Book Section:
Mayland, C.R. (2024) Chapter 15: Palliative care in head and neck cancer. In: Homer, J.J. and Winter, S.C., (eds.) Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition. The Journal of Laryngology & Otology, 138 (S1). Cambridge University Press (CUP) , S83-S95.

https://doi.org/10.1017/s0022215123001615

VOLUME 138 | NUMBER S1 | APRIL 2024 ISSN: 0022-2151

The Journal of Laryngology & Otology

Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition

Edited by Jarrod J Homer and Stuart C Winter

ENDORSED BY:

Association of Palliative Medicine (APM)

British Association of Endocrine and Thyroid Surgeons (BAETS)

British Association of Head and Neck Oncologists (BAHNO)

British Association of Head and Neck Oncology Nurses (BAHNON)

British Association of Oral and Maxillofacial Surgeons (BAOMS)

British Association of Plastic Reconstructive and Aesthetic Surgeons (BAPRAS)

ENT UK

Restorative Dentistry UK (RD-UK)

Royal College of Speech and Language Therapists (RCSLT)

The Royal College of Pathologists (RCPath)

The Royal College of Radiologists (RCR)

Founded in 1887
By Morell Mackenzie and Norris Wolfenden

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

The Journal of

Laryngology & Otology

Founded in 1887 by Morell Mackenzie and Norris Wolfenden

Email: managing-editor@jlo.co.uk. Website: http://www.jlo.co.uk

The Journal of Laryngology & Otology (ISSN 0022-2151) is published monthly in both print and electronic form and distributed on behalf of the proprietors, JLO (1984) Ltd, by Cambridge University Press
Registered Charity No 293063

SUBSCRIPTIONS, LICENSING, ADVERTISING AND REPRINTS

The Journal of Laryngology & Otology (ISSN 0022-2151) is published monthly in both print and electronic form and distributed on behalf of the proprietors, JLO (1984) Ltd, by Cambridge University Press.

Subscriptions: Volume 138, 2024 (Monthly)
Both standard and online-only subscription prices entitle subscribers to access all of the archival online content, which dates back to Volume 1 (1887). For further details please go to Cambridge University Press.

Institutions print and electronic: £828/$1649. Institutions electronic only: £550/$1088. Individuals print plus electronic: £420/$837. Member rates available – please enquire. Special rates available for Trainees. Print ISSN 0022-2151. Electronic ISSN 1748-5460.

Orders are regarded as firm, and payments are not refundable. All orders and enquiries, including online licensing and consortia enquiries, should be sent to: Journals Subscription Department, Cambridge University Press.

*Periodicals postage paid at Rahway, NJ. US Postmaster: send address changes to *The Journal of Laryngology & Otology*, c/o Mercury Airfreight International Ltd, 365 Blair Road, Avenel, NJ 07001, USA.

Advertising sales
Contact: Ad sales, Journals, Cambridge University Press.
Tel: +44 (0)1223 325757
Fax: +44 (0)1223 325801
E-mail: UK: ad_sales@cambridge.org
US: USAdSales@cambridge.org

Other business correspondence
All other business correspondence, should be sent to: JLOProduction@cambridge.org Journals Department, Cambridge University Press. Enquiries about reprints should be sent to Ad sales: special_sales@cambridge.org

Typeset by Techset and printed in the UK by CPI Group (UK) Ltd.

This Journal issue has been printed on FSC™-certified paper and cover board. FSC is an independent, non-governmental, not-for-profit organization established to promote the responsible management of the world's forests. Please see www.fsc.org for information.

SUMMARY GUIDANCE FOR AUTHORS

The Journal of Laryngology & Otology (*JLO*) is a peer-reviewed publication, and is indexed/abstracted in most major databases including Index Medicus, MEDLINE/ PubMed, Science Citation Index, Current Contents and EMBASE.

Only a very brief summary of the submission requirements is presented here: when preparing their manuscripts, authors must consult and comply with the full Instructions for Authors on the *JLO* website at **http://www.jlo.co.uk/docs/submittingarticles.htm** Adherence to these will speed up the editorial process.

All contributions are considered for publication on the understanding that they have been submitted solely to the *JLO* and that they have not previously been published. Contributions in the following categories will be considered: Main Articles (reporting clinical research or audit), Review Articles, Historical Articles, Short Communications (including 'How I do it'), Clinical Records (case reports), and Letters to the Editors.

Submission
Please submit articles electronically using the ScholarOne Manuscripts submission site: https://mc.manuscriptcentral.com/jlo

The text of the manuscript (incorporating all tables and the figures legends, but ***not*** the figures themselves) must be saved as a Microsoft Word document or an RTF file (i.e. 'rich text format'). Use double-spaced, unjustified text throughout. The title page must contain the full title of the paper; the names and qualifications of all authors; the departments(s) and institution(s) where the work was carried out; and the name, postal and e-mail address, and telephone and fax numbers of the author responsible for all communications about the manuscript and proofs. An Abstract (maximum 150 words) and Key words must be provided for all contributions (except Letters).

References should be identified in the text by superscript Arabic numerals and listed at the end of the manuscript in the order in which they are first cited in the text. The tables feature of the word processor should be used to prepare Tables, and both these and the list of Figure legends should appear on separate pages at the end of the manuscript. All Figures must be saved as separate TIFF files at a resolution of 600 dpi.

The authors of all material accepted for publication will be required to assign copyright to JLO (1984) Ltd; a form for this purpose and for ordering offprints will accompany the proofs. The proofs will be sent by e-mail to the corresponding author as a PDF file, and should be corrected and returned within three working days.

The Journal of

Laryngology & Otology

Volume 138, Number S1, April 2024

Head and Neck Cancer:

United Kingdom National Multidisciplinary Guidelines, Sixth Edition

Edited by:

Jarrod J Homer
Consultant Surgeon and Professor of Otolaryngology-Head and Neck Surgery
Manchester Head and Neck Centre, Manchester University NHS Foundation Trust,
Manchester Academic Health Sciences Centre

Stuart C Winter
Consultant Otolaryngologist, Head and Neck Surgeon
Associate Professor, University of Oxford

Endorsed by:

Sponsored by:

JLO (1984) Ltd

Publication of this Supplement was supported by JLO (1984) Ltd.

These guidelines have been reviewed by the Guest Editors and may be cited.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

The Journal of Laryngology & Otology

cambridge.org/jlo

Guidelines

Jarrod J Homer and Stuart Winter take responsibility for the integrity of the content of the paper

Cite this article: Homer JJ, Winter SC. Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition. *J Laryngol Otol* 2024;**138**:S1–S224. https://doi.org/10.1017/S0022215123001615

Received: 10 September 2023
Accepted: 10 September 2023

Corresponding authors:
Jarrod J Homer;
Email: jarrod.homer@mft.nhs.uk
Stuart C Winter;
Email: stuart.winter@nds.ox.ac.uk

Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition

Jarrod J Homer[1,2] and Stuart C Winter[3,4]

[1]Manchester Head and Neck Centre, Manchester University NHS Foundation Trust, Manchester, UK, [2]Manchester Academic Health Sciences Centre, University of Manchester, UK, [3]Department of Otolaryngology, Head and Neck Surgery, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK and [4]Blenheim Head and Neck Unit, Churchill Hospital, Oxford, UK

Introduction

This is the sixth iteration of *Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines*, produced by a broad range of UK professionals involved in the care of patients with head and neck cancer (see Author List).

The Guidelines are divided into 30 chapters that aim to cover all aspects of care for patients with head and neck cancer, ranging from the provision of services, management in general, to the management of specific tumours. Rather than a simple update to the last iteration, most chapters have been rewritten. The major change is the increased emphasis on multidisciplinary care. With that in mind, the Guidelines are split into three sections. These are: (Section 1) general issues underpinning the basis of care of patients with head and neck cancer, which apply across the spectrum of management; (Section 2) patient support, describing mainly the support required throughout the patient journey, and the pre-, peri- and post-treatment provided by various health professionals; and (Section 3) site-specific chapters, as in the previous iteration. An addition to these Guidelines is a chapter dealing with head and neck paraganglioma. Although not usually a malignant disease, it is an area that involves input from a variety of disciplines and is probably subject to significant variation in management.

The Guidelines have been authored by over 170 UK-based authors covering 22 specialties (anaesthetics, clinical nurse specialists, dermatology, dietetics, endocrinology, endocrine surgery, otolaryngology – head and neck surgery (ENT), genetics, oral maxillofacial surgery, oncology, oral surgery, palliative care, pathology, physiotherapy, pharmacology, plastic surgery, psychology, public health, radiology, restorative dentistry, speech and language therapy, and vascular surgery).

The Guidelines have been endorsed by 12 national bodies:

- Association of Palliative Medicine ('APM')
- British Association of Endocrine and Thyroid Surgeons ('BAETS')
- British Association of Head and Neck Oncologists ('BAHNO')
- British Association of Head and Neck Oncology Nurses ('BAHNON')
- British Association of Oral and Maxillofacial Surgeons ('BAOMS')
- British Association of Plastic Reconstructive and Aesthetic Surgeons ('BAPRAS')
- British Dietetic Association
- ENT-UK
- Restorative Dentistry – UK
- Royal College of Speech and Language Therapists
- The Royal College of Pathologists ('RCPath')
- The Royal College of Radiologists (Faculty of Clinical Oncology)

The aim has been to set standards of care and best practice. The Guidelines can be also used as an educational resource for clinicians, and for insight into head and neck cancer care for non-clinicians involved in commissioning and managing services for patients with head and neck cancer.

As with the last Guidelines, summary recommendations appear throughout the document. These are qualified by '(R)' or '(G)'. '(R)' can be taken as an accepted standard of care and/or with a strong evidence base (an evidence-based recommendation). It can be interpreted as equivalent to 'offer' in National Institute for Health and Care Excellence (NICE) guideline parlance. '(G)' can be taken as something that should be at least considered, with some supporting evidence (a good practice point). It can be interpreted as equivalent to 'consider' in NICE guideline parlance. When recommendations concern the provision of services, these terms may be replaced with '(E)' (essential) and '(D)' (desirable).

The Guidelines are guidelines, and not black and white diktats of what constitutes acceptable and non-acceptable care. Every patient has different individual circumstances (tumour, patient, environment), and care is therefore variably nuanced.

The variety of treatment options can be difficult for a patient to navigate through. It is thus critical that the clinical team help patients to make very difficult decisions, with the provision of clear and understandable information on the risks and benefits associated with treatments offered.

There have been some significant developments in practice since the last Guidelines. These mainly have involved increasing recognition and understanding of the nature of human papillomavirus related squamous cell carcinomas, increasing experience of systemic therapies, in particular immunotherapy, and the updated staging classification (*TNM Classification of Malignant Tumours*, eighth edition) by the American Joint Committee on Cancer ('AJCC') and Union for International Cancer Control ('UICC'). However, perhaps the most powerful area of change is the continued development of prehabilitation, which features prominently in Section 2, and involves input from various health professionals with large areas of overlap.

Chapters on non-melanoma skin cancer and cancer of an unknown primary follow previous consensus-gathering initiatives, with more detail regarding evidence sources and wider input by those taking part in these consultations. This may be a model to follow in future.

The authors of each chapter were invited to suggest areas in which research or evidence is required, and to indicate important on-going clinical trials that are due to report in the next few years.

UK clinical trials can be found via the National Cancer Research Institute, which supports a wide variety of clinical trials in head and neck cancer (https://www.ncri.org.uk (search portfolio maps)). Major USA trials undertaken by the NRG co-operative group can be viewed here: https://www.nrgoncology.org/Clinical-Trials/Protocol-Search. Other global trials can be found at: https://clinicaltrials.gov.

The guidelines have been generously peer reviewed (Appendix 1).

Endorsements

Association for Palliative Medicine (APM)

British Association of Endocrine & Thyroid Surgeons (BAETS)

British Association of Head & Neck Oncologists (BAHNO)

It gives me great pleasure to write a foreword for the 6th edition of the Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines.

In the five years since the last edition was published, a significant evidence base has accrued in the management of head and neck cancer, especially for oropharyngeal cancer and recurrent metastatic cancer. Additionally, the impact of the coronavirus disease pandemic, which has been felt across all domains of clinical practice, has certainly changed practice in the realms of cancer diagnoses.

Professors Jarrod Homer and Stuart Winter are to be congratulated on compiling this edition of the guidelines, with comprehensive multidisciplinary stakeholder engagement, which significantly builds on the previous edition. Having very carefully sieved through the 30 chapters that comprise the guidelines, I believe this truly captures the best of British expertise in head and neck cancer care. The multidisciplinary authorship reflects the clinicians, researchers and thought leaders in the specialty, who make recommendations based on existing evidence and current practice. I am only too well aware of the long and arduous hours it takes to put together a work of this kind, and the quality of the contributions indicates that the guidelines will be well received by the head and neck oncology community.

In addition to the clinical recommendations, these guidelines have also used a new approach to generate consensus across areas that are not supported by high-level evidence. Working collaboratively with six stakeholder organisations, novel comprehensive methodology was used to achieve consensus recommendations; this is demonstrated to good effect for the unknown primary.

On behalf of the British Association of Head & Neck Oncologists, I whole heartedly endorse these guidelines for practice within these Isles and beyond.

Vinidh Paleri MS FRCS

President, British Association of Head & Neck Oncologists (BAHNO)

British Association of Head & Neck Oncology Nurses (BAHNON)

On behalf of the British Association of Head & Neck Oncology Nurses Committee, we are delighted to endorse this document. This multidisciplinary document will have a positive impact on the delivery of the highest standard of research-based patient care for many years to come. It will be a valuable resource to all members of the multidisciplinary team. I would like to take the opportunity to thank the authors and editors for all their hard work.

Maria Smith

Vice Chair, CNS, Royal Alexandra Hospital/Queen Elizabeth University Hospital – NHS Greater Glasgow & Clyde

British Association of Oral and Maxillofacial Surgeons (BAOMS)

On behalf of the British Association of Oral and Maxillofacial Surgeons, as the Oncology Subspecialty Interest Group Leads,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

it is a privilege to write a foreword for this essential scientific document.

Best practice is driven by robust guidelines, which in turn must derive from a high-quality evidence base. The complexity and relatively low incidence of head and neck cancer renders this task extremely challenging.

The 6th edition of Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines embrace the current best available evidence, with comprehensive multidisciplinary specialist team consensus, for practices in caring for head and neck cancer patients.

The publication addresses the challenges met in the complex field of head and neck cancer, but also offers succinct insight into new scientific approaches, such as non-surgical systemic treatments and minimally invasive procedures, either for diagnosis or definitive management.

Whilst cure is the primary goal in the management of patients with head and neck cancer, the document also guides us well regarding the palliative patient, with a focus on quality of life, and updates on psychosocial support and targeted novel treatments.

With a high calibre authorship of renowned experts, this guidance document undoubtedly offers a state-of-the-art overview in head and neck cancer and its management.

We congratulate the cohesive collegiate teamwork in producing this superb set of guidelines.

Brian Bisase and Mr Leandros (Leo) Vassiliou DDS (Hons) MD (Hons) MRCS MSc FRCS (OMFS)

Subspecialty Interest Group Leads for Head and Neck Oncology
British Association of Oral and Maxillofacial Surgeons

BAOMS
British Association of Oral and Maxillofacial Surgeons

British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)

On behalf of the British Association of Plastic, Reconstructive and Aesthetic Surgeons, I am delighted to endorse the publication of these guidelines, and for British Association of Plastic, Reconstructive and Aesthetic Surgeons to be involved in such a collaborative effort, bringing together the knowledge of a truly multidisciplinary group of specialists involved in the management of patients suffering from cancer of the head and neck. The latest guidelines will continue to support multidisciplinary teams and to help provide the best possible outcome for patients.

Mr Maniram Ragbir

President, British Association of Plastic, Reconstructive and Aesthetic Surgeons

BAPRAS
British Association of Plastic
Reconstructive and Aesthetic Surgeons

ENT-UK

I am delighted to write a short introduction to the 6th edition of the Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines. I have been privileged to contribute to all of the previous excellent editions, and without doubt this edition of the guidelines is the most comprehensive to date. The multidisciplinary team (MDT) model is the core of head and neck services in the UK, and the list of authors clearly demonstrates the truly multidisciplinary nature of these guidelines. There was no shortage of excellent authors from all specialties who were keen to contribute to these guidelines, which indicates how important this established publication has become amongst the head and neck specialty. Stuart Winter and Jarrod Homer should be congratulated on the tremendous amount of work they have put in, and it is reflected in a comprehensive, concise, contemporary and eminently readable textbook. These guidelines will be essential reading for all those involved in the management of head and neck cancer, and will form an excellent reference to help inform MDT decisions.

Sanjai Sood MBChB, FRCS, FEBE-ORLHNS

President, ENT-UK Head & Neck Society

ENTUK

Restorative Dentistry – UK (RD-UK)

We are fortunate to have so many talented and dedicated colleagues involved in delivering healthcare across the UK. Our patients benefit so much more when we work together, within well-structured multidisciplinary teams. We therefore have the opportunity, and, indeed, the responsibility, to collaborate with others, sharing what we currently believe is best practice, caring deeply for our patients, and being open to both teaching and learning, so that we are well prepared for those who will need us in the future.

On behalf of Restorative Dentistry – UK and our specialty of restorative dentistry, I am delighted to endorse the 6th edition of these essential guidelines, and welcome the recognition of our specialty as a core member of the multidisciplinary head and neck cancer team. Restorative dentistry is for those patients who have complex dental problems, requiring multidisciplinary, specialist care for their oral rehabilitation. These guidelines confirm the need for and benefit of restorative dentistry at all stages of the head and neck cancer pathway, ensuring better clinical and personal outcomes for our patients, throughout their treatment and recovery.

These guidelines are, once again, a considerable step towards ensuring that high standards of care are delivered to our patients. We congratulate and thank all those who have contributed to writing, collating and publishing this edition.

Professor Martin Ashley BDS (Hons) FDSRCS (Eng) FDS (Rest Dent) RCSEng MPhil MFCI

Chair, Restorative Dentistry – UK

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Royal College of Speech and Language Therapists (RCSLT)

The Royal College of Speech and Language Therapists is pleased to endorse this high-quality document, in which a great deal of thought and effort has gone into its creation. It will be a very useful resource for speech and language therapists working in head and neck cancer, providing key point summaries and detailed information on speech and language therapy interventions at different stages of the cancer pathway. Clear guidance will be invaluable to speech and language therapists, enabling them to perform their best, which will benefit patients and their families, and foster interprofessional working.

Kamini Gadhok and Judith Broll

Chief Executive Officer, Royal College of Speech and Language Therapists and Director of Professional Development, Royal College of Speech and Language Therapists

The Royal College of Pathologists (RCPath)

On behalf of The Royal College of Pathologists, I am delighted to endorse the latest update of these guidelines, and I thank the editors and authors for their hard work, particularly Drs Betts, Damato, Robinson and Thavaraj and Prof. Hunter, who contributed the pathology content. The guidelines are testament to the importance of collaborative working between specialties in the treatment of head and neck cancer, and rightly acknowledge cellular pathology as a core component of this. An exciting addition to the guidelines is the molecular testing of head and neck tumours, which has developed immeasurably since the last edition, and places cellular pathology at the centre of diagnosis, prognostication and therapy. This quality-assured pathology guidance provides reassurance to clinical teams that pathology information is based on good evidence, robustly accredited, and has the confidence of members of the College. Congratulations on an excellent document.

Professor Michael Osborn BSc MBBS MRCS FRCPath

President of The Royal College of Pathologists

The Royal College of Radiologists (RCR)

On behalf of The Royal College of Radiologists, I am delighted to welcome this 6th edition of the Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines. These guidelines are a key clinical resource for all those involved in the treatment of patients with head and neck cancer, and I hope this new edition will continue to support essential multidisciplinary working in this field and promote the highest possible standards of patient care. I would like to congratulate the editors and authors – who include a number of Fellows of the Royal College of Radiologists – for their hard work and dedication in producing these excellent guidelines.

Dr Katharine Halliday

President, The Royal College of Radiologists

Authors

Elizabeth C Abbey, Department of Palliative Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Chapter 15)
Hiba Aga, Head and Neck Department, Nottingham University Hospitals, Nottingham, UK (Chapter 26)
Reshma Agrawal, Histopathology, University College London Hospitals NHS Trust, London, UK (Chapter 25)
Derfel ap Dafydd, Radiology, Royal Marsden NHS Foundation Trust, London, UK (Chapter 29)
Takhar Arunjit, Department of Otolaryngology – Head and Neck Surgery, St George's Hospital NHS Trust, London, UK (Chapter 30)
Patrick Axon, Department of ENT, Addenbrookes Hospital, Cambridge, UK (Chapter 22)
Eleanor Aynsley, Department of Oncology, James Cook University Hospital, Middlesbrough, UK (Chapter 18)
Izhar N Bagwan, Histopathology, Royal Surrey County NHS Foundation Trust, Guildford, UK (Chapter 29)
Arun Batra, Department of Radiology, North Tees University Hospital, Stockton-on-Tees, UK (Chapter 18)
Donna Begg, Clinical Nursing, University Hospitals Birmingham, Birmingham, UK (Chapter 29)
Jonathan M Bernstein, Department of Otolaryngology – Head and Neck, Surgery, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK (Chapters 17, 24 and 30*)
Guy Betts, Adult Histopathology Department, Manchester Royal Infirmary, Manchester, UK (Chapters 3 and 21)
Colin Bicknell, Department of Vascular Surgery, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK (Chapter 30)
Brian Bisase, Department of Oral and Maxillofacial Surgery, Queen Victoria Hospital, East Grinstead, UK (Chapter 7*)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Grainne C Brady, Department of Speech, Voice and Swallowing, Royal Marsden NHS Foundation Trust, London, UK (Chapter 10)
Peter Brennan, Oral and Maxillofacial, Head and Neck Surgery, Portsmouth Hospitals NHS Trust, Portsmouth, UK (Chapter 16*)
Aina Brunet, Department of Otorhinolaryngology, Head and Neck Surgery, and Head, Neck Thyroid Cancer Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapter 20)
Val Bryant, Patient representative, Sunderland, UK (Chapter 8)
Linda Cantwell, University of Liverpool School of Health Sciences, Liverpool, UK, and Department of Dietietics, Merseycare NHS Foundation Trust, Liverpool, UK (Chapter 8)
Ashish Chandra, Department of Cellular Pathology, St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapter 25)
Preetha Chengot, Department of Pathology, Leeds Teaching Hospitals, Leeds, UK (Chapter 24)
Melvin L K Chua, Division of Radiation Oncology, National Cancer Centre, Singapore (Chapter 19)
Peter Clarke, Department of ENT, Imperial College Healthcare NHS Trust, London, UK (Chapter 23)
Gemma Clunie, Complex Laryngology/Airways Service, National Centre for Airway Reconstruction, Imperial College Healthcare NHS Trust, London, UK (Chapter 10)
Margaret Coffey, Speech and Language Therapy, Imperial College Healthcare NHS Trust, London, UK (Chapter 10)
Clare Conlon, Department of Anaesthesia, Manchester University Hospitals NHS Foundation Trust, Manchester, UK (Chapter 8)
David I Conway, School of Medicine, Dentistry, and Nursing, University of Glasgow, Glasgow, Scotland, UK (Chapter 6)
Florence Cook, Head and Neck Centre, University College London Hospital NHS Foundation Trust, London, UK (Chapter 9*)
Matthew R Cooper, Librarian, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Chapter 15)
Declan Costello, Otolaryngology, Head and Neck Surgery, Wexham Park Hospital, Slough, UK (Chapter 16*)
Ben Cosway, Department of Otolaryngology, James Cook University Hospital, Middlesbrough, UK (Chapter 18)
Neil J A Cozens, Department of Radiology, Royal Derby Hospital, Derby, UK (Chapter 25)
Grant Creaney, School of Medicine, Dentistry, and Nursing, University of Glasgow, Glasgow, Scotland, UK (Chapter 6)
Gahir K Daljit, Clinical Oncology, University Hospital of North Midlands NHS Trust, Stoke-on-Trent, UK (Chapter 26)
Stephen Damato, Department of Cellular Pathology, John Radcliffe Hospital, Oxford, UK (Chapter 3)
Joe Davies, Department of Oncology, Poole Hospital, Poole, UK (Chapter 16)
Katharine S Davies, Department of Otolaryngology, Head and Neck Surgery, Aintree Hospital, Liverpool University Hospitals Trust, Liverpool, UK (Chapter 2)
Alina D Dragan, Radiology Department, Royal Marsden Hospital, London, UK (Chapter 26)
Yong Du, Department of Nuclear Medicine and PETCT, Royal Marsden NHS Foundation Trust, Sutton, UK (Chapter 30)
Mark R D Edmond, Department of Otolaryngology, Head and Neck Surgery, Poole Hospital, Poole, UK (Chapters 16 and 29)
Stefano Fedele, Department of Oral Medicine, University College London Eastman Dental Institute, London, UK (Chapter 16*)
Harriet Finze, Physiotherapy, Churchill Hospital, Oxford, UK (Chapter 11)
Jason C Fleming, Liverpool Head and Neck Centre, Liverpool University Hospitals NHS Foundation Trust/University of Liverpool, Liverpool, UK (Chapter 23)
Bernadette H Foran, Weston Park Cancer Centre, Sheffield, UK (Chapter 21)
Beth Fordham, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK (Chapter 11)
Mohammed M A S Foridi, Clinical Pharmacy, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Chapter 15)
Lesley Freeman, Department of Nutrition and Dietetics, Sunderland Royal Hospital, Tyneside and Sunderland NHS Foundation Trust, Sunderland, UK (Chapter 9)
Katherine E Frew, Palliative Medicine, Wansbeck General Hospital, Northumbria Healthcare NHS Foundation Trust, Ashington, UK (Chapter 15)
Pallavi Gaitonde, Restorative Dentistry, Castle Hill Hospital, Hull and East Ridings NHS Trust, Cottingham, UK (Chapter 13)
Victoria Gallyer, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK (Chapter 11)
Fraser W Gibb, Department of Endocrinology, NHS Lothian, Edinburgh, Scotland, UK (Chapter 25)
Sinclair M Gore, Blenheim Head and Neck Unit, Churchill Hospital, Oxford, UK (Chapters 1 and 17)
Mark Gormley, MRC Integrative Epidemiology Unit, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK (Chapter 6)
Roganie Govender, Head and Neck Academic Centre and Research, University College London, London, UK (Chapter 10)
J Greedy, Head and Neck Cancer, Beacon Cancer Centre, Musgrove Park Hospital, Taunton, UK (Chapter 12)
Teresa Guerrero Urbano, Department of Clinical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapter 20)
Dorothy Gujral, Department of Clinical Oncology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK (Chapter 30)
David W Hamilton, Department of ENT, Freeman Hospital, Newcastle upon Tyne, UK (Chapter 21)
John C Hardman, Department of Head and Neck Surgery, Royal Marsden Hospital, London, UK (Chapter 27*)
Kevin Harrington, Department of Oncology, Royal Marsden NHS Foundation Trust, London, UK (Chapters 27 and 29)
Samantha Holmes, Speech and Language Therapy, Oxford University Hospitals NHS Trust, Oxford, UK (Chapter 8)
Jarrod J Homer, Manchester Head and Neck Centre, Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, UK (Introduction, and Chapters 1, 25 and 30)
Deborah Howland, Department of Nutrition and Dietetics, Torbay Hospital, Torbay and South Devon NHS Foundation Trust, Torquay, UK (Chapter 9)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Gerald Humphris, Medical School, University of St Andrews, St Andrews, Scotland, UK (Chapter 14*)
Keith D Hunter, Academic Unit of Oral Medicine and Pathology, School of Clinical Dentistry, Sheffield, UK (Chapter 3)
Kate Ingarfield, Centre for Trials Research, Neuadd Meirionnydd, Cardiff, Wales, UK (Chapter 6)
Richard Irving, Department of Otolaryngology, Queen Elizabeth Hospital NHS Foundation Trust, Birmingham, UK, and Department of Otolaryngology, Diana, Princess of Wales Hospital for Children, Birmingham, UK (Chapter 30)
Kristina Isand, Department of Endocrinology, Oxford University Hospital, Oxford, UK (Chapter 16)
Yatin Jain, Department of Radiology, Christie Hospital NHS Foundation Trust, Manchester, UK (Chapters 2 and 21)
Sachin Jauhar, Restorative Dentistry, Glasgow Dental Hospital, Glasgow, Scotland, UK (Chapter 13)
Sarra Jawad, Restorative Dentistry, Guy's Hospital, London, UK (Chapter 13)
Glyndwr W Jenkins, Department of Maxillofacial Surgery, Freeman Hospital, Newcastle upon Tyne Hospitals Trust, Newcastle upon Tyne, UK (Chapter 2)
Anil Joshi, name retracted as author of Ch 28 (as per Jarrod Homer) (Chapter 28)
Anastasios Kanatas, Department of Head and Neck Surgery, St James Institute of Oncology, Leeds Dental Institute, Leeds General Infirmary and University of Leeds, Leeds, UK (Chapter 16*)
Stephen Keohane, Department of Dermatology, Portsmouth Hospitals NHS Trust, Portsmouth, UK (Chapter 28)
Cyrus J Kerawala, Head and Neck Unit, Royal Marsden Hospital, London, UK (Chapters 17 and 29)
William Keys, Restorative Dentistry, Aberdeen Dental Institute, Aberdeen, Scotland, UK (Chapter 13)
Emma V King, Department of Otolaryngology, Head and Neck Surgery, Poole Hospital, Poole, UK (Chapters 16* and 29*)
Anthony Kong, Comprehensive Cancer Centre, Guy's Campus, King's College London, London, UK, and Department of Clinical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapters 5 and 20)
Fiona Lalloo, Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University Foundation Trust, Manchester, UK (Chapter 30)
Kirsten Laws, Department of Oncology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK (Chapter 4)
Samuel C Leong, Liverpool Head and Neck Centre, Liverpool University Hospitals NHS Foundation Trust/University of Liverpool, Liverpool, UK (Chapter 23)
Shane Lester, Department of Otolaryngology, James Cook University Hospital, Middlesbrough, UK (Chapter 18*)
Miles Levy, Department of Endocrinology, University Hospitals of Leicester, Leicester Royal Infirmary, Leicester, UK (Chapter 30)
Ken Lingley, Carer representative, UK (Chapter 29)
Gitta Madani, Department of Radiology, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK (Chapter 30)
Navin Mani, Manchester Head and Neck Centre, Manchester Royal Infirmary, Manchester, UK (Chapter 22*)
Bipin Mathew, name retracted as author of Ch 28 (as per Jarrod Homer) (Chapter 28)
Paolo L Matteucci, Department of Plastic and Reconstructive Surgery, Castle Hill Hospital, Cottingham, UK (Chapter 28*)
Catriona R Mayland, Department of Palliative Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK, and Yorkshire Cancer Research, Harrogate, UK (Chapter 15*)
James McCaul, Department of Maxillofacial/Head and Neck Surgery, Queen Elizabeth University Hospital, Glasgow, Scotland, UK (Chapter 24)
Lorna K McCaul, Restorative Dentistry, Glasgow Dental Hospital, Glasgow, Scotland, UK (Chapter 13*)
Pádraig McDonnell, Clinical Psychology, Greater Manchester Mental Health NHS Foundation Trust, Manchester, UK (Chapter 8)
Andrew McPartlin, Department of Clinical Oncology, Christie Hospital, Manchester, UK (Chapter 19)
Valeria Mercadante, Department of Oral Medicine, University College London Eastman Dental Institute, London, UK (Chapter 16)
Zoe Merchant, Occupational Therapy and Prehab4Cancer Programme, Christie NHS Foundation Trust, Manchester, UK (Chapter 8)
Radu Mihai, Department of Endocrine Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK (Chapter 25)
Mufaddal T Moonim, Histopathology, Imperial College NHS Healthcare Trust, London, UK (Chapter 25)
John Moore, Division for Anaesthesia, Critical Care and Peri-operative Medicine, Manchester University Hospitals NHS Foundation Trust, Manchester, UK (Chapter 8*)
Paul Nankivell, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK, and Department of Otolaryngology, University Hospital Birmingham, Birmingham, UK (Chapter 5*)
Sonali Natu, Histopathology, University Hospital of North Tees and Hartlepool NHS Foundation Trust, Hartlepool, UK (Chapter 25)
A Nelson, Macmillan Head and Neck, Northwick Park Hospital, London North West University Healthcare NHS Trust, Harrow, UK (Chapter 12)
Pablo Nenclares, Oncology, Royal Marsden NHS Foundation Trust, London, UK (Chapter 29)
Kate Newbold, Oncology, Royal Marsden Hospital, London, UK (Chapter 25)
Carrie Newland, Oral and Maxillofacial Surgery, Royal Surrey NHS Foundation Trust, Guildford, UK, and School of Medicine, University of Surrey, Guildford, UK (Chapter 28)
Ailsa J Nicol, Restorative Dentistry, Newcastle Dental Hospital, Newcastle upon Tyne, UK (Chapter 13)
Iain J Nixon, ENT Department, NHS Lothian, Edinburgh, Scotland, UK (Chapter 25*)
Rupert Obholzer, Department of ENT, Guy's Hospital, London, UK (Chapter 22)
James T O'Hara, Department of ENT, Freeman Hospital, Newcastle upon Tyne, UK (Chapters 16* and 21*)
S Orr, Nursing, Colchester Hospital, East Suffolk and North Essex Foundation Trust, Colchester, UK (Chapter 12*)
Vinidh Paleri, Head and Neck Unit, Royal Marsden Hospital, London, UK (Chapters 26, 27* and 29)
James Palmer, Department of Oncology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Chapter 15)
Rachel S Parry, Palliative Medicine, Wirral University Teaching Hospitals NHS Trust, Birkenhead, UK (Chapter 15)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Claire Paterson, Beatson West of Scotland Cancer Centre, Glasgow, Scotland, UK (Chapters 5 and 17)
Gillian Patterson, Patient representative, UK (Chapter 29)
Joanne M Patterson, Liverpool Head and Neck Centre, School of Health Sciences, University of Liverpool, Liverpool, UK (Chapter 10*)
Miranda Payne, Medical Oncology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK (Chapter 29)
L Pearson, Workforce and Education, Worcester Acute Hospitals NHS Trust, Worcester, UK (Chapter 12)
David N Poller, Department of Pathology, Queen Alexandra Hospital, Portsmouth, UK (Chapter 25)
Jonathan Pollock, Department of Plastic Surgery, Nottingham University Hospitals, Nottingham, UK (Chapter 28)
Stephen Ross Porter, Department of Oral Medicine, University College London Eastman Dental Institute, London, UK (Chapter 16)
Matthew Potter, Department of Plastic and Reconstructive Surgery, John Radcliffe Hospital, Oxford, UK (Chapters 22 and 23)
Robin J D Prestwich, Leeds Cancer Centre, St James's University Hospital, Leeds, UK (Chapters 4 and 19)
Ruth Price, Department of Physiotherapy, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK (Chapter 8)
Mani Ragbir, Department of Plastic and Reconstructive Surgery, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK (Chapter 7*)
Meena S Ranka, Restorative Dentistry, Luton and Dunstable University Hospital, Luton, UK (Chapter 13)
Max Robinson, Department of Cellular Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, UK (Chapters 3 and 18)
Justin W G Roe, Department of Speech, Voice and Swallowing, Royal Marsden NHS Foundation Trust, London, UK, and Complex Laryngology/Airways Service, National Centre for Airway Reconstruction, Imperial College Healthcare NHS Trust, London, UK (Chapter 10)
Tom Roques, Department of Oncology, Norfolk and Norwich University Hospital, Norwich, UK (Chapters 1, 4* and 27)
Aleix Rovira, Department of Otorhinolaryngology, Head and Neck Surgery, and Head, Neck Thyroid Cancer Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapter 20)
Sajid Sainuddin, Department of Oral and Maxillofacial Surgery, Manchester University NHS Foundation Trust, Manchester, UK (Chapter 7*)
I J Salmon, Macmillan Head and Neck, Bedford Hospital NHS Trust, Bedford, UK (Chapter 12)
Ann Sandison, Department of Head and Neck/Oral Pathology, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapter 23)
Andy Scarsbrook, Leeds Institute of Health Research, University of Leeds, Leeds, UK, and Department of Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK (Chapter 5)
Andrew G Schache, University of Liverpool Cancer Research Centre, Liverpool, UK (Chapters 6, 17* and 23)
A Scott, Macmillan Head and Neck, Mount Vernon Cancer Centre, East and North Hertfordshire NHS Trust, Northwood, UK (Chapter 12)
Diane Sellstrom, Department of Voice and Swallowing, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK (Chapter 10)
Cherith J Semple, School of Nursing, Ulster University, Belfast, UK (Chapter 15)
Jagrit Shah, Radiology, Nottingham University Hospitals NHS Foundation Trust, Nottingham, UK (Chapter 23)
Praveen Sharma, Restorative Dentistry, University of Birmingham School of Dentistry, Birmingham, UK (Chapter 13)
Richard J Shaw, Oral and Maxillofacial/Head and Neck Surgery, University of Liverpool, Liverpool, UK (Chapter 16*)
Somiah Siddiq, Head and Neck Department, University Hospitals Birmingham, Birmingham, UK (Chapter 26*)
Priyamal Silva, Head and Neck Surgery, Oxford University Hospitals NHS Foundation Trust, Oxford, UK (Chapter 29)
Ricard Simo, Department of Otorhinolaryngology, Head and Neck Surgery, and Head, Neck Thyroid Cancer Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK (Chapter 20*)
Rabin P Singh, Maxillofacial, Head and Neck Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK (Chapter 16*)
Maria Smith, Macmillan Head and Neck, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Glasgow, Scotland, UK (Chapter 12*)
Rebekah Smith, Department of Nutrition and Dietetics, Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK (Chapter 9)
Toby Oliver Smith, Warwick Clinical Trials Unit, University of Warwick, Coventry, UK, and School of Health Sciences, University of East Anglia, Norwich, UK (Chapter 11*)
Sanjai Sood, Otolaryngology, Head and Neck Surgery, Bradford Teaching Hospitals, Bradford, UK (Chapters 24* and 27)
Francis W Stafford, Otolaryngology – Head and Neck Surgery, Sunderland Royal Hospital, Sunderland, UK (Chapters 1* and 27)
Neil Steven, Medical Oncology, University Hospitals Birmingham, Birmingham, UK (Chapter 29)
Kay Stewart, Department of Palliative Medicine, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Chapter 15)
Lisa Stoner, Physiotherapy, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK (Chapter 11)
Steve Sweeney, Patient representative, Manchester, UK (Chapter 8)
Andrew Sykes, Department of Clinical Oncology, Christie Hospital, Manchester, UK (Chapter 28)
Carly L Taylor, Restorative Dentistry, University Dental Hospital of Manchester, Manchester, UK (Chapter 13)
Selvam Thavaraj, Head and Neck Pathology, Guy's Hospital, London, UK (Chapters 3* and 17)
David J Thomson, Department of Oncology, Christie NHS Foundation Trust, Manchester, UK, and Division of Cancer Sciences, University of Manchester, Manchester, UK (Chapters 4, 22 and 23)
Jane Thornton, Department of Speech and Language Therapy, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK (Chapter 10)
Neil S Tolley, ENT Surgery, Imperial College NHS Healthcare Trust, London, UK (Chapter 25)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Nancy Turnbull, Melanoma Focus, Cambridge, UK (Chapter 29)
Sriram Vaidyanathan, Department of Nuclear Medicine, St James's University Hospital, Leeds, UK (Chapter 19)
Leandros Vassiliou, Oral and Maxillofacial Surgery, Royal Blackburn Hospital, Blackburn, UK (Chapter 1)
John Waas, Department of Endocrinology, Oxford University Hospital, Oxford, UK (Chapter 16*)
Kelly Wade-McBane, Department of Nutrition and Dietetics, Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, UK (Chapter 9)
Donna Wakefield, Department of Palliative Medicine, University Hospital of North Tees, North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees, UK (Chapter 15)
Amy Ward, Department of Oncology, Barking, Havering and Redbridge University Hospitals NHS Trust, Romford, UK (Chapter 4)
Laura Warner, Department of Otolaryngology, Head and Neck Surgery, Freeman Hospital, Newcastle upon Tyne Hospitals Trust, Newcastle upon Tyne, UK (Chapter 2*)
Laura-Jayne Watson, Speech and Language Therapy, South Tyneside and Sunderland NHS Foundation Trust, Sunderland, UK (Chapters 8* and 10)
H Watts, Macmillan Head and Neck, Northampton General Hospital NHS Trust, Northampton, UK (Chapter 12)
Christina Wilson, Beatson West of Scotland Cancer Centre, Glasgow, Scotland, UK (Chapters 4 and 17)
Stuart C Winter, Department of Otolaryngology, Head and Neck Surgery, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, and Blenheim Head and Neck Unit, Churchill Hospital, Oxford, UK (Introduction, and Chapters 16* and 18)
Winson Wong, Department of Otolaryngology, Head and Neck Surgery, Hull University Teaching Hospitals, Hull, UK (Chapter 18)
Chui-Yan Yip, Clinical Pharmacy, Wheatfield's Hospice and St Gemma's Hospice, Leeds, UK (Chapter 15)
Kent Yip, Clinical Oncology, Ipswich Hospital, East Suffolk and North Essex NHS Foundation Trust, Ipswich, UK (Chapter 29)

*Indicates chapter lead author

Index

Section 1: Generic issues in head and neck cancer management

Section 2: Patient support

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Section 3: Site-specific guidelines

Appendices

*Indicates chapter lead author

Section 1: Generic issues in head and neck cancer management

Chapter 1: Provision of head and neck cancer services for diagnosis and treatment centres

Table of Contents

Key recommendations

- Head and neck cancer services should be organised around specialist multidisciplinary teams (MDTs), comprising health professionals within a head and neck cancer treatment centre including surgical and oncological services that can provide comprehensive treatment and management for patients with head and neck cancers (essential (E))
- Diagnostic services outside of the head and neck cancers should have agreed protocols with the referral centre regarding the diagnosis and referral of patients with head and neck cancer (E)
- In-reach models of service delivery in which surgeons primarily located at a peripheral diagnostic unit travel to a centre to perform cancer surgery is not recommended (desirable (D))
- Where geographically possible, there should be the maximum consolidation into as few head and neck treatment centres as possible. In these circumstances, a head and neck treatment centre should comprise a single surgical centre and a single oncological centre (D)

Introduction and current service provision

The initial development of head and neck cancer services in UK was based upon the National Institute for Health and Care Excellence (NICE) Improving Outcomes Guidelines 2004.[1] Subsequent UK guidelines, standards, quality assessment metrics and commissioning standards essentially all mirror the structure outlined in the original NICE Improving Outcomes Guidelines.

Head and neck cancer services in the UK are generally based on a hub-and-spoke model of treatment centres (surgery and oncology) (Figure 1), in which MDTs are centrally based, and peripheral 'spoke' diagnostic units offer diagnostic services, as

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

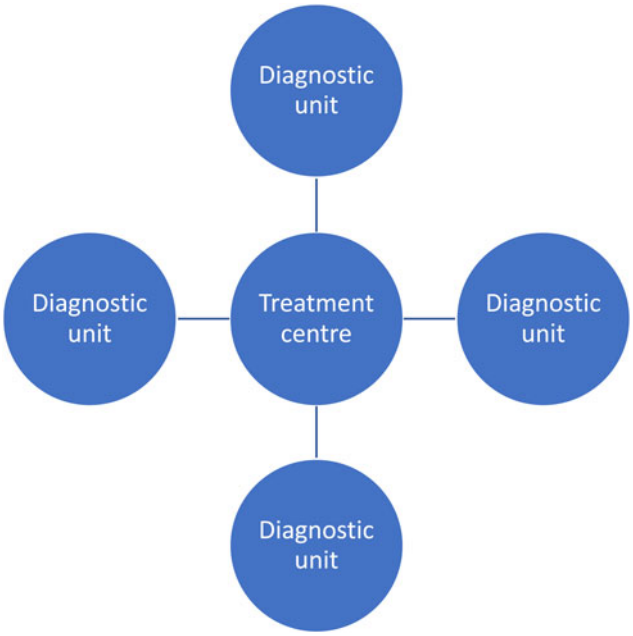


Figure 1. Hub-and-spoke model of treatment centres.

well as, ideally, ongoing post-treatment support and follow up, closer to patients' homes. There is variation in the nature of this set-up. Diagnostic units are important, potentially maximising the proportion of the patient journey closer to home.

Diagnostic units can be entirely separate from treatment centres, provided that patient-centred communication and co-ordination is not compromised, and the pathway remains streamlined (Figure 2). This requires clinicians working to agreed MDT diagnostic and follow-up guidelines. However, the alternative arrangement is that MDT surgeons from the treatment centre may 'out-reach' to provide diagnostic and follow-up services in peripheral units. Less commonly and less ideally, surgeons from a peripheral unit 'in-reach' to the treatment centre to perform surgery on patients who are diagnosed with cancer in their unit. Many have concerns over this model, with a limited presence in the main surgical treatment centre and disjointed care models. Similar in-reach and out-reach models can be applied to other disciplines, such as allied health and specialised nursing professionals.

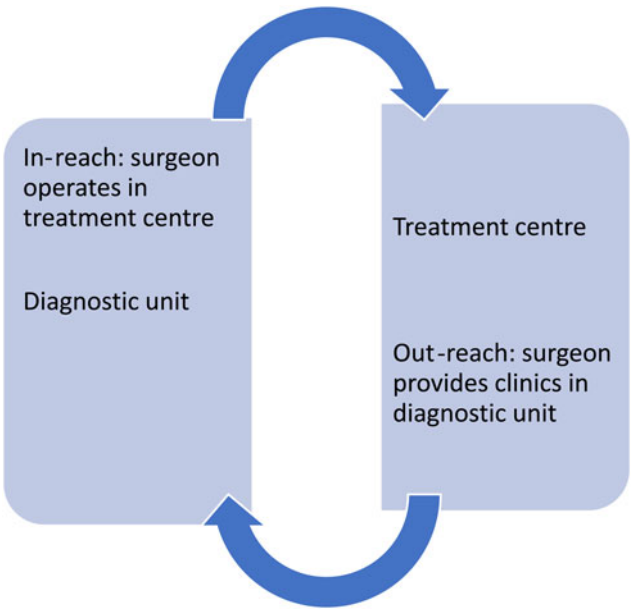


Figure 2. In-reach and out-reach model of treatment centres.

There is variation in this model in the UK, and variation in MDT size (e.g. as defined by the population served). In England, in 2017, one region had a population of 2.4 million with 1 MDT and an annual caseload of 548 new patients. Another with a population of 2.7 million had 6 MDTs and a caseload of 584, with only 2 of the units seeing more than 100 new cases. Some MDTs have more than one surgical and radiotherapy centre. In addition, the incidence of head and neck cancers in the UK varies significantly. The UK average is 18.8 per 100 000 per year, higher in Scotland and Wales.[2]

The economic and clinical value in various different set-ups is unclear, and may vary according to population density, incidence, and geographical area and spread.

Diagnostics and follow-up units

The purpose of diagnostic units is to provide early diagnosis and appropriate investigation, as well as staging, for patients with head and neck cancer in the locality which they serve. Additionally, where appropriate, patient follow up can be delivered in these units, at least in part, maximising care nearer to home. Each head and neck cancer centre will also act as the diagnostic unit for its locality or secondary referral population. The process of diagnostic investigation is discussed in Chapter 2 of these guidelines. Essential and desirable specifications are shown below (Table 1).

Table 1. Diagnostic units: essential and desirable

Parameter	Essential	Desirable
Specific surgical clinics for patients referred with suspected H&N cancer	X	
Fibre-optic endoscopy	X	
Fibre-optic endoscopy with image capture & storage		X
Neck lump clinics	X	
Neck lump clinics with one-stop USS, with guided FNAC & Rapid On-site Evaluation		X
Access to diagnostic imaging (CT, MRI, PET-CT* & USS)	X	
Access to urgent theatre for biopsy & endoscopy	X	
Photo-documentation in operating theatre for MDT referral		X
Access to histopathological services expert in H&N cancer diagnosis	X	
Dedicated cytopathological expertise in H&N cancers		X
Clinical nurse specialist with expertise in H&N cancers	X	
SLT with expertise in H&N cancers	X	
Dietetic services expertise in H&N cancers	X	
Multidisciplinary follow-up clinics		X
Links to community services (e.g. nutrition, palliative services, nursing)	X	

*The facility to request a positron emission tomography/computed tomography (PET-CT) scan (rather than provide PET-CT scans). H&N = head and neck; USS = ultrasound scanning; FNAC = fine needle aspiration cytology; CT = computed tomography; MRI = magnetic resonance imaging; MDT = multidisciplinary team; SLT = speech and language therapist

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Head and neck cancer treatment centres

A treatment centre must provide comprehensive management for all patients with head and neck cancer. The head and neck cancer MDT is at the heart of this, comprising all health professionals and allied staff required to provide this and support patients. Suggested core and extended MDT members are listed in Table 2. Core members are required to provide input into patients' care, and should be available for every patient who needs their expertise or input. Whether this takes the form of physical attendance at the MDT meeting and/or at an MDT clinic with the patients will vary, but, in general, core members are expected to attend (physically or virtually) the weekly MDT meeting (see below). Extended members are professionals whose input is less regular, and who would not be expected to routinely attend MDT meetings and clinics.

Multidisciplinary team meetings

Head and neck MDT meetings improve decision-making and diagnosis, impacting positively on both staging and treatment.[3–8] Effective MDTs reduce the time from diagnosis to definitive treatment. An MDT management approach is associated with improved survival rates after treatment for head and neck cancer.[9]

Table 2. H&N MDT members

Core MDT members
Specialist surgeons including:
– ENT surgeons
– Oral & maxillofacial surgeons
– Reconstructive surgeons (who may come from plastic surgery, oral & maxillofacial surgery, or ENT backgrounds, but who have a special interest & training in H&N reconstruction, including microvascular reconstruction)
Clinical oncologists (some MDTs also have medical oncologists)
Pathologists with expertise & special interest in H&N pathology, including H&N cytopathology
Radiologists with special interest in H&N
Specialist restorative dentists
Clinical nurse specialists including tracheostomy & gastrostomy support
SLTs or swallowing therapists, including therapists competent to run voice clinics & support surgical voice restoration
Dieticians with links to feeding teams for gastrostomy support
Senior nurses &/or ward managers from H&N ward
MDT co-ordinators & patient pathway co-ordinators
Clinical trials practitioners & nurses
Extended MDT members (given the often-complex needs of H&N patients, MDTs should be encouraged to include following staff)
Anaesthetists with specialist interest in H&N surgery & difficult airway management. These doctors should participate in pre-operative H&N assessment, & should be engaged in local enhanced recovery pathways
Occupational therapists
Clinical psychologists
Physiotherapists who understand rehabilitation requirements of both resection sites & any flap donor sites
Specialist palliative care nurses or doctors
Dental hygienist
Ophthalmologist
Pain specialist
Therapeutic radiographers
Maxillofacial or dental technician
Data manager

H&N = head and neck; MDT = multidisciplinary team; SLT = speech and language therapist

The MDT meetings to record a patient's care will take place at different stages during a cancer journey. This includes:

- Upon initial diagnosis, to ensure diagnosis and staging is accurate, that no further investigations are required, and to determine appropriate treatment options according to agreed national and local protocols
- After surgery, to discuss histopathology and options for post-operative adjuvant treatment
- After primary chemoradiotherapy, where there is concern for residual disease on post-treatment imaging
- For suspected or confirmed recurrence, or second primary cancers, after initial diagnosis and treatment

The MDT should meet at least weekly. Every meeting should have appropriate input from core members (see above). External imaging is generally reviewed by an MDT radiologist. Some or all external pathology findings may also need reviewing according to local policy.

The MDT meeting offers an opportunity to collect data and to offer clinical trials, where appropriate, for eligible patients.

Each head and neck cancer MDT should have an operational policy setting out the roles and responsibilities of its core members, including attendance required at MDT meetings. These will vary between specialist groups: all surgeons and oncologists should be expected to attend most meetings, whilst radiologists and pathologists may attend according to a rota. Most core member groups need at least two individuals, to allow for cover in case of leave.

The MDT meeting should have an appropriately trained chair who leads the meeting; this individual also ensures that a clear summary is documented after each case is discussed and that recorded data are accurate. The agreed diagnosis and staging, relevant discussions, and treatment plans should be documented in real time and circulated to the MDT members immediately afterwards, along with the person responsible for confirming the outcome to the patient. The MDT co-ordinator role is crucial to the preparation and smooth running of the meeting, and in disseminating information after the meeting. Enquiries for the co-ordinator should be sent to a generic monitored e-mail address, so that absence is covered. The co-ordinator(s) are also responsible for uploading data to cancer waiting times databases and cancer registries.

An annual report documenting MDT activity, including workload, outcomes, significant events such as staff changes, waiting time targets, critical incidents, and 'never events' should be written.

The head and neck MDT should have formal links with inter-dependent MDTs for other related tumour types, such as skull base or neurosurgical, sarcoma, skin cancer and melanoma, thyroid, teenage and young adult, cancer of unknown primary, and lung MDTs.

Following MDT discussions, patients should be reviewed in an MDT clinic, in which core members can provide input for each patient depending on their needs in one visit. This would typically include, for example:

- Primary clinician(s) (surgical or oncological) offering prime treatment or explaining treatment options
- Clinical nurse specialist

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Allied health professionals (speech and language therapy, or dietetics), as required
- Dental assessment including orthopantomagram X-ray
- Anaesthetic assessment (ideally) for patients needing surgery
- Clinical trial nurse if clinical trial option is available

Surgery and radiotherapy within treatment centre

Surgery

A comprehensive head and neck cancer centre should be able to offer all patients the surgical treatment they require. It is accepted that not every head and neck cancer surgical centre will offer treatment for rarer cancers, or in niche areas, such as skull base cancer surgery.

Surgeons should have job plans reflecting their commitment to specialist practice. Subspecialty training in head and neck oncology is essential, ideally including a fellowship after completion of training.

Staffing numbers in all aspects of care need to be large enough to provide a sustainable service 24 hours a day, 7 days a week, allowing cover for holidays and unexpected absences. Case numbers need to be large enough to maintain individual expertise amongst all the personnel, whilst providing case experience for trainees.

The essential and desirable services that the main head and neck cancer surgical centres should offer are shown in Table 3 below. This assumes the provision of the MDT members listed above.

Radiotherapy

Radiotherapy is already centralised in 62 UK centres, most but not all of which treat head and neck cancer. Case numbers are relatively small – there were 5987 courses of curative head and neck cancer radiotherapy delivered in England in 2017, compared with 30 708 for breast cancer.[10] In 2020, there were 149 UK clinical oncologists treating head and neck patients.[11]

Head and neck radiotherapy is one of the most complex treatments given by clinical oncologists. The 2019 NHS England Service Specification for Radiotherapy Operational Delivery Networks states that each consultant clinical oncologist should be responsible for at least 25–50 cases of radical radiotherapy per year for each tumour site treated.[12] The '25–50' number is empirical and not supported by strong evidence. As different head and neck subsites are also managed differently, it could be argued that nasopharyngeal cancer, for example, is so rare in the UK and so different to other tumour subsites that it should be super-specialised and treated by a very small number of clinical oncologists.

Rather than trying to establish an ideal number of cases to be treated by a radiotherapy team, it is perhaps more sensible for commissioners to examine surrogate indicators of radiotherapy quality which are likely to reduce unwarranted variation between clinical teams and centres (Table 4).

Follow up and data collection

The purpose of interactions with patients following treatment for head and neck cancer is not just about tumour surveillance. Restoring quality of life is as important as cancer cure. Follow-up services should have speech and language therapists, dietitians, clinical nurse specialists, and restorative dentistry at their core, delivered as close to home as possible. Psychological support is often less readily available.

The collection of survival metrics, patient-reported outcome and experience measures is key to assess and improve care. Each MDT should be able to collect and publish its outcomes. Follow-up services should be designed and funded with the ability to collect such data from every patient. Completing simple, validated digital tools before a clinic visit can enable more patient-focused appointments, and their analysis can help drive improvements in the quality of the clinical service.

Table 3. Essential and desirable services that the main H&N cancer surgical centre (the 'hub') should provide

Main H&N surgical centre services
Essential services
A dedicated H&N in-patient ward with appropriately airway-trained nursing staff
Critical care capacity for post-operative care after complex surgery &/or for patients with significant co-morbidities
Support from medical subspecialties: cardiology, renal medicine, endocrinology etc.
On-site imaging facilities (CT, MRI, USS & interventional (including vascular) radiology)
Cancer nurse specialist support
AHPs: SLTs, dieticians, physiotherapists, occupational therapists
Pre-operative assessment & anaesthesia by consultants with special interest in H&N surgery (including expertise in difficult airway anaesthesia)
Reconstructive surgery including composite & chimeric free-flap options when appropriate
24/7 free-flap salvage rota (microvascular on-call rota), with provision for rapid access to operating theatres for salvage surgery
Surgical voice restoration
RIG &/or PEG services
Restorative dentistry including maxillofacial & dental laboratory for intra-oral rehabilitation
Pathology department on-site for capability to allow intra-operative frozen sections
Infrastructure & support for enrolment & participation in national audits & clinical trials
Desirable services
Equipment for minimal invasive transoral procedures (robot &/or laser &/or endoscopic facility for oropharyngeal surgery)
Laryngology service including transnasal oesophagoscopy
Nuclear medicine to allow for sentinel node biopsy
Interdependencies or other relevant specialties: vascular surgery, ophthalmology & oculoplastic surgery, neurosurgery, cardiothoracic surgery
Maxillofacial & dental laboratory for extra-oral rehabilitation & prosthetics
In-house 3D planning & printing facilities

H&N = head and neck; CT = computed tomography; MRI = magnetic resonance imaging; USS = ultrasound scanning; AHP = allied health professional; SLT = speech and language therapist; 24/7 = 24 hours a day, 7 days a week; RIG = radiologically inserted gastrostomy; PEG = percutaneous endoscopic gastrostomy; 3D = three-dimensional

The future: evidence for minimal treatment volumes and further centralisation?

The importance of concentrating patient volumes in specialised head and neck services through reconfiguration and centralisation has been illustrated in reports from Canada, USA,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Surrogate indicators of radiotherapy service quality

Surrogate indicators
Adherence with overall H&N cancer guidelines, including NICE & BAHNO
Adherence to RCR H&N cancer consensus statements
Use of internationally agreed radiotherapy contouring guidelines to minimise unwarranted variation in practice
Ensuring all H&N radiotherapy contours have prospective peer review before treatment starts
Establishing functional cross-centre networks to enable peer support for decision-making & for contouring of more complex cases (e.g. nasopharynx)
All patients having a dental assessment before curative radiotherapy starts
Appropriate patients having dietetic & SLT assessment, before, during & after RT
All patients seen in multidisciplinary on-treatment review clinics to support management of acute side effects
Evidence of recruitment into NCRN-adopted clinical trials

H&N = head and neck; NICE = National Institute for Health and Care Excellence; BAHNO = British Association of Head and Neck Oncologists; RCR = Royal College of Radiologists; SLT = speech and language therapy; RT = radiotherapy; NCRN = National Cancer Research Network

UK and Europe. The weight of opinion has moved away from the 100 new cases recommended by the NICE Improving Outcomes Guidelines in 2004.

The questions that arise are: what is the minimum or optimal size of a head and neck cancer centre?; and is it practical and affordable? The difficulty in addressing these within the UK is exemplified by the lack of any update on guidance since 2004.

There are consistent data that support a relationship between hospital or institutional volume or caseload and various measures of quality, mainly improved patient survival and a reduction in complications.[13–17] However, the definition of what defines a low-volume and high-volume unit are often empirical. The largest analysis of 351 052 head and neck squamous cell carcinoma cases treated in 1229 centres found that low-volume units treating less than 54 cases per year had significantly higher mortality rates than moderate volume units (54–164 cases per year), and high-volume units with over 165 cases per year were even better.[18]

The recent Getting It Right First Time review of oral and maxillofacial surgery services[19] suggested that the figure of 250 new cases per MDT was optimal.

Figures taken from analysis of the 2013 *Data for Head and Neck Oncology* ('DAHNO') audit, and presented by the initial head and neck surgery clinical reference group to NHS England, formed the basis of estimated caseload, and effect upon MDT numbers was considered if alterations were made to the required caseload. The data were illustrative, rather than definitive, and are shown in Table 5.

Table 5. Projected number of surgical treatments based on annual H&N MDT caseload

Annual MDT caseload (new patients) (*n*)	Major surgical therapeutic interventions (*n*)	Neck dissections (*n*)	Free flaps (*n*)
200	100	67	20
250	125	80	25
300	150	100	30

H&N = head and neck; MDT = multidisciplinary team

If it is assumed that a centre must have a comprehensive free-flap service, then a minimum number of free flaps per year (and per reconstructive surgeon) could be considered. There is no UK consensus on this. Canadian guidelines stipulate 20 free flaps per surgeon per year. Assuming 3 surgeons are required to support a 24 hours a day, 7 days a week service, but perhaps factoring in more than 1 reconstructive surgeon per case, this would suggest an annual case load of at least 300 might be required (Table 5). The figures in Table 5 (essentially 1 free flap per 10 new patients with head and neck cancer) are consistent with the known incidence of head and neck cancer in England (average of 10 053 cases in 2016–2018)[2] and coded free flaps per year for head and neck cancer (average of 1184 cases in 2003–2013).[20]

Hence, it is difficult to define a metric that defines minimal caseload or throughput. The variance in cancer incidence and geographical spread or population density within the UK also needs to be factored in.

A reasonable conclusion is that, where geographically possible, the provision of head and neck cancer services should follow the evidence, i.e. have as high volume as possible. Within cities and conurbations, there should be the maximum consolidation into as few head and neck treatment centres as possible. In these circumstances, a head and neck treatment centre should comprise a single surgical centre and a single oncological centre (and co-location is ideal). For more rural, less populated areas, a practical compromise might entail having smaller centres within a service offering restricted services (e.g. no microvascular surgery) linked to a large centre with the same operational policies and linked MDT meetings.

Chapter 2: Clinical assessment, diagnosis and imaging

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

Head and neck malignancy is the fourth commonest reason for referral on a cancer pathway, yet the eighth commonest cancer diagnosed in England.[21] Diagnosis at an early stage is a challenge in head and neck cancer, as many patients arise from lower socio-economic groups and late presentation is common. Best practice timed pathways in secondary care aim to expedite and streamline diagnosis. However, the lack of patient engagement with primary care services remains a fundamental issue.

