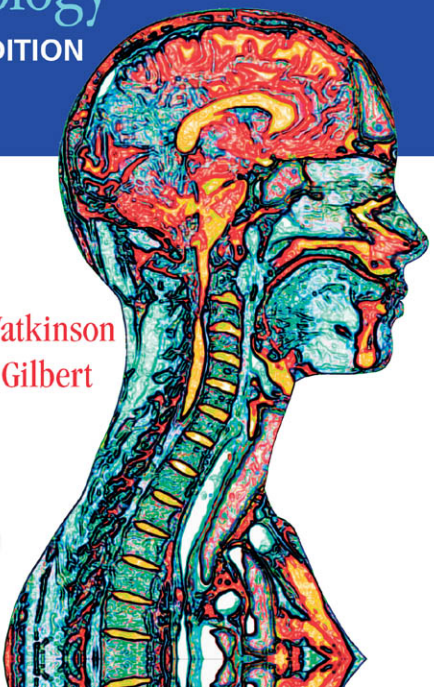
Stell & Maran's Textbook of Head and Neck Surgery and Oncology

FIFTH EDITION

Edited by
John C Watkinson
Ralph W Gilbert



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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)

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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.

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.

Contents

Key to reference annotations

Seminal primary article = ●
Key review paper = ♦
First formal publication of a management guideline = ✻

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Foreword from Arnold Maran

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

Foreword from Janet Wilson

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 where 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 (COMMANDO) 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 shrunk 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

Preface

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

2D	two-dimensional
3D CRT	three-dimensional conformal radiotherapy
3D	three-dimensional
ABG	arterial blood gas
ACC	adenoid cystic carcinoma
ACE	adult comorbidity evaluation
ACTH	adrenocorticotropic hormone
ADC	apparent diffusion coefficient
ADH	alcohol dehydrogenase; antidiuretic hormone
ADMH	autosomal dominant mild hyperparathyroidism
AF	atrial fibrillation
AFAP	attenuated familial adenomatous polyposis
AFTN	autonomously functioning thyroid nodules
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALDH	acetaldehyde dehydrogenase
ALT	anterolateral thigh
APUD	amine precursor and uptake decarboxylase
ARDS	adult respiratory distress syndrome
ARF	acute renal failure
ARSAC	Administration of Radioactive Substances Advisory Committee
ART	antiretroviral therapy
ASA	American Society of Anesthesiologists
ASSIDS	Assessment of Intelligibility of Dysarthric Speech
ATA	American Thyroid Association
ATLS	Advanced Trauma Life Support
ATP	adenosine triphosphate
BAETS	British Association of Endocrine and Thyroid Surgeons
BAHA	bone anchored hearing aid
BAHNO	British Association of Head and Neck Oncologists
BAMMF	buccinator artery myomucosal flap
BCC	basal cell carcinoma
bFGF	basic fibroblast growth factor
BFHH	benign familial hypocalciuric hypercalcaemia
BIPP	bismuth and iodoform paraffin paste
BMI	body-mass index
BMP	bone morphogenic proteins
BRAF	B-Raf
BTA	British Thyroid Association
CADCAM	computer-aided design, computer-aided manufacture
CAP	College of American Pathologists
CBC	complete blood count
CCH	C cell hyperplasia
CCI	Charlson comorbidity index
CCRT	concomitant cheoradiotherapy
CD	Cowden's disease
CDK	cyclin-dependent kinases
CEA	carcinoembryonic antigen
CFD	colour flow Doppler
CFDS	colour flow Doppler Sonography
CGCL	central giant cell lesion
CGRP	calcitonin gene-related peptide
CHEP	cricohyoidoepiglottopexy
CHP	cricohyoidopexy
CJD	Creutzfeldt–Jakob disease
CML	chronic myeloid leukaemia
CN	cranial nerve
CNS	central nervous system
CNS	clinical nurse specialist
COF	conventional ossifying fibroma
COG	Children's Oncology Group
COPD	chronic obstructive pulmonary disease
CRF	corticotrophin-releasing factor
CRH	corticotrophin-releasing hormone
CRP	C-reactive protein
CRT	chemoradiotherapy
CSA	circumflex scapula artery
CSCCHN	cutaneous SCC of the head and neck
CSF	cerebrospinal fluid
CSR	calcium-sensing receptor
CT	calcitonin
CT	computed tomography
CTRT	chemoradiation
CTV	clinical target volume
CUP	carcinoma of unknown primary origin
CV	central venous
CVP	central venous pressure
CXR	chest x-ray
DAHNO	Data for Head and Neck Oncology
DAT	digital audiotape
DCIA	deep circumflex iliac artery
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DLBCL	diffuse large cell B-cell lymphoma
DLT	dose-limiting toxicities
DM	distant metastasis
DMSA	dimercaptosuccinic acid
DNES	diffuse neuroendocrine system
DTC	differentiated thyroid carcinoma
DVH	dose–volume histograms
DVT	deep vein thrombosis
DWI	diffusion-weighted imaging

EA	early intracellular antigen
EAC	external auditory canal
EAM	external auditory meatus
EBRT	external beam radiation therapy
EBSLN	external branch of the superior laryngeal nerve
EBV	Epstein–Barr virus
ECD	extracapsular dissection
ECG	electrocardiogram
ECOG	Eastern Co-operative Oncology Group
ECS	extracapsular spread
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ELS	endoscopic laser surgery
EMA	epithelial membrane antigen
EMG	electromyogram; electromyography
EMI	elective mucosal irradiation
END	elective neck dissection
ENT	ear, nose and throat
ENoG	electroneuronography
EORTC	European Organisation for Research and Treatment of Cancer
EPI	electronic portal imaging
EPSTSSG	European Paediatric Soft Tissue Sarcoma Study Group
ESR	erythrocyte sedimentation rate
ETA	European Thyroid Association
ETE	extrathyroidal extension
EUA	examination under anaesthesia
FACT	Functional Assessment of Cancer Therapy
FAMM	facial artery muscular mucosal
FAP	familial adenomatous polyposis
FBC	full blood count
FD	fibrous dysplasia
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FEES	flexible endoscopic evaluation of swallowing
FEESST	flexible endoscopic evaluation of swallowing with sensory testing
FESS	functional endoscopic sinus surgery
FGF	fibroblast growth factor
FHH	familial hypercalcaemic hypocalciuria; familial hypocalciuric hypercalcaemia
FIHP	familial isolated hyperparathyroidism
FMTC	familial medullary thyroid cancer
FNA	fine needle aspiration
FNAB	fine needle aspiration biopsy
FNAC	fine needle aspirate cytology
FND	functional neck dissection
FSH	follicle-stimulating hormone
fT3	free T3
fT4	free T4
FTC	follicular thyroid carcinoma
FTSG	full-thickness skin grafts
FTT	free tissue transfer
FTUMP	follicular tumour of uncertain malignant potential
FVPTC	follicular variant of papillary thyroid carcinoma
G-CSF	granulocyte colony-stimulating factor
GBR	guided bone regeneration
GCS	Glasgow Coma Score
GCT	giant cell tumour
GDNF	glial cell line-derived neurotrophic factor
GFR	growth factor receptor
GH	growth hormone
GHRH	GH-releasing hormone
GI	gastrointestinal
GORTEC	Groupe d'Oncologie Radiotherapie Tête et Cou
GTV	gross tumour volume
H&E	haematoxylin and eosin
HA	hydroxyapatite
HBO	hyperbaric oxygen
HCTA	helical CT angiography
HDR	high-dose rate
HIF	hypoxia inducible factor
HIV	human immunodeficiency virus
HL	Hodgkin's lymphoma
HLA	human leukocyte antigen
HMWCK	high molecular weight cytokeratins
HNC	head and neck cancer
HNPG	head and neck paragangliomas
HNSCC	head and neck squamous cell carcinoma
HPT-JT	hyperparathyroidism or hereditary hyperparathyroidism with jaw tumours
HPT	hyperparathyroidism
HPV	human papilloma virus
HRQOL	health-related quality of life
HSV	herpes simplex virus
HTA	hyalinizing trabecular adenoma
HTT	hyalinizing trabecular tumours
IAC	internal auditory canal
ICA	internal carotid artery
ICIDH	International Classification of Impairment Disabilities and Handicaps
ICP	intracranial pressure
ICRU	International Commission on Radiation Units and Measurements
ICU	intensive care units
ID	inferior dental
IG	image guidance
IGF	insulin-like growth factors
IGRT	image-guided radiotherapy
IHC	immunohistochemistry
IJV	internal jugular vein
ILN	inferior laryngeal nerve
IM	internal margin
IMAP	internal mammary artery perforator
IMRA	immunoradiometric
IMRT	intensity-modulated radiotherapy

IONM	intraoperative nerve monitoring
IPSS	inferior petrosal sinus sampling
ISH	*in-situ* hybridization
ISO	International Organization for Standardization
ITA	inferior thyroid artery
ITU	intensive treatment unit
JNA	juvenile nasopharyngeal angiofibroma
KD	Kikuchi disease
KFI	Kaplan–Feinstein index
KIN	keratinocyte intraepithelial neoplasia
KS	Kaposi's sarcoma
KSHV	Kaposi sarcoma-associated virus
KTP	potassium titanyl phosphate
KWD	Kawasaki disease
LAT	lateral aberrant thyroid
LDH	lactate dehydrogenase
LDR	low-dose rate
LH	luteinizing hormone
LIN	laryngeal intraepithelial neoplasia
LMWH	low molecular weight heparin
LND	anterolateral neck dissection
LOH	loss of heterozygosity
LRC	locoregional control
LRF	locoregional flaps
LTBR	lateral temporal bone resection
MAB	monoclonal antibodies
MACH-NC	Meta-analysis of Chemotherapy on Head and Neck Cancer
MACS	minimal access cranial suspension
MALT	mucosa-associated lymphoid tissue
MAPK	mitogen activated protein kinase
MARCH	Meta-analysis of Radiotherapy in Carcinomas of the Head and Neck
MCC	Merkel cell carcinoma
MCT	medium chain triglyceride
MDADI	MD Anderson Dysphagia Inventory
MDCT	multirow detector computed tomography
MDT	multidisciplinary team
MDTM	multidisciplinary team meeting
MEMS	microelectromechanical systems
MEN	multiple endocrine neoplasia
MFH	malignant fibrous histiocytoma
MI	myocardial infarction
MIBG	metaiodobenzylguanidine
MIFC	minimally invasive follicular carcinoma
MIP	minimally invasive parathyroidectomy
MIRA	Minimally Invasive Robotic Association
MIS	minimally invasive surgery
MIVAT	minimally invasive video-assisted thyroidectomy
MLC	multileaf collimators
MMM	mucosal malignant melanoma
MMP	matrix metalloproteinases
MND	modified neck dissection
MNG	multinodular goitre
MOFT	multiple oxyphil follicular tumours
MPNT	malignant peripheral nerve sheath tumour
MPT	maximal phonation time
MR	magnetic resonance
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRND	modified radical neck dissection
MRSA	methicillin resistant *Staphylococcus aureus*
MSI	microsatellite instability
MSK	Memorial Sloan Kettering
MSLT	Melanoma Sentinel Lymph Trial
MST	maximum stimulation test
MTC	medullary thyroid carcinoma
MVD	mean vessel density
NCASP	National Clinical Audit Support Programme
NCDB	National Cancer Database
NCDS	National Cancer Dataset
NEC	neuroendocrine carcinoma
NEMS	nanoelectromechanical systems
NET	nerve excitability test
NET	neuroendocrine tumour
NF1	neurofibromatosis 1
NFA	non-functioning adenoma
NG	nasogastric
NGF	neural growth factor
NHL	non-Hodgkin lymphomas
NHS	National Health Service
NIC	National Institute of Cancer
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes for Health
NMSC	melanoma and non-melanoma skin cancer
NOS	not otherwise specified
NOTES	natural orifice transluminal endoscopic surgery
NPC	nasopharyngeal carcinoma
NSHPT	neonatal severe HPT
NTM	non-tuberculous atypical mycobacterial adenitis
NTTBR	near total temporal bone excision
OAR	organs at risk
OD	osseous dysplasias
OGTT	oral glucose tolerance test
OIN	oral intraepithelial neoplasia
ONB	olfactory neuroblastoma
OPG	orthopantomogram
OPSCC	oropharyngeal squamous cell carcinoma
OPSE	oropharyngeal swallow efficiency
ORF	open reading frames
OTT	overall treatment time
PAS	periodic acid Schiff
PC	parathyroid carcinoma
PCNSL	primary central nervous system lymphoma
PCR	polymerase chain reaction
PDGF	platelet-derived growth factor

PDTC	poorly differentiated thyroid carcinoma
PE	pharyngo-oesophageal
PE	pulmonary embolism
PEEP	positive end expiratory pressure
PEG	percutaneous endoscopic gastroscopy
PET	positron emission tomography
PF	cisplatin, 5-fluorouracil
PGL	persistent generalized lymphadenopathy
PHTS	PTEN hamartoma tumour syndrome
PIF	palatal island flap
PIF	prolactin inhibitory factor
PIN	penile intraepithelial neoplasia
PL	partial laryngectomy
PLAT	paraganglioma-like adenoma of the thyroid
PLND	posterolateral neck dissection
PORT	postoperative radiotherapy
PPAR	peroxisome proliferation activated receptor
PSSHN	Performance Status Scale for Head and Neck
pT	primary tumour
PTAH	phosphotungstic acid haematoxylin
PTC	papillary thyroid carcinoma
PTFE	polytetrafluoroethylene
PTG	parathyroid glands
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
PTU	propylthiouracil
PTV	planning target volume
PVC	polyvinylchloride
QoL	quality of life
QRT-PCR	quantitative reverse transcriptase-polymerase chain reaction
RAI	radioactive iodine
RFLP	restriction fragment length polymorphism
rhTSH	recombinant human TSH
RIS	radiation-induced sarcoma
RLN	recurrent laryngeal nerve
RLNP	recurrent laryngeal nerve palsy
RND	radical neck dissection
RP	rapid prototyping
RT-PCR	reverse transcription-polymerase chain reaction
RT	radiation therapy; radiotherapy
Rb	retinoblastoma
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
SALT	speech and language therapist
SAN	spinal accessory nerve
SCC	squamous cell carcinoma
SCCHN	squamous cell cancer of the head and neck
SCM	sternocleidomastoid muscle
SCN	solid cell nests
SCPL	supracricoid partial laryngectomy
SEER	Surveillance Epidemiology and End Results
sEMG	surface electromyography
SI	signal intensity
SIADH	syndrome of inappropriate ADH secretion
SIGN	Scottish Intercollegiate Guidelines Network
SIN	squamous intraepithelial neoplasia
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SLN	superior laryngeal nerve
SLT	speech and language therapist
SM	set-up margin
SMA	smooth muscle actin
SMAS	superficial musculoaponeurotic system
SNB	sentinel node biopsy
SND	selective neck dissection
SNUC	sinonasal undifferentiated carcinoma
SOFT	solitary oxyphil follicular tumour
SOHND	supraomohyoid neck dissection
SPA	salivary pleomorphic adenoma
SPECT	single photon emission computed tomography
SPIO	superparamagnetic iron oxide
SSND	superselective neck dissection
SSRI	selective serotonin reuptake inhibitors
STIR	short tau inversion recovery
STS	soft tissue sarcomas
STSG	split-thickness skin grafts
SUS	Secondary Uses Services
SVR	secondary voice restoration
TB	tuberculosis
TCP	tricalcium phosphate
TDAA	thoracodorsal angular artery
TEP	tracheoesophageal
TFT	thyroid function tests
TG	thyroglobulin
TGFα	transforming growth factor-alpha
TGF-β	transforming growth factor-beta
THORP	titanium hollow osseointegrated reconstruction plate
THW	thyroid hormone withdrawal
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
TLM	transoral laser microsurgery
TMJ	temporomandibular joint
TND	therapeutic node dissection
TNF	tumour necrosis factor
TNM	tumour, node, metastasis
TO	tracheo-oesophageal
TOM	therapy outcome measure
TORS	transoral robotic surgery
TPF	docetaxel, cisplatin, 5-fluorouracil
TPF	temporoparietal fascia
TPN	total parenteral nutrition
TPO	thyroid peroxidase
TR	thyroid hormone receptor
TRH	thyrotropin releasing hormone
TSG	tumour suppressor genes
TSH	thyroid-stimulating hormone
TTF-1	thyroid transcription factor-1
Tg	thyroglobulin

UADT	upper aerodigestive tract
UCNT	undifferentiated carcinoma of nasopharyngeal type
UICC	Union Internationale Contre le Cancer
URLNP	unilateral RLNP
US	ultrasound
USPIO	ultrasmall superparamagnetic iron oxide
USS	ultrasound scanning
UV	ultraviolet
UW-QoL	University of Washington Quality of Life
VA	Veterans Affairs
VAPP	Voice Activity and Participation Profile
VCA	viral capsid antigen
VEGF	vascular endothelial growth factor
VFSS	video fluoroscopy swallowing study
VHI	Voice Handicap Index
VPQ	Voice Performance Questionnaire
VoiSS	Voice Symptom Scale
WBC	white blood cell
WBS	whole body scan
WHO	World Health Organization
WIFC	widely invasive follicular carcinoma
XIAP	X-linked inhibitor of apoptosis protein
ZES	Zollinger Ellison syndrome

1

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, 551–478BC

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 3000BC, 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 Samhita* (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 600BCE to 1000AD. 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.[3] 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.[4]

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[5] 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 laryngofissure approach to remove laryngeal tumours in 1851. The famous Viennese surgeon, Theodore Bilroth, introduced techniques of bilateral mandibular ostetomy 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.[6] In 1885, Henry Butlin published his work on diseases of the tongue.[7] 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.[8] 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 Soerensen arguably became the foundation of modern laryngopharyngeal ablative and reconstructive surgery.[9]

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.[10]

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.[11] 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.[12]

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.[13] In 1952, Conley and Pack extended concepts of vascular surgery to neck tumours, describing approaches to vascular tumours and malignancy involving the carotid.[14]

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.[15, 16] 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] Medina[19] 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. Jako 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 Steiner[20] 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, Stammberger[21] 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 Snyderman[22] 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 States[23] 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 McGregor[24] 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 Ariyan[26] 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 1983[28] and popularized for oral cavity and oromandibular reconstruction by Soutar; the free fibular transfer originally described by Taylor in 1977[29] and popularized by Hidalgo and Rekow for mandibular reconstruction in 1995;[30] and the anterolateral thigh flap described by Song *et al.* in 1984[31] 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.[33]

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 advances, as did Sir Thomas Dunhill in Australia who pioneered 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.[34]

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 proteinomic 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.

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PART ONE

INTRODUCTION TO HEAD AND NECK SURGERY

Section editor: René Leemans

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2

Epidemiology and prevention of head and neck cancer

IAN GANLY AND SNEHAL G PATEL

> 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.

