuperscript{59} While many of these patients have poor performance status and/or are elderly, there is a subpopulation of younger, fitter patients with disease limited within the laryngeal skeleton that would be good potential recipients of a transplant. Immunosuppressed patients are, of course, more likely to develop cancers. However, correcting for premorbid smoking and drinking habits, there is little concrete evidence for an increase in head and neck cancer in transplant recipients.\textsuperscript{53} Furthermore, increasing numbers of liver transplants are being carried out for patients with hepatic cancer, with good overall results. Although some patients might argue otherwise, it is counterintuitive to immunosuppress someone in order to provide a short-term quality of life gain, only for them to die much sooner from recurrent disease. This is not only what happened to the 1969 patient,\textsuperscript{51} but also to the world’s first tongue transplant recipient, who also had advanced squamous cancer, in 2004.\textsuperscript{50} When we asked laryngectomies this very question, they also flagged this as a major concern.\textsuperscript{61}

Part of the problem here lies in our limited understanding of laryngeal and tracheal immunology, although, as with other areas of transplant research, detailed scientific study has led to as many questions as answers to date.\textsuperscript{62} For example, there is an unexplained, but possibly significant, difference in graft dendritic cell responses to transplantation between subsites of the same organ, which may lead to differential rates of rejection (Figure 60.3). The present documented human laryngeal transplant is maintained on tacrolimus, which may raise the potential for recurrence if applied to patients who have had a cancer laryngectomy. A major breakthrough may have been reached, however, by the startling discovery that rapamycin, and its derivative everolimus, is not only an effective immunosuppressant, but also inhibits the growth of squamous cell cancer \textit{in vitro} and in a rat model.\textsuperscript{63} Although the potential effects on wound healing may mitigate against using rapamycin as part of a starting regimen,\textsuperscript{64} its early introduction thereafter is almost certainly indicated. This may bring clinical trials in the main, and increasingly a large, target population much closer than we previously thought.

Almost certainly, however, the key issue in determining the viability of laryngeal transplantation is the establishment of functional reinnervation. It has long been known that direct repair of the recurrent laryngeal (main motor) nerve in man does not lead to functional recovery, but rather to a functionless synkinesis where adductor and abductor nerve fibres do not return to their appropriate target muscles.\textsuperscript{65} This conundrum has led to nerve and muscle transfer techniques, which ‘rob Peter to pay Paul’ with mixed evidence of clinical effectiveness to date.\textsuperscript{66–68} Although improvements are possible with careful selective intralaryngeal reinnervation.\textsuperscript{69} We and others have hypothesized that part of the failure of these techniques lies in the slow rate of progression of reinnervation (1 mm/day), which allows aberrant intralaryngeal sprouting to occur.\textsuperscript{70} Thus, we have applied neurotrophins \textit{in vitro} and in nerve transfer experiments in pigs with the aim of improving the speed and accuracy of reinnervation with encouraging results.\textsuperscript{71} These methods are now undergoing clinical trials in equine patients with recurrent nerve paralysis and favourable outcomes here should pave the way for similar trials in man. Meanwhile, progress is being made in the development of laryngeal pacemakers, triggered to stimulate abductor (opening) muscles on inspiration. Such devices offer the prospect of immediate return of appropriate respiratory function to a transplanted larynx and might be
useful either on a long-term basis, or as a ‘babysitter’, preserving muscle fibre morphology and type-distribution until reinnervation occurs as a result of selective or transfer techniques, with or without neurotrophin support.

As alternatives to transplantation for patients where conventional reconstruction techniques will not suffice, several experimental and clinical lines of research have been evaluated for tracheal replacement: synthetic substitutes, modified to avoid tissue reaction; implantation of nonviable tissues, including fixed trachea; adaptation and transfer of autogenous tissues, with or without scaffolding of foreign materials as patches or tubes; and tissue engineering as above. All but the latter, which is still developing, have ultimately failed to reproduce a predictable or dependable tracheal substitute, the Achilles heels being the unique vascular supply of the cervical and intrathoracic trachea and biological issues.