This chapter outlines suggested best practice, and summarises the available evidence concerning the initial assessment and diagnosis of patients with suspected head and neck cancer, from primary care referral through to diagnosis. The focus is predominantly upon upper aerodigestive tract head and neck squamous cell carcinoma (SCC) and salivary cancers. Diagnosis of thyroid and skin pathology are covered in dedicated chapters.

The process of a patient with potentially suspicious symptoms can be broken down into three steps, culminating with a patient confirmed with cancer and appropriately investigated and staged (Figure 1). Each of these steps has its challenges.

Public awareness and referral from primary to secondary care

Recommendations

- Co-ordinated public awareness campaigns to boost recognition of the early signs of head and neck cancer should be promoted (desirable (D))
- Improved primary care awareness of the early signs of head and neck cancer is needed to reduce time to diagnosis and emergency late-stage presentation (D)
- Collaboration between cancer alliances and primary care is required to agree upon clear and appropriate two-week-wait referral criteria (essential (E))
- Use and adoption of validated risk calculators is recommended to assist with urgent referral (accepted standard of care (evidence-based recommendation (R))

On average 100 000 new head and neck referrals are seen in each year, with only 2.8 per cent on the cancer waiting time pathway resulting in a cancer diagnosis; yet only 35–56 per cent of patients diagnosed with cancer present via this route in England.[21,22]

These data demonstrate deficiencies in the current referral process for head and neck cancer. Whilst urgent clinics are full of patients without cancer, nearly half of head and neck malignancies present via other routes, too frequently with advanced disease. The negative impact of delayed diagnosis upon survival and quality of life is well proven.[23]

Figure 1. Process for a patient with potentially suspicious symptoms. GP = general practitioner; MDT = multidisciplinary team

Table 1. NICE guidelines 2015

Laryngeal cancer (patients aged ≥45 years)
– Persistent unexplained hoarseness
– An unexplained lump in neck
Oral cancer
– Unexplained ulceration in oral cavity lasting >3 weeks
– A persistent & unexplained lump in neck
– Lump on lip or in oral cavity
– Red or red & white patch in oral cavity consistent with erythroplakia or erythroleukoplakia
Thyroid cancer
– Unexplained thyroid lump

NICE = National Institute for Health and Care Excellence

Table 2. Suggested referral criteria after Tikka *et al.*[26]

Persisting hoarseness for >3 weeks
Unexplained oral ulceration or mass for >3 weeks
Unexplained persistent swelling in parotid or submandibular gland for >3 weeks
Unexplained neck mass for >3 weeks or recently appeared neck mass
Dysphagia for >3 weeks
Odynophagia for >3 weeks
Unexplained otalgia with normal otoscopy
FOSIT with presence of blood in mouth
FOSIT with unexplained otalgia & normal otoscopy

FOSIT = feeling of something in throat

The National Institute for Health and Care Excellence (NICE) refined their referral guidelines in 2015 to include symptoms with a positive predictive value above 3 per cent (Table 1).[24] These adjustments were made in response to consistent data proving no discernible difference between the numbers of patients being diagnosed through the urgent and non-urgent pathways. Regrettably, the detection rate remains low despite these changes.[25]

An alternative list of referral criteria has been proven to correlate well with a head and neck cancer diagnosis (Table 2).[26] This has formed the basis for a risk calculator to guide primary care referral or triage (www.orlhealth.com/risk-calculator.html). This has been refined and validated, and shown to be effective for triage during the coronavirus disease 2019 (Covid-19) pandemic. It uses symptoms such as intermittent hoarseness and globus sensation as negative predictors of malignancy.[27,28]

More fundamentally, early diagnosis is contingent on patients seeking medical attention with suspicious symptoms. Public awareness campaigns have successfully increased numbers of patients with lung cancer referred and diagnosed at an early stage. The same is required for head and neck cancer, particularly in deprived populations.

Assessment in secondary care and best timed pathways

Recommendations

- Use of validated risk calculators is recommended to assist initial assessment and triage (evidence-based recommendation (R))

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Trusts should commit to achieving the faster diagnosis standard, with communication of the outcome to patients and general practitioners (essential (E))
- Patients with suspected cancer should be seen in a dedicated ENT, oral and maxillofacial surgery or neck lump specialist clinic (R)
- Best timed pathways centred around one-stop clinics for diagnosis of head and neck cancers should be implemented, enabling same-day investigations and expedient booking of diagnostic imaging and general anaesthesia procedures (R)
- Equipment for endoscopy, and biopsy in clinic and dental procedures must be readily available (R)
- Video monitors and facilities for photographic documentation should be available (good practice point (G))
- Narrow band imaging or optical florescence imaging can assist with the identification of malignancy and dysplasia (R)
- Diagnostic imaging should be performed prior to biopsy under anaesthesia if possible, but biopsy in clinic should not be delayed and should be carried out initially if possible (G)
- Patients with cervical lymphadenopathy require fibre-optic nasopharyngolaryngoscopy (R)
- A neck lump clinic should include same-day ultrasound and ultrasound-guided biopsy (fine needle aspiration cytology (FNAC) or core biopsy) (G)
- Ultrasound-guided biopsy should be performed by an experienced head and neck radiologist, ultrasonographer, or appropriately trained surgeon capable of performing diagnostic ultrasound imaging and both FNAC and core needle biopsy (G)
- Immediate FNAC adequacy checking improves the rate of diagnostic sampling (R)
- Rapid cytopathological assessment of FNAC samples is desirable (G)

The National Health Service's (NHS's) long-term plan aims to achieve 55 000 extra patients surviving five years after treatment, with an early-stage diagnosis for 75 per cent of patients (with a commitment to achieving a 'faster diagnosis standard', either confirming malignancy or the exclusion thereof, within 28 days of referral).[29]

Alternative methods of assessment using tele- and video-consultations, straight-to-test pathways, and so on were implemented in response to Covid-19 and may prove to be effective post-pandemic. Although originally intended to assist with the selection of cases for urgent referral from primary care, the refined and validated risk calculator (www.orlhealth.com/risk-calculator.html) has been shown to be effective for initial telephone triage or assessment during the Covid-19 pandemic.[28] This appears to be a safe and effective means of selecting those patients who should remain on an urgent diagnostic pathway and determining those who can be seen routinely. At this stage, allocation to the appropriate clinic can be carried out (e.g. ENT clinic, oral and maxillofacial surgery clinic, neck lump clinic). Hence, assessment in secondary care may comprise any of the following steps:

- Triage
- Initial telephone assessment
- Investigations before clinic attendance
- Clinic attendance
- Investigations during or after clinic attendance

For those patients on an urgent diagnostic pathway in secondary care, best practice or optimal pathways should be adopted and implemented. This involves early, appropriate investigations and a reduction of unnecessary investigations, together with the simplification of diagnostic pathways. Such pathways may vary and be tailored to the facilities and practices within the hospital concerned.

Out-patient assessment

In addition to pertinent head and neck symptoms and risk factors, co-morbidities, performance status and social circumstances should be recorded for those patients who have or may have cancer. This is vital information to inform multidisciplinary team (MDT) discussion and treatment planning.

Detailed description of examination findings should be documented. Photographic documentation is recommended, to aid MDT discussion and disease monitoring.

Patients with oral cavity lesions should be seen in a clinic with the capabilities for dental radiography and local anaesthetic biopsy. Palpation of lesions clinically is useful to estimate thickness and depth. Pre-malignant-looking oral lesions should be investigated as early oral cavity cancers.

Patients with pharygolaryngeal or sinonasal symptoms and those with neck lumps that may be metastatic lymph nodes require flexible nasopharyngolaryngoscopy. Video equipment offers higher definition images, which are helpful for training and peer review of appearances. Narrow band imaging and optical fluorescence imaging may improve the detection of subtle malignant and pre-malignant lesions.[30]

Transnasal oesophagoscopy can be considered; it enables enhanced views of the hypopharynx and upper oesophagus compared to conventional flexible laryngoscopy, and offers benefit when excluding oesophageal pathology in patients with upper dysphagia or globus symptoms.[31]

A representative biopsy in clinic should be performed for accessible lesions (oral cavity, and some nasal or oropharyngeal lesions). This allows for early confirmed diagnosis and greater understanding of the tumour biology, for example depth of invasion, peri-neural or lymphovascular invasion, which inform pertinent management decisions. Whilst diagnostic imaging prior to biopsy may be preferable to avoid distortion of anatomy, the impact upon accurate disease staging is inconclusive,[32] and it is recognised that diagnostic time pressures may impact upon this ideal pathway.

Biopsy of laryngeal and pharyngeal lesions with transnasal oesophagoscopy or a channelled flexible laryngoscope offers a safe and effective means of gaining a histological sample in out-patients, avoiding general anaesthetic in a significant proportion.[33] The depth of biopsy can be a limiting factor in some cases.

Neck lumps

The key features of assessment are:

- Complete head and neck examination, including fibre-optic nasopharyngolaryngoscopy and skin inspection, if the lump is possibly a lymph node
- Ultrasound (as part of a one-stop clinic ideally)
- Ultrasound-guided tissue sampling (FNAC or core biopsy) (see also Chapter 3 on pathology)

The evidence for ultrasound guidance in needle biopsy sampling of neck masses to reduce sampling errors is compelling.[34]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Adequacy check and rapid on-site evaluation

On-site assessment of the adequacy of cytopathology samples by biomedical scientists reduces pathway delays due to non-diagnostic specimens. Rapid on-site evaluation by cytopathologists goes one step further. Not only are non-diagnostic sampling rates further reduced,[35] but also same-day diagnosis offers unmeasurable advantages from the patient's perspective, and speeds up subsequent steps on the diagnostic or staging pathway. Furthermore, ancillary tests such as core biopsy for suspected lymphoma can then be performed immediately, if necessary.

Fine needle aspiration cytology versus core needle biopsy

Core biopsy, although more invasive, may offer increased accuracy rates over FNAC for immunohistochemical staining (and prevents the need for incision or excision biopsy), particularly when lymphoma is suspected, in cases of salivary gland tumours[36] and for unusual tumours (see also Chapter 3 on pathology).

Preference between core biopsy and FNAC may depend on local cytopathological expertise. Because core biopsy may not be suitable for smaller lesions or those within proximity to neurovascular structures, it is recommended that the personnel sampling the neck masses are familiar with both techniques.

Many lateral cystic neck masses in patients aged over 40 years prove to be malignant, most commonly metastatic human papillomavirus (HPV)-associated SCC from an oropharyngeal primary.[37] Achieving diagnosis by FNAC or core biopsy can be difficult when the lymph node is mainly cystic. Targeting the cyst wall can help optimise accuracy (see Chapter 27, dealing with unknown primary cancer).

Open biopsy (by incision or excision) should be a last resort to achieve histological diagnosis. The FNAC and core biopsy should be performed prior to this, as well as imaging to identify a possible primary in the case of suspected lymph node metastasis (suspected carcinoma of unknown primary).

Unknown primary: metastatic squamous cell carcinoma

This topic is covered in more detail in the dedicated chapter (Chapter 27). Most patients with carcinoma of unknown primary SCC will present to neck lump clinics and should be managed as outlined above.

Panendoscopy or examination under anaesthesia and biopsy of primary cancer

Many lesions will not be amenable to clinical staging and biopsy in clinic. This should be carried out after other investigations and imaging.

When examination under anaesthesia and biopsy is required, a panendoscopy, examination of all of the upper aerodigestive tract (oral cavity, pharynx, larynx and cervical oesophagus), should ideally be performed, although the detection rate of second primary malignancies is very low through this.

For carcinoma of unknown primary, positron emission tomography/computed tomography (PET-CT) should be carried out before this step and requested as soon as carcinoma of unknown primary is suspected. Chapter 27 discusses what should be biopsied and how.

Imaging in head and neck cancer

Recommendations

- Magnetic resonance imaging is recommended for suprahyoid primary lesions, and for cases of carcinoma with an unknown primary (good practice point (G))
- Computed tomography is recommended to assess bony involvement where required (evidence-based recommendation (R))
- Computed tomography thorax is mandated for systemic staging in advanced disease and may be used to exclude synchronous primary lung malignancies in the early stage of disease (R)
- Positron emission tomography/CT is advocated for the assessment of distant metastasis in advanced tumour (T) stage (T_4) nasopharyngeal and hypopharyngeal malignancies, and in examination of nodal (N) stage N_3 cancers (R)
- Positron emission tomography/CT is recommended for the post-treatment assessment of nodal disease following non-surgical treatment (R)
- Post-treatment assessment of primary tumours should follow the original modality used for primary staging (G)

The roles of imaging for head and neck cancers are: to assess and characterise a suspected lesion, and to stage local, regional and distant metastatic disease; and to detect second primary malignancy. The Royal College of Radiologists published guidelines in 2014.[38]

Imaging modality and primary tumour considerations

Computed tomography

Advantages:

- Widely available
- Short scanning time
- Excellent anatomical resolution
- No contraindications through ferrous implants
- Limited problems for patients with claustrophobia

Limitations:

- Radiation exposure
- Risk of contrast-induced nephropathy
- Distortion from dental amalgam artefact
- Limited contrast resolution inherent to the technique means that magnetic resonance imaging (MRI) is often preferred, particularly in the suprahyoid neck, salivary glands, sinonasal areas, nasopharynx and skull base, but increasingly for the larynx and hypopharynx. However, CT is still extremely valuable for patients in whom MRI is contraindicated, to provide bony detail and when rapid scan acquisition is required.[39]

A variety of techniques can be used with CT to improve visualisation in certain subsites, including: shallow free breathing for laryngeal lesions; e-phonation for lesions of the laryngeal ventricle, anterior commissure and aryepiglottic folds; and the 'puffed cheek' technique for buccal mucosa lesions. Slice thickness depends upon scanning capability, but, in general, sections are acquired at 0.625–1.25 mm and reformatted no greater than 2.5 mm for viewing. Intravenous contrast improves the delineation of tumour extent and the detection of lymph nodes. Traditionally, a scan delay of 50–75 seconds was used to allow adequate enhancement of primary tumour and accurate differentiation of cervical lymph nodes from vessels, although a delay of 90 seconds is thought to improve this further and is now used widely.[40]

Magnetic resonance imaging

Advantages:

- Superior contrast resolution

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- No radiation
- The risks of intravenous gadolinium-based contrast are also lower than with iodinated CT-based contrast[39]

Limitations:

- Longer scanning times
- More susceptible to image degradation and therefore technically more challenging
- Magnetic resonance imaging may also be contraindicated in the presence of metallic implants and cardiac devices
- Difficult for patients with claustrophobia

With superior contrast resolution, MRI is the preferred modality for multiple subsites.

Scanning times are longer causing restricted availability, and MRI therefore may be reserved for select cases when CT findings are inconclusive.

Protocols vary, but they include axial and coronal T1- and T2-weighted imaging with further post-contrast T1-weighted sequences. Diffusion-weighted imaging may increase the conspicuity of small lesions, but has a role mainly in post-therapy imaging. A variety of new MRI sequences are being introduced to help in certain situations, for example for better evaluation of peri-neural tumour spread.[41]

Ultrasound scanning

Ultrasound scanning is particularly useful in the evaluation of neck nodes. All imaging modalities use size criteria for the evaluation of lymph nodes (generally, a short axis of more than 10 mm), but there is no perfect size threshold. Morphological ultrasound characteristics such as extracapsular spread, non-hilar vascular pattern, parenchymal granular echoes, necrosis, as well as the clustering of nodes are features that suggest malignancy. Ultrasound scanning with ultrasound-guided fine needle aspiration remains the most accurate test for the differentiation of benign from malignant nodal disease.[42]

Ultrasound assessment of primary tumour sites is limited, with high resolution ultrasound occasionally performed at a small number of centres to aid in tumour (T) staging and to determine the depth of invasion of some oral cavity or laryngeal tumours.[43]

Positron emission tomography/computed tomography

Combined 18F-fluoro-2-deoxyglucose (18F-FDG) PET-CT is useful for:

- The detection of the unknown primary cancer (see Chapter 27)
- The detection of metastatic disease in the setting of locoregional advanced cancers with a high risk for distant metastatic disease
- Post-treatment imaging (particularly after chemo-radiotherapy)

Combined 18F-FDG PET-CT is also useful to exclude distant metastatic disease when contemplating salvage surgery for recurrent cancer.

In the setting of a cancer with an unknown primary, accurate identification of occult primary sites is clearly important. The 18F-FDG positron emission tomography (PET) scan detects 25 per cent of tumours not apparent after conventional investigation.[44]

The PET-CT has enhanced sensitivity (83 per cent) and specificity (96 per cent) for the detection of metastatic disease in patients with head and neck cancer; the corresponding values for conventional imaging methods are 44 per cent and 96 per cent, respectively. These results show the advantage of using 18F-FDG PET-CT over conventional imaging methods to detect distant metastatic disease.[45]

Current NICE guidelines indicate the use of PET-CT for T_4 cancers of the hypopharynx and nasopharynx and N_3 cancers which are most likely to have distant metastases.[46]

Metastatic disease

Cervical lymph node metastases:

- Regional lymph nodal involvement is typically determined with the cross-sectional imaging modality used for delineation of the primary site
- Where uncertainty exists, ultrasound scanning (with or without needle biopsy) is advocated

Diffusion-weighted MRI shows promise in the detection of malignant nodes, but there is some difficulty in the translation of apparent diffusion co-efficient values between MRI systems, and the results are variable.[47]

Positron emission tomography/CT does not demonstrate significant improvement in sensitivity and specificity in comparison to conventional cross-sectional imaging, limited by small size of some metastatic nodes and inflammatory uptake.[48]

Distant metastasis

The lung is the commonest site of distant metastasis, representing 66 per cent of haematogenous metastases, with mediastinum, bone and liver sites also recognised.[49] The NICE guidelines suggest CT of the chest for the detection of metastatic lung disease in higher risk tumours, excluding T_1N_0 and T_2N_0 tumours.[46] A dilemma exists regarding the use of CT of the thorax as lung screening, given the similar risk factors and high instance of synchronous lung cancer in head and neck patients.[50] The National Comprehensive Cancer Network classifies head and neck cancer patients with a 20 pack-year smoking history as high risk and recommends annual screening. Many centres therefore follow a pragmatic approach of routinely performing CT of the chest in patients with head and neck carcinoma, irrespective of primary stage.

As above, PET-CT should be used for T_4 cancers of the hypopharynx and nasopharynx and N_3 cancers which are most likely to have distant metastases.[46] It could also be considered for unusual tumours at higher risk of non-lung distant metastasis.

Post-treatment imaging

Post-treatment imaging is primarily aimed at identifying residual or recurrent disease but also detects late effects of treatment and second primary malignancies.

Positron emission tomography/CT is advocated for patients who have been treated with radical chemoradiotherapy for oropharyngeal, hypopharyngeal or laryngeal primaries with nodal involvement, following the outcomes of the 'PET-NECK' trial,[51] typically at 10–12 weeks post treatment.

For other tumours, imaging usually follows the original modality used for staging, to allow for comparison. In some of these situations, for example in laryngeal cancer without nodal disease treated non-surgically, PET-CT demonstrates

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Summary of recommended imaging

Site	Primary tumour	Neck	Thorax*
Oral cavity	MRI ± CT for mandible	MRI or CT	CT
Oropharynx	MRI	MRI	CT
Larynx	MRI or CT	MRI or CT	CT
Hypopharynx	MRI	MRI	CT
Nasopharynx	MRI ± CT	MRI	CT
Sinonasal	CT & MRI	MRI	CT
Salivary gland	MRI ± CT	MRI ± CT	CT
CUP	MRI/PET-CT	MRI/PET-CT	PET-CT & CT

*Positron emission tomography/computed tomography (PET-CT) is recommended instead for nodal stage N_3 disease, tumour stage T_4 cancer of the nasopharynx and T_4 cancer of the hypopharynx. MRI = magnetic resonance imaging; CT = computed tomography; CUP = carcinoma of unknown primary

non-inferiority in comparison to direct laryngoscopy, as shown within the 'RELAPS' (REcurrent LAryngeal carcinoma PET Study) trial.[52]

Having a post-treatment baseline scan is also useful for the comparison of future imaging, should it be needed; thus, the effects of surgery and radiotherapy on imaging can be factored in through reference to the baseline imaging.

A summary of recommended imaging is shown in Table 3. More specific detail can be found in the relevant site-specific chapters.

Staging of head and neck cancer

In conjunction with the Union for International Cancer Control ('UICC'), the eighth edition of the *TNM Classification of Malignant Tumours* was released in December 2016.[53] The major changes from the seventh edition are as follows:

- A new classification group for HPV-associated oropharyngeal cancers
- Carcinoma of unknown primary: stage groupings now differentiate between non-viral, HPV-related and Epstein–Barr virus (EBV)-related
- A new N_{3b} stage reflecting the prognostic importance of extra-nodal extension
- Oral cavity T-staging: the impact of depth of invasion
- Thyroid cancer staging reflects survival rather than risk of recurrence

The detail of the staging for each site can be found in the relevant chapter.

The eighth edition of the *TNM Classification of Malignant Tumours* acknowledges the distinct biological behaviour of HPV-associated oropharyngeal cancers with a new classification group. The main difference relates to regional metastasis, where there is recognition that multiple ipsilateral lymph nodes are frequently encountered in HPV-associated disease and do not carry the poor prognosis seen in non-HPV-related cancers. It also differentiates the clinical and post-surgical nodal staging.

Carcinoma of unknown primary stage groupings now differentiate between non-viral, HPV- and EBV-related. Alterations reflect differences in prognosis, with non-HPV-related carcinoma of an unknown primary including only stages III and IV, and EBV-related carcinoma of an unknown primary including stages II–IV, to acknowledge the poorer prognosis when compared to HPV-associated disease which includes stages I–IV. In other non-viral related cancers there are new clinical and pathological nodal staging categories,

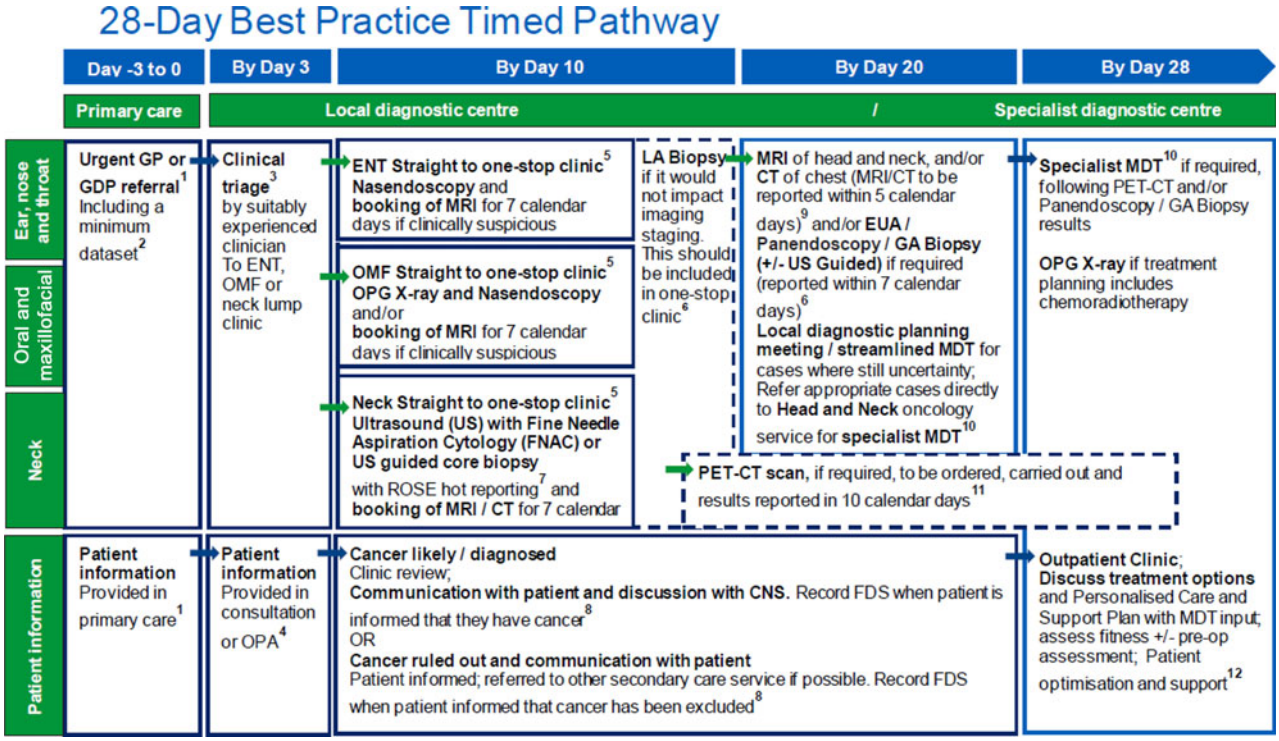


Figure 2. Twenty-eight-day best practice timed pathway for neck lumps and upper aerodigestive tract symptoms. GP = general practitioner; GDP = general dental practitioner; OMF = oral and maxillofacial; MRI = magnetic resonance imaging; OPG = orthopantomogram; ROSE = rapid on-site evaluation; CT = computed tomography; LA = local anaesthetic; EUA = examination under anaesthesia; GA = general anaesthetic; MDT = multidisciplinary team; PET = positron emission tomography; OPA = out-patient appointment; CNS = clinical nurse specialist; FDS = faster diagnosis standard; pre-op = pre-operative

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

where the prognostic implication of extra-nodal extension is recognised with a new N_{3b} stage.

Changes in oral cavity T-staging recognise the impact of depth of invasion, and in nasopharyngeal cancers amendments to both the primary tumour and nodal staging are seen. The changes to the staging of differentiated and anaplastic thyroid malignancies in the eighth edition of the *TNM Classification of Malignant Tumours* aims to represent the risk to life from a thyroid cancer diagnosis, as opposed to risk of recurrence as seen in previous staging and risk stratification systems.

Exclusion of second primary malignancies

Recommendations

- Patients with new and recurrent upper aerodigestive tract cancers should undergo comprehensive clinical examination, including endoscopic nasopharyngolaryngoscopy, as part of diagnostic investigation (evidence-based recommendation (R))
- Cross-sectional imaging, appropriate for tumour site, should be performed to screen for upper aerodigestive tract and thoracic second primary cancer (good practice point (G))

Head and neck cancers have the highest propensity of all malignancies for synchronous and metachronous cancers,[54] with reported incidences of around 13 per cent.[55] Second head and neck primaries are commonest, followed by oesophageal cancers and lung cancers.[56]

The rate of synchronous second primary malignancies, i.e. present at or around the time of diagnosis of the index tumour, is around 5 per cent.[55]

These sites are usually encompassed by imaging performed for the primary diagnosis and staging (including the thorax).

Panendoscopy under general anaesthetic offers a low diagnostic yield in the absence of significant symptoms in patients with head and neck cancers,[57] and has fallen out of favour as a screening tool in this population. Incidental second oesophageal primaries are more likely to be better detected with outpatient endoscopy and imaging alone. However, transnasal oesophagoscopy could play an important role in the exclusion of both second head and neck and oesophageal primaries.[31]

Best timed pathways

Best timed pathways (also known as optimal pathways) put together all the elements described above, with a view to fast diagnosis in as few hospital visits as possible. They are somewhat idealised and can be difficult to adhere to (e.g. when an initial biopsy is non-diagnostic).

Examples of these have been described by NHS Wales.[58]

Simplified examples for neck lumps and upper aerodigestive tract symptoms can be found in Figure 2. The selection of the investigations will depend on the clinical situation, and this has been described in earlier sections.

Important issues to be answered

These include:

- Refinement and development of cost-effective methods to improve rates of early-stage diagnosis
- Optimisation of systems to discern suspicious head and neck symptoms from those suggestive of benign disease
- Understanding of the role of transnasal oesophagoscopy in diagnosis and detection of second primary malignancies

Clinical trials due to report

'EVEREST-HN' (2022–2028): EVolution of a patiEnt-REported symptom-based risk stratification sySTem to redesign the suspected Head and Neck cancer referral pathway (https://fundingawards.nihr.ac.uk/award/NIHR202862).

Chapter 3: Head and neck cancer pathology

Table of Contents

Key recommendations

- The head and neck multidisciplinary team (MDT) should understand the scope and limitations of histopathology and cytopathology in order to inform multidisciplinary discussion. This requires effective communication between

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

clinicians and pathologists within the MDT (evidence-based recommendation (R))
- A clinically suspected diagnosis of malignancy should be confirmed by biopsy or cytology prior to oncological treatment (R)
- Participation in the National Head and Neck Histopathology External Quality Assurance Scheme is essential (R)
- The current World Health Organization (WHO) dysplasia grading system for oral cavity and larynx should be used (R)
- The meaning of the descriptors 'carcinoma in situ' and 'severe epithelial dysplasia' should be well understood between the reporting pathologist and the MDT (good practice point (G))
- Correct orientation of resection specimens and accompanying clinical information are essential (R)

Introduction

Pathologists have critically important roles in confirming or excluding specific diseases, assessing the adequacy of treatment, recognising key predictive and prognostic factors, and contributing to the evidence-based stratification of clinical outcomes for audit and research purposes. This document is aimed at providing a broad overview of the key elements of pathology services required to underpin best practice for the multidisciplinary management of head and neck cancer patients. These guidelines also aim to provide salient aspects of the pathology report that surgeons, oncologists and allied health professionals should consider when discussing the implications of a diagnosis and management options with patients and the MDT. The recommendations for pathology practice are based on published evidence as well as accepted standard practice, and have been endorsed by the Royal College of Pathologists. These guidelines are largely based on the WHO Classification of Head and Neck Tumours, and the histopathology reporting datasets published by the Royal College of Pathologists and the International Collaboration on Cancer Reporting.[59–66]

Head and neck pathology services

Quality management for head and neck pathology services

Robust internal and external quality assurance programmes are inherent in any head and neck pathology service. The pathology service should be embedded within a medical laboratory that is accredited against the international standard ISO15189:2012 by the UK Accreditation Service and integrated within local Cancer Alliances.[67–69] Local departmental consensus reporting for all borderline malignant or equivocal cases is encouraged.

Multidisciplinary team working

Histopathologists and cytopathologists are core members of cancer MDTs, and are essential to the provision of a successful service. Participation in the National Head and Neck Histopathology External Quality Assurance Scheme is essential.[69–71] The MDT should be able to review external pathology, in accordance with a risk-based approach, particularly for patients who have had diagnostic biopsies performed at non-specialist centres. For all newly diagnosed thyroid malignancies (including Thy4 (abnormal, suspicious of malignancy) and Thy5 (diagnostic of malignancy) cytology specimens), a central cancer network pathology review by a specialist thyroid MDT pathologist is necessary.[72,73] Evaluation of excision completeness may not be possible for resections specimens that have been processed at other centres.

Tissue pathways

Patient management should be guided primarily by pre-operative biopsy and/or fine needle aspiration cytology (FNAC).

Frozen sections

The sensitivity of frozen sections for margin assessment is sub-optimal, but there may be clinical utility in certain intra-operative scenarios, including determining the extent of margin involvement, and confirmation or exclusion of lymph node metastasis.[74] When required, frozen sections should be pre-arranged with the histopathology department. Clear annotation of the anatomical location of frozen sections enables correlation with the main resection specimen for final margin evaluation. The indications of frozen sections for intra-operative diagnosis are highly limited and its routine use is discouraged.

Resection specimens

Some specimens may require sampling of fresh tissue for purposes such as biobanking, special diagnostic tests and research. Following sampling of fresh tissue, specimens should be fully submerged in 10 per cent neutral buffered formalin in at least four times the volume of the specimen as soon as possible, to avoid denaturing. The site, laterality, clinical stage and nature of each specimen should be clearly indicated on the request form. The form must include the clinical indication for the operation, pre-operative radiotherapy or chemotherapy, details of previous biopsies or cytological investigations, and relevant biochemistry (particularly for thyroid diseases). Correct orientation of the specimen is of paramount importance and needs to be clearly communicated to the pathologist, preferably with the use of labelled diagrams, sutures or other markers on important structures, and peri-operative clinical photographs. Macroscopic photography of specimens is highly beneficial when communicating post-surgical pathological findings at MDT meetings.[75]

Resection specimens containing calcified tissue

Optimal decalcification is a balance between preservation of histomorphology and timeliness. Decalcification end-point testing requires experienced laboratory technical staff with optimised standard operating procedures. In resection specimens containing bone, at least one non-decalcified tissue block containing tumour should be obtained. This is to preserve the quality of antigens and nucleic acids for immunohistochemistry and molecular testing, should these be required. Decalcification may take several days or weeks. If necessary, a provisional report on the soft tissue components of the specimen may be issued for adjuvant treatment planning purposes.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Neck dissection specimens

Neck dissections should be orientated with all important structures (e.g. internal jugular vein) clearly labelled, and the nodal groups indicated, preferably with a diagram.[63,76] Avoiding errors in the interpretation of post-operative neck levels is challenging.[77]

Ancillary testing

Immunohistochemistry

Immunohistochemistry plays an important role in the correct diagnosis of primary head and neck cancers, particularly for the less common entities. The addition of novel diagnostic antibodies to the repertoire should be part of the laboratory quality assurance programme. Except for p16, the prognostic use of immunohistochemistry in head and neck cancer is less established.

In situ hybridisation

DNA and RNA in situ hybridisation is used to determine the presence of human papillomavirus (HPV) and Epstein–Barr virus (EBV) in head and neck cancers.

Human papillomavirus testing

The HPV testing should be undertaken on all primary squamous cell carcinomas (SCCs) arising in the oropharynx and neck metastases from carcinomas of unknown primary.[62,78] The sensitivity of DNA in situ hybridisation testing on fine needle aspiration (FNA) material is suboptimal.[79] Routine HPV testing is not recommended for head and neck SCC outside the oropharynx.

Epstein–Barr virus testing

The EBV testing should be undertaken on all suspected primary nasopharyngeal carcinomas and neck metastases from carcinomas of unknown primary in which primary nasopharyngeal cancer is possible.[62] The EBV testing may be indicated in certain lymphomas, but should always be performed as part of a wider lymphoma testing panel.

Carcinoma of unknown primary

Morphologically similar poorly differentiated carcinomas arising in the oropharynx and nasopharynx, and their nodal metastases, may be distinguished by the presence of HPV and EBV infection, respectively. In patients with metastatic malignancy in cervical lymph nodes without evidence of primary disease, the morphological features of the metastatic tumour may be useful, e.g. thyroid and salivary neoplasms. Immunocytochemical investigation of FNA or biopsy material does not reliably distinguish between primary SCC sites, but may be helpful in identifying metastatic carcinomas originating from the lungs, breast, gastrointestinal tract, mediastinum, genitourinary tract or prostate. Clinicians should note that immunohistochemical markers are very rarely specific for particular tissues, and that opinions on likely primary sites are based on the assessment of a panel of different markers, the availability of patient history and the balance of probabilities. Imaging studies and correlation with clinical features are essential for accurate multidisciplinary assessment of these patients. Molecular genetic profiling of head and neck cancers is not currently recommended outside the research setting.

Molecular testing

Access to accredited molecular testing facilities is essential. Tissue preparation and transfer between cellular and molecular pathology laboratories should adhere to standard operating procedures.[80] Gene mutation, rearrangement, amplification and deletion studies are important in some thyroid, salivary gland and sinonasal neoplasms, carcinomas with unknown primary, or when the nature of malignancy is unclear. A directory for genomic tests under NHS England and NHS Scotland describes the available tests.[81,82] All molecular testing results should be interpreted in the context of clinical, histomorphological and immunohistochemical findings, and integrated into the final pathology report.[80]

PD-L1

The PD-L1 (programmed death-ligand 1) testing should only be undertaken on cases requested by the MDT following clinical assessment of suitability for immunotherapy. The MDT should clearly state which immunotherapy drug is being considered, and convey whether the combined percentage score or tumour percentage score is required.[83,84] Specific companion diagnostic antibodies and automated platforms are matched to the immunotherapy drug being considered. Diagnostic validation following a period of training is required prior to combined percentage score and tumour percentage score reporting. Because inter-observer variation is recognised, it is prudent that a combined percentage score or tumour percentage score close to the 1 per cent cut-off be the consensus scored by two pathologists.[85]

Squamous cell carcinoma of upper aerodigestive tract

Squamous cell carcinoma, conventional type

Practical problems that may preclude definitive diagnosis on diagnostic biopsies include incomplete clinical information, poor orientation, necrotic or inflammatory debris, small samples containing few cells, and crush artefact. The edges of laser resection specimens often show thermal artefacts, making detailed interpretation impossible. Extensive scarring, radiation-associated nuclear atypia and loss of the normal anatomical landmarks in post-radiation specimens may make assessment difficult. A good chemo-radiotherapeutic response may leave a mass of necrotic tissue containing degenerate keratinocytes. Viable carcinoma may be difficult to identify even after extensive histological sampling, and immunohistochemistry may be of use in this setting to detect viable keratinocytes.

Morphological variants of squamous cell carcinoma

Some variants of SCC are associated with particular difficulties in diagnosis and clinical assessment, but should be managed, stage for stage, in line with conventional SCC.[65]

Papillary squamous cell carcinoma

Papillary SCC is typified by an exophytic growth pattern, with fronds of fibrovascular tissue covered by squamous epithelium showing marked atypia; areas of invasive carcinoma are often small and limited in extent. Definitive invasion may not be demonstrable in diagnostic biopsies despite a bulky tumour, and close correlation with clinical impression and radiological features are required. The prognosis is relatively good because of the limited invasive component.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Verrucous squamous cell carcinoma

Verrucous SCC has exophytic and endophytic components. It is formed by well-differentiated squamous epithelium, with minimal atypia and abundant surface keratin. The defining criterion of verrucous SCC is a broad 'pushing' invasive front, extending deeper to adjacent non-neoplastic surface epithelium. It may not be possible to make the diagnosis of verrucous SCC on superficial diagnostic biopsies, which do not include the deep invasive front. Repeated biopsies, and appreciation of the discrepancy between a clinically obvious malignancy and minimal microscopic atypia are sometimes required to make a diagnosis of verrucous SCC.

Spindle cell (sarcomatoid) squamous carcinoma

Spindle cell carcinomas typically present as polypoid tumours with an ulcerated surface, and are formed by sheets of atypical spindle cells, often raising the possibility of sarcoma. Sarcomas of mucosal origin are extremely rare in adults, but a definitive diagnosis of spindle cell carcinoma may only be possible on resection specimens when small areas of surface dysplasia or more typical invasive carcinoma are identified. Immunohistochemistry only identifies squamous epithelial differentiation in approximately 60–70 per cent of cases.

Basaloid squamous cell carcinoma

Basaloid SCC forms sheets and rounded nests of basaloid cells with palisaded nuclei of peripheral cells. Comedo-necrosis and stromal hyalinisation are frequently present. While most tumours are submucosal, continuity with dysplastic surface epithelium should be demonstrable. As morphological squamous differentiation may be absent, immunohistochemistry may be necessary to distinguish basaloid SCC from adenoid cystic (solid type) and neuroendocrine carcinomas. When located in the oropharynx, the term 'basaloid SCC' should not be used interchangeably with 'conventional HPV-associated, non-keratinising SCC'.[86]

Adenosquamous carcinoma

Adenosquamous carcinoma is a rare variant of SCC arising from surface epithelium, characterised by biphasic squamous and glandular elements. This variant is clinically more aggressive than conventional SCC. The main differential diagnosis is mucoepidermoid carcinoma; a combination of cytogenetic testing and demonstration of local surface origin may be useful in distinguishing between these entities.

Histopathology reporting

Diagnostic biopsies

The histological features from diagnostic biopsies may be limited, but it should normally be possible to determine whether any carcinoma is invasive or in situ. For invasive carcinomas, a provisional estimate of the degree of differentiation and the growth pattern should be made, but the MDT should appreciate that diagnostic sampling may not be representative, and the final grade and pattern of invasion are proffered based on the definitive resection specimen. In the oral cavity, the depth of invasion or tissues involved (e.g. muscle or bone) may guide the extent of surgery.

Resection specimens

Resection specimens provide sufficient tissue for pathological staging and to describe the full range of prognostic information.[87] The evidence base for this prognostic information is provided in guidelines published by the Royal College of Pathologists, and varies between anatomical head and neck subsites.[59–64,72,73] All Royal College of Pathologists dataset items should be included in the histopathology reports of resection specimens. The International Collaboration on Cancer Reporting may be used for reporting odontogenic carcinomas, mucosal melanomas and malignant neoplasms of the ear and temporal bone.[88–90]

Tumour–node–metastasis classification

For the purposes of local treatment protocols and continuity in clinical trial stratification, both the seventh and eighth editions of the *TNM Classification of Malignant Tumours* should be referred to. It is important to note the difference in clinical and pathological neck staging in p16 positive oropharyngeal cancer (Table 1),[91] which reflects the need for different stratification of patients having primary radiotherapy (with or without chemotherapy) versus the need for adjuvant treatment in patients receiving primary surgery.

Other important advances in the seventh and eighth editions of the *TNM Classification of Malignant Tumours* are:

- The incorporation of the depth of invasion for tumour (T) category in oral cavity carcinoma
- Separate staging systems for p16 positive and p16 negative oropharyngeal carcinoma
- The inclusion of extra-nodal extension for neck staging in all head and neck cancer except mucosal melanoma, nasopharyngeal and p16 positive oropharyngeal carcinoma
- A separate staging system for carcinoma of unknown primary, head and neck skin cancer[33,34]

Neck dissections

The presence of extra-nodal extension (formerly termed 'extracapsular spread') is considered by many to be the most important prognosticator in the majority of head and neck cancer subtypes.[93] Extra-nodal extension may be further

Table 1. Differences between clinical and pathological neck staging for p16 positive oropharyngeal cancer

Clinical nodal (cN) staging		Pathological nodal (pN) staging	
cN_X	Regional lymph nodes cannot be assessed	pN_X	Regional lymph nodes cannot be assessed
cN_0	No regional lymph node metastasis	pN_0	No regional lymph node metastasis
cN_1	Unilateral metastasis in lymph node(s), all ≤6 cm in greatest dimension	pN_1	Metastasis in 1–4 lymph node(s)
cN_2	Contralateral or bilateral metastasis in lymph node(s), all ≤6 cm in greatest dimension	pN_2	Metastasis in 5+ lymph nodes
cN_3	Metastasis in lymph node(s), >6 cm in dimension		

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Summary of WHO grading system for oral cavity and laryngeal dysplasia

WHO dysplasia grading system	
Oral cavity	3-tier system of mild, moderate & severe dysplasia. Carcinoma in situ is synonymous with severe dysplasia in oral cavity
Larynx	2-tier system of low- & high-grade dysplasia. Low-grade dysplasia relates to previous categories of mild dysplasia, whereas high-grade dysplasia encompasses previous moderate & severe dysplasia categories. The WHO system allows high-grade dysplasia to be further subdivided into high-grade dysplasia & carcinoma in situ if a 3-tier system is preferred[65]

WHO = World Health Organization

subdivided into minor or major categories, based on whether the metastasis has extended less than 2 mm or more than 2 mm beyond the lymph node capsule, respectively.[87] As the presence of extra-nodal extension informs adjuvant treatment, consensus reporting of incipient extra-nodal extension is recommended, as suboptimal inter-observer reproducibility has been reported.[94,95]

Dysplasia

Squamous cell carcinoma results from a combination of genetic alterations, some of which may manifest as precursor lesions characterised by morphological changes in epithelial cells, collectively referred to as dysplasia. An increasing degree of dysplasia is positively correlated with a greater risk of transformation to carcinoma. The various commonly used grading systems utilise the cumulation of microscopic architectural and cytological features to provide a continuous spectrum. The current WHO grading system for dysplasia of the oral cavity and larynx is recommended, summarised in Table 2.[65]

Management of dysplasia should take account of the microscopic grade of the lesion and its clinically assessed extent. While dysplasia grading remains subjective, with suboptimal inter-observer agreement, consensus reporting is likely to enhance diagnostic reliability.[96–98] Clear communication between the pathologist and clinician is necessary to convey the degree of concern regarding malignant transformation. 'Carcinoma in situ' is often used interchangeably with 'severe epithelial dysplasia', and may be appropriate in certain circumstances if the meaning is well understood between the reporting pathologist and the MDT. It is important to note the small but significant risk of concurrent invasive carcinoma in lesions biopsied and reported as severe epithelial dysplasia. The presence of severe epithelial dysplasia at resection margins should be included in pathology reports of resection specimens, as it may predict local recurrence.[59,61]

Diagnosis and management of neck lumps

Fine needle aspiration and core biopsy

Fine needle aspiration cytology is an important first-line investigation for mass lesions in the head and neck, and it can also be useful as part of staging procedures for patients with known head and neck cancer.[99] The sample collected should be high-quality, cellular, well-spread (if it is smear preparation) and not overly contaminated with blood. Aspirates should be obtained under ultrasound guidance unless very superficial. Depending on the clinical circumstance, rapidly air-dried direct smear preparations and/or needle washings into preservative solution may be required; the latter are useful for ancillary tests such as immunostaining. Rapid on-site evaluation of specimen adequacy by a biomedical scientist can reduce the number of non-diagnostic aspirates, but this has workload and cost implications.[100,101]

Reasonable cytological expertise should be available for interpreting the findings and for recognition of the diagnostic pitfalls. In the assessment of lymphadenopathy, FNAC shows high diagnostic specificity for granulomatous lymphadenitis, metastatic carcinoma, high-grade lymphoma and Hodgkin's lymphoma. Immunohistochemistry for p16 should be performed on FNAC specimens that show SCC. Cytology can be useful in the evaluation of cystic neck masses, particularly if the cyst wall is targeted, but definitive characterisation is not always possible, e.g. the differentiation between a lympho-epithelial cyst and cystic SCC metastasis. Such cases require close clinical and radiological assessment. The diagnostic sensitivity and specificity for low-grade lymphoma on cytological morphology is low, and ancillary investigations such as flow cytometry and immunocytochemistry on cytology specimens are not universally available.

The choice between FNAC and core biopsy may depend on the extent of cytopathological expertise, and the site and nature of the lesion. Core biopsy may be preferred, for example, for salivary gland tumours and lesions that require an immunohistochemistry panel or molecular testing, such as lymphoma or malignancies that require further characterisation.

Lymphoma, sarcoma, skin cancer and mucosal melanoma

The diagnostic and tissue pathways for lymphoreticular neoplasms, sarcomas, skin cancers and mucosal melanomas should be subject to local and cancer network standard operating procedures.

Role of pathologist in clinical trials

The Standard Protocol Items: Recommendations for Interventional Trials ('SPIRIT') statement provides evidence-based recommendations for the minimum content of clinical trial protocols, and is widely endorsed by the research community.[102] The Cellular Molecular Pathology Initiative ('CM-Path'), hosted by the National Cancer Research Institute, has recently published an extension to the Standard Protocol Items: Recommendations for Interventional Trials statement, to provide the details required to effectively incorporate pathology support into clinical trial protocols; the guidance is called 'SPIRIT-Path'.[103]

Important questions to be answered

Head and neck pathology is a rapidly evolving field that is continuously being shaped by technological advances. Developments likely to influence the practice of head and neck pathology in the near future include the following points.

- *Routine use of diagnostic digital pathology.* This is likely to facilitate streamlining of the diagnostic pathway and rapid pathology review across cancer networks. High throughput digital pathology will also advance artificial intelligence algorithms for computer-assisted diagnosis and the development

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

of biomarkers. Incorporation of whole slide images linked to tissue biobanks, with associated clinical metadata, will underpin the drive to greater refinement of personalised medicine.
- *Characterisation of the tumour microenvironment.* Better understanding of the function of interplay between the tumour, immune cells and the extracellular matrix is likely to lead to the identification of individuals most likely to benefit from immunomodulatory oncology drugs.
- *Whole genome sequencing.* Routine whole genome sequencing of fresh tumour samples in selected tumour types may identify actionable mutations in head and neck cancer.[104]
- *Integration of pathology support in clinical trials.* There is a growing need for clinical trials with pathology support for biomarker-driven stratification and embedded translational studies, to develop novel molecular-based diagnostic, prognostic and predictive biomarkers.
- *Multiplex risk stratification.* The integration of morphological, molecular and digital pathology signatures with radiomic, microbiome and serological biomarkers can be used to improve the stratification of patients with a risk of tumour recurrence and determine progression.

Chapter 4: Non-surgical head and neck cancer treatment

Table of Contents

Introduction

The ability of ionising radiation to kill tumour cells makes it an ideal curative treatment for head and neck cancers where the rates of metastasis are relatively small. Many of the developments in radiotherapy techniques over the last 20 years have been applied to great effect in head and neck cancers to target smaller treatment volumes and reduce side effects. For many years, cisplatin has been combined with radiotherapy to increase cure rates and used in palliative chemotherapy regimens. The promise of newer drugs such as immunotherapies is now beginning to be realised in head and neck cancers.

Curative radiotherapy

Recommendations

- Use intensity-modulated radiotherapy techniques and international consensus contouring guidance when treating head and neck cancers with curative intent (evidence-based recommendation (R))
- Use Royal College of Radiologists' recommended dose fractionation schedules e.g. 70 Gy in 35 fractions over seven weeks and 65–66 Gy in 30 fractions over six weeks (R)
- Review patients weekly during treatment by a multidisciplinary team (MDT), with particular focus on nutrition and swallowing assessment and therapy (R)
- Dental assessment with extraction if necessary should be carried out before radiotherapy for dentate patients (R)
- Smoking cessation management is a key component of radiotherapy treatment (R)

Definitive or 'radical' radiotherapy treatment offers the potential for cure with organ preservation for many head and neck cancer anatomical sites.

Radiotherapy planning initially involves fabrication of a mask to keep the patient still and precisely positioned for each fraction of treatment, followed by a planning computed tomography (CT) scan performed whilst in the mask, usually with the administration of intravenous contrast. There is then a period of time whilst planning takes place before treatment is ready to be commenced. For a course of radical radiotherapy, a clinician will contour target volumes using diagnostic imaging such as magnetic resonance imaging (MRI), CT and positron emission tomography (PET)-CT, sometimes co-registered to improve the accuracy of target delineation. This is followed by the generation of a radiotherapy plan by dosimetrists or physicists using advanced computing.

Intensity-modulated radiotherapy is now the standard of care – highly conformal dose distributions are achieved by shaping or modulating multiple beams, allowing the sparing of nearby organs at risk. It has been demonstrated that intensity-modulated radiotherapy offers superior disease control for nasopharyngeal carcinoma and a reduction in radiotherapy-induced xerostomia.[105,106] Intensity-modulated radiotherapy allows the delivery of different doses to differing target volumes (e.g. tumour-bearing tissues and elective lymph node regions) within each fraction of treatment. For each fraction, a patient will typically be in the treatment room for 10–20 minutes. Image-guided verification of treatment accuracy is a key part of modern radiotherapy treatment with the recently updated UK guidelines.[107]

Recommended dose fractionation schedules are summarised in the Royal College of Radiologists' guidance.[108] Schedules of 70 Gy in 35 fractions over seven weeks and 65–66 Gy in 30 fractions over six weeks are radiobiologically similar, and represent standard schedules in the UK for definitive radiotherapy. For primary non-surgical treatment of locally advanced disease, combining radiotherapy with concurrent chemotherapy is standard for patients aged less than 70 years with a good performance status.[109] For patients unsuitable for chemotherapy, modest acceleration of radiotherapy (e.g. delivering six rather than five fractions per week) has been shown to offer some improvement in local control but not overall survival, with the benefit diminishing with increasing age.[110] For early glottic cancer, hypofractionated schedules are superior to conventional fractionation e.g. 55 Gy in 20 fractions over four weeks.

Radiotherapy often has both short-term (acute) and long-term (late) side effects, which are dependent upon the dose delivered, target volumes, and patient fitness and co-morbidity. Short-term side effects gradually build up during a course of fractionated treatment, and can last for weeks or months after treatment. These include skin reaction, mucositis, xerostomia,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Summary of Radiotherapy Therapy Oncology Group Common Toxicity Criteria 2.0 scoring for skin, oral mucositis and pharynx

	Grade			
Toxicity	1	2	3	4
Skin	Faint erythema, dry desquamation	Moderate to brisk erythema, or patchy moist desquamation, mostly confined to skin folds or creases, moderate oedema	Confluent, moist desquamation >1.5 cm in diameter not confined to skin folds, pitting oedema	Skin necrosis or ulceration of full thickness of dermis, may include bleeding
Mucositis due to radiation	Erythema	Patchy pseudomembranous reaction (patches generally <1.5 cm in diameter, non-contiguous)	Confluent pseudomembranous reaction (contiguous patches, generally >1.5 cm in diameter)	Necrosis or deep ulceration, may include bleeding
Dysphagia – pharyngeal, related to radiation	Mild dysphagia, but can eat regular diet	Dysphagia, requiring mainly pureed, soft or liquid diet	Dysphagia, requiring feeding tube, IV hydration, or hyperalimentation	Complete obstruction, ulceration with bleeding

IV = intravenous

dysgeusia, throat secretions, risk of aspiration pneumonia and voice changes. Common toxicity criteria are often used to grade acute toxicity. Table 1 summarises grading for acute radiation-related skin, mucositis and dysphagia toxicity.[111] Long-term side effects are highly variable, and can include long-term swallowing dysfunction, osteoradionecrosis, xerostomia, dysgeusia, lymphoedema, hypothyroidism, skin and subcutaneous fibrosis, and radiotherapy-induced cancer in the treated area many years later.

The provision of supportive care prior to, during and after a course of treatment is a key component of the delivery of radiotherapy. This includes restorative dental, nursing, dietetic, and speech and language therapy input. Some patients may suffer with significant treatment-related anxiety and claustrophobia, and can receive individualised support. Continued smoking during head and neck radiotherapy has been shown to approximately double the risk of locoregional treatment failure and the risk of mortality, along with increased late toxicity.[112] Smoking cessation management is a key component of radiotherapy treatment.

Unscheduled interruptions in radiotherapy for head and neck cancers can allow tumours to repopulate, with a detrimental impact upon cure rates. The Royal College of Radiologists has published guidance on the appropriate management of unavoidable gaps in treatment, with options including weekend or bi-daily treatment administration.[113]

Response to (chemo)-radiotherapy is often best assessed clinically. A PET-CT performed three months after treatment is often used in node-positive disease to assess the need for a neck dissection, as evidenced by the 'PET-NECK' trial.[51] It can be helpful to repeat diagnostic imaging (e.g. MRI) three months after radiation, but it can be difficult to distinguish radiotherapy-induced oedema from tumour recurrence with imaging alone.

Post-operative radiotherapy

Recommendations

- Discuss all surgical resection histology at an MDT meeting with input from a clinical oncologist, pathologist and operating surgeon, to decide on suitability for post-operative radiotherapy (evidence-based recommendation (R))
- Commence post-operative radiotherapy within six weeks of surgery if the patient has recovered well enough (R)

Radiotherapy should be considered after surgery when there is a significant risk of locoregional recurrence. In practice, this usually means considering post-operative radiotherapy in pathologically staged $T_{3/4}$ tumours, node-positive disease or combinations of other risk factors. There are some specific cases where radiotherapy is also recommended in early stage disease, for example adenoid cystic cancer. As a rule of thumb, locoregional recurrence rates are halved by post-operative radiotherapy, but with relatively little effect on overall survival.

Tumour histology should be discussed at an MDT meeting with the surgeon present. The team should consider indications for irradiating the primary site, dissected neck and undissected neck. Absolute and relative indications for post-operative radiotherapy are summarised in Table 2 and discussed further in the relevant site-specific chapters.

Some patients may not feel able to undertake six weeks of adjuvant radiotherapy having just recovered from a major operation if the benefit of radiotherapy is relatively small. The decision to administer post-operative radiotherapy may depend as much on patient fitness, their support network and their preferences as on the tumour factors listed above. If patients present with disease that is locally advanced (e.g. T_4 disease or with obvious extra-nodal extension on diagnostic imaging) a plan to offer surgery and post-operative radiotherapy should be discussed with the patient and oncologist before the operation. Putting someone through a major resection for locally advanced disease when they cannot complete post-operative radiotherapy may not be to their advantage.

Post-operative radiotherapy should ideally commence within six weeks of surgery. This can be challenging to achieve, particularly if there have been post-operative complications. It generally takes several weeks from a decision to offer adjuvant radiotherapy to commencing treatment, so efficient MDT organisation is important in order to review post-operative pathology promptly and to allow the oncologist to meet the patient in a timely fashion. Sometimes it may be advantageous to organise post-operative radiotherapy before histology results are available (e.g. in a tumour that was T_4 at diagnosis), or to start radiotherapy planning, but not treatment itself, before a fistula or wound is fully healed. The absence of a tumour to contour and the altered anatomy after surgery often make radiotherapy contouring more challenging for the oncologist than in definitive radiation cases. Marginal and out-of-field recurrences are more common than following definitive radiotherapy, and hence target volume delineation needs to be generous.[114]

As with curative radiotherapy, the support of an MDT, comprising dietitians, speech and language therapists, clinical

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Absolute and relative indications for post-operative radiotherapy

Radiation site	Absolute indication	Relative indication
Radiation to primary site	– Involved margin where further resection not possible – Close margin – Surgeon concern regarding recurrence risk – T_4 cancer	– Lymphovascular invasion – Perineural invasion – Non-cohesive tumour edge – T_3 cancer – Grade 3 cancer
Radiation to dissected neck	– Extra-nodal extension, >1 involved nodes	– 1 involved node, especially if >30 mm
Radiation to undissected neck	– Primary tumour crossing midline – Multiple involved nodes	
Radiation to undissected neck – oral tongue primary	– T_3 or T_4 cancer – Primary tumour is within 10 mm of midline – 2+ involved nodes in ipsilateral neck – Extra-nodal extension in ipsilateral neck	– 1 involved node, with no extra-nodal extension in ipsilateral neck

nurse specialists, and therapy radiographers, is critical to ensure patients complete the treatment course.

Palliative radiotherapy

Recommendations

- Consider palliative radiotherapy to ameliorate local symptoms in people who are not able to receive curative treatment (evidence-based recommendation (R))

Primary palliative radiotherapy can be used as a first-line treatment in those who are not fit enough to undergo curative-intent treatment with surgery or radiation. The aims of this include longer-term local control of an incurable tumour, and short-term palliation of distressing symptoms such as pain, bleeding or fungation. Typical dose fractionation schedules can range from a single fraction to 30 Gy in 10 fractions or even longer schedules.[108]

Radiation toxicity during and after treatment can temporarily make symptoms worse, so patient selection is key, and the overall aims of treatment need to be carefully considered. Doses should be chosen to minimise toxicity and travelling where possible. Close working with palliative care teams can be invaluable.

Palliative re-irradiation can be considered for symptomatic local recurrences after a prior definitive or adjuvant radiotherapy treatment, though the increased availability of systemic treatments such as immune checkpoint inhibitors means other treatment options may be preferable. The role of stereotactic ablative radiotherapy in this context remains uncertain and it is not routinely commissioned within the National Health Service (NHS).

Palliative radiotherapy has a role in the management of symptomatic systemic metastatic disease, especially for painful bone metastasis. Stereotactic ablative radiotherapy is increasingly used in oligometastatic disease. This is defined as the presence of one to three sites of metastatic disease, typically within the lung, bone, lymph nodes or liver, presenting six months or more after primary treatment. This has been shown to be well tolerated, with local control rates of 80–90 per cent, and the promise of improved overall survival in other cancer types.[115,116]

Proton beam therapy

Recommendations

- Consider proton beam therapy for adults with head and neck cancer who meet appropriate commissioning criteria, or as part of randomised, controlled trials (evidence-based recommendation (R))

Proton beam therapy is routinely used in preference to standard photon radiotherapy for children and young adults, where the reduced integral dose lessens effects on organ growth and lowers the risk of secondary cancers.[117] Because of the complex anatomy and proximity of sensitive organs at risk in the head and neck region, proton beam therapy may also benefit adult patients, by reducing early and late treatment toxicities, or by improved optimisation of target volume coverage in areas of dose-limiting structures, for example the base of the skull.

The distinct physical properties of protons result in a sharp distal fall-off in dose beyond the target volume, with minimal 'exit-dose'.[118] Compared with standard treatment using photons, there is a reduction in the low-to-intermediate dose delivered to normal tissues. Proton treatment planning is complex; it factors in possible variation in the relative biological effectiveness (protons compared to photons),[119] as well as the nature of tissues the beam passes through, changes in patient weight or variation in air cavity, all of which can alter the dose distribution. Changes in patient anatomy are carefully monitored for alteration in the dose distribution, with re-planning routinely needed during head and neck cancer treatments.

There are observational data to support the benefits of proton beam therapy for the treatment of head and neck cancers. In oropharynx cancer, patients were less likely to require a feeding tube during treatment;[120] or to develop grade 3 weight loss or require a feeding tube at three months (odds ratio = 0.44; 95 per cent confidence interval (CI) = 0.19–1.0; p = 0.05) or one year after treatment (odds ratio = 0.23; 95 per cent CI = 0.07–0.73; p = 0.01).[121] Patients with nasopharynx cancer were less likely to develop any grade 2 or higher acute adverse events (odds ratio = 0.15; 95 per cent CI = 0.03–0.60; p = 0.01)[122] or require feeding tube placement (20 per cent *vs* 65 per cent; p = 0.02).[123] In a systematic review of non-comparative sinonasal cancer observational studies, subgroup analysis showed higher disease-free survival at five years (relative risk = 1.44, 95 per cent CI = 1.01–2.05; p = 0.045) and locoregional control at the longest follow up (relative risk = 1.26, 95 per cent CI = 1.05–1.51; p = 0.011) using proton beam therapy.[124]

NHS England now has high-energy proton beam therapy centres in Manchester and London, and is well-placed to systematically evaluate the potential benefits of proton beam

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

therapy, through a combination of randomised clinical trials,[125] pre-commissioning studies and outcome monitoring.[126] Rigorous assessments are needed to justify the routine use of a specialist and constrained resource, the increased treatment costs, and the inconvenience to patients and their families in accessing a centralised service.