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

	Estimated cases			Estimated deaths		
	Both sexes	Male	Female	Both sexes	Male	Female
Oral cavity/oropharynx	34 360	24 180	10 180	7550	5180	2370
Tongue	9800	6930	2870	1830	1180	650
Mouth	10 660	6480	4180	1860	1110	750
Other oral cavity	2100	1460	640	1680	1270	410
Oropharynx	11 800	9310	2490	2180	1620	560
Larynx	11 300	8960	2340	3660	2900	760
Thyroid	33 550	8070	25480	1530	650	880

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 7690 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 cancers 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, 9310 male and 2490 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, slated 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 premaligant lesion oral submucus 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

retained in the inferior gingivobuccal sulcus and leads to cancer in this site.[26] Toombak, the form used in the Sudan, has been extensively studied. It contains very high levels of nitrosamines.[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.[28] A study from Memorial Sloan Kettering Cancer Center reported an overall risk of 2.6 compared to non-users.[29]

Alcohol

Alcohol is believed to act in a synergistic fashion with tobacco in the aetiology of oral and oropharyngeal cancer.[30, 31, 32] However, some case–control and cohort studies have shown an increased risk of cancer even in non-smokers.[33] Over the past few decades, alcohol consumption has been steadily increasing and this matches the increase in oral cancer mortality.[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.[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.[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.[36] Painful or loose fitting dentures have also been associated with oral and oropharyngeal cancer.[37, 38] This may also be due to chronic inflammation. There is some evidence suggesting mouthwashes containing alcohol may also be important,[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,[40] as well as pharyngeal and laryngeal cancer.[41] Occupations involving exposure to organic chemicals and coal products are also at increased risk.[41]

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.[13, 42] In particular, between 30 and 100 per cent of verrucous carcinomas have HPV.[43] The proportion of cancers with HPV varies with site with a strong association with tonsil cancer.[44, 45] Steinberg[43] 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.[46] High risk types are associated with premalignant lesions and squamous cell carcinoma and include HPV 16, 18, 31, 33, 35, 39.[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.[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.[50] This allows uncontrolled cell proliferation which can result in genomic instability and cellular transformation.[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 tonsillar carcinoma.[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.[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.[53] 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.[54] 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.[55] 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.[56, 57] La Vecchia *et al.*[58] 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.[59, 60]

Inflammatory

Gastro-oesophageal reflux disease

Reflux has been documented in 36–54 per cent of patients,[61, 62] 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.[63] 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.[64, 65, 66, 67] There is a genetic susceptibility in the capacity to metabolize carcinogens and repair consequent DNA damage. This involves polymorphisms in *GST* genes,[68, 69, 70] *CYP* genes[71, 72] and the cytochrome P450 system.[73]

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.[74]

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 radiation 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.[75]

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 'precancerous'. This is referred to as 'field cancerization'.[76, 77] 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.[78] 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.[79] Clinical trials using gene therapy and vaccine therapy are also underway.[80, 81]

Cancer of the larynx and hypopharynx

EPIDEMIOLOGY

The American Cancer Society estimated that 11 300 new cases of laryngeal cancer (8960 in men and 2340 in women) would be diagnosed, and 3660 people (2900 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 supraglottic 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.[82] 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.[83] 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[84, 85] with 50:1 in France.[86] Postcricoid lesions show a female preponderance 1.5:1.[87, 88, 89]

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.[90] Environmental tobacco smoke also increases the risk of laryngeal cancer.[91]

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.[92, 93, 94] 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.[95] 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.[96, 97]

Occupational factors

Laryngeal cancer is associated with nickel and mustard gas exposure.[98] There may also be association with asbestos exposure.[99, 100] Machinists and car mechanics are at increased risk.[101, 102] Long-term exposure to sulphuric and hydrochloric acid in battery plant workers have increased risk.[103]

Radiation

Postcricoid carcinoma is associated with previous radiation[87, 104] and sideropenic dysphagia.[87, 88, 89] 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.[105]

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.[106, 107]

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. Ho[116] has reported accumulation of carcinogenic nitrosamines in salted fish. In southeast China, the rate of this cancer is dropping as people begin eating a more 'western' diet.

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.[117]

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)[118] 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.[119, 120]

AETIOLOGY

Diet low in iodine

Thyroid cancer is more common in areas of the world where diets are low in iodine.[121]

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.[122] 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.[123, 124, 125]

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 syndrome type A (MEN-2A) associated with parathyroid disease and 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.[126, 127] Patients can now be stratified into

high-, intermediate- and low-risk groups according to the type of RET mutation.[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.[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.[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.[130] Industrial exposure to radioactive substances and also accidental exposure from atomic bomb blasts also increase the risk of salivary gland cancer.[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.[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.[132] Female patients with salivary gland tumours are also 0.5 times more likely to develop breast cancer.[133] Diets low in vegetables and high in animal fat may also be an important factor.[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)[135] and those arising from bone (osteosarcoma).[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.[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[137] 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.[138]

Other factors

Patients with chronic lymphoedema have an increased incidence of soft tissue sarcoma formation.[139] Patients with Paget's disease of bone, particularly the skull, are predisposed to osteogenic sarcoma.[140, 141]

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 postcricoid 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 Kaposi's sarcoma.
- Genetic predisposition in neurofibromatosis includes Li–Fraumeni syndrome and Gardner's syndrome.

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3

Molecular biology as applied to head and neck oncology

VOLKERT B WREESMANN AND BHUVANESH SINGH

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

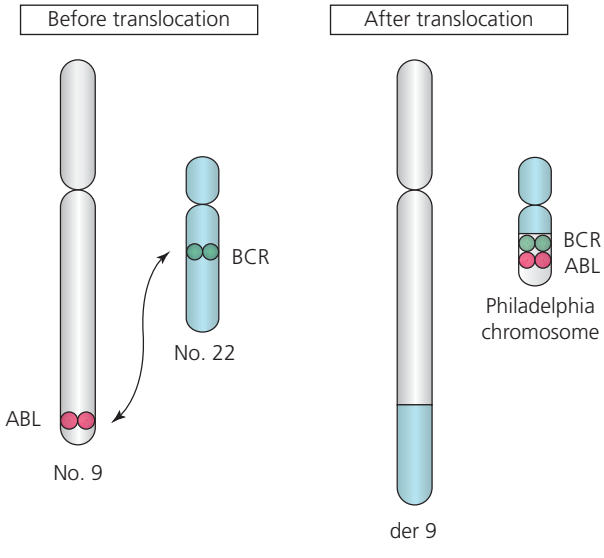

Figure 3.1 Creation of the Philadelphia chromosome through reciprocal exchange of genetic material between chromosomes 9 and 22. Fusion of the c-Abl-containing region of distal chromosome 9 to the BCR-containing region of chromosome 22 results in formation of a chimeric oncogene that causes chronic myeloid 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.[4] 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.[5] 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, asz-arenes (dibenz[*a*,*h*]acridine and 7H-dibenzo[*c*,*g*]carbazole), *N*-nitrosamines (*N*-nitrosodiethylamine), 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.[6]

Chronic alcohol exposure results in increased cancer incidence in animal models, confirming its carcinogenic role.[7] 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.[8] 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.[9] 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).[10] 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.[11] In addition, immunosuppression has been suggested to increase the risk for infection and development of HPV-related HNSCC.[12]

INHERITED SUSCEPTIBILITY TO HNSCC

Susceptibility to the carcinogenic effects of tobacco, alcohol and HPV varies widely between individuals, and is dependent on hereditary factors.[13] 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.[14, 15] Several studies and meta-analyses suggest that

Table 3.1 Genetic cancer syndromes associated with HNSCC.

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

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).[16] 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.[17, 18] 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.[19] 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.[18, 20, 21, 22, 23, 24] 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 (**Table 3.1**). 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).[18] 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**).[25]

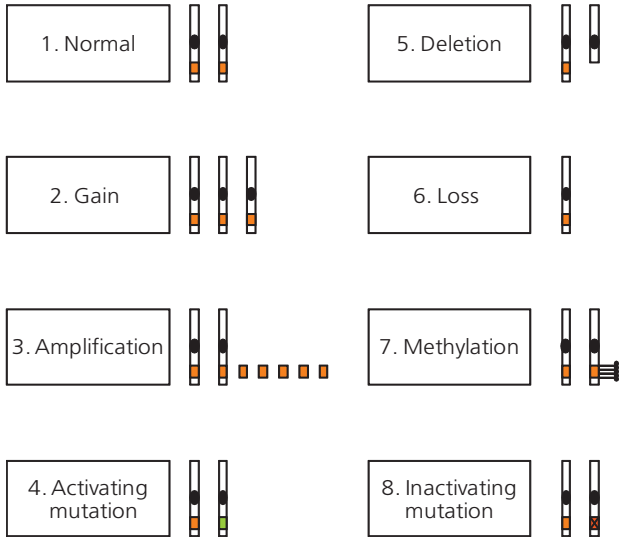

Figure 3.2 Normal pair of (paternally and maternally derived) chromosomes with centromere represented by black dot and both alleles of target gene sequence represented by orange regions (1), and most common genetic alterations that affect the gene sequence to activate it (in the case of the oncogene, 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 promotor 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 $p14^{arf}$. 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

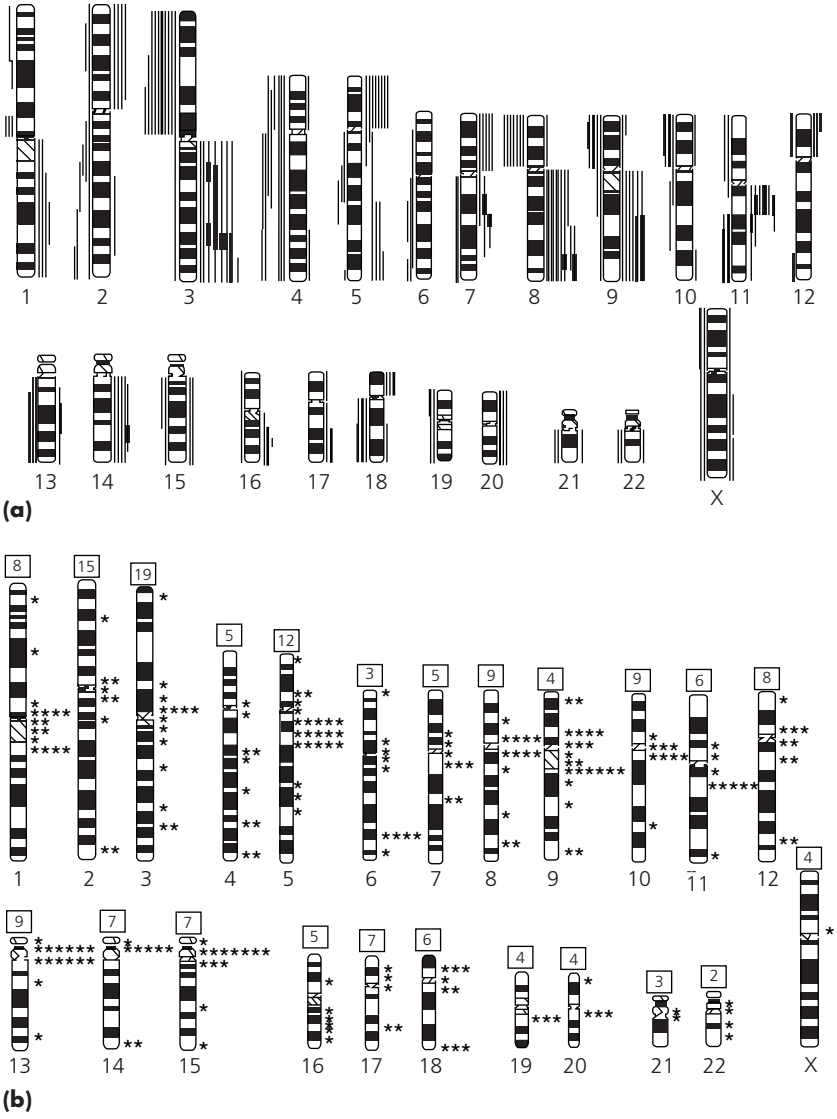

Figure 3.3 (a) Ideogram showing common chromosomal alterations identified by comparative genomic hybridization (CGH) in HNSCC. Each vertical line on either side of the ideogram represents an aberration detected in a single tumour. Thin vertical lines indicate losses (left) and gains (right) of the chromosomal 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.

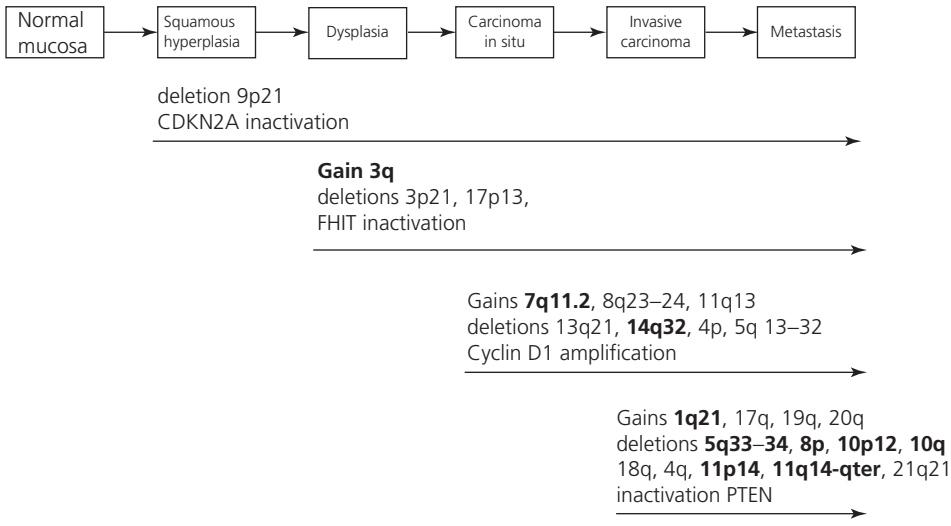

Figure 3.4 Tumour progression model for HNSCC, showing that histologic progression from normal mucosa to invasive carcinoma and ultimately metastasis is associated with a stepwise accumulation of specific genetic alterations (genetic alterations associated with metastatic progression are highlighted in bold).

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.[31] 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.[32] The p53 pathway is activated by cellular stress resulting in either cell cycle arrest to allow repair or apoptosis in case of severe event. 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 $p14^{ARF}$ 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.[33] Detrimental alterations in components of the Rb pathway are required for cancer development, as shown from their ubiquitous presence in human cancer, including HNSCC.[5, 34] 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. In addition, the pRB protein is sequestered and tagged for degradation by the E7 protein in HPV-infected tumours. HPV positivity and intrinsic p16 silencing are mutually exclusive events, suggesting that they are functionally redundant. Activation of cyclin D1, a proto-oncogene that

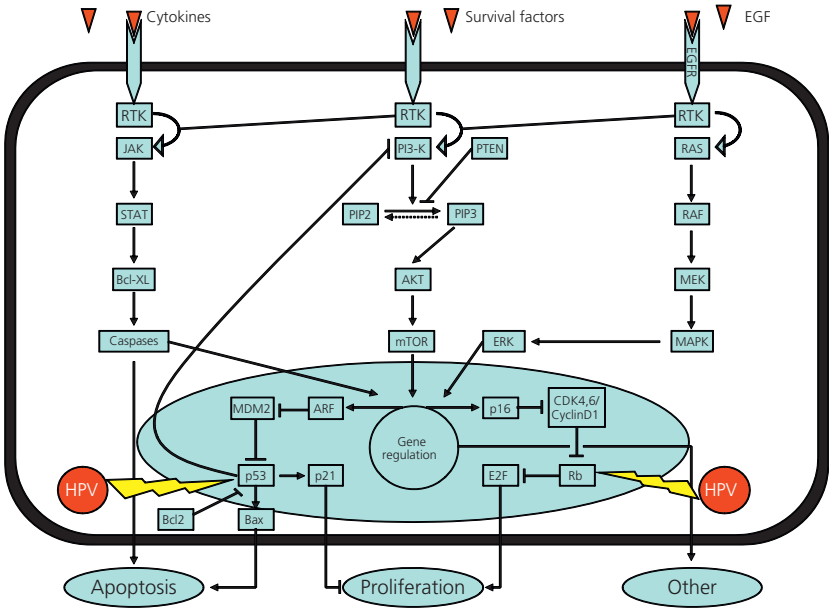

Figure 3.5 Simplification of most common signalling pathways affected in HNSCC. Activational relationships between sequential factors are represented by arrows, whereas inhibition is represented by barred lines. Transmembrane receptor tyrosine kinase (*RTK*) receptors including *EGFR* and several other unidentified receptors are activated by various extracellular ligands (represented by red triangles) and activate cytoplasmic protein cascades, such as RAS-MAPK pathway, PI3-kinase/AKT pathway and JAK-STAT pathway, ultimately resulting in modulation of the intranuclear gene regulation machinery. As a result, the activity of the two most important intranuclear signalling pathways including the p53 pathway and the Rb pathway is modulated, resulting in a shifted balance between cell death (apoptosis) and cell survival (proliferation) signals. In addition, altered gene regulation results in modulation of several other cellular properties including induction of angiogenesis, invasion and metastasis. Human papilloma virus (HPV) is typically present in cytoplasmic vesicles (episomes) and degrades p53 and Rb proteins with the use of its E6 (p53) and E7 (Rb) proteins.

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] ERBb 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.[36]

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 disputed 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 superfamily. 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

aspirates and associated reduction of survival.[50] Also, Califano and colleagues[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.[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.[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.[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.[59] These studies confirm *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.[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.[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.[62]

Human papillomavirus is well known to compromise p53 and Rb pathways (see above under The retinoblastoma pathway) in oropharyngeal cancers is one of the strongest outcome predictors. Overall, HPV-positive tumours have improved outcomes relative to HPV-negative cases.[63] The prognostic value of HPV positivity is well defined in oropharyngeal carcinoma patients treated with chemoradiotherapy.[64] Studies from Worden *et al.*[65] and Kumar *et al.*[66] strongly suggest that oropharyngeal carcinoma patients treated with chemoradiation should be stratified for HPV status in clinical management and trials. Recent work indicates that the genetic composition of HPV-positive and HPV-negative cancers may be different, suggesting putative molecular markers that may be of predictive value.[67] Kumar and colleagues[66] report an association between *p16* and HPV status, suggesting that *p16* may serve as a surrogate marker for HPV infection. Recent work suggests that combining the EGFR expression status with HPV status may improve prognostic analysis of chemoradiotherapy treatment.[68, 69]

Alterations in EGFR and several of its downstream effectors have been associated with prognostic significance in multivariate analyses.[34] These studies suggest that constitutive activity of the EGFR pathway results in aggressive tumour behaviour. Multiple studies have reported EGFR overexpression as an independent predictor of poor outcome after surgery ± radiation therapy.[70] Also, EGFR overexpression is associated with chemotherapy and chemoradiation resistance.[70] These findings are in line with the observed modulation of chemotherapy and radiation therapy resistance of other human tumours by ErbB receptors.[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.[71] Also, overexpression of AKT provides an independent survival benefit in patients with HNSCC.[72, 73] A prognostic role for other EGFR-induced survival factors, such as the STATs, the PLC/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.[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.[40]

Table 3.2 Clinical relevance of molecular factors in HNSCC.

Molecular alteration	Prognostic significance	Therapeutic agents
P53 pathway	P53	ONYX-15, adP53
Rb pathway	Cyclin D1	In progress
EGFR pathway	EGFR	Cetuximab, panitumumab gefitinib, erlotinib
PI3K/AKT pathway	PI3 K, AKT	Everolimus, temsirolimus
Human papilloma virus	HPV	Vaccination, immunotherapy
Angiogenesis	VEGF	Bevacizumab
DNA repair	Unclear	PARP inhibitors

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.[74] 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.[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.[76, 77] The molecular signature was an independent predictor of disease outcome in 295 patients and has been validated in several independent patient groups.[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).[79, 80] Pramana and colleagues[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.[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.[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 prognostic 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.