The five-year survival of patients undergoing laryngectomy is around 40 per cent. Thus, many people live for years without a larynx. Although there is a very active minority who make the most of things and a few who actually return to work thereafter, the impact on quality of life is profound. A functioning larynx is necessary for normal speech, swallowing, lifting, coughing, straining, sniffing, smelling, tasting and even kissing. These are the very functions that allow us to function in human society, and the impact of their loss should not be underestimated. Many patients become reclusive and depressed, despite putting a brave face on when presenting for follow up in clinic.72 The loss of a long segment of trachea is, of course, incompatible with life. Our survey of the views of laryngectomees on the acceptability of laryngeal transplantation demonstrated widespread support for the idea, provided the questions of reinnervation and immunosuppression were satisfactorily addressed.61 Thus, while for some people laryngectomy represents a challenge to be fought and overcome, for many it represents withdrawal from society and most would accept the risks of a transplant if it meant a return to normal functioning and to normal human society.

The arguments against laryngeal transplantation are strong, but may be balanced, individually, by counterarguments. We propose that a twin track of research into airway transplantation, alongside research into tissue-engineering strategies, is essential if we are to be confident that we may ultimately offer functional alternatives to the dehumanizing effects of a mutilating operation (laryngectomy) which has changed little in 150 years.73

Figure 60.9 A double concave hydrocarbon buckycatcher, a crystal structure of molecular tweezers composed of two corannulene pincers clasping a C60 fullerene. (Copyright of M Stone).

Figure 60.10 Self-assembled DNA nanostructures. (a) DNA ‘tile’ structure consisting of four branched junctions oriented at 90° intervals. These tiles serve as the primary ‘building block’ for the assembly of the DNA nanogrids shown in (b). Each tile consists of nine DNA oligonucleotides as shown. (b) An atomic force microscope image of a self-assembled DNA nanogrid. Individual DNA tiles self-assemble into a highly ordered periodic two-dimensional DNA nanogrid. (Copyright Wikimedia (http://upload.wikimedia.org/wikipedia/commons/5/55/DNA_nanostructures.png)).

**NANOTECHNOLOGY**

Another exciting development that promises much for the future is nanotechnology or nanomedicine. The term ‘nanotechnology’, derived from the Greek nanos or ‘dwarf’, generally refers to engineering and manufacturing at the molecular or nanometre length scale. One nanometre (nm) is 1 billionth, or $10^{-9}$ of a metre. To put that scale in context, the comparative size of a nanometre to a metre is the same as that of a marble to the size of the earth. Or put another way, a nanometre is the amount a man’s beard grows in the time it takes him to raise the razor to his face. Nanoscale devices are smaller than human cells (10,000–20,000 nm in diameter) and organelles and similar in size to large biological macromolecules, such as enzymes and receptors. Haemoglobin, for example, is approximately 5 nm in diameter, while the lipid bilayer surrounding cells is 6 nm thick. Nanoscale devices smaller than 50 nm could easily enter most cells, while those
smaller than 20 nm could transit in and out of blood vessels. As a result, nanoscale devices can readily interact with biomolecules on both the cell surface and within the cell, in ways that do not alter the behaviour and biochemical properties of those molecules.

Constructing nanoscale machines involves two main concepts. In the first, called the ‘bottom-up’ approach, materials and devices are built from molecular components which assemble themselves chemically by principles of molecular recognition. A variety of molecular machines have been synthesized in this way, including molecular motors, switches, sensors and tweezers. DNA nanotechnology is an interesting area of current research that uses the bottom-up, self-assembly approach for nanotechnological goals. In DNA nanotechnology, the unique molecular recognition properties of DNA and other nucleic acids is utilized to create self-assembling branched DNA molecules with useful properties. In this application, DNA is used as a structural material rather than as a carrier of biological information to construct three-dimensional structures, such as lattices or tiles.