Chemotherapy and other drugs concomitant with radiotherapy

Recommendations

- Offer concomitant cisplatin with curative radiotherapy to patients who are young and fit enough to tolerate the likely increased toxicity when they have $T_{3/4}$ tumours and/or node-positive disease (evidence-based recommendation (R))
- Offer concomitant cisplatin with post-operative radiotherapy to patients with R1 (presence of microscopic cancer cells) or R2 (presence of macroscopic residual tumour) resections, or extracapsular nodal extension (R)

Concomitant chemotherapy given with radiotherapy is now a standard of care in advanced disease, both in the primary and adjuvant setting. It has been shown to improve locoregional control, and adds a small survival benefit to radiotherapy alone but with the downside of greater toxicity. The mechanism of action is still not fully understood. Chemotherapy may act as a radiosensitiser by impairing pathways to repair tumour DNA damage caused by radiotherapy. It may also have a role in sterilising microscopic metastatic disease cells.[127]

The Meta-Analysis of Chemotherapy in squamous cell Head and Neck Cancer ('MACH-NC') database demonstrated that concomitant chemotherapy improved overall survival. The 2021 update assessed 19 805 patients in 107 trials (excluding nasopharyngeal cancer) and showed an absolute survival benefit of 6.5 per cent at 5 years and 3.6 per cent at 10 years for concomitant chemotherapy compared to radiotherapy alone. The benefit decreased with increasing age, with no significant benefit for patients aged over 70 years (hazard ratio of 0.78 for those aged less than 50 years, compared with 0.97 for those aged 70 years or more).[109] Concomitant cisplatin should be considered for patients who are young and fit enough to tolerate the likely increased toxicity when curative radiotherapy is used for $T_{3/4}$ tumours and/or with node-positive disease.

Concomitant chemotherapy in the post-operative setting has also been shown to improve local control and survival in those with poor prognostic factors and a high recurrence risk, particularly if there are involved resection margins or extracapsular nodal extension. In a separate meta-analysis, the five-year absolute benefit rate with concomitant chemotherapy versus radiotherapy alone was 7.9 per cent.[128,129]

The international standard treatment regimen is cisplatin 100 mg/m[106] three-weekly, but because of the intensiveness and morbidity of treatment, chemotherapy modification (delays, omission and dose modification) is not uncommon. Weekly cisplatin 30–40 mg/m[106] is preferred by some centres in the belief that it is better tolerated and more flexible in delivery, as occasional weeks can be missed with less risk of compromising total dose. Regardless of treatment schedule, it has been shown in studies that a cumulative dose of around 200 mg/m[106] gives the best therapeutic benefit.

A meta-analysis published in 2017 concluded that, although no difference in treatment efficacy was seen for three-weekly versus weekly cisplatin regimens, the studies analysed were often flawed in terms of balance and study numbers, and few trials were prospective and randomised.[130,131] Subsequently, Noronha *et al.* reported a prospective phase 3 randomised study of 300 patients (93 per cent adjuvant), and showed a two-year locoregional control benefit rate of 58.5 per cent for weekly cisplatin versus 73.1 per cent for three-weekly.[132] Other studies have reported conflicting results and so conclusions remain difficult to draw.[133]

Cetuximab has also been extensively investigated in combination with radiotherapy. Although the initial major study showed a benefit for cetuximab compared to radiotherapy alone, subsequent studies have shown cetuximab to be inferior to cisplatin, particularly in human papillomavirus (HPV)-positive groups.[134–136]

Immunotherapy (discussed in the next section for recurrent and metastatic disease) may have a place in the radical setting in combination with surgery and/or radiotherapy. The global multicentre, multicohort phase I/II trial 'Checkmate-358' assessed the safety of neo-adjuvant nivolumab prior to surgery, and the 'CompARE' (Comparing Alternative REgimens for escalating treatment of intermediate and high-risk oropharyngeal cancer) trial is currently recruiting patients with intermediate and high-risk oropharyngeal tumours receiving radical (chemo)radiotherapy with durvalumab as one of the investigation arms. There are many more studies open or in development that are focused on assessing the benefit of immune checkpoint inhibitors; this is an exciting era for concomitant systemic therapy in radical head and neck cancer.

Palliative systemic therapies

Recommendations

- Explain the potential benefits of different systemic therapies and their possible negative effects (side effects, time taken for treatment, likelihood of treatment not working) to patients and families before agreeing a treatment plan (evidence-based recommendation (R))
- Measure PD-L1 (programmed death-ligand 1) biomarkers in all patients who are considering systemic palliative therapies (R)
- Offer palliative immunotherapy as an alternative to chemotherapy, in line with current NHS commissioning guidance* (R)

*NHS England currently funds single-agent pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma (SCC), provided the combined positive score is 1 or more. Nivolumab is funded for patients who have progressed during or within six months of platinum-based chemotherapy.

Palliative chemotherapy can be considered in cases of recurrent or metastatic head and neck SCC that are not amenable to local therapies and where the patient continues to have a good World Health Organization performance status classification, of 0–2 (ranging from asymptomatic to symptomatic and in bed less than 50 per of the day). In recurrent and metastatic disease, overall survival is generally poor, and measured between 6 and 12 months in most series. Responses to systemic therapies can be of limited duration and toxicity rates can be high, so it is important to discuss the risks of treatment compared to best supportive care alone, particularly taking into account a patient's fitness for treatment and their preferences and wishes when life expectancy is short. Medications

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

and strategies aimed at improving symptom control are essential, along with good palliative care and clinical nurse specialist and allied health professional support. It is important to consider clinical trials if available.

Chemotherapy and cetuximab

Traditional first-line palliative chemotherapy is platinum and 5-fluorouracil, in combination with cetuximab, a monoclonal antibody directed against epidermal growth factor receptor (the 'EXTREME' regimen). The inclusion of cetuximab in this combination only has NHS England approval for oral cavity tumours. This combination produces an overall response rate of 36 per cent and an overall survival of 10 months, in comparison to 7.4 months for chemotherapy alone.[137] It is, however, associated with substantial toxicity, including skin toxicity, hypomagnesaemia and sepsis, and so patients should have a good performance status. Simpler schedules of similar drugs may offer reduced toxicity and reduced duration of day-unit or in-patient stay, but have less evidence to support them (e.g. carboplatin and capecitabine).

If the patient remains fit after progression, second-line chemotherapy options include carboplatin and paclitaxel, which demonstrates an overall response rate of 25.9 per cent and median overall survival of eight months, with a reasonable toxicity profile.[138] Further options include single-agent cetuximab, taxanes or methotrexate, each of which can be associated with response rates of 10–27 per cent, but with no overall survival benefit.[139,140]

Immunotherapy

Immune checkpoints modify immune responses to prevent autoimmune reactions. One such check point is the PD1 protein (programmed cell death protein 1), expressed by T cells. This ligates with PD-L1 on cancer cells, which often overexpress PD-L1, therefore providing a means of tumour immune escape by suppressing the immunological response of the T cell.

Anti-PD1/PD-L1 immunotherapy agents, such as pembrolizumab and nivolumab, block this signalling through the PD-L1 pathway and thereby enhance immune activity.

Immune check point inhibitors have recently been shown to improve outcomes in recurrent or metastatic head and neck SCC, in both the first-line setting in comparison to traditional chemotherapy, and in platinum-resistant tumours.

Pembrolizumab as a single agent or in combination with platinum and 5-fluoruacil is now the most effective first-line treatment in recurrent or metastatic head and neck SCC cases. The PD-L1 biomarker testing should be routinely assessed in patients with recurrent or metastatic head and neck SCC in order to determine eligibility for pembrolizumab, using the combined positive score or tumour positive score measure (combined positive score of more than 1). Up to 85 per cent of head and neck SCC patients have a PD-L1 combined positive score of 1 or more.

Combination pembrolizumab and chemotherapy demonstrates an overall survival of 13.6 months, compared to 10.4 months for standard chemotherapy.[141] Single-agent pembrolizumab also demonstrates an improved overall survival of 12.3 months. Single-agent pembrolizumab is generally well tolerated, with a favourable safety profile in comparison to standard chemotherapy or the pembrolizumab chemotherapy combination (7 per cent had grade 3–5 treatment-related adverse events, compared to 39–47 per cent for the combination or standard treatment). NHS England currently funds single-agent pembrolizumab for untreated metastatic or unresectable recurrent head and neck SCC, provided the combined positive score is 1 or more, but not the combination with chemotherapy. Typical potential toxicity includes fatigue, endocrine toxicity including hypothyroidism, gastrointestinal disturbance, and anaemia. A subgroup of patients demonstrates prolonged survival when treated with immunotherapy, with a survival rate at 24 months of 38 per cent for pembrolizumab as a single agent and 29 per cent for pembrolizumab in combination with chemotherapy.

Monotherapy with both nivolumab or pembrolizumab has demonstrated efficacy in patients who have progressed during or after platinum-based chemotherapy compared to standard second-line single-agent chemotherapy, with an improved toxicity profile.[142,143]

Current trials that may change practice and future directions

The National Cancer Research Institute supports a wide variety of clinical trials in head and neck cancer. Studies that are open to recruitment or in the set-up stage can be viewed here via: https://www.ncri.org.uk (search portfolio maps). Major USA trials undertaken by the NRG co-operative group can be viewed here: https://www.nrgoncology.org/Clinical-Trials/Protocol-Search. There are perhaps three major research areas that may change practice within the next five years.

In HPV-associated oropharyngeal cancer, there are many studies exploring different de-intensification strategies: reducing radiation dose, treatment volumes or concomitant therapies in order to maintain high cure rates with less toxicity. There is almost a risk that the plethora of trials with different strategies will make the optimal treatment paradigm difficult to assess. Key UK phase III trials that should report in the next few years are 'PATHOS' (a trial of risk-stratified, reduced-intensity adjuvant treatment in patients undergoing transoral surgery for HPV-positive oropharyngeal cancer) and Torpedo (a trial of intensity-modulated proton beam therapy *vs* intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer).

The cure rates for other head and neck SCC have not changed much for decades, so trials are also exploring improving survival rates in these cancers, often by adding new treatment options such as immunotherapy to existing protocols. In the UK, the 'CompARE' trial has almost completed accrual.

Systemic therapy for many cancers has changed hugely in the last decade, with major advances being made in melanoma and lung cancer in particular. It is hoped that continued immunotherapy and targeted-therapy research will also improve survival rates in head and neck cancers.

The head and neck oncology community worldwide has produced an excellent series of practical guidelines for radiotherapy target volume contouring and selection in the last decade.[144–146] These have been supplemented with the Royal College of Radiologists' head and neck cancer consensus statements, and other associated UK national guidance on topics such as radiotherapy contour quality assurance and dose fractionation.[107,108,147] If implemented in every radiotherapy centre, such guidelines have huge potential to reduce variation and improve outcomes. Future guidelines, for example on post-operative radiotherapy contouring, are eagerly awaited.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Chapter 5: Follow up, surveillance and recurrent disease

Table of Contents

Introduction

Follow up is an essential component of the management of patients who have undergone radical treatment for head and neck cancer. The rationale for follow up is multifactorial:

- Monitoring of treatment effectiveness
- Early detection of recurrent disease
- Surveillance for second primary tumours
- Assessment of treatment morbidity and functional deficit
- Education of patients and caregivers
- Risk factor modification

Approximately 25 per cent of patients treated for head and neck cancer develop cancer recurrence, most of which is locoregional, and the majority of recurrences occur within the first two years after treatment.[148]

Patients with head and neck cancer are also at risk of developing metachronous second primary tumours, with the risk of a second primary tumour doubled (compared to patients without head and neck cancer). Over 10 years, around 17 per cent of patients will develop a second primary tumour, mostly in the head and neck or lung.[149]

Most protocols adopt shorter intervals between clinic visits in the first two years (when the risk of locoregional recurrence is known to be at its highest), with gradually lengthening intervals through to five years.

Despite the accepted importance of follow up, current strategies, including imaging protocols, are largely based on consensus opinion rather than prospective data, with significant variation in practice.[150]

This chapter covers the principles of follow up and surveillance, and the management of disease recurrence. Site- and tumour-specific guidance can be found in the relevant chapters. Imaging is discussed in more detail in Chapter 2 and non-surgical treatment for recurrence is described in Chapter 4. The aspects of patient support and survivorship – crucial parts of follow up – are discussed in more detail in Chapters 9–14.

Follow up

Recommendations

- Patients should undergo follow up on at least a two-monthly basis for two years, then three- to six-monthly thereafter for a minimum of five years (good practice point (G))
- Patients should be able to access urgent clinical assessment for suspicious symptoms at any time during follow up (evidence-based recommendation (R))
- Follow up and clinical examination with imaging, if indicated, should aim to identify cancer recurrence as early as possible and to detect second primary tumours (R)
- Patients should undergo follow up in clinics at, or linked to, a head and neck treatment centre, and have access to the wider multidisciplinary team (MDT), including clinical nurse specialists, speech and language therapists, and dieticians (R)
- Patients receiving radiotherapy or chemoradiotherapy for stage 3 and 4 disease should undergo post-treatment surveillance imaging to assess for disease response, as well as for baseline imaging (R)
- Baseline imaging should be considered after primary surgery in which anatomy is altered (G)
- Patients should undergo regular thyroid function monitoring after treatment for head and neck cancer (R)

Detection of recurrent disease

Recurrent head and neck cancer poses significant challenges for treatment and is associated with a poor prognosis. However, early detection of recurrence means that the patient has a greater chance of being a candidate for surgical salvage,[151] as well as for active treatments such as radiotherapy if not already employed, and systemic therapies including immunotherapy.

Of the 25 per cent of patients who will develop cancer recurrence, around 65 per cent of recurrences are in the primary site, 36 per cent in regional lymph nodes and 22 per cent are distant.[148] The majority occur within the first two years after treatment (62 per cent in first year, 82 per cent within two years).

Hence, standard follow-up protocols with short intervals in the first two years, followed by less frequent follow up, would seem appropriate. However, it is not clear what impact regular scheduled follow up has on either the detection of recurrence or on overall survival. In a study of 4839 patients with locoregional recurrent head and neck cancer, more than 60 per cent presented at an advanced stage (stage III and IV disease).[152] In

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

another study, only 27 per cent of patients with detected recurrence were suitable to undergo salvage surgery.[153]

There are consistent data showing that most recurrences detected in clinic arise when a patient has become symptomatic and therefore expedited their clinic appointment.[150] For example, one study showed that the detection rate rose from 0.2 per cent in asymptomatic patients to 56 per cent in those with symptoms.[154]

In the detection of the response to treatment, post-treatment response evaluation using ^{18}Fluorine-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) has become the standard of care to evaluate patients after (chemo)radiotherapy and to determine the need for neck dissection.[51] Yet the positive predictive value in this setting is low, and is affected by both treatment and tumour biology (being lower in human papillomavirus (HPV)-positive tumours).[155] Therefore, changes to the timing of post-treatment imaging for HPV-positive tumours, from three to four months, has been proposed, to reduce the rates of equivocal scans from involuting disease, which is known to be slower in HPV-associated disease.[156]

For the detection of recurrence (rather than persistence), clinical assessment remains the mainstay of cancer surveillance. Baseline post-treatment imaging, usually by magnetic resonance imaging (MRI), typically performed three to four months after the completion of treatment, is recommended for any patient having undergone surgical or non-surgical treatment that may alter anatomy or imaging. This serves as a means of comparison if further imaging is later required.

When recurrence is clinically suspected, axial imaging should be organised and compared to baseline imaging (using the same modality).

Ultrasound provides rapid assessment of regional nodal recurrence and facilitates accurate concurrent pathological sampling. It may be available at the time of the clinic appointment. It may also have a role for monitoring an untreated neck with a significant chance of cervical lymph node metastases, although such cases should generally have had elective treatment or sentinel node biopsy in cases of oral cavity cancer.

Imaging may be the only means of assessing the recurrence status of clinically inaccessible tumours, e.g. the maxilla or midface after reconstruction, or the anterior and lateral skull base. However, there is no consensus on the frequency of such imaging.

^{18}Fluorine-fluorodeoxyglucose PET-CT offers potential advantages in the detection of recurrences, with evidence suggesting a role for FDG PET-CT imaging at one year post treatment, outperforming other imaging modalities and showing additional benefit over clinical examination alone.[157]

Head and neck adenoid cystic carcinoma is a rare indolent cancer, but is characterised by late recurrence, both locally and to lungs and bone. Long-term interval imaging with low-dose computed tomography (CT) is proposed as a means of early metastasis detection. However, the evidence for improved survival with metastasectomy is mixed and the cumulative radiation risk from serial imaging, especially in younger patients, needs to be considered.[158] Hence, there is no evidence-based or consensus position on this.

Detection of second primary disease

Patients with head and neck cancer are not only at risk from recurrence of the index tumour, but also from the development of metachronous second primary tumours. The standardised incidence ratio of second primary tumours is estimated to be more than double in patients who have already had head and neck cancer, with an excess absolute risk of 167.7 per 10 000 per year (essentially, 17 second primary tumours in 100 treated head and neck cancer patients over 10 years of follow up).[149] This risk remains stable over time and relates to previous and continued exposure to known carcinogens, such as tobacco and alcohol, leading to widespread genomic instability or field change.[159,160]

Overall, most second primary tumours are lung cancers, although other oral cavity cancers are the commonest for patients with an index oral cavity cancer. The anatomical subsite of the first tumour affects the risk of second primary tumours, with the risk being highest for hypopharyngeal tumours and lowest for laryngeal tumours.[149]

While the risk of a second primary tumour from oropharyngeal cancer appears to have decreased in the era of HPV-related disease, the presence of any HPV-induced malignancy (including head and neck) exposes patients to a significantly increased risk of a second HPV-induced tumour.[161]

As for recurrent disease, second primary tumours in the head and neck will often give rise to symptoms that may be reported by a patient and may then be detected via clinical examination or by imaging. However, as many second primary tumours may be both asymptomatic and arise outside the head and neck (in particular, the lung and oesophagus), the role of prolonged imaging surveillance is discussed, yet remains controversial. Low-dose CT appears more effective than chest X-ray alone, yet the outcome for patients with secondary lung primaries is poor and therefore raises the question of its effectiveness in this setting.[162] The PET-CT scan may offer advantages over CT and MRI, with an increasing sensitivity and specificity the longer after treatment completion it is used.[163,164] Currently, no robust prospective data have yet confirmed a survival advantage from regular surveillance imaging.

Monitoring and managing symptom burden

Because of their anatomical location, head and neck tumours and their treatment result in significant morbidity, including problems with speech and voice, swallowing, pain, and disfigurement. Consequently, head and neck cancer has one of the highest disease burdens of any cancer type.[165] In addition, neurological morbidity and endocrinopathies may pose long-term challenges to rehabilitation.

Follow up provides an opportunity to both assess symptom burden in the early phase after treatment, but also monitor for late and long-term effects. Examples of late effects include xerostomia, dysphagia, dental problems, osteoradionecrosis and lethargy. Some late effects of treatment, such as dysphagia, may have a period of stability for several years before late deterioration.[166] The wide range of morbidity experienced by head and neck cancer survivors demonstrates the need for a multidisciplinary input into follow-up services. This includes access to speech and language therapy, dieticians, clinical psychology or counselling, physiotherapy, and dental rehabilitation. Longer-term follow up also provides an opportunity to support patients with smoking and alcohol cessation, as well as psychological support regarding fear of cancer recurrence (see also Chapters 9–16).[167]

Endocrinopathies are not uncommon after treatment for head and neck cancer.[168] Particular attention should be paid to the development of hypothyroidism. This may occur in

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

25–40 per cent of patients undergoing radiation treatment, but rises to greater than 60 per cent in patients undergoing total laryngectomy and radiotherapy, with an average time to detection of eight months.[169]

Follow-up guidelines

Following from the issues and evidence explained above, it is possible to arrive at guidelines for the follow up of patients after treatment for head and neck cancer.

Setting

Patients should be followed up in specialist head and neck oncology clinics, where they can be seen by clinicians with a specialty interest in head and neck cancer, and with access, in clinic, to an MDT, dependent on an individual patient's needs. Studies of specialist nurse counselling and intervention after treatment, in conjunction with regular clinical follow up, have demonstrated improvements in health-related quality of life and depressive symptoms.[170] Continuity of care is an important issue to patients.[171] There should be access to all aspects of patient support, i.e. clinical nurse specialists, dieticians, speech and language therapists, physiotherapy, dentistry, and psychological support. There should also be access to smoking cessation services.

There should be access to urgent CT and MRI, if required, when recurrence is suspected. Ultrasound can ideally be performed in clinic.

There may be a tension between all follow up taking place at a head and neck treatment centre and travel or access issues, but models of service delivery with out-reach peripheral spokes can provide the required level of MDT input, as close as possible to home (see Chapter 1).

Frequency

Current UK national guidelines recommend that patients undergo clinical follow up every two months for the first two years after treatment, and then every three to six months for the next three years, consistent with the aim to align with the risk of locoregional recurrence.

The fact that most recurrences are detected because the patient has symptoms (rather than through routine examination) has led to the consideration of alternative flexible patient-led follow-up strategies. It is not yet clear if they will be any more effective in detecting recurrences at an earlier stage,[172] or whether these will replace or add to traditional follow up.

The use of patient-reported outcome measures may assist patients with describing, recording and temporally monitoring relevant symptoms within this setting.[173] In the absence of high-quality prospective trial data, follow-up schedules should remain in line with international standards, although current evidence would support additional patient-initiated follow up.

The use of patient-reported outcome measures and holistic need assessments can also assist with the identification of patients requiring more support.

Duration

Patients should undergo follow up for a minimum of five years, a point in time at which the risk of recurrence is very low and tends to plateau in many cancers. Many clinicians extend beyond this, and patient preference will play a role in the shared decision-making after the five-year period, especially in the presence of significant ongoing fear of cancer recurrence. Other situations that may benefit from prolonged follow up include where patients experience ongoing symptom burden or when delayed recurrence is known to occur. For example, distant failures can occur much later in HPV-positive cancers.[174] How the early detection of late distant metastases can best be achieved has yet to be defined.

Nature

Follow up should include:

- Post-treatment imaging after chemoradiotherapy, usually by PET-CT scan at three to four months
- Baseline axial imaging for patients with altered anatomy or imaging as a result of treatment
- Clinical examination including, when indicated, flexible nasopharyngolaryngoscopy
- Access to a wider MDT for patient support
- Access to urgent imaging for suspected recurrence

Recurrent disease

Recommendations

- Consider curative, palliative and supportive options for patients with recurrent disease (evidence-based recommendation (R))
- Biopsy is required before active treatment and should include PD-L1 (programmed death-ligand 1) testing for immunotherapy (R)
- The decision-making process is highly complex and requires multidisciplinary input (R)
- Patients and their families should be aware of the prognosis, chance of treatment efficacy and complications when making decisions about possible treatment (R)
- Consider PET-CT before active treatment (good practice point (G))

General principles

The development of recurrent disease after head and neck cancer is common and, on the whole, carries a poor prognosis. In general, management options include:

- Surgery for local or regional recurrence
- Chemoradiotherapy (if not already given) for local or regional recurrence
- Re-irradiation (see Chapter 4)
- Chemotherapy (generally palliative, see Chapters 4 and 15)
- Immunotherapy (see Chapter 4)
- Local targeted therapies (e.g. photodynamic therapy or electrochemotherapy)
- Best supportive care

Many patients will be offered, or choose, best supportive care alone, either through having disease that is not amenable to treatment, or by being too frail to tolerate therapy and jeopardising their quality of life. However, there are patients who can benefit from surgical and non-surgical treatment in the recurrent setting. Careful patient selection is fundamental, taking into consideration specific tumour, patient and prognostic factors, as well as the effects of prior treatment. The complexity of recurrent cancers necessitates management by an MDT that can offer a full range of both surgical and non-surgical

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

treatments, as well as significant functional support and rehabilitation. The early involvement of palliative and supportive care services is important in all patients with recurrent disease.

Assessment

Patients with recurrent disease require careful evaluation, essentially repeating the same assessment processes used for primary disease, but with greater emphasis on co-morbidities, functional limitations from prior treatment and current performance status, to help determine the patient's level of frailty and their ability to tolerate therapy. Crucially, the social context and support systems in place for patients also need to be considered. Continued smoking or significant alcohol intake should be addressed at this stage, as these are likely to increase treatment complication rates.[175]

Biopsy is mandatory if further treatment is to be considered. This should include molecular profiling in this era of evolving systemic therapies (e.g. combined positive score and PD-L1 for immunotherapy – see Chapter 4).

Imaging

The role of imaging is similar to the assessment of primary disease. Baseline imaging (after primary treatment, before recurrence) helps in the delineation between distorted anatomy, inflammation, fibrosis and recurrent tumour. There is evidence that techniques such as diffusion-weighted MRI may help with this.[176]

^{18}Fluorine-fluorodeoxyglucose PET-CT imaging can struggle to differentiate metabolic activity and inflammation from tumour recurrence. However, it has two significant advantages in the recurrent setting. The first is a high negative predictive value, both for disease in the primary site and the neck, which persists even at 12 and 24 months.[164] In addition, it may detect occult recurrence including distant metastases, absent on clinical examination, as well as second primary tumours.

Salvage surgery

Selection

Organ preservation protocols have emerged as a standard of care for locally advanced head and neck cancer. Approximately 25 per cent of patients develop a locoregional recurrence. In this setting, salvage surgery provides the best opportunity for long-term survival.[151] Even then, the effectiveness of salvage surgery has been reported at only 39 per cent in a meta-analysis of 1080 patients.[177] Some anatomical subsites offer a better chance of salvage, for example a five-year survival rate of 83 per cent for early larynx cancer recurrence. Yet salvage surgery also comes with significant and serious risks – complications after salvage surgery have been reported to be as high as 68 per cent.[178] These two factors of poor overall control and high morbidity to the patient mandate open and detailed discussions with patients before committing to surgery.

Efforts have been made to identify prognostic factors in order to better select those patients with the highest chance of success with salvage surgery. Broadly, these can be divided into: (1) patient factors; (2) prior treatment factors; and (3) tumour factors.

Patient factors: Patient age and co-morbidity are significant factors in determining outcome after salvage surgery. In a study of 191 patients, the pre-salvage Charlson–Age Comorbidity Index ('CACI') was identified as an independent risk factor for death at one year post salvage surgery.[179] The Eastern Cooperative Oncology Group ('ECOG') performance status may also be used to determine general health. Continued smoking and excessive alcohol use lead to higher complication rates and should be addressed before surgery.[175] Nutritional deficits are likely to be present, either because of ongoing swallowing difficulties from previous treatment or because of the disease process itself. These will need correcting through dietetic and nutritional support. Other pre-operative optimisation to aid tissue healing will include normalising thyroid function, improving diabetic control, and the cessation of any immunosuppressive agents where possible.

Prior treatment factors: Previous treatment with radiotherapy or chemotherapy is associated with poor outcomes after salvage surgery. A study of 39 patients with recurrent oral cavity cancer undergoing salvage surgery had a 43 per cent overall five-year survival rate. Yet this was reduced to 10 per cent in those who had undergone previous irradiation.[180] Patients with a short duration between primary treatment and recurrence have a poor prognosis. If this interval is less than six months, it is likely that this represents persistent rather than recurrent disease. Conversely, a longer disease-free interval has been demonstrated to lead to a lower risk of death.[181] This is likely reflective of the inherent aggressiveness of the biology of the disease.

Tumour factors: Advanced stage of either the primary tumour or the recurrence negatively impacts prognosis, which appears to be independent of anatomical site.[177,182] Other tumour factors considered poor prognosticators include positive margins, recurrence in the neck and locoregional recurrence (as opposed to local recurrence only). Human papillomavirus positive recurrent disease has a better prognosis than HPV-negative disease.

Combining prognostic factors to develop stratification scores for post salvage surgery survival has been attempted. In a study of 38 patients undergoing salvage surgery, initial advanced stage, and concurrent local and regional failures, were demonstrated to be independent poor predictors for decreased survival. Two-year overall survival rates for patients with two, one or none of these predictive factors were 0 per cent, 49 per cent and 83 per cent, respectively.[151]

Neck recurrence

Treatment failure in the neck may occur in isolation, or combination with primary site recurrence. As with other recurrent disease, meticulous assessment is required to exclude distant disease, and determine the extent of nodal disease, the presence of extra-nodal extension and the involvement of adjacent structures. Progression of neck disease may lead to fungation, and subsequently poor quality of palliation for a patient. Therefore, even in the presence of limited distant disease, with careful consideration given to patient expectations and wishes, there may be a rationale for considering salvage neck surgery to control regional disease.

Traditionally, salvage neck dissection has been undertaken with either a radical or modified radical approach. In this situation, the occurrence of complications, including wound infection, dehiscence, chyle leak or bleeding, are common. In the era of HPV-positive disease, there has been a move towards a more selective, and even super-selective approach to the extent of nodal levels dissected. The evidence for this is not yet definitive.[183,184]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Oligometastatic disease

The prognosis of metastatic head neck cancer is poor. The current standard of care is palliative intent treatment with systemic therapies, or best supportive care. Hellman and Weichselbaum proposed a transitional state between minimal detectable metastatic burden (more recently thought of as five lesions or fewer) and more widespread disease – the concept of oligometastasis.[185] Patient selection for the treatment of oligometastasis should consider similar factors as those discussed for recurrent disease. Treatment of the metastatic disease should not be undertaken without concurrent treatment of locoregional disease. Broadly, the options are between surgery (metastasectomy) or stereotactic body radiation therapy. There are too few studies to accurately compare the effectiveness of the two approaches in head and neck cancer.[186] Few data exist of treatment of oligometastasis from the oral cavity, or laryngeal or hypopharyngeal cancer. In nasopharyngeal cancer and HPV-positive oropharyngeal cancer, there are data to support improved overall survival in patients with oligometastatic disease treated aggressively, compared to those receiving systemic treatment alone.[186]

Targeted local therapies

Photodynamic therapy

Photodynamic therapy is an ablative treatment that relies on localised cell and tissue destruction by the activation of a photosensitising agent. It largely preserves connective tissue, minimising disfigurement and maintaining function. Importantly, it is repeatable, even in previously irradiated areas. Photodynamic therapy may have a role in patients with locoregional recurrent disease. A study of 128 patients undergoing photodynamic therapy, for whom standard multimodality treatment had failed, was conducted to evaluate the overall clinical benefit, demonstrating a complete response rate of 16 per cent. This rose to 30 per cent in those who had favourable characteristics, namely smaller, more superficial tumours amenable to surface illumination.[187] Patients with a complete response had a much greater one-year survival rate compared to those with a non-complete response (73 per cent *vs* 32 per cent). These results were subsequently validated in a study of 39 patients unsuitable for further salvage treatment. Here, a higher complete response rate of 49 per cent was demonstrated, with the difference in overall one-year survival again being significantly different between the complete response and non-complete response groups (86 per cent *vs* 28 per cent).[188]

Electrochemotherapy

Electrochemotherapy is a localised therapy whereby cytotoxic agents are applied either locally or topically, and entry to tumour cells is gained through the application of pulsed electrical currents. These electric pulses temporarily depolarise the cell membrane, thereby increasing the permeability of tumour cells. A systematic review of its use in mucosal head and neck cancer only identified a total of 128 patients who had received electrochemotherapy in the palliative setting.[189] In this group, a response rate (either complete or partial) of 73.1 per cent was demonstrated, with little apparent deterioration in quality of life scores after treatment. More prospective data are required before the effectiveness of electrochemotherapy can be judged.

Important questions to be answered and future developments

Remote consultation

Prior to the emergence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), it is unlikely that either patients or clinicians would have been widely accepting of remote clinical review. Alongside telephone assessment of urgent head and neck cancer referrals, follow up also moved to a model of remote consultations via telephone or video call initially, with few face-to-face appointments. This was further refined, and evidence from UK centres indicates that care has now moved to a hybrid model of both remote and face-to-face consultations based on risk stratification.[190]

Patient-initiated follow up

Limited evidence for the effectiveness of routine follow-up schedules, increasing pressure on head and neck cancer services, and patients' desires for a more flexible system, mean that alternative strategies are being explored. Patient-initiated follow up, a model where patients have more control over when and where their care is delivered, has been demonstrated to improve satisfaction and quality of life, without deleterious effects on outcome.[191] This approach may be particularly effective when used in conjunction with the stratification of follow up based on an individual's risk of recurrence (e.g. via imaging with PET-CT, or associated clinical or pathological factors). A retrospective study examining different intensities of follow up, stratified by the patient's risk of recurrence based on PET-CT imaging, found that the time to recurrence detection, overall survival, and proportion of salvageable recurrences were similar between the two cohorts. A PET-CT stratified follow up reduced the mean number of visits and led to a significant cost saving per patient (£2738 over five years of follow up).[192] Although these strategies have not yet been widely evaluated in head and neck cancer, clinicians appear willing to engage and test this hypothesis.[172]

Liquid biopsies

Technologies to develop blood- or saliva-based biomarkers, in the form of either circulating fragments of DNA or circulating whole tumour cells, have developed rapidly. These liquid biopsies allow serial monitoring and may overcome the issue of tumour heterogeneity – a significant factor in head and neck cancer. There is early evidence that in HPV-positive disease, HPV circulating tumour DNA may be able to complement imaging to predict and detect recurrent disease.[193] Prospective trial data will be required before the incorporation of liquid biopsies into surveillance strategies.

Management of early metastatic disease

Earlier detection through imaging and liquid biopsies is likely to open new considerations about how best to manage patients with early metastatic disease, especially those with oligometastatic disease. Limited data currently exist on how best to manage this in head and neck cancer patients.

Studies due to report

'PETNECK 2' trial

The efficacy and cost-effectiveness of FDG PET-CT to guide follow up after treatment for head and neck cancer has been

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

posed as an outstanding research recommendation by the National Institute for Health and Care Excellence.[194] The 'PETNECK2' trial has been funded by the National Institute for Health Research and will assess an alternative active surveillance strategy (using PET-CT-guided, patient-initiated, symptom-based follow up), compared to the current standard-of-care routine regular clinical follow up. This randomised, controlled trial will complete in April 2026.

Chapter 6: Epidemiology of head and neck cancer: definitions, trends and risk factors

Table of Contents

Key points

- Both globally and in the UK, head and neck cancer incidence is increasing, and is projected to continue to rise, largely driven by increases in oropharyngeal cancer.
- Mortality rates in the UK over the last decade have started to increase, reflecting the rising incidence and static survival rates.
- The major risk factors for oropharyngeal cancer are: tobacco smoking, alongside alcohol consumption and tobacco used in combination; betel chewing in Southeast Asian populations; and human papillomavirus (HPV).
- Head and neck cancers are clearly socio-economically patterned, with individuals from the most deprived backgrounds having the greatest burden and poorest survival outcomes, and this socio-economic risk is not entirely explained by smoking and alcohol consumption behaviours.
- Head and neck cancer incidence is higher among men than women, and is more common in older age groups, although oropharyngeal cancer incidence peaks around 10 years younger at around 60–65 years.

Definitions of head and neck cancer

Approximately 90 per cent of head and neck cancers are squamous cell carcinoma that arise from the epithelial lining of the oral cavity, pharynx and larynx.[195] There are many types of head and neck cancer, which are discretely categorised on the basis of their anatomical location using the International Classification of Diseases, 10th revision ('ICD-10'), from the World Health Organization.[196] In addition, the subsites that are included under the definition of 'head and neck cancer' often vary across studies, particularly with relation to the oral cavity and oropharynx.[197,198] Because of differences in definition, it is important that anatomical subsites are clearly specified when reviewing the epidemiological literature (ideally by using corresponding International Classification of Diseases codes).

Global incidence trends in head and neck cancer

Head and neck cancer is the seventh most common cancer globally, accounting for more than 660 000 new cases and 325 000 deaths annually. The overall incidence of the disease continues to rise, with a predicted increase of 30 per cent (over one million) new cases annually by 2030.[199,200] This increase in incidence has been recorded across both developed and developing countries.[201] Southeast Asia and Asia-Pacific regions have particularly high incidences of oral cancer, which are strongly associated with chewing of the areca nut (betel quid), with or without tobacco.[202] Oral cancer is therefore expected to rise within Southeast Asia, in line with population growth.[203] The increasing rates of head and neck cancer in the USA and Europe have been attributed to a rise in oropharyngeal cancer, linked to HPV infection (Figures 1 and 2).[204,205] Over the next 20 years, it is expected that the majority of head and neck cancers will be HPV-positive, with projections that in some European countries, such as the UK, oropharyngeal cancer incidence will overtake cancer of the oral cavity.[197]

Worldwide, laryngeal cancer incidence and prevalence have increased by 12 per cent and 24 per cent, respectively, during the past three decades.[206] However, age-adjusted rates for new laryngeal cancer cases have been falling in countries with a higher sociodemographic index, perhaps reflecting changes in smoking and alcohol drinking behaviours.[206] Overall, head and neck cancer affects males two to four times more than females, with estimates reaching over 20 per 100 000.[207] For men in developing countries, lip and oral cavity cancer is the second most common cancer (10 per 100 000). Male incidence of oral and oropharyngeal cancer has declined over recent years in France (−12.6 per cent), Slovakia (−4.0 per cent), Spain (−10.8 per cent), Brazil (−26.7 per cent) and Hong Kong (−10.5 per cent), while it increased in the UK (18.8 per cent), Australia (8.7 per cent), Japan (21.3 per cent) and in the USA (3.7 per cent).[208] The risk of head and neck cancer increases with age across populations, with the majority of cases diagnosed in those aged over 50 years.[209] Similarly, there has been a rise in cases amongst females, predominantly in European countries, which may be explained by sex-specific patterns of tobacco and alcohol consumption.[207,208]

Trends in head and neck cancer in the UK

As described previously, head and neck cancer rates are also rising in the UK. Studies have shown that from 1995 to 2011, oropharyngeal cancer incidence increased by 7.3 per cent for males and 6.5 per cent for women in England, with oral cavity cancer showing a 2.8 per cent rise in men and 3.0 per cent rise in women over the same period.[210] Incidence rates are highest in Scotland, where oropharyngeal cases were shown to have increased by 85 per cent from 2011 to 2012.[211] These rates are continuing to rise according to most recent UK Cancer Registry Data, which show a 34 per cent increase in total cases diagnosed across the four nations from 2011 to 2018. The burden of head and neck cancer is strongly socio-economically patterned, with the highest rates being observed among people living in the most socio-economically deprived communities.[211,212] These cancer registry data also demonstrate that the majority of head and neck cancers are diagnosed at an advanced stage.[213] For the UK as a whole, 58.5 per cent of head and neck cancers with a known stage are diagnosed at an advanced stage, III or IV,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

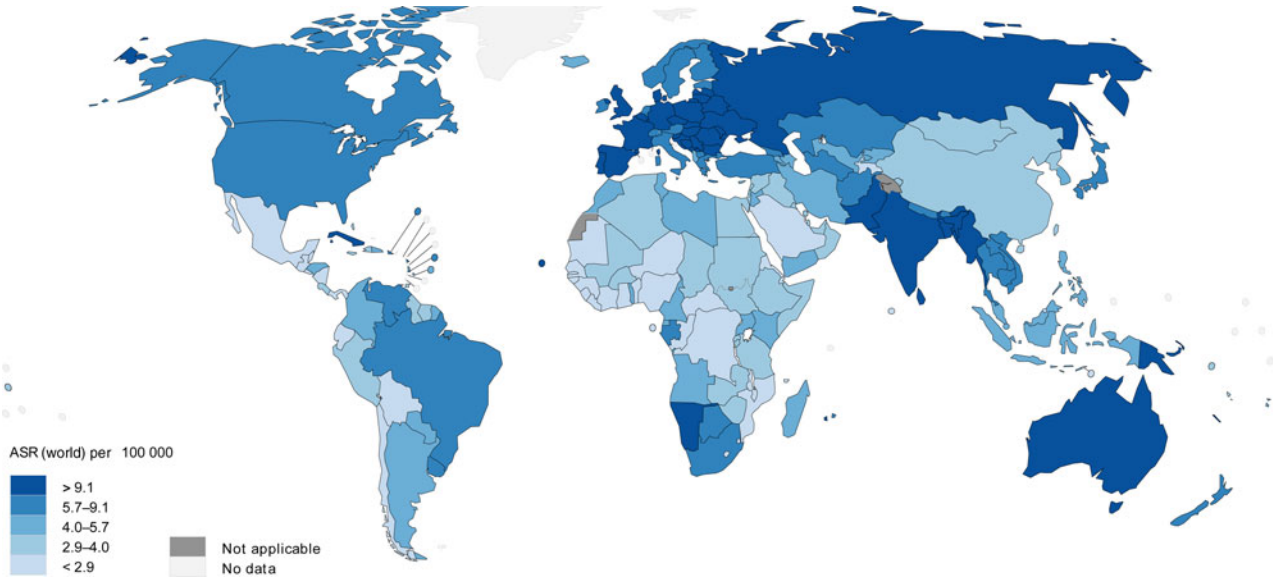


Figure 1. Global age-standardised incidence rates (ASR) of head and neck cancer. Reprinted with permission from the World Health Organization International Agency for Research on Cancer 'Cancer Today – Data visualization tools for exploring the global cancer burden in 2020' (in: http://gco.iarc.fr/today, accessed August 2021). The map was generated using the Global Cancer Observatory ('Globocan') website mapping tool by selecting the 'lip, oral cavity', 'oropharynx', hypopharynx' and 'larynx' cancer sites. Estimated age-standardised rates of head and neck cancer incidence worldwide are shown for both sexes.

in accordance with the *TNM Atlas*, seventh edition.[214] The highest rates of advanced disease are found in Scotland and Northern Ireland, where 67.6 per cent are at an advanced stage. Stage IV is the most common stage at diagnosis for oral and oropharyngeal cancer, whereas stage I is most common for laryngeal cancer.[213]

Mortality and survival trends in head and neck cancer in the UK

In 2018, there were 4078 deaths attributable to head and neck cancer in the UK, accounting for approximately 2 per cent of all cancer deaths annually.[215] Variation in national head and neck cancer mortality rates (European age-standardised rate per 100 000 population) was apparent between nations of the UK: Scotland (rate = 8.7) and Northern Ireland (rate = 8.4) had worse outcomes than England (rate = 6.2) and Wales (rate = 5.8). Age-specific mortality that is attributable to head and neck cancer rises from the fifth decade of life onwards, towards a peak mortality in those aged over 90 years – a phenomenon most pronounced in males. In the UK, since the early 1970s, the combined head and neck cancer mortality for men and women has fallen by 11 per cent overall (age-standardised rate per 100 000 population = 7.3 in 1971 and 6.5 in 2018); however, the last decade has seen a gradual rise in mortality rates from a low in 2006 (age-standardised rate per 100 000 population = 5.6), possibly reflecting the changes in disease incidence and static survival rates.[215]

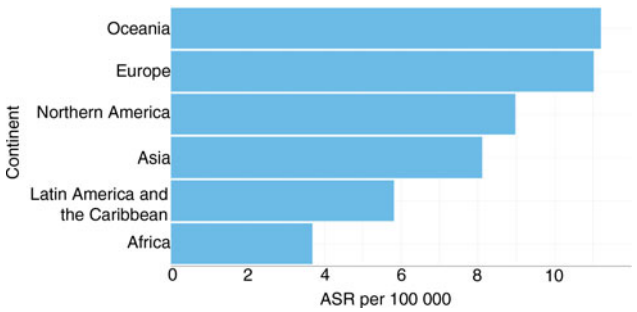


Figure 2. Age-standardised incidence rates (ASR) of head and neck cancer, by continent. Reprinted with permission from World Health Organization International Agency for Research on Cancer 'Cancer Today – Data visualization tools for exploring the global cancer burden in 2020' (in: http://gco.iarc.fr/today, accessed August 2021). The map was generated using the Global Cancer Observatory ('Globocan') website mapping tool by selecting the 'lip, oral cavity', 'oropharynx', hypopharynx' and 'larynx' cancer sites. Estimated age-standardised rates of head and neck cancer incidence by continent are shown for both sexes.

Survival rates can vary significantly according to geographical location, tumour site, HPV association (associated with increased chances of survival),[216] and, most prominently, stage at diagnosis. Those diagnosed with advanced disease have notably poorer outcomes than those with early disease. Analysis of a large cohort in the USA showed that patients with HPV-positive cancers had a better chance of long-term survival compared to those with non-HPV cancers, confirming previous studies also suggesting this phenomenon.[216] There are several studies within the recently established Head and Neck Cancer in South America and Europe ('HEADSpAcE') international consortium[217] that are exploring the factors associated with relatively poor survival among people with head and neck cancer. Analysis of routinely collected data and from large prospective cohort studies, such as Head and Neck 5000,[218] have demonstrated that significant socio-economic inequalities in head and neck cancer survival exist in the UK, not all of which can be explained by behavioural factors.[219]

Risk factors associated with head and neck cancer

Tobacco smoking and alcohol consumption are well established risk factors for head and neck cancer. However, a detailed understanding of these somewhat complex behaviours in terms of precise estimates of risk, recognising the joint tobacco–alcohol effect, the dose–response, and the benefits of quitting both smoking and alcohol, remains less well established. The role of other risk factors in head and neck cancer

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

risk, such as smokeless tobacco, betel chewing, diet, oral health and hygiene, and hormonal, genetic, occupational and socio-economic status, is also poorly understood. A major challenge in elucidating detailed information from the epidemiological literature is the heterogeneity in study designs and populations from often small observational studies. The dominant effects of tobacco smoking and alcohol drinking also overshadow other minor risk factors.

A recent umbrella review of systematic reviews and meta-analyses (Conway *et al.*[220]) has been combined with pooled analyses at the individual level data from studies from around the world, by The International Head And Neck Cancer Epidemiology ('INHANCE') Consortium.[221] These data confirm that tobacco smoking and alcohol drinking behaviours, separately and in combination, are major risk factors for head and neck cancer, accounting for 72 per cent of cases when used in combination.[222] Recent evidence has shown an independent causal effect of alcohol consumption, when controlling for smoking (odds ratio = 2.1), suggesting that the role of alcohol may have been previously underestimated.[223]

High-risk HPV, especially HPV type 16, is a major risk factor for oropharyngeal cancer,[224] thought to be sexually transmitted via oro-genital contact.[205] Smoking has been shown to interact with HPV and increase risk.[225] Those who have HPV-negative oropharyngeal tumours are more likely to be heavier smokers, with an increased risk of death for every additional pack-year, compared to HPV-positive cases.[226] Genetic susceptibility to head and neck cancer has also been investigated,[227] with the largest genome-wide association study of oral and pharyngeal cancer (6034 cases and 6585 controls from Europe, North America and South America), detecting seven unique loci.[228] Genetic variants in alcohol-metabolising genes, such as alcohol dehydrogenase (*ADH*), are associated with increased head and neck cancer risk. This study also found a strong protective association at a chromosome within the human leukocyte antigen class II region in oropharyngeal subgroup analysis.[228] Going forward, this could help explain why some individuals are more at risk of developing the disease following HPV infection.

Chapter 7: Reconstructive considerations in head and neck surgical oncology

Table of Contents

Key recommendations

- Microsurgical free-flap reconstruction should be the primary reconstructive option for most defects of the head and neck that need tissue transfer (good practice point (G))
- Composite free tissue transfer should be offered as the first choice to all patients needing mandibular reconstruction (evidence-based recommendation (R))
- Free flaps should be offered as the first choice of reconstruction for all patients needing circumferential pharyngoesophageal reconstruction (R)
- Free-flap reconstruction should be offered for patients with class III or higher defects of the maxilla (R)
- Patients undergoing salvage total laryngectomy should be considered for vascularised flap reconstruction, to reduce pharyngocutaneous fistula rates (R)
- For reconstruction involving the upper and lower jaws, or involving rhinectomy or orbital exenteration, pre-operative multidisciplinary decision-making should include restorative dentistry or dental prosthodontists (R)
- Tubing over and use of a salivary bypass tube appear to decrease complication rates with anterolateral thigh and radial forearm free flaps (G)
- Each head and neck centre should have a protocol for free-flap monitoring and rescue (G)

Introduction

Reconstructive surgery for head and neck cancer defects can be complex and challenging. Priorities of reconstruction include restoring oral and upper aerodigestive tract lining, maintaining oral competence along with the function of speech and swallowing, and providing an acceptable aesthetic result.

These guidelines have been divided into the management of defects in the oral cavity soft tissues, mandible, maxilla and midface, oropharynx, laryngopharynx, and neck soft tissue. Where tumour ablation or reconstruction involves the possible need for orofacial implants and oral rehabilitation or prosthetics, close collaboration with the consultant restorative dentist or oral rehabilitation team is required. This is discussed in detail in Chapter 13. Options for facial palsy are discussed in Chapter 22 (lateral skull base), and skull base defects are also discussed in Chapters 22 (lateral) and 23 (anterior).

There is little evidence relating to the optimal reconstruction of head and neck defects. While many mandibular and soft tissue upper aerodigestive tract reconstruction techniques are fairly standard, some controversy remains regarding the midface and maxilla because of the complexity of the defects and the possibility of using a dental or facial prosthesis, especially with the advent of three-dimensional (3D) digital planning and printing. Flap selection is usually determined based on the expertise and experience of the individual surgical teams, as well as on patient co-morbidities, the exact nature of the surgical defect, any future possible treatments including radiotherapy, and donor site morbidity.

The 'work horse' microvascular and pedicled flaps that a head and neck surgical centre should provide, and which serve the majority of defects in the head and neck, are summarised in Table 1.

Most reconstructions are performed primarily following tumour ablation. Modern techniques aim for one-stage reconstruction utilising vascularised tissues, with a high success rate and good overall results. However, secondary reconstructions

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Principal microvascular and pedicled flaps for head and neck reconstruction

Type	Flap	Main applications
Soft tissue microvascular flap	Radial artery free flap	Oral cavity, oropharynx, pharyngolaryngectomy, limited maxilla or midface defects
	Anterolateral thigh flap	Oral cavity, oropharynx, pharyngolaryngectomy, midface or skull base
Composite microvascular flap	Fibula	Mandible
	Deep circumflex iliac artery flap	Maxilla or midface, mandible
	Scapula (tip or lateral)	Maxilla or midface, mandible
Soft tissue pedicled	Pectoralis major flap	Non-circumferential pharyngolaryngectomy, salvage laryngectomy, neck soft tissue or skin
	Supraclavicular artery island flap	Neck skin

are also undertaken to treat problems such as fistulae, osteoradionecrosis or previously obturated maxillary defects.

Oral cavity soft tissues

Oral soft tissues include the tongue, floor of mouth, buccal mucosa and the retromolar trigone extending to the tonsillar area. Because of the close proximity of these areas, cancers of these sites occasionally cross over to one another. Reconstructive access is usually determined by the extent and access of the surgical resection.

Free tissue transfer provides the mainstay of oral soft tissue reconstruction, as it allows importation of large volumes of healthy tissue from sites distant to prior surgical or radiotherapy fields. The radial artery forearm flap and anterolateral thigh perforator flap remain the 'go to' options for most significant oral soft tissue defects. Other options exist, as detailed in Table 2.[229,230]

Regional flaps such as pectoralis major, submental island artery, supraclavicular artery island and nasolabial flaps can be effective in importing tissue, but are not optimal choices.

Mandible

Reconstruction of the mandible must address the site and size of the bony defect, associated soft tissue loss and the desirability of dental rehabilitation. Free tissue transfer is the mainstay of mandibular reconstruction, as it allows the importation of bone which can be tailored to fit the desired shape, is well vascularised and is amenable to osseointegration. The main flap options are:

- Fibula flap
- Deep circumflex iliac artery flap
- Scapular flap

Dental rehabilitation is a key part of most mandibular reconstructions, and pre-operative liaison with the restorative team, including consideration of 3D planning and osseo-integrated implants, is recommended (see Chapter 13).

The fibular flap allows harvest of a long piece of bone that is of adequate height for osseointegration and can be osteotomised several times for contouring. This is now made easier with the availability of 3D software to plan the osteotomies at the mandible and on the fibula prior to transfer. It is relatively easy to harvest as an osseous or osteoseptocutaneous flap, with or without muscle. This versatility means it is the workhorse for mandibular reconstruction in most centres. One drawback of the flap is its relative lack of height.

The deep circumflex iliac artery flap provides for a high bony segment, and the natural curve of the ilium lends itself to lateral mandibular defects where an osteotomy may not be necessary. The donor site defect can be problematic (pain restricting mobility, hernia and mesh infection), and its skin paddle is usually reserved for external use although muscle can be incorporated for oral reconstruction.

The scapular flap allows for harvest of a relatively small amount of bone. The main advantage of this flap is the large volume of skin and muscle (latissimus dorsi), which can be used in a chimeric fashion. The bone is a good height, but two-team flap harvesting is generally not possible.

A composite radial forearm flap is rarely used for bone reconstruction as only a small volume of bone of low height can be harvested. There is also a risk of subsequent fracture of the radius, which can be debilitating.

A new classification of the mandibular defect has been described based on the four corners of the mandible, which are both angles and both canines (Figure 1).[231]

Table 2. Mainstream and promising options for oral cavity soft tissue reconstruction

Flap	Type	Advantages	Disadvantages
Radial artery forearm flap	Microvascular	Large, thin, pliable flap with excellent reliability & simplicity of harvest; long pedicle; options include bone, fascia, adipose tissue	Poor donor site aesthetics when skin grafting is required
Anterolateral thigh flap	Microvascular	Bulk; long pedicle; minimal donor site morbidity; options include multiple paddles, fascia lata, muscle & nerve	Too bulky for many oral defects (can be minimised if raised as a perforator flap)
Medial sural artery perforator flap[229]	Microvascular	Thin & pliable; minimal donor site morbidity	Vessel diameter can be smaller than the radial forearm fasciocutaneous flap & anterolateral thigh flap; shorter pedicle
Superficial circumflex iliac artery perforator flap[230]	Microvascular	Thin & pliable; long pedicle; minimal donor site morbidity	Small pedicle, technically more difficult to harvest
Local intra-oral mucosal flaps	Rotation	Simple, quick	Only for very small defects
Facial artery myomucosal flap	Axial	Simple, quick	For small defects e.g. limited floor of mouth, palate

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

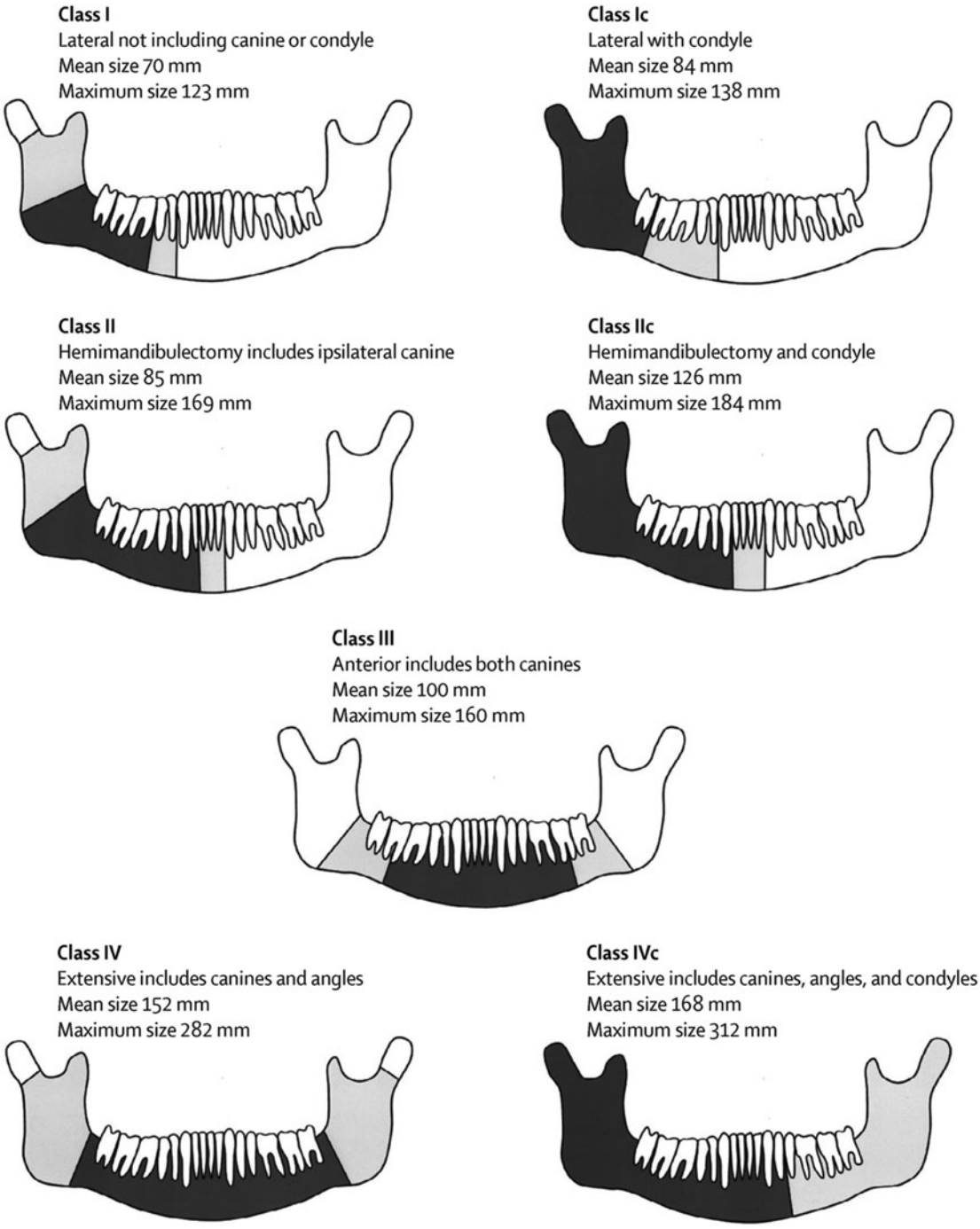


Figure 1. Classification of mandibular defects.[231]

Although not in the official classifications in Figure 1, posterior mandibular defects distal to the second lower molar, involving the ramus of the mandible but sparing the subcondylar/condylar segment, may be amenable to a soft tissue only flap with a reinforced titanium plate. This is on the premise that dental rehabilitation is not required, but it risks plate fracture or extrusion. In order to minimise the latter, a robust chimeric flap such as an anterolateral thigh flap with vastus muscle would be recommended.

Maxilla and midface

The level of evidence is very weak in all areas of reconstruction, but more particularly in the maxilla and midface because of the differing complexity of the defects, and the potential for skull base involvement.

All cases involving the loss or ablation of the maxilla and/or midface should be discussed in a multidisciplinary setting. The choice of reconstruction or prosthetics requires discussion among the ablative and reconstructive teams, prosthodontist, maxillofacial technician, patient and family. There are clear advantages in simplifying the surgery and using prosthetic options, but this choice becomes more difficult to deliver, and makes it more difficult for the patient to cope, as the defect becomes larger and more complex.

The use of the maxillectomy defect classification is recommended (Figure 2).[232]

The choice of a prosthetic option or reconstruction depends on the nature of the defect. In class I and II defects, an

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Defect	Comments
Class I (70 mm) or class Ic (84 mm)	Most of the flaps described above will work well, as the length of this defect is around 7–8 cm and so all bone donor sites are adequate. In the lateral defect, the reconstruction height is less problematic
Class II (85 mm) or class IIc (126 mm)	The iliac crest can work well, as the shape of the ipsilateral hip may reduce osteotomy preparation, and a scapula may not be sufficiently long for a class IIc when soft tissue is seldom an issue
Class III (100 mm) (includes both canines, but neither angle)	Flap choice depends more on the rehabilitation plan and height of chin support. The fibula flap can be double-barrelled to increase height, but scapula and radius are often difficult to implant successfully for complete oral rehabilitation
Class IV (152 mm) or class IVc (168 mm)	The fibula flap is usually the best option for faithful reconstruction, but the mandible may need to be made smaller for such major resections, especially if there is maxillary teeth loss

Figure 1. Continued.

obturator is a reasonable option, but this becomes less favourable with orbital adnexae involvement (class III), orbital exenteration (class IV), and when the midface defects are of an orbitomaxillary (class V) or nasomaxillary (class VI) nature. In addition to the vertical component, the extent of the dental or alveolar part of the resection is relevant to the prosthodontist in deciding on appropriate obturation. A summary of the options can be found in Table 3.

Class I: Resections of the alveolar bone not resulting in an oroantral fistula can either be left to granulate or treated with a local flap. Palatal defects can be obturated or reconstructed with a soft tissue flap. For larger defects not requiring implants, a vastus lateralis muscle flap based on the descending branch of the lateral circumflex femoral artery may be used. This has a low donor site morbidity, and matures with shrinkage and some fibrosis to mimic the pre-morbid hard palate.

Class II: This is the standard hemi-maxillectomy not involving the orbital floor or adnexae. Obturation is often very successful for this form of defect, as the orbit does not require support, and if the defect is small enough for retention and stability of the prosthesis. In more extensive cases (classes IIc–d), the options are an implant-retained prosthesis or composite flap. Reconstruction with the fibula flap has also shown good outcomes. The deep circumflex iliac artery flap, with greater height, and which includes the iliac crest and internal oblique muscle, will give better support to the peri-nasal area. The scapula flap can be supplied by the circumflex scapular artery that supplies the lateral scapula (scapula flap) through periosteal perforators along its length, or the angular branch of the thoracodorsal artery which supplies the scapula tip. The advantage of the scapula tip option is that the pedicle is considerably longer than the circumflex scapula artery option, which is a great advantage in the maxilla and midface as the recipient vessels are more distant.