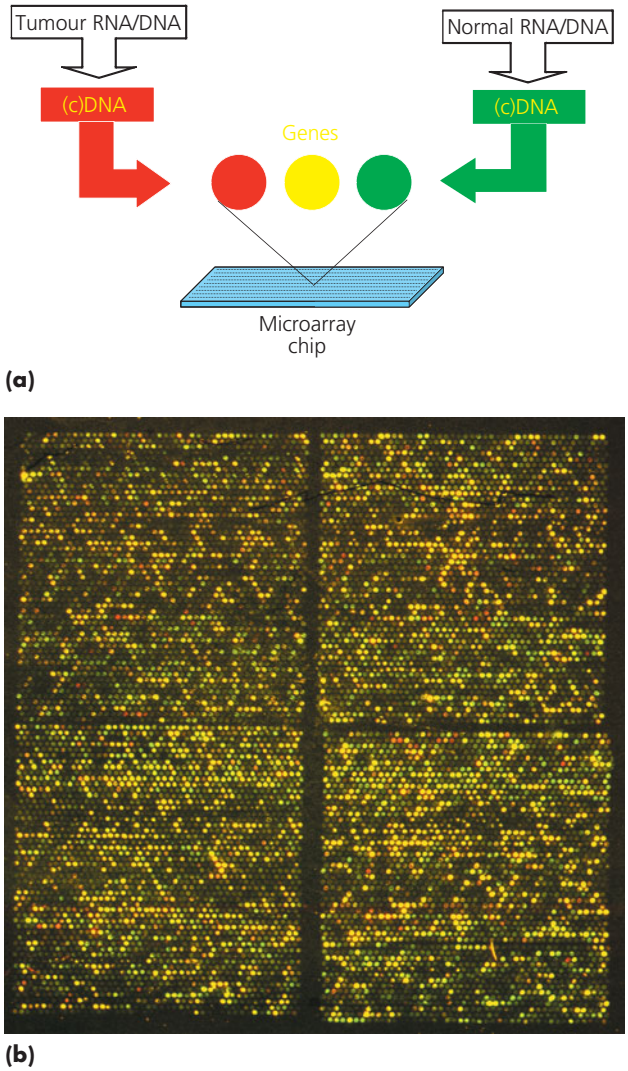

Figure 3.6 (a) Schematic description of microarray analysis. Tumour and normal reference RNA (or DNA) is reversely transcribed into complementary DNA (cDNA) (or directly used in case of DNA) and differentially labelled with a red fluorescent and green fluorescent agent, respectively. Equal amounts of labelled tumour and reference DNA are hybridized onto chips dotted with several thousands of individual gene sequences. With the use of a computer-assisted microscope and spectral analysis, the green-to-red colour ratio for each dot (gene) is calculated, the intensity of which represents overrepresentation (red-to-green ratio >1), underrepresentation (red-to-green ratio <1) or equal representation (red-to-green ratio $=1$) of the sequence in tumour tissue relative to the normal reference tissue. (b) Image of dotted microarray chip after hybridization, showing clear variations of green-to-red ratio (= gene expression level or DNA copy number) between dots.

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 chemotherapy 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] ONYX-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 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.[1, 2, 3, 4, 25, 26, 27, 86]
- 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]

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 in individual cells.
- Critical molecular alterations for cancer development typically activate genes that promote oncogenesis (proto-oncogens) or inactivate genes that limit oncogenesis.

- 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 anaemia, 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.

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4

Assessment and staging

NICK ROLAND

Measure twice, cut once.

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.

Grade	Description
0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90–100)
1	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)
2	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)
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30–40)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair (Karnofsky 10–20)

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) scheme[1] 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 posssible 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)[3, 4] 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**).[4] 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

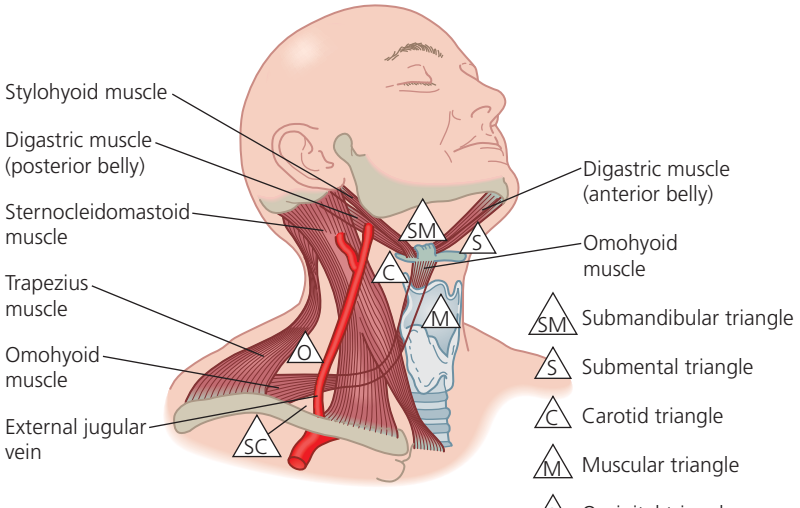

Figure 4.1 The triangles of the neck.

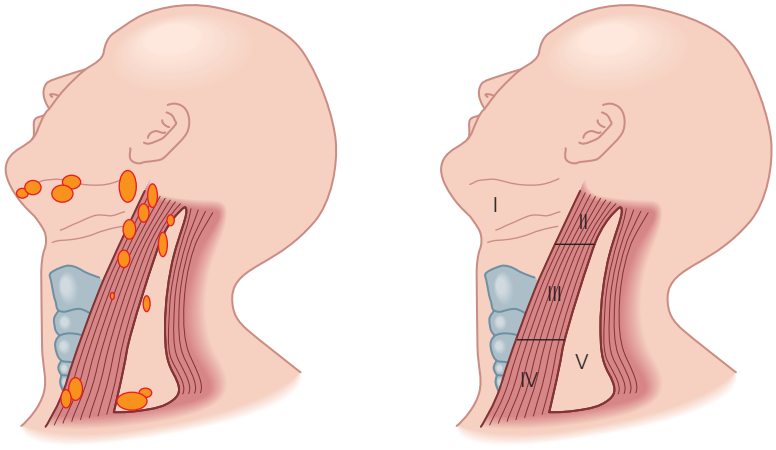

Figure 4.2 Lymph node levels.

Table 4.2 Lymph node levels.

Level	Nomenclature of anatomical site of lymph node
I	Contains the submental and submandibular triangles bounded by the posterior belly of the digastric muscle, the hyoid bone inferiorly and the body of the mandible superiorly
II	Contains the upper jugular lymph nodes and extends from the level of the hyoid bone inferiorly to the skull base superiorly
III	Contains the middle jugular lymph nodes from the hyoid bone superiorly to the cricothyroid membrane inferiorly
IV	Contains the lower jugular lymph nodes from the cricothyroid membrane superiorly to the clavicle inferiorly
V	Contains the posterior triangle lymph nodes bounded by the anterior border of the trapezius posteriorly, the posterior border of the sternocleidomastoid muscle anteriorly and the clavicle inferiorly
VI	Contains the anterior compartment lymph nodes from the hyoid bone superiorly to the suprasternal notch inferiorly. On each side, the medial border of the carotid sheath forms the lateral border
VII	Contains the lymph nodes inferior to the suprasternal notch in the upper mediastinum

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 C_1 and C_2 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 CYTOLOGY

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

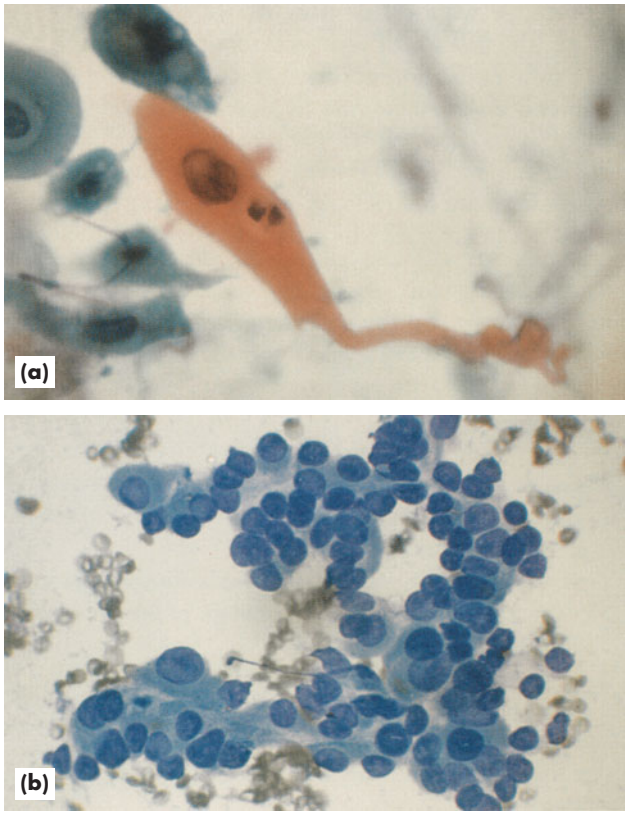

Figure 4.3 Fine-needle aspiration cytology showing (a) squamous cell carcinoma and (b) papillary carcinoma of the thyroid gland.

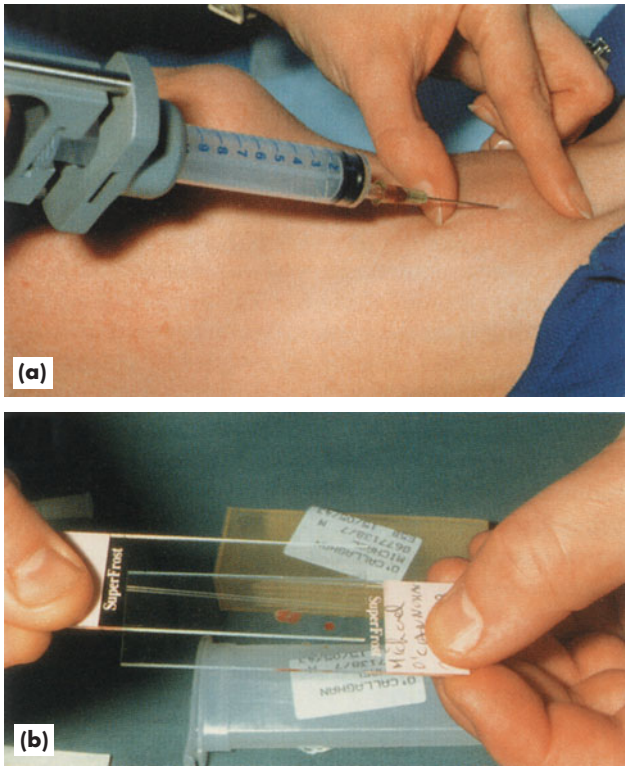

Figure 4.4 Technique for fine-needle aspiration cytology showing (a) aspiration of a solitary thyroid nodule and (b) smearing.

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 cytologist. 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. In addition, they should be air-dried for May–Grünwald–Giemsa 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 cytospin 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

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.[6, 7, 8] 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.[9] 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 jejunostomy 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

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

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. T_1-weighted images carry a great deal of spatial resolution with excellent depiction of detailed anatomy. T_2-weighted images are better at highlighting abnormal tissues. The short tau inversion recovery (STIR) sequence retains this positive attribute of a T_2-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

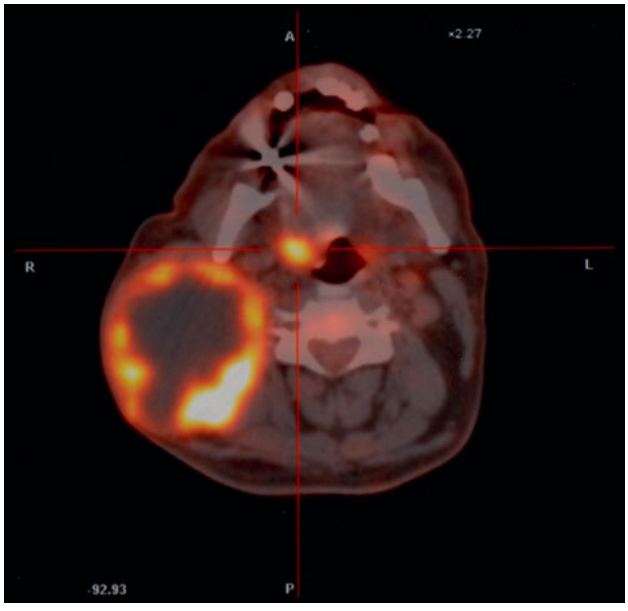

Figure 4.5 Positron emission tomography and computed tomography scan illustrating a large nodal metastasis with a small tonsil primary.

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

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 hypoharyngeal 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.[10, 11]

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° fibreoptic and 30° and 70° angled fibreoptic 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 oesophagoscopy 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.[12] 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.[13] 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. Multifocality 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 pN_0 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.

Grade	G, Histopathological grading
GX	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

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 conventional treatment 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.

Box 4.2 Benefits of staging

- An aid to planning therapy
- Indication of prognosis
- Comparison of results of treatment
- Facilitate exchange of information between treatment centres

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.[3, 4]

Details can be found in the current UICC handbook.[3] 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 histopathological classification, designated pTNM). 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.[4]

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.[3]

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.[3, 4]

T_0 is used when there is no evidence of a primary tumour, T_{1s} used when the primary is non-invasive or carcinoma *in*

Table 4.4 Primary tumour classification.

Stage	T, Primary tumour
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1, T2, T3, T4 (T4a, T4b)	Increasing size and/or local extent of the primary tumour

Table 4.5 Nodal status classification.

N-stage	N, Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node. 3 cm or less in greatest dimension
N2	N2a: Metastasis in a single ipsilateral lymph node, more than 3 cm, but not more than 6 cm in greatest dimension N2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Table 4.6 Stage grouping.

Stage			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1, T2	N1	M0
	T3	N0, N1	M0
IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
IVB	Any T	N3	M0
	T4b	Any N	M0
IVC	Any T	Any N	M1

situ and T_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_0 and not T_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.[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.[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.[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.[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_1 or M_0, respectively. M_1 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 metastic 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).[3, 4]

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 (T_0) 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.[21]

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.[22] 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.[23]

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 T_1, whereas in the glottis this will almost certainly be a T_3. 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 T_{1a}. The same tumour may be deeply infiltrating into the vocalis muscle and yet the stage will still remain T_{1a}. 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.[24]

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 T_1 or T_4 tumour, but problems can occur when the tumour measures between 1.5 and 3 cm. Furthermore, increasing severity with a T_4 tumour is reflected in deep invasion into muscle, bone or adjacent structures. Bony invasion of the mandible demonstrated radiographically is classified as T_4 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 T_2 and T_4 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.[22]

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 T_2 classification, but when oral carcinoma involves the antrum (erosion of the inferior wall of the sinus), the classification is T_{4a}. 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.[25] Furthermore, palpable nodes do not always harbour tumour. 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.[5] 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[20] and now it is included in the current classification.[4] 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).[4] It is advised that specific lymph node level (as well as U/L category) be documented in the case file and on the database, for ease in future use.

The immunological and pathological status of lymph nodes is not included. This is not so surprising as the evidence for importance of immunology of lymph nodes is conflicting. For example, it has been stated by some authorities that the presence of reticular hyperplasia[26] and evidence of lymphocytic stimulation[27] in lymph nodes is a good prognostic sign, whereas a double-blind retrospective study has shown no correlation between lymph node morphology and survival or metastases.[28]

The presence of extracapsular nodal spread has been shown to be associated with significant decline in survival and high rate of local-regional recurrence.[29] Extracapsular spread is noted in a majority of lymph nodes larger than 3 cm and in a significant number of nodes less than 2 cm.[30] The situation is even worse when there is tumour freely extending through into the soft tissues of the neck.[31] Imaging studies showing amorphous spiculated margins of involved nodes or involvement of internodal fat resulting in loss of normal oval or round nodal shape strongly suggest extracapsular tumour spread. However, despite the obvious importance, extracapsular spread is not an integral part of N status classification.

In addition, inclusion of bilateral or contralateral disease as N_2 is confusing since it implies a better prognosis than N_3 disease. The word fixation has, at least, been removed from previous nodal classifications since it was open to wide and varied subjective interpretation. However, it is worth noting that the present classification of N_3 disease includes nodes which are greater than 6 cm in size which are usually fixed.

LIMITATIONS OF PATHOLOGICAL STAGING

The pathological assessment of the primary tumour (pT) entails a resection of the primary tumour or biopsy adequate to evaluate the highest pT category. The system, even with the aforementioned guidelines, is open to sampling errors and inter- and intraobserver errors. It is advised that pT is derived from the actual measurement of the unfixed tumour in the surgical specimen, as up to 30 per cent shrinkage occurs.

Direct extension of the primary tumour into lymph nodes is classified as a lymphn-node metastasis. Of course, it could be argued that this extension has a completely different biology and perhaps outcome to a tumour that has truly metastasized. Similarly contentious is that a tumour nodule in the connective tissue of a lymph drainage area without histological evidence of residual lymph node is classified in the pN category as a regional lymph node if it has a smooth contour. A tumour with an irregular contour is classified in the pT category, i.e. discontinuous extension.[3]

In contrast to clinical staging, when size is a criterion for pN classification, measurement is made of the metastasis, not of 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,[17] 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.[32, 33] Vascular and nerve sheath invasion also increases the probability of lymphn-node metastases.[34] 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).[35]

While some studies report a close correlation between histological malignancy scores and the outcome of

disease,[35, 36] other investigations have found no significant improvement on conventional grading.[37] Critics of these grading systems have pointed out that they are extremely labour intensive and the criteria used have a subjective element with wide inter- and intraobserver error by the histopathologist.[38] In addition, it is argued that the pooling of statistically significant and less important parameters results in a compromised conclusion of no clinical value.[37] Hence, these systems have not been adopted for regular use in clinical practice nor do they form part of pathological staging.

The challenge seems to be how to incorporate non-anatomic prognostic factors with the TNM system. For example, the use of biomolecular markers and measures of cell kinetics have been suggested as potential prognostic indices for tumour behaviour. Some studies have found that certain markers influence outcome, but the results are not consistent and they too have not found regular use in clinical practice.[39, 40, 41, 42, 43]

LIMITATIONS OF STAGE GROUPING

Despite the obvious value of staging, both in the management of individual patients, and for the grouping of patients in trials and reports of treatment, it does have its limitations. The most insidious of these is that attempts to increase the accuracy of staging leads to greater complexity, and hence paradoxically to more errors and an increased likelihood of non-compliance by the person responsible for staging. Advances in methods of collecting and recording data will hopefully reduce these errors.

There are now seven stages for head and neck cancers arising at mucosal sites (0, I, II, III, IVa, IVb, IVc) and six stages for salivary gland cancers (I, II, III, IVa, IVb, IVc). Differentiated thyroid cancers also have six stages (I, II, III, IVa, IVb, IVc) with undifferentiated (anaplastic) cancers having three as all cases are stage IV (IVa, IVb, IVc). Many authorities have concluded that problems exist with the current staging system.[44, 45, 46, 47] One of the main criticisms is that the size of some groups defined by the combinations of the TNM classifications is small, preventing accurate prediction from previous experience.

Compelling arguments have been advanced suggesting the different ways grouping the same T, N and M categories may result in an improved system.

The TANIS score combines the integers of the T and N to create a new score. Thus, a T1N0 would be a TANIS 1 and T2N2 would be a TANIS 4, etc. First reported by Jones *et al.*,[47] this is an easy system to use evaluated primarily for cancers of the oral cavity and oropharynx. It treats T and N as equivalent with respect to survival. The advantages of the TANIS score are its ease of application, ability to define a reasonable number of groups, and ability to be applied retrospectively if the TNM score is known. The main disadvantage is that the concept of T and N equivalence does not hold true. Many studies have confirmed the more significant impact of N status over T status. For example, a T2N0 carcinoma does not have the same survival as a T1N1 at any site, though both of these would be TANIS 2.

Others have also tried to improve on the current stage grouping and TANIS system with subtle variations.[48, 49, 50] They more or less all claim that their system is an improvement on any other. Lydiatt *et al.*[51] 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.[51]

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[52] and comorbidity[53] 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.[3, 4]

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

Table 4.7 Comparison of results of treatment for cancer using an old and a new staging system.

Stage	Old staging systems			New staging systems		
	No. of patients	% Cured	No. cured	No. of patients	% Cured	No. cured
I	30	80	24	25	84	21
II	30	50	15	25	60	15
III	30	20	6	25	28	7
IV	10	10	1	25	12	3
All	100	46	46	100	46	46

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'.[54] 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 T_2N_0 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.

Table 4.8 Follow-up frequency after treatment for squamous cancer of the head and neck.

Time after treatment	Good possibility of successful salvage, if local or nodal relapse	Little chance of successful salvage
First year	Monthly	Six-weekly
Second year	Two-monthly	Three-monthly
Third year	Three-monthly	Six-monthly
Fourth year	Six-monthly	Six-monthly
Fifth year	Six-monthly	Six-monthly
After five years	Annually or discharge	Annually or discharge

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 T_2N_0 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

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.