In the second, ‘top-down’ approach, nano-objects are constructed from larger entities without atomic-level control. These methods create smaller devices by using larger ones to direct their assembly. Microelectromechanical systems (MEMS) is the technology of the very small, and merges at the nanoscale into nanoelectromechanical systems (NEMS) and nanotechnology. NEMS have become practical as they are constructed using modified semiconductor fabrication technologies, normally used to make electronics. These include moulding and plating, wet and dry etching and electro discharge machining, and other technologies capable of manufacturing very small devices. Examples of such nanomachines are shown in Figure 60.11.

In the United States, the current potential applications for molecular and NEMS nanoscale technology are being targeted as an important part of the future portfolio of both the National Institute of Health (NIH) and National Institute of Cancer (NIC). Examples of future nanotechnology include ‘Trojan Horse’ photoactive tumoricidal nanoparticles delivered via monocytes to facilitating cancer therapies in hypoxic areas of tumours. Researchers are also developing nano-devices that can deliver therapeutic doses of radiotherapy within tumours (nanobrachytherapy) with reduced side effects to the surrounding tissues. Gold-coated nanoparticles preferentially accumulate in tumours and research is

Figure 60.11 Nanoelectomechanical systems (NEMS). (a) Spider mite with legs on a mirror drive assembly; (b) a gear chain with a mite approaching; (c) triple-piston microsteam engine. Water inside three compression cylinders is heated by electric current and vaporizes, pushing the piston out. Capillary forces then retract the piston once the current is removed. (Courtesy of Sandia National Laboratories, SUMMIT™ Technologies, www.memes.sandia.gov).
underway using associated or combined laser technology to selectively thermocoagulate malignant tissue. The Apple Corporation recently announced progress on the development of a ‘smart pill’ allowing patients, with the use of their Apple computer, to program the specific timed release of their medication based on their individual needs. In the future, we may possibly see multifunctional nanoscale devices called ‘nanoclinics’ that will have the capability to make in vivo diagnosis with molecular nanosensors, treat tumours with a variety of tumoricidal nanodevices and report back their findings while monitoring response to therapy and recurrence.

**CONCLUSIONS**

It is not possible in a chapter of this size, as the saying goes, to cover the full exciting vista of biotechnology now and in the future. We believe that whether or not complete medical ‘cures’ for squamous cell carcinoma of the head and neck are developed, the head and neck surgeon of the future will have twin roles as ‘pilot’ of high-tech outpatient and operating room procedures, and as restorer of normal structure and function in those marked by disease. Head and neck surgeons must engage with our universities’ top bioscientists to keep treatment of our patients at the forefront of advance. Finally, we must equip our future specialists with the scholarship to walk alongside the scientists and to adapt to whatever future, this or a completely different one, is presented to them.

**KEY LEARNING POINTS**

- Minimally invasive surgery (MIS) represents an emerging philosophy in head and neck cancer. Advantages include less morbidity, fewer tracheostomies and reconstructions, shorter hospital stays and improved function compared with traditional surgical and non-surgical techniques.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)
- In the near future, advancements we can expect to see in robotic surgery will be in scale and in integration of robotics with fusion technologies, such as image guidance and computer control.
- Tissue engineering, stem cell technology and nanotechnology all offer the possibility of creating ‘off-the-shelf’ tissues and organs. We have already successfully used tissue-engineered patches to reconstruct trachea and bronchus in the clinic,\(^6\)\(^7\) and have used fat-derived stem cells to generate nerve and Schwann cells for reinnervation, while others have ‘grown’ tissues such as muscle, and ‘organs’ from stem cells.\(^8\)\(^9\) Tissue engineering will offer a better way for long segment replacement of the tracheal airway than transplantation.

**REFERENCES**

1112 Robotics, laryngeal transplantation, gene therapy, growth factors and facial transplantation

Notes
As the subject of this book is head and neck cancer, general entries under these terms have been kept to a minimum: readers are advised to look under more specific entries. vs. indicates a comparison or differential diagnosis.
To save space in the index, the following abbreviations have been used:
CT – computed tomography
FNAC – fine needle aspiration cytology
MRI – magnetic resonance imaging
PET – positron emission tomography
PORT – postoperative radiotherapy

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