Class III: In these cases, there is loss of the orbital support, and often a part of the nasal bones may also require

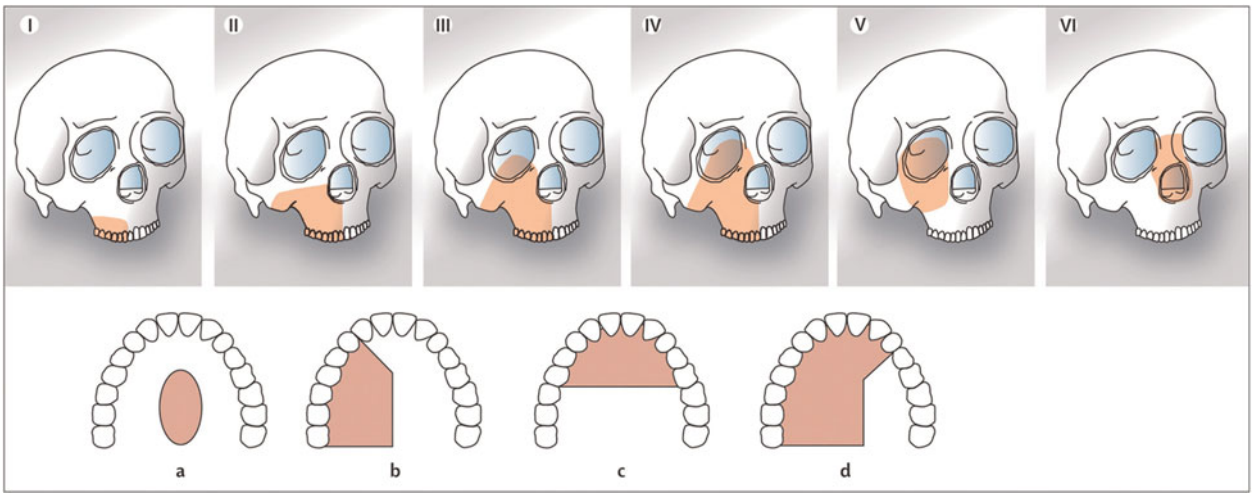


Figure 2. Classification of the maxillary and midface defects. Classes I–VI relate to the vertical component of the defect, including orbitomaxillary (class V) and nasomaxillary (class VI) defects, when often the palate and dental alveolus are intact. Classes a–d relate to the increasing size of the palatal and dento-alveolar parts of the defect, indicating increasing difficulty in obtaining good results with obturation.[232]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Recommended reconstruction method, according to midface and maxillectomy defect classification[232]

Reconstruction method	I	II	III	IV	V	VI
Obturation	+	+	–	–	–	–
Local pedicled flaps						
– Temporoparietal, temporalis	+	+(b)	–	–	–	–
Soft tissue free flaps						
– Radial, anterolateral thigh	+	+(a,b)	–	–	+	–
– Rectus abdominus, latissimus dorsi	–	–	–	+	–	–
Hard-tissue or composite flaps						
– Radial	+	+(b,c)	–	–	+	+
– Fibula	–	+	–	–	–	–
– Deep circumflex iliac artery*/ internal oblique	–	+	+	+	–	–
– Scapula	–	+	+	+	–	–
– Thoracodorsal angular artery† (with scapula tip)	–	+	+	+	+	+

Letters (a, b, c) refer to the horizontal classification (Figure 2). *Supplies the iliac crest. †Supplies the scapula tip. + = recommended; – = not recommended

reconstruction. There is good consensus in the literature that the restoration of orbital support with vascularised tissue (pedicled or free flap) is essential to ensure healing of the bone graft, and to reduce soft tissue problems such as epiphora and ectropion. The deep circumflex iliac artery with internal oblique provides the best solution if an implant-retained prosthesis is planned, but the scapula tip flap using latissimus dorsi muscle is also a good option with a more reliable pedicle. The fibula is also described for this defect, but considerable skill in the adaptation of this flap for the defect is required, with variable results. Obturation alone will result in facial collapse, poor support of the orbit, and a high risk of vertical orbital dystopia and ectropion. In children, the scapula tip will probably be the best option, as the iliac crest has a cartilaginous cover and the vessels are much smaller.

Class IV: Reasonable results can be achieved with a soft tissue flap alone such as rectus abdominus or vastus lateralis, but this will result in poor definition of the orbital defect and some facial collapse. The choice is similar to class III in that the iliac crest with internal oblique offers better implant options, but the scapula tip and fibula flaps are also good options.

Class V: In the orbitomaxillary defect, the main aim is not to obturate the orbital space with too much soft tissue, to allow space for an orbital prosthesis. The temporalis or temporoparietal flap are ideal, but in more extensive defects it is worth considering the radial or anterolateral thigh flap in a thinner patient. Some patients may prefer the natural 'eye patch' option provided by a thicker flap to a prosthesis. Thicker flaps will atrophy in time and can be thinned secondarily.

Class VI: If there is loss of the facial skin between the orbits and nasal bones, then free tissue transfer is probably essential. The composite radial artery forearm flap can be ideal if harvested with fascia to line the nasal side of the radial strut and the skin to restore the face. This can be augmented with a glabella or forehead flap.

A classical rhinectomy can be rehabilitated with a prosthesis, and of course the surgeon can check the margins of resection and resect more tissue if required. There are very successful full rhinectomy reconstructions performed, which can give a permanent biological solution if preferred. In this defect, attention must be paid to the restoration of the cartilaginous scaffolding and nasal bones with vascularised tissue, to prevent complications during and following radiotherapy. Frequently used combinations are radial artery forearm flap (inner lining), non-vascularised auricular cartilage and bone grafts, and a paramedian forehead flap (external surface).

Skull base reconstruction

The primary intentions are to seal the cranial cavity off and prevent cerebrospinal fluid leaks. This critical defect requires careful planning by all teams and surgeons involved in the case. This is discussed in more detail in Chapters 22 (lateral skull base) and 23 (anterior skull base).

Oropharyngeal reconstruction

Most tumour ablation involving the oropharynx is now transoral, after which there is usually no requirement for reconstruction. However, transoral surgery for tumour recurrence after radiotherapy may require reconstruction, for example, if the carotid sheath is left exposed, as the vitality of remaining tissue will have already been compromised. Other indications include soft palate reconstruction and tongue base reconstruction.

When required, radial artery forearm flap can be used and inset transorally following transoral tumour ablation. Anterolateral thigh flaps might be useful when more bulk is required. A posteromedially based musculomucosal flap, facial artery musculomucosal flap or radial artery forearm flap microvascular flaps can be used for soft palate reconstruction.[233]

When open surgery is performed, microvascular options are preferred, mainly radial artery forearm or anterolateral thigh flaps.

Pharyngolaryngectomy reconstruction

Non-circumferential (partial) pharyngeal defects

Defects that result in insufficient pharyngeal mucosa for a primary repair will require a 'patch' flap. Options include the pectoralis major myocutaneous flap, and the supraclavicular artery island flap which does not have the bulk of the pectoralis major muscle. Free flaps, such as radial artery forearm flap, anterolateral thigh flap and medial sural artery perforator flap,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

may also be used. The use of a salivary bypass tube appears to decrease fistula rates.[234]

A pectoralis major myocutaneous flap or myofascial flap is also a good option for persistent fistula after total laryngectomy.

If the pharyngeal mucosal remnant is very narrow (less than 1 cm in width), then it is often better to excise the remnant and undertake a total circumferential reconstruction.

Total circumferential pharyngolaryngectomy defects

There are several options for reconstruction following circumferential pharyngolaryngectomy, summarised with an historic context by Patel *et al.*[235] The main options are, however:

- Tubed* anterolateral thigh flap
- Tubed* radial artery forearm flap
- Jejunal free flap

*Tubing around a salivary bypass tube with two-layered closure (fascia and skin) appears to decrease fistula rates.[234]

Expertise and experience with these options may vary, particularly concerning jejunal free flaps. However, most published experience with regard to voice and swallowing, as well as morbidity, favours cutaneous flaps rather than a jejunal free flap.[235] Problems due to hyper-peristalsis and a 'wet' sounding voice are common with the jejunal free flap, which also carries a morbidity rate associated with abdominal complications (approximately 5 per cent). For cutaneous flaps, the choice between an anterolateral thigh flap and radial artery forearm flap may reflect the size of the patient's legs and their forearms. Around 30 per cent of patients may need a subsequent dilatation for stricture.

The use of a pectoralis major myocutaneous flap is not generally applicable, except as a last resort. It is very difficult to tube, although it can be used as a 270-degree flap with the prevertebral fascia.

For salvage circumferential pharyngolaryngectomy after chemoradiotherapy, especially for extensive defects with poor tissue vitality, additional options may include gastro-omental free flaps. Limited case series suggest that these may have an advantage associated with the availability of the omentum. This can be wrapped around the anastomotic site to decrease the possibility of leakage and improve the overlying skin quality. However, the complication rate is significant, although may in part reflect patients in whom this option is considered.[236,237] Additional vascularised tissue can be included with the anterolateral thigh as a chimeric flap to resurface the neck, in cases where there is poor quality skin or contracted skin that would not safely close post-operatively.

When oesophageal resection is significantly intrathoracic, there may be insufficient access for the lower anastomosis, even with various forms of manubriumectomy. In such cases, a gastric pull-up may be used. This technique carries significant morbidity and mortality associated with the need to enter three visceral cavities. However, the mortality rate associated with gastric pull-up has dropped to less than 10 per cent in more modern case series.[238] Colonic transposition is an alternative but is rarely used in the modern era.

Vascularised tissue after salvage laryngectomy

Pharyngocutaneous fistulae are known to occur in nearly one-third of patients who undergo salvage total laryngectomy after chemoradiation. Recent meta-analyses suggest that there is an advantage in using vascularised tissue from outside the radiation field in the laryngectomy defect, either as a buttress or to augment the circumference of the pharynx.[239] This may be in the form of myocutaneous inset of free or pedicled soft tissue (e.g. anterolateral thigh or pectoralis major respectively), or myofascial onlay, usually a pectoralis major myofascial flap. This intervention reduces the risk of pharyngocutaneous fistulae by one-third to a half.

Reconstruction of soft tissue neck defects

After extended neck dissections for neck disease with skin involvement, with loss of skin, a pectoralis major myocutaneous flap should be considered. Most of these cases will also involve loss of the sternocleidomastoid muscle, and this provides both skin cover and protection of the otherwise exposed carotid artery through its volume and muscle. A supraclavicular artery island flap can also be used for skin cover, but does not have the bulk.

In cases without a skin defect, when the neck dissection has included the sacrifice of the sternocleidomastoid muscle, and either chemoradiotherapy is planned or the neck dissection is for salvage treatment of recurrent disease after chemoradiotherapy, a pectoralis major myofascial flap can be considered in order to provide vascularised carotid artery cover and lessen the risk of breakdown causing catastrophic haemorrhage.

Care of patients after microvascular free-flap surgery

Microvascular reconstruction using free tissue transfer is standard practice in head and neck reconstruction. The literature demonstrates success rates in excess of 95 per cent.[240,241] The early detection of and intervention for flap failure forms an important part of ensuring low failure rates.

There is no universally agreed protocol regarding the duration and method of flap monitoring. However, the following should be considered:

- The critical period for flap vascular complications is 24–48 hours post-operatively[241]
- The probability of flap salvage is inversely related to the duration of ischaemia, and successful flap salvage is highly unlikely after 12 hours[241]
- Clinical flap monitoring includes using capillary refill, skin colour, cutaneous temperature and arterial Doppler signal. It is highly accurate and effective, with 85–95 per cent flap success rates using clinical assessment alone[242]
- The use of an implantable Doppler may be considered for buried flaps or to augment clinical monitoring, with some improvement in reducing flap failure but possibly at the expense of false alarms[242]

A typical protocol for monitoring is:

- One-hourly observation on post-operative day 1
- Two-hourly observation on post-operative day 2
- Four-hourly observation on post-operative day 3

While late flap vascular complications are reported, even at day 7 post-operatively, both the probability of their occurrence and their salvage is low, as these are usually related to intrinsic flap problems, which are not easily correctable.[243]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Section 2: Patient support

Chapter 8: Patient preparation for treatment and enhanced recovery

Table of Contents

Key points

- Patients and family members should be at the centre of their care. They should receive education and information regarding prehabilitation and enhanced recovery after surgery early in their pathway, so that they can provide informed consent and engage in preparation.
- Prehabilitation and enhanced recovery after surgery relies on interdisciplinary teams involving a range of professionals, including those who may traditionally fall outside healthcare, e.g. voluntary sector, health and leisure centres, to ensure that the optimum patient outcome is achieved.
- Healthcare workers require the appropriate training, governance and operational support to be able to enact this guidance and embed the recommendations into their practice. It is recommended that clinical services identify champions within their organisation to effectively implement organisational change with appropriately resourced audit data collection.
- There may be barriers present for some head and neck cancer patients that prevent them from engaging in prehabilitation and enhanced recovery after surgery programmes; for example, difficulty in changing maladaptive behaviours, and/or psychological factors including the lived experience of trauma. All attempts should be made to gain awareness of such barriers, and to support patients in overcoming these issues in order to achieve the benefits offered from prehabilitation and enhanced recovery after surgery programmes.
- Prehabilitation and enhanced recovery after surgery programmes are more effective when delivered across a pathway that also includes rehabilitation.

Introduction

The following guidelines cover the provision of interdisciplinary team prehabilitation and enhanced recovery after surgery services required for head and neck cancer patients. An overview of the current literature in prehabilitation and enhanced recovery after surgery is provided, alongside an overview of each element. Recommendations for services are divided into key time points across the patient journey. Each section is then separated into recommendations that are considered 'essential' and 'desirable'.

It is recommended that this chapter is cross-referenced with the following other chapters available in these guidelines, including those on: nutritional management in the treatment of head and neck cancer; physiotherapy and exercise; psychological management; speech, voice and swallowing rehabilitation; and the clinical nurse specialist's role.

Additionally, the following resources provide further information for both head and neck cancer clinicians and patients involved in prehabilitation and enhanced recovery after surgery programmes:

- Mouth Cancer Foundation, in: https://www.mouthcancerfoundation.org/
- The Swallows, in: https://www.theswallows.org.uk/
- Heads2gether, in: https://www.heads2gether.net/home/
- Prehab4cancer, in: www.prehab4cancer.co.uk
- 'ERAS+' (enhanced recovery after surgery plus), in: www.erasplus.co.uk
- SafeFit, in: https://safefit.nhs.uk/
- National Health Service – Exercise, in: https://www.nhs.uk/live-well/exercise/
- The Royal Marsden – Exercise at home, in: https://www.royalmarsden.nhs.uk/your-care/living-and-beyond-cancer/exercise-home
- 'CURE' (treating tobacco addiction), in: www.thecureproject.co.uk
- MacMillan Cancer Support – The building-up diet, in: https://www.macmillan.org.uk/cancer-information-and-support/stories-and-media/booklets/the-building-up-diet; Swallowing, in: https://www.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1601-10061/swallowing-tcm9-355063; and Dry mouth and changes in saliva after head and neck cancer treatment, in: https://www.macmillan.org.uk/cancer-information-and-support/impacts-of-cancer/dry-mouth-and-changes-in-saliva-after-head-and-neck-cancer-treatment
- Maggie's cancer support, in: https://www.maggies.org/cancer-support/our-support/
- 'PINNT' (Patients on Intravenous and Naso-gastric Nutrition Treatment), in: https://pinnt.com/Home.aspx

Prehabilitation

Cancer prehabilitation is an intervention commonly defined as occurring from the time of diagnosis to the commencement of acute treatment. Macmillan prehabilitation guidance (2019)[244] outlines a set of principles to empower people with cancer to prepare for treatment, through promoting healthy behaviours and needs-based prescribing of exercise, nutrition and psychological interventions. We would suggest that cancer prehabilitation is best viewed as a continuum throughout the patients' journey, from diagnosis to treatment, into rehabilitation and to survivorship.[245]

The treatments for head and neck cancer are often multimodal and complex, and include primary surgery and reconstruction, and/or adjuvant radiotherapy with or without chemotherapy. These treatments are associated with both acute nutrition impact symptoms and long-term side effects, including dysphagia, pain, taste changes, mucositis and dry

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

mouth, which result in a decline in nutritional and physical function that negatively affects quality of life (QoL) and survivorship.[246,247] In addition, many patients present with higher rates of smoking and alcohol consumption, low socioeconomic status, and many co-morbidities; these result in low physical, nutritional and emotional well-being, which can negatively impact treatment outcomes. On diagnosis, up to 60 per cent of patients have been identified as malnourished or are at risk of malnutrition.[248] Subsequent treatment often serves to worsen malnutrition status, and leads to sarcopenia development in over 50 per cent of head and neck cancer patients, which is associated with worse outcomes.[249]

Despite the downward trend of smoking, the incidence of head and neck cancer in the UK continues to rise, with approximately 50 per cent of oropharyngeal cases related to human papillomavirus.[250,251] With this increasing prevalence, and the significant patient burden of head and neck cancer disease and treatment, interventions such as prehabilitation are particularly attractive, as they aim to improve the patient's physical, nutritional and mental resilience. This process aims to mitigate against the impact of treatment-related side effects, and to improve QoL as well as longevity.

A review of the literature identified several systematic reviews demonstrating the positive impact of prehabilitation amongst cancer patients.[252–256] Prehabilitation that includes an exercise component can improve physical function prior to surgery, and demonstrates positive effects on length of hospital stay and post-operative surgical complications.[252,255] One review, which aimed to identify whether prehabilitation improves health outcomes (physical function, nutritional status and patient-reported outcome measures) after more than 30 days post-treatment, concluded that prehabilitation improved gait, cardiopulmonary function, urinary continence, lung function and mood.[253] In a study of older adults with cancer that examined the efficacy of nutritional and exercise interventions on health-related QoL, the majority of interventions were exercise only, with variations in exercise modalities, duration and location.[254] Despite this heterogeneity, improvements in QoL were identified, highlighting the potential benefits of prehabilitation in the older adult population. Further robust and personalised interventions are recommended.

Implementing prehabilitation strategies commonly requires motivation, self-efficacy support and behaviour change in patient cohorts. Eating As Treatment ('EAT') is a psychological intervention that aims to improve the nutritional status in patients undergoing radiotherapy.[257] Dietitians were trained to include motivational interviewing and cognitive behavioural therapy strategies into their dietary counselling. This resulted in positive significant differences in nutritional status, as measured by the Patient-Generated Subjective Global Assessment ('PG-SGA') Short Form, weight loss and treatment interruptions. In addition, although not significant, global QoL was reported to have improved.

Currently, recommendations for head and neck cancer prehabilitation and its optimal delivery are limited by the volume of published research. This is likely because of the difficulties posed by the more complex treatment pathways in head and neck cancer when compared with abdominal and thoracic cancer resection surgery, which have tended to dominate the large prehabilitation trials. There is also a focus on more urgency in head and neck cancer surgery, potentially giving less time for prehabilitation interventions to be included in patient pathways. Additionally, there can often be difficulties associated with delivering treatment across increased geographical areas, as the head and neck cancer tertiary centre model may make the distance for patients to travel appear impractical.

Despite these challenges, there is confirmed safety and efficacy for exercise and nutrition interventions during chemo/radiotherapy in head and neck cancer patients.[258] Exercise interventions included a combination of strength and aerobic exercises and were performed up to five times per week. Nutritional interventions were predominantly dietary counselling personalised to meet estimated energy and protein requirements, with oral nutritional supplements being used to meet any deficit. Additionally, a 7-day prehabilitation intervention in head and neck cancer and abdominal surgery patients, including a nutritional (oral nutritional supplements), exercise (step targets), breathing technique and skin cleaning regimen, has confirmed the feasibility of short interventions by demonstrating significant improvements in post-operative mobility and improved prevention of pulmonary morbidity.[259]

Despite the paucity of published research specifically in head and neck cancer, it is clear from the burden of the disease and its treatment that this group of patients can significantly benefit from many of the processes inherent in prehabilitation. These recommendations have been developed by drawing upon the current evidence, clinical expertise in head and neck, knowledge from established prehabilitation programmes, and the lived experience of head and neck cancer proton pump inhibitor (PPI) groups.

Pre-treatment (general to all head and neck cancers)

The recommendations are summarised in Table 1.[260–262]

During treatment

Surgery-specific

The recommendations are summarised in Table 2.

Chemo/radiotherapy-specific

The recommendations are summarised in Table 3.[263,264]

Post-treatment (general to all head and neck cancers)

The recommendations are summarised in Table 4.

Enhanced recovery

Enhanced recovery after surgery pathways are used in some surgical pathways with the aim of improving post-operative recovery by optimising pre-operative function and by reducing the post-operative stress response.[265] Whilst novel in its application to head and neck cancer surgical pathways, enhanced recovery after surgery has been implemented for decades in both general and colorectal surgery, with demonstrated long-term improvements in patient outcomes.[266] Established enhanced recovery after surgery pathways in these specialties recommend principles that could be applied to head and neck cancer patients, including pre-operative counselling, nutrition optimisation, standardised analgesic and anaesthetic regimens, and early post-operative mobilisation for all surgical patients.

Despite this proven evidence for benefit in other cancers and surgical specialties, current research exploring enhanced recovery after surgery in head and neck cancer surgery

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Prehabilitation: pre-treatment recommendations general to all head and neck cancers

Essential	Desirable
The concept of prehabilitation should be introduced at time of diagnosis, to all patients (evidence-based recommendation (R)) Where available, referral should be made to prehabilitation services within 48 hours of diagnosis, depending on service provision (good practice point (G)) If services are not currently available, patient should be signposted to available self-directed resources (G)	Location of prehabilitation services should be based on patient screening & assessment, whereby patients could be offered prehabilitation within community & not exclusively within hospital setting (G)
Expectation setting for prehabilitation should be discussed with patients, including what it involves, why it is important & reassurance about its safety. This should be provided in both written & verbal form (R)[260]	Offer patient choice – how & where they are best to engage, i.e. hospital, home, or community health & leisure centres (G)
Core prehabilitation team should include (G): • Physiotherapist &/or level 4 cancer & exercise specialist • Dietitian • Speech & language therapy • Clinical nurse specialist	Additional (R): Lifestyle services: • Psychological therapies • Occupational therapy • Consultant ENT, oncologist, anaesthetics, OMFS, dental • Therapy assistant or navigator
All patients should have measurements taken of physical function & outcome measures, which includes baseline physical activity, cardiovascular fitness, upper & low body muscle strength & function (e.g. 6-minute walk test or incremental shuttle test, sit-to-stand test, handgrip strength test, timed up & go test, physical activity questionnaire) (R)	
Where appropriate, patients should be offered an exercise prescription, stating intensity, dose etc. This should be based on patient's baseline, & may be adjusted in accordance with any improvements or change to exercise tolerance (R)	Patients should engage in physical activity (i.e. walking for 30 minutes daily) as an adjunct to exercise prescription (G)
All patients should have a nutritional screen using a validated screening tool (i.e. PG-SGA SF, NRS, MUST) & referral to dietitian for those at risk of malnutrition (R)	All patients referred to dietitian for assessment (R)
All patients should have a nutritional assessment that includes subjective assessment of body composition & sarcopenia risk (i.e. PG-SGA, SARC-F, handgrip strength test) (R)*	All patients should have an objective measure of body composition using BIA, CT or DEXA scan (for those identified through screening as at risk of sarcopenia &/or malnutrition) (G)
All patients should have a nutritional care plan that includes targets for calories & protein. Oral nutritional supplementation or enteral feeding should be used to meet deficits that cannot be met orally (R)*[261]	Patients complete daily diet diaries or use application software (apps) to monitor dietary intake & support self-efficacy (G) Recommend taking protein containing snack or supplements post exercise (G)[262]
Patients should have nutrient biochemical screening & treatment if clinically indicated: vitamins D & B12, folate, ferritin, iron, HbA1c, & random glucose (R)	Patients should have nutrient biochemical screening if clinically indicated: zinc, selenium, copper (G)
Patients should be offered psychological or mental well-being screening (G) From there, consideration & assessment of mental health well-being, history, & biopsychosocial function. When needed, patients should be directed to self-help i.e. IAPT, changing faces†	All clinicians should have advanced communication skills training (G)
Protocols should be in place to support anyone identified or presenting at risk following any mental health screening (R)	
Lifestyle – patient should be supported with smoking cessation, screened for alcohol consumption & offered an alcohol detox programme where appropriate (R)	
All patients should be offered access to SLT for assessment & management of swallowing &/or communication. This should include collection of clinician- & patient-reported outcome measures (R)†	Patients should be offered tailored swallowing &/or communication exercises e.g. traditional swallow therapy, voice care advice (G)
Peer & social support: patient's support network should be identified, & patients should be provided with local & national support information (G)	
Validated QoL measures should be used with all patients i.e. EORTC QLQ-30, EORTC QLQ-H&N35, PCI, SF-36 (G)‡	Measurement of QoL taken at baseline, pre-treatment & end of treatment, for all patients (G)
All patients should be offered & complete a holistic needs assessment (R)	

*See chapter on nutritional management in the treatment of head and neck cancer for further details. †See chapter on psychological management for further details. ‡See chapter on speech, voice and swallowing rehabilitation for head and neck cancer for further details. OMFS = oral and maxillofacial surgery; PG-SGA SF = Patient-Generated Subjective Global Assessment Short Form; NRS = nutrition risk screening; MUST = Malnutrition Universal Screening Tool; SARC-F = Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls questionnaire; BIA = bioelectrical impedance analysis; CT = computed tomography; DEXA = dual-energy X-ray absorptiometry; HbA1c = haemoglobin A1c; IAPT = improving access to psychological therapies; SLT = speech and language therapy; EORTC = European Organization for the Research and Treatment of Cancer; QLQ-30 = 30-item Quality of Life Questionnaire Core Module; QLQ-H&N35 = 35-item Quality of Life Questionnaire Head and Neck Module; PCI = Patient Concerns Inventory; SF-36 = 36-item Short Form Health Survey; QoL = quality of life

remains limited in number and variable in study design.[267] The key concepts that have been explored to date focus on early oral feeding following major head and neck cancer surgery,[268–271] early tracheostoma fistula closure, and aspects of service delivery including predictors of complications.[272–276] Dort and colleagues' (2017)[273] systematic review of recommendations for peri-operative care in head and neck cancer surgery with free-flap reconstruction identified 17 topic areas, and reported their evidence levels. Ten of these topic areas are applicable to all head and neck cancer patients,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Prehabilitation: intra-treatment recommendations specific to surgery

Essential	Desirable
Patients should be part of an enhanced recovery after surgery programme, as described below (evidence-based recommendation (R))	

Table 3. Prehabilitation: intra-treatment recommendations specific to chemo/radiotherapy

Essential	Desirable
All patients should have ongoing monitoring. Adjustments need to be made to exercise prescription & other aspects of prehabilitation interventions in response to patient's tolerance of chemo/RT. Interventions should be complementary & not contraindicated at this time (evidence-based recommendation (R))	Record of treatment interruptions (good practice point (G))
Physical activity should be encouraged, & is safe & effective for fatigue management (R)[263]	
All patients on chemo/RT are referred to dietitian for nutritional assessment (G)	
Weight & tolerance to nutritional care plan monitored weekly with all patients (R)	
Patients should have access to SLT to support oral intake & prophylactic exercises throughout treatment (R)[264]	

Chemo/RT = chemo/radiotherapy; SLT = speech and language therapy

Table 4. Prehabilitation: post-treatment recommendations general to all head and neck cancers

Essential	Desirable
All patients should have repeat outcome measures collected (physical, nutritional, QoL) (good practice point (G))	Patients should have input from consistent healthcare professionals, from prehabilitation into rehabilitation, building on trust & rapport already developed in prehabilitation, for continued enhanced psychosocial support (G)
SMART goals should be set, which are based on patient's wishes & needs to direct rehabilitation provision (G)	Patients should have access to group delivery of interventions (G)
Patients should be supported to adopt healthy lifestyle behaviours, with long-term aim of preventing cancer recurrence & other long-term health conditions such as pulmonary & cardiac based illnesses (evidence-based recommendation (R))	Patients should be offered therapy, which can be delivered via a patient-centred approach, to enhance behavioural change. For example, enabling patients to engage in exercise that they enjoy & which suits their preferences e.g. attending a local walking club (R)
Self-management should be a key focus with all patients, especially as they approach discharge (R)	
All patients should have a repeated holistic needs assessment to understand any unmet needs, & should liaise with other agencies to address these (R)	

QoL = quality of life; SMART goals = specific, measurable, achievable, relevant and time-bound goals

and are supported by other research.[277] It is for this reason that they are included in this guideline.

Whilst there are acknowledged limitations in the current literature, findings from the most recent studies are encouraging;[273,277] and it must be recognised that the concept of enhanced recovery after surgery has potential to positively influence head and neck cancer patient outcomes and service provision.[267] For this to be achieved, audit cycles of changes in clinical practice should be conducted in all head and neck cancer services adopting enhanced recovery after surgery protocols in the UK.

As we know, there are a wide range of head and neck cancer surgical procedures offered to patients in the UK, ranging from 'minor' to 'major' surgery. Some enhanced recovery after surgery principles may vary depending on the extent of surgery (e.g. timing of re-commencing oral intake); however, the general principles of enhanced recovery after surgery should be applicable to all head and neck cancer surgery patients, irrespective of their surgery.

Therefore, the following recommendations are generalised to all head and neck cancer patients undergoing surgical procedures, pre-treatment, during treatment and post-treatment care. These guidelines have been developed based on critical literature appraisal, expert consensus and PPI involvement. It is recommended that they be used as a model for clinical services and applied to patients on an individualised basis. We recommend referring to the speech and language therapy chapter for more specific recommendations on laryngectomy, if required.

Pre-treatment

The recommendations are summarised in Table 5.

During treatment

The recommendations are summarised in Table 6.

Post-treatment

The recommendations are summarised in Table 7.

Research

The evidence base for both prehabilitation and enhanced recovery after surgery in head and neck cancer is emerging, with promising outcomes. In addition, trials that aim to investigate the effectiveness of prehabilitation within the head and neck cancer population are underway.[278]

However, there is a continuing need for high-quality studies with replicable methods and statistical analysis. This will support the implementation and evaluation of evidence-based standardised prehabilitation programmes and peri-operative enhanced recovery after surgery pathways for head and neck cancer patients. This is reinforced by a number of National Cancer Research Institute ('NCRI') key research priorities.[279]

In order to evaluate the effectiveness of developed programmes or pathways, there are key research questions and areas that should be addressed in future studies:

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 5. Pre-treatment recommendations for enhanced recovery

Essential	Desirable
All patients should have pre-op speech, voice & swallow screening assessment, including collection of patient-reported outcome measures (see SLT chapter for recommended measures) (evidence-based recommendation (R))	All patients should be offered pre-op home assessment to prepare for any potential discharge requirements or services e.g. equipment (good practice point (G))
All patients should have pre-op nutritional assessment. This should include screening & treating for risk of re-feeding syndrome, & plan for nutritional optimisation (R)* Decision on whether, how & when to treat should be documented	All patients should be screened for sarcopenia (G)
All patients should be screened for alcohol consumption, & offered an alcohol detox programme where appropriate. This should commence within 48 hours pre-op (R) Assessment & outcome should be documented	Where appropriate, patients should be offered a pre-treatment visit with a volunteer patient matched to their planned treatment (G)
All patients should be screened for smoking status, & offered access to smoking cessation advice where appropriate (R) Assessment & outcome should be documented	There should be access to baseline respiratory function tests where appropriate e.g. patients with COPD, & for initiation & optimisation of therapy (G)
All patients should be offered practical information to prepare them for their in-patient stay. This should include direct information, such as a list of expectations & items to bring in to hospital (G)	Where available, all patients should be offered access to surgery school for co-ordination of enhanced recovery programmes e.g. Greater Manchester ERAS+ programme (R)
All patients should have pre-op assessment of their activities of daily living, including functional evaluation (G)	
All patients should be offered pre-op exercise optimisation programme (R)	Where appropriate, patients should be offered pre-emptive analgesia (G)
All patients should be offered medical optimisation that includes diabetes, anaemia & respiratory function. Therapy & treatment should be started, as appropriate (R)	
There should be access to baseline cognitive & frailty assessments from occupational therapist, to inform treatment planning, manage intra-op risks & inform post-op care (G)	
All patients should have a pre-op evaluation by head & neck anaesthetist (R)†	
Pre-op fasting duration should be minimised (R)	
All patients undergoing major surgery should be offered pre-op carbohydrate treatment, excluding patients who have uncontrolled diabetes or gastroparesis (G)	
All patients should have access to pre-op psychological screening service (G)	

*See chapter on nutritional management of head and neck cancer for further information. †An anaesthetist who specialises in the management of difficult airways. SLT = speech and language therapy; pre-op = pre-operative; COPD = chronic obstructive pulmonary disease; ERAS+ = enhanced recovery after surgery plus; intra-op = intra-operative; post-op = post-operative

- Patient-reported outcomes or experiences are not currently routinely represented in enhanced recovery after surgery literature. These should be explored in both prehabilitation and enhanced recovery after surgery services, and outcomes should be incorporated into any future pathway development to measure outcomes, ensuring the patient report and experience are at the core
- Clinician-reported experiences are not currently represented in the literature. Future work should explore this, as a deeper understanding of clinician perspectives could benefit implementation through increasing compliance with enhanced recovery after surgery pathways
- There should be understanding of cost-effectiveness and workforce provision of prehabilitation and enhanced recovery after surgery interventions, to support services in providing prehabilitation and enhanced recovery after surgery
- Facilitator and barriers to the integration of prehabilitation with enhanced recovery after surgery programmes should be investigated
- Prehabilitation that includes patients undergoing primary (chemo)radiotherapy treatment should be explored
- Comprehensive multimodal prehabilitation trials should be conducted, which include a combination of nutrition, exercise, behaviour and/or swallowing interventions
- The impact of delaying treatment to enable prehabilitation should be assessed
- The impact of including peer, caregiver and family support within prehabilitation and enhanced recovery after surgery programmes should be evaluated

Future research into both prehabilitation and enhanced recovery after surgery must demonstrate quality improvement, efficiency and embed patient-reported outcomes. This will enable prehabilitation and enhanced recovery after surgery models to become the standard of care, and allow thorough evaluation of the services offered to head and neck cancer patients in the UK. This also supports a number of National Cancer Research Institute key research priority questions, including: (1) How can the short-term, long-term and late effects of cancer treatments be (a) prevented, and/or (b) best treated and managed?; and (2) What specific lifestyle changes (e.g. diet, exercise and stress reduction) help with recovery from treatment, restore health and improve QoL?

Future aspects of prehabilitation and enhanced recovery after surgery

Prehabilitation and enhanced recovery after surgery programmes have the potential to benefit long-term patient

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 6. Intra-treatment recommendations for enhanced recovery

Essential	Desirable
Patients should be given antibiotics 60 minutes prior to skin incision (evidence-based recommendation (R))	Depth of anaesthesia monitoring (R)
Repeat antibiotic dosing should be given at appropriate intra-op intervals (R)	Where appropriate, overnight sedation & avoidance of tracheostomy should be considered (R)
All patients should have management of VTE prophylaxis; e.g. anti-embolic stockings, pneumatic compression devices & prophylactic low-molecular weight heparin unless contraindicated (R)	Where indicated, patients should be provided with appropriate reflux management (R)
Patients should have peri-op glucose management (R)	
All patients should have access to multimodal analgesia (R)*	
All patients should have appropriate management & maintenance of normothermia (R)	
All patients should have access to goal-directed fluid therapy (R)	
All patients should be evaluated & treated by an H&N anaesthetist (good practice point (G))	
If patients are at risk of post-op pulmonary complications, they should be offered lung protective ventilation (R)	
All patients should have preventative management of post-op nausea & vomiting (R)	

*Indicates the use of more than one modality to control pain. Intra-op = intra-operative; VTE = venous thromboembolism; peri-op = peri-operative; H&N = head and neck; post-op = post-operative

Table 7. Post-treatment recommendations for enhanced recovery

Essential	Desirable
All patients should have appropriate tools to implement oral care within 24 hours post-op (good practice point (G))	Where appropriate, early oral trials should be considered, with patients commencing sterile water within 1–3 days post-op (evidence-based recommendation (R))
All patients should be encouraged to start swallowing saliva within 24 hours post-op (G)	There should be access to a 7-day therapies service including SLT, dietetics, occupational therapy, physiotherapy (G)
All patients should have access to alternative communication methods within 24 hours of surgery (G)	Early swallow rehabilitation exercises should be offered to optimise swallowing outcomes (R)
All patients should have access to SLT for functional communication rehabilitation, i.e. adjustment therapy (R)	Patients should be offered impairment-based communication rehabilitation when indicated (R)
Early pulmonary assessment & rehabilitation should be provided by physiotherapy, particularly for high-risk patients (R)	Where appropriate, remote support with patients' clinical team, e.g. clinical nurse specialist, should be provided (G)
Where appropriate, early catheter removal should be considered, to reduce risk of UTI (R)	All patients should be provided with alternative forms of information, e.g. written leaflets & videos, outlining clear post-treatment recovery guidelines for enhanced recovery (G)
Return to activities of daily living should be encouraged within 72 hours of surgery, particularly early mobilisation, for all patients (R)	Alternative forms of therapy should be available to all patients for their general health & well-being, & psychological health. Examples could include art or music therapy (G)
All patients & their families should have either face-to-face or remote communication with key clinical team within 24 hours post-op (G)	
All patients should be cared for on a ward with specialist head & neck nursing staff (G)	
Where possible, tracheostomy should be avoided. If required, timely decannulation & early suturing of tracheostoma should be considered (R)	

post-op = post-operative; SLT = speech and language therapy; UTI = urinary tract infection

outcomes and experience, as well as cost-effectiveness of clinical services. Participants of the Greater Manchester Prehab4Cancer and recovery programme[259] provided clear positive feedback around being able to 'take back control' of their cancer journey. Many patients anecdotally felt stronger than the cohort of patients with similar conditions who did not take part. One patient said, 'I was out of bed faster than everyone on my ward'. They were unanimous about the positive mental benefits of the exercise programme. Engagement with personal trainers was critically important, as well as feeling part of a group within an environment in which they could participate and share experiences with other patients. The group universally would recommend an exercise dose as part of their cancer journey, and felt this should be offered to all relevant cancer patients. This should be considered in future aspects of both prehabilitation and enhanced recovery after surgery services.

Head and neck cancer services in the UK will need to be expanded to achieve optimum prehabilitation and enhanced recovery after surgery services. These services should have interdisciplinary working at their core, so that the optimum patient outcome is achieved. This recommendation is echoed

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

by feedback (from a head and neck cancer PPI group), with one person saying: 'I think setting bespoke individual goals is an excellent idea if constructed in an achievable way. I like goals, things to aim for but emphasis must be on the positive'.

Therefore, both prehabilitation and enhanced recovery after surgery services should have access to:

- Community well-being and leisure services that support engagement in exercise
- Patient and public involvement groups
- Digital healthcare technology
- Social prescribing and other primary care personalised care initiatives
- Third sector provision such as Macmillan and Maggie's charities, for information and support

Chapter 9: Nutritional management in the treatment of head and neck cancer

Table of Contents

Key points

- Specialist dietitians should be part of head and neck cancer multidisciplinary teams (MDTs) throughout patients' continuum of care.
- Clear pathways between primary, secondary and tertiary care across organisational boundaries should be maintained, reviewed and monitored to ensure seamless delivery of dietetic support.
- Patients with head and neck cancer are at a high risk of malnutrition because of the impact of disease and subsequent treatment.
- At diagnosis, all patients should be screened for malnutrition using validated tools, e.g. Malnutrition Universal Screening Tool ('MUST'). Any patient at risk of malnutrition, or likely to become malnourished as a result of treatment should be referred to a dietitian for early intervention, and assessed for malnutrition using validated tools, e.g. Patient-Generated Subjective Global Assessment ('PG-SGA'). Malnutrition screening and assessment should be repeated at various intervals throughout patients' continuum of care.
- All patients should receive a pre-treatment appointment prior to any treatment that is expected to impact on the ability to maintain nutritional status. This should include counselling on enteral tube feeding options, where appropriate.
- Nutritional requirements can be estimated using evidence-based equations; however, patients' anthropometry and tolerance of nutrition support should be monitored to ensure adequacy of intake.
- Prophylactic gastrostomy placement should be considered on an individualised basis, where the MDT should take account of the following: performance status and social factors, baseline nutritional status, tumour stage, tumour site, pre-existing dysphagia, and impact of planned treatment.
- Patients having nasogastric tubes in the community should all have a nasogastric tube risk assessment completed.
- All patients undergoing a surgical intervention should be provided with carbohydrate loading and have tube feeding initiated within 24 hours of surgery (where oral intake is contraindicated) as part of enhanced recovery after surgery protocols.
- All patients at severe nutritional risk, who are not meeting nutritional requirements, should receive nutrition support for 10–14 days prior to surgery. Delaying surgery to achieve this may be necessary but has to be weighed against the risk of delaying treatment.
- All patients undergoing radiotherapy should receive a dietetic review at least once weekly during treatment, fortnightly for six weeks after treatment, and as appropriate thereafter for up to a minimum of three to six months.
- Dietitians can become advanced clinical practitioners and extend their scope of practice within their MDTs. This includes becoming non-medical supplementary prescribers with appropriate supervision in place from MDT members.
- All patients having palliative treatment should have access to a dietitian. The advantages and disadvantages of nutrition support and/or artificial feeding should be discussed with the MDT based on a goal of maintaining patients' quality of life.
- Patients who have completed rehabilitation and are no longer at risk of malnutrition should be offered cancer prevention and healthy eating advice. Where appropriate, this should include encouraging physical activity as per national recommendations.
- Dietitians should offer telehealth appointments where appropriate to support service flexibility.
- Dietetic provision in proton beam therapy services should mirror existing intensity-modulated radiation therapy services.

Head and neck cancer dietetic service provision and delivery

Nutritional intervention and support is integral in the management of head and neck cancer patients. It is estimated

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

that 35–75 per cent of patients present malnourished at diagnosis.[280,281] In addition, the obesity epidemic has led to more patients presenting as overweight or obese at diagnosis, and recent research suggests that these individuals have increased rates of malnutrition and sarcopenia during treatment.[282]

Dietetic services within head and neck cancer units should be seamless, and ensure access at each stage of the patient pathway from diagnosis to survivorship and/or palliation. As part of the National Health Service (NHS) 'Long Term Plan', 'Cancer Plan' and 'Cancer Reform Strategy', head and neck cancer services in the UK have been restructured to facilitate the centralisation of services, MDT unification and the streamlining of surgical treatments at tertiary centres.[283] Dietitians are key stakeholders in ensuring that the process of centralisation allows access to adequate nutritional screening, support and intervention, to optimise patients' experience and outcomes (Table 1). Furthermore, it is integral that pathways are maintained and reviewed, to ensure continuity of care between primary, secondary and tertiary facilities across organisational boundaries in order to prevent fragmented service delivery.[284]

The British Association of Head and Neck Oncologists recommend that all head and neck cancer units have a specialist dietitian with at least 50 per cent of their time dedicated to head and neck cancer.[71] Early, frequent dietetic counselling is associated with improvements in nutrition, patient-centred outcomes, quality of life, compliance and tolerance to treatment (Table 1).[285]

Malnutrition and body composition screening

Emerging research highlights the importance of body composition on identifying malnutrition, sarcopenia and/or cachexia. These can affect treatment outcomes, hence should be taken into consideration by the MDT when planning treatment.[286]

Malnutrition within cancer is the negative energy balance and skeletal muscle loss driven by a combination of reduced food intake and metabolic derangements. It is adversely associated with survival, morbidity, mortality, quality of life and treatment response, impacting on clinical outcomes, cost and patient experience.[287] Table 2 depicts how malnutrition can be generally identified, and the consequences, but it is important that screening and assessment for this is undertaken. Patients with head and neck cancer are at risk of malnutrition because of the site of their cancer, the impact of the disease process and treatment, and lifestyle factors.[288,289] More recently, it has been reported that patients who are overweight or obese at baseline are at higher risk of becoming malnourished during and after head and neck cancer treatments.[282]

Unintentional weight loss (independent of presenting body mass index) of 10 per cent or more in the six months preceding diagnosis[288,290] can lead to the adverse effects detailed in Table 2.[289–291]

Cancer cachexia is difficult to diagnose as it is multifactorial in nature. It is characterised by the loss of weight, skeletal muscle and adipose tissue, alongside an imbalance of metabolic regulation and reduced food intake. It negatively affects treatment outcomes and quality of life. Management is difficult in light of limited agreed treatment options. Evidence to support pharmacological treatments remains inconclusive. Improvement has been reported with fish oil supplements; however, palatability limits compliance.[292]

Sarcopenia can be defined by the combination of low grip strength plus low muscle mass.[293] Sarcopenia and myosteatosis (infiltration of muscle with fat) can be significant negative

Table 1. Recommendations for dietetic provision in head and neck cancer services

Essential	Desirable
Specialist dietitian for HNC should be part of MDT (evidence-based recommendation (R))	Dedicated time for research & service development for HNC dietitians within job plans (good practice point (G))
All HNC units should have a specialist dietitian with ≥50% of their clinical time dedicated to HNC (R)	
Dietetic service provision to reflect capacity & demand of HNC units (G)	
Clear pathway & communication for service delivery between acute & community dietetic services & within centralised HNC services (G)	
Dietetic representation on pathway boards for centralised services across organisational boundaries (G)	

HNC = head and neck cancer; MDT = multidisciplinary team

Table 2. Identification and consequences of malnutrition

Identification[289–291]
Malnutrition can be diagnosed following nutritional screening & assessment using validated tools. The top 5 ranked criteria by the Global Leadership Initiative on Malnutrition include 3 phenotypic criteria (weight loss, low BMI, reduced muscle mass) & 2 aetiological criteria (reduced food intake or assimilation, & disease burden or inflammation). To diagnose malnutrition, at least 1 phenotypic & 1 aetiological criteria should be present[291]
People at risk of malnutrition:
– BMI of <18.5 kg/m[281]
– Unintentional weight loss (regardless of BMI) of: >10% in 3–6 months; &/or BMI <20 kg/m[281] with unintentional weight loss of >5% in last 3–6 months
– Poor nutritional intake (<60% requirements in preceding 5–10 days) &/or likely to have minimal nutrition for the next ≥5 days
– Poor absorptive capacity, increased nutritional needs e.g. catabolism &/or high nutrient losses
Consequences of malnutrition
Increased:
– Risk of infection
– Treatment interruptions
– Length of hospital stay
– Risk of falls
– Unplanned admissions
– Post-operative complications
Reduced:
– Wound healing
– Treatment response
– Quality of life
– Muscle mass & function
– Overall survival

BMI = body mass index

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

predictors of overall survival, and muscle status evaluation should be considered during treatment planning.[286] Methods for identifying sarcopenia include the Strength, Assistance with walking, Rising from a chair, Climbing stairs and Falls ('SARC-F') questionnaire, computed tomography (CT) defined assessment, anthropometry, and bioelectrical impedance. Treatment for sarcopenia requires a combined approach, including physical activity and nutrition support, which should be offered as part of a prehabilitation programme (see 'Patient preparation for treatment and enhanced recovery' chapter for further information).

Screening and assessment

Malnutrition screening tools are used to identify patients promptly who are at risk of malnutrition and require further dietetic intervention, and should be used throughout the patient's pathway. Subsequently, malnutrition assessment tools can be used to diagnose malnutrition.[287,294] Some examples are illustrated in Table 3.[287] Several of these tools have been validated, but this may differ for various parameters including age and clinical settings. The most highly recommended assessment tool is the Patient-Generated Subjective Global Assessment. Screening should be agreed locally using a validated screening tool for the patient population. Following this, any patient identified at risk of malnutrition should be referred to a dietitian for full nutritional assessment (detailed in Table 4) using a validated nutritional assessment tool.

Patients who are malnourished, or at risk of malnutrition, may be identified by various members of the MDT, and should be referred to the dietitian for assessment. Dietitians should attend MDT meetings and MDT head and neck cancer clinics to support rapid referral (Table 5).

Nutrition support

Interventions can have a profound impact on the ability to eat and drink or take adequate nutrition orally, related to loss of function and treatment side effects such as nausea, vomiting, xerostomia, pain, mucositis and dysphagia.

Pre-treatment

All patients scheduled to undergo treatment that is likely to impact on nutritional status should be offered a dietetic pre-treatment appointment in order to assess baseline nutritional status, and provide dietary intervention as appropriate to maintain nutritional status and prevent decline (Table 6).[295,296] The British Dietetic Association care pathway (Table 7) should be used to collect relevant baseline information alongside a malnutrition assessment tool.[297]

The appointment should also provide counselling to assist informed decision-making and manage expectations on the impact of upcoming treatment on nutritional status. This includes possible changes to dietary textures, the requirement for enteral tube feeding in the short and long term, and side effects of treatments affecting the ability to take nutrition.[298]

Prehabilitation

Prehabilitation promotes healthy behaviours such as exercise, optimal nutrition and psychological support, to maximise resilience to treatment and improve long-term health. All patients should be counselled on the importance of prehabilitation, and services should be developed to facilitate access for all head and neck cancer patients.[299] Further information can be found in the 'Patient preparation for treatment and enhanced recovery' chapter.

Table 3. Malnutrition screening and assessment tools[287]

		Type & purpose of tool	
Tool name	Description	Screening	Assessment
Revised MNA-SF	Screening tool for rapid detection in older adult population	X	
PG-SGA Short Form	Patient-generated screening tool	X	
Malnutrition Screening Tool	Screening tool that does not require patient weights	X	
Nutrition Risk Screening 2002 tool	Screening tool used in hospital setting, & widely used & recommended by several international organisations	X	
Royal Marsden Nutrition Screening Tool	Screening tool with good sensitivity for identifying in-patients at risk of malnutrition	X	
Malnutrition Universal Screening Tool	Screening tool currently used by most trusts across UK	X	
Short Nutritional Assessment Questionnaire	Screening tool for early detection of malnutrition in in-patient setting	X	
Mini Nutritional Assessment	Used in grading nutritional status in older adults, in in-patient & out-patient settings. High sensitivity in older adults, but low specificity in cancer patients aged 32–81 years	X	X
Nutrition Impact Symptom Assessment Tool for HNC patients (NIS)	Used specifically in HNC patients		X
Subjective Global Assessment	Includes assessment on nutritional status, history & physical examination		X
PG-SGA	Adaptation of Subjective Global Assessment; it is patient-generated, with good sensitivity, specificity & predictive values; recommended as benchmark in cancer patients globally		X

MNA-SF = Mini Nutritional Assessment *Short-Form;* PG-SGA = Patient-Generated Subjective Global Assessment; HNC = head and neck cancer; NIS = nutritional impact symptoms

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Nutritional screening and assessment recommendations

Essential	Desirable
Patients with HNC should be screened and assessed for malnutrition at diagnosis using a validated tool (e.g. MUST) (good practice point (G))	Patients with HNC should be nutritionally assessed using PG-SGA (evidence-based recommendation (R))
Malnutrition screening and assessment should be repeated at intervals during treatment, and as appropriate therefore, using validated tools, to prevent deterioration & allow early intervention (R)	
Patients identified at risk of malnutrition should be promptly referred to dietitian to allow early intervention & prevent deterioration (R)	
Patients offered treatment that is likely to impact on nutritional status should be offered dietetic support at any stage of pathway, despite baseline nutritional status (G)	
Access to nutritional support & treatment for malnutrition without delay, with appropriate feeding route (R)	

HNC = head and neck cancer; MUST = Malnutrition Universal Screening Tool; PG-SGA = Patient-Generated Subjective Global Assessment

Table 5. MDT and combined head and neck clinic recommendations

Essential	Desirable
Dietitian to attend ≥1 HNC MDT meeting as core member of MDT (evidence-based recommendation (R))	Offer further out-patient pre-treatment appointment in conjunction with clinical nurse specialists & SLTs) for: information-giving, assessment of baseline nutritional status, & individualised decision-making regarding enteral feeding support (good practice point (G))
Provide specialist input to inform treatment decision-making, especially regarding impact on nutritional status, enteral feeding requirements & functional outcomes (R)	
Attend combined MDT clinic consultation with surgeon & oncologist if appropriate. Advise on hospital admission if required (G)	
Early referral to dietetics for high-risk patients for early intervention (R)	

MDT = multidisciplinary team; HNC = head and neck cancer; SLT = speech and language therapist

Table 6. Pre-treatment assessment recommendations

Essential	Desirable
All HNC patients with existing or anticipated dysphagia &/or requirement of enteral feeding, regardless of treatment modality, should be offered a pre-treatment dietetic consultation (good practice point (G))	Offer pre-treatment consultation in conjunction with clinical nurse specialists & SLTs for: information-giving, assessment of baseline function, & decision regarding enteral feeding support (G)
Maintain & improve nutritional status & prevent decline for those malnourished at baseline or at risk of becoming malnourished (evidence-based recommendation (R))	Dietetic-led gastrostomy service, where dietitians lead decision-making, screening & assessment for tube insertions & removal, with support from gastroenterology, radiology & core HNC MDT members, including consultant physician, enteral clinical nurse specialist & SLT18 (G)
All patients considered for prophylactic gastrostomy should be selected individually & as per criteria in Table 10, to ensure appropriate decision-making for gastrostomy. All patients should be counselled on tube feeding options to assess suitability & optimal placement method (R)	Day-case gastrostomy services approach where appropriate within centres & as agreed with key stakeholders e.g. endoscopy & radiology (G)
All patients considered for NG tube use in community, or likely to require this for any part of their treatment, should be counselled on tube feeding options to assess suitability. Community support available for NG tube use that affects ability to self-manage; social support & ability to self-manage should be investigated beforehand & as applicable. MDT-supported NG tube use risk assessment should be completed for all patients with NG tube in community (G)	
Check patient's understanding of diagnosis, planned treatment, & their expectations of functional changes & outcomes. Provide further information & clarify as appropriate, & arrange follow up (G)	

HNC = head and neck cancer; SLT = speech and language therapist; MDT = multidisciplinary team; NG = nasogastric

Estimation of nutritional requirements

Total energy expenditure and protein requirements can be estimated using a variety of calculations, detailed in Table 7.[287,297,300–302]

Requirements will vary depending on many factors including: infection; biochemical and physical parameters indicating metabolic stress and reactions to treatment; body composition; activity levels; clinical condition; and type of treatment.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 7. Nutritional assessment and dietetic care pathway recommendations[297]

Parameter	Essential	Desirable
Anthropometry	Height; weight; weight history; % weight change; BMI of <18.5 kg/m[281] suggests undernutrition; clinical signs of weight loss e.g. ill-fitting dentures, clothing, jewellery	Triceps skinfold thickness (indicates fat stores); mid arm muscle circumference (indicates lean tissue mass); hand grip strength (assesses muscle function); bioelectrical impedance analysis (assesses skeletal muscle mass, fat mass, fat free mass, visceral fat, fluid); cross-sectional analysis (assesses muscle status)
Biochemistry	Urea & electrolytes (indicate fluid status, although can be disrupted by disease state & treatment). Albumin (not a good indicator of nutritional status given its long half-life (17–20 days) & it is affected by metabolic stress associated with raised C-reactive protein (indication of acute phase response)). Refeeding syndrome (see section below for details)	Pre-albumin (shorter half-life of 2–3 days, but also affected by infection & stress). Transferrin (affected by inflammation & infection). Total lymphocyte count (affected by infection)
Clinical	Gather information on relevant medical, social & drug history. Consider impact of HNC diagnosis, & proposed treatment on current & future nutritional status	Social history to gather information on alcohol intake, smoking, substance abuse, dentition, & social & financial status, which can affect access to initiatives, to aid nutritional support e.g. kitchenware & social support. Joint assessment with MDT members, including but not limited to: consultant surgeon, oncologist, clinical nurse specialist, speech & language therapist, therapeutic radiographer
Dietary history	Use of appropriate dietary recall method e.g. 24-hour recall, food frequency questionnaire, including following additional factors: – Ability to chew & swallow, & liaison with SLT if reporting any signs of aspirating, e.g. coughing, chest infections – Fluid intake – Changes in texture – Reports of fullness – Length of time & effort taken to eat – Changes in appetite – Gastrointestinal function – Medical history that may affect nutritional intake, e.g. co-morbidities & pharmacotherapy	Joint assessments with SLT where feasible
Estimated nutritional requirements (see section for full details)	– Energy: (1) ESPEN = 25–30 kcal/kg/day,*[287,300,301] or (2) BDA Parenteral & Enteral Nutrition Group = 22–25 kcal/kg/day + combined factor for physical activity level & dietary induced thermogenesis (1–1.4)†[302] – Protein: (1) 1.2–1.5 g/kg/day;*[287,300,301] or (2) 1–1.5 g/kg/day‡[287,302]	
Dietetic diagnosis	Evaluate impression & dietetic diagnosis of patient's nutritional status as per BDA framework	
Dietetic aim	Formulate overall aims & objectives for dietetic intervention	
Dietetic plan & implementation	Formulate 'SMART' (specific, measurable, achievable, relevant & time-bound) based patient-centred goals for nutritional intervention & support where appropriate	
Monitoring, evaluation & review	Set review date with patient, to assess effectiveness & compliance with dietetic recommendations, & review accordingly	Routine use of outcomes measures to assess & evaluate effectiveness of interventions

*Denotes ideal body weight. †Denotes body mass index (BMI) of 18.5–30 kg/m^2. ‡Denotes BMI of 18.5–30 kg/m^2. Adjust for obesity (use 75 per cent value for BMI over 30 kg/m^2; 65% value for BMI over 50 kg/m^2; start at upper end of range for BMI less than 18.5 kg/m^2 and monitor regularly). BMI = body mass index; HNC = head and neck cancer; MDT = multidisciplinary team; SLT = speech and language therapy; ESPEN = European Society for Parenteral and Enteral Nutrition; BDA = British Dietetic Association

Equations may be less accurate, and may be inadequate, for patients who are severely malnourished or morbidly obese. Therefore, it is essential to monitor anthropometric changes to ensure adequacy.[300]

Previous guidance recommended 25–35 kcal/kg, aiming for at least 30 kcal/kg. Updated European Society for Parenteral and Enteral Nutrition ('ESPEN') guidance recommends 25–30 kcal/kg.[287] It is important to note that this recommendation is for all cancer diagnoses, and may not be accurate for head and neck cancer patients, where equations often underestimate requirements.[300] Thus, it is recommended that estimated requirements for head and neck cancer patients currently undergoing treatment should start at 30 kcal/kg, and increase as required, as radiotherapy with or without chemotherapy and surgery can increase energy requirements significantly. Alternatively, the British Dietetic Association Parenteral and Enteral Nutrition Group head and neck cancer guidelines can be used, with a physical activity level of 1.4, as this gives similar results to previous guidelines.[302]

Vitamins and minerals should be provided as per daily recommendations, unless considered deficient. Particular attention should be given to patients on long-term home enteral feeding and ensuring nutritional completeness of enteral feed.

Refeeding syndrome

Refeeding syndrome consists of metabolic disturbances that occur as a result of the reintroduction of nutrition (namely carbohydrates) to patients who are severely malnourished. Head and neck cancer patients may be at a high risk of refeeding syndrome, and it can occur irrespective of nutrition route.[303]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Refeeding syndrome is characterised by hypophosphataemia, hypokalaemia and hypomagnesaemia, as well as abnormal sodium and fluid balance, changes in glucose, protein and fat metabolism, and thiamine deficiency.[302,303]

Management for refeeding syndrome includes the gradual reintroduction of nutrition, supplementation of thiamine/B vitamins, and monitoring, with or without replacement of electrolytes. Latest guidance from the American Society of Parenteral and Enteral Nutrition ('ASPEN') have been included (Tables 8 and 9), but clinicians should also be guided by locally agreed policies for identification, avoidance and management. Identification and management will differ for paediatric patients; guidance is available from the American Society of Parenteral and Enteral Nutrition.[303]

Nutrition support

Nutrition support should be considered where malnutrition is diagnosed following screening and assessment, to optimise nutritional status. There are three main methods of nutrition support: oral, enteral and parenteral. Parenteral nutrition is rarely used in head and neck cancer, but should be considered if clinically indicated e.g. chyle leak, post-operative ileus, no enteral access route.

Oral nutrition support

Oral nutritional support aims to address deficiencies and minimise further nutritional compromise. Nourishing dietary advice including food-first fortification should be recommended, but may not meet the nutritional deficit alone because of the impact of disease and treatment. In order to meet these deficits, more intensive support such as nutritionally complete oral nutritional supplements can also be prescribed. There are a wide variety of products available, and choice will depend on patient preference, compliance and local policy.

Enteral nutrition

Enteral feeding is often required to support patients in meeting their nutritional requirements, to prevent weight loss, and to maintain good nutritional status on a short- and long-term basis. Enteral feeding tubes include the nasogastric tube, nasojejunal tube, orogastric tube, oesophageal-fistulae tube, gastrostomy tube (with or without jejunal extension) and jejunostomy tube. The type of tube placed should account for tumour type and size, treatment plan, anticipated length of enteral feeding, and patient choice, with patients being included in the decision-making process.[304]

The most common approaches for head and neck cancer patients with tube feeding in the community are prophylactic gastrostomies and reactive nasogastric tubes. The impact of tube type and timing in head and neck cancer is controversial, leading to variation in practice. Controversy exists because of a lack of consensus on whether a prophylactic or reactive approach leads to improved patient outcomes.