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5

Imaging

ALISON PAGE AND JULIE OLLIFF

A picture is worth a thousand words.

attributed to Frederick R Barnard (1921)

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.[1] 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.[2] 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.[3]

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.

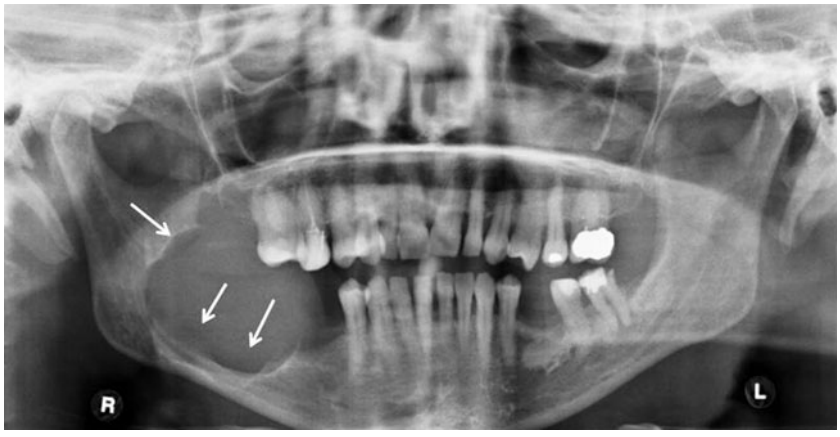

Figure 5.1 Orthopantomogram showing large ameloblastoma in the right mandible with smooth bone erosion (arrows).

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.[4] 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.[5]

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 cinefluoroscopy. 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.

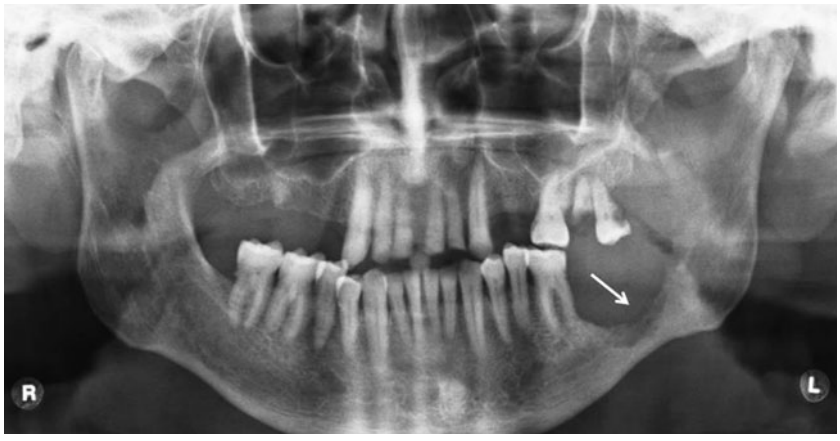

Figure 5.2 Orthopantomogram demonstrating local erosion of the alveolar surface of the left angle of the mandible due to squamous cell carcinoma (arrow).

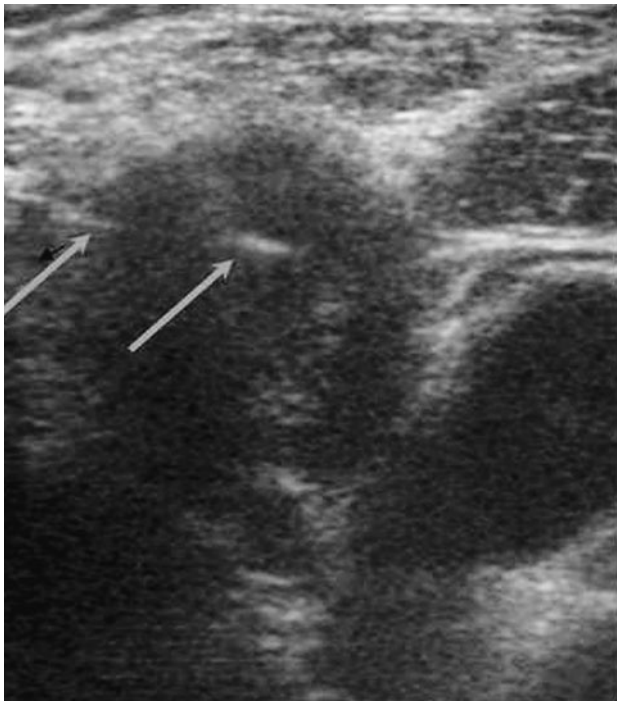

Figure 5.3 Ultrasound image showing a metallic needle (arrows) positioned within a necrotic level I node.

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

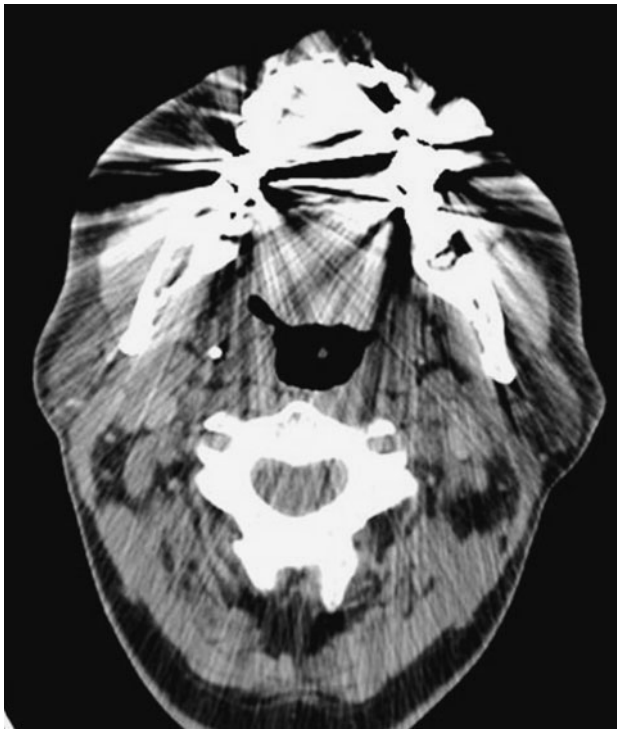

Figure 5.4 Beam hardening artefact from dental amalgam on computed tomography.

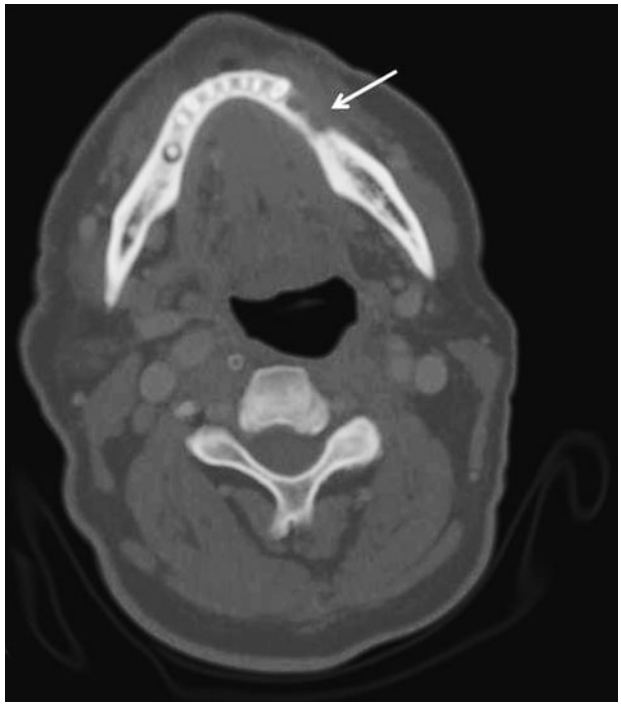

Figure 5.5 Focal erosion of the buccal surface of the left body of mandible on computed tomography (bone windows).

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.[12] MRI scanning in an interventionally configured (open) magnet may be appropriate in claustrophobic patients who fail examination in a conventional magnet without sedation.[13]

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.[14] 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.[15]

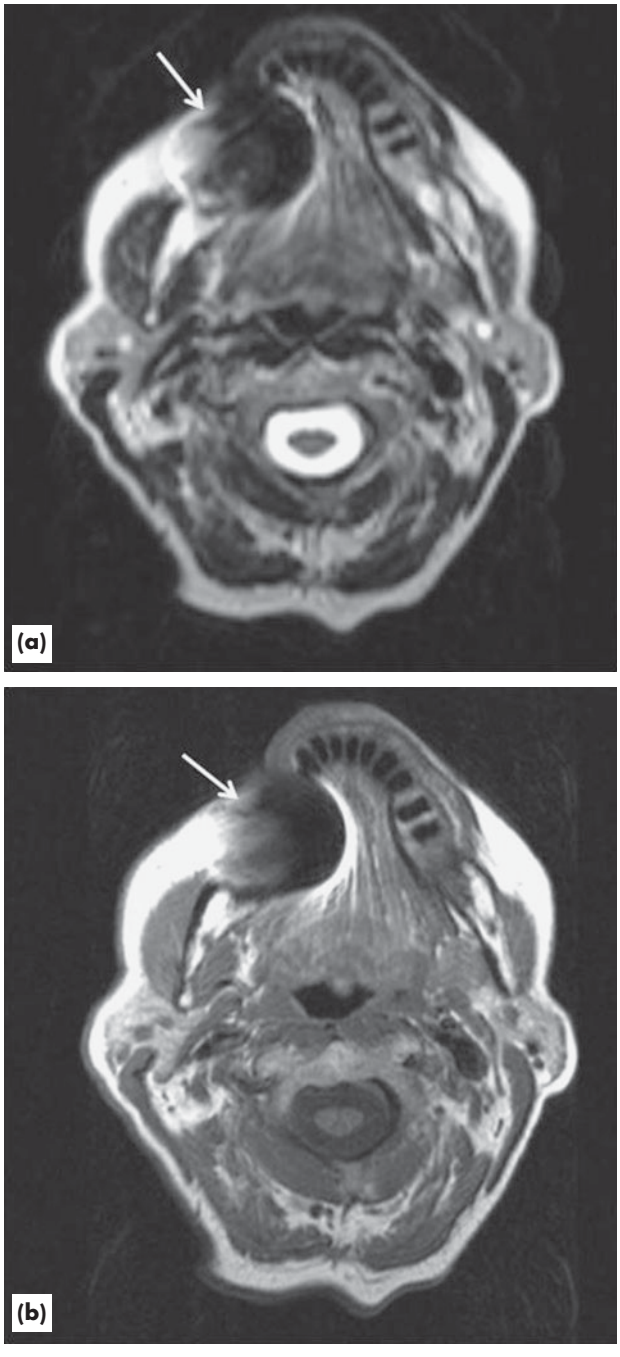

Figure 5.6 T2-weighted (a) and T1-weighted (b) axial magnetic resonance images demonstrating signal loss around a metallic dental bridge.

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.[16] 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**).

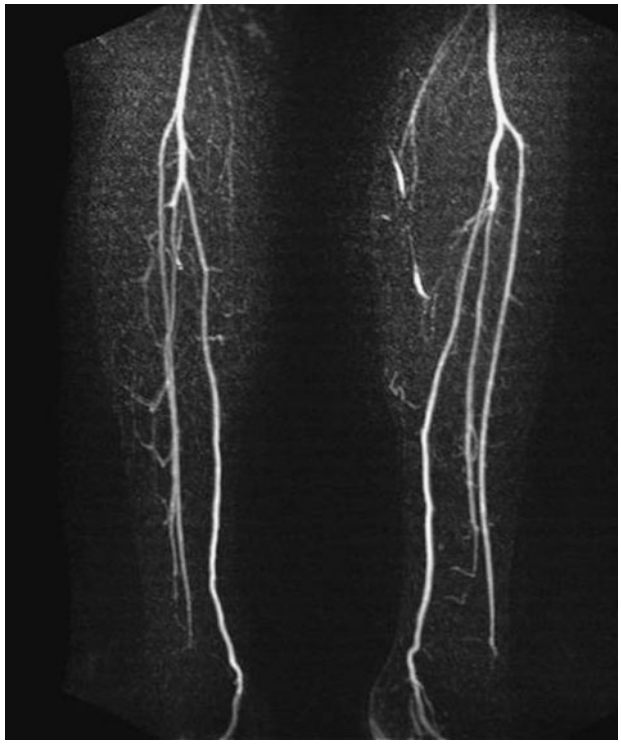

Figure 5.7 Magnetic resonance angiography of distal leg vessels.

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 (^{99m}Tc) 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, ^{99m}Tc 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.[17]

Suspected postoperative pulmonary emboli can be confirmed using a ventilation-perfusion scan (VQ scan). These utilize ^{99m}Tc-labelled macroaggregated albumin to demonstrate blood flow within the pulmonary capillary network and either Xenon-127 gas or nebulized ^{99m}Tc 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 (^{123}I). Iodine-131 (^{131}I) 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.[18]

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.[19, 20]

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**).[21] 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.[22]

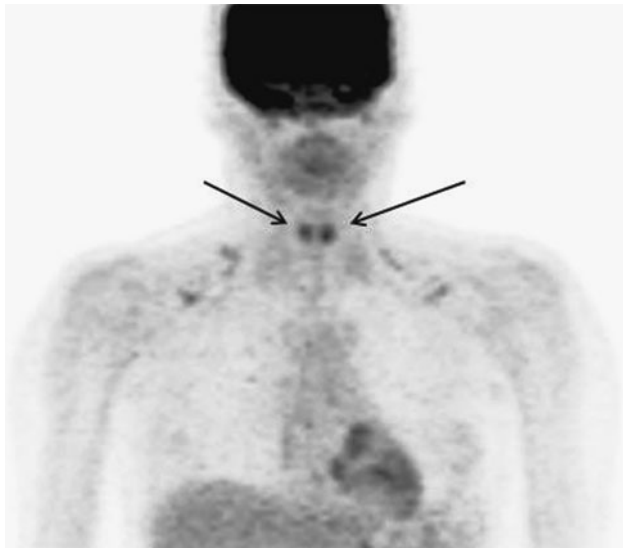

Figure 5.8 ^{18}F-FDG PET-CT demonstrating physiological tracer uptake in the glottis.

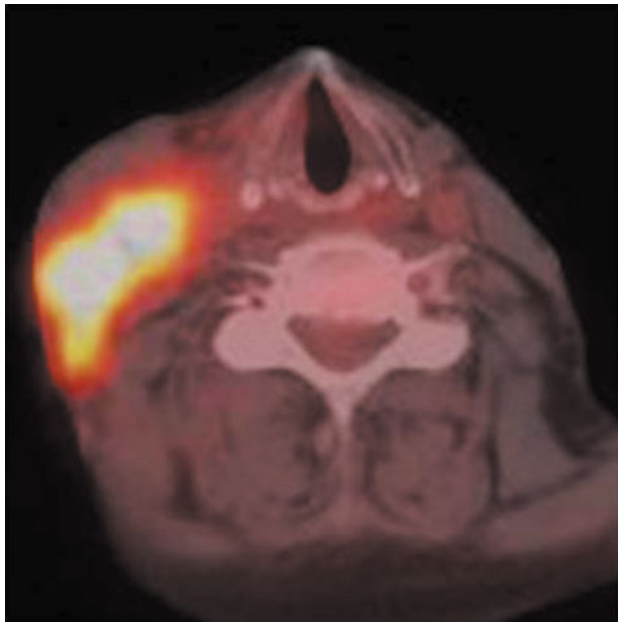

Figure 5.9 Avid tracer uptake within pathological right neck nodes on ^{18}F-FDG PET-CT. Unknown primary.

NASOPHARYNGNEAL 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 carcinosarcoma 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

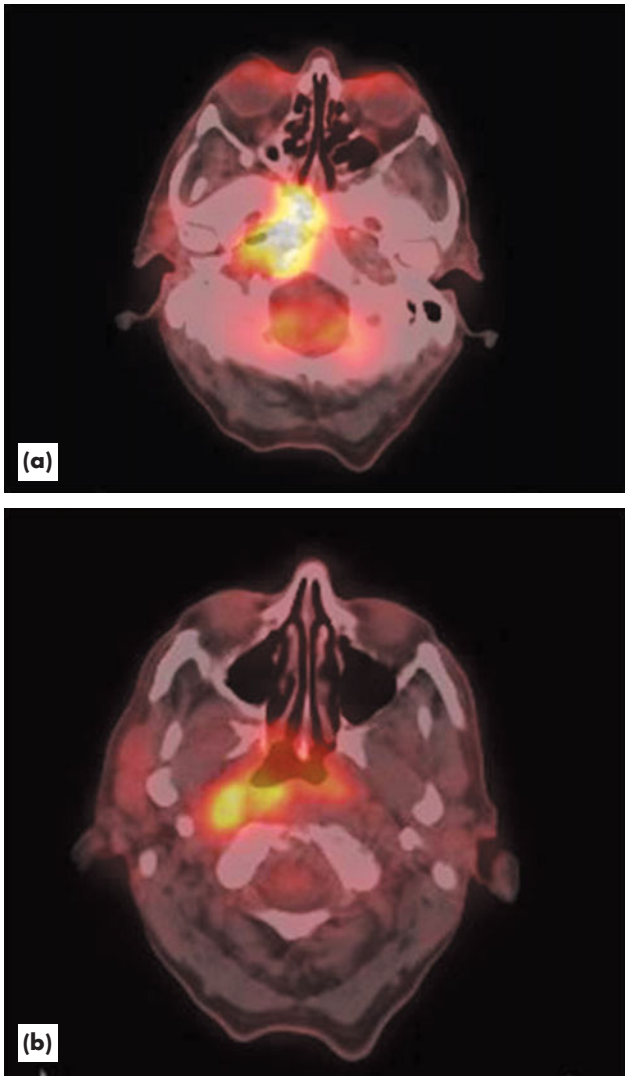

Figure 5.10 (a,b) ^{18}F-FDG PET CT showing recurrent oropharyngeal tumour invading the skull base post-radiotherapy and photodynamic therapy (PDT).

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

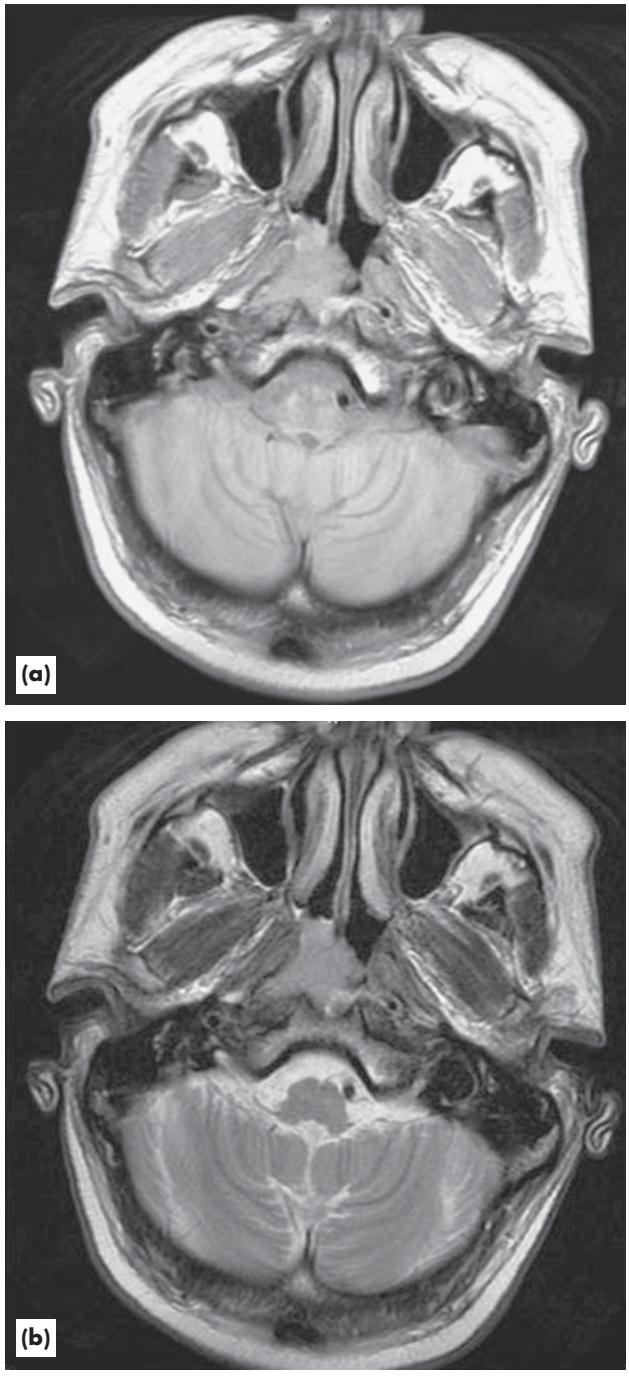

Figure 5.11 Axial T1-weighted (a) and T2-weighted (b) magnetic resonance images demonstrating a right-sided nasopharyngeal tumour filling the fossa of Rosenmüller.

and/or recurrent disease following treatment at the primary site. The combined use of both modalities was more accurate for restaging.[23]

PARAPHARYNGEAL SPACE PATHOLOGY

The parapharyngeal space extends from the skull base to the styloglossus muscle at the level of the angle of the mandible.