Prophylactic approaches mainly consist of gastrostomy placement prior to head and neck cancer treatment where it is likely that enteral feeding will be required for a long-term period. 'Long-term' is not always well defined; within the UK, the National Institute for Health and Care Excellence (NICE) suggests gastrostomy tubes should be considered when enteral feeding is required for more than four weeks.[288] The advantages of prophylactic gastrostomy include improved nutritional outcomes and quality of life, in addition to reduced incidences of malnourished patients, hospital admissions or treatment interruptions when compared with reactive feeding approaches.[305] The disadvantages include the risk that some tubes are not used,[306] but patient compliance and appropriateness of decision-making for tube placement in such studies are unclear. Furthermore, it has been argued that prophylactic gastrostomies lead to poorer swallowing outcomes related to prolonged tube use. These conclusions are limited because of a lack of high-quality studies including a nutritional outcome analysis. Recent studies have not shown a relationship between long-term swallowing dysfunction and prophylactic gastrostomy.[307]

Gastrostomy placement is generally considered a safe procedure, but can result in complications; however, major complications are rare. Placement can be endoscopic, radiological or surgical, and no nationally agreed selection criterion on placement method currently exists. All patients should be screened and assessed for suitability and optimal method,

Table 8. Refeeding syndrome identification for adults*

Risk identification	Moderate risk: 2 risk criteria needed	Significant risk: 1 risk criterion needed
BMI	16–18.5 kg/m[281]	<16 kg/m[281]
Weight loss	5% in 1 month	7.5% in 3 months; or >10% in 6 months
Caloric intake	None or negligible oral intake for 5–6 days; or <75% of estimated energy requirement for >7 days during an acute illness or injury; or <75% of estimated energy requirement for >1 month	None or negligible oral intake for >7 days; or <50% of estimated energy requirement for >5 days during an acute illness or injury; or <50% of estimated energy requirement for >1 month
Abnormal prefeeding serum potassium, phosphorus or magnesium concentrations†	Minimally low levels or normal current levels with recent low levels necessitating minimal or single-dose supplementation	Moderately or significantly low levels, or minimally low or normal levels with recent low levels necessitating significant or multiple-dose supplementation
Loss of subcutaneous fat	Evidence of moderate loss	Evidence of severe loss
Loss of muscle mass	Evidence of mild or moderate loss	Evidence of severe loss
Higher-risk co-morbidities‡	Moderate disease	Severe disease

*American Society of Parenteral and Enteral Nutrition ('ASPEN') consensus criteria for identifying adult patients at risk for refeeding syndrome, adapted and reproduced with permission.[303] †Please note electrolytes may be normal despite total body deficiency, which is believed to increase the risk of refeeding syndrome. ‡These include: acquired immunodeficiency syndrome; chronic alcohol or drug use disorder; dysphagia and oesophageal dysmotility (e.g. eosinophilic oesophagitis, achalasia, gastric dysmotility); eating disorders (e.g. anorexia nervosa); food insecurity and homelessness; failure to thrive, including physical and sexual abuse and victims of neglect (particularly children); hyperemesis gravidarum or protracted vomiting; major stressors or surgery without nutrition for prolonged periods of time; malabsorptive states (e.g. short-bowel syndrome, Crohn's disease, cystic fibrosis, pyloric stenosis, maldigestion, pancreatic insufficiency); cancer; advanced neurological impairment or general inability to communicate needs; post-bariatric surgery; post-operative patients with complications; prolonged fasting (e.g. individuals on hunger strikes, anorexia nervosa); refugees; protein malnourishment. BMI = body mass index

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 9. Refeeding syndrome management for adults*

Aspect of care	Recommendations
Initiation of calories	Initiate with 100–150 g of dextrose or 10–20 kcal/kg for first 24 hours; advance by 33% of goal every 1–2 days. This includes enteral & parenteral glucose
	In patients with moderate to high risk of refeeding syndrome, with low electrolyte levels, consider holding the initiation or increase of calories until electrolytes are supplemented &/or normalised
	Initiation or increase of calories should be delayed in patients with severely low phosphorus, potassium or magnesium levels, until corrected
	Consider infusing calories from IV dextrose solutions & medications in dextrose in the levels shown above, &/or initiated with caution in patients at moderate to severe risk for refeeding syndrome. If a patient has received significant amounts of dextrose for several days, from maintenance IV fluids &/or medications in dextrose, & has been asymptomatic with stable electrolytes, calories from nutrition may be reintroduced at a higher amount than recommended above
Electrolytes†	Check serum potassium, magnesium & phosphorus before initiation of nutrition
	Monitor every 12 hours for first 3 days in high-risk patients. May be more frequent based on clinical picture
	Replete low electrolytes based on established standards of care
	If prefeeding levels are normal, no recommendation can be made regarding whether prophylactic dosing of electrolytes should be given
	If electrolytes become difficult to correct or they drop precipitously during nutrition initiation, decrease calories or grams of dextrose by 50%, & advance dextrose or calories by approximately 33% of the goal every 1–2 days based on clinical presentation. Recommendations may be changed based on practitioner judgment & clinical presentation; cessation of nutrition support may be considered when electrolyte levels are severely &/or life-threateningly low or dropping precipitously
Thiamine & multivitamins†	Supplement thiamine 100 mg before feeding or before initiating dextrose-containing IV fluids in patients at risk
	Supplement thiamine 100 mg/day for 5–7 days or longer in patients with severe starvation, chronic alcoholism, or other high risk for deficiency &/or signs of thiamine deficiency
	Routine thiamine levels are unlikely to be of value
	Multivitamin injectable is added to parenteral nutrition daily, unless contraindicated, as long as parenteral nutrition is continued. For patients receiving oral or enteral nourishment, add complete oral or enteral multivitamin once daily for 10 days or greater, based on clinical status & mode of therapy
Monitoring & long-term care†	Recommend vital signs every 4 hours for first 24 hours after initiation of calories in patients at risk
	Cardiorespiratory monitoring is recommended for unstable patients or those with severe deficiencies, based on established standards of care
	Daily weights with monitored intake & output
	Evaluate short- & long-term goals for nutrition care daily during first several days until patient is deemed stabilised (e.g. no requirement for electrolyte supplementation for 2 days), & then based on institutional standards of care

*American Society of Parenteral and Enteral Nutrition ('ASPEN') consensus recommendations for avoidance and treatment of refeeding syndrome in at-risk adults, adapted and reproduced with permission.[303] †Management will depend on local refeeding syndrome guidelines and policies; thus, these recommendations should be used as a general guide only. IV = intravenous

accounting for local resources and policy. Endoscopic placement is generally associated with fewer complications compared to radiological gastrostomy; however, the former may be contraindicated in head and neck cancer (e.g. tumour location, trismus), and gastrotomy tubes are often retained by an internal bumper which requires endoscopic removal.[308] Radiologically placed tubes are usually retained with a balloon filled with water, which can be deflated and removed at bedside. This is advantageous for enabling prompt removal, but corresponds with an increased risk of unintentional tube dislodgement.

Reactive approaches involve the placement of a gastrostomy or nasogastric tube during or after treatment. Advantages of this approach include avoidance of: the risk of placing a tube that may not be used and gastrostomy-related complications. Nasogastric tubes have the advantage of being quick to insert and remove, and thus may remain in place for less time than a gastrostomy tube. Dietitians can be trained to become competent with tube insertions, to streamline services. Disadvantages of this approach include tube visibility, dislodgement, discomfort, fear or worry of tube displacement, pharyngeal irritation, and the public reaction, which has been reported negatively by service users.[304] In addition, complications associated with tube management in the community are not well documented (e.g. tube displacement requiring emergency department attendance, with or without tube replacement and chest X-ray).

In the UK, the discharge of patients with a nasogastric tube from the acute to community setting is not always permitted by some NHS trusts because of the potential risk of feeding into the lungs causing a 'never event'. This has resulted in many district nursing services refusing to support patients with nasogastric tubes in the community, but continuing to provide support for gastrostomy tubes. Therefore, patients who require a nasogastric tube at home are often expected to self-manage or have family support. This can complicate discharge planning, thus early identification is crucial. The NHS requires all patients discharged with a nasogastric tube to have an MDT-supported nasogastric tube risk assessment completed, and a care plan in place to assess suitability and mitigate any risks.[309] Success with prolonged nasogastric tube use (more than 28 days) in the community has been reported,[310] with some units developing out-patient nasogastric tube services, which is advantageous in reducing in-patient admissions.[311] These factors highlight the importance of dietetic pre-treatment appointments to aid informed decision-

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

making on feeding options, accounting for individualised needs and preference at the point of diagnosis.[312]

In summary, the evidence base remains inconclusive, with insufficient evidence to suggest an optimal feeding route.[312–314] Guidelines have been developed based on predictors of prolonged tube use to aid clinicians with appropriate decision-making for placing prophylactic gastrostomy tubes. These include overall clinical stage, tumour site, clinical tumour (T) and nodal (N) stage, and patient age.[315,316] The NICE guidelines suggest individualised multidisciplinary decision-making at diagnosis, accounting for predictors as detailed in Table 10.[317]

There are a wide variety of enteral nutrition products available, and the volume and type will depend upon the patient's requirements, tolerance and local contractual agreements.[288]

Monitoring nutrition support

The monitoring of enteral feeding regimens is essential given issues of: potential inaccuracies of nutritional requirement equations, compliance, and tolerance. Dietitians should be informed by any member of the MDT if signs of intolerance are reported, to ensure an optimal regimen is in place, and adjustments made accordingly.

On treatment

Nutritional considerations during surgery

Pre-operative nutrition

Inadequate oral intake for more than 14 days is associated with a higher mortality. These patients should receive nutrition support prior to major surgery. Delaying surgery to achieve this may be necessary but has to be weighed against the risk of delaying treatment.[318]

Enhanced recovery after surgery

Surgery is associated with reduced muscle function, prolonged fatigue, poor wound healing, increased morbidity and a longer length of hospital stay.[319] Enhanced recovery after surgery protocols help ameliorate these effects; for example, increased carbohydrate utilisation leads to an anabolic state promoting enhanced recovery, which is well established in many centres. Nutritional interventions include pre-operative carbohydrate loading of 100 g carbohydrate the night before surgery and 50 g carbohydrate 2 hours before surgery. In order to avoid harm, carbohydrate loading should not be given for patients with uncontrolled diabetes or gastroparesis, and is unlikely to be beneficial for those with type 1 diabetes.[320] Further information can be found in the 'Patient preparation for treatment and enhanced recovery' chapter.

Table 10. Gastrostomy selection criteria in head and neck cancer*

MDT to assess at diagnosis & take following into account:
Performance status & social factors
Nutrition status (weight loss, high or low BMI, ability to meet estimated nutritional requirements)
Tumour stage
Tumour site
Pre-existing dysphagia
Impact of planned treatment (such as radiation treatment volume & dose-fractionation, concomitant chemotherapy, & extent & site of surgery)

*Adapted from National Institute for Health and Care Excellence with permission.[317] MDT = multidisciplinary team; BMI = body mass index

Post-operative nutrition

Early post-operative enteral tube feeding (within 24 hours) should be commenced in patients if early oral nutrition cannot be initiated.[321] Early oral feeding in the absence of contraindications after primary total laryngectomy and free-flap surgery has been reported to reduce length of stay, without increasing peri-operative complications. Further research is required to support the uptake of this approach, and studies vary in their definition of 'early oral feeding'.[270,322]

Chyle leaks

If a chyle leak is suspected, it can be confirmed by testing for triglycerides and chylomicrons. Nutritional interventions (Table 11) are often used alongside medical options, such as somatostatin analogues, pressure dressings and suction drainage. (Further information can be found in the 'Complications of treatment' chapter.)

Radiotherapy

Dietary counselling during radiotherapy for head and neck cancer patients with nutrition support is recommended to manage treatment-induced toxicities (e.g. mucositis, pain, increased secretions, odynophagia, dysphagia), to prevent weight loss (Table 12). Significant weight loss (more than 10 per cent) cannot be completely prevented by nutritional counselling and intervention alone,[301] and can lead to re-planning of radiotherapy fields and interruptions in treatment. Patients should be reviewed by a dietitian at least once a week during radiotherapy, and some centres offer twice-weekly review.

Patients should be encouraged with optimising the nutrition and tolerance of oral diet for as long as safely possible during radiotherapy, in conjunction with speech and language therapy advice. Enteral feeding should be considered if treatment impacts on swallowing and the ability to meet full nutritional requirements orally for weight maintenance. The timing and type of enteral feeding is controversial (discussed in the 'enteral feeding' section). The choice of tube should be MDT led, and should account for local resources, patient preference and high-risk factors of prolonged tube use (oral plus bilateral chemoradiotherapy, midline oropharyngeal/nasopharyngeal/pharyngeal plus chemoradiotherapy, dysphagia and/or severe malnutrition at presentation).[317] Patients should be counselled on an individualised basis, with the risks and benefits of both reactive and prophylactic approaches discussed before treatment.

Post-treatment care

All head and neck cancer patients should be reviewed in the first three months post radiotherapy or major surgery to prevent decline in nutritional status, and thereafter on an individual basis. The goal of dietetic input post treatment is to reduce reliance on enteral feeding and/or nutritional supplements if possible, whilst assisting a return to healthy eating, accounting for possible chronic changes, e.g. texture modification (Table 13). It should be noted that patients' experiences after treatment will vary greatly, with some returning to pre-treatment function rapidly and others needing long-term input.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 11. Nutritional management recommendations for surgery, including suspected and confirmed chyle leak cases

Essential	Desirable
Pre-surgery	
– Commence nutritional support if malnutrition present or patient at risk of malnutrition, without delay (evidence-based recommendation (R))	– Consider pre-operative admission for nutrition support ± enteral feeding for 7–14 days prior to major surgery for patients diagnosed with severe malnutrition using a validated assessment tool (good practice point (G))
– ERAS protocol in place with carbohydrate loading, for all patients undergoing major HNC surgery (100 g carbohydrate the night before surgery & 50 g carbohydrate 2 hours before surgery), excluding patients who have uncontrolled diabetes or gastroparesis (G)	
Within 72 hours of surgery	
– Initiate enteral feeding within 24 hours of surgery unless contraindicated & in patients where oral feeding cannot be established (R)	– Implement H&N protocols for rapidly increasing enteral feed to target rates (G)
– Patients should be seen for assessment & implementation of enteral feeding regimen (R)	– Consider early oral feeding after primary laryngectomy (R) & flap surgery (G), as guided by ERAS protocols & in the absence of any contraindications
– Collaboration with MDT members e.g. surgeons & SLTs on when & what type of oral intake can be resumed & progressed (G)	
During acute in-patient stay	
– Chyle leaks to be confirmed by analysis of drainage fluid. Commence medium chain triglycerides or low-fat diet, as required & using appropriate enteral feeds or oral supplement products (R). Consider parenteral nutrition in severe cases (G)	
– Consider enteral feeding if oral intake not adequate to meet nutritional requirements (R)	– Regular attendance to surgical & oncological ward rounds, to optimise management & early discharge planning, especially for patients requiring home enteral feeding (G)
– Use standard 1.0–1.5 kcal/ml polymeric feed ± fibre unless otherwise contraindicated (G)	

ERAS = enhanced recovery after surgery; HNC = head and neck cancer; H&N = head and neck; MDT = multidisciplinary team; SLT = speech and language therapists

Table 12. Recommendations for management during radiotherapy

Essential	Desirable
Pre-radiotherapy	
– Pre-treatment dietetic assessment & counselling on tube feeding options during treatment, including prophylactic gastrostomy as per locally agreed guideline criteria (evidence-based recommendation (R))	– Joint pre-treatment appointments with SLTs & clinical nurse specialists (good practice point (G))
	– Dietetic-led gastrostomy & NG tube pathways (G)
During radiotherapy	
– Weekly dietetic review & intervention for all patients receiving radiotherapy, to monitor & optimise nutritional status, prevent weight loss, & minimise treatment interruptions (R)	– Twice-weekly dietetic review (G)
	– Out-patient NG tube service to help reduce on-treatment acute admissions for enteral feeding, if appropriate, in locally agreed pathways & supporting infrastructure (G)
– MDT approach in encouraging patient adherence to analgesia, & mouth care plan to support oral intake (R)	– Support for non-medical supplementary prescribing post-graduate courses, training & supervision for HNC dietitians working in radiotherapy services, to assist with prescribing medications for symptom management (e.g. analgesics, laxatives, anti-emetics, PPIs) affecting ability to tolerate nutrition within scope of practice & patient's clinical management plan (see extended scope section) (G)
– Monitor anthropometric measurements regularly & monitor weight at least bi-weekly (R)	– Access to bioelectrical impedance scales to measure sarcopenia, e.g. fat free mass changes during treatment & hand grip strength (G)

SLT = speech and language therapist; NG = nasogastric; MDT = multidisciplinary team; HNC = head and neck cancer; PPI = proton pump inhibitor

Head and neck cancer patients can experience treatment-related side effects in the short and long term that may impact quality of life and functional status. These include xerostomia, dysphagia, trismus, dental problems, difficulty chewing, taste alterations and mucositis.[323] Patients may need ongoing nutrition support to manage these symptoms, and weight loss has been shown to continue for up to a year post treatment.[324]

Late effects of treatment such as progressive dysphagia, pharyngoesophageal stenosis and osteoradionecrosis can lead to ongoing poor nutritional intake, and food avoidance may lead to vitamin and mineral deficiencies.[325,326] This may necessitate further dietetic input, and nutrition screening should continue in order to identify these patients if they have been previously discharged from dietetics.[324]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 13. Post-treatment care recommendations

Essential	Desirable
Offer dietetic support & intervention for 3 months post treatment (with minimum fortnightly review for 6 weeks post radiotherapy) & as required thereafter (evidence-based recommendation (R))	Joint rehabilitation appointments with SLT, to support acute toxicity phase & build tolerance with oral diet, whilst reducing enteral tube feeding dependency where indicated or appropriate (good practice point (G))
Monitor weight & adjust nutritional provision as required, as estimated nutritional requirements may remain elevated post treatment (R)	Development of a specialised late effects clinic, to reassess treatment effects. Ideally, this should be completed alongside SLT (G)
Dietary counselling & education should be given, highlighting that oral intake is unlikely to return to normal following treatment, including strategies on dietary modifications, coping mechanisms & avoiding nutrient deficiencies longer term (G)	Patients no longer at risk of malnutrition should be offered cancer prevention & healthy eating advice. This should encourage physical activity as per national recommendations, if appropriate (G)
Patients should be reviewed until nutritionally stable following treatment completion, to reduce tube dependency, prevent weight loss, provide psychological support with eating & drinking, & maintain quality of life (G)	QoL, nutrition & swallowing measured at regular intervals (G)
Dietitians should encourage good oral hygiene to prevent dental caries & thrush (G)	Access to services to support patients in the community on long-term enteral feeding, e.g. support groups such as PINNT (G)
Nutritional screening to identify post-discharge patients who may benefit from full dietetic assessment because of late effects. Early referral back to dietetic services if recurrence is affecting nutritional status (R)	

SLT = speech and language therapist/therapy; QoL = quality of life; PINNT = Patients on Intravenous & Nasogastric Nutrition Therapy

In the absence of disease recurrence or late effects, cancer survivors who are no longer at risk of malnutrition should be offered healthy eating and physical activity advice, to prevent long-term morbidity. This should be tailored on an individualised basis given the complexity of head and neck cancer.[287]

Palliative care

Patients may be offered palliative chemotherapy, radiotherapy or immunotherapy to reduce symptoms caused by cancer. Patients should be nutritionally assessed early in this pathway, and the aim of nutritional interventions should be to maintain quality of life and reduce the symptoms, with early anticipation of any deterioration (Table 14). Dietitians should discuss the advantages and disadvantages of artificial feeding with patients and their family, as nutrition is likely to be affected by treatment and disease progression.

Palliative care patients can develop symptoms as a result of the tumour, and may also be suffering from the long-term side effects of previous cancer treatment.[327] Dietitians should work collaboratively with other MDT members to ensure that informed decisions are made regarding palliative and end-of-life care, including the appropriateness of commencing artificial feeding and/or gastrostomy tube placement within the context of risk, benefit and prognosis.[328] Further information is discussed in the palliative care chapter.

Future aspects and important research questions

Immunonutrition

Immune-enhanced nutrition are feeds containing amino acids, nucleotides and lipids. The evidence base for outcome measures including length of stay, wound infection, mortality and feed tolerance is lacking.[329] A systematic review of cancer patients receiving immunonutrition[330] has suggested a reduced risk of post-operative infectious complications, a decreased risk of anastomotic leakage and a reduced hospital stay. Current studies are low in quality, at a high risk of bias and vary in regard to supplemental regimens, and thus should be interpreted with caution. Further high-quality and larger studies are required to justify routine usage.[331]

Immunotherapy

Immunotherapy is a fast-emerging treatment used for people with head and neck cancer. The nutritional management of

Table 14. Palliative care management recommendations

Essential	Desirable
Access to a dietitian as part of palliative care team, because of presence of dysphagia & malnutrition within this population (evidence-based recommendation (R))	Where possible, joint appointments with other MDT members & patient's family should be undertaken (good practice point (G))
Early referral back to dietetic services if recurrence is affecting nutritional status (R)	
Goals of nutritional intervention guided by prognosis, & maximising comfort & QoL on patient-centred basis (R)	
Clarify patient's understanding of prognosis, palliative treatment & disease progression effects on functional outcomes, & how this may affect QoL (G)	
Access to enteral feeding where appropriate. Patients who are likely to deteriorate in terms of ability to take adequate nutrition, & who have prognosis of ≥3 months, should be considered for a gastrostomy or long-term enteral feeding tube (G)	
Risks & benefits of gastrostomy insertion discussed, with consultation from MDT members, nutrition support teams, radiology & endoscopy (R)	

QoL = quality of life; MDT = multidisciplinary team

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 15. Future considerations for dietitians working in head and neck cancer services

Essential	Desirable
Specialist dietitians working within PBT services to develop, monitor & evaluate dietetic service pathways across organisation boundaries, to ensure seamless delivery of dietetic care, from diagnosis to rehabilitation or discharge (good practice point (G))	Specialist dietitians working within PBT, with dedicated non-clinical time for research & service development (G)
Dietetic input into PBT services should reflect existing IMRT services, with ≥1-weekly dietetic review or intervention until further research on treatment effects on nutritional outcomes have been established & evaluated (G)	Routine evaluation of patient's experience with telehealth appointments (G)
Offer telehealth appointments (e.g. virtual, video, telephone) to patients where appropriate (G)	Collection of dietetic & patient-related outcomes, e.g. SGA, PG-SGA (G)
	Support for dietitians to become advanced clinical practitioners & extend their scope of practice within their MDTs, e.g. non-medical supplementary prescribing (see radiotherapy section) (G)

PBT = proton beam therapy; IMRT = intensity-modulated radiation therapy; SGA = Subjective Global Assessment; PG-SGA = Patient-Generated Subjective Global Assessment; MDT = multidisciplinary team

complications and individualised assessment are required. Further research is needed in this area.

Proton beam therapy

Proton beam therapy has recently been implemented within NHS services on two UK sites (University College London Hospital and The Christie in Manchester) following the strategic outline case published by the Department of Health. Eligibility is via a national panel, and dietitians are essential members of the MDT for managing patients during their treatment pathway.

Emerging research suggests that patients undergoing proton beam therapy may have reduced toxicity related side effects affecting ability to take adequate nutrition, and are therefore likely to have better nutritional outcomes and reduced tube dependency.[332] The Torpedo trial is currently underway, and aims to compare proton beam therapy with intensity-modulated radiotherapy in regard to late treatment-related toxicities in patients with locally advanced oropharyngeal squamous cell carcinoma. Patient-reported toxicity, feeding tube dependence and severe weight loss at 12 months post treatment will all be measured.[125]

Telehealth

The delivery of dietetic services is changing, as indicated by the NHS 'Long Term Plan', enhancing the use of digital technologies through the provision of new service models supported by the Royal College of Physicians (2018).[283,333,334] The unprecedented coronavirus disease 2019 pandemic has accelerated this, with rapid adoption of telehealth across the NHS.

Telehealth can assist in optimising healthcare resource utilisation and efficiency, whilst enabling improved flexibility, patient satisfaction and experience. However, limitations include access to equipment from service users, especially in older and low-income populations.[335]

Encouraging results have been reported that support the use of virtual clinics for head and neck cancer patients, from prehabilitation through to post treatment and supportive care.[336] Feasibility studies have investigated a home-based telehealth model for the delivery of speech and language therapist and dietetic reviews.

Extended scope of practice

There is opportunity for dietitians to become advanced clinical practitioners and extend their scope of practice within their MDTs (Table 15). Some options include post-graduate training for non-medical supplementary prescribing, assisting with enteral tube placement and care, and prehabilitation. The agreed scope of practice should be documented formally within job plans, with a clear framework, mentorship and supervision in place.

Non-medical supplementary prescribing may include reviewing symptoms of acute radiotherapy toxicity, alongside their impact on nutritional intake, and prescribing medication where appropriate. This aims to alleviate side effects within the agreed patient clinical management plan, whilst liaising closely with the medical team.[334]

Future research

Further research questions associated with the nutrition management of head and neck cancer include:

- The reliability and validity of dietetic assessment and monitoring tools that can easily be adapted to virtual consultations
- Standardised outcome measures that can be obtained virtually
- Patient satisfaction and experience with telehealth
- Use of imaging technology (e.g. positron emission tomography/CT) to measure body composition change
- Use of diet counselling skills (e.g. cognitive based therapy) to improve patient outcomes
- Investigation of diet-based management of taste and smell training to improve taste changes
- High-quality studies to investigate the routine use of immunonutrition in head and neck cancer

Chapter 10: Speech, voice and swallowing rehabilitation for head and neck cancer

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Key points

- Patients with speech, voice or swallowing dysfunction should be identified, assessed, and offered rehabilitation by a speech and language therapist with specialist skills.
- All multidisciplinary teams (MDTs) should have rehabilitation patient pathways covering all stages of the patient's journey, including multidisciplinary and pre-treatment clinics, with clear mechanisms for re-entry.
- Rehabilitation needs to begin early in the care pathway, involving comprehensive evaluation and tailored evidence-based interventions, from pre-treatment and including end-of-life care.
- Instrumental evaluation is integral to assessment and rehabilitation pathways given the complex relationships between function and altered anatomy and pathophysiology in head and neck cancer patients.
- Services should strive for robust collection of functional outcome measures at specified time points to incorporate clinician-rated and patient-reported tools.
- Healthcare professionals need to remain vigilant for signs of late treatment effects where the downward trajectory of speech, voice and swallowing function, and airway compromise pose complex challenges and involve careful MDT management.
- Although speech and language therapists hold a key role, MDT discussion is essential to attain optimal patient outcomes. This may involve collaboration with other healthcare professionals, as appropriate, to optimise care, e.g. oral hygiene and laryngectomy stoma care.
- The support of carers is an important part of the speech and language therapist's role when gathering and delivering information, developing a tailored rehabilitation package, and/or guiding patients in a decision-making process.
- Patient involvement in decision-making is crucial, with high importance being attributed to functional outcomes when weighing up treatment and management options. Speech and language therapists engage in eliciting patient priorities and values, and give realistic information about alterations to function and the impact on daily living and health.
- Speech and language therapists are involved in generating and contributing towards research and audit for improved patient outcomes and service delivery.
- Clear pathways for access and re-referral to speech and language therapists need to be in place, with excellent communication between central and locality-based services with a robust training and supervision programme for specialist knowledge and skill development and maintenance.

Introduction

Head and neck cancer treatment can have a major deleterious impact on communication and swallowing function. Poor functioning can result in low mood, distress, reduced quality of life, and difficulties returning to work and socialising.[337] Furthermore, dysphagia can have serious medical consequences, such as malnutrition, dehydration and aspiration-associated pneumonia.[338] A conservative estimate of dysphagia prevalence is between 50 and 60 per cent, with evidence of further deterioration over time.[339,340] The presence of dysphagia extends hospital stay and increases associated costs by 60 per cent.[341] Emerging evidence suggests that early speech and language therapist and dietetic intervention may contribute to reduced health and patient costs for some head and neck cancer patients.[342,343]

The following guidelines cover the provision of voice, speech and swallowing services, delivered by speech and language therapists with specialist competencies. They are divided into key timepoints across the patient journey, with a dedicated section for laryngectomy rehabilitation. Each section is separated into recommendations that are considered 'essential' and 'desirable'. The delivery and measurement of outcomes associated with speech and language therapy is an essential component of delivering effective and high-quality services; recommendations for the selection and timing of measures are described in the final section.

In addition to these guidelines, the following resources provide further support to both speech and language therapists and patients with head and neck cancer:

- Macmillan head and neck cancer information and support, in: https://www.macmillan.org.uk/cancer-information-and-support/head-and-neck-cancer
- Maggie's Centres, in: https://www.maggies.org
- Cancer Research UK, in: https://www.cancerresearchuk.org
- Head & Neck Cancer UK, in: http://hancuk.org
- The Swallows Head & Neck Cancer Support Group, in: https://theswallows.org.uk/ (@swallowsgroup, X, formerly Twitter)
- Saving Faces UK, in: https://savingfaces.co.uk
- National Association of Laryngectomee Clubs, in: https://www.laryngectomy.org.uk

Pre-treatment

The majority of individuals undertaking head and neck cancer treatment are likely to experience some level of difficulty or alteration to their swallowing and/or communication during their cancer care journey, with as many as 60 per cent presenting with problems at diagnosis.[344] The impact of oncological interventions on function and the likely trajectory of recovery can reasonably be predicted,[345,346] which therefore offers an opportunity for early intervention. A pre-treatment consultation should thus include informational counselling about the upcoming cancer treatment, and about the impact on swallowing and communication, and, where indicated, could provide a window for prehabilitation that may include prophylactic swallowing exercises (Table 1).[347]

Early post-operative phase

Surgery results in loss of tissue, with changes to the anatomy and structural relationships. Post-operative voice, speech and swallowing impairments can change over time, with oedema and/or pain being more prevalent in the early post-operative period, and atrophy or scarring with a reduced range of motion being more common in the long term.[348] Surgery can also result in nerve damage, leading to motor and sensory deficits. The severity of voice, speech and swallowing

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Recommendations for MDT meetings and combined head and neck clinic

Essential	Desirable
Attendance by at least 1 SLT as core MDT member Provide specialist input to inform treatment decision-making, especially regarding functional outcomes	Offer further out-patient appointment in conjunction with clinical nurse specialists & allied healthcare professionals, for: information-giving; assessment of baseline function; decision regarding enteral feeding support
Attend consultation with surgeon or oncologist if appropriate	Discuss prophylactic swallowing exercises & manoeuvres, with voice care advice as indicated
Be an advocate for patients who may feel overwhelmed by the diagnosis & the large volume of information provided	
All HNC patients with existing or anticipated swallowing &/or communication problems should be offered pre-treatment SLT consultation, regardless of treatment modality	
Check patient's understanding of diagnosis, planned treatment, & their expectations of functional changes & outcomes. Provide further information & clarify as appropriate	

MDT = multidisciplinary team; SLT = speech and language therapist; HNC = head and neck cancer

impairment depends on factors such as tumour site, the volume resected and the nature of the reconstruction. The inevitable functional impairments coupled with aesthetic changes, in addition to activity limitations and participation restrictions, can have a profound psychological impact on the patient. Rehabilitation, including very early engagement and interaction, can be both healing and therapeutic for patients (Table 2).[349]

During radiotherapy

Painful and uncomfortable mucositis side effects, xerostomia, dysgeusia, and increased secretions are frequently experienced by patients during radiation treatment. There is an increasing body of evidence investigating strategies introduced before or during radiation treatment to reduce the incidence and severity of dysphagia.[350,351] Patients are encouraged to continue to eat and drink throughout radiotherapy, where safe, avoiding periods of nil by mouth status.[348] On-treatment rehabilitation is generally provided in an MDT setting to ensure that analgesia and mouth care are optimised, to allow ongoing oral intake and exercises as indicated (Table 3).[352–354]

Rehabilitation following head and neck cancer treatment

Rehabilitation of swallowing should aim to optimise oral intake, reduce reliance on enteral feeding and supplements, and facilitate psychosocial adjustment. Studies support the use of exercises to improve swallowing function.[355–358] Postures such a chin tuck and head rotation can be effective in controlling bolus flow, to reduce or eliminate aspiration.[359] Manoeuvres including the super supraglottic swallow[360] and effortful swallow[361] can also be utilised to control specific aspects of the oropharyngeal swallow, improving function. The use of expiratory muscle strength training may improve airway protection in those with chronic radiation-induced aspiration.[362] Combining cognitive behavioural therapy with swallowing therapy has highlighted the importance of addressing the emotional, behavioural and cognitive components of dysphagia alongside the physical impairment.[363]

Voice can be impaired by both radiotherapy and chemotherapy,[364,365] and by laser surgery.[366] Phonatory changes as a result of head and neck cancer treatment may include reduced vocal intensity, impaired pitch, compromised breath support, as well as roughness, breathiness, hoarseness and vocal fatigue. Specific therapy techniques[367,368] utilised with non-cancer patients may be considered to enable the patient to achieve the optimum voice quality.

Speech may be impaired as a result of surgical resection, or chemoradiotherapy side effects such as xerostomia and trismus. Intelligibility will largely be dependent on the site of the lesion, the extent of the resection and the flexibility of tissue. In some instances, referral for dental or prosthetic enhancement may optimise communication and/or swallowing function (Table 4).

Table 2. Recommendations for early post-operative management

Essential	Desirable
Within 72 hours of surgery	
– Patients should be seen for communication, with or without swallowing review	– Patients should have documented MDT tracheostomy management & weaning plan
– Early & regular review to optimise communication	
– Early & regular review to support secretion management	
During acute in-patient stay	
– Following consent from surgical team, SLT should assess appropriacy for commencement of oral intake & communicate diet recommendations using IDDSI framework (https://iddsi.org/)	
– Provision of exercise regimen when surgical wound healed sufficiently, to maximise & optimise recovery	

MDT = multidisciplinary team; SLT = speech and language therapist; IDDSI = International Dysphagia Diet Standardisation Initiative

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Recommendations for management during radiotherapy

Essential	Desirable
Weekly review of patients receiving: ≥60 Gy to a defined clinical target volume in oral cavity or oropharynx, or neck levels Ia/b; or bilateral radiotherapy fields &/or concurrent chemotherapy Access to SLT for all patients identified with communication ± swallowing difficulties	Dietitian, clinical nurse specialists & radiographer should have set of screening questions regarding swallowing in absence of SLT
Encourage & support patients to avoid periods of being nil by mouth where appropriate & safe[353]	
MDT approach encouraging patient adherence to analgesia & mouth care plan, to support oral intake & prophylactic exercises throughout treatment[352]	

SLT = speech and language therapy/therapist; MDT = multidisciplinary team

Table 4. Recommendations for rehabilitation

Essential	Desirable
Patients with persisting communication & swallowing difficulties post-treatment should be seen within 4 weeks of completion or discharge following definitive treatment, for review of rehabilitation needs & intervention planning	Voice amplification options should be provided as appropriate
Tailored compensatory dysphagia therapy techniques, strengthening exercises, biofeedback & diet modification	Augmentative communication options, as required
All patients should have access to specific voice therapy techniques	
All patients should have access to communication rehabilitation including articulation therapy &/or indirect use of compensatory strategies	

Total laryngectomy

Laryngectomy surgery results in permanent anatomical and physiological changes that affect communication,[369] swallowing,[370,371] breathing,[372] olfaction[373] and appearance.[374] Intervention from speech and language therapy is essential along each stage of the pathway, from diagnosis to long-term management, to support individuals in reaching and adjusting to their new optimum functional potential (Table 5).

Late treatment effects

Progressive functional deterioration following treatment for head and neck cancer needs careful MDT assessment and management. Where disease recurrence is excluded, these symptoms are likely to represent 'late-stage' treatment effects. The gradual and insidious development over a period of time can make early identification of patients challenging,[375] but healthcare professionals need to remain vigilant. Education of the wider MDT and community teams is key, so they are alert to 'red flag' symptoms like chest infections, dehydration, weight loss and airway difficulties.

Patients may report increased swallowing difficulty, weight loss, recurrent chest symptoms, as well as speech, voice and breathing changes.[376,377] The sequelae can be devastating on both physical and emotional well-being,[339,378] as complex choices between airway, swallowing and voice functions can be required (Table 6).[379]

Palliative care

Patients with advanced incurable head and neck cancer have a high number and diverse range of complex symptoms. Difficulty eating and weight loss are some of the most frequently reported problems.[380,381] These symptoms can result in numerous hospital visits, which is particularly problematic with the centralisation of head and neck cancer services.

Early identification of functional changes is essential to providing high-quality and pre-emptive speech and language therapy services, with good communication between central and locality-based therapists and the wider palliative care team (Table 7).

Outcome measures

A combination of clinician- and patient-reported outcome measures should be collected at pre-determined time intervals. Systems should be developed to enable data to be collected, stored and protected in a robust manner. At a local level, data can be used for clinical purposes to: highlight rehabilitation needs for individuals; inform the MDT of functional outcomes post treatment; direct future service developments; and provide stakeholders with information regarding effectiveness. On a larger scale, quality data can identify trends in functional changes. This is especially relevant for new and emerging treatment regimens where gaps in understanding can be identified, providing direction for future research topics. Patient-reported outcome measures provide a subjective evaluation of symptom burden.[71] Quality of life patient-reported outcome measures are integral to a complete dataset, and can be collected by any member of the head and neck cancer MDT (Table 8).[382–398]

Important research questions

Over the next few years, results from national and international trials will further our knowledge on whether alterations to treatment modalities – including intensity-modulated radiation therapy versus dysphagia optimised intensity-modulated radiation therapy,[399] de-escalation of post-operative adjuvant (chemo)radiotherapy for oropharyngeal cancer,[400] intensity-modulated proton beam therapy[125] – impact on swallowing outcomes. Secondary analysis of these data will inform our

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 5. Recommendations for total laryngectomy

Essential	Desirable
Pre-treatment	
– Assessment & counselling regarding suitability for communication methods	– Patients should be offered pre-treatment visit with volunteer laryngectomee
Early post-operative rehabilitation	
– Offer regular SLT to facilitate adjustment to patient's new communication method	– Alongside MDT team, consider contrast swallow study for extended surgery patients, prior to commencing oral intake
– All patients should be considered for baseplate & HME rehabilitation. Commence early pulmonary rehabilitation via HME cassette use, within 24 hours of surgery if possible	
– All patients should complete stoma care competencies to independently manage & maintain a safe airway	
– Complete voice prosthesis cleaning competencies if a prosthesis is in place	
– Documented plan for post-operative eating & drinking	
– Registered with emergency services via 999 text service	
– Registered with a prescription delivery service for laryngectomy supplies e.g. brushes, HMEs	
Post-treatment rehabilitation	
– All patients should have SLT rehabilitation to reach maximum post-operative function for: (1) Communication (2) Swallowing (3) Pulmonary (4) Psychosocial adjustment	– Instrumental swallow evaluation, e.g. videofluoroscopy, air insufflation & FEES, to holistically problem solve swallowing & voice issues
– If not suitable for primary puncture, & if appropriate, offer assessment for secondary SVR	– Air insufflation to assess potential for SVR
– All SVR patients should be assessed & offered hands-free option if suitable	– Access to out-of-hours valve changing by SLT-trained nursing staff &/or ENT
– All SVR patients should complete self-management competencies for trouble-shooting & emergency management	– Patients should be provided with emollient for peristomal irritation
– All SVR patients should be offered a self-changing competency programme if appropriate	
– All patients should be provided with neck breather emergency card or bracelet	
– Monitor weekly during radiotherapy for the following: (1) Maintenance of adequate stoma size & safe, humidified airway (2) Voice prosthesis review & maintenance of functional communication (3) Peristomal skin review, & baseplate & HME management (4) Maintenance of swallow	

SLT = speech and language therapy; MDT = multidisciplinary team; HME = heat and moisture exchanger; FEES = fibre-optic endoscopic evaluation of swallowing; SVR = surgical voice restoration

Table 6. Recommendations for late effects of treatment

Essential	Desirable
Instrumental assessment because of known higher incidence of silent aspiration & complex pathophysiology	Specialist airway services referral
Tailored SLT intervention that aims to optimise & maintain function	Prehabilitation programmes prior to airway surgery

SLT = speech and language therapy

Table 7. Recommendations for palliative care

Essential	Desirable
Early & integrated access to SLT for palliative care relating to function	SLTs to be part of an integrated multidisciplinary palliative care HNC clinic
Clear pathways & sign-posting for referral & (re-)access to SLT services	SLTs to conduct regular 'check-ins' (remote or face to face) with patients with functional problems, according to patient & family needs
Clear sign-posting for rapid & timely access to local or central SLT services	

SLT = speech and language therapy/therapist; HNC = head and neck cancer

understanding of swallowing outcome measures. Findings may then be translated into treatment selection, improved shared decision-making tools and more accurate patient information.

Further work is indicated in the arena of speech and language therapy interventions, to include: exploration of novel technologies; investigation of specific time points, e.g. early post-operative and late effects of dysphagia; examination of defined populations, e.g. recurrent disease; and consideration of impairment, as well as the psychosocial sequelae of speech, voice and swallowing problems. It is also important to take a holistic view, being inclusive of the needs of carers. These

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 8. Recommendations for outcome measures

Essential	Desirable
Who	
– Patients planned for surgical or non-surgical treatment where an effect on speech, voice or swallow is anticipated	Patients referred because of late effects of treatment
When	
– Baseline – Early post-treatment (3–6 months) – Late post-treatment (6–12 months) or prior to discharge from SLT	– First contact post-treatment – 3 months post-completion of treatment (±4 weeks) – 12 months post-completion of treatment (±6 weeks) – Annually, as a way of monitoring functional status long-term
What	
– Voice (GRBAS scale)[382] – PSS-HN – Normalcy of Diet subscale[383] – Timed Water Swallow Test[384] – Speech, voice swallowing specific PROM	Selected measures according to clinical indication: *Patient-reported*: – Speech Handicap Index[385] – Voice Handicap Index[386] – MDADI[387] – Swallowing Outcomes after Laryngectomy questionnaire[388,389] *Clinician-rated*: – PSS-HN – Eating in Public subscale[383] – PSS-HN – Understandability of Speech subscale[383] – Functional Oral Intake Scale[390] – Maximum interincisal opening – TOMs[391] – Sunderland Tracheoesophageal Voice Perceptual Scale[392]
	Instrumental assessment of swallowing to include a rating scale: – Penetration Aspiration Scale[393] – DIGEST scale[394] – New Zealand Secretion Scale[395,396] – Yale Pharyngeal Residue Severity Rating Scale[397] – Patterson Edema Scale[398]
	Discharge report to contain final outcome measures, to act as reference for any patient referred back with late treatment effects

SLT = speech and language therapy; GRBAS scale = grade, roughness, breathiness, asthenia, strain scale; PSS-HN = Performance Status Scale for Head and Neck Cancer Patients; PROM = patient-reported outcome measure; MDADI = MD Anderson Dysphagia Inventory; TOMs = therapy outcome measures; DIGEST = Dynamic Imaging Grade of Swallowing Toxicity

interventions are defined as 'complex'; specifically, they have a number of interacting components, require new behaviours by those receiving the intervention and can have a variety of outcomes (e.g. patient-reported outcomes, measurements of physiology). For this reason, it is imperative that we understand issues of take-up, adherence and retention, in conjunction with testing for effectiveness.

The context of coronavirus disease 2019 has bought many challenges in the delivery of speech and language therapy services and rehabilitation. In response to this, future research needs to address:[401]

- Reliability and validity of non-invasive voice and swallowing screening and assessment tools, including those that can be conducted remotely
- Collection of standardised outcome measures, utilising digital technologies where possible

Service delivery and models of care need evaluation and further development as to how we can best support patients, the workforce and the National Health Service as a whole. Examples of priorities include:

- Provision of remote highly specialist care for our most vulnerable patients
- Models of telehealth for ENT speech and language therapy services
- Implementation of ENT speech and language therapist-led clinics and triaging

Conclusion

The majority of head and neck cancer patients incur changes to their speech, voice and swallowing function as a result of their disease and/or treatment. The role of the speech and language therapist can therefore be pertinent at any stage from presentation to palliation. Even in those patients with good survival outcomes, treatment sequelae can result in a return to the care of the speech and language therapist for management of complex late side effects. Working collaboratively with MDT colleagues will ensure patients receive and reach optimal potential. Consistent recording of an agreed set of outcome measures is needed to capture the burden of disease and thus inform services of existing patient needs, and identify gaps in understanding.

Chapter 11: Physiotherapy and exercise

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Key points

- The evidence base is of low-quality or very low-quality evidence, based on underpowered trials that are of high risk of bias.
- There is insufficient evidence to understand whether and how pre-operative rehabilitation should be provided to patients prior to neck dissection for head and neck cancer.
- There is low-quality evidence to justify the role of physiotherapy during the in-patient stay, and uncertainty over what exercise prescription should be offered to patients following neck dissection. Given the heterogeneity in the clinical presentation and functional impairments of these individuals, each patient should be assessed for the potential for post-operative complications, and exercises should be prescribed, tailored to the individual, which aim to prevent complications, optimise range of motion and symptom management, and enhance function.
- There is very low-quality evidence supporting the provision of exercises for people who undergo neck dissection following hospital discharge. There is uncertainty regarding what these exercises should be, but there is some promise that progressive resistance and strengthening exercises may offer benefit over simple range of motion exercises. There is evidence that out-patient physiotherapy may offer benefit over self-directed exercises, but this is based on underpowered trials.
- Further evidence is required to understand what components of treatment are required for this population, and to determine when they should be offered.
- There remains uncertainty as to whether some patients are at greater risk of poor outcome and would benefit more from physiotherapy. It is suggested that people who experience an intra-operative spinal accessory nerve injury may be at risk. Further evidence is required to determine whether this population should routinely be reviewed in out-patient physiotherapy, and explore whether certain patients are of lower risk of poor outcome and may be better managed through a self-directed approach.

Introduction

Head and neck cancer affects 700 000 people worldwide and over 11 000 in the UK annually.[402–404] Whilst the incidence of head and neck cancer is increasing, prognosis and survival in the UK continues to improve.[405,210] As such, the proportion of people living with the effects of this cancer and its treatment is increasing.

Post-operative complications are common following neck dissection.[406–409] Early complications can include shoulder pain and infection. Late complications may not appear until three months post treatment, and can continue to present over five years.[410,411] These late complications include shoulder movement dysfunction, and speech, swallowing and musculoskeletal problems, such as cervical contracture and muscle wastage.[410] Psychosocial complications are also highly prevalent post-operatively – predominantly fatigue, anxiety, depression, sleep disturbance and social isolation. Shoulder dysfunction and psychosocial complications are strongly associated with reduced return to work, with up to 50 per cent of patients ceasing working because of shoulder disability alone.[409,412]

The treatment pathway for head and neck cancer is complex given the varied anatomical sites of disease and the needs of the patient. Treatment for head and neck cancer requires treatment of the primary site, e.g. tonsil and larynx, as well as the neck. The neck is included when there is spread to the lymph nodes or a high probability of spread. Treatment involves surgery, radiotherapy or chemoradiotherapy, used as single treatments or in combination. Treatment of the neck requires a neck dissection or inclusion in the radiotherapy fields. Side effects from surgery can be significant, including swallowing problems, neck and shoulder girdle problems, difficulties sleeping, fatigue, and anxiety.[413] Accordingly, physiotherapy and exercise prescription are considered interventions that may manage these surgical complications.

There has been no agreement on what UK practice for head and neck cancer neck dissection rehabilitation consists of.[414] The role of physiotherapy in the in-patient and out-patient (post-discharge phase) broadly includes: reducing the risk of early or later complications, including respiratory, musculoskeletal and neurological complications; optimising normal recovery and healing; restoring functional and occupational capabilities; and maximising psychosocial enhancement and outcomes.

Accordingly, usual in-patient physiotherapy frequently commences day 1 post-operatively and involves:

- Early mobilisation to reduce risk of post-operative pulmonary complications
- Additional respiratory support for airway clearance and alveolar recruitment, as indicated
- Prescription of a personalised exercise programme, including neck and shoulder range of motion and progressive shoulder strengthening exercises, to minimise the risk of post-surgical contracture, optimise neck and shoulder function, and potentially help optimise movement of muscles used in swallowing
- Education on body positioning to reduce pressure and pull on the shoulder girdle, protection advice for the eyes and mouth in the presence of facial nerve palsy and pain management, and pacing activities to optimise levels of comfort and function
- Assessment of the spinal accessory nerve

Post-operatively, there remains, in the UK, less consistency of physiotherapy provision.[414] However, two key themes exist:

- Assessment of the need for post-discharge physiotherapy, to minimise complications such as reduced shoulder and neck range of motion, strength and function. This may be particularly important for those who have experienced an intra-operative spinal accessory nerve injury or have pre-operative reduced joint range of movement and function.
- Provision of advice and guidance (with or without supporting educational materials in the form of a paper-based leaflet or online) on post-operative self-management strategies, including exercise, pain management and return to work, and activities of daily living.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

As acknowledged, currently there is no national standard best practice for rehabilitation following head and neck cancer. Physiotherapy practice varies across the UK.[414] Rehabilitation, in the form of physiotherapy, is not routinely available to patients with head and neck cancer, in either in-patient or out-patient settings.[413] Nonetheless, rehabilitation was the focus of 1 of the 22 key questions in the 2016 National Institute for Health and Care Excellence (NICE) Clinical Guideline[415] on the management of head and neck cancer. The guideline recommends clinicians 'consider progressive resistance training for people with impaired shoulder function, as soon as possible after neck dissection'. The review highlighted that the evidence was from small trials with a high risk of bias. The NICE guideline concluded that a prospective randomised trial was required to understand how best to promote recovery following head and neck cancer.[415] Uncertainty therefore remains regarding the effectiveness of physiotherapy in reducing post-operative complications following neck dissection for head and neck cancer.

In addition to these guidelines, the following resources provide further support to both physiotherapists and patients with head and neck cancer:

- MacMillan Cancer Support – recovering from head and neck cancer surgery (www.macmillan.org.uk)
- UK National Health Service – head and neck cancer (www.nhs.uk)
- American Head and Neck Society – neck dissection (www.ahns.info)
- UK NICE – cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over (www.nice.org.uk)

Pre-operative physiotherapy and exercise prescription

No studies were identified that assessed the effectiveness of pre-operative physiotherapy interventions for people before neck dissection for head and neck cancer. This is a major limitation to the evidence base. Table 1 outlines the essential and desirable pre-operative physiotherapy and exercise recommendations, based solely on clinical recommendations and transferable evidence in other surgical specialties.

Based on other surgical specialties such as general surgery, there is moderate quality evidence that a multimodal prehabilitation intervention, including respiratory and whole-body exercises, education and advice, and psychological support, may be beneficial for patients in terms of reducing length of hospital stay (mean difference = 3.68 days; 95 per cent confidence interval (CI) = 0.92, 6.44).[416] There was moderate quality evidence that this may improve pre-operative functional capacity, as measured in terms of 6-minute walk test distance (mean difference = 33.09 metres; 95 per cent CI = 17.69, 48.50), but this may not necessarily translate into a reduced risk of post-operative complications (odds ratio = 0.81; 95 per cent CI = 0.55, 1.18) or post-operative mortality (odds ratio = 0.95; 95 per cent CI = 0.43, 2.09).[416]

Table 1. Recommendations for pre-operative physiotherapy and exercise intervention

Essential	Desirable
Education on expected surgical procedure & post-operative recovery, including role of physiotherapy (good practice point (G))	Provision of cardiovascular exercises (G)
Advice on preparation for surgery with regard to work, home or social pursuits (G)	Prescription of neck & shoulder range of motion & strength exercises prior to surgery, particularly if limited pre-operatively or undergoing pre-operative radiotherapy treatment (G)

Across the pre-operative (non-head and neck cancer) literature, there is evidence that pre-operative education is important for patients and their family members to prepare for surgery. This may concern shaping expectations of the hospital admission and post-hospital discharge recovery, and particularly to inform of the risks of spinal accessory nerve injury during surgery, and associated neck and shoulder complications.[417] This may also include practical recommendations on 'normal' recovery, preparing the home and living arrangements for after surgery, or liaising with workplaces and other people important in the patients' home and work life to prepare for before and after hospital.

There is insufficient evidence on how and when prehabilitation interventions should be delivered for people undergoing neck dissection for head and neck cancer.[418] Given the timescales between listing for surgery and the hospital admission, it may not be feasible to provide prehabilitation interventions weeks in advance of surgery. However, there is potential that patients may receive support pre-operatively, with tailored guidance on their personal prehabilitation programme before surgery.

Post-operative physiotherapy and exercise prescription – hospital admission

The recommendations for a post-operative physiotherapy and exercise intervention commencing during the in-patient hospital phase for patients undergoing neck dissection for head and neck cancer are presented in Table 2. Two trials have investigated physiotherapy interventions prescribed to patients following neck dissection surgery in the hospital setting.[419,420]

Takamura *et al.*[420] assessed the prescription of a stretching and range of motion exercise programme to improve and optimise shoulder and neck motion. This programme was monitored by a nurse or doctor whilst in hospital, and was supported with an exercise leaflet. Outcomes were compared to a comparator group who were encouraged to return to normal movement, but without a specific stretching or exercise programme. There was low-quality evidence, downgraded because of risk of bias and imprecision, that those who received the supported exercise programme were less likely to experience pain at 1 month (odds ratio = 0.55; 95 per cent CI = 0.36, 0.84), 6 months (odds ratio = 0.47, 95 per cent CI = 0.28, 0.78) or 12 months (odds ratio = 0.47; 95 per cent CI = 0.27, 0.83) post-operatively. There was no difference in the probability of experiencing a complication between the groups (odds ratio = 1.17; 95 per cent CI = 0.39, 3.53). There was no substantial difference between the groups in terms of length of hospital stay (mean difference = 0.50 days; 95 per cent CI = 1.02, 0.02).

In the study by Steegmann *et al.*,[419] both the comparator and experimental groups received range of motion shoulder and neck exercises; patients allocated to the experimental group received those exercises and an individual cardiovascular exercise programme. Based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Recommendations for post-operative physiotherapy and exercise intervention commenced during the in-patient hospital phase

Essential	Desirable
Assess & provide individualised programme with aim of regaining shoulder & neck range of motion at earliest, safe opportunity (evidence-based recommendation (R))	Provision of a general exercise programme to meet needs of patient's hospital & post-discharge goals (R)
Provide exercise materials, either paper-based or online, to re-enforce exercises prescribed (R)	Assess for & provide advice on facial nerve palsy, goal setting, pacing, pain management, scar management & limb positioning where appropriate (good practice point (G))
Assess & manage any post-operative respiratory complications that may present during hospital stay (G)	
Assess & manage safe & supported discharge of patients to their post-discharge residence (G)	
Assess for appropriateness of post-discharge physiotherapy follow up (G)	

approach, there was low-quality evidence (downgraded because of risk of bias and imprecision) of a significant difference between the groups in terms of length of hospital stay, with those who received mobilisation and general exercise demonstrating a mean difference of 5.40 days (95 per cent CI = 8.08, 2.72) compared to the control group. Whilst there was no difference in complication score (assessed using a 0–10 visual analogue scale) for neurological, cardiovascular, respiratory, musculoskeletal, sleep, concentration or anxiety complications ($p > 0.05$), there was low-quality evidence (downgraded because of risk of bias and imprecision) that those patients randomised to the general exercise group experienced fewer complications regarding their digestion (mean difference = 2.10 points; 95 per cent CI = 3.48, 0.72) and less fatigue (mean difference = 1.60 points; 95 per cent CI = 2.98, 0.22) compared to the range of motion alone exercise group.

There was no evidence identified concerning the requirement for a respiratory assessment or the need to assess for factors for a safe discharge to the post-hospital residence. The review authors recommend that these aspects are considered, in addition to an assessment of whether patients require post-discharge physiotherapy, to ensure safe and effective hospital care. A recent survey of UK provision of physiotherapy following neck dissection surgery acknowledged that 78 per cent of the nine regional centres surveyed offered post-discharge physiotherapy for those who had symptoms.[414] The assessment of symptoms is therefore important within the pre-discharge assessment, and may be particularly important for those with spinal accessory nerve neuropraxia. Whilst there remains insufficient evidence justifying the essential recommendation for physiotherapists to ensure that patients are given advice regarding goal-setting, pacing, pain management, scar management and limb positioning (when appropriate), these are considered potentially valuable skills that can be taught to patients prior to discharge.[421] It is therefore considered desirable that these skills are shared with patients, particularly those who are experiencing or at risk of complications following discharge.[421]

Post-operative physiotherapy and exercise prescription – post-hospital admission

The recommendations for physiotherapy and exercise interventions for patients undergoing neck dissection for head and neck cancer following hospital discharge are presented in Table 3. A number of different physiotherapy programmes for people who have undergone neck dissection surgery for head and neck cancer, which begin after hospital discharge, have been evaluated and reported in the literature. These include: the assessment of progressive resistance exercises, muscle energy technique exercise programmes, the use of acupuncture, the provision of self-help interventions, the prescription of yoga and the use of a multimodal rehabilitation programme.

Three trials (reported across four papers) have assessed the outcome of progressive shoulder resistance exercise training compared to active shoulder range of motion exercise programmes.[422–424] On meta-analysis that pooled outcomes, there were no differences between those who received progressive shoulder resistance exercises compared to active shoulder range of motion exercises in terms of flexion range of motion at 12 weeks (mean difference = 9.27 degrees; 95 per cent CI = −2.97, 17.51) or abduction at 12 weeks (mean difference = 15.93 degrees; 95 per cent CI = −0.92, 32.78), although those who were randomised to the progressive resistance exercise programme demonstrated significantly greater external rotation range at 12 weeks (mean difference = 12.0 degrees; 95 per cent CI = 1.56, 22.44). McGarvey *et al.*[425] reported 12-month data. There were no differences between the two

Table 3. Recommendations for post-operative physiotherapy and exercise intervention commenced following hospital discharge

Essential	Desirable
For patients with a spinal accessory nerve injury, patients should be reviewed in out-patient clinic to monitor scapula position, shoulder function, range of motion & pain post-hospital discharge (good practice point (G))	Where possible, all patients should be reviewed by physiotherapy team member in out-patient setting, to provide education & advice on recovery & exercises, both range of movement & strengthening exercises, across temporomandibular, neck & shoulder joints (evidence-based recommendation (R))
	Consider prescribing whole-body exercises to promote global range of motion, flexibility & strengthening following hospital discharge (G)
	Provide patients with advice regarding expectations & goals to achieve in their recovery (G)
	Provide patients with contact information so they can seek help if these recovery milestones, particularly around return to work and hobbies, are not met when self-directed rehabilitation is offered (G)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

exercise programmes at this timepoint in terms of flexion (mean difference = 1.70 degrees; 95 per cent CI = −14.10, 17.50) or abduction (mean difference = −4.50; 95 per cent CI = −31.28, 22.28). There was no difference in health-related quality of life when measured using the Functional Assessment of Cancer Therapy – General ('FACT-G') questionnaire[426] at 12 weeks (mean difference = 7.18 points; 95 per cent CI = −0.85, 15.24) or at 12 months (mean difference = 1.50 points; 95 per cent CI = −7.20, 10.20). This was the same for pain at 12 weeks, which was assessed in McNeely *et al.*[422] (mean difference = 1.60 points; 95 per cent CI = −17.50, 20.70), and for shoulder function both at 12 weeks (standardised mean difference = 0.01; 95 per cent CI = −0.35, 0.38) and 12 months (standardised mean difference = 0.18; 95 per cent CI = −0.45, 0.82). However, for all outcomes, this evidence was judged as very low-quality based on the GRADE assessment, downgraded because of risk of bias, imprecision and inconsistency.

Two trials investigated outcomes comparing physiotherapy when delivered in a supervised out-patient setting compared to being self-directed by patients at home, after receiving instructions on hospital discharge.[421,427] There was very low-quality evidence, based on the GRADE assessment (downgraded because of risk of bias, imprecision and inconsistency), that those randomised to out-patient-based physiotherapy had significantly greater neck and shoulder function at 6 weeks (mean difference = 29.68 points; 95 per cent CI = 15.27, 44.09) but no difference at 12 weeks (mean difference = −9.81 points; 95 per cent CI = −23.18, 3.56). However, there were no differences in shoulder range of motion in respect to: flexion at 6 weeks (mean difference = 1.40 degrees; 95 per cent CI = −9.78, 12.58) or 12 weeks (mean difference = 3.65 degrees, 95 per cent CI = −7.80, 15.10); abduction at 6 weeks (mean difference = 4.08 degrees; 95 per cent CI = −17.54, 25.70) or 12 weeks (mean difference = 8.09 degrees; 95 per cent CI = −11.63, 27.81); or external rotation at 6 weeks (mean difference = 3.87; 95 per cent CI = −2.61, 10.35) or 12 weeks (mean difference = −2.98; 95 per cent CI = −9.40, 3.44). There was no difference between the groups in respect to pain scores at 6 weeks (mean difference = 1.11 points; 95 per cent CI = −0.36, 2.58) or 12 weeks (mean difference = 1.20 points; 95 per cent CI = −0.15, 2.55).

Thomas *et al.*[428] compared the prescription of a muscle energy technique exercise programme for the shoulder versus an active range of motion exercise programme for this population. They reported that whilst there was no difference between the exercise programmes at 10 days for abduction (mean difference = −1.28 degrees; 95 per cent CI = −11.12, 8.56) or internal rotation range (mean difference = 1.06 degrees; 95 per cent CI = −3.70, 5.82), those who received the muscle energy technique exercises demonstrated greater flexion (mean difference = 15.35 degrees; 95 per cent CI = 6.34, 24.36) and external rotation (mean difference = 5.94 degrees; 95 per cent CI = 0.82, 11.06). There was no difference between the groups in pain scores at 10 days (mean difference = 0.13 points; 95 per cent CI = −0.79, 0.53). However, the evidence was judged as very low-quality given a high risk of bias and imprecision, being based on a single, underpowered trial.

One trial was identified that investigated the use of acupuncture following neck dissection, assessing outcomes at six weeks post-intervention.[429] They reported very low-quality evidence (downgraded three levels because of risk of bias and imprecision) indicating that, whilst there was no difference between people who received acupuncture versus those who did not and followed the usual care for shoulder function at six weeks (mean difference = 6.30 points; 95 per cent CI = −3.73, 16.33), the acupuncture patients demonstrated significantly lower pain scores at this timepoint (mean difference = 2.20; 95 per cent CI = −3.41, −0.99).

One trial (reported in two papers) compared the outcomes of prescribing a self-help exercise programme and self-care education programme versus a self-care education programme alone.[430,431] They reported that, whilst there was no difference in health-related quality of life, measured using the European Organization for the Research and Treatment of Cancer 30-item Quality of Life Questionnaire ('EORTC QLQ-C30') (global health status)[432] at three months (mean difference = 4.80; points; 95 per cent CI = −4.39, 13.99), those who received self-directed education and exercise demonstrated greater health-related quality of life compared to people who only received self-directed education (mean difference = 8.00 points; 95 per cent CI = 0.48, 15.52). Similarly, people who received both self-directed exercises and education demonstrated better pain outcomes compared to those who only received education, both at three months (mean difference = −14.60 points; 95 per cent CI = −25.44, −3.76) and at six months follow up (mean difference = −12.20 points; 95 per cent CI = −22.75, −1.65). There was also a significant benefit in favour of people who received the education and exercise intervention for neck and shoulder function when measured using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (functional scale)[432] at three months (mean difference = 10.40 points; 95 per cent CI = 3.39, 17.41) and at six months (mean difference = 8.80 points; 95 per cent CI = 0.54, 17.06). Whilst providing support for the provision of exercises with education, the evidence for these outcomes was based on low-quality evidence, downgraded for risk of bias and imprecision. It is interesting to note that only one-quarter of these patients were randomised within six months of their operation, suggesting patients might still be able to benefit from physiotherapy input later post-operatively.

One trial reported the outcomes of shoulder range of motion, pain and anxiety in people who were prescribed a yoga programme for eight weeks compared to those who did not and followed usual care following neck dissection for head and neck cancer.[433] The data were presented as medians and interquartile ranges, precluding the ability to perform meta-analysis. The paper reported significantly greater shoulder range of motion for active and passive abduction and external rotation for those who receive the yoga compared to those who did not ($p < 0.05$). They also reported significantly lower pain interference scores and anxiety scores, both at four weeks and eight weeks, compared to the usual care group ($p < 0.05$). The evidence was judged low in quality because of a high risk of bias and being underpowered.

Chen *et al.*[434] used a multimodal intervention that included pain management, scar massage, stretching, active and passive shoulder range of motion and scapular setting exercises, with education on scapular setting and positioning. Their control group was the same multimodal programme, but without the scapular setting component. Both groups commenced their intervention post-operatively for the first three weeks post-discharge. The authors reported a significant improvement in shoulder abduction within the scapular setting group compared to the general shoulder exercise group ($p < 0.05$). Whilst pain significantly decreased in both groups over the three-week follow-up period, there was no significant difference between the groups for pain score ($p > 0.05$).

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Important research questions

As highlighted, the current evidence base presents a number of issues. Recommendations are largely based on clinical reasoning rather than robust evidence. There is therefore a major gap in knowledge that urgently requires addressing. Key research themes arising from the current state of the evidence base are listed below.

Prehabilitation for people scheduled for neck dissection to treat head and neck cancer

There is currently uncertainty as to what interventions should be included in a prehabilitation programme for this population. The composition, timing, frequency, duration, personnel and setting to deliver such an intervention remain unknowledge. There is a gap in knowledge regarding the effectiveness of such an intervention, and it is unclear whether effectiveness would vary for those with different stages of cancer and different surgical requirements, and for concomitant treatments with radiotherapy or chemotherapy.