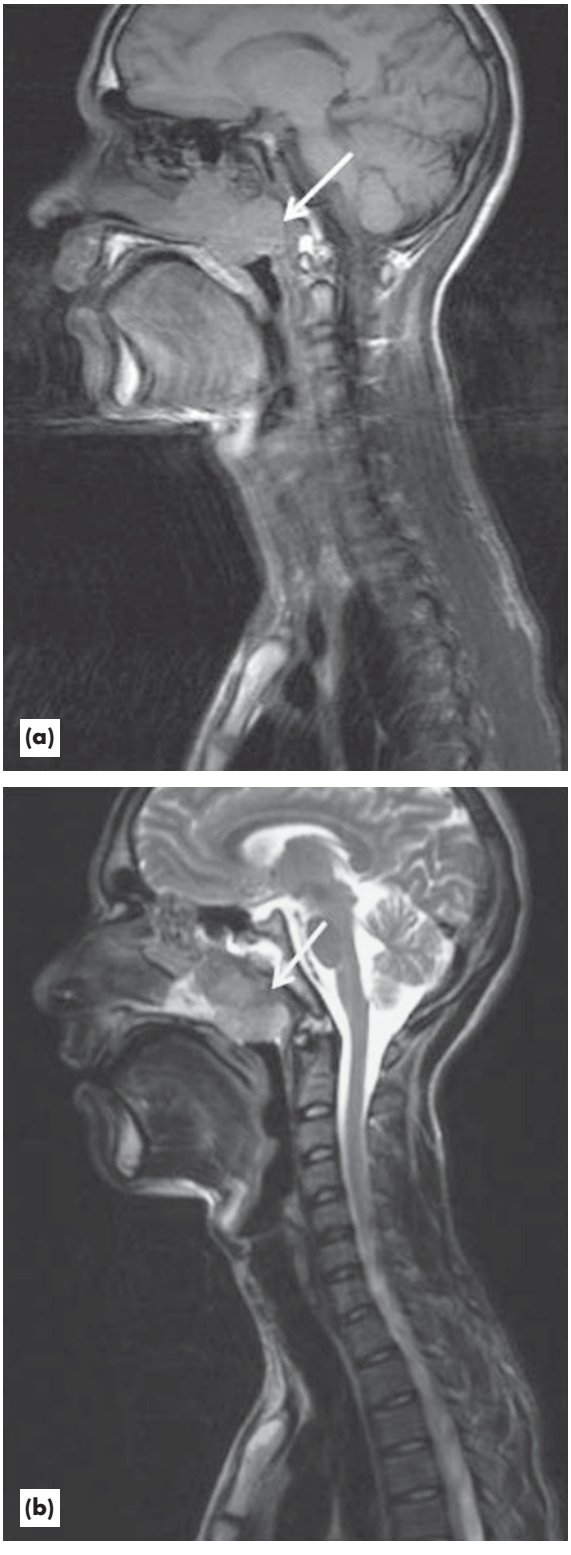

Figure 5.12 Sagittal T1-weighted (a) and T2-weighted (b) magnetic resonance images demonstrating a bulky nasopharyngeal tumour with direct extension into the clivus (arrows).

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

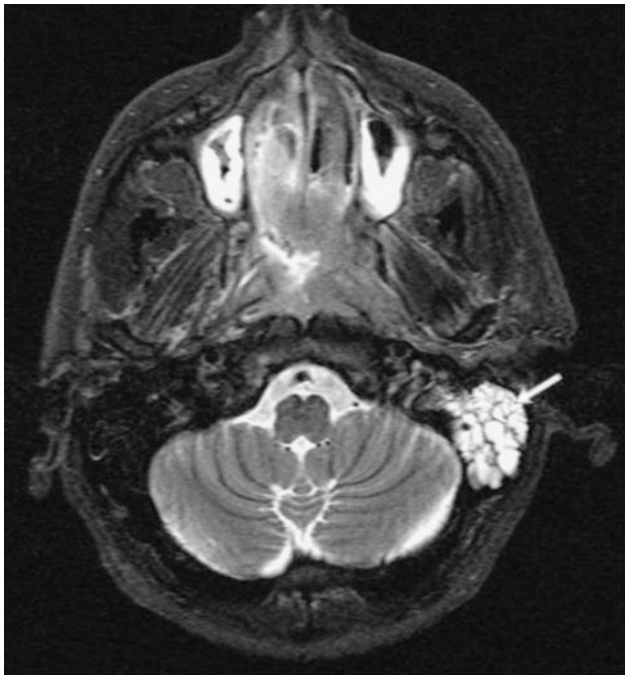

Figure 5.13 Large nasopharyngeal tumour invading the nasal cavity with loss of the pharyngobasilar fascia and obstruction of the left Eustachian tube resulting in opacification of the left mastoid air cells (small arrow).

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.[24] 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.[25, 26] 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

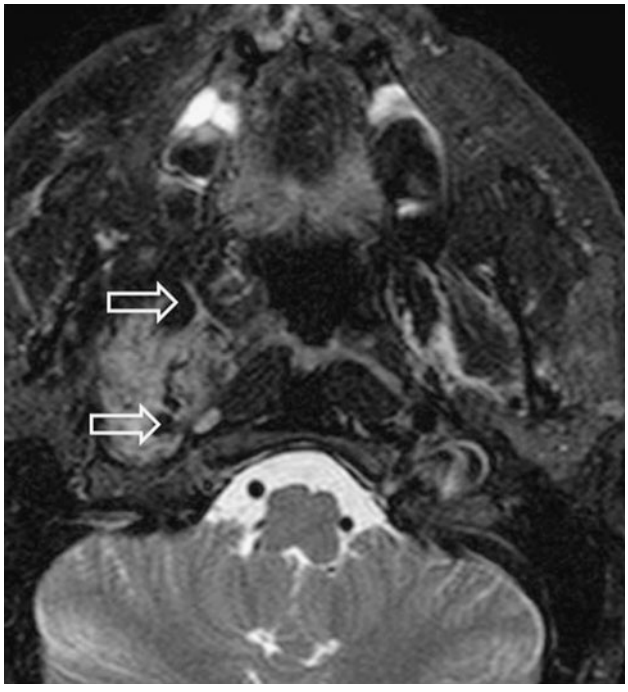

Figure 5.14 STIR (short tau inversion recovery) magnetic resonance image demonstrating flow voids (open arrows) in a large right high T2 signal parapharyngeal paraganglioma.

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.

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.[27] 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.[28] 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).[29] Another group,[30] however, found that although MR was sensitive it had a poor positive predictive value for mandibular invasion. In a further study, ^{99m}Tc 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.[31]

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.

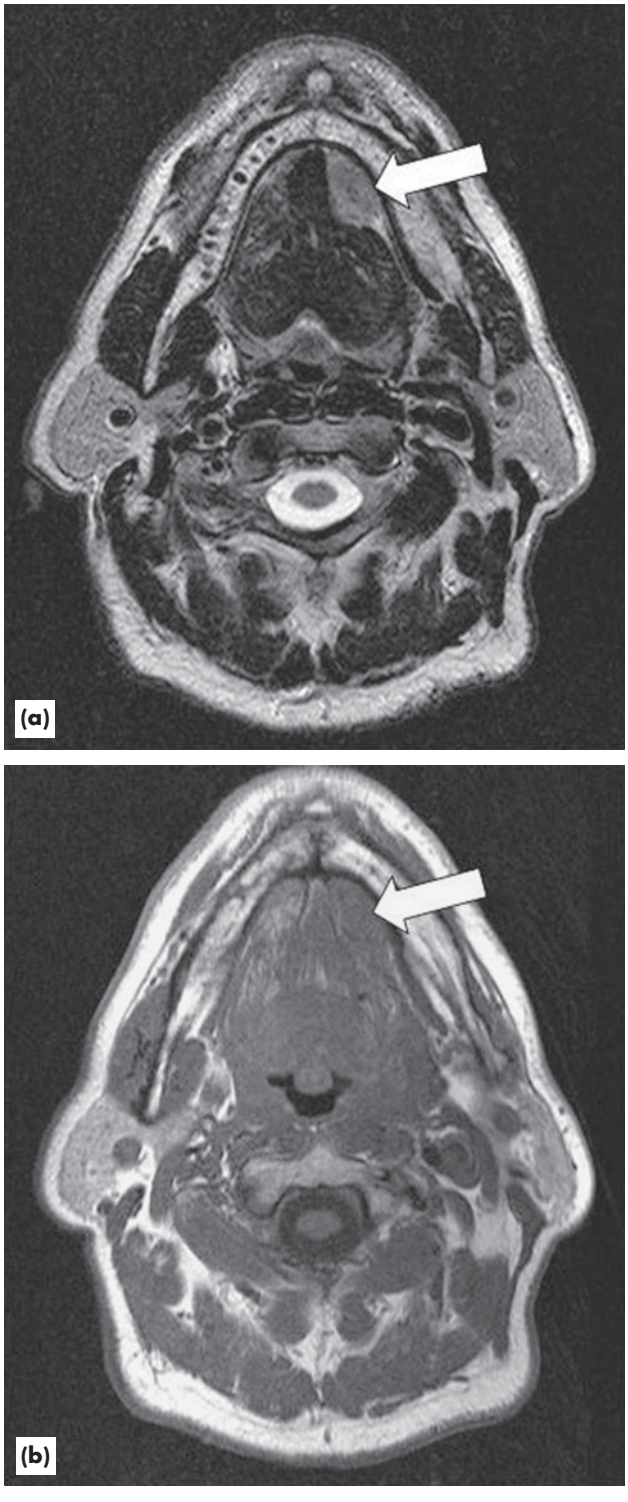

Figure 5.15 Axial T2-weighted (a) and T1-weighted (b) magnetic resonance images of a localized tumour in the anterior left floor of the mouth (solid arrow).

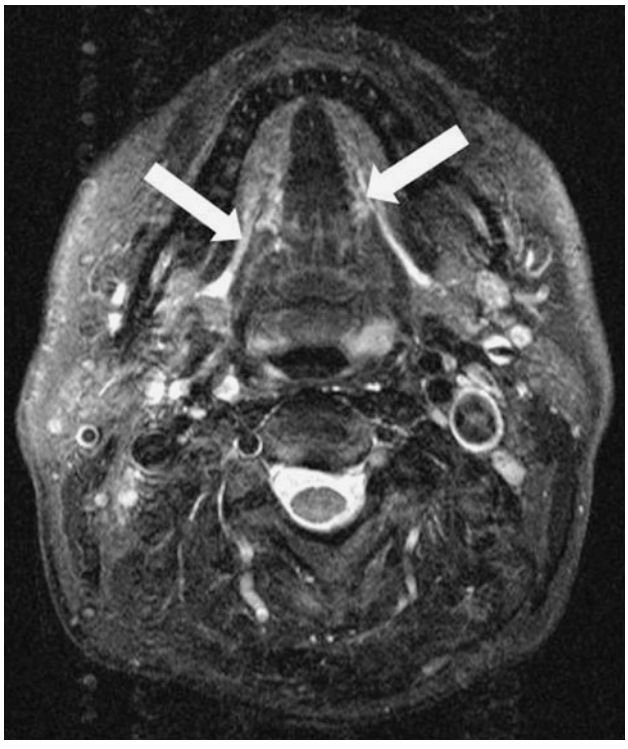

Figure 5.16 Axial STIR magnetic resonance image showing bilateral submandibular salivary gland duct obstruction (white arrows).

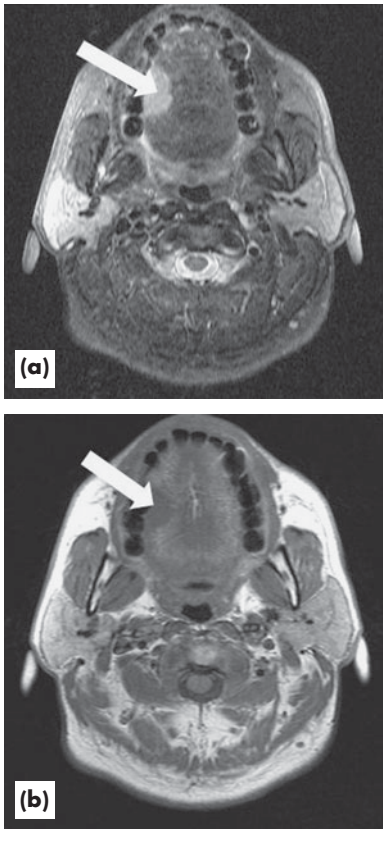

Figure 5.17 STIR (a) and T1-weighted (b) axial magnetic resonance images of a small right lateral tongue tumour (white arrow).

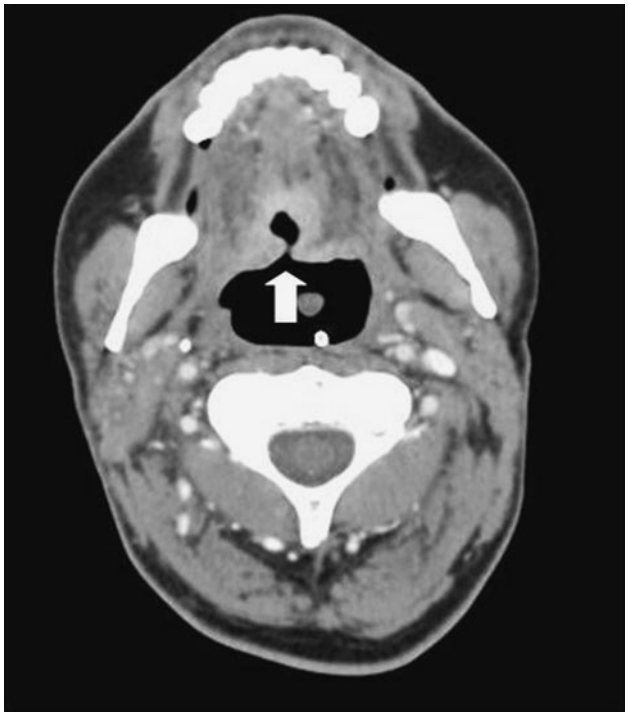

Figure 5.18 Contrast-enhanced computed tomography demonstrates a small superficial tumour of the tongue base crossing the midline (white arrow).

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.[32]

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

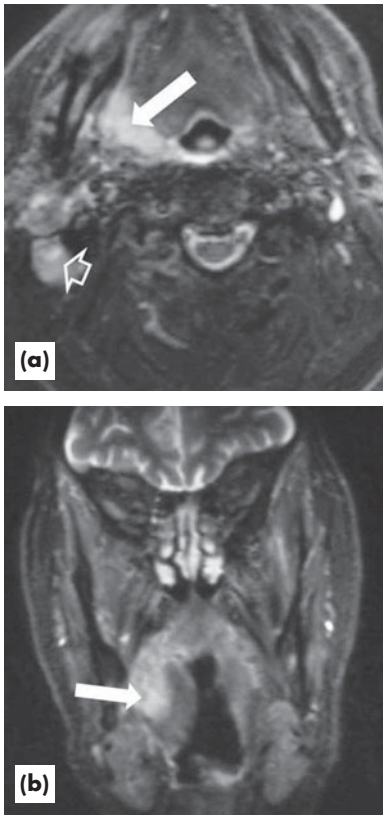

Figure 5.19 STIR axial (a) and STIR coronal (b) magnetic resonance images demonstrating a right tonsillar tumour (white arrows) with pathologically enlarged right level II nodes (arrowhead).

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. Multirow detector computed tomography-calculated tumour volume has been shown to have a high level of agreement with histology, with

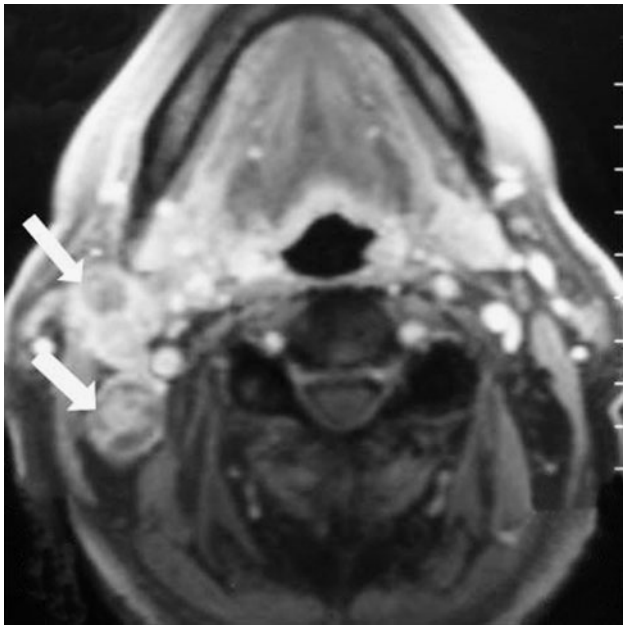

Figure 5.20 T1-weighted fat-saturated contrast enhanced axial magnetic resonance image demonstrating a right tonsillar tumour with pathologically enhancing nodes (white arrows).

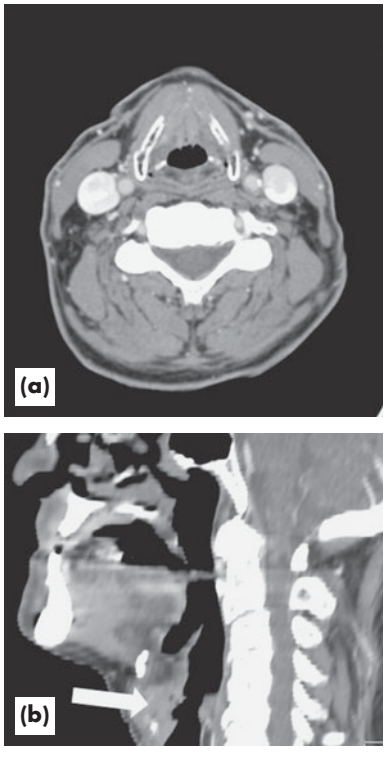

Figure 5.21 Contrast-enhanced axial computed tomography scan (a) with sagittal reformat (b) showing pre-epiglottic spread (arrow).

a slight tendency of MDCT to overestimation proportional to the size of the tumour.[33] 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 on MR 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.[34] Work performed by Murakami and colleagues[35] 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 inter-observer variation in the assessment of tumour volume, cartilage invasion and cartilage sclerosis on the basis of CT imaging, apparently limiting its clinical significance.[36] 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.[37]

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.[38]

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 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.[39, 40] 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).[39]

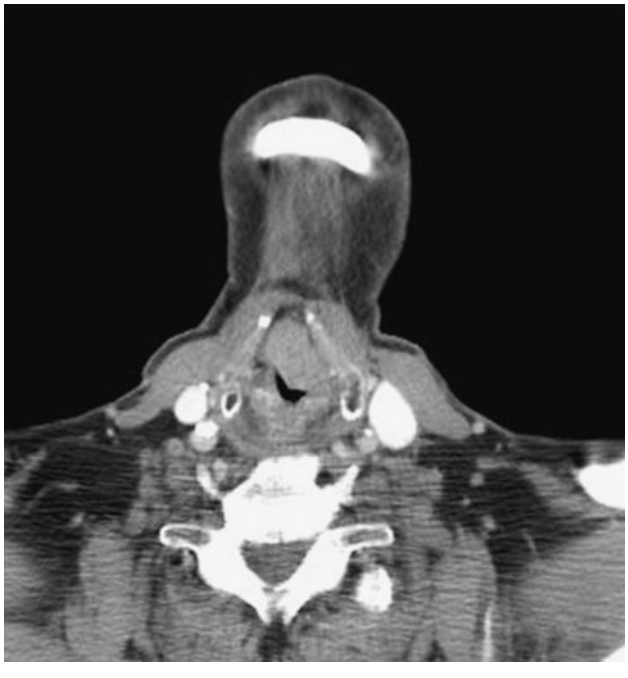

Figure 5.22 T3 left cord tumour with thickening of the anterior commissure on contrast-enhanced computed tomography.

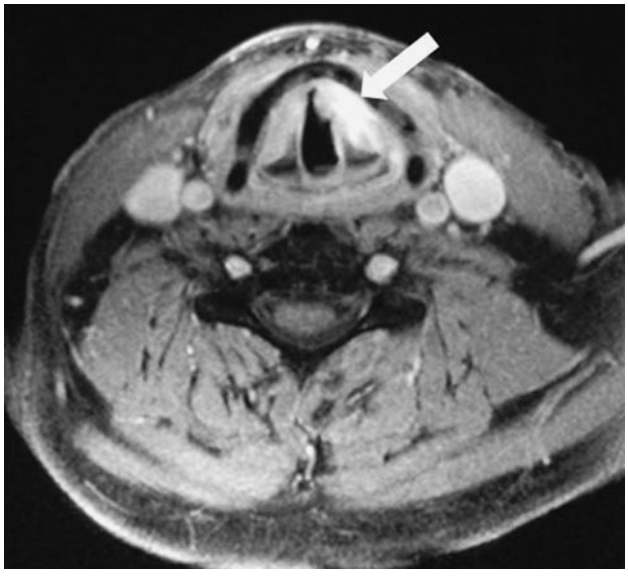

Figure 5.23 Fat-saturated T1-weighted spin echo axial magnetic resonance post-contrast demonstrating a left cord tumour with paraglottic spread (white arrow).

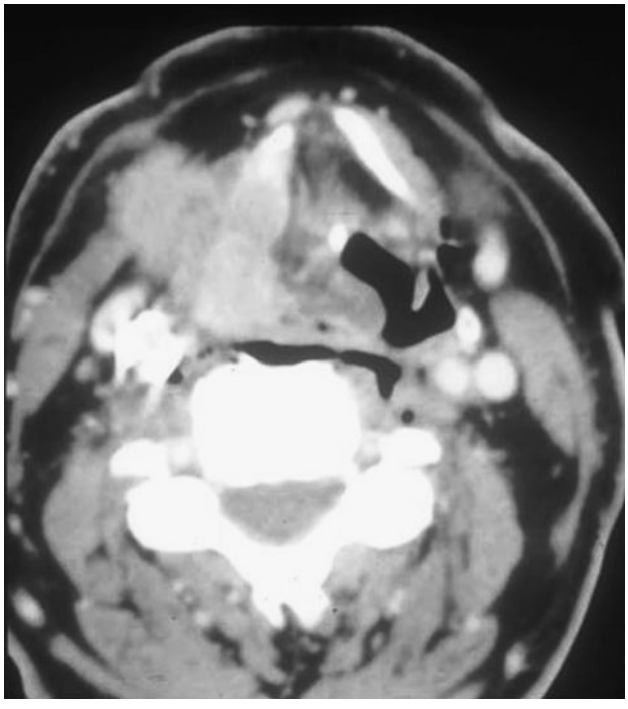

Figure 5.24 Contrast-enhanced axial computed tomography demonstrating extralaryngeal tumour and lysis of the right thyroid lamina.

A study examining 111 laryngeal cartilages comparing CT with histopathology,[41] 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.[41] The presence of arytenoid cartilage sclerosis can be due to invasion or to the presence of tumour adjacent to the perichondrium.[42, 43] Some authors[44] 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,[45] 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.[46] The term 'abnormal signal intensity in the cartilage' rather than 'invasion of cartilage' has been suggested.[47] 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.[37] New criteria have been suggested:[48] 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[45] 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.[49]

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

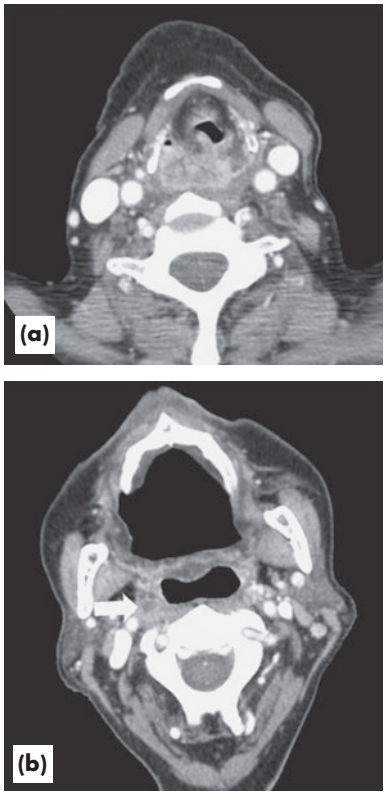

Figure 5.25 Contrast-enhanced computed tomography demonstrating a primary posterior pharyngeal wall tumour (a) with a rim enhancing right retropharyngeal node (b).

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.[50] The width of this stripe is, however, variable from patient to patient and from superior, where it is wider, to inferior.[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

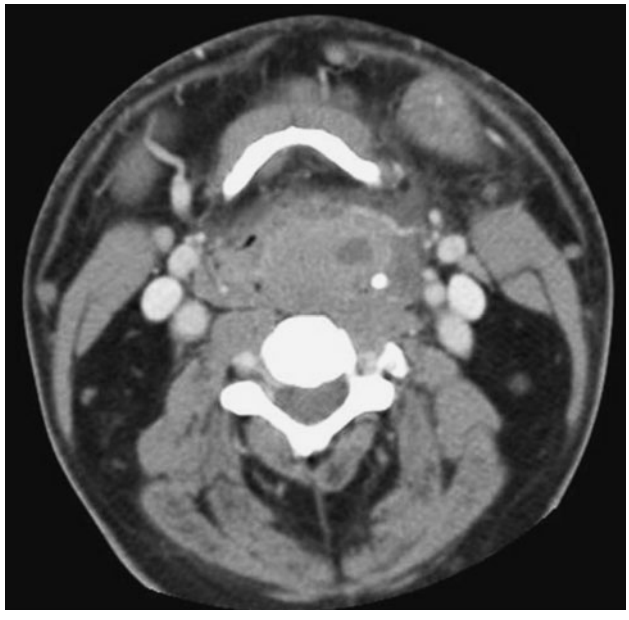

Figure 5.26 Axial-enhanced computed tomography scan showing bulky pharyngeal tumour with retropharyngeal fascia invasion.

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.[51]

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.

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

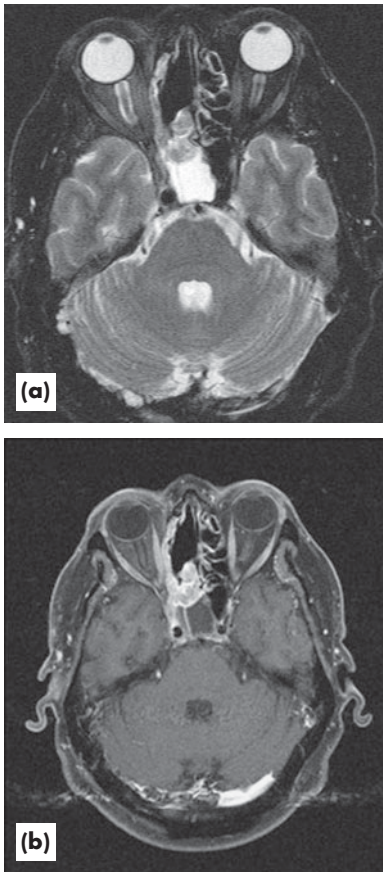

Figure 5.27 Fat-saturated T2-weighted (a) and fat-saturated T1-weighted magnetic resonance following intravenous contrast (b). Recurrent enhancing enthesioneuroblastoma in the right nasal cavity with obstruction of the right sphenoid sinus.

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

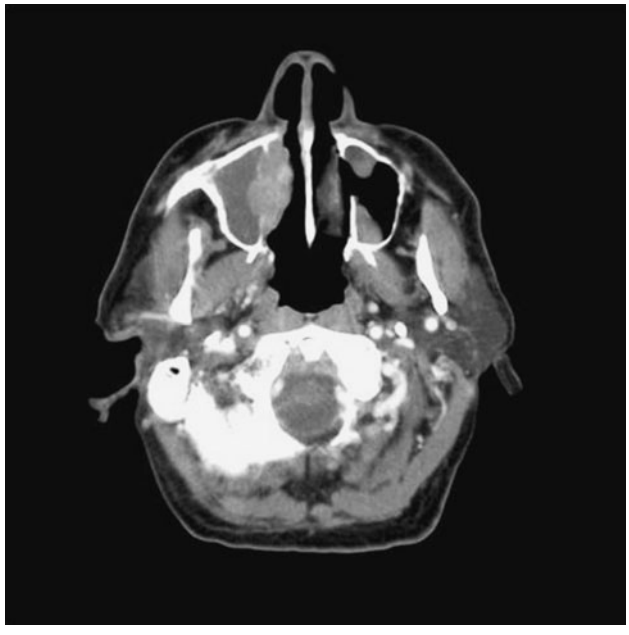

Figure 5.28 Contrast-enhanced axial computed tomography scan demonstrating a destructive enhancing soft tissue mass (melanoma) involving the medial wall and with obstruction of the right maxillary antrum.

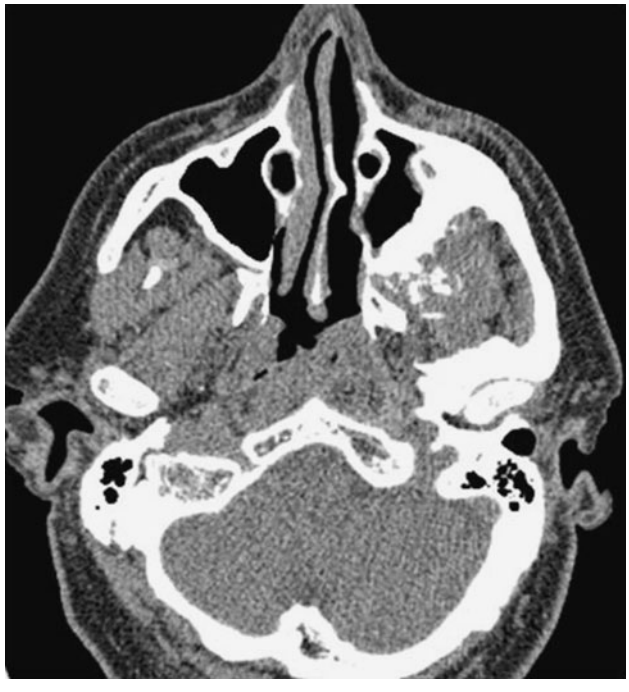

Figure 5.29 Contrast-enhanced axial computed tomography scan showing chondrosarcoma of the posterior wall of the left maxillary antrum extending into the infratemporal fossa.

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

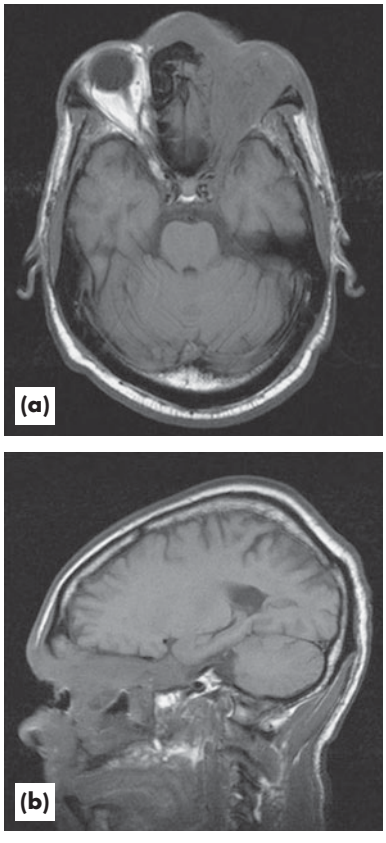

Figure 5.30 Axial T1-weighted (a) and sagittal T1-weighted (b) magnetic resonance image demonstrating tumour extension into the orbit and anterior cranial fossa.

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

The salivary glands are divided into two groups: the major salivary glands and the minor salivary glands. The three pairs

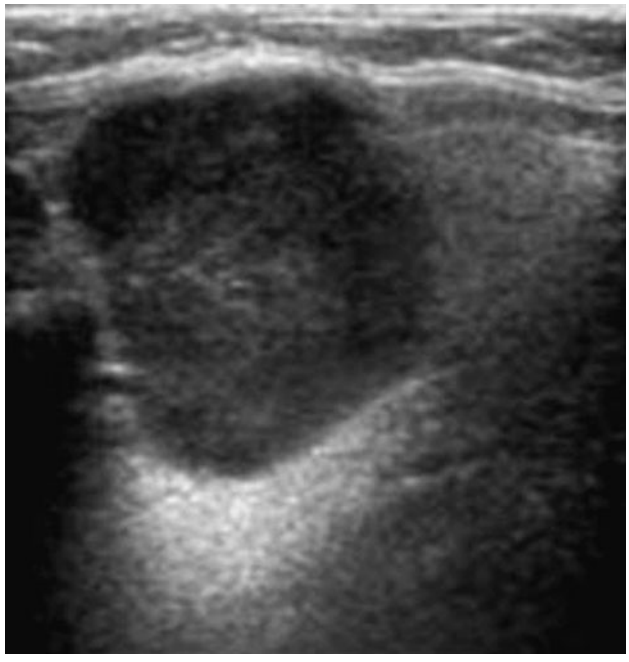

Figure 5.31 Ultrasound of a pleomorphic adenoma demonstrating a well-defined hypoechoic mass with typical through transmission.

of major salivary glands are the parotids, submandibular and sublingual glands. The numerous small glands distributed throughout the oral cavity mucosa, the sinonasal cavity, the hard and soft palates, the pharynx and the larynx comprise the minor salivary glands.

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.[55] 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.[56]

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.

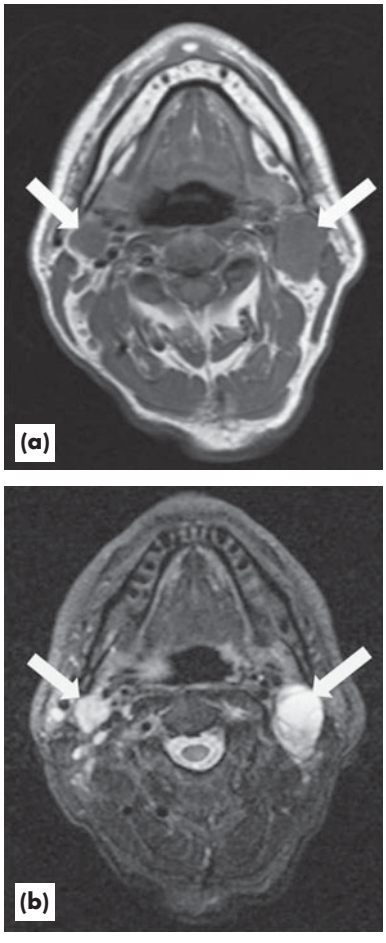

Figure 5.32 T1-weighted (a) and STIR (b) axial images demonstrating a small pleomorphic adenoma within the tail of both parotid glands (arrows).

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

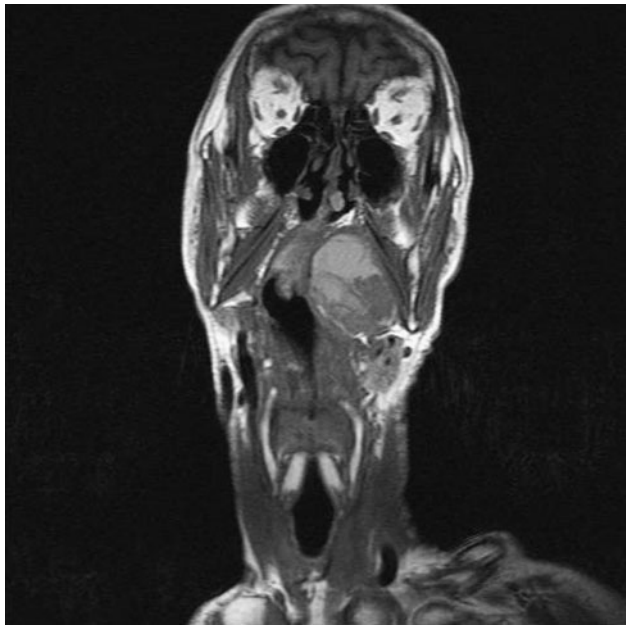

Figure 5.33 T1-weighted coronal magnetic resonance image demonstrating a large haemorrhagic Warthin's tumour in the left parapharyngeal space.

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

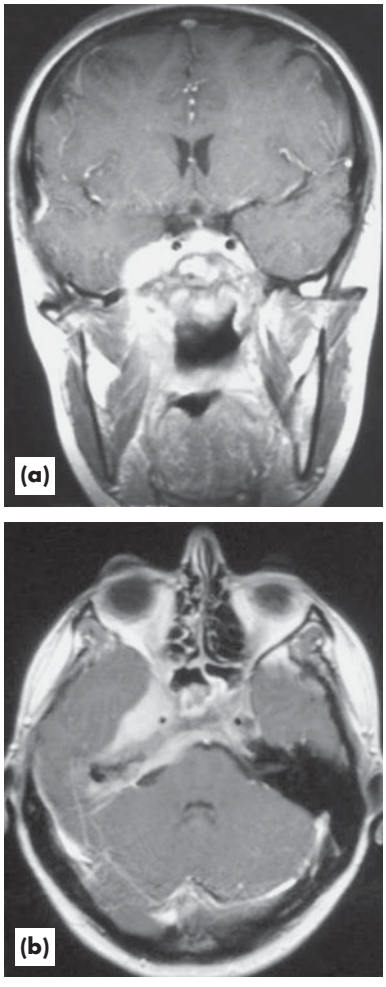

Figure 5.34 Contrast-enhanced T1-weighted coronal (a) and axial (b) magnetic resonance image demonstrating perineural spread from adenoid cystic carcinoma.

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.[57] 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

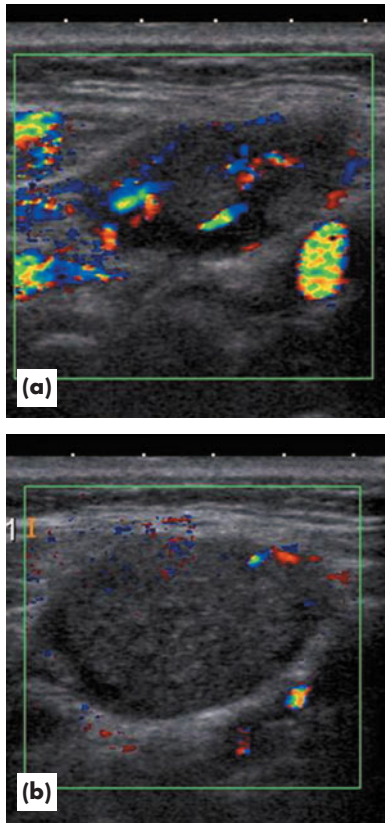

Figure 5.35 Involved nodes with disordered flow (a) and peripheral flow (b) on colour Doppler ultrasound.

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**).[58] 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.[59]

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.[60]

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.