In-patient and out-patient physiotherapy requirements for people undergoing neck dissection to treat head and neck cancer

Current physiotherapy and exercise management for people who undergo neck dissection to treat head and neck cancer is geographically varied. It remains unclear from the evidence whether there is a subgroup of patients who have greater requirement for in-patient or out-patient physiotherapy, or whether all patients who undergo physiotherapy have the potential to benefit. Given the diverseness of the population, there is potential heterogeneity in terms of the need for physiotherapy, the composition of a programme and dosage (frequency, duration, intensity). Future research should be prioritised to determine who has the potential to benefit from such an intervention, and whether a flexible model should be adopted to account for varying clinical presentations within hospital and community settings. Assessing the effectiveness of such a programme and approach to treatment is then required, with a sufficiently powered and robust pragmatic clinical trial.

Outcome measures for people recovering from neck dissection conducted to treat head and neck cancer

The literature review identified that whilst pain and active shoulder flexion, abduction and external rotation are frequently reported outcome measures in trials of physiotherapy interventions for this population, there is no consistency on outcomes reported, or on the outcome instruments or tools reporting these domains. There is no core outcome set for trials assessing physiotherapy interventions in people recovering from neck dissection conducted to treat head and neck cancer. Accordingly, outcome domains that may be important to patients, healthcare professionals and other stakeholders (including health utilisation or psychosocial outcomes such as anxiety, depression, return to work or social pursuits) have not been reported in the literature. The development of such a core outcome set would be valuable to aid standardisation of outcome reporting, allowing comparison between interventions across trials, whilst also facilitating meta-analysis once the evidence base develops in this area.

Future aspects of physiotherapy

There is evidence that patients value physiotherapy following neck dissection conducted to treat head and neck cancer.[435] However, the provision of such treatment is restricted by service provision and capacity. This may be overcome by healthcare providers if a stronger evidence base existed to justify the clinical and cost-effectiveness of physiotherapy for these patients. The role of physiotherapy for these patients may therefore develop as the evidence develops.

Neck dissection surgery is frequently undertaken in a smaller number of specialist centres in the UK.[414] This is particularly the case for more complex head and neck cancer surgery. In such an instance, patients are frequently required to travel distances for follow-up care and, if provided, specialist physiotherapy. With the growing interest in offering telerehabilitation through video conferencing and computer platforms, physiotherapy for this patient group may develop through a more virtual approach.[436] However, this may present with challenges, particularly when assessing neuromusculoskeletal function where face-to-face examination may be preferable, and when patients present with communication challenges post-operatively that may be exacerbated in a virtual rather than face-to-face approach. Consideration of the approaches of such a platform may be examined in the future.

The population who are treated with neck dissection for head and neck cancer is changing. Historically, this was an older population whose risk of developing head and neck cancer was increased through smoking and alcohol consumption. More recently, people affected by and surviving head and neck cancer in the UK are younger and more active than previous generations,[210] attributed to human papillomavirus[251] being an increasing cause of the disease. With this change in demographic, there has been a change in recovery expectation, with patients now being more physically active, with social and occupational pursuits, interests and requirements. However, still approximately 50 per cent of patients are unable to return to their work post-surgery.[408,413] The role of physiotherapy has adapted accordingly. Therefore, a greater emphasis on vocational rehabilitation and a return to occupational goals is required to support the personal needs of our patients. Consideration on how we deliver this, and how this relates to the timing of other interventions such as chemotherapy or radiotherapy, should be considered.[435]

Conclusion

Physiotherapy for people who have undergone neck dissection in the management of head and neck cancer may be beneficial. This is largely based on clinical recommendation and a low-quality evidence base. With a changing demographic of patients, determining who can benefit from physiotherapy, and when and in what form physiotherapy and exercise should be provided, is a research priority. Through developing the evidence, it is anticipated that physiotherapists, and the wider head and neck cancer multidisciplinary team, will be able to justify the provision of this intervention, which may offer considerable benefits to the health and well-being of this growing patient population.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Chapter 12: The clinical nurse specialist role in head and neck cancer care

Table of Contents

Key points

All multidisciplinary teams (MDTs) should make adequate provision of clinical nurse specialist posts or individuals to ensure the following essential care elements can be provided at all times:

- Clinical nurse specialist contact with individuals at the time of diagnosis
- Clinical nurse specialist involvement in all MDT meetings
- Psychosocial support and care co-ordination for all individuals being managed within the MDT (to varying extents) by all modalities of treatment
- Availability to provide co-ordination of multiprotection care pathways
- Accessibility as a point of contact for expert advice to primary care physicians, district nurses, specialist palliative care teams etc. (e.g. tracheostomy and gastrostomy care, wound care)
- Co-ordinated, tailored approach to the provision of support for individuals living with the effects of cancer and long-term consequences of cancer treatment. This should include end of treatment summaries, health and well-being advice, signposting to resources available, and appropriate follow up

Introduction

Head and neck cancers are complex, and are managed with a range of arduous treatments. Head and neck cancer and its treatment is physically debilitating, and the psychological impact is immense. Patients and carers often require assistance and support, from diagnosis and treatment through to long-term support, to help them live well with the impact of the disease.

Specific aspects of clinical nurse specialist role

The role of the clinical nurse specialist is diverse, involving the co-ordination and signposting of patients and carers, for advice, information and support, from diagnosis through to the later stages of disease. Clinical nurse specialists act as the gate-keeper to the patients' cancer pathway, to deliver a seamless journey.[437]

There are specific core aspects of the clinical nurse specialist role; these are described within this chapter (Table 1).[438–442] It is essential that the clinical nurse specialist works closely with the speech and language therapy and dietetic teams as significant others, in order to deliver a multidisciplinary approach in which to achieve the best possible outcomes. Whilst the roles may overlap, their reliance on one another is imperative.

Surgery

Surgery is one of the key modalities used in head and neck cancer treatment. Surgery can have permanent effects on structures essential for normal human activities, therefore affecting speech, mastication and breathing.[443]

Head and neck cancer is complex and life-changing, often having a traumatic and devastating impact on the patient and their family, both physically and psychologically, because of the impact on highly important functions.[444]

Table 1. Specific aspects of clinical nurse specialist role

Essential	Desirable
– Initiate cessation of smoking, drug & alcohol use, with referral to local & national agencies for intervention – Discussion in conjunction with clinician regarding HPV, & counsel patients accordingly – Teach patients & carers in relation to specific care needs: airway, feeding, valve management – Teach other professionals in relation to patients' specific care needs – Deliver information, education materials & training sessions, on a face-to-face, telephone or written basis, to community hospitals, hospices, homecare agencies & other staff within the trust & region	– Offer pharmacotherapy options to patients who decline referral – Continue to support cessation throughout, & during relapse – NHS Stop Smoking Services[438] – Provide local & national written information to support www.throatcancerfoundation.org[439] – Involvement in speaking valve changes in surgical voice restoration patient, in conjunction with SLT services – Self-changing of speaking valves by patients who are able, thus reducing hospital attendance
– Support & act as a resource for national & local patient support groups for head & neck & thyroid cancers	– Encourage patient development with groups: www.laryngectomy.org.uk;[440] www.theswallows.org.uk;[441] and www.butterfly.org.uk[442]
– Complex wound management: flaps, grafts, radiotherapy skin reaction – Care of patients at risk of major haemorrhage: local guidelines in conjunction with palliative care teams – Support for patient, family & carers	– Involvement of other professionals: radiotherapy, tissue viability (if indicated). Referral for community nurse support. Teach & help other professionals in supporting individual patients

HPV = human papillomavirus; NHS = National Health Service; SLT = speech and language therapy

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Support is required before, during and after treatment, to help the patient adjust to the physical, social and emotional effects, sometimes with disfigurement, on quality of life (Tables 2 and 3).[445]

The head and neck cancer clinical nurse specialist plays a pivotal role throughout the disease trajectory. For example, information given at diagnosis often includes working uniquely with the MDT (speech therapist, dietician, physiotherapist, oncologist etc.), setting realistic expectations with patients and their families before 'life-changing surgery or treatment', and this is often a challenging process. In addition, managing disease symptoms and treatment side effects requires complex care management with issues such as complex airway management, or bleeding that could signify a life-threatening situation and which needs to be urgently assessed and addressed. This highlights the importance of advocacy, which is an MDT responsibility.[446]

The clinical nurse specialist can develop a unique relationship with the patients and their carers. This is established through using expert clinical skills, decision-making skills and judgement, together with experience and intuition. Practising within this field can be both challenging and rewarding.

From surgery through to post-treatment care, the clinical nurse specialist helps to build an appropriate care pathway for each patient given their everyday challenges. By providing rationale and advice for each treatment option, the patient is included in the decision-making process and feels engaged in their care.[447]

'It has been recognised that care co-ordination individualised to the patient during and after treatment is vital to deliver appropriate person-centred care'.[437]

Table 3. Role of clinical nurse specialist during admission for surgery

Essential	Desirable
Within 72 hours of surgery	
– Patients should be seen post-operatively to assess physiology & psychology	
– Early & regular review to optimise & maximise recovery	
– Support nursing & medical staff in patient management	
During acute in-patient stay	
– Regular review on high-dependency units & wards	
– Optimise & maximise recovery	
Post discharge	
– Provide major surgery patients with home visit or video call, for ongoing support & advice	
– Clinic follow up (face to face, video or telephone) to manage side effects & late effects of treatment	
– Quality-of-life questionnaire	

Prehabilitation is vital in the preparation for potentially life-changing surgery and treatment. It is a continuum to rehabilitation, and focuses on personal empowerment by improving physiological function and psychological well-being, therefore improving resilience to the effects of cancer treatment.[446]

Prehabilitation, described in detail in a separate dedicated chapter, should be implemented as soon after diagnosis as

Table 2. Role of clinical nurse specialist pre-treatment (pre-surgery)*

Essential	Desirable
– Attendance by ≥1 CNS as a core member of MDT – Provide CNS input to inform treatment decision-making, especially regarding aim of surgery & functional outcomes – Advocacy	– Offer further out-patient appointment, in conjunction with AHP for information-giving, for: assessment of baseline function & decisions regarding enteral feeding support
– Attend consultation with surgeon & oncologist	
– Be an advocate for patients who may feel overwhelmed by the diagnosis & the large volume of information provided	
– All HNC patients should be offered a pre-treatment consultation in the form of prehabilitation (AHP, CNS & physiotherapist). This can provide a teachable moment to discuss alcohol & smoking cessation – Enhanced recovery after surgery clinic appointment, for advice & information-giving, in the case of major surgery with free flap repair	
– Check patient's understanding of diagnosis, planned treatment, & their expectations regarding functional changes & outcomes – Provide further information in the form of head & neck booklet (Macmillan or locally produced)	
– Provide contact details for CNS service. Explain role of telephone service (emotional support, symptom control, co-ordination of investigations) – Advise on out-of-hours contact (GP, district nurses or emergency department)	
– Offer all patients a health needs assessment – Address symptoms & arrange for review of symptoms, either by telephone or face to face	
– Pre-operative ward visit if admitted pre-surgery – Liaise & refer to appropriate members of MDT (alcohol team, psychology team)	
– Refer to community services & liaise appropriately – Refer patients for laryngectomy to district nurse once patient made aware of treatment plan, so that community equipment can be ordered in advance	

*Multidisciplinary team (MDT) meeting and combined head and neck clinic. CNS = clinical nurse specialist; AHP = allied health professional; HNC = head and neck cancer; GP = general practitioner

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

possible to enable maximal benefit in advance of treatment. These interventions aim to reduce post-operative complications and minimise functional decline following surgery.

Macmillan Cancer Support published 'Principles and guidance for prehabilitation within the management and support of people with cancer' in 2019.[448] This document sets out principles with which people with cancer can be prepared for treatment, through a multimodal approach that promotes healthy behaviours, exercise prescription, nutrition and psychological interventions appropriate to their needs.

Early intervention, engagement and interaction can be both healing and therapeutic for patients post-surgery.[449] Regular patient reviews for support and information are vital in the recovery, as this is often a particularly anxious time for the patient and family as they adjust to the post-operative changes. Recent research has also indicated that the prevalence of mental health disorders in people with head and neck cancer increases by 10 per cent after diagnosis.[449]

The head and neck nursing team also play an active role in educating junior nursing staff, student nurses, allied health professionals and medical staff whilst reviewing patients in the clinical environment. The clinical nurse specialist's experience, mentoring and educational support of colleagues is a valuable resource.

In 2020, the British Association of Head and Neck Oncologists set out clear guidance for the management of head and neck cancer patients, both in the hospital and community setting, as described below.[71]

In-patient nursing staff

(1) The nurse in charge on each shift should have a specialist qualification in a related discipline and a minimum of five years of experience.
(2) Two other nurses on the staff should have, or be preparing for, a specialist qualification in related disciplines.
(3) Nursing staff, including healthcare assistants, should have competencies associated with altered airway management and major haemorrhage in the head and neck setting.

Nurses should be informed and aware of ongoing clinical research projects, audits and clinical trials.

Crisis planning

- All units and hospices managing individuals with head and neck cancer should adhere to local guidelines for tracheostomy blockage and major haemorrhage.
- All specialist head and neck ward nurses should be aware of these protocols.
- Individuals (and their carers) at risk of these crises should be made aware of the warning signs in all cases, unless the patient has expressed a wish to not be provided with this information.

Role of clinical nurse specialist during oncology treatment

The role of the oncology clinical nurse specialist is equally as important (Table 4). This can be a difficult period for patients

Table 4. Role of clinical nurse specialist during oncology treatment

Essential	Desirable
– Pre-treatment session with MDT (SLT & dietician) for patients undergoing radiotherapy/chemoradiotherapy; written information given at this point	– Such sessions should ideally be MDT joint reviews; however, separate CNS appointments are a minimum – Offer attendance at local head & neck support group prior to treatment, as this can help alleviate fears for anxious patients
– Pre-treatment review & telephone call for patients commencing chemotherapy or immunotherapy; written information given at this point	
– All patients should be given contact details, & have access to, a CNS or support nurse who has experience in managing radiotherapy & chemotherapy side effects	– Follow-up call from CNS prior to starting treatment
– All patients should have a pre-treatment holistic needs assessment, with onward referrals as required	
– Weekly review on treatment for management of radiotherapy side effects in MDT clinic – Treatment toxicities, such as oral mucositis, pain, fatigue, thick mucus, skin desquamation, nausea, constipation & dysphagia, should be assessed & documented by a qualified individual using a recognised tool, e.g. NCI CTCAE version 5.0	– Midweek review from CNS to ensure self-management & compliance with medication & mouthwashes
– Pre-cycle clinic review for patients undergoing chemotherapy or immunotherapy – Toxicity & fitness for treatment assessed at this point	– Mid-cycle review & telephone call from head & neck oncology CNS
– Regular post-treatment assessment & support when recovering, occurring weekly initially then as determined by healthcare professional running the clinic	– CNS-led follow up for patients when recovering from radiotherapy/chemoradiotherapy
– CNS should have the ability to lead & contribute to teaching other healthcare professionals in caring for HNC patients, including ward, out-patient & community nurses	
– CNSs should be part of local & national initiatives for health promotion, especially within treatment & recovery period	
– CNS should contribute to treatment summaries. This should become part of practice to provide good communication between primary & secondary care, to enable continuity of care for patient	

MDT = multidisciplinary team; SLT = speech and language therapist; CNS = clinical nurse specialist; NCI = National Cancer Institute; CTCAE = Common Terminology Criteria for Adverse Events; HNC = head and neck cancer

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

as they move from one treatment modality to another. Anxiety is often high and information is key.

Supportive care, appropriate information and individualised care planning is key to improving the experience of the patient and the carer.[437]

This is also often a point of change of key worker. It is vital the oncology clinical nurse specialist meets the patient and carer at the start of the oncology treatment period. This starts at the pre-treatment clinics, where there is an opportunity for patients and carers to meet the clinical nurse specialist and other allied health professionals prior to treatment. It allows the giving of information, the explanation of treatment and the implementation of a health needs assessment. A health needs assessment ensures that the patients' and carers' physical, emotional and social needs are met in a timely and appropriate way, and that advice and support are available from the right source at the right time.[450]

Radiotherapy or chemoradiotherapy side effects from treatment are often debilitating. Up to 89 per cent of patients having treatment develop oral mucositis and require analgesia.[451] Patients should have a clear explanation of what to expect during this period. Side effects build during treatment to a peak on the final week and the week after completion. In general, side effects develop from week two onwards, and treatment toxicity should be assessed and scored with a recognised grading tool. This can help guide consultations and required interventions. Patients should have weekly reviews to ensure compliance with medications and supportive measures. Effective MDT communication will be vital in supporting the patients through this period. Offer onward referral for psychological support if required and if the patient is struggling with treatment.

The clinical nurse specialist should always be a source of information and comfort for the patient undergoing treatment. They should be contactable within working hours and available to review the patient outside of the clinic setting if needed (either face to face or by telephone).

Those patients undergoing chemotherapy or immunotherapy only are generally on treatment with palliative intent. In addition to toxicity management, the clinical nurse specialist should assess the level of support required and arrange community palliative care support if required.

Living with cancer

An individual approach to living with cancer (last 12 months of life), including clear documentation and communication with each relevant team providing palliative care, must be employed for all individuals. This may include liaison with primary care and specialist palliative care teams. Clear offers must be made to discuss and implement advance care plans with all patients. These may reasonably include patients' preferred place of care, agreed thresholds or ceilings of treatment.

For those recognised to be dying (last days of life), an individualised care plan should support care for all individuals.

Late effects of treatment

The role of the clinical nurse specialist incorporates support with late effects of treatment, in relation to chemotherapy, radiotherapy, surgery or combined modality treatment (Table 5).[440–442,452] Macmillan defines 'late effects' as side effects that do not disappear after treatment, or that do not materialise until months or even years after treatments have taken place.[446] Such effects differ between patients, both in terms of the effects and the timing at which they occur.

The clinical nurse specialist works closely with other team members in supporting patients with late effects, such as lymphoedema teams, late effects radiographers and core members of the MDT.

Community, palliative and supportive care

The head and neck clinical nurse specialist is instrumental in ensuring that support, advice and appropriate signposting is available to patients and their carers when a referral to the acute setting for suspected cancer is made (Table 6).[437,443,450]

Table 5. Late effects of treatment and role of clinical nurse specialist

Essential	Desirable
Referral for lymphoedema management services	Rule out any suspicion for recurrent disease before referral
Advice & support for dry mouth	Advise on suitable treatments to try, over-the-counter products, complimentary therapies, NHS or private sources
Management for post-treatment fatigue	Referral for physiotherapy input & exercise tolerance
Dental issues post treatment: risk of osteoradionecrosis	Ensure referral to restorative services & local general dental practitioners; reinforce oral hygiene standards
Encourage engagement with regular dental check-ups	Oral hygiene standards
Difficulties with swallowing	Referral to acute or community SLT & dietetic services, to assess swallow & maintain adequate nutritional intake
Taste changes post treatment; taste dysfunction is reported in patients who receive radiotherapy[452]	Advice from dietitians regarding food preparation & modification
Changes in hearing following radiotherapy & chemotherapy	Referral to local audiology departments for assessment & therapy
Stiffness in jaw with trismus; maintain exercises set by SLT team	Monitor for effectiveness & to determine whether further management required
Changes in appearance after surgery or treatment; support & counsel	Referral to skin camouflage services & Changing Faces, nationally or locally: www.changingfaces.org.uk
Changes in mood, fear of recurrence; normalise & support	Referral for local counselling & or psychology input if indicated
Access & use head & neck support groups, thyroid cancer & laryngectomy groups, for patient & carer support	Encourage interaction & support from patient-led groups, learning from others in similar positions: www.laryngectomy.org.uk[440]; www.theswallows.org.uk[441]; www.butterfly.org.uk[442]

NHS = National Health Service; SLT = speech and language therapy

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 6. Palliative and supportive care

Essential skills	Desirable skills
Manages common HNC symptoms, such as pain, excessive mucous production, difficulty in swallowing, problems eating, drinking & chewing; manages abnormal changes in bowel habits & nausea or vomiting; advises on managing fatigue	Is able to advise other staff members on management of more specialised scenarios, such as a potential compromised airway or catastrophic bleeding, & ensures that anticipatory medications are prescribed in preparation. Often this needs to be the primary care team if the patient is at home
Offers holistic needs assessment & completes appropriate care plan for any identified needs[450]	Participates in completion of 'advanced care planning', where discussions & decisions around resuscitation, type & amount of treatment to be given (in cases of incapacity), & 'preferred place of death', can be started by CNS & communicated to other professionals, both in community & acute settings
Refers on to welfare team, who can ensure that patient is in receipt of appropriate finances, housing & 'blue badge' for easier parking	Signposts carers to appropriate bereavement services, if required
Completes a 'DS1500' form, which is an application for enhanced rate of benefit, or requests that a GP or consultant completes	Advises specialist palliative care team on specialist symptoms
Refers to specialist palliative care team & ensures that appropriate ongoing care continues for patients in community setting	
Is trained in advanced communication skills[443]	
Assesses & supports psychological needs of patients & their carers, & makes onward referrals to psychology team, as required	

HNC = head and neck cancer; CNS = clinical nurse specialist; GP = general practitioner

If discussions at the MDT meeting conclude that it is not possible to cure a patient of their cancer, a less radical course of treatment known as 'treatment with palliative intent' may be offered to help control symptoms and slow down progression of the disease. For some patients, it may be recommended that no active treatment be given, if the MDT feels treatment would not be beneficial or may worsen their current symptoms; this is known as 'supportive care'. Whilst a diagnosis for palliative treatment or supportive care may be given at initial presentation to the acute service, a patient may also be given this diagnosis at any later stage of the pathway, even if the initial intention was for cure. In any case, the clinical nurse specialist acts as the patient's advocate at the MDT, and ensures that sufficient support and advice are available whilst the patient remains under the care of the hospital team.[443]

Palliative and supportive care

Depending on local service provision and a patient's wishes, specialist palliative care support can be provided, no matter what the care setting, dependent on complexity of needs.[453] It is important that the clinical nurse specialist recognises when further input from a specialist palliative care team is required, and that they ensure a timely referral is made so that a seamless transition of care takes place. Involvement from these different teams and other allied health professionals (such as dietitians, speech therapists and physiotherapists) will require the clinical nurse specialist to have a sound knowledge of local service provision and an understanding of how an onward referral to these teams may occur.

Table 6 lists some essential and desirable skills for the clinical nurse specialist to possess when dealing with a patient being treated with palliative intent.

Community care

As a patient's condition deteriorates, there is frequently an emphasis on managing palliative patients within the community setting (Table 7). This concerns those patients with distant metastasis, late-stage disease or cancer that is life-limiting, and/or those with a prognosis of 6–12 months. Given that head and neck cancer is a very specialised area of care, some localities provide hospital out-reach services for their patients, which can be beneficial in supporting community staff to manage more complex and specialised situations.

In order to facilitate greater community working, the clinical nurse specialist should have the skills listed in Table 7.

Psychology in the management of head and neck cancer

A diagnosis of head and neck cancer is often described by patients as physically and psychologically debilitating, with significant psychosocial implications on physical, emotional, spiritual, financial and interpersonal interactions (Table 8). Unlike other tumour sites, head and neck cancer and its treatment cannot be hidden, often because of disfigurement, altered anatomy, and lasting effects on eating and communication. Whilst some patients adapt to their altered anatomy with little support, others experience a loss of confidence in social interactions because of self-image,[454] and go through significant periods of adjustment to obtain an acceptable level of quality of life. Windon *et al.*[455] identified that head and neck patients experienced feelings of regret post treatment, particularly following multiple treatment modalities despite curative treatment intention. This signifies the crucial role that psychological support has within the complex and challenging management of head and neck cancer.

Often patients share a fear of recurrence as a primary concern, whilst milestones such as post-treatment investigations, follow-up appointments and physical reminders of treatment frequently trigger patients back into psychological turmoil. Collectively, head and neck cancer patients display an increased

Table 7. Community care

Essential skills	Desirable skills
Has an awareness of local community care provision, & can make onward referrals to access appropriate local community care services, as needed	Out-reaches & supports patients, carers & staff in community setting, as required. (In some localities, there is a dedicated community team to provide these services)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 8. Psychological support*

Essential skills	Desirable skills
Undertakes psychological level 2 training	Provides access to clinical psychologist
Undertakes an advanced communication course	
Undertakes comprehensive holistic assessment & care planning, in line with national directives, ensuring that physical, social, psychological, emotional & spiritual needs are identified & met at key points in the pathway	
Supports patients in making informed decisions about treatment & care	
Screens patients for psychological distress using recognised tool	
Provides psychological level 2 support or, where appropriate, refers to clinical psychology for complex level 3 or 4 support	
Supports patients in developing self-management strategies	

*Psychology management in head and neck cancer

frequency of depression associated with the multifaceted consequences of cancer and the effects of treatment decreasing quality of life for patients.[456] Declines in performance status and functional ability collectively impact on many aspects of daily living, including employment, in the head and neck patient.[457] Interviews have shown that survivors of head and neck cancer call themselves the 'visible minority', stemming from their noticeable disfigurement.[458] The need for psychological support is supported by the author's reflection on a case study, whereby, despite the patient's remission, he was left looking in the mirror at a reflection that overwhelmed him with feelings of shock and regret. This patient acknowledged that the late and physically permanent effects of cancer treatment were undoubtedly worse than the initial cancer diagnosis itself.

As key worker and patient advocate, the clinical nurse specialist is level 2 trained in providing timely psychological interventions, utilising advanced communication skills. The clinical nurse specialist ensures frequent opportunities for one-to-one supportive conversation to meet patients' information needs around their cancer diagnosis and potential treatment options, but also identifying and responding to psychological needs. This undoubtedly helps to inform therapeutic relationships, and enhance holistic patient-centred care and choice. Involving patients in decisions around their care will help to enable a sense of partnership between the patient and healthcare professional. Screening for psychological distress using a recognised tool and providing ongoing psychological support throughout the entire pathway are imperative in improving the quality of life of those diagnosed with head and neck cancer.

Future roles and development

Advanced nursing roles such as clinical nurse specialist advanced practitioner and advanced nurse practitioner are clinical expert roles that require academic degrees. Healthcare delivered by nurses in these advanced roles has proven to impact important care quality factors such as patients' experiences, safety, symptom burden and cancer care co-ordination. By improving communication between and within the teams, advanced nursing care can reduce re-admissions. Advanced nursing roles can contribute to improving clinical practice and patient centeredness, through education, developing guidelines and spanning organisational boundaries, to progress the patient through the system.

The clinical nurse specialist is the clinical nursing role with in-depth knowledge of cancer care and symptom management, supporting both the patient and their families through the cancer journey. The clinical nurse specialist's knowledge enables them to offer expert care to patients with all stages of cancer, including screening for early detection, making a diagnosis, administrating treatments, and discussing survivorship. Most clinical nurse specialists perform advanced tasks; these can be nurse-led clinics for pre-treatment, on treatment and after treatment, with clinical nurse specialists often seeing the patient weekly to support with symptom management. The clinical nurse specialist is recognised as the first point of contact for patients.

Some clinical nurse specialists offer additional advanced roles, which include nurse-led tracheostomy tube changes for patients requiring long-term airway management, and joint valve clinics with speech and language therapists. In order to address local demands, nurses working in partnership with physicians may select a group of patients that can be seen independently within a risk-stratified nurse-led clinic, which could include nasendoscopy follow up and working alongside ultrasound clinics for rapid access.

Chapter 13: Restorative dentistry and orofacial rehabilitation for patients with head and neck cancer

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Key points

- Consultants in restorative dentistry are core multidisciplinary team (MDT) members. Their close collaboration with the MDT is essential. The restorative dentistry consultant should be proactive in the MDT, contribute to research and audit, and act as an advocate for optimum oral health outcomes.
- Consideration of oral rehabilitation needs to begin early in the surgical and non-surgical treatment pathways. By managing the pre-treatment pathway optimally, the restorative dentistry consultant can facilitate prevention or reduction of complications.
- Patient involvement in decision-making regarding the oral and dental care plans is essential, and should be underpinned by written and verbal information regarding the expected impact of treatment on appearance, ability to speak, eat and chew. A clear understanding of patient expectations and priorities is essential to providing individual counselling on likely outcomes and personalised plans.
- The possibility of implant rehabilitation should always be considered early, as timely implant rehabilitation can improve patient outcomes, reduce overall treatment times and decrease costs where appropriate.
- Referral pathways for management post treatment should be clear.

Introduction

Impact on patients

Patients diagnosed with head and neck cancer are referred to a specialist head and neck cancer MDT for treatment, which may include surgery, chemotherapy or radiotherapy, or a combination of these. These treatment modalities can have significant and long-lasting adverse effects on orofacial and dental function, appearance and quality of life (QoL). In a recent study of the Patient Concerns Inventory, 'dental health and teeth' was the second most commonly selected concern at the baseline clinic, alongside 'fear of the cancer coming back'. Oral health-related issues were selected in four of the top five issues at this stage in the pathway. Of the health professionals that patients wanted to see at baseline, the dentist was the most selected professional.[459]

Thus, the impact on patients can be devastating, adding to the trauma of a cancer diagnosis. Some of these effects are preventable or can be minimised by early intervention from the specialist restorative dentistry team.

The management of long-term oral and dental complications can have a protracted, often lifelong pathway, with attendant costs. There is a marked increase in consumption and costs for dental care in the first two years following diagnosis compared with those for patients without head and neck cancer.[460] In the UK, some of these costs currently fall out of National Health Service (NHS) provision and, consequently are borne by patients themselves.

Standardised, specialist delivery of oral and dental prehabilitation and rehabilitation

Predicting and managing oral and dental complications is complex and highly specialised. For this reason, it is recommended that, at a minimum, each MDT should have at least one consultant in restorative dentistry as a core member of the team.[461–463] Specialist restorative dentistry is for patients who have complex dental problems requiring multidisciplinary, specialist dental care.[464]

The restorative dentistry consultant functions as implant surgeon, maxillofacial prosthodontist and 'dental oncologist'. Outside the UK, the term 'dental oncologist' is used to describe specialists in the dental side effects of head and neck cancer non-surgical treatment. Such multiplicity of roles facilitates a clinically effective pathway for patients treated surgically or non-surgically, and optimises service delivery.

The incorporation of the restorative dentistry consultant to UK head and neck cancer MDTs has developed significantly in the last 15 years. The increase in human papillomavirus associated disease in younger, usually dentate patients, who are expected to survive for longer, the development of new technologies in relation to osseointegrated implants and new approaches to radiotherapy cement the importance of this specialist input.

Outline of requirements for a service

All head and neck cancer services must have continuous service provision by a consultant-led restorative dentistry team, and should have a dedicated specialist dental hygienist and maxillofacial prosthodontic technician or reconstructive scientist technical support.

Digitally planned implant placement in head and neck cancer patients is highly complex, and requires ready access to cone beam computed tomography, digital planning software, optical scanning devices, dedicated software and three-dimensional (3D) printing facilities.

Guideline principles

This paper provides guidelines on planning and treatment for oral and dental prehabilitation and rehabilitation for patients having treatment for head and neck cancer. They were devised with consensus meetings from members of the Restorative Dentistry UK ('RD-UK') Head and Neck Cancer Clinical Excellence Network from eight major treatment centres across the UK.

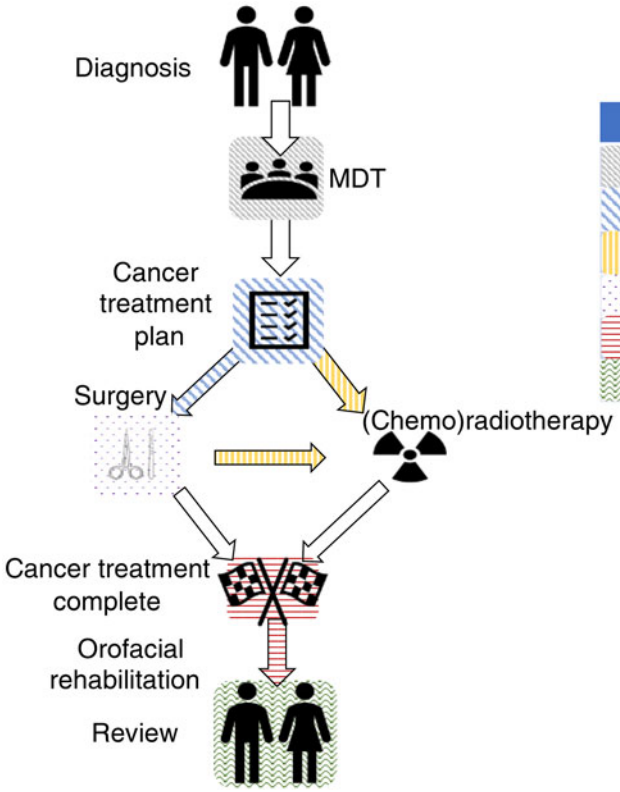
These guidelines cover oral rehabilitation planning and management for patients undergoing radiotherapy or surgery or multimodality treatment. Input is needed at key times: before, during and after cancer treatment. Therefore, the paper is set out along these lines (Figure 1). Each section is separated into recommendations that are considered either 'essential' or 'desirable'. Future roles, and areas for research and audit are described in the final section. In addition to these guidelines, the guidelines produced by Restorative Dentistry UK[465] will provide further information for the MDT.

Pre-treatment

Patients whose cancer treatment will affect oral and dental function and appearance will require oral rehabilitation planning (Tables 1 and 2).[461,462,465] This generally includes patients scheduled for surgical intervention that alters oral anatomy, patients requiring radiotherapy where the treatment field includes any part of the maxilla, mandible or salivary glands, and patients with specific dental concerns or pre-existing conditions.

Clinically edentulous patients may have retained roots, buried teeth or local bony pathology, and should also be considered for prehabilitation. This stage is often referred to as

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press



Timepoint	Role of consultant restorative dentist
	• Attendance at HANC MDT
	• Pre-surgical restorative planning
	• Pre-(chemo)radiotherapy restorative planning
	• CRD in theatre
	• Orofacial rehabilitation
	• Post-(chemo)radiotherapy & post-surgical review

Figure 1. Restorative dentistry consultant role in the patient pathway. MDT = multidisciplinary team; HNC = head and neck cancer; CRD = consultant restorative dentist

'screening' or 'assessment', which belies a highly complex planning and initial treatment stage with time pressures. It should be more accurately viewed as planning or oral and dental prehabilitation. It presents challenges, as the outcomes of cancer treatment for the individual patient are not yet known. Risk assessment for adverse oral and dental outcomes, therefore, is key.

Some dental pathology is preventable if appropriate early interventions are put in place. Primary implant placement should always be considered as part of surgical planning. For patients having dual modality treatment, this may be the only opportunity to place implants. Secondary implant placement may extend the rehabilitation pathway, but allows more time for comprehensive planning and assessment of any post-treatment challenges. However, implants may not be appropriate in some cases. Patients should be counselled by the restorative dentistry consultant regarding expected prosthodontic oral rehabilitation outcomes from the start.

Success in implant rehabilitation is improved by early digital planning. Digital workflows can greatly facilitate the planning and execution of implant based orofacial rehabilitation, allowing rapid treatment completion.[466,467] The restorative dentistry consultant should be involved in planning with surgical colleagues from the outset.

Software used for digitally planned osseous reconstruction following resection allows dental implant planning with guided surgical stents, and should be undertaken jointly with the restorative dentistry consultant and maxillofacial surgeons during the early planning stage utilising a prosthetically driven approach to optimise rehabilitation outcomes.[468] This helps achieve more predictable outcomes in terms of function, biology and aesthetics,[469] which contribute to improving QoL.

Dental extractions for head and neck cancer patients can be a traumatic, highly emotive experience. Extraction of teeth, if indicated, should be organised as early as possible after the cancer treatment plan is known, to maximise healing time and expedite the pathway. However, care should be taken to avoid unnecessary dental extractions, especially where the cancer treatment plan is not yet clarified. Where multimodality treatment is definite or where gross dental pathology exists, extraction during primary surgery should be considered.

The essential and desirable aspects of the pre-treatment restorative planning appointment before surgery and before radiotherapy are outlined in Table 1.

Peri-treatment

Osseointegrated implants can improve the support and retention of prostheses, help raise self-esteem and body image, and improve overall QoL.[470] Primary implant placement in head and neck cancer patients involves placing dental implants at the time of the ablative surgery, to allow osseointegration to take place prior to any necessary adjunctive radiotherapy. It facilitates more rapid rehabilitation,[471] while avoiding further surgery and further in-patient treatment costs. Disadvantages include reduced planning time, and the risk of implants not being used because of tumour recurrence or changed anatomy during or following surgery.[472]

Peri-surgical maxillectomy defect management can involve prosthetic obturation or surgical reconstruction of the defect. Dental implants can help to retain an obturator or can support a fixed dental bridge in conjunction with a free flap. The latter may involve placing implants into native bone, composite free flaps or remote anchorage in the zygomatic buttress. Overall, the literature fails to demonstrate the superiority of obturation or reconstruction, as a result of unique patient presentation and a lack of data reporting standardisation.[473] Limited evidence suggests that surgical reconstruction may offer improved QoL over prosthodontic rehabilitation.[474] Individual studies have demonstrated comparable masticatory function with

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Pre-oral and maxillofacial surgery and ENT surgery planning

Essential	Desirable
MDT meeting	
– Attendance of CRD	
MDT planning clinic (OMFS & restorative dentistry)	
– Discussion with patient about: (1) Expected impact of surgery on oral, dental & facial function, access & appearance (2) Options for replacing missing orofacial structures (including estimated timeframe) (3) Check maximum inter-incisal opening or equivalent if edentulous or partly dentate	– Psychological support
– Joint oral rehabilitation planning with CRD & OMFS to determine most suitable reconstructive techniques to facilitate oral rehabilitation where possible	
– For primary implants in osseous free flaps or native bone: joint implant position planning with CRD & OMFS, using a 'tooth down' approach to digital planning of free flap position where possible	
– Use of digital implant planning software & 3D printing	
– Maxillectomy with surgical reconstruction: impressions for construction of surgical obturator to be held in reserve	
– Maxillectomy without surgical reconstruction: impressions for obturator; check patient's understanding & expectations, & if manual dexterity is limited, organise for support	
– Intra-oral impressions & occlusal registration where appropriate	– Access to intra-oral optical scanner
	– Clinical photographs
– Arrange treatment of any dental disease needed to render the patient dentally fit before surgery	
– Plan extractions at primary surgery if dual modality treatment is definite	
MDT planning clinic (ENT & restorative dentistry)	
– If extractions are required for surgical access, liaise with ENT surgeons & CRD to determine most suitable teeth & their replacement	
– Plan extractions at primary surgery if dual modality treatment is definite	
	– Access to facial scanning equipment, digital planning software & 3D printing facilities
	– Joint planning with ENT, CRD & maxillofacial technicians utilising digital workflows for orbital exenteration, rhinectomy & craniofacial resections where implant rehabilitation is planned
	– Pre-operative nasal & facial impressions, extraoral photographs, & 3D photography if extraoral resection is planned
	– Assessment by CRD & fabrication of protective prosthesis for patients receiving transoral robotic surgery

MDT = multidisciplinary team; CRD = consultant in restorative dentistry; OMFS = oral and maxillofacial surgery; 3D = three-dimensional

implant supported obturators and surgical reconstruction, both superior to conventional obturation in low-level defects.[475,476] Implants can also be used to help retain facial prostheses, obviating the need for tissue adhesives. There are multiple case reports and case series on the use of zygomatic implants for orofacial and nasal prostheses, with good results.[477]

Zygomatic implants have been used for over 20 years. They can be used splinted or un-splinted. There are multiple implant designs for post-resection orofacial rehabilitation.[478] A recent review highlighted current evidence for the use of zygomatic implants in the midface and maxillary rehabilitation of patients with head and neck cancer.[479] Overall survival rates of 77–100 per cent were reported, with few complications.

Zygomatic implant positioning for intra-oral prostheses should be restoratively driven.[480] Involvement of the restorative dentistry consultant in planning and surgical placement should reduce the risks of malposition and improve the potential for rehabilitation (Table 3).[481]

Post-treatment

Some of the most commonly reported issues for patients during the early post-treatment phase are dry mouth, problems with chewing or eating, dental health and teeth issues, fear of recurrence, and salivation problems.[482] As the late effects of treatment develop, oral and dental concerns are a noted priority for patients in most patient-related outcome measures. Ongoing management of dental issues is, therefore, essential.[483]

For some patients, placement of osseointegrated implants can positively impact health-related QoL outcomes.[484]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Pre-radiotherapy planning

Essential	Desirable
MDT meeting	
– Attendance of CRD	
MDT planning clinic (oncology & restorative dentistry)	
– Discussion regarding long-term impact of radiotherapy on oral, dental & facial function & appearance, including written information on trismus, hyposalivation (xerostomia), osteoradionecrosis & radiotherapy side-effect associated caries	– Collaborate with oncology, SLT & dietitian to align healthcare information & delivery
– Advice on active jaw mobility exercises in conjunction with SLTs	– Physiotherapy support
	– Dry mouth gels & saliva substitutes
– Plan for dental extractions as soon as possible, to allow for adequate healing	– Extractions ≥10 days prior to radiotherapy; oncologists to consider recent extraction socket(s) from teeth as 'organs at risk'
	– Design & fabrication of radiation stents where appropriate
– Arrange for provision of dental restorations where appropriate	
– Discuss cariogenic potential of nutritional supplements with patient. Collaborate with dietitians to balance optimisation of nutritional status with prevention of rampant dental caries	
– Arrange prescription for 1.1% sodium fluoride toothpaste & fluoride mouth rinse 0.05% for patients at risk of caries	– Arrange for supply of toothpastes containing casein phosphopeptide amorphous calcium phosphate for patients at risk of caries, e.g. Tooth Mousse®
– Instruction on maintenance of good oral hygiene: effective toothbrushing, interdental cleaning (dentate patients) & denture hygiene delivered by appropriately trained dental care professional, e.g. dental hygienist or therapist	
– Record minimum dataset: maximum inter-incisal opening or equivalent if edentulous or partly dentate; perception of limited opening; xerostomia	

MDT = multidisciplinary team; CRD = consultant in restorative dentistry; SLT = speech and language therapist

Table 3. Peri-treatment

Essential	Desirable
OMFS head & neck surgical procedures	
– CRD to place primary implants where appropriate & as agreed with OMFS team	
– CRD collaboration with OMFS team in theatre during maxillectomy without surgical reconstruction for: impressions for interim obturator; surgical obturator fit	– Provision of surgical obturator to be held in reserve for maxillectomy cases planned for surgical reconstruction
– CRD collaboration with OMFS team in theatre during zygomatic implant placement	– CRD to place zygomatic implants
Radiotherapy	
– Liaison with oncology & cancer specialist nurses, SLTs, dietetics, & oral surgery team via development of communication network & agreed peri-treatment oral care management plans	
– Access to dental hygienist as part of pre-radiotherapy assessment to ensure oral hygiene instruction & hygiene treatment for each patient	

OMFS = oral and maxillofacial surgery; CRD = consultant in restorative dentistry; SLT = speech and language therapist

Post-surgery

Following maxillofacial surgery for head and neck cancer, most patients will have residual dental or orofacial derangement in their anatomy (Table 4).[485] This may be a result of pre-surgical dental extractions, and/or the removal of teeth and hard or soft tissues to achieve clear margins. Prosthetic replacement of teeth and associated hard and soft tissue may be achieved using conventional or implant-retained prostheses. Dental implants have been shown to be an appropriate treatment modality.[486] Smokers, patients who cannot maintain adequate oral hygiene and those with a history of previous osteoradionecrosis are less suitable for implant treatment because of an increased risk of complications.

A post-resection assessment should be undertaken – ideally in formal joint restorative dentistry and maxillofacial clinics – to discuss prosthetic oral rehabilitation, and to plan any pre-prosthetic surgery such as vestibuloplasty, the release of tethered flaps and the use of free gingival grafts needed to facilitate prosthetic rehabilitation. Second-stage surgery to expose primary implants will also be planned at this stage.

Where primary implants have not been placed, secondary intra-oral implants may now be planned and placed in native (maxillary, zygomatic or mandibular) bone, or in grafted bone. Implants may also be used extra-orally for orofacial prostheses.

In a scoping literature review, the pooled five-year survival rate for primary placed implants was 92.8 per cent (95 per cent

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Post-maxillofacial surgery

Essential	Desirable
Post-surgery oral rehabilitation clinics to consider: – Pre-prosthetic surgery – Planning second-stage surgery on primary implants – Secondary implant placement	Joint OMFS & CRD collaboration in formal oral rehabilitation clinics
CRD to plan & place secondary implants	CRD theatre list for secondary reconstructive procedures
Definitive conventional rehabilitation	Work in conjunction with maxillofacial prosthetists & reconstructive scientists for orbital, nasal & extraoral prostheses retained with or without implants
Definitive maxillectomy rehabilitation with obturators & secondary zygomatic implants ± conventional implants	
Close collaboration with oncologists regarding radiotherapy fields & dose when planning for secondary implants close to or in radiotherapy fields	
Discharge to primary care on completion of oral rehabilitation with management plan & point of contact for re-referral to CRD	

OMFS = oral and maxillofacial surgery; CRD = consultant in restorative dentistry

confidence interval (CI) = 87.1–98.5), and for secondary placed implants it was 86.4 per cent (95 per cent CI = 77.0–95.8), demonstrating a higher rate for primary placement. A higher survival rate has been reported for primary implants when compared to secondary implants;[472,487] however, a confounding factor may be that less complex cases are selected for primary implant placement, whereas delayed placement is favoured in more complex cases or more extensive tumours, which inadvertently affects survival rates. In a systematic review by Barber *et al.*,[488] primary implants had a survival rate of 96–100 per cent, with a follow up ranging from 15 to 96 months.

Implants placed in grafted bone have been shown to require further surgical soft tissue manipulation because of the lack of keratinised mucosa around the implants,[471] but still have a survival rate of 82–100 per cent up to 12 years later.[489]

Dental implants can be placed before or after radiotherapy. The survival of dental implants placed 12 months before or after radiotherapy showed no significant difference,[490] although those placed 6–12 months after radiotherapy have shown a minimally greater risk of failure than those delayed further.[491] Studies prior to 2007 show a difference in survival between implants placed in radiated and non-radiated bone, but more recent studies fail to show a difference.[492] In irradiated bone, the survival rates are 74–97 per cent.[493–495] Radiotherapy doses over 55 Gy have been shown to impact on implant success,[496,497] but bone grafting, smoking and implant positioning have an even greater impact, with higher failure rates in irradiated grafted bone.[497] Radiotherapy should therefore not be considered a frank contraindication to implant placement,[495] although doses over 60 Gy should be considered with caution, especially when placing implants in the maxilla.[494]

Placing secondary implants in irradiated patients carries the risk of osteoradionecrosis development. The results of the 'HOPON' (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis) trial do not recommend consideration of hyperbaric oxygen for dental extractions or implant placement in irradiated mandibles.[498]

Because of the increased time to rehabilitation in secondary implant cases[471], and the lack of evidence that radiotherapy post-placement results in implant failure or osteoradionecrosis,[499] there is an increasing trend to support primary placement where this is logistically possible. However, costs and resources such as 3D scanning and implant planning software can be a limiting factor.[500]

Post-(chemo)radiotherapy

Patients who were seen prior to radiotherapy will be reviewed again soon after treatment is completed given the increased risk of dental disease in the immediate post-(chemo)radiotherapy phase (Table 5). The main oral side effects of trismus, xerostomia, caries and osteoradionecrosis are assessed. Periodontal therapy prior to (chemo)radiotherapy, and periodontal maintenance thereafter, is advised.[501]

Treatment of head and neck cancer and its associated side effects can adversely affect patients' health-related QoL.[502] Health-related QoL is integral for patient care[503] and should be regularly assessed. Information from health-related QoL questionnaires can help improve patient care and can be used in treatment decisions.[502] The patient will remain under the care of the restorative dentistry consultant until oral side effects have stabilised and are manageable by the patient. Discharge to primary care can then take place, with clear instructions on providing care for the patient as well as information on when to refer back, if needed.[504]

Research

Predicting and managing the oral and dental complications of head and neck cancer treatment is complex, and requires the input of highly specialised clinicians. Following the NHS Getting It Right First Time approach, Restorative Dentistry UK have produced clear guidance on best practice.[465]

The quality of patient care and outcomes can be improved by developing clinical networks. The Restorative Dentistry UK Head and Neck Cancer Clinical Excellence Network aims to connect consultants and specialty trainees in restorative dentistry across the UK in order to work at improving outcomes, facilitating multicentre research and audit, and reducing variation, so that the quality of, and access to, patient care are improved. Crucially, the Restorative Dentistry UK Head and Neck Cancer Clinical Excellence Network works with the other MDT clinical specialties, including ENT and maxillofacial surgery, oncology, cancer specialist nurses, dietitians, and speech and language therapists, so that outcomes are meaningful and not produced in a clinical vacuum.

Now that 100 per cent of Scottish and Welsh MDTs and over 80 per cent of English MDTs have restorative dentistry consultant input, the development of multicentre studies is possible. As part of holistic, patient-centred care, future research and audit should aim to improve dentally focused

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 5. Post-(chemo)radiotherapy

Essential	Desirable
Review by CRD team soon after completing treatment	Close collaboration with oncology, SLT & dietetics at immediate post-treatment stage
Record minimum dataset each visit: – Maximum inter-incisal opening (equivalent for edentulous or partly dentate) – Perception of limited opening – Xerostomia – Oral nutritional supplement use	
Reinforce jaw mobility exercises	Collaboration with SLT
For patients with xerostomia, consider use of saliva substitutes for symptomatic relief	Saliva substitute when prescribed for dentate patients should ideally be neutral & not acidic
Check for healing of any extraction sockets	
Lifelong continuation of prescription for 1.1% sodium fluoride toothpaste for patients at risk of caries	
	Continue toothpaste containing casein phosphopeptide amorphous calcium phosphate for patients at risk of caries
Review by appropriately trained dental hygienist for advice regarding oral hygiene & dental care, especially in presence of nutritional supplements in liaison with oncology team	
– If dental extractions are unavoidable post-radiotherapy, then consider referral to specialist oral & maxillofacial surgeon – Post-radiotherapy extractions should be carried out with minimal trauma & preferably with primary wound closure – Oncologist may provide information regarding radiotherapy dose & field	
Candidal infections should be treated with antifungal drugs & chlorhexidine gluconate, & denture hygiene should be recommended where appropriate	
Continue review in specialist head & neck unit until patient: – Has ceased nutritional supplement use or is managing caries prevention methods effectively – Can comfortably tolerate treatment by a dental hygienist – Can use fluoride products comfortably	
Discharge to primary care with management plan & point of contact for re-referral to restorative dentistry	

CRD = consultant in restorative dentistry; SLT = speech and language therapist

pre-surgical planning, as supported by patient-related outcome measures with the use of the Patient Concerns Inventory. A focused Patient Concerns Inventory in relation to oral and dental health would be useful. The introduction of minimum dataset collection – including the number of decayed, missing and filled permanent teeth ('DMFT'), and implant placement and rehabilitation – will help inform future research. Service delivery and workforce data from various centres will help develop and deliver best treatment to patients of this cohort.

In the future, the role of the restorative dentistry consultant will continue to evolve to address oral impacts of emerging technologies such as robotic surgery, immune therapy and proton beam therapy. Ongoing engagement with consultants in restorative dentistry will be essential to maximise the benefit of these technologies for patients.

Chapter 14: Psychological management in head and neck cancer

Table of Contents

Key points

- Develop information services for patients and carers. Consider introducing new technology to collect routine patient self-report data on health behaviour, psychological responses to care received, outlining of key messages and outcome assessments.
- Develop decision-making tools (such as explanatory tablet applications, e.g. Patient Concerns Inventory) to aid patients in entering into discussion with the multidisciplinary team (MDT) to agree on a treatment plan.
- Collect routine psychological assessments at key points during the course of care. These indicators must be supported with dedicated and tailored interventions to prevent neglecting identified psychological distress or depression.
- Focus on the level of support and intervention that the current team can realistically provide with the current level of resources; remain cautious when introducing change, but strengthen and build upon supports already available.
- Develop more comprehensive support services by improving generic communication skills training for current staff, and ensure consistency of message-giving to patients and/or carers across the MDT.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Introduce staff training to assist with the management of potential burnout in MDT staff; consider flexible responses including secondments, study breaks and peer-support programmes.
- Audit current psychological services applied in the head and neck cancer service; identify current usage and gaps in service, and develop forward plans to address these gaps.
- Assess current capability of specialist clinical nurse skills to support head and neck cancer patients psychologically, and introduce dedicated training and supervision programmes.
- Actively search for clinical psychology service input and negotiate improved access and response time; estimate likely demand of service.
- Consider appointing sessional input of a clinical or counselling psychologist or psychotherapist to the cancer network.
- Identify liaison psychiatry service, and negotiate referral pathway and response time.

Introduction

The patient with head and neck cancer and their carers have considerable challenges to overcome.[505] First, the initial meeting of the patient with the care team is regarded with foreboding by the patients and family. An MDT approach to concentrate diagnostic data collection has shown considerable advantages for patients in enhancing speed of curative or palliative interventions.[506] A study to predict the variation of delay in initial treatment has shown that there is no simple systematic factor or sets of factors responsible, other than possibly the severity of illness.[507] The second major challenge is the psychological experience of the patient with head and neck cancer. This has been closely described in a systematic review and meta-synthesis.[508]

In addition to the negative psychological effect of a diagnosis and treatment of this cancer, there is a recognisable economic burden, with wider implications for the patient, their family and health service when suffering mental duress.[509] Although many patients appear to cope surprisingly well, a sizeable minority experience considerable psychological effects, including uncertainty about the return of cancer, disruption to daily life, a diminished self, attempts to understand the changes that occur and finding a plan forward. Treatment recovery may be hampered by mood changes, whereas longer-term psychological states may feature some months and even years following initial treatment.[510] The field of clinical and health psychology has expanded in the past five years, and provides both firmer evidence and more diverse approaches for care teams to explore and incorporate enhanced service features. This chapter expands and supports the previous edition.

Communication of diagnosis and treatment

Evidence from areas of treating cancer at other sites has demonstrated clearly that the way in which the diagnosis is presented to the patient is important to their psychological response to the disease and treatment.[511,512] It is important that the patient is told explicitly that they have a cancer and its nature is described, and that all treatment available is presented to them in an unambiguous manner. This information needs to be relayed consistently by all members of the team, so that the patient and carer are able to adapt, especially to be sensitive in the relaying of 'bad' news. This needs to be closely exercised, as this is often the first contact the patient has with the head and neck team. The initial contact has great impact, over and above the actual time spent. Evidence shows that delivering information without interruption, avoiding jargon and showing appropriate empathy are important features of the diagnostic interview that help prevent illness concerns developing.[512] Decision-making and designing of tools to improve communication between clinician and patient are improving rapidly, and highlight an important growth area for the future of head and neck cancer care where complex choices are discussed and commitments made with patients.[513,514] Surgery, a major treatment modality, has received considerable attention regarding how to assist patients in coping with procedures. Providing early psychological support and frequent distress screening were features identified for improving outcomes.[515]

Delivering information about treatment and recovery

Considerable efforts have been expended to determine the information needs of head and neck cancer patients.[516,517] Poor satisfaction with information supplied by the team was predictive of patients' lowered mood and quality of life (QoL) in the longer term.[518] More information was required on financial advice, support groups and ability to return to work. Virtually no studies have been reported on patients' desire to be involved in treatment decision-making. The nature of the disease and its complex profile of mixed treatment methods have favoured the MDT's sole authority to determine treatment regimens. However, large datasets of 'normative' QoL estimates linked to various treatment options have been compiled, which enable the team to start sharing the potential risks and benefits of certain treatment packages, and tailoring to patient preferences of retained functions on recovery.[519]

Managing psychological distress

The use of routine assessments for psychological distress such as the Distress Thermometer and the Hospital Anxiety and Depression Scale are being considered as means to identify those patients who may suffer during the process of treatment preparation, the treatment itself, the initial stages of recovery and the follow-up out-patient appointments.[520] These assessments have the ability to capture those patients who would not necessarily be identified by the MDT as needing psychological support.[521] Two issues are raised, however: an increased number of patients in need of assistance; and screening measures that may indicate substantial distress when there is none because of measurement error. Hence, it is recommended as essential that service heads organise links with local health service providers to input directly into the MDT and create a referral pathway.

The types of psychological distress require attention and definition. The classical typology of mental distress includes anxiety and depression. In addition, assessments of recurrence fears (the most frequently reported concern of head and neck cancer patients), facial disfigurement, body image, loneliness and sexual dysfunction may also be compiled within an MDT assessment profile library for occasional use when required.[522,523] Recurrence fears have been found to be linked closely to depression in patients, and some evidence exists that patients can stimulate these fears in their carers.[524] Furthermore, it is now recognised that high recurrence fears promote more requests for medical services, incurring higher treatment and surveillance costs.[525] Acknowledgement of the patient's experience of the severity and longevity of these

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

fears is important, and more in-depth approaches may be required to alleviate debilitating distress.[526] It is widely accepted that the patient's treatment and tumour characteristics are not good predictors of who will experience high fear of cancer recurrence levels.[527,528] The exception to this generality is patient age. The young patient reports a greater reported fear of cancer recurrence level.[529] Gender may also be implicated, but less so.[530,531] Two types of patient experience of fear of cancer recurrence have been found in the six months following diagnosis. The first is a 'low declining' group and a sizeable minority (20 per cent) of 'high stable' fear of cancer recurrence sufferers.[532] This fear of cancer recurrence characterisation of head and neck cancer patients strongly suggests that regular assessment of fear of cancer recurrence using a brief assessment is indicated, especially as patients tend not to volunteer their concern unless explicitly questioned.[533]

The profile of staff expertise and skills needs close inspection to enable a flexible and tailored matching of needs to professional training of support or specialist staff. The MDTs need to plan their services to provide an escalating level of care according to the specific psychological difficulties presented by the patient. Stepped-care approaches are being developed and tested.[534] Initial support and educational approaches can be offered widely by the MDTs, with brief structured interventions provided by staff with additional training or a mental health qualification (counselling) to those patients with an identifiable psychological problem. More extensive interventions for patients with complex psychological difficulties can be offered, usually by referral to clinical psychologists, psychotherapists and liaison psychiatrists. A recent review and meta-analysis of fear of cancer recurrence structured interventions has been conducted.[535] The effect size of the Adjustment to the Fear, Threat or Expectation of Recurrence ('AFTER') intervention designed for patients with head and neck cancer is comparable to other well developed but more general programmes ('Conquer Fear' and Survivors' worries of recurrent disease ('SWORD') interventions). The services offered would consist of complex psychotherapeutic approaches. A simple example of a stepped-care pathway is presented (Figure 1) for those patients with moderate or extensive fears of cancer recurrence. The pathway is triggered by simple and regular assessments using a four-question patient-rated outcome measure called the Fear of Cancer Recurrence scale ('FCR4') (Figure 2).[536]

The changes in service delivery precipitated by the coronavirus disease 2019 (Covid-19) pandemic, some of which may continue, can produce feelings of isolation and abandonment for those diagnosed with head and neck cancer.[537] Close attention is needed to offset the use of triage procedures due to the virus or delays in diagnostic reports. Successful communication of the team members becomes even more vital to provide consistency of messaging to patients and carers.