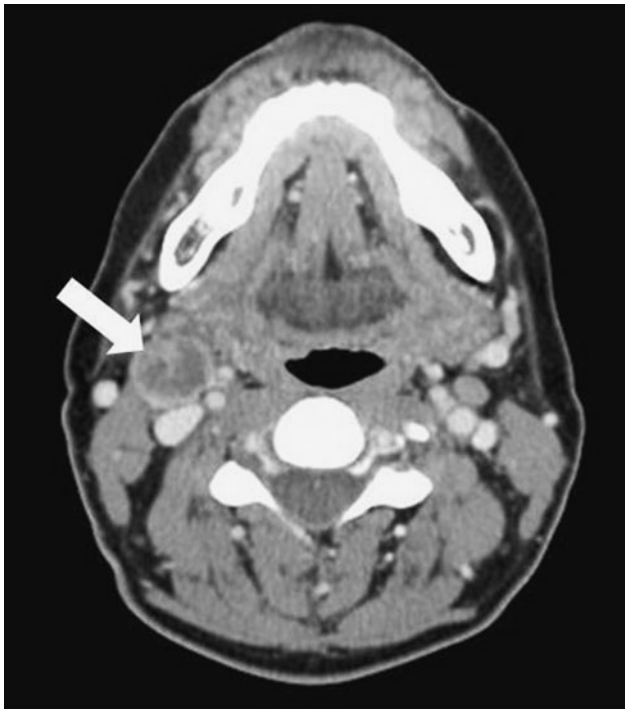

Figure 5.36 Pathological node on contrast-enhanced computed tomography (arrow).

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.[61] 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.[62] 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).[63]

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.[61]

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.[64] However, the clinical usefulness of USPIO agents is unfortunately limited by technical problems (motion and susceptibility

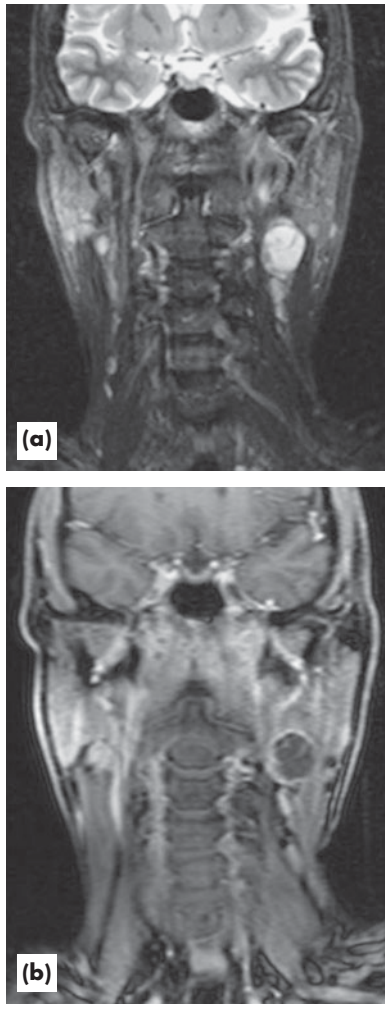

Figure 5.37 STIR coronal image precontrast (a) demonstrating a left level II node and fat-saturated T1-weighted coronal image following gadolinium chelate (b) demonstrating a rim enhancement and central necrosis.

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.[65]

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.[66] 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.[67]

^{18}F-FDG PET-CT

Combined ^{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.[68]

^{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 ^{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.[69]

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.[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.[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

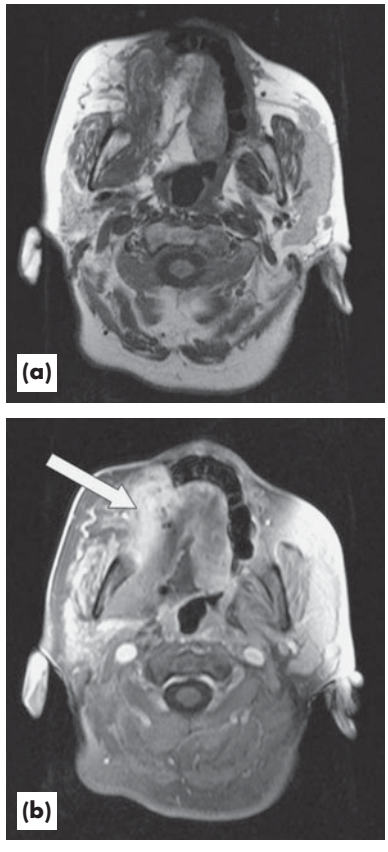

Figure 5.39 Axial T1-weighted magnetic resonance image of a radial free forearm flap reconstruction of the right floor of mouth (a) with enhancement of the denervated muscle (arrow) on fat-saturated axial T1-weighted post intravenous gadolinium (b).

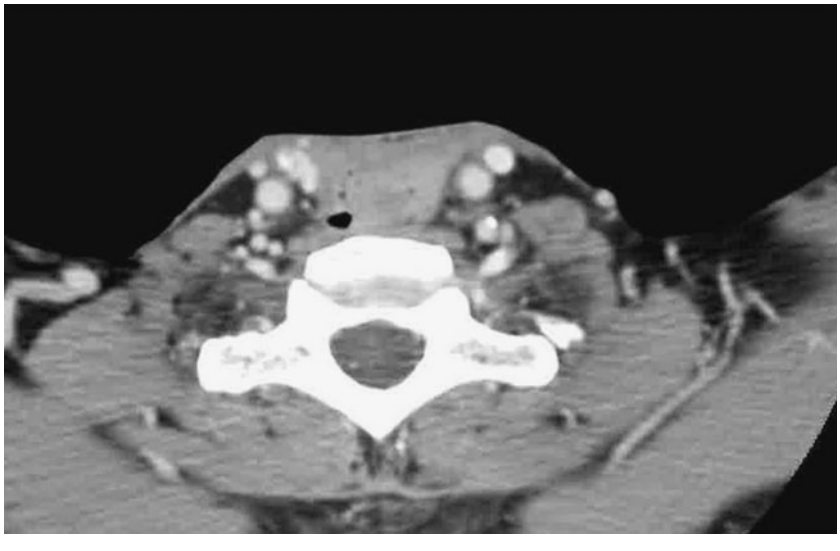

Figure 5.38 Asymmetric thyroid post laryngectomy.

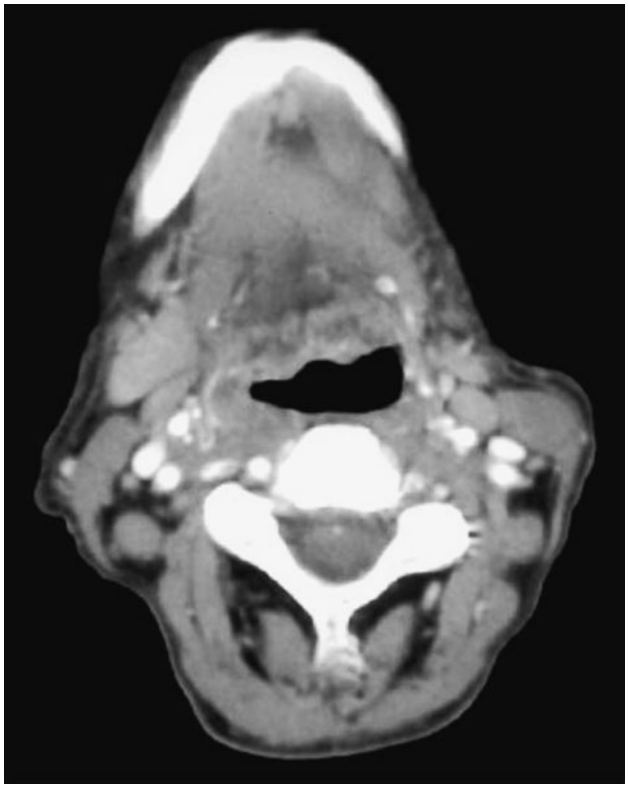

Figure 5.40 Contrast-enhanced computed tomography scan post left neck dissection with resection of the left submandibular gland.

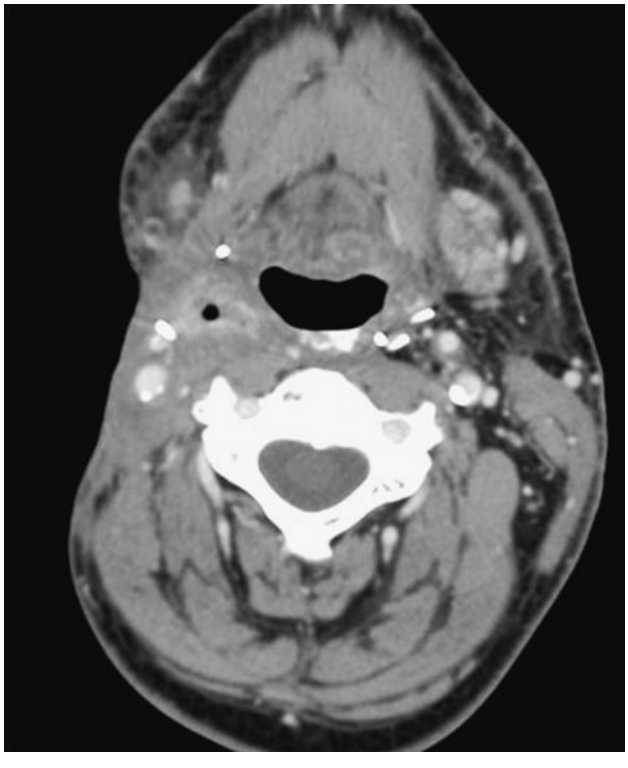

Figure 5.41 Contrast-enhanced computed tomography scan post right neck dissection with loss of fat planes.

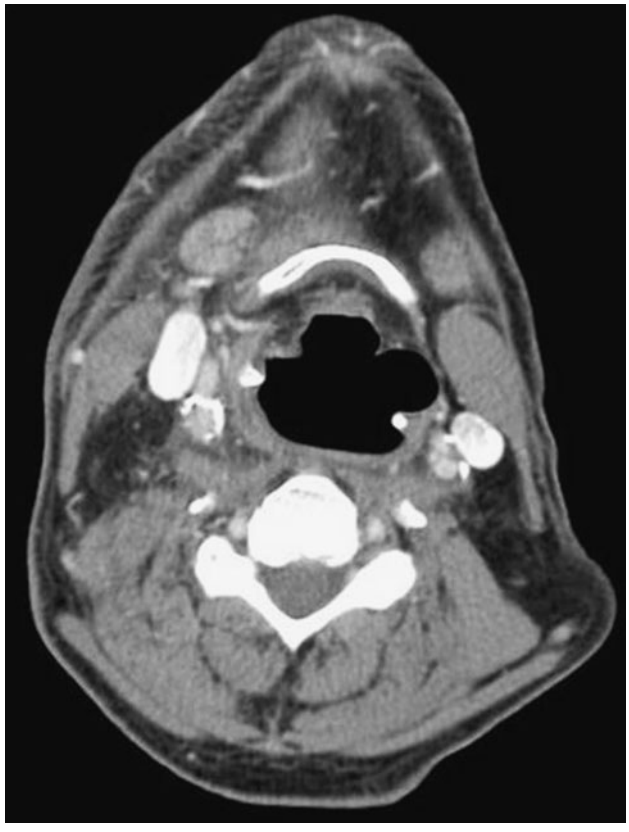

Figure 5.42 Computed tomography scan demonstrating thickening of the right subcutaneous fat and platysma muscle post radiotherapy.

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.[72] 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 ^{18}F-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 (V_2) and foramen rotundum
  - Faucial tonsil to masticator space involving branches of V_3 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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6

Head and neck pathology

RAM MOORTHY AND ADRIAN T WARFIELD

> We recognize only what we see; we see only what we know.
>
> JW Goethe (1749–1832)

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 Papanicolau (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–Grünwald-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**).[2]

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.

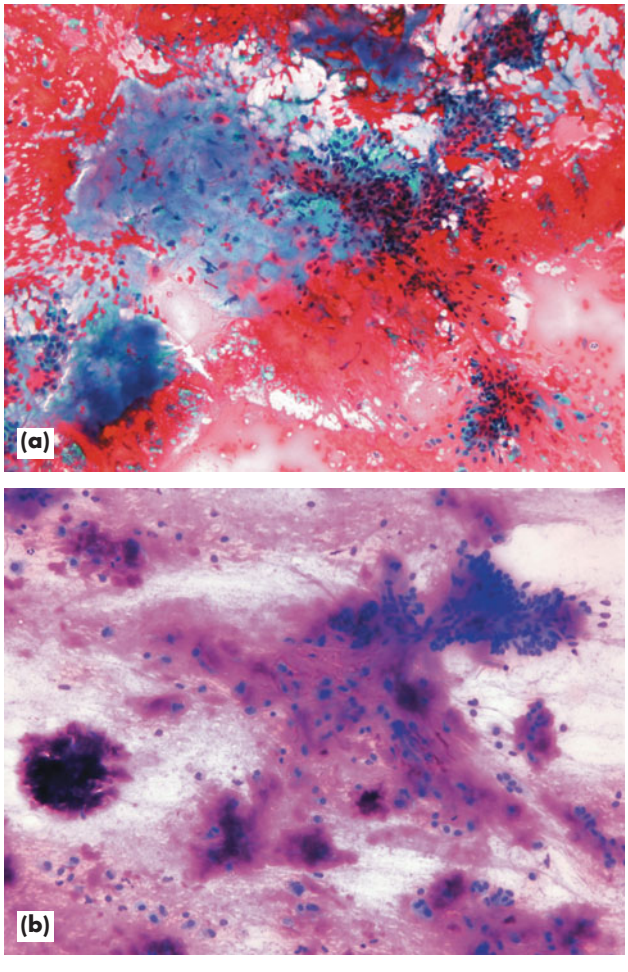

Figure 6.1 Fine needle aspiration cytology (FNAC) preparations from a salivary pleomorphic adenoma. (a) This alcohol-fixed slide depicts weakly stained, feathery stroma intimately admixed with loosely cohesive, isomorphic epithelioid and spindle cells (Pap stain, medium magnification). (b) This air-dried slide from the same tumour at identical magnification highlights the intensely stained myxoid ground substance, which obscures cytological detail in areas (May–Grünwald-Giemsa (MGG) stain, medium magnification).

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.[9] 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**).

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

Type of sample	Advantages	Disadvantages
Fine needle aspiration	(1) Relatively risk free	(1) Primary cytological diagnosis by FNAC must be confirmed by histology prior to radical treatment for head and neck cancer
	(2) Quick	(2) Diagnostic yield is both lesion sensitive and operator dependent and there can be a high non-diagnostic rate,[3, 5] but this may be improved with the use of ultrasound[3]
	(3) Can be undertaken in outpatients	(3) Analysis is limited by cytopathological expertise and has been a rate-limiting step
	(4) Does not usually compromise future management	(4) Clinicians must be aware of inherent limitations including a risk of false-positives and false-negatives
	(5) In assessment of cervical lymphadenopathy FNAC has been shown to have a sensitivity of 76–98%[3] and a sensitivity typically of >90%.[3] The rates can vary with regards salivary gland and thyroid masses[3, 4, 5]	(5) FNAC is of limited help in the diagnosis of lymphoma. Flow cytometry may be helpful in excluding a diagnosis of lymphoma[5]
Core biopsy	(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[6]	(1) Appropriate precautions are required in patients on anticoagulation therapy undergoing core biopsy to prevent bleeding and haematoma formation
	(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	(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[6, 7, 8]
	(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[7]	
Incision biopsy	(1) Can provide definitive histological diagnosis	(1) Can affect definitive management of the tumour
		(2) Can require admission as a day-case
		(3) May require a general anaesthetic
		(4) Higher complication rate than FNAC or core biopsy
		(5) Costlier than FNAC or core-biopsy
Excision biopsy	(1) Can provide definitive diagnosis	(1) Higher risk of complication compared to other biopsy techniques
	(2) Can be definitive treatment of the tumour	(2) Can require admission and the need for general anaesthetic
		(3) Costliest method of obtaining a biopsy

FNAC, fine needle aspiration cytology.

Request form

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.

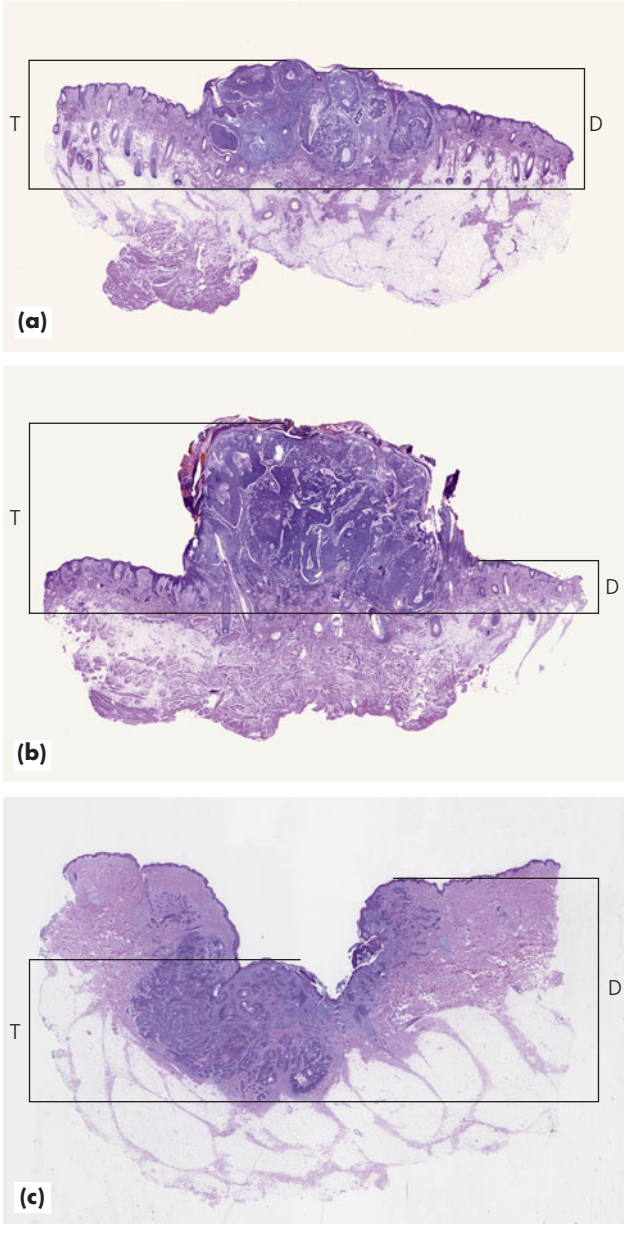

Figure 6.2 The potential discrepancy between tumour thickness and tumour depth. (a) Employing the uppermost granular layer, or actual surface discounting non-vitalized slough if ulcerated, as a fiducial point this relatively flat contoured tumour's thickness is roughly comparable to its depth (H&E stain, 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.)

- 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.

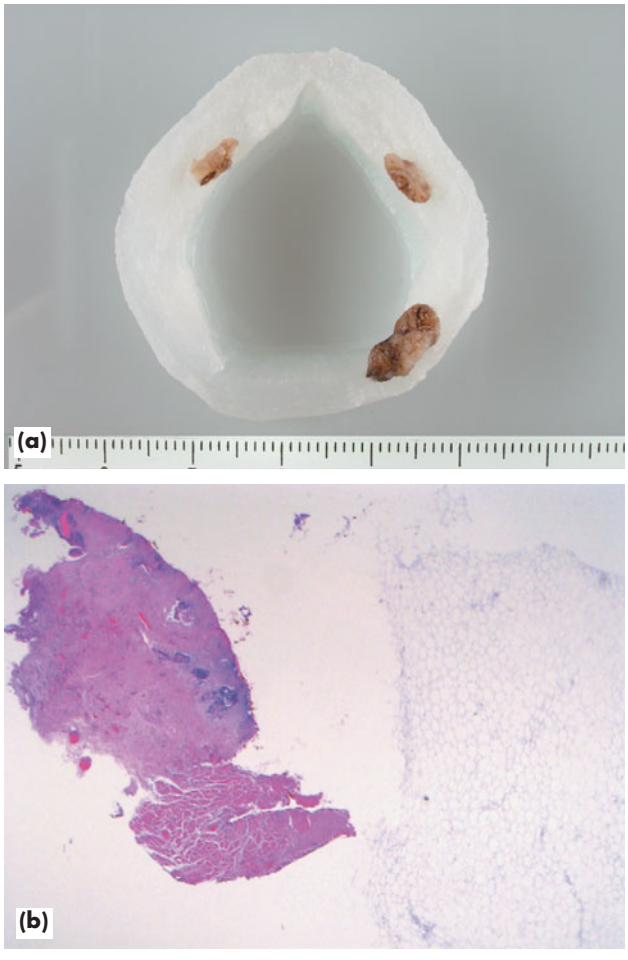

Figure 6.3 Biopsy orientation using a biomount. (a) Three laryngoscopic biopsies glued to a dehydrated cucumber (*Cucumis sativus*) biomount in order to maintain correct orientation in the laboratory. An accompanying endoscopic digital photograph further assists handling of such small biopsies. These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

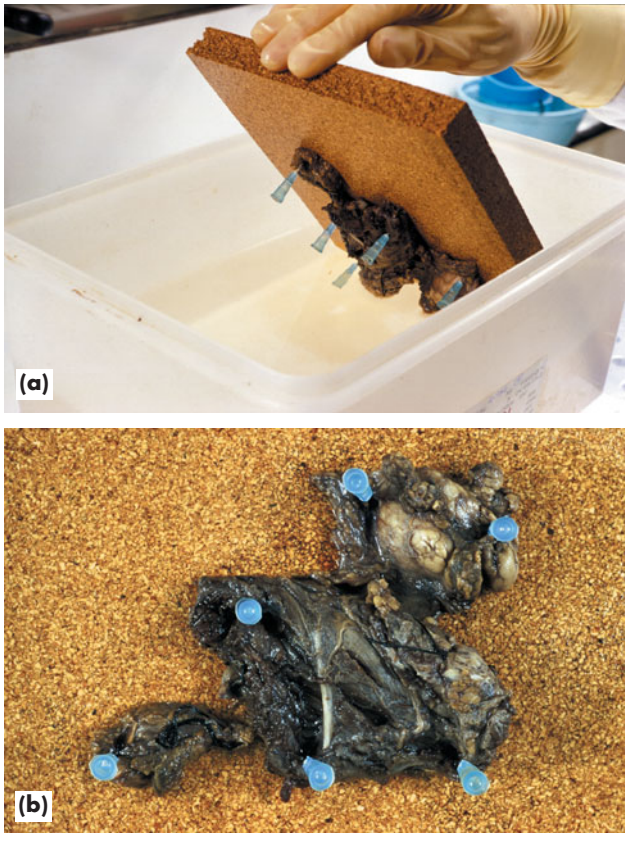

Figure 6.4 Resection specimen orientation utilizing corkboard. (a) Radical neck dissection specimen pinned to cork block, inverted and immersed to float in formalin. Hypodermic needles or other pins should not be pushed completely through the corkboard to obviate the risk of injury to laboratory personnel. (b) The fixed specimen as received in the laboratory, ready for trimming and block selection. This was accompanied by separate annotation by the surgeon. Alternatively, the surgeon may prefer to separate the levels in theatre and place them individually in labelled pots.

section examination, molecular studies or microbiology must be despatched without delay to the laboratory, cognizant that it constitutes an infectious biohazard.

Upon receipt in the laboratory, the specimen identity is corroborated and a unique accession number is allocated. Following an appropriate period of fixation, either the pathologist or senior biomedical scientist staff will describe the specimen macroscopically, dissect and submit representative tissue slices for additional microscopical study, observing relevant protocols and minimum data set guidelines according to their professional experience and discretion. In most laboratories, these slices are inserted into proprietary sealable cassettes appropriately labelled.

After a further period of fixation, the tissue slices undergo cycles of dehydration, clearing, infiltration and embedding in preparation for microtomy. During dehydration, alcohol replaces the aqueous fixative within the tissue. Clearing replaces the alcohol with an antemedium, such as xylene. Molten paraffin wax then replaces the clearing agent and 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

a final conclusion depends on many factors, including detailed site-specific knowledge coupled with experience of normality, familiarity with the manifold appearances of many disease processes at various stages in their natural history, awareness of mimics and artefacts plus cognizance of the limitations of the technique, in conjunction with patient-specific details and the clinical context. Without consideration of these and appropriate correlation with clinical, radiological and other relevant background information, a pathological slide is in danger of becoming a two-dimensional, brightly stained artefact, which may be as misleading as it can be potentially helpful.

Subsites of the head and neck

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

Table 6.2 Head and neck site and subsites.

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

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.[10, 11] 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**.

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.[13] The annual incidence is reported as 2.4–3.05/100 000 and shows a slight female preponderance,[11] as do most salivary gland tumours (**Figure 6.5**).

Table 6.3 Classification of tumours by histogenesis with examples.

Cell type		Examples	
		Malignant	**Benign**
Epithelial		Squamous cell carcinoma Basal cell carcinoma	Papilloma
Neuroectodermal	Central	Olfactory neuroblastoma	
	Peripheral	Malignant Melanoma Neuroendocrine carcinoma Merkel cell tumour	Paraganglioma
Mesenchymal	Lymphoproliferative	Lymphoma	
	Vascular	Angiosarcoma	Nasopharyngeal angiofibroma
	Bone	Osteosarcoma	Osteoma
	Odontogenic		Ameloblastoma
	Cartilage	Chondrosarcoma	Chondroma
	Nerve	Nerve sheath tumour	Schwannoma
	Smooth muscle	Leiomyosarcoma	Leiomyoma
	Skeletal muscle	Rhabdomyosarcoma	Rhabdomyoma
	Adipose tissue	Liposarcoma	Lipoma
	Fibrous	Fibrosarcoma	Fibroma
Salivary gland	Epithelial and myoepithelial	Mucoepidermoid carcinoma Adenocarcinoma	Pleomorphic adenoma Warthin's tumour
	Non-epithelial	Lymphoma Sarcoma	Haemangioma Lipoma

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

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

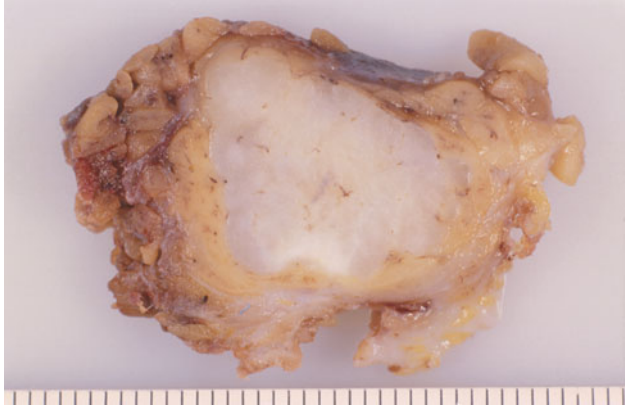

Figure 6.5 Salivary pleomorphic adenoma. The cut surface of a typical salivary pleomorphic adenoma displaying a solid blue/grey hue characteristic of chondromyxoid matrix. More cellular examples tend to be tan or cream/white. Note the localized sessile capsular herniation.

MACROSCOPIC APPEARANCE

SPAs tend to be well demarcated, round or ovoid with broad-based surface bosellations, 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

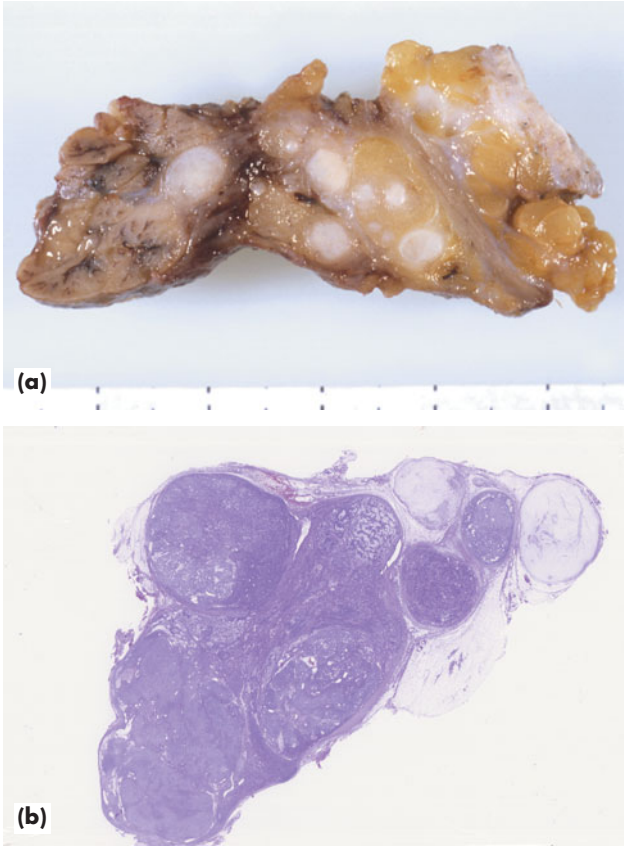

Figure 6.6 Recurrent salivary pleomorphic adenoma. (a) Excision of multinodular recurrence of salivary pleomorphic adenoma encompassing the original surgical field, consequent upon incomplete removal at first operation. (b) Whole mount section of another local recurrence showing secondary seeding of 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).

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. pseudoadenoid cystic, clear cell, epithelial/myoepithelial carcinoma-like, basaloid, giant cell, spindle cell, acinar, plasmacytoid, oncocytoid), crystalloid deposition, dysplasia and malignant transformation.

Table 6.5 Seifert's classification of salivary pleomorphic adenoma.[15]

Subtype	Stromal content
1 (classical SPA)	30–50%
2	80%
3	20–30% and similar epithelial differentiation as subtype 1
4	6% with a relatively monomorphic epithelial structure

Table 6.6 Alternative subclassification system for salivary pleomorphic adenoma.[17, 18]

Subtype	Histological features
Myxoid (stroma-rich)	80% stroma
Cellular	80% cellular
Mixed (classical SPA)	

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 nodes[11, 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]

It can occur over a wide age range, but is common in the sixth decade for women and seventh decade for men.[22] It is more common in males but the male : female ratio has reduced over the last few decades.[11]

There is a link between Warthin's tumour, cigarette smoking[23] 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. Paucilymphocytic Warthin's tumours may closely mimic oncocytic adenoma (oncocytoma) of salivary origin. Malignant transformation, either carcinomatous or lymphomatous is exceptionally rare (**Figure 6.7**).

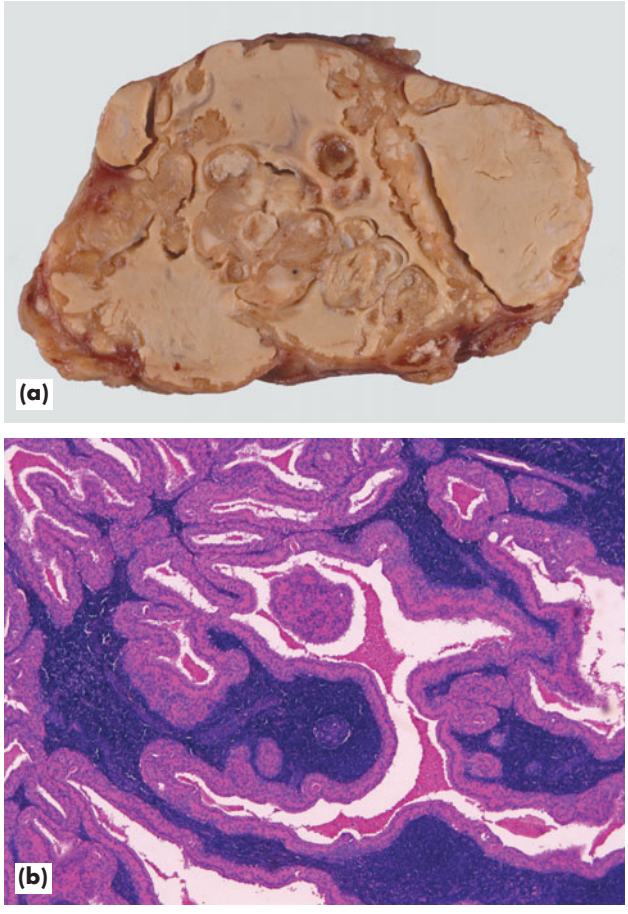

Figure 6.7 Warthin's tumour. (a) The characteristic papillocystic cut surface appearance of Warthin's tumour. Oncocytic epithelium is typically mid-brown. The light tan micronodules correspond to reactive lymphoid follicles. The coagulated cyst contents have retracted slightly during fixation. (b) Well-polarized fronds of oncocytic epithelium supported by hyperplastic lymphoid stroma surrounding cystic lumina are obvious microscopically (H&E stain, ultralow magnification).

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 polypoidal 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.[11] There is convincing evidence that recurrent respiratory papillomatosis is due to human papillomavirus (HPV) infection, with HPV6 and 11 as the dominant subtypes.[28]

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.[16]

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.[29]

Table 6.7 Pathological features of oral cavity and oropharynx papillomas.

Subtype	Squamous papilloma or verruca vulgaris	Condyloma acuminatum	Focal epithelial hyperplasia, Heck's disease
HPV status	Approximately half are associated with HPV infection, typically for squamous papilloma HPV6 and 11 and HPV2 and 57 for verruca vulgaris.[24] Other HPV subtypes implicated include 4, 13 and 32[25]	Associated with HPV6, 11.[11, 26, 27] Transmission is venereal or autoinoculation and there is an association with genital condyloma	HPV13 and 32. Disease of children, adolescents and young adults
Macroscopic appearance	Wart-like exophytic lesion	Dome-shaped exophytic nodules which are usually larger than squamous papilloma	Multiple clusters or patches of soft, plaque-like lesions

HPV, human papilloma virus.

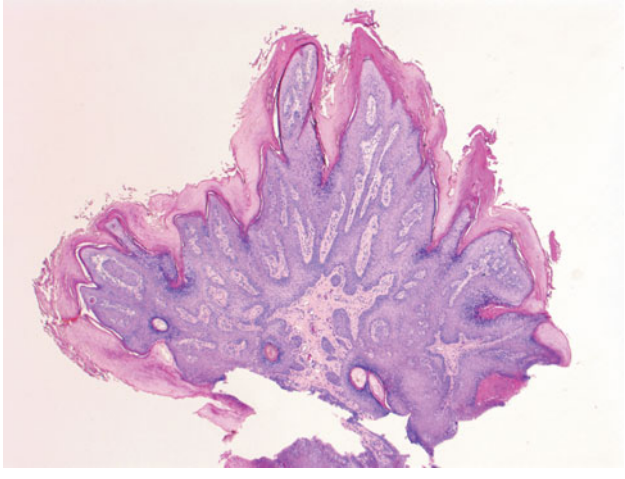

Figure 6.8 Exophytic/fungiform nasal papilloma. Classical exophytic/fungiform nasal papilloma characterized by its radially symmetrical, acrohyperkeratotic outline (H&E stain, ultralow magnification).

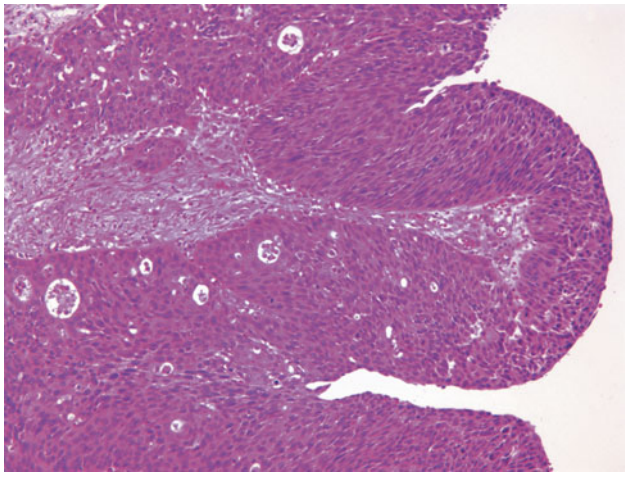

Figure 6.9 Inverted sinonasal papilloma. Inverted sinonasal papilloma illustrating a papilliform surface. This is composed of non-keratinizing squamous and transitional cell-like epithelium with scattered intraepithelial microabscesses. There is no significant cytonuclear atypia in this field (H&E stain,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

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.

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,[11] vestibular schwannoma and a common site of occurrence is the neck,[10] but it is rare in the oral cavity.[30]

NF2 gene is a tumour suppressor gene which is inactivated in 67 per cent of schwannoma, which are in the main sporadic in origin.[31, 32, 33]

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**).

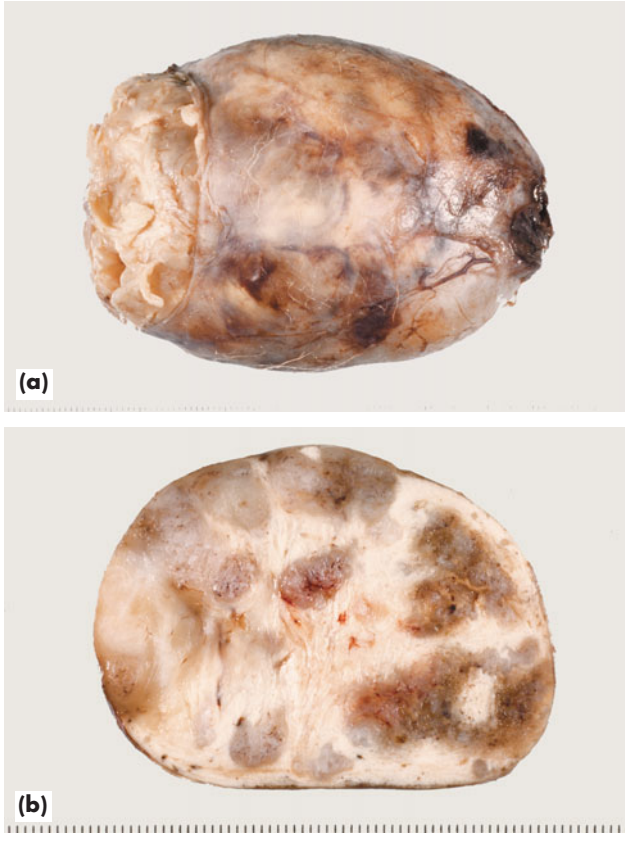

Figure 6.10 Schwannoma. (a) Encapsulated schwannoma from parapharyngeal space giving a smooth surfaced nodal appearance, although the capsule is deficient at one pole. This arises eccentrically from nerve trunk in contrast to neurofibroma, which expands the nerve fibres in a fusiform fashion. (b) The cut surface displays a variegated texture corresponding to areas of Antoni A and Antoni B growth pattern.

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.[11]

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.[34] 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.[34] The affected genes code for subunits of succinate dehydrogenase protein, a mitochondrial enzyme. The genes are found on chromosome 1 and 11.[35]

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 focally 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.[38] The group as a whole accounts for over 8000 cases and 2700 deaths per year in England and Wales.[39] 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 6.8 Site and features of head and neck paragangliomata.

Name of paraganglion	Location	Features
Carotid body	Carotid bifurcation	Most common site (60%) for paraganglioma in head and neck.[36] 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[11] 31% of familial tumours are bilateral compared to 4% of sporadic[36]
Jugulotympanic	Jugular bulb (glomus jugulare) and promontory on medial of middle ear cleft (glomus tympanicum)	Second most common site for head and neck paraganglioma. The sporadic form is more common in females, while the familial form is more common in males[36]
Vagal	Found within or adjacent to the vagus nerve usually near the ganglion nodusum (largest and most inferior of the three ganglia)	Account for less than 5% of head and neck paragangliomas.[36] Most are sporadic, more common in women and occur over a wide age range[11]
Laryngeal	Superior and inferior paraganglia of the larynx	Rare, more common in women and over a wide age-range[11]
Miscellaneous	Orbit[37] Thyroid gland[36] Sinonasal[36]	