Family and social support

Developments are progressing to design interventions that assist communication between patient and carers, with initial results indicating success.[538] It is important for the MDT to raise survivorship issues with patients.[539] Not only does the patient remain watchful for indicators and symptoms that may raise concern for life-reducing disease processes, but also to maintain function for as long as possible. Two areas are pertinent here. First, carers and spouses should be encouraged to use techniques to enhance the adherence of follow-up MDT recommendations. Second, and closely related, is the use of social media to link other members of the local community with similar health conditions and survivorship concerns, who can share information and provide extended social support outside the hospital boundaries. Finally, use of brief telephone contact to assist fear of cancer recurrence concerns, for example, may be considered cost-effective,[540] and, in some

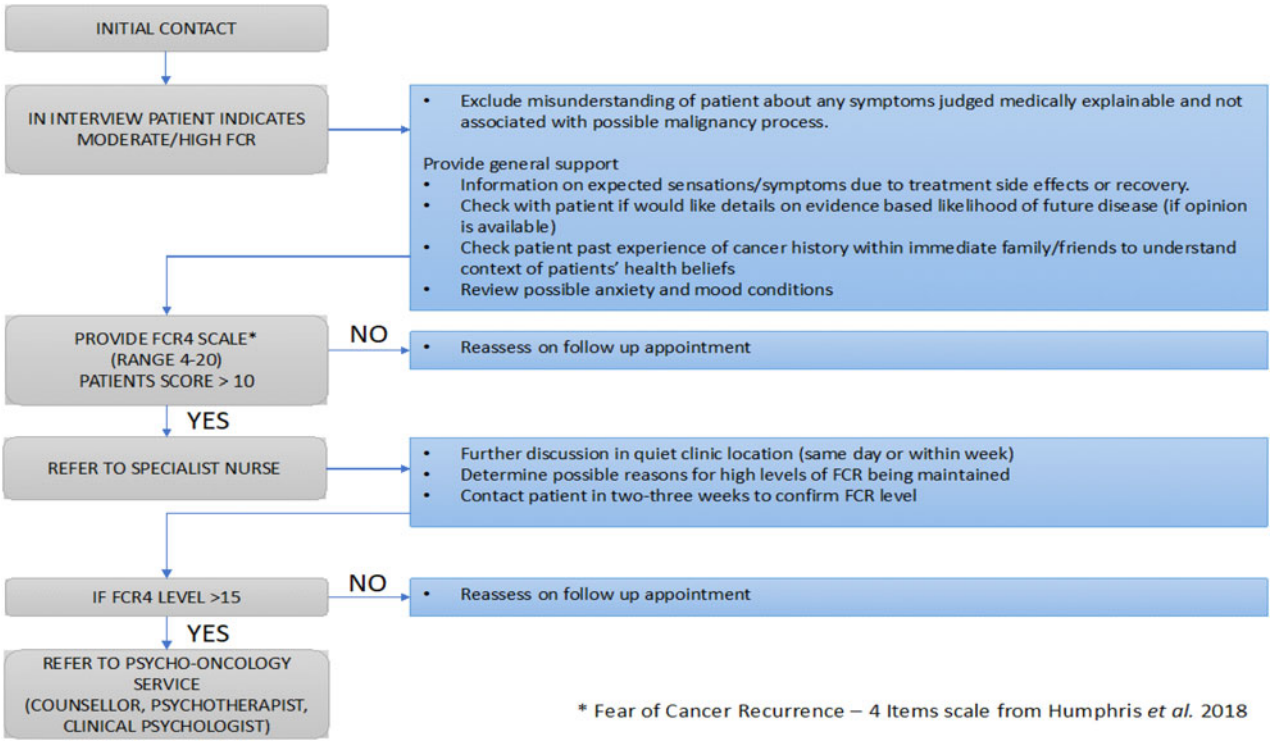


Figure 1. Example of a stepped-care pathway for managing patients' fear of cancer recurrence (FCR). FCR4 = four-item Fear of Cancer Recurrence scale[536]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

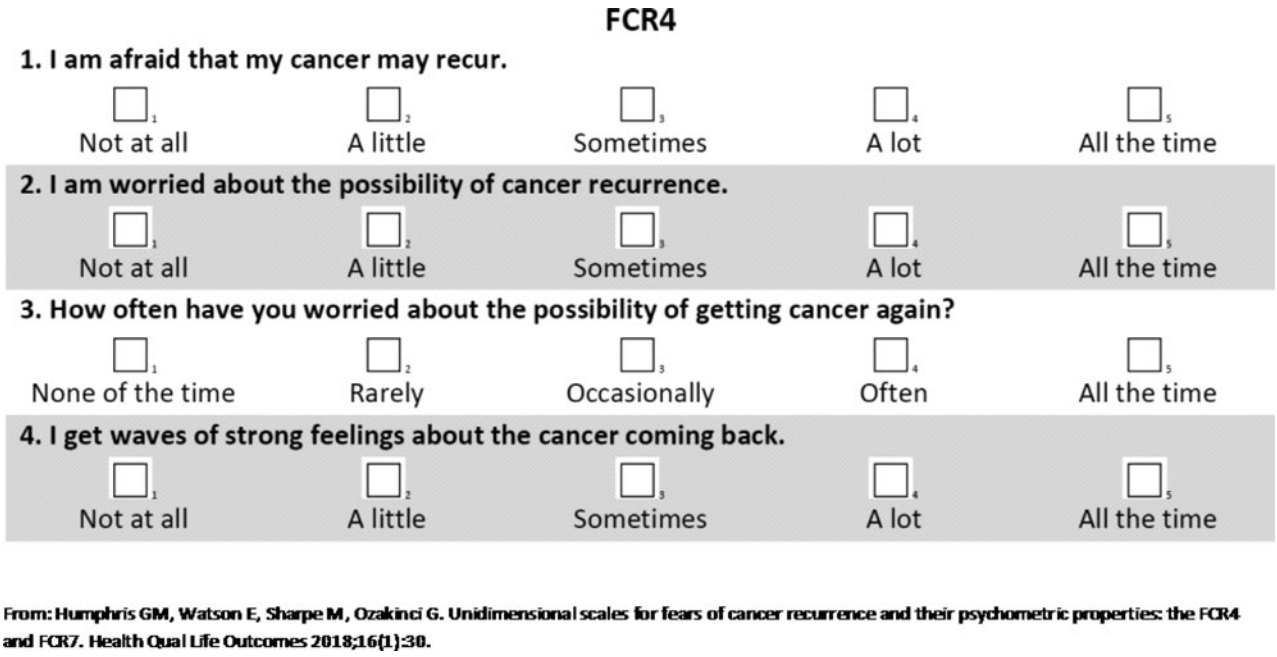


Figure 2. 'FCR4' – four-item Fear of Cancer Recurrence scale.[536]

cases, online psychological interventions may be offered as a way to reduce face-to-face contact.[541]

End-of-life issues

Communication with the patient assumes even greater importance when curative treatment options are not available and care focuses towards a palliative approach.[542] Areas such as assessing patient preferences concerning life expectancy and control of pain, and managing fears of uncertainty and family reactions, are features of these discussions with the staff of the MDT and palliative care services.

Pressure on multidisciplinary teams and staff burnout

The psychological burden to staff requires recognition, supervision and training. A recent qualitative study identified themes that describe staff experiences in providing a comprehensive service to patients.[543] The authors recommended advanced communication skills training, trauma sensitivity training and self-compassion. Excellent leadership qualities are essential in running such MDTs.[544] This field requires further study and development to enable staff to maintain their exemplary service levels.[545]

Chapter 15: Palliative care in head and neck cancer

Table of Contents

Key points

The key points concerning the role of specialist palliative care teams within the provision of palliative care are:

- Integration of a multidisciplinary, person-centred approach to care (good practice point (G))
- Liaison with both primary care and specialist palliative care teams (G)
- Clear communication of treatment options to facilitate decision-making on the treatment pathway (G)

> 'Palliative care is an approach that improves the quality of life of patients and their families who are facing problems associated with life-threatening illness. It prevents and relieves suffering through the early identification, correct assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual'. (World Health Organization (WHO), 2020)[546]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

The WHO's encompassing definition of palliative care outlines the aim to achieve the best quality of life for patients and their families.[546] This is especially pertinent for those with head and neck cancer who often have numerous and complex palliative care needs, including a high degree of symptom burden. Every healthcare professional has a role and responsibility towards providing palliative care. In order to offer a collaborative approach, each member of the multidisciplinary team (MDT), including community healthcare practitioners, should have core palliative care knowledge and skills.

The following guidelines provide an overview of the key palliative care issues related to those with head and neck cancer. These include:

- The role of specialist palliative care teams within the provision of palliative care
- Management of common physical symptoms for those with incurable head and neck cancer
- Bleeding, airway and wound management
- Principles involved in advance care planning including resuscitation and care for the dying patient
- An overview of the key areas where further research is needed

Within these guidelines, we have used the American Society of Clinical Oncology definition of 'advanced cancer', namely 'those with distant metastasis, late-stage disease, cancer that is life limiting, and/or with prognosis of 6 to 24 months' as a general reference point.[547]

How palliative care should be delivered

Palliative care for those with head and neck cancer, in its broadest remit, should be delivered within a multi-professional context. As a minimum, this should include a surgeon, oncologist, specialist palliative care clinician, clinical nurse specialist, dietitian, speech and language therapist, emotional support team, and community team, all embedded within a clear communication framework across the acute and community settings. Developing effective working relationships, pathways and closer integration of specialist palliative care teams and the referring surgical and oncology teams is imperative.[547–549] Models within the in-patient and out-patient setting have been developed,[547,550] e.g. 'co-rounding' of specialist palliative care and oncology teams.[551] When there is a shift in treatment intent from curative to incurable, this should correlate with a directional move of care delivery from the surgical and oncology team to include the specialist palliative care MDT.

Open and honest communication is fundamental to enable optimal delivery of palliative care, as advanced head and neck cancer can be unpredictable, necessitating complex decisions with uncertain outcomes. Discussions should be centred on prognostication information, and the establishment of treatment goals based on patient and family priorities. Research has demonstrated that head and neck cancer patient preferences and clinicians' priorities are often out of line,[552] which accentuates the need for skilful communication by the healthcare team to explicitly inform patients of anticipated benefits and burdens of available treatments. Palliative care delivery should be underpinned by the principles of person-centred care, shared decision-making and respect for patients, given the vulnerability of this patient population.[553]

When specialist palliative care teams should be involved

The importance of timely identification of head and neck cancer patients who may benefit from specialist palliative care services is widely recognised.[552,381] The key challenges for clinical teams are identifying who should be referred to specialist palliative care services and determining when is the optimal time (Table 1). When referrals are too late, head and neck cancer patients can be denied the full benefit of specialist palliative care, including timely symptom management and advance care planning conversations.[554] Conversely, referrals that are too early may result in patients with few concerns being assessed, thus inappropriate use of a specialist resource.[550]

Common physical symptoms

Within this section, we have focused on pain, nausea and vomiting, constipation, and the management of secretions. This is not an exhaustive list; for other details about specific symptoms and medications, we would advise reference to texts such as the *Palliative Care Formulary*[555] and *British National Formulary*.[556] As the evidence base has limitations, we have provided advice for commonly used medications. Consultation with the local pharmacy and specialist palliative care teams is advisable in case of regional variations. Within specialist palliative care teams, medications that are 'off-label' or used in unlicensed ways are generally accepted. Note that 'unlicensed medicine' refers to a medicinal product that does not have a UK marketing authorisation;[555] 'off-label use' refers to the use of a medicine with a UK marketing authorisation for an indication outside of its licensing.[555]

Pain

Key recommendations for the management of pain:

- A detailed, individualised pain history should be taken (evidence-based recommendation (R))
- Awareness of the signs and symptoms of opioid toxicity is important. This may include drowsiness, confusion, vivid dreams, hallucinations, myoclonus and pin-point pupils, occurring before respiratory rate reduces and level of consciousness decreases (good practice point (G))
- Consider the addition of adjuvant medications, local analgesics and disease-modifying treatments when managing pain (G)
- First-line adjuvants include gabapentin, pregabalin and amitriptyline (R)
- Review and reassess effectiveness (G)

Table 1. Reasons to prompt referral for specialist palliative care team involvement

High degree of symptom burden (diverse & complex)
Enhanced communication needs, e.g. complex decision-making with uncertainty about treatment outcome; advance care planning
Anticipated risk of terminal haemorrhage or airway difficulties
Complex psychosocial issues, including limited social support structures
Complex end-of-life care issues, including issues likely to arise in bereavement

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Detailed pain assessment*

Character: document patient's own words, e.g. 'sharp' or 'dull'
Site: primary tumour site, around nodal disease, whether radiating to other areas
Severity: can be recorded on numerical pain rating scale of 0–10 (0 = no pain; 10 = worst pain imaginable)
Exacerbating factors: relationship to eating, swallowing, movement
Relieving factors: positioning, medication effectiveness, heat, cold
Other influencing factors: psychological, social & spiritual, in keeping with 'total pain' concept

*Including, but not limited to, the listed factors

An estimated two-thirds of patients with advanced head and neck cancer have severe pain requiring management with opioids (Table 2).[557] The pain is often multifactorial, relating directly to the tumour and/or occurring as a result of treatment. Initiating analgesia can be guided by using the WHO analgesic 'pain ladder', a simple three-step approach to managing cancer pain (Figure 1).[558,559]

This approach, however, must be used as a general guide only, alongside an individualised assessment of pain and a management plan tailored to the individuals' specific needs. In practice, especially for those with severe uncontrolled cancer pain, it would be appropriate to progress directly to step 3 and prescribe a strong opioid, with steps 1–2 being omitted.[560] A recent open-label randomised, controlled trial[559] supported a two-step approach (omitting the weak opioid step) as an alternative option for cancer pain management, which is associated with few side effects and is cost-effective.

Assessing pain

A detailed pain assessment should be conducted (Table 2).[561] This can help identify the primary cause of the pain and in turn indicate which treatment(s) might be most effective, including the use of non-pharmacological interventions and disease-modifying treatments. Consideration should be given to the overall holistic needs of the patient, as additional factors such as psychological, social and spiritual problems can influence the patient's pain experience and response to treatment, a concept referred to as 'total pain'.[562]

Types of pain and their management

Nociceptive pain may be present as a result of direct tumour invasion of soft tissue and bone. Oral morphine would usually be the first choice because of familiarity and availability (Tables 3 and 4).[563,564] It is important to explain clearly to patients the difference between the immediate release and modified release preparations, as confusion can lead to opioid toxicity (Table 3).

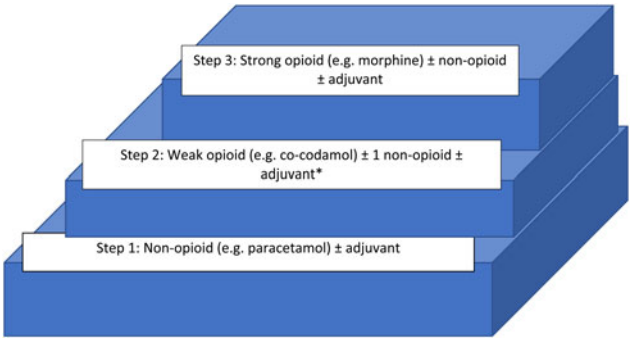


Figure 1. The World Health Organization analgesic ladder.[558] *Note that recent evidence[559] supports that step 2 may be omitted. An individualised approach should be taken, tailored to the patient.

Neuropathic pain may be present because of the compression or infiltration of nerves. Opioids may provide limited relief for such pain, and the use of an adjuvant (a drug that has a primary indication for something other than pain, but which can have an analgesic effect) may be required. First-line adjuvants would be amitriptyline, gabapentin or pregabalin (Table 5).[565,566] The choice of medication can be influenced by factors such as side effect profile, contraindications, patient co-morbidities and dosing regimen.

Oral mucosal pain is common in head and neck cancer patients, but there is a lack of robust evidence supporting the management of oral mucositis.[567] Treatment should focus on the underlying cause, maintaining oral hygiene, providing pain relief, protecting ulcerated areas and treating any secondary infection. Topical anaesthetics such as benzydamine and/or oxetacaine can be used. The regular application of coating agents (such as Orabase™ and Gelclair™) may provide some short-term relief. The use of topical opioids can be helpful, although immediate release morphine (oral solution, which contains alcohol) may exacerbate oral pain. Some centres can prepare a special-order morphine, which can be held in the mouth for a local analgesic effect. Otherwise, consider the use of oxycodone liquid, as this is alcohol-free.

Patients may have other types of pain related to their cancer, including visceral pain from metastatic disease. The same approach to pain assessment should be taken, with additional consideration given to specific types of pain. For example, patients with liver capsule pain may benefit from a trial of dexamethasone. Pain management can be complex and supported through discussion with the specialist palliative care team, including escalation to medications used under specialist supervision such as methadone or ketamine, if required.

Nausea and vomiting

Key recommendations for the management of nausea:

- Identification of the underlying cause(s) can help direct management (good practice point (G))
- Non-pharmacological and pharmacological methods should be used to manage nausea and vomiting (G)
- Choose the most suitable anti-emetic depending on the likely cause(s) (G)
- Consider the most appropriate route of administration, formulation and dose (G)

Nausea is defined as an 'unpleasant sensation of the need to vomit', presenting with or without vomiting,[568] and often in conjunction with other autonomic symptoms, e.g. cold sweats, tachycardia and diarrhoea. Persistent nausea and frequent vomiting significantly reduce quality of life, and can result in complications like dehydration and malnutrition.[569] In a similar approach to pain management, comprehensive assessment is needed to identify and treat the cause(s), and both non-pharmacological (Table 6) and pharmacological methods should be used.

Many different causes can contribute to nausea and vomiting in those with head and neck cancer (Table 7).[568–570] Identification of the underlying cause(s) can help direct pharmacological management (Table 8).[555,568,569,571] We

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Commonly prescribed short-acting opioids

Opioid	Formulation(s)	Route(s)	Starting dose(s)	CSCI?	Cautions & contraindications
First-line: morphine sulphate, immediate release	Oral solution (Oramorph™)	By mouth or via gastrostomy tube	Suggested starting dose 5 mg by mouth (check local guidelines)	No	Consider a lower starting dose in renal impairment or older adult patients. Contraindicated in renal failure cases. If morphine not tolerated because of side effects, may convert to oxycodone
	Tablets (Sevredol™)	By mouth		No	
	For injection	Subcutaneous (IV – rarely)	Half the oral dose	Yes	
Commencing opioids:					
– If not already taking an opioid, consider commencing immediate release morphine (check local guidelines)					
– Many centres recommend initially using this as required only, with a minimum 1-hour interval; others additionally prescribe immediate release morphine 4 times per day					
– After 24–48 hours, review response & any side effects, & use this as guide for commencing dose of modified release morphine 12-hourly					
– Calculate breakthrough dose of immediate release morphine as 1/6th of total 24-hour dose (to nearest practical dose)					
Oxycodone, immediate release	Oral solution	By mouth or gastrostomy tube	Suggested starting dose of 2.5 mg by mouth (check local guidelines)	No	Contraindicated in moderate–severe liver impairment. Requires dose reduction or increased dose interval in renal impairment cases
	Capsules		1.5–2 times more potent than oral morphine	No	
	For injection	Subcutaneous (IV – rarely)	Half the oral dose	Yes	
Alfentanil	For injection	Subcutaneous	Some centres use when required subcutaneously for pain in renal failure (check local guidelines); if unfamiliar with use, please seek local specialist advice	Yes	Alfentanil syringe driver in renal failure (eGFR <30). Some centres use fentanyl (check local guidelines)
Fentanyl	Sublingual tablet or buccal lozenge	Oromucosal	Specialist use – seek advice	No	Some centres use fentanyl syringe drivers in renal failure cases (check local guidance)
	For injection	Subcutaneous	Used in some centres. If unfamiliar with use, seek local specialist advice	Yes	

Note: when initiating opioids, make patients aware of the associated driving regulations.[574] CSCI = continuous subcutaneous infusion; IV = intravenous; eGFR = estimated glomerular filtration rate (in ml/minute/1.73 m^2)

have not specifically mentioned chemotherapy- or radiotherapy-induced nausea and vomiting, or post-operative causes, as local management guidelines are often in place.

Generally, the oral route of administration may not be available or appropriate (if there is persistent nausea or vomiting); therefore, the subcutaneous route and continuous subcutaneous infusions can be used. Intravenous and intramuscular administration is usually avoided because of issues with venous access and pain on or after administration. In patients unable to swallow or who have enteral feeding tubes, the NEWT Guidelines[571] can be used to help identify alternative routes and administration methods.

Constipation

Key recommendations for the management of constipation:

- Assess stool frequency and consistency, to determine whether stimulant and/or softener required (good practice point (G))
- Assess patient's previous experience of laxatives and tolerability (taste, volume, frequency) (G)
- When initiating opioids, also prescribe a regular low-dose stimulant or osmotic agent (G)

Constipation is a distressing symptom, and those with head and neck cancer are particularly vulnerable because of dietary factors (struggling to obtain adequate fibre or hydration), and iatrogenic causes (opioid analgesia, serotonin antagonists for nausea, and chemotherapeutic agents). Favourable management of constipation is preventative, ensuring patients are adequately provided with laxatives if requiring constipating therapies.[572,573] Individual patient needs should be considered, so if a patient has prior experience with laxatives, the preferred agent may be revealed. Otherwise, consider factors such as available routes and tolerance of volume for your patient. Generally, continue with one agent from each class and titrate (Table 9). It is worth noting that an additional class of 'bulk-forming' laxatives exist, but are not generally recommended in palliative care. Suppositories may be required, followed by enemas, to prevent faecal impaction in severe cases.

Opioid-induced constipation is common, so, when initiating opioid treatment, also start a regular low-dose stimulant or osmotic agent, and titrate to affect.[574] If constipation persists beyond a few days despite regular laxatives, a rectal examination with or without enema is the next step. If these methods fail, specialist palliative care advice can be sought for use of peripheral opioid antagonists such as naloxegol and methylnaltrexone.[573,574]

Secretions

Key recommendations for the management of secretions:

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Commonly prescribed long-acting opioids*

Opioid	Formulation(s)	Route(s)	Starting dose	Cautions & considerations
Morphine, modified release	Tablets (MST Continus™)	By mouth	Use response to immediate release morphine to guide starting dose of modified release morphine (except if already on weak opioid such as codeine, then convert this to find appropriate starting dose)	Avoid, or convert to alternative, in renal failure cases
	Capsules (Zomorph™)	By mouth or gastrostomy tube – open capsules		
Oxycodone, modified release. If morphine not tolerated because of side effects, consider conversion	Tablets	By mouth; only available in tablets, so might be difficult for patients unable to swallow	As above, use immediate release oxycodone over 24–48 hours to guide modified release oxycodone titration	Avoid in liver impairment & significant renal failure cases
Morphine or oxycodone	For patients who are vomiting or are unable to take medications via mouth, or via gastrostomy or NG tubes, may need syringe driver over 24 hours	Syringe driver	CSCI per 24-hour dose = half the total 24-hour oral dose	
Alfentanil/fentanyl	Required in renal failure cases; consult local guidance or seek specialist advice	Syringe driver	Seek specialist advice	
Fentanyl	Patch	Transdermal	Fentanyl patch (changed every 72 hours). Do not start in opioid-naive patient. Lowest dose patch is 12 μg/hour (equivalent to oral morphine 30 mg in 24 hours)	Fentanyl patches can be used in severe renal failure cases, when no oral route, or according to patient preference; however, these are not recommended in unstable pain cases
Buprenorphine	Patch	Transdermal	Buprenorphine patch (changed every 3, 4 or 7 days depending on preparation & strength). Lowest dose patch is 5 μg/hour (equivalent to oral morphine 10 mg in 24 hours)	

Note: when initiating opioids, make patients aware of the associated driving regulations.[564] *Including syringe drivers, which although are short-acting preparations, are administered over 24 hours and so provide long-acting pain relief. NG = nasogastric; CSCI = continuous subcutaneous infusion

Table 5. Commonly prescribed neuropathic pain agents

Neuropathic agent	Formulation(s)	Route(s)	Dose	Side effects	Cautions & considerations
Amitriptyline	Tablets or solution	By mouth or gastrostomy tube	Typical starting dose of 10 mg at night. Can increase to 25 mg every night after 3–7 days	Dry mouth, sedation, postural hypotension	Avoid in patients with arrhythmias, heart block, congestive heart failure. May reduce seizure threshold
Gabapentin	Tablets, capsules or solution	By mouth or gastrostomy tube (use solution; if unavailable, capsule contents can be dispersed in water)	Typical starting dose of 300 mg o.d., increasing every few days to t.d.s.	Sedation, dizziness, ataxia	Reduce dose in older adult or frail patients, or those with renal impairment (e.g. 100 mg, & titrate more slowly)
Pregabalin	Capsules or solution	By mouth or gastrostomy tube (use solution; if unavailable, capsule contents can be dispersed in water)	Typical starting dose of 75 mg b.d. Can increase by 75 mg every few days	Sedation, dizziness, ataxia	Reduce dose in older adult or frail patients, or those with renal impairment (e.g. 25 mg b.d., & titrate more slowly)

o.d. = once a day; t.d.s. = three times a day; b.d. = twice a day

- Identification of the underlying cause(s) of secretions will help identify potentially reversible causes of the secretions (good practice point (G))
- Detailed assessment of the types of secretions is essential, as thick or thin or secretions at the end of life are managed differently (G)
- Non-pharmacological methods should be considered to help manage all types of secretions (G)

Although xerostomia (dry mouth) is common in head and neck cancer patients, excess secretions and/or the inability to swallow or clear secretions are often troublesome.[575,576]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 6. Non-pharmacological interventions to manage nausea and vomiting

Control odours (e.g. fungating tumours, wounds, colostomies)
Minimise triggering factors (e.g. sight of food, smell of cooking, noise & motion)
Encourage regular small portions of meals & sips of drink (e.g. starchy foods, cold or fizzy drinks). If gastrostomy feeding tube in situ, discuss with dietetics (e.g. reduce feed volume or rate or changing feed)
Consider acupressure wrist bands
Maintain a peaceful environment where possible (reduce anxiety level)

Potentially reversible causes should be considered (Table 10).[555,576,577]

Reduced salivary production, xerostomia and thick salivary secretions are the most commonly observed complication of radiotherapy.[575] The management of thick, tenacious secretions involves largely conservative measures, such as suctioning, using pineapple juice as a lytic agent, employing a cough assist device, and reducing or stopping the medication potentially causing the secretions if appropriate.[575,578] Humidification, sodium chloride nebules and mucolytics can be considered as treatment for these secretions. Sodium chloride nebules can help loosen the secretions; however, they are unsuitable for patients who cannot expectorate, as it can increase production of liquid sputum. Mucolytics can reduce the viscosity of the secretions, especially in the context of chronic obstructive airways disease (Table 11).[576,578,579]

Drooling or sialorrhoea

The role for palliative care in the management of drooling or sialorrhea will be primarily for patients who have not previously received radiotherapy. Despite the burden of excessive saliva accumulation (sialorrhea) and subsequent drooling having a significant negative impact on the patient's quality of life, there is little research to guide management.[575] Pharmacological management would include antimuscarinics or tricyclic antidepressants (Table 12).[575] Occasionally, under specialist supervision, botulinum toxin injection could be considered if standard treatment is ineffective.[575]

Secretions at end of life

Noisy secretions caused by fluid collecting in the upper airways, also known as the 'death rattle,' occur in about 50 per cent of dying patients.[555,580] If unconscious, this is unlikely to be distressing to the patient, but can cause distress to family and friends witnessing it, so reassurance is important.[555,576,580] Non-pharmacological treatment such as positioning, suctioning and mouthcare can help.[576,580] Antibiotics may be indicated for symptom relief if the secretions are caused by profuse purulent sputum in a semi-conscious patient.[555,576] Pharmacological treatment should be initiated as soon as the first sign of secretions occurs, as they reduce further secretion production, but do not dry out existing secretions.[555,576] A Cochrane review suggests subcutaneous antimuscarinics are of limited benefit, but established practice accepts their use for patients approaching the end of life (Table 13).[555,576,580] If the rattle is associated with distressing breathlessness in a semi-conscious patient, supplement the recommendations above with an opioid and an anxiolytic sedative.[555]

Bleeding, airway and wound management

Key recommendations for bleeding, airway and wound management in the palliative context:

- Rule out any reversible cause, e.g. infection or contributing medications, and consider whether oncological or surgical intervention remains appropriate (good practice point (G))
- Be proactive in initiating advance care planning discussions, especially where risks of acute events could arise (G)
- In an acute, potentially life-threatening event, it is vital that the patient is never left alone (G)
- Manage distress and associated symptoms with both pharmacological and non-pharmacological measures (G)

Generally, it is important to identify individuals with head and neck cancer who are at risk of acute, potentially life-threatening events such as a bleeding episode or airway difficulties. These types of events are estimated to occur for 6–11 per cent of head and neck cancer patients.[581] Identification of the risk enables timely discussions to occur within the MDT about whether further investigation and interventions may be indicated, such as embolisation or radiotherapy.

Table 7. Choosing most suitable anti-emetic by possible cause of nausea and vomiting

Possible nausea & vomiting causes	Possible features	Anti-emetic of choice
Gastric stasis or gastrointestinal tumour infiltration	Ascites, fullness, nausea relieved by vomiting, functional or partial obstruction	Metoclopramide or domperidone
Gastrostomy complications	Abdominal bloating, cramps, excess feed administration	Metoclopramide or domperidone
Chemical- or drug-induced	– Metabolic: hypercalcaemia, renal impairment, hyperuraemia – Drugs: opioids or analgesics, antibiotics, etc.	– 1st line: haloperidol (metoclopramide has a central action & can be used) – 2nd line: levomepromazine
Raised intracranial pressure or intra-cerebral causes	Headache, visual disturbance	– Dexamethasone (if inflammation suspected) – Cyclizine
Vestibular disorders	Vertigo, nausea on motion, other neurological signs	– 1st line: cyclizine – 2nd line: hyoscine hydrobromide or prochlorperazine
Psychological factors	Fear, anxiety, anticipatory nausea	Lorazepam
Cause unknown	Terminal phase (last days of life), unable to determine cause, unable to examine patients	– 1st line: cyclizine or haloperidol – 2nd line: levomepromazine if likely to be multifactorial & broad-spectrum anti-emetic required

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 8. Common choices of anti-emetics used in pharmacological management of nausea and vomiting

Anti-emetics	Receptor sites affinities	Formulation(s)	Doses & routes	Cautions & considerations
Domperidone	Dopamine (D_2) antagonist	– Tablet – Suspension	– By mouth = 10 mg t.d.s. – If unable to swallow tablets, use suspension – Gastrostomy or NG tubes – use suspension mixed with equal volume of water	– Avoid giving with antimuscarinic drugs, e.g. do not combine with cyclizine – Avoid if colicky pain present – Contraindicated with other QT-prolonging drugs
Metoclopramide	Dopamine (D_2) antagonist & 5-HT_4 agonist	– Tablet – Oral solution – Injection	– By mouth, or IV or subcutaneous injection = 10 mg t.d.s. – CSCI = 30–80 mg/24 hours – If unable to swallow tablets, use solution – Gastrostomy or NG tubes – use solution & flush tube with water	– Avoid giving with antimuscarinic drugs, e.g. do not combine with cyclizine – Do not use in Parkinson's patients – Avoid if colicky pain present – Contraindicated in those with epilepsy
Cyclizine	Histamine (H_1) antagonist & acetylcholine antagonist	– Tablet – Injection	– By mouth, or IV or subcutaneous injection = 50 mg t.d.s. – CSCI = 50–150 mg/24 hours (max) – Gastrostomy or NG tubes – tablets can be crushed & dispersed in water	– Incompatibility issues with CSCI – check syringe driver handbook or seek specialist advice if needed – Injections can be painful; may cause CSCI site irritation – Avoid giving with antimuscarinic drugs, e.g. do not combine with metoclopramide – Parenteral administration can cause hallucinations
Haloperidol	Dopamine (D_2) antagonist	– Tablet – Oral solution – Injection	– By mouth or subcutaneous injection = 0.5–1.5 mg when required (max 5–10 mg/24 hours) – CSCI = varying dose; consult local guidance – If unable to swallow tablets, use solution – Gastrostomy or NG tubes – use solution & flush tube with water	– Do not use in Parkinson's patients – Contraindicated with other QT-prolonging drugs
Levomepromazine	Histamine (H_1), 5-HT_2, dopamine (D_2) & acetylcholine antagonist	– Tablet – Injection	– By mouth or subcutaneous injection = 6.25 mg every night or 2-hourly when required (max 25 mg/24 hours) – CSCI = 6.25–25 mg/24 hours – Gastrostomy or NG tubes – tablets can be dispersed in water	– Sedating – Caution in older adult patients with dementia, liver dysfunction or cardiac disease (lower starting doses may be needed) – Available as 6 mg unlicensed tablet in some centres
Hyoscine hydrobromide	Acetylcholine antagonist	– Tablet – Transdermal patch	– By mouth = 150–300 μg 6-hourly when required (max 900 μg/24 hours) – Transdermal = 1.5 mg patch every 72 hours – If unable to swallow, consider using the patch. Tablets can be sucked & absorbed via mucosa – Gastrostomy or NG tubes – tablets can be dispersed in water	– Do not confuse with hyoscine butylbromide – Apply patch behind the ear; alternate ears when changing patches
Dexamethasone	Mechanism unknown	– Tablet – Soluble tablet – Oral solution – Injection	– By mouth = 4–16 mg o.d. (or divided) – Subcutaneous injection = 4–16 mg o.d. (or divided) – Not used 'when required' – If unable to swallow tablets, these can be dispersed in water, or can use soluble tablets or oral solution – Gastrostomy or NG tubes: as above. Consider parenteral route	– Consider gastro-protection – Give morning & lunchtime for divided doses. Avoid evening dosing to prevent night-time restlessness – Ensure adequate mouth care to prevent candidiasis – Monitor blood glucose – Note different strengths of dexamethasone solution for injections. Refer to local formulary for product & dosing
Ondansetron	5-HT_3 antagonist	– Tablet – Orodispersible tablet – Oral solution – Injection	– By mouth or subcutaneous injection = 4–8 mg, 2–3 times a day – CSCI = 8–24 mg/24 hours – If unable to swallow tablets, oral solution or orodispersible tablets can be used – Gastrostomy or NG tubes: solution can be given via gastrostomy tube. Consider parenteral route	– Constipating – Can also consider granisetron as alternative
Lorazepam	GABA mimetic	– Tablet – Oral solution – Injection	– By mouth or sublingually = 0.5–1 mg up to 4-hourly when required (max 4 mg/24 hours) – If unable to swallow tablets, solution can be used	– Can be sedating – Use lower doses in older adults, & those with renal or hepatic impairment

t.d.s. = three times a day; NG = nasogastric; 5-HT = 5-hydroxytryptamine; IV = intravenous; CSCI = continuous subcutaneous infusion; max = maximum; o.d. = once a day; GABA = γ-aminobutyric acid

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 9. Commonly prescribed types of laxatives

Class	Laxative	Formulation(s)	Route(s)	Starting dose	Cautions & considerations
Osmotic	Polyethene glycol, e.g. Movicol®, Laxido®, CosmoCol®	– Sachet – for dissolving in water – Movicol 'ready to take' sachets	– By mouth – Via gastrostomy tube	1–3 sachets daily, in divided doses	– Sachets require 125 ml water to dissolve – 'Ready to take' sachets are 25 ml
	Lactulose	Syrup	– By mouth – Via gastrostomy tube	15 ml b.d.	Can cause unpleasant bloating & cramps. Not first-line
Stimulant	Senna	– Tablets – Syrup	– By mouth – Via gastrostomy tube	7.5–15 mg every night	Contraindicated if obstruction suspected
	Bisacodyl	– Tablet – Suppository	– By mouth – Via rectal examination	– By mouth = 5–10 mg every night – Via rectal examination = 10 mg o.d. when required	Contraindicated if obstruction suspected
Softener	Docusate	– Capsule – Oral solution	– By mouth – Via gastrostomy tube	100–200 mg b.d.	
	Glycerol	Suppository	Via rectal examination	4 g o.d. when required	

b.d. = twice a day; o.d. = once a day

Table 10. Choosing most suitable treatment by possible cause of secretions

Possible cause	Treatment considered
Pulmonary oedema	Diuretics (e.g. furosemide), by mouth, or subcutaneous or IV injection
Respiratory infections	Antibiotics, short-acting bronchodilators (e.g. salbutamol) & mucolytics (e.g. carbocisteine)
Gastric reflux	Metoclopramide, H_2 receptor antagonists (e.g. famotidine, nizatidine) & PPIs (e.g. omeprazole)

IV = intravenous; H_2 = histamine type 2; PPI = proton pump inhibitors

Planning ahead

It is important to proactively clarify whether specific anti-cancer treatments are options, and to conduct conversations surrounding the focus and limitations of further care, and the likelihood of an acute and terminal event. These discussions need to be had with the patient (where possible), and their family or caregivers. Airway difficulties and bleeding are frightening situations, and being told there is 'nothing that can be done' does not alleviate anxiety. Rather, an explanation of symptom management as an active way of providing care should be undertaken. The aim is to understand the patient's priorities and care needs, and to develop an individualised care plan in the case of a significant event. In situations involving bleeding, it is important to acknowledge that not all patients with disease near major arteries will suffer a terminal haemorrhage. This topic should be discussed sensitively, emphasising that any plans are in case of a bleed, rather than this being a certainty.

Patients and carers may be traumatised by an acute episode of airway compromise or bleeding. If the patient survives, fear of further episodes may impact future care plans, including place of care and death. If the event was precipitated, for example by infection, thick secretions or poor tracheostomy care, addressing these issues may help prevent another episode. It is essential that relevant healthcare professionals are made aware of the likelihood of a further event, and know what actions to take in this situation. For those patients returning to their own home, discussions with community services, such as their general practitioner and district nurses, are imperative.

Table 11. Choice of medication to help with thick, tenacious secretions

Medication	Formulation(s)	Route	Dose
Sodium chloride 0.9%	– Nebules – If nebules are not available, plastic ampoules for injections can be used instead as a nebule	Inhalation	2.5–5 ml q.d.s. when required
Carbocisteine (mucolytic)	– Capsulev – Liquid (in bottle or sachet)	– By mouth – Via gastrostomy tube	750 mg t.d.s. for 4 weeks. Review at 4 weeks: if ineffective, cease treatment; if effective, reduce dose to 750 mg b.d.
Acetylcysteine	Effervescent tablet	– By mouth – Via gastrostomy tube	600 mg o.d.

q.d.s. = four times a day; t.d.s. = three times a day; b.d. = twice a day; o.d. = once a day

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 12. Choice of medication to help with sialorrhoea

Classification	Medication	Formulation(s)	Routes	Dose	Cautions & considerations
Antimuscarinic	Hyoscine hydrobromide	– Transdermal patch (Scopoderm®) – Tablets – not effective via oral route & not used for secretions	Transdermal; oral route available but ineffective	Apply 1 patch every 72 hours. Each 1.5 mg patch delivers 1 mg over 72 hours	Do not use hyoscine hydrobromide in end-stage renal failure or hepatic failure cases, increased risk of delirium
	Glycopyrronium	– Tablet (1 mg & 2 mg strength) – Oral solution (1 mg/5 ml)	By mouth, a sublingual route or via gastrostomy tube – tablets can be dispersed in water or oral solution given	See manufacturer's summary of product characteristics or seek specialist advice regarding dose	– Recommended as first-line treatment if cognitive impairment is an issue, because it has fewer central nervous system effects – Tablets are only available as special order from manufacturer; liquid is available but efficacy is unpredictable
	Atropine	1% eye drops	Sublingual route	4 drops sublingually every 4 hours when required	Unlicensed for this symptom. Benefits only last a few hours, so may be more suitable for specific, timed events such as appointments
Tricyclic antidepressant	Amitriptyline	– Tablet – Oral solution	By mouth or gastrostomy tube – oral solution can be given	Starting dose of 10 mg at night. Usual range of 10–25 mg at night	Can cause sedation

Table 13. Choice of antimuscarinic medication for secretions at end of life

Medication	Peripherally active?	Centrally active?	Duration of action	Immediate & 'when required' dose	CSCI dose	Cautions & considerations
Hyoscine butylbromide	Yes	No	<2 hours	20 mg	20–120 mg	Considered first-line (check local guidance)
Glycopyrronium	Yes	No	7 hours	200 µg	600–1200 µg	Some localities will use this first-line
Hyoscine hydrobromide	Yes	Yes	1–9 hours	400 µg	1200–1600 µg	Not routinely used for end-of-life care; can cross blood–brain barrier & can cause confusion & agitation. Contraindicated in end-stage renal & hepatic impairment cases

Note: The dose of the syringe driver should be increased if two or more 'when required' doses are needed. CSCI = continuous subcutaneous infusion

Table 14. Risk factors for bleeding

Risk factors for general bleeding	Risk factors for a potential terminal bleed
Rapid tumour growth	Pulsations from artery, tracheostomy or wound site
Previous head & neck radiation, or post-operative complications such as infection or flap necrosis	Infection, skin discolouration or oedema
Superficial fungating lesions	Ballooning of an artery
Concurrent anticoagulation or antiplatelet medications	Patient may become restless or irritable
Malnutrition or cachexia with >10–15% reduction in body weight	Scans may suggest patient is at risk with disease close to a major artery – CT angiograms are most accurate at identifying these patients
Systemic features such as increased age, diabetes, atherosclerosis	Minor or 'herald' bleeds previously

Note: there may be no warning at all. CT = computed tomography

Witnessing an acute death from airway compromise or terminal haemorrhage can be very distressing for family members and healthcare professionals alike, and it is important to offer a debrief and ongoing support.

Bleeding

The identified risk factors for minor and potentially terminal bleeds are shown in Table 14.

Minor bleeding

A minor or 'herald' bleed resolves spontaneously or with minimal intervention. They often, however, signal a risk of ongoing acute events, including terminal bleeding, and should trigger advance care planning discussions. Several factors and treatments should be considered to reduce the risk of bleeding and taken into account when treating minor bleeds (Table 15).

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 15. Prevention and treatment of minor and major bleeding

Reducing risk of bleeding	Management of minor bleeding	Management of major bleeding
Treat any superimposed infection	Consider a blood transfusion if symptomatic	Remain calm & ensure patient is never left alone, even to administer medications
Review medications: consider stopping anticoagulants, antiplatelets & NSAIDs	Topical agents: – Gauze soaked in 1:1000 adrenaline, monitoring for signs of rebound bleeding – Silver nitrate sticks applied to visible bleeding points – Tranexamic acid soaks & mouthwashes	– Maintain dignity – use of curtains or screens & dark towels to apply gentle pressure – Suction if blood is causing airway compromise or distress; only suction what is visible – If patient has tracheostomy, consider inflating cuff, inserting cuffed tube
Consider starting tranexamic acid: this does not prevent a terminal bleed, but may reduce frequency of further bleeding. It does not increase risk of arterial or venous thrombus formation	Symptom control: – Low-dose benzodiazepines, e.g. sublingual lorazepam 0.5–1 mg or midazolam 2.5–5 mg via subcutaneous injection – Anticipatory medications if patient is not suitable for invasive management	– Midazolam 5–10 mg IV or IM (because of peripheral circulation shut down) – Will prevent anxiety or distress if patient survives (retrospective amnesia) – Will not hasten death

NSAIDs = non-steroidal anti-inflammatory drugs; IV = intravenous; IM = intramuscular

Table 16. Management of breathlessness and distress

Medication	Formulation(s)	Route(s)	Starting dose(s)	CSCI?	Cautions & contraindications
Lorazepam	– Tablet – Oral solution	Via sublingual route or gastrostomy tube	0.5–1 mg (max 4 mg in 24 hours)	No	– Can be administered by a lay person, if access to sublingual area is available & moist (to ensure adequate dissolving) – Use a lower dose in older adults or those with renal impairment
Midazolam	– Injection – Oromucosal solution	Via subcutaneous injection or buccal route	– 2.5–5 mg for distress – In acute catastrophic airway obstruction, can be given IM or IV, & at larger doses of 5–10 mg (check local guidance)	Yes	– Subcutaneous injections will need to be given by healthcare professional, or trained carer – Buccal route treatment can be given more easily at home by a lay person
Opioids	– Oral solution – Tablet – Injection	By mouth, gastrostomy tube or subcutaneous injection	– For opioid-naive patient with normal renal function, morphine sulphate (immediate release) 5 mg by mouth (or 2.5 mg via subcutaneous injection) – First-line choice of opioids varies depending on co-morbidities & local guidance	Yes	If patient requires multiple doses, consider using modified release formulations of opioids (if able to take orally), or using transdermal route or starting a CSCI

CSCI = continuous subcutaneous infusion; max = maximum; IM = intramuscular; IV = intravenous

Terminal haemorrhage

Three to four per cent of head and neck cancer patients experience a terminal haemorrhage, where the volume of blood loss causes circulatory collapse.[582] In the majority of terminal haemorrhages, the patient will lose consciousness before any medication can be administered or have time to take effect. Remaining with the patient for psychological support is the most important treatment (Table 15).[582]

Airway management and breathlessness

Airway management in a palliative situation, where a definitive treatment or procedure is not planned, involves measures to control symptoms. These include tracheostomy and laryngectomy care (if already in place), and the use of adrenaline nebulisers and steroids (despite a lack of supporting evidence),[583] and are usually guided by local policies. Additionally, end-of-life guidance on managing breathlessness may have local variation, but is likely to include the use of opioids and benzodiazepines (Table 16).

If the patient survives an acute event but remains terminal, the use of continuous benzodiazepines and opioids (e.g. via a syringe driver) will control ongoing symptoms. If the patient survives an event and is able to take oral medication, consider benzodiazepines and/or opioids.

Complex wound management

Head and neck cancers often result in wounds that are unusually shaped, in a prominent position, are painful, result in fistulas or gross disfigurement, can bleed, become infected, or are malodorous. Once nutritional status and pressure area care are optimised, and palliative oncological or surgical intervention have been considered, a stepwise management approach can be taken:

- Exclude or confirm infection by microbiology swabbing and treat appropriately: for systemic or local infections, see local antibiotic policies; for malodour, use metronidazole, orally or topically). Infection can change a wound – make it

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 17. Key considerations in wound management

Considerations	Notes
Non-adherent dressings	Reduce pain, bleeding & disruption of epithelialisation at dressing removal or change
Moisture control	If wound surface is dry, use dressings to maintain degree of moisture, to allow some protection & healing, whilst preventing surface cracking (which increases vulnerability to infection & can worsen bleeding)
Exudate control	If wound surface is very wet, exudate may wet clothes or bedding, & cause moisture damage on surrounding normal skin. Consider alginate dressings – these are dry to apply, & soak up & retain moisture
Malodour control	Consider dressings containing charcoal to absorb malodour; these will not work if they become wet
Control of infection	Dressings are available with silver to reduce infection risk
Fistula	A small stoma bag (e.g. paediatric sized) placed over a fistula can collect any leaking fluids
Difficulty placing & fixing dressings	Burns compression garments can hold dressings in awkward places or reduce need for adhesives
Allergies	Be aware of patient allergies when choosing dressings (silicone, iodine, latex etc.)

more painful, induce colour change, cause healing to remain static or deteriorate, and worsen pain, odour or exudate. Superadded infection, particularly of a fungating wound, is an important reversible cause for minor bleeding.

- Treat the pain (as per previous subsection); consider topical opioid on a dressing and providing pain relief prior to anticipated dressing changes.
- Appropriate dressings – general principles are outlined in Table 17; refer to local tissue viability formularies.
- Psychological support for the patient or carers if disfigured. This could be a simple conversation whilst changing dressings, or more formal psychological support if available.

Advance care planning and end-of-life care

Key recommendations for advance care planning and end-of-life care:

- Consider advance care planning whenever there is a 'trigger' or transition in care (good practice point (G))
- Prepare for end-of-life care at the earliest opportunity and discuss preferences ahead of time (G)
- Plan ahead for anticipated symptoms or events (G)
- Recognition that a person might be in the last days of life is critical to providing good end-of-life care (G)

Advance care planning in head and neck cancer patients can be challenging (Table 18).[584] Communication about illness trajectories and outcomes is critical to the initiation of advance care planning discussions. Studies of head and neck cancer patients demonstrate differences in the understanding and interpretation of information between healthcare professionals, patients and carers, alongside differences in preferences regarding openness to prognostic discussions.[585] Whilst acknowledging that there will be differences in the desire to discuss the future, the opportunity for such a discussion may affect patients' access to palliative care and hospice care at the end of life.[586]

Table 18. European Association of Palliative Care definition of advance care planning

ACP enables individuals who have decisional capacity to identify their values, to reflect upon meanings & consequences of serious illness scenarios, to define goals & preferences for future medical treatment & care, & to discuss these with family & healthcare providers
ACP addresses individuals' concerns across physical, psychological, social & spiritual domains
ACP encourages individuals to identify a personal representative, & to record & regularly review any preferences, so that their preferences can be taken into account should they, at some point, be unable to make their own decisions

ACP = advance care planning

There are many different models that support discussions relating to advance care planning; these can be helpful frameworks to support clinicians when initiating conversations. Models such as the Serious Illness Conversation Guide[586] and mnemonic frameworks (e.g. 'REMAP', which stands for Reframe, Expect emotion, Map out patient goals, Align with goals, and Propose a plan[587]) focus on eliciting patients' values and preferences for care, alongside their goals of care. Advance care planning should be considered to support options for care, including the continuation of further lines of therapy, alongside less interventional approaches and end-of-life care planning.[585] Importantly, advance care planning may not reduce hospital attendance for patients with head and neck cancer, as has been anticipated in patients with other conditions; rather, the difficulty of managing symptoms such as bleeding, airway obstruction and complex wounds in the home setting frequently necessitates hospital-based care. Crucial to introducing advance care planning into practice is the recognition of key 'triggers' that prompt the clinician to consider and raise conversations regarding such planning (Table 19).

Resuscitation

Patients with head and neck cancer often have a treatment course characterised by frequent interventions and a high

Table 19. Examples of triggers for introducing conversations about advance care planning

Triggers	Example
Prognostic-related triggers	Would you be surprised if patient died in the next year?
Disease-related triggers	'Herald' bleeding or airway obstruction
	Progression in disease despite maximal treatment
Treatment-based triggers	Change in treatment intent from curative to palliative
	Stopping systemic, disease-modifying treatment because of progressive disease
Patient-based triggers	Frequent hospital admissions
	Deteriorating physical function (performance status)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 20. Indicators that an individual is entering last days of life

Signs such as progressive weight loss, agitation, deterioration in level of consciousness, mottled skin, noisy respiratory secretions & then Cheyne–Stokes breathing
Symptoms such as increasing fatigue & loss of appetite
Functional observations such as changes in communication, deteriorating mobility or performance status, or social withdrawal

level of tertiary based care.[381] There is some evidence to suggest these patients may be less likely than others to accept 'Do not attempt cardiopulmonary resuscitation' forms.[588] The integration of resuscitation discussions into structured advance care planning discussions is recommended, and may increase the readiness of patients to understand and accept the limitations of medical care.[589] Thus, discussions about resuscitation should be prompted by transitions in the patient journey; these may be similar triggers to those used for prompting advance care planning conversations. For those at risk of catastrophic events, this is critical, with the recognition that should such an event take place, cardiopulmonary resuscitation would be ineffective.

End-of-life care

It can be difficult to be certain that a person is in the last days of life (Table 20). Anticipating this, however, is critical to allow a person to communicate with loved ones, have the potential to be in a place of their choosing, complete any important rituals or attend to spiritual care needs. Care in the last days

Table 21. Care in last days of life

Recommendation	Detail
Recognise dying	Identify most appropriate member(s) of the team to communicate & provide ongoing care & support
	Use an MDT approach
	Review at least every 24 hours
	Where uncertainty exists, seek advice from colleagues more experienced in providing end-of-life care
Communicate	Establish & consider communication needs
	Discuss prognosis, & listen to fears & anxieties
	Involve those important to the person (e.g. relatives or carers)
	Document discussions & their outcomes
Shared decision-making	Establish how much the person is able to, & wishes to, be involved in decision-making & planning for last days of life
	Provide individualised care through discussion with the person & those important to them, especially regarding:
	– Personal goals & wishes
	– Preferred care setting
	– Preferences for symptom management
	– Needs for care after death if any are specified
	– Personal care needs, or need for additional support
	Ensure impeccable documentation of discussions
Maintaining hydration	Support dying person to drink if they wish to & are able to
	Assess for any swallowing problems or risk of aspiration
	Provide regular mouth & lip care as tolerated, & support family & those with the patient to administer if wished
	Discuss risks & benefits of clinically assisted hydration with dying person & those important to them
	Advise them that, for someone who is in last days of life:
	– Clinically assisted hydration may relieve distressing symptoms or signs related to dehydration, but may cause other problems such as fluid overload
	– It is uncertain whether giving or not giving clinically assisted hydration will prolong life or extend the dying process
	– Make an individualised decision, with the patient & those important to them, regarding clinically assisted hydration. Where there is a desire to use clinically assisted hydration, consider a trial, with assessments at least every 24 hours to determine its benefit or side effects
	– For those with established clinically assisted hydration (enteral or parenteral), use same principles & assessments to form an individualised plan & review regularly
Pharmacological interventions	Review all medications & form an individualised approach with the person & those important to them
	Continue medication that is clinically appropriate (e.g. those which provide symptom control)
	Consider alternative routes (subcutaneous) for important medication that cannot be taken or tolerated
	Avoid intramuscular injections
	Consider using a syringe pump to deliver medicines for continuous symptom control if more than 2–3 doses of any 'as required' medicines have been given within 24 hours

MDT = multidisciplinary team

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 22. Summary of first-line options for anticipated symptoms at end of life*

Symptom	Drug	Route & initial 'when required' dose
Pain	Morphine	Subcutaneous injection, 2.5–5 mg
Breathlessness	– Morphine &/or – Midazolam	– Subcutaneous injection, 2.5–5 mg – Subcutaneous injection, 2.5–5 mg
Nausea &/or vomiting	– Cyclizine, or – Levomepromazine or – Haloperidol	– Subcutaneous injection, 50 mg – Subcutaneous injection, 6.25 mg – Subcutaneous injection, 1.5 mg
Agitation	Midazolam	Subcutaneous injection, 2.5–5 mg
Noisy secretions	Hyoscine butylbromide	Subcutaneous injection, 20 mg
Terminal haemorrhage	Midazolam	Subcutaneous injection, 5–10 mg

*Refer also to previous relevant sections about symptom control

of life should follow National Institute for Health and Care Excellence (NICE) recommendations (Table 21).[590]

For those approaching the last days of life with established artificial nutrition (enteral or parenteral), similar challenges to those with clinically assisted hydration can arise. It is important for patients and/or those individuals close to them to understand that there is a change in the goal of the nutritional support, from maintaining a good nutritional status, to providing comfort and symptom control. The manner in which this happens should be tailored to the individual, and their preferences and needs. For many, stopping the feed when in the last days of life allows the best balance between the burden of the feeding and the clinical benefit (which is minimal at this stage of life).[591] Given the emotional and sometimes spiritual importance of feeding, however, it might be important to discuss a gradual reduction in feeding rather than an abrupt stopping, depending on the person's wishes.

Medication at end of life

'Anticipatory' medications should be prescribed to ensure there is no delay in the administration of a required drug, especially for a symptom or situation that can be anticipated (Table 22).[590]

'One Chance to Get it Right' details the principles for caring for dying people, and highlights five key priorities for care (Table 23).[592] This advocates the use of an individualised care plan in the last days of life and supports all members of the patient's care team to adopt an appropriate focus of care for the patient, alongside attention to supporting carers. Detailed plans, such as those described above, for anticipated emergencies, are considered essential.

Current and future research

Over the last decade, many trials have been conducted assessing the merits of palliative care.[593,594] Generally, it is advocated that palliative care be integrated into standard oncological care early in the illness trajectory, often alongside active anti-cancer treatments.[547] Within an Indian healthcare context, early routine specialist palliative care input for those with head and neck cancer did not improve quality of life at three months.[595] Models of care, however, need to be targeted to individual populations. Questions therefore remain about the optimum model of care needed to improve outcomes for this complex population. Addressing variability in terms of clinical outcomes is essential. Geographical and socio-economic inequalities persist, and ultimately affect place of death.[596]

Table 23. The five priorities for caring for a dying person

1. Recognise dying
2. Communicate
3. Involve the patient & family in all decisions
4. Listen to those who are important to the dying person
5. Tailor care to the individual & deliver with compassion

The limited evidence base for symptom control highlights the need for further work and dedicated funding. Within cancer research, less than 0.3 per cent of the £500 million is allocated to palliative care.[597] Clinical trials need to extend inclusion beyond those patients with good performance status, and be combined with novel methodologies to help overcome practical and ethical challenges.

Improving the general palliative care skills and knowledge of the head and neck cancer MDT, and integrating a needs-driven mechanism for access to specialist palliative care services, seem essential.[598] Models of integrated care, which include community providers, are pertinent to avoid 'silo' working,[548] and to enhance decision-making and advance care planning, encourage mutual learning, and optimise quality of life for patients and their family carers.

Chapter 16: Management of treatment effects and complications

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

This chapter aims to describe the investigations and management for some of the specific common effects of treatment for patients treated for head and neck cancer.

Chyle leak following head and neck cancer surgery

Recommendations

- Surgery to the supraclavicular region on both sides of the neck should necessitate careful inspection for a potential chyle leak at completion (evidence-based recommendation (R))
- If an intra-operative chyle leak is identified, every effort should be made to repair or close the damaged thoracic duct at the time of surgery (R)
- Biochemical testing to be undertaken to confirm a clinically suspected post-operative chyle leak (good practice point (G))
- Monitor fluid balance, electrolytes, protein levels and white cell count (R)
- Consider non-operative measures that can be implemented to reduce chyle flow (R)
- Operative interventions will be influenced by local experience and available resources (G)
- Consideration should be given to involving interventional radiology and thoracic teams, even if not available locally for persistent leaks (G)

Introduction

Lymph returns proteins and excess interstitial fluid to the bloodstream. It also transports fats from the digestive system via chylomicrons, and is rich in electrolytes, fat-soluble vitamins, trace elements, glucose and white blood cells. Flow rates in the thoracic duct are such that damage to it can result in significant fluid shifts.

The thoracic duct originates from the cisterna chyli, at the level of the second lumbar spinal vertebra (L2), and drains lymph from the left side of the body and the right side below the diaphragm. The right lymphatic duct receives lymph from the right chest, arm, and head and neck region. The thoracic duct ascends through the thoracic cavity to enter the route of the neck, with the duct extending up to 5 cm above the clavicle before terminating into the venous circulation.[599] Whilst this is most commonly into the left internal jugular vein (IJV), it can also drain into the confluence of the IJV and subclavian vein, the subclavian vein, or even into the brachiocephalic vein, external jugular vein or vertebral vein, or, even more rarely, to the right-sided vessels. Furthermore, whilst a single duct is most common, there may also be multiple drainage channels.[600,601]

Iatrogenic damage to the thoracic ductal drainage system during head and neck surgery resulting in a chyle leak occurs in 0.5–1.4 per cent of thyroidectomies and in 2–8 per cent of neck dissections.[599] The variable anatomy and fragile composition of the thoracic duct render it prone to inadvertent injury. The head and neck surgeon may also encounter a chyle leak as a result of penetrating neck trauma, cervical rib resection, or following sentinel or cervical node biopsy.[600]

A chyle leak into the neck can have serious consequences, in terms of additional interventions, delayed discharge and wound healing. Systemic effects of a large volume of chyle leak can result in hypovolaemia, electrolyte imbalances (hyponatraemia, hypochloraemia and hypoproteinaemia), malnutrition and immunosuppression. Local effects of a chylous collection include delayed wound healing, infection, wound breakdown and fistula formation. The presence of chyle within a contained space may decrease tissue perfusion, resulting in skin or flap necrosis. It is also possible that chyle may penetrate the chest, forming a chylothorax.[599,600]

Intra-operative diagnosis and treatment

Surgery to the supraclavicular region on both sides of the neck should necessitate careful inspection for a potential chyle leak

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

at completion. Identifying a chyle leak can be aided by manoeuvres that increase the intrabdominal and/or intrathoracic pressure. These include Trendelenburg positioning, a Valsalva manoeuvre or abdominal compression. Meticulous haemostasis, careful drying and observation of the area can aid the detection of even small chyle leaks.

If an intra-operative chyle leak is identified, every effort should be made to repair or close the damaged thoracic duct at the time of surgery. If clearly visible, ligation of the thoracic duct can be readily achieved with clips or by over-sewing the duct. Additionally, the use of locoregional muscle flaps to cover the area should be considered. A number of these flaps have been proposed, including the clavicular head of the sternocleidomastoid, the scalenus medius and the omohyoid; one or more of these can be raised and rotated into the space (usually posteriorly to the IJV). Alternatively, a regional pedicled flap such as a pectoralis major flap can be used to fill the space. A number of glues, such as fibrin- or cyanoacrylate-based products, have been proposed to help.[599,600] If using such products, care should be taken to isolate nerves (such as the vagus) traversing the region. Figure 1 shows a flow chart summarising the identification and management of a chyle leak following surgery for head and neck cancer.

Post-operative diagnosis and treatment

Table 1 summarises the clinical and biochemical features of a chyle leak. Whilst the classical creamy or milky appearance of the drain fluid is highly indicative of a chyle leak, this may not be evident for a few days, especially if there is serosanguinous discharge or a delay in enteral feeding.[602,603]

The volume of chyle produced in a 24-hour period is one of the main determinants of treatment. Low output chyle leaks (less than 500 ml/day) are initially managed with conservative non-operative treatment, whilst persistent high output chyle leaks (more than 500 ml/day) will usually require operative treatment. However, volume alone is not the only determinant of treatment. Management will also be influenced by patient factors, the duration of the chyle leak and the impact of losing a large volume of electrolyte-rich fluid. Further factors to consider include the response of the drain output to treatment measures, individual surgeon preference and the range of local services available.[599,600,604] It is important to note that large fluid shifts can occur, so fluid balance and electrolytes should be monitored regularly, along with white cell counts, blood glucose and albumin levels.

Table 1. Clinical and biochemical diagnosis of chyle leak

Clinical diagnosis	Biochemical analysis of drain fluid
Increasing drain output	Drainage triglyceride & cholesterol levels > serum levels
Creamy or milky drain fluid	Chylomicrons
Skin erythema	

Non-operative interventions

Physical activity increases chyle flow, so bed rest, with elevation of the head of the bed, along with measures to reduce straining such as the use of stool softeners, are helpful.

Dietary modifications with a fat-free, low-fat or medium-chain fatty acid diet should be instigated. Medium-chain fatty acids are largely water-soluble and are absorbed via the portal venous circulation, reducing lymphatic flow. This diet can be administered enterally or parenterally.[605] For high-volume chyle leaks (more than 500 ml), parenteral nutrition can be considered as nutritional intervention.

For output of less than 500 ml, enterally fed patients should receive either a fat-free nutritional product or a medium-chain triglyceride-based feed.

For patients who are able to eat and drink a low-fat diet, supplements that are fat-free or where the fat is made up of medium-chain triglycerides should be used to meet nutritional requirements. A low-fat diet may be defined as providing less than 5 kcal per serving of food. Compliance with a low-fat diet can be low.

Pressure dressings, suction drainage and negative-pressure therapy have all been described to reduce the available space for chyle to accumulate. These measures need to be balanced against the risks of impaired flap perfusion and inducing an exudate with suction.[599]

Systemic drug therapy with somatostatin or a somatostatin analogue such as octreotide has been shown to slow chyle production and is effective in a chyle leak following a neck dissection. The timing of starting octreotide does vary, as does the treatment dose, although 100 µg subcutaneously every 8 hours is a common regimen.[599,600,604,606]

Sclerosing agents introduced via drainage tubes have been described. However, these should be used with caution given the potential problems if re-operation is required.

Surgical interventions

The decision to surgically explore a chylous fistula requires careful planning, and will be influenced by surgeon choice

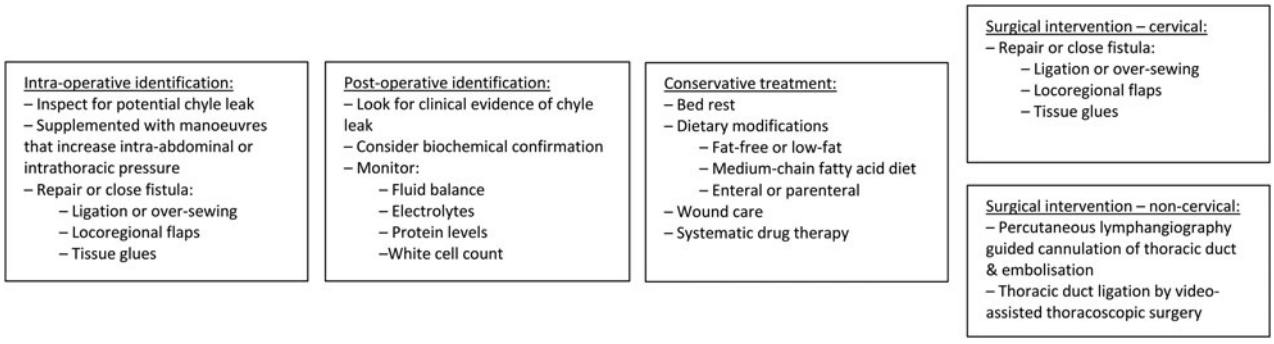


Figure 1. Flow chart summarising the identification and management of chyle leak following surgery for head and neck cancer.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

and locally available resources. There is no high-level evidence for a particular intervention.

The aim of surgical exploration of the neck is to facilitate surgical repair to stop or reduce a chyle leak, or to ligate the thoracic duct. However, as a result of the small size of lymphatic vessels, it is quite often difficult to identify specific leakage points, and there may be multiple sites responsible. As described above, identification of the leak site can be helped with manoeuvres that increase the intrabdominal or intrathoracic pressure, including: Trendelenburg positioning, Valsalva manoeuvre or abdominal compression.[599]

Closure of the supraclavicular space can be aided by locoregional flaps. The use of sclerosing agents, adhesive agents or mesh can also help.[600] Once again, care is required to protect other vital structures (vagus and phrenic nerves, and the brachial plexus) when using these agents.

Interventional radiology and cardiothoracic interventions

If local neck control cannot be achieved, percutaneous lymphangiography guided cannulation of the thoracic duct and its embolisation has been reported to have a high success rate. Thoracic duct ligation can be achieved by a number of techniques, including video-assisted thoracoscopic surgery, and has been found to have a high success rate. Several other procedures, including thoracotomy, pleurodesis and decortication, pericardial 'window', and pleura-venous and pleura-peritoneal shunts, have been described.[599,607]

Osteoradionecrosis following head and neck cancer treatment

Recommendations

- For early osteoradionecrosis, pragmatic conservative and symptomatic management involves debridement of sharp and exposed necrotic bone, analgesia, antiseptic mouthwash, and antibiotics (good practice point (G))
- Minor bone spicules may heal with entirely conservative management (evidence-based recommendation (R))
- The role of rim resection and saucerisation, i.e. resection of all necrotic bone in cases of Notani stage 1 and 2 osteoradionecrosis, remains uncertain (G)
- The use of hyperbaric oxygen in the management or prevention of osteoradionecrosis is not supported by recent randomised, controlled clinical trials (R)
- The efficacy of the pharmacological therapy with pentoxifylline, vitamin E and clodronate ('PENTOCLO') protocol requires further evaluation in controlled trials (R)
- In patients with Notani stage 3 (advanced) osteoradionecrosis or in those with disease refractory to medical or conservative management, definitive surgical resection and reconstruction is likely to be necessary. This may result in acceptable healing outcomes, but with significant complications and compromised function (R)

Introduction

Osteoradionecrosis has been defined as 'exposed irradiated bone that fails to heal over a period of three months in the absence of local tumour'.[608] This is a much-feared complication of (chemo-)radiotherapy occurring in 5–10 per cent of irradiated patients.[609] This is associated with pain, infection, fistulation, haemorrhage and progressive disfigurement. In the most common site, the mandible, osteoradionecrosis is often associated with trismus, leading to malnutrition and fracture. Osteoradionecrosis may also occur in the midface, skull and even cervical spine. A parallel condition of the cartilage (chondroradionecrosis) may affect the larynx. Osteoradionecrosis may co-exist with late radiation toxicities of adjacent tissues, such as xerostomia, atrophic mucosae, fibrosis, skin telangiectasia, trismus and neuropathic pain, any of which may complicate treatment and compromise outcomes. Osteoradionecrosis is associated with significant mortality in its own right, but also is occasionally coincident with the presentation of local tumour recurrence.

Classification

Classifications of osteoradionecrosis, in particular for the mandible, have been used to categorise and manage osteoradionecrosis in clinical practice and in the context of prospective trials. Some prior classifications have depended on progression, or responses to a particular therapy, or presumed indications for one treatment over another. After a recent review of various classifications,[610] Notani and colleagues' classification of osteoradionecrosis has shown many pragmatic advantages.[611] They classify mandibular osteoradionecrosis by: cases limited to the dentoalveolar process (Notani stage 1), cases involving the body of the mandible above the inferior dental canal (Notani stage 2), and cases with full thickness, fracture or extra-oral fistulation (Notani stage 3). One recent additional category by virtue of its favourable prognosis is minor bone spicules (less than 20 mm[600] exposed bone),[610] which often heal without intervention.[498] There are no commonly used classifications of osteoradionecrosis outside the mandible, but it is recommended that the extent and anatomy of exposed bone and involved necrotic bone are described.

Management

Conservative and supportive care

Conservative measures include: oral hygiene improvement, irrigation, antibiotic therapy, analgesia and nutritional status optimisation.[612] There is a paucity of data on the natural history and course of osteoradionecrosis treated with conservative management. In advanced osteoradionecrosis, conservative approaches are neither cost-effective nor effective, and have been criticised given the lack of evidence.

Combined pharmacological therapy with pentoxifylline, vitamin E and clodronate

A better understanding of the pathophysiology of osteoradionecrosis, especially the radiation-induced fibro-atrophic theory, has resulted in diverse treatments, including attempts at medical management. Delanian *et al.*[613] presented details of the medical management of osteoradionecrosis with a combination of pentoxifylline, and vitamin E with clodronate. Each patient was given a daily combination of twice-daily 400 mg pentoxifylline (800 mg/day) plus 500 IU vitamin E (1000 IU/day) and once-daily 1600 mg/day clodronate from Monday to Friday (5 days per week), alternated with 20 mg prednisone plus 1000 mg ciprofloxacin on the weekend (2 days per week). It was concluded that long-term pharmacological therapy with pentoxifylline, vitamin E and clodronate ('PENTOCLO') treatment is curative for refractory osteoradionecrosis, and induces mucosal and bone healing with significant symptom improvement. That was a phase II trial, with most patients having a

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

defect of less than 2 cm (Notani stage 1), with the median time for healing of six months. Limited studies to date have demonstrated the effective pharmacological use of 'PENTOCLO' in treating osteoradionecrosis,[614] and controlled trials are essential in order to confirm these results.

Hyperbaric oxygen

Prior enthusiasm for the use of hyperbaric oxygen in the management of osteoradionecrosis arose from uncontrolled case series and a single-centre randomised, controlled trial of prevention following dental extractions.[615] Since then, two multicentre randomised, controlled trials have shown no benefit of hyperbaric oxygen in the management of established osteoradionecrosis, either used alone[616] or as an adjunct to surgical excision.[617] A recent randomised, controlled trial of hyperbaric oxygen to prevent osteoradionecrosis following high-risk surgical procedures to the mandible showed no benefit, with the rate in both study arms of around 6 per cent, lower than had been previously reported in trials.[498]

Surgery

Surgical interventions should be appropriate for the stage of osteoradionecrosis. Surgical procedures include sequestrectomy, marginal or rim resection ('saucerisation'), and segmental resection, usually implying oromandibular reconstruction with a composite free flap. The goal of surgery is usually the removal of bone with compromised perfusion, whilst retaining viable bone in order to promote healing. There is no convincing evidence that either sequestrectomy or rim resection have superior outcomes to conservative or medical management. A concern following surgery is that vascularised soft tissue coverage of the resultant bony defect is often compromised. One relatively novel and untested approach worthy of further investigation is the use of marginal resection of Notani stage 1 and 2 mandibular osteoradionecrosis and subsequent revascularisation with a free flap bearing periosteum.[618] Segmental reconstruction with free flap reconstruction has acceptable microvascular patency, with a recent meta-analysis reporting patency in over 90 per cent of cases.[619] However, healing and functional outcomes are understandably compromised in a surgical field affected by late radiation toxicity, and are associated with significant complications (40 per cent) including fistula, infection and hardware exposure.[619] For many Notani stage 3 cases, there is sometimes no acceptable alternative than to undertake major resection and reconstruction. The outcomes of surgery can be improved by virtual planning, but will ultimately be informed by access to suitable vessels, co-morbidities and the need for occlusal rehabilitation.

Role of palliative care

In a small group of patients, mandibular osteoradionecrosis may be present in combination with: affected sites such as the base of skull, temporomandibular joint (TMJ) distraction with extradural or subdural collections, and middle-ear complications. In addition, patients with a history of extensive treatment for head and neck cancer often present with significant co-morbidities. Patients with mandibular osteoradionecrosis demonstrate reconstructive challenges associated with poor healing, soft tissue defects and vessel-depleted necks. Surgical complications such as wound infection, skin necrosis, salivary fistulae and partial flap loss, and in rare instances carotid blow-out, have also been reported. In a patient with significant co-morbidities, extensive craniofacial osteoradionecrosis may be beyond any surgical intervention, and best supportive care may be the only pragmatic option; these patients have symptoms that are very difficult to manage and they often succumb to these complications.

Overall prognosis

Patients with early osteoradionecrosis (minor bone spicules and Notani stage 1), can be managed successfully through conservative management with occasional support in an outpatient clinic. Advanced osteoradionecrosis is a debilitating condition with significant adverse effects to a patient's health-related quality of life. Early surgical intervention can contribute to a successful outcome.[619]

Trismus following head and neck cancer treatment

Recommendations

- The primary focus should be directed towards prevention by identifying high-risk patients before treatment of head and neck cancer (evidence-based recommendation (R))
- The mainstay of treatment is physiotherapy; jaw-stretching exercises with a trismus device should be commenced as soon as feasible following surgery and/or radiotherapy (RT) (R)/(good practice point (G))
- Every effort should be made to establish the cause of trismus for targeted investigations and treatment (G)
- Mouth-opening distance should be measured and recorded at each follow-up consultation, and a realistic goal for mouth opening agreed with the patient (G)

Introduction

Trismus is a common but often overlooked sequelae of head and neck cancer treatment involving surgery and/or RT that involves the masticatory system. It can have a significant impact on the physical, psychological and social well-being of patients, and is generally defined as a reduced jaw opening of 35 mm or less.[620,621]

Trismus is associated with several potential complications that lead to a poor overall quality of life for patients. It may result in poor nutrition due to difficulty chewing and poor dentition, and periodontal disease as a result of limited access for both oral hygiene and dental treatment. Chewing and speech difficulties may cause patients to avoid eating in public, leading to social isolation, and even anxiety and depression. Restricted mouth opening may compromise cancer surveillance, and may complicate airway management during general anaesthesia for procedures that may be required down the line. Impaired clearance of oropharyngeal secretions may also lead to a risk of aspiration.[621–623] It is therefore important that trismus is actively addressed and dealt with by clinicians as soon as possible (Table 2).

Causes

There are several possible causes of trismus in patients treated for head and neck cancer. Disease progression or tumour recurrence must be considered in the differential diagnosis and excluded with utmost urgency.

More commonly, trismus may be a result of surgical resection causing scarring and tissue contracture in the masticatory apparatus, or occur following damage to the neural

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Summary of management of trismus post head and neck cancer treatment

Determine cause
– Disease progression or recurrence
– Surgical scar & contracture
– Radiation-induced fibrosis & contracture
– Odontogenic cause
Investigations
– Clinical examination & flexible nasoendoscopy
– Imaging – CT, MRI & PET-CT
– Examination under general anaesthesia & biopsy
Treatment
– Focus on prevention & early intervention
– Treat infection & tumour progression or recurrence
– Early physiotherapy
– Trismus appliances

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography

innervation to masticatory muscles. Surgical resection extending into the masticator space, thereby affecting muscles of mastication such as the masseter, temporalis, medial pterygoid and superior head of lateral pterygoid muscles, are particularly inclined to cause trismus. Similarly, tumour resections involving the infratemporal fossa, parapharyngeal space and TMJ may also result in trismus.

The prevalence of trismus in head and neck cancer patients treated with RT ranges from 30 to 50 per cent,[601] and concomitant chemoradiotherapy may be associated with a higher prevalence of trismus.[622] Trismus may begin towards the end of radiation treatment, and the adverse effect of progressive fibrosis may continue for years.

It is important to consider odontogenic causes of restricted mouth opening. Odontogenic infection originating from dental (apical) abscesses or periodontal disease with bacterial spread into the masticator space may cause inflammation and pain, resulting in trismus. Head and neck cancer patients may struggle with maintaining oral hygiene, and may suffer from xerostomia, which can lead to the rapid deterioration of dentition and subsequent orofacial infections. Infected or failed reconstructive fixation metal plates and screws can cause pain and restricted mouth opening. Dislocated condyles or stress-induced TMJ dysfunction syndrome may also be the cause of restricted mouth opening.

Investigations

Thorough clinical examination may not be possible because of restricted access. Flexible nasoendoscopy is useful not only to examine the nasal cavity and rest of the upper aerodigestive tract, but also to visualise the oral cavity and oropharynx by passing the scope tip through a small gap between the incisor teeth (if present).

Any suspicion of residual disease or recurrence should be excluded with imaging modalities such as computed tomography (CT), magnetic resonance imaging or positron emission tomography-CT. Interpretation of these scans may be difficult because of post-surgical and radiation changes, which may warrant multiple imaging modalities for the accurate interpretation of radiological findings.

Examination under general anaesthesia may be required in some patients, and focused histological sampling should be considered, guided by clinical examination and radiological findings.

Management

Management of trismus requires a multidisciplinary approach with the primary focus aimed at prevention and early intervention.

Prevention

Preventative measures are important because, once the trismus is established, many patients will not return to a pre-treatment level of mouth opening.[623] Identifying high-risk patients may help facilitate early preventative measures and intervention. Patients with tumours affecting, or in close proximity to the masticatory apparatus, should be prepared for possible restricted mouth opening following treatment. Every attempt must be made to reduce the impact of surgical resection and radiation exposure to adjacent structures, whilst balancing the importance of oncologically safe treatment. Decreasing the radiation dose delivered to the surrounding structures involved in mastication, using intensity-modulated RT, reduces the incidence rate and severity of radiation-induced trismus after RT.[624]

Physiotherapy should begin as early as possible after surgery and/or RT, to maintain or improve jaw mobilisation. Those patients with reconstructive fixation plates should be approached judiciously. Early intervention is likely to result in better long-term outcomes.[622,624]

Primary reconstruction of surgical defects at the time of tumour ablation is advocated, to prevent excessive scarring and contraction. Prophylactic removal of the coronoid process (where the temporalis muscle inserts) is recommended for surgery involving resection of the posterior maxilla and mandible. The temporalis muscle is at high risk of contracture and fibrosis post-surgery and/or RT, which can result in jaw tightening and closure. It may be beneficial to detach the insertions of masseter and medial pterygoid muscles as a part of the surgical resection if appropriate.

Comprehensive dental examination and restorative care, and extraction of teeth with guarded prognosis, at the time of resection surgery or prior to RT commencement, reduces the risk of odontogenic infections. Strict oral hygiene measures, a low-sugar diet and fluoride treatment are recommended to prevent dental caries and the rapid deterioration of dentition, especially in such patients with radiation-induced xerostomia. Artificial saliva, frequent sips of water or sialagogues to encourage saliva flow may be considered.

Treatment

It is important to determine the cause of trismus so that the treatment can be guided appropriately. Mouth opening should be measured and recorded regularly at follow-up consultations, and a realistic target agreed with patients.

For trismus related to surgery and/or RT, the first line of treatment is jaw mobilisation exercises using various jaw-opening devices. Jaw exercises with a vertical and horizontal range of movements should commence as soon as possible, and should be undertaken several times a day. Exercises may have to be continued for one to two years to maintain the

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

results.[622] Input from both physiotherapy and speech and language therapy teams will be invaluable in instigating this treatment.

Trismus appliances that are commonly used in dentate or partially dentate patients include wooden spatulas (tongue depressors), the TheraBite® Jaw Motion Rehabilitation System™, the Dynasplint® Trismus System and corkscrews. Readily available tongue depressors are easy to use and can be employed early in patients with restricted mouth opening. Care should be taken not to cause excessive discomfort or pain whilst using these devices, to avoid damage to dentition or soft tissue. In a randomised feasibility study of 71 patients, there was improved mouth opening in both groups of patients using either wooden spatulas or the TheraBite system at six months, with no significant difference between the two groups.[625]

A systematic review found large variations in the stretching techniques, duration of stretching and frequency of exercises. In the studies analysed, both preventative and therapeutic measures were found to increase mouth opening after exercise therapy. There was a considerable range in jaw-opening changes, and a no stretching technique was superior to others. Multiple studies in the systematic review reported post-stretching mouth opening, which remained at less than 35 mm, indicating that trismus persisted in many patients despite treatment.[602] Other adjunctive measures, such as heat therapy, low-level laser therapy, pentoxiphylline and botulinum A toxin injection, have been reported in the literature, but overall evidence for their effectiveness is lacking.

There may be scope for surgical intervention in some patients, but the risk of complications is high in this group of patients. Consideration may be given to the excision of scar tissue and fibrotic bands (e.g. buccal mucosa bands). If mandibular coronoidectomy was not performed at the time of primary surgery, this may be considered, particularly if temporalis muscle contracture is suspected. Manipulation of the jaw under anaesthesia, followed by the maintenance of mouth opening with physiotherapy, may also be considered.

Aspiration and dysphagia following head and neck cancer treatment

Recommendations

- Functional and radiological swallowing assessment should be considered in all patients with post-treatment dysphagia and aspiration (evidence-based recommendation (R))
- Endoscopic dilatation should be offered to patients with a symptomatic pharyngeal stricture (R)
- Multidisciplinary team (MDT) input and shared decision-making with the patient must support consideration of a functional laryngectomy (R)
- Gastrostomy and tracheostomy insertion are reasonable interventions to manage laryngeal and pharyngeal dysfunction following head and neck cancer treatment (good practice point (G))
- Cross-sectional imaging should be performed prior to major surgical intervention, to exclude recurrent disease (G)

Introduction

Radiotherapy and surgery induced fibrosis can affect many patients who are cured following their head and neck cancer treatment. Laryngeal and pharyngeal dysfunction due to fibrosis leads to unpredictable levels of dysphagia, aspiration risk and airway compromise. The mainstay of managing post-treatment dysphagia and/or aspiration should be speech and language therapy and dietetic input (Chapters 9 and 10). This chapter will concentrate on potential surgical interventions to treat these treatment-related sequelae.

Tracheostomy

Tracheostomy may be required to relieve airway compromise. Conservative methods to improve the airway, such as transoral laser cordectomy or arytenoidectomy, are unlikely to be appropriate in this particular patient group as the aspiration risk may be exacerbated. A tracheostomy may worsen dysphagia,[626] causing further impairment of laryngeal elevation, and is unlikely to reduce aspiration risk, although it may be used to help manage symptomatic aspiration.

Gastrostomy

Gastrostomy is an option for patients at risk of aspiration and who struggle to meet their oral calorie intake. Reducing the need for oral intake may allow a more targeted oral diet with a lower aspiration risk. Whilst a gastrostomy may help to reduce the risk of aspiration and pneumonia for some patients with severe long-term fibrosis effects, a gastrostomy may not reduce this risk.[339]

Dilatation

Dilatation is frequently performed for pharyngeal stenosis. Oropharyngeal and supraglottic stenoses are less common, and are more challenging to manage. Endoscopic dilatation can be performed under general anaesthesia via direct sight with serial bougies or balloon dilatations. The main risk is perforation. Endoscopic dilatation can be performed under local anaesthetic with or without sedation. More challenging stenoses can be dilated using radiological guidance with bougies or balloons inserted over a guide wire, to reduce the risk of creating a false passage and perforation risk. Complete pharyngeal stenoses can be approached in a retrograde fashion via a gastrostomy. A narrow gastroscope can be directed superiorly within the oesophagus to the pharyngeal stricture, or a guide wire can be advanced superiorly in the oesophagus with radiological confirmation. The stricture can then be opened under direct transoral visualisation towards the light of the endoscope or by blunt dissection towards the guide wire – the so called 'rendezvous' procedure.[627]

Case series show that pharyngeal dilatation is successful in improving swallowing in up to 75 per cent of patients.[628] Poor swallowing outcomes may be expected for patients with fibrotic strictures who require repeat procedures.[629]

Functional laryngectomy

'Functional laryngectomy' is an option for patients with a dysfunctional larynx leading to aspiration and dysphagia, with or without airway compromise. It is infrequently performed, and therefore very little best practice evidence exists. The long-term results of the Radiation Therapy Oncology Group 'RTOG 91-11' trial showed that 9 out of 148 patients undergoing laryngectomy did so for functional reasons.[630]

Patients must be managed in an MDT approach, with the opportunity to discuss the option with speech and language

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

therapists and dietetic specialists, and ideally with a similar patient. The main aims of surgery are often to prevent aspiration and pneumonia. The secondary aim is to improve swallowing. Many patients achieve their aim of swallowing, with a proportion requiring ongoing enteral feeding.[631] Speech rehabilitation with a tracheoesophageal puncture voice is likely to be more variable than following primary laryngectomy, but can be achieved in the majority of carefully selected patients.[631]

Patient selection is key to potentially successful functional outcomes. An assessment of the extent of fibrosis is required prior to surgery, ideally under general anaesthesia to assess for hypopharyngeal stenosis. Cross-sectional imaging is recommended to exclude recurrence or distant metastases. Speech and language therapy input should include a functional and radiological evaluation of swallowing, to counsel on potential outcomes. The most favourable scenario is that of a dysfunctional larynx with an otherwise healthy pharynx. In this situation, surgical dissection can be kept to a minimum, with the possible preservation of the strap muscles and hyoid bone (a narrow field laryngectomy).

If pharyngeal fibrosis and structuring is present, a pharyngectomy to excise the scarred mucosa and reconstruction should be considered, to augment the pharyngeal diameter. These cases are far more challenging than the straightforward functional laryngectomy. The fibrotic process may continue following surgery, affecting the reconstruction and leading to further stricture formation.

Reconstruction after pharyngolaryngectomy is discussed in Chapter 7.

Other surgical interventions

Other surgical interventions have been described to manage post-treatment dysphagia and aspiration that may be considered prior to laryngectomy or for patients refusing laryngectomy who wish to preserve their laryngeal voice.

Cricopharyngeal myotomy has been described for this group of patients.[632] Hyoid suspension is another technique, generally preserved for patients with neurological laryngeal dysfunction. This tends to have poor results in the irradiated patient because of immobility of the larynx. Many patients will have global pharyngeal weakness and fibrosis causing their dysphagia following RT. The potential improvements from these specific interventions require careful consideration.

Tubed supraglottic closure has been recently described, with encouraging results.[633] Laryngeal voice in the presence of a tracheostomy can be achieved whilst minimising the aspiration risk by reducing the supraglottic aperture.

Radiotherapy-induced xerostomia

Recommendations

- All patients should be asked about dry mouth symptoms (xerostomia) as part of their post-treatment clinical reviews (evidence-based recommendation (R))
- Salivary substitutes and oral lubricants in a variety of forms (sprays, gel, mouthwash, slow-release adhesive discs) may be recommended for the pragmatic temporary reduction of dry mouth symptoms. When residual saliva gland function is present, tactile stimulation of the salivary reflex with topical sialagogues (sugar-free gums, pastilles and lozenges) may temporarily increase natural salivation and reduce dry mouth symptoms. Evidence behind both interventions is not robust, and the perceived benefits can vary widely (good practice point (G))
- When residual salivary gland function is present, and topical sialagogues do not offer satisfactory relief from persistent xerostomia, systemic sialagogues (e.g. the parasympathomimetic cholinergic agonist pilocarpine hydrochloride) should be considered if there are no absolute contraindications in the patient's medical history. The efficacy of pilocarpine in increasing salivary flow and reducing xerostomia is supported by robust evidence. Adverse effects are common but usually mild, and should be discussed with the patient (R)
- If the above strategies are not effective, clinicians may consider acupuncture or neuro-electrostimulation (intra-oral or extra-oral devices). The evidence supporting these strategies is not robust, and availability may vary widely (G)

Introduction

Xerostomia is defined as the subjective sensation of oral dryness, whereas hyposalivation reflects an objective, measurable decrease in salivary flow.[634]

Radiation exposure of salivary glands located within the treatment portal results in a dramatic loss of gland function within the first week of treatment, with a subsequent permanent decrease in salivary flow rate in the vast majority of patients.[635,636] The critical dose limit for parotid and submandibular salivary gland tissue is less than 30 Gy; exceeding this limit typically leads to the acute and eventually progressive, irreversible loss of saliva-producing acinar cells, impaired parasympathetic innervation, and injury to glandular vascular structures.[637] Hyposalivation and xerostomia can also be associated with chemotherapy, although function loss and associated symptoms tend to be less severe and often transient.[638]

More than 60 per cent of individuals with head and neck cancer receiving radiation as a monotherapy or in combination with chemotherapy develop irreversible hyposalivation and experience permanent xerostomia.[639] Intra-oral discomfort, difficulties with speech, chewing and swallowing, as well as increased risks of secondary oral infection (e.g. candidiasis and suppurative sialadenitis) and dental disease are commonly seen as consequences of hyposalivation in head and neck cancer survivors.[640] Dental disease in turn may increase the risk of jawbone osteoradionecrosis. Ultimately, a restriction in daily activities, reduced quality of life, poorer general health, social disability and malnutrition may be observed.[641,247]

This chapter proposes a working management plan for hyposalivation and xerostomia (Figure 2).

Oral mucosal lubricants and saliva substitutes

Various oral mucosal lubricants and saliva substitutes with constituents resembling the chemical-physical properties of saliva have been developed, and are commercially available in the form of moisturising gels, mouthwashes, sprays or adhesive discs. As individual preferences and perceived responses to different types of salivary substitutes can vary widely, it is difficult to suggest the superiority of one formulation over another. Evidence supporting the use of oral mucosal lubricants and saliva substitutes is limited, and a clear understanding of the magnitude of their effect is lacking. Realistically, only mild and short-lived xerostomia alleviation may be expected.[642] Nevertheless, oral mucosal lubricants and saliva

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

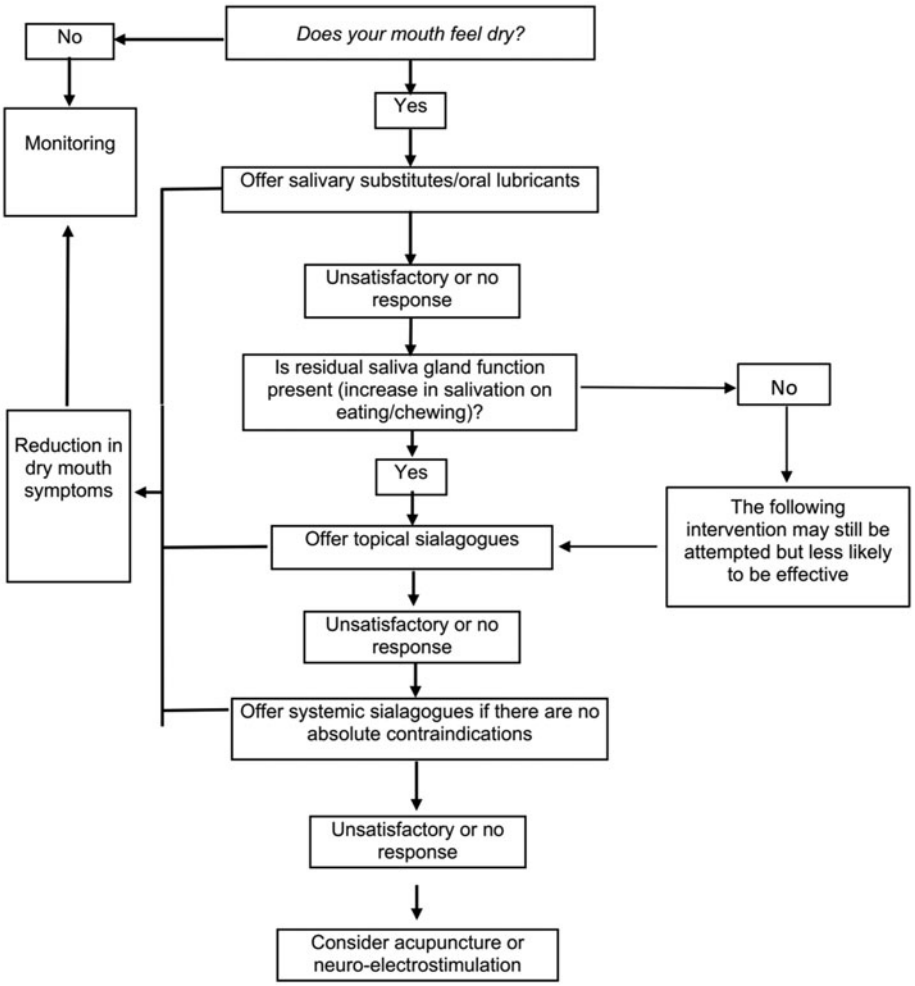


Figure 2. Flow chart summarising a working management plan for hyposalivation and xerostomia.

substitutes have a very safe profile, with very few, if any, adverse effects.

Topical sialagogues

The residual secretory capacity of the salivary glands, if any, may allow increased secretion of natural saliva, which arguably can provide the best protection for the oral tissues and relief from uncomfortable dry mouth symptoms. This can be attained by means of mechanical and gustatory stimuli, with sugar-free chewing gums, and pastilles or lozenges being able to trigger the salivary reflex, increase whole saliva secretion and lessen xerostomia.[643,644] Topical sialagogues have a very safe profile; however, the evidence supporting their efficacy is limited. Clinical experience suggests that the beneficial effects of topical sialagogues may be short-lived.

Systemic sialagogues

Randomised, placebo-controlled trials have provided convincing evidence that patients with RT-related xerostomia can experience increased salivation and reduced dry mouth symptoms with regular use of pilocarpine 5 mg tablets, one tablet three times a day.[645,646] Adverse effects are common but not severe, and include sweating, increased urinary frequency, dizziness, gastrointestinal discomfort and nausea, palpitations, and asthenia.[647] Contraindications include uncontrolled asthma, cardio-renal disease and chronic obstructive pulmonary disease.[647]

Acupuncture

Acupuncture may be offered to patients with radiation-induced xerostomia, especially where the above topical treatments have proven unsatisfactory, and systemic pilocarpine is not effective, is contraindicated or is poorly tolerated. Stimulation of residual salivary functional capacity by acupuncture may increase whole salivary flow rates and alleviate xerostomia up to six months following RT completion.[648,649] The evidence is, however, limited by the lack of true controls in clinical studies and by the considerable heterogeneity in acupuncture protocols.[650,651] In the available studies, no serious adverse events were attributed to acupuncture, although somnolence, tiredness, and minor bruising or bleeding at the puncture site have been reported.[652] Furthermore, acupuncture services are not widely available.

Neuro-electrostimulation of salivary glands

Non-pharmacological, non-invasive electrostimulating devices, such as transcutaneous electrical nerve stimulation, have been developed and tested, with the aims of conveying pulsed electrical currents across the intact surface of the skin or oral mucosa, and stimulating the underlying nerves that modulate salivary gland function. Clinical trials of transcutaneous electrical nerve stimulation devices and intra-oral electrostimulators have reported increased saliva secretion and possible reductions in dry mouth symptoms, although the evidence is limited by differences and inconsistencies in terms of the duration and type of electrical stimulation used, as well as the study design.[653]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

No serious adverse events have been reported with the use of available salivary neuro-electrostimulating devices.

Unilateral vocal fold paralysis following treatment for head and neck cancer

Recommendations

- All patients with a unilateral vocal fold palsy should be assessed by a speech and language therapist (evidence-based recommendation (R))
- Transection of the recurrent laryngeal nerve at the time of surgery should be followed by primary repair where skills allow for this (good practice point (G))
- Early medialisation should be considered in all patients (G)

Introduction and presentation

Unilateral vocal fold paralysis is not uncommon in patients undergoing treatment for head and neck cancer, particularly following surgery for thyroid cancer. Symptoms of unilateral vocal fold paralysis include a breathy and quiet voice. Many patients will also instinctively tension the vocal folds, resulting in a high-pitched voice.

The loss of adequate glottic closure affects swallow function, with aspiration of solids and liquids, but also saliva. Spontaneous coughing on the patient's own secretions is not uncommon. The loss of glottic competence also means that the strength of the cough is diminished (characteristically described as 'bovine'). It is now recognised that silent aspiration results in excess morbidity and mortality.[654] Figure 3 shows a suggested algorithm for the management of unilateral vocal fold paralysis.

Features of unilateral vocal fold paralysis:

- Breathy, weak voice
- Altered pitch (often high-pitched)
- Vocal fatigue
- Hyperventilation
- Ineffective cough
- Aspiration (particularly liquids)
- Pneumonia

The degree of breathy dysphonia is variable and depends on the position of the paralysed vocal fold; a vocal fold sitting in a median or paramedian position results in better glottic closure, and hence a stronger voice. Conversely, a vocal fold in a lateral position will result in a very breathy voice. Most treatments for unilateral vocal fold paralysis are aimed at pushing the paralysed vocal fold into a more medial position (vocal fold augmentation or medialisation). Some patients will still aspirate despite good compensation, and this may be related to sensory deficits from the injury.

Management

The management of unilateral vocal fold paralysis has changed significantly in recent years; in the past, a period of clinical observation ('watchful waiting') was advocated. However, with the advent of newer injectable and absorbable materials, combined with better out-patient endoscopic systems, medialisation procedures are now relatively straightforward to undertake in the clinic in an awake, unsedated patient.

Patients with unilateral vocal fold paralysis should be seen by the speech and language therapy team without delay. If there is evidence of aspiration, appropriate action is necessary (see section on aspiration, above).

Procedures to medialise or augment the paralysed vocal fold aim to provide bulk to the paraglottic space, pushing the medial vibratory edge of the vocal fold to the midline so that glottic closure can be improved. The medialisation material may either be injected directly into the vocal fold (vocal fold medialisation injection (injection laryngoplasty)) or may be placed into the paraglottic space via a window in the thyroid cartilage (Isshiki type 1 thyroplasty (medialisation laryngoplasty)).

Medialisation (augmentation) injection

Vocal fold medialisation injection (injection laryngoplasty) is relatively easy to perform under local anaesthesia in the clinic setting. Equipment requirements are minimal: a distal chip endoscopic system, local anaesthetic and the injection material itself.

Early medialisation following the onset of unilateral vocal fold paralysis improves long-term outcomes. A series of studies has demonstrated that the longer the delay in performing a medialisation procedure, the more likely it is that the patient

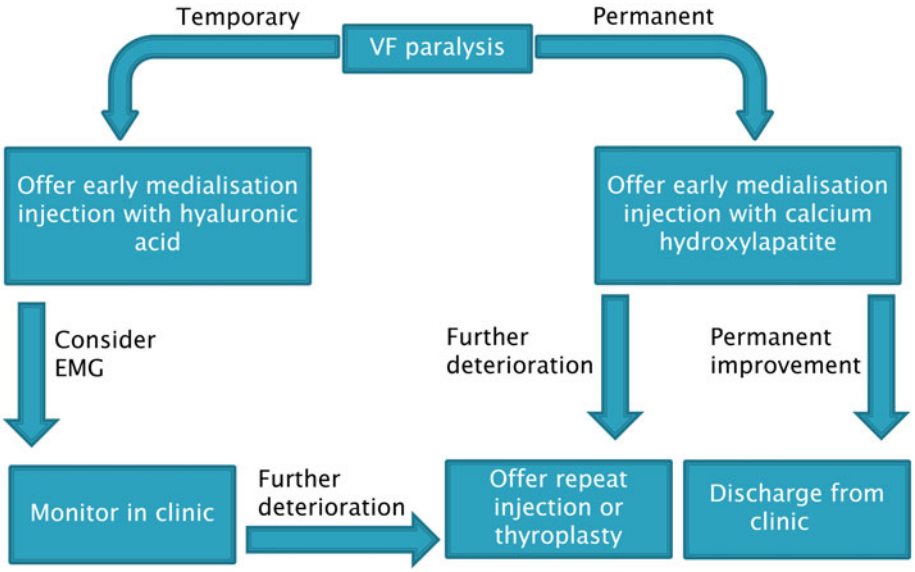


Figure 3. Suggested algorithm for the management of unilateral vocal fold (VF) paralysis. EMG = electromyography

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

will require a thyroplasty in the future.[655–658] There is therefore little justification for 'watchful waiting', and this is radically altering clinical practice amongst laryngologists.

Different materials can be used, the most common of which are:

- Calcium hydroxylapatite (Prolaryn™ Plus, Renú® Voice), which is easy to handle and requires no specific preparation. Its typical duration of action is around 12–18 months.
- Hyaluronic acid (various proprietary preparations, including Restylane®). This typically lasts around four months. It is therefore ideally suited to those patients in whom resolution of the unilateral vocal fold paralysis is anticipated, restoring the voice for the intervening recovery period.
- Dissolvable gels (Renú® Gel, Radiesse™ Voice Gel, Prolaryn™ Gel) are synthetic products that have a similar short duration of action (typically a few months) to hyaluronic acid, and these are used in similar situations to hyaluronic acid.

Injection medialisation can be performed percutaneously or per-orally. All the local anaesthetic techniques described below take just a few minutes to perform, and the patient will typically leave the clinic a few minutes after it is completed. The options are:

- Percutaneous injection under endoscopic guidance (transhyoid, transcricothyroid, transthyroid cartilage)
- Transoral injection under endoscopic guidance

Isshiki type 1 thyroplasty (medialisation laryngoplasty)

Thyroplasty has the advantage of being a 'definitive' procedure, with an implant that (in theory) will not resorb or move. In long-standing cases of unilateral vocal fold paralysis, particularly when previous injections have been performed, a thyroplasty is often the most appropriate choice of procedure.

This procedure is performed in the operating theatre under local anaesthesia. A window in the thyroid cartilage is made at the level of the paralysed vocal fold; an implant material (which may be Silastic™, Gore-Tex® ribbon, metal or other) is placed through the window into the paraglottic space.

Laryngeal reinnervation

If the recurrent laryngeal nerve is transected at the time of neck surgery, it can be primarily repaired, with or without the use of a nerve interposition graft.

Non-selective reinnervation procedures aim to restore tone and bulk to the paralysed vocal fold, but do not achieve normal laryngeal movement. A branch of the ansa cervicalis can be anastomosed to the distal stump of the recurrent laryngeal nerve. Early studies have shown promising results,[659] but improvements in voice often take several months to be seen, so the reinnervation is often combined with a temporising medialisation injection with (for example) hyaluronic acid.

Studies are planned to compare thyroplasty with laryngeal reinnervation, and a feasibility study is underway.[660]

Thyroid testing and dysfunction following head and neck cancer treatment

Introduction

Radiation damages the thyroid gland and can cause, in patients treated for head and neck cancers, mainly two disorders: short-term thyroiditis and long-term hypothyroidism.[661] Less frequently, central hypothyroidism (pituitary irradiation), Graves' disease (hyperthyroidism), including Graves' ophthalmopathy (through the release of thyroid antigens) and benign nodularity, and radiation-induced thyroid carcinoma may occur.[662]

Radiation-induced hypothyroidism

The importance of recognising hypothyroidism cannot be understated. Manifestations of hypothyroidism include slowed mentation, depression, skin dryness, pleural and pericardial effusions, decreased gastrointestinal tract motility, weight gain, and cold intolerance.[169]

Radiation-induced hypothyroidism is the most common post-RT thyroid complication. The incidence of post-treatment hypothyroidism among patients with head and neck cancer is 10–40 per cent.[661,663] It can develop at any time after RT, as long as 10 years post treatment, but with peak occurrence at 1–3 years after RT.[661]

Patients treated with total laryngectomy and RT are at the greatest risk for developing radiation-induced hypothyroidism.[169]

Primary hypothyroidism can be divided into clinical and sub-clinical states. Clinical hypothyroidism is characterised by an elevated thyrotropin (thyroid-stimulating hormone (TSH)) level with a decreased thyroxine (T4) level, or TSH of 10 mIU/l or more, regardless of symptoms. In these cases, hormone replacement with levothyroxine is recommended.[662] Patients with sub-clinical hypothyroidism have an elevated TSH level with normal free T4 levels.[169] If the patient has symptoms of hypothyroidism and TSH is higher than 5 mIU/l, it is reasonable to start a six-month trial of levothyroxine monotherapy to see whether symptoms improve.[664]

Thyroid function studies should be considered before beginning treatment, with further thyroid function tests at 3–6 months after the completion of therapy, and then at 12-month intervals for 2 years followed by annual evaluation, being considered reasonable. Other radiation-induced thyroid disorders (thyroiditis, Graves' disease, thyroid cancer) are rarer, and treatment is similar to that employed in spontaneously occurring conditions.[662]

Clinical management of radiation-induced hypothyroidism

- All patients with overt hypothyroidism (TSH level over 10 mIU/l) should be treated with levothyroxine.[665]
- Initial treatment should entail thyroxine in lower doses in: older adult patients, patients with coronary artery disease and patients with long-standing, severe hypothyroidism.[665]
- In primary hypothyroidism, treatment is monitored in terms of serum TSH levels, with the target level being less than 2.5 mIU/l.

Sub-clinical radiation-induced hypothyroidism

- Consider treatment with levothyroxine for: patients in whom serum TSH is between 5 mIU/l and 10 mIU/l along with symptoms of hypothyroidism, patients with infertility, and patients with goitre or positive anti-thyroid peroxidase antibodies.[71,72]
- When treatment is indicated, a three to six month therapeutic trial is justified. If the patient feels improved by therapy, it is reasonable to continue treatment.[667]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- In patients with central hypothyroidism, treatment is tailored according to free or total T4 levels, which should be maintained in the upper half of the normal range for age.[665]

Treatment with levothyroxine

- Treatment with levothyroxine is lifelong.
- The levothyroxine starting dose should be 25–100 µg.
- In older adults with a history of ischaemic heart disease, the levothyroxine dose can be raised by 25 µg increments at six-week intervals until the TSH goal is attained.[666]
- Thyroid-stimulating hormone should be checked only after six weeks after any dose change; once stabilised, TSH should be checked on an annual basis.[666]
- Levothyroxine is best taken in the morning, with water, on an empty stomach, at least half an hour before eating and drinking anything.[667]
- In patients with persistently elevated TSH despite an apparently adequate replacement dose of T4, consider poor compliance, coeliac disease, malabsorption and the presence of drug interactions.[665]
- Over-replacement is common; it is associated with an increased risk of atrial fibrillation and osteoporosis, and hence should be avoided.[665]

Hearing loss and tinnitus following head and neck cancer treatment

Recommendations and key points

- Where surgical resection (most commonly temporal bone resection) is thought to disrupt any anatomy integral to hearing, it is vital that these patients undergo thorough audiological testing and counselling pre-operatively (evidence-based recommendation (R))
- Total or near-total unilateral hearing loss: consider referral for a bone conduction hearing implant or a bilateral contralateral routing of signals ('BiCROS') aid (good practice point (G))
- Numerous therapeutic agents have been proposed as potentially protective from the ototoxic effects of cisplatin; however, none have clinically significant evidence to support their use. There are less ototoxic alternatives to cisplatin; however, they lack the survival benefit that is evidenced with cisplatin (R)
- The management of otitis media with effusion (OME), commonly encountered in the context of post-RT nasopharyngeal carcinoma (NPC), remains controversial. Conservative measures to manage nasopharyngeal and middle-ear inflammation, as well as hearing aids to rehabilitate hearing, should be considered prior to offering more invasive treatments (R)
- Identifying patients who are at risk of developing ototoxicity pre-treatment can help tailor treatment in the chemoradiotherapy setting, to try and minimise the impact on their quality of life (G)

Introduction

Hearing loss and tinnitus are potential post-treatment sequelae of all modalities used to treat head and neck cancer, namely:

- Cochlear toxicity from chemotherapy
- Cochlear toxicity from RT
- Direct effects of surgery on the external ear canal and/or middle ear
- Effects of surgery and/or RT on Eustachian tube function, causing middle-ear effusion

Hearing loss and tinnitus can have profound effects on a patient's quality of life, particularly in older adults.[668] It is therefore essential to not only help patients in their rehabilitation after treatment, but also to explore how to limit the ototoxic effects of treatment whilst maintaining excellent oncological outcomes. Hearing loss and tinnitus are both included in the National Cancer Institute Common Terminology Criteria for Adverse Events.[669]

Surgery

Temporal bone resection can result in total or near-total conductive hearing loss, and, if extended to the inner ear, sensorineural hearing loss (SNHL) and balance impairment.

Pre-operative audiological assessment of the ipsilateral ear is necessary, and audiological involvement is recommended. Both conductive hearing loss and SNHL can be rehabilitated through a bone conduction hearing implant or a bilateral contralateral routing of signals aid. A bone conduction hearing implant may be contraindicated within any post-operative RT field however.

Chemotherapy

Cisplatin is the most commonly used chemotherapeutic agent in head and neck oncology. Cisplatin-induced ototoxicity results in high frequency SNHL, which may be permanent and is often associated with tinnitus.[670] Fifty per cent of patients receiving more than 200 mg/m[600] have a significant reduction in their hearing, with a severe to profound loss in both ears.[670–672] It is therefore part of pre-treatment counselling to make patients aware of these potential side effects and to screen them for pre-existing hearing loss. It is also important to advise patients to contact the chemotherapy hotline or other appropriate service should they develop hearing loss or tinnitus during their treatment. This allows clinicians to then consider means of mitigating ototoxicity.

Fractionating the cisplatin regimen to weekly doses reduces the likelihood of ototoxicity occurring.[673] There are alternative chemotherapeutic agents with potentially more favourable ototoxicity profiles. Carboplatin is a second-generation platinum-based drug that has a similar mode of action; however, it is associated with less ototoxicity, and less nephrotoxicity and peripheral neuropathy.[674] Carboplatin, however, has failed to demonstrate the same survival benefit as cisplatin.[675]

If there was a scenario where patient-specific factors such as occupation or hobbies, or pre-existing profound hearing loss, were very significant and chemotherapy was indicated, then the above alternatives can be considered. It would obviously be important to counsel the patient thoroughly on the potential reduction in the efficacy of their treatment and to involve the wider MDT in the decision-making process.

There have been attempts to see whether any steps can be taken to protect the inner ear from the ototoxic effects of cisplatin. A wide variety of therapeutics, both systemic and intratympanic, have been proposed to try and ameliorate the ototoxic effects of cisplatin. Unfortunately, to date, none have demonstrated any convincing protection.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Radiotherapy

Radiotherapy causes ototoxicity by a number of proposed mechanisms, including effects on outer hair cells, atrophy of the vestibulocochlear nerve[676] and endarteritis affecting the cochlear blood vessels.[677] It has been established that the effects of RT on hearing are dose-related, and combination chemoradiotherapy exacerbates ototoxicity. Radiotherapy ototoxicity generally causes a high frequency SNHL (4–8 kHz) that may be transient.[678]

The advent of intensity-modulated RT and subsequently volumetric-modulated arc therapy has allowed a reduction of the radiation dose received by the cochlea. The critical cochlear dose to cause an SNHL is unclear, and is quoted as anywhere between 24.2 Gy and 60 Gy in different patient populations.[679,680] Even with these modern advancements in RT techniques, in the context of NPC, it is hard to limit the radiation dose to the cochlea to less than 15 Gy.[681] As a consequence, some authors have advocated pre-treatment risk stratification to try and identify patients who are at high risk of developing ototoxicity, so patients can be appropriately counselled and RT planning tailored.[682,683] Increasing age, cochlear dose, the addition of cisplatin and poor pre-existing hearing have all been identified as risk factors for developing clinically significant ototoxicity following RT.[684]

Otitis media with effusion

Specific attention should be given to OME in relation to patients with NPC. Interestingly, over 40 per cent of patients with NPC will present with OME due to tumour occlusion or Eustachian tube dysfunction.[685] Radiotherapy with or without chemotherapy is the mainstay of treatment for the majority of these patients (see above). The incidence of post-radiation OME ranges between 7.1 per cent and 53 per cent.[686–688] This wide range is likely dose-related; however, the advent of intensity-modulated RT has not significantly reduced the incidence.[689,690] Pre-treatment OME is understandably an adverse risk factor for it remaining following treatment.

The management options for patients with OME with associated hearing loss are the same as in other settings. Many authors have historically advocated a hearing aid, as this rehabilitates both conductive and SNHL and is non-invasive.[691,692] Myringotomy and grommet insertion remain controversial, and there is conflicting evidence in the literature; some authors go as far as to say grommets are contraindicated, quoting persistent otorrhoea rates of 68 per cent and highlighting almost certain recurrence in a condition that is known to last for as long as 10 years following treatment.[691] A more contemporary (2017) randomised, controlled trial comparing observation versus grommet insertion demonstrated more favourable outcomes in patients with grommets, finding that only 10 per cent of patients suffered from persistent otorrhoea.[693]

It is reasonable to suggest that a stepwise approach is sensible in this patient cohort. Conservative measures such as a hearing aid, managing nasopharyngeal inflammation with topical nasal steroids, and salt-water nasal douches should be instigated first. If these fail to rehabilitate symptoms effectively, more invasive measures such as myringotomy and grommets can be discussed. Informing a patient that this treatment is unlikely to be definitive and may result in a chronically discharging ear is vital in the joint decision-making process.

Tinnitus

Tinnitus is a notoriously difficult condition to manage, even in a non-cancer setting. Problematic tinnitus (as recorded by the Tinnitus Handicap Inventory)[694] is more prevalent in patients undergoing chemoradiotherapy rather than RT alone.[695] The management of tinnitus post treatment should be carried out as in other settings, with patient counselling, noise distraction and cognitive behavioural therapy as the mainstays of treatment. Some patients with Eustachian tube dysfunction may experience autophony or tinnitus associated with patulous Eustachian tube dysfunction.[677] There is no evidence-based treatment for patulous Eustachian tube dysfunction in the setting of post-cancer treatment.

Section 3: Site-specific guidelines

Chapter 17: Oral cavity and lip cancer

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

Cancers of the lip and oral cavity are common, with over 377 000 incident cases annually worldwide.[199] In the UK, there are over 3500 new diagnoses each year. The incidence is increasing[210] and represents currently approximately 1 per cent of cancer incidence.[696] Cancers of the lip are the most common group of malignant tumours affecting the head and neck region.

Within the oral cavity, the tongue and floor of the mouth are the most common subsites affected. Cancers of the lip require separate consideration as their natural history may differ from oral cavity disease.

The overwhelming majority of oral cavity cancers are squamous cell carcinomas (SCCs). Those not of squamous origin are pre-dominantly derived from salivary tissues and are discussed elsewhere in these guidelines. Surgical resection is the primary treatment modality for the vast majority of oral and lip cancers.

There are significant functional and cosmetic sequelae of the management of oral cavity tumours, as well as frequent medical co-morbidities and social issues in this patient group. Hence, multidisciplinary team (MDT) management is particularly important.

Pathology

Oral cavity squamous cell carcinoma and dysplasia

Oral cavity SCC may develop *de novo*, or from a pre-malignant dysplastic lesion that appears clinically as leukoplakia, erythroplakia or a combination of the two. In both instances, chronic exposure to carcinogens such as tobacco and/or alcohol is thought to be important. Dental trauma can also be a risk factor, especially in the lateral tongue.

Malignant and pre-malignant lesions of the lip and oral cavity present as a spectrum of disease with varying degrees of cellular atypia, ranging from mild dysplasia to widely invasive carcinoma.[65] Malignant transformation is reported to occur in approximately 12 per cent of dysplastic oral lesions.[697]

Oral dysplasia should be reported according to the World Health Organization (WHO) classification, i.e. a three-tier system of mild, moderate and severe dysplasia, with carcinoma in situ being synonymous with severe dysplasia (see Chapter 3, on pathology).

Histological subtypes of oral cavity SCC have prognostic relevance. For example, verrucous carcinoma has a better prognosis compared to spindle cell carcinoma which generally has a poor outcome. Oncogenic human papillomavirus (HPV) infection is detected in only a small proportion (5 per cent) of oral cavity SCC cases, and there is some evidence to support differential outcomes on the basis of HPV status,[698,699] but not to the extent seen in the oropharynx.[700,701]

Depth of invasion is particularly important in oral cavity SCC, hence its incorporation into the most recent staging, as per *AJCC Cancer Staging Manual* (eighth edition)[87] (see below). Oral tongue SCC of greater than 4 mm tumour thickness is considered to represent a risk of occult cervical lymph node metastasis of greater than 20 per cent.[702]

Tumours with a non-cohesive invasive front, lymphovascular and/or vascular, with lymphatic or perineural invasion, are associated with an increased risk of locoregional relapse. These pathological factors therefore supplement the tumour–node–metastasis (TNM) classification and are now incorporated in histopathology reporting datasets.

Lip

Squamous cell carcinoma is the commonest histological tumour type in lip cancers, followed by basal cell carcinoma. The clinical behaviour of lip SCC is similar to that of skin cancer (see also Chapter 27, on non-melanoma skin cancer). Aetiological factors for lip cancer include solar radiation, tobacco smoking and viruses.

The most common non-mucosal form of lip cancer arises from minor salivary glands, which (in contrast to SCC of the lip) occurs in the upper lip more commonly than the lower.

Clinical presentation and diagnosis

Presentation

Most oral cavity SCCs (over 95 per cent) present as ulcers or masses. Early lesions can be subtle, and appear as flat, discoloured areas (leukoplakia or erythroplakia[703]). A non-healing ulcer is the most common presentation. Advanced tumours may present with invasion of neighbouring structures, causing tooth mobility, trismus, sensory change, referred otalgia and extraoral masses.

The clinical presentation of cancer of the lip is usually that of an exophytic, crusted lesion with variable invasion into underlying muscle (related to the size of the primary tumour). The adjacent lip often shows features of actinic sun damage such as colour change, mucosal thinning, and various associated areas of leukoplakia.[704] About 90 per cent of tumours arise in the lower lip, with 7 per cent occurring in the upper lip and 3 per cent at the oral commissure.

Diagnosis

A systematic approach of examination must be adopted to include the primary site and neck, with an assessment of the index tumour size as well as any potential invasion of local structures.

Diagnosis is confirmed histologically by biopsy for any lesion suspected to be either dysplastic (providing grade of dysplasia) or malignant, and is typically performed in the outpatient setting under local anaesthesia for accessible lesions. The use of flexible nasendoscopy facilitates both the assessment of primary tumours posteriorly positioned in the oral cavity and the assessment of adjacent mucosal structures at risk of synchronous primary malignancies. Examination under anaesthesia (EUA) might be necessary for more posterior lesions, for mapping biopsies, and/or to aid with staging and operation planning.

Imaging

Imaging should ideally be conducted before biopsy, but not at the expense of diagnostic delay. In practice, this means that biopsy in clinic is typically performed before imaging, but imaging should be carried out before EUA. It should be borne in mind that inflammation caused by biopsy might alter the radiological size of some smaller oral cancers and regional lymph nodes.

Oral cavity SCC should be staged with cross-sectional imaging as routine, by either computed tomography (CT) or magnetic resonance imaging (MRI). The chest should be imaged to exclude synchronous primary lung cancer and/or distant metastases.[705] This may also demonstrate other

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

simultaneous pulmonary parenchymal disease. National Institute for Health and Care Excellence (NICE) guidance (NG36) recommended cessation in systemic staging for $T_{1/2}N_0$ disease unless indicated otherwise.[706] However, most patients continue to have systemic staging, similarly to laryngeal cancer, factoring the importance of detecting synchronous lung primary cancers.

Imaging of the primary site in early-stage tumours of the lip is usually not indicated. However, advanced tumours, particularly if they are adherent to the adjacent mandible, require CT or MRI to allow complete staging and treatment planning with regard to resection margins which may include adjacent bone. Where cross-sectional imaging is not indicated, ultrasound assessment of the clinically N_0 neck should be considered, to adequately stage the neck (bilaterally).

Table 1 shows the recommendations for routine imaging modalities in the staging of oral cavity SCC.[706]

Staging

Staging of primary cancer of the lip and oral cavity (according to the *AJCC Cancer Staging Manual*, eighth edition) is summarised in Tables 2–4.[87] The main change in the eighth edition, specific to the oral cavity, is the inclusion of the impact of depth of invasion. The presence of bone invasion carries a negative influence on disease-specific survival (approximately halving survival).[707] This is reflected in the TNM staging classification, whereby the presence of bone invasion (beyond merely superficial cortical erosion) upstages tumours to T_4.

Cancers of the lip vermilion are staged as oral cavity and lip; those arising from outside of the vermilion are staged as skin cancers.

Management – oral cavity cancers

Recommendations

- Surgery is the mainstay of management for oral cavity tumours (evidence-based recommendation (R))
- Offer surgical excision of resectable lesions with a high risk of malignant transformation (R)
- Tumour resection should be performed with a clinical clearance of 1 cm, vital structures permitting (good practice point (G))
- Proactive or elective neck treatment should be offered for all oral cavity tumours (R)
- Elective neck dissection for clinically node-negative disease should include levels I–III (R)
- Therapeutic neck dissection for clinically node-positive disease should include at least levels Ia, Ib, IIa, IIb and III (R)

Table 2. Tumour (T) staging for oral cavity and lip cancer[87]*

T stage	Primary tumour – oral cavity & lip
T_X	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T_1	Tumour ≤2 cm, ≤5 mm DOI†
T_2	– Tumour ≥2 cm, DOI >5 mm & ≤10 mm; – Or tumour >2 cm but ≤4 cm, & ≤10 mm DOI
T_3	– Tumour >4 cm – Or any tumour >10 mm DOI
T_{4a}	Moderately advanced local disease: – (Lip) tumour invades through cortical bone, or involves inferior alveolar nerve, floor of mouth, or skin of face (e.g. chin or nose); – (Oral cavity) tumour invades adjacent structures only (e.g. through cortical bone of mandible or maxilla, or involves maxillary sinuses or skin of face)‡
T_{4b}	Very advanced local disease; tumour invades masticator space, pterygoid plates or skull base, &/or encases ICA

*As per *AJCC Cancer Staging Manual* (eighth edition). †'DOI' is depth of invasion; tumour thickness is not necessarily synonymous with depth of invasion. ‡Note: superficial erosion of bone or tooth socket (alone) by a gingival primary is not sufficient to classify a tumour as T_{4a}. ICA = internal carotid artery

- Post-operative radiotherapy (RT) should be considered for locally advanced disease (R)
- Adjuvant chemoradiotherapy in the presence of advanced neck disease (extracapsular spread) or positive margins improves control rates (R)

General principles

Whilst there are no data from randomised, control trials exclusively comparing the different treatment modalities available in the management of oral cavity cancer, it is generally accepted that the primary treatment modality in suitable patients is surgery.

Two-year crude survival rates are around 85 per cent for stage I disease, 70 per cent for stage II disease,[708] 50 per cent for stage III disease and 40 per cent for stage IV (non-metastatic) disease.[709]

Management of oral dysplasia

Management of oral pre-malignant lesions remains controversial and lacks level I evidence to support practice. The overall malignant transformation rate in a recent systematic review was 27 per cent.[710]

Intervention should be guided by risk stratification for malignant transformation. Grade (either by WHO grading or by two-tier classification) is only one factor that predicts transformation. Risk assessment is an evolving field. In addition to the

Table 1. Recommendations for routine imaging modalities in oral cavity SCC staging

Disease spread	Oral cavity cancer	Lip cancer	
	Any stage	Early tumour stage ($T_{1/2}$)	Late tumour stage ($T_{3/4}$)
Primary tumour	MRI ± CT for mandible*, ± X-ray OPG†	Imaging not necessary	MRI ± CT for mandible*, ± X-ray OPG†
Regional (neck)	MRI or contrast-enhanced CT	Consider MRI &/or ultrasound	MRI or CT
Distant	CT or PET-CT‡	Imaging not routinely indicated	CT or PET-CT‡

*Magnetic resonance imaging (MRI) is superior for assessing soft tissue involvement (e.g. tongue); computed tomography (CT) is superior in the assessment of mandible erosion. †An orthopantomogram (OPG) should be taken to assess the adjacent dentition, and may support the determination of bone invasion alongside clinical assessment and cross-sectional imaging. ‡National Institute for Health and Care Excellence guidance (NG36) recommends cessation in systemic staging for $T_{1/2}N_0$ disease unless indicated otherwise;[706] positron emission tomography (PET)-CT is utilised for N_3 disease. SCC = squamous cell carcinoma

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Node (N) staging for oral cavity and lip cancer[87]*

N stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node sized ≤3 cm in greatest dimension & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node sized ≤3 cm in greatest dimension & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node sized <3 cm & with extra-nodal extension; Or metastasis in a single ipsilateral node sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node sized >6 cm in greatest dimension & with no extra-nodal extension	Metastasis in a lymph node sized >6 cm in greatest dimension & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node sized >3 cm in greatest dimension & with extra-nodal extension; Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, or any with extra-nodal extension; Or metastasis in a single contralateral node of any size & with extra-nodal extension

*As per *AJCC Cancer Staging Manual* (eighth edition).

Table 4. Group staging for oral cavity and lip cancer[87]*

Group stage	Tumour (T)	Node (N)	Metastasis (M)
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	T_{1-3}	N_1	M_0
IVA	T_{1-4a}	N_2	M_0
	T_{4a}	N_{0-1}	M_0
IVB	Any T	N_3	M_0
	T_{4b}	Any N	M_0
IVC	Any T	Any N	M_1

*As per *AJCC Cancer Staging Manual* (eighth edition).

grade of dysplasia, site (floor of mouth and lateral tongue), size, appearance (erosive appearance or erythroplakia), carcinogen exposure and past oral cancer history influence risk.[711]

Whilst decision-making will vary, low-risk cases may be observed clinically with an appropriate review regime and interval clinical photography instigated. It should be ascertained that the biopsy sample was representative of the clinically affected area. Patients with resectable lesions that have a high risk of transformation should be offered surgery, but some lesions are pan-oral or so extensive that surveillance is the only pragmatic option. Where surgical intervention is elected, excision should be undertaken to facilitate histological assessment of the specimen.

Surgery – primary cancer

Curative surgery for cancer of the oral cavity involves resection of the tumour with an appropriate uninvolved margin. Primary reconstruction in order to restore functional integrity should be offered when required. The size and location of the primary tumour determines the need for adjuncts such as access procedures and/or temporary tracheostomy. A full description of surgical techniques is beyond the scope of these guidelines; however, important principles are set out below:

- The primary aim of surgery in oral cavity cancer is tumour resection with a clinical clearance of ideally 1 cm (vital structures permitting) to achieve a histopathological margin of at least 5 mm.
- Most tumours in the anterior aspect of the oral cavity can be accessed via the transoral route. This is ideal, as in so doing the circumferential muscular sphincter is maintained and scars avoided.
- As tumours increase in volume and/or are positioned more posteriorly in the oral cavity, a controlled resection may be facilitated by a lingual release or lip-split mandibulotomy.
- The method of ablation, be it by scalpel, laser, diathermy or Coblation®, is a matter of surgeon preference.
- The use of intra-operative frozen sections to assist marginal clearance is resource-intensive and its benefits remain controversial.[712] Although specificity is good, there is suboptimal sensitivity, which can give a false sense of security and invariably prolongs operative time.
- Attempts to reduce the incidence of dysplastic or in situ disease at the margins with topical adjuncts, such as Lugol's iodine, to guide assessment have been investigated in clinical trials, although definitive outcomes are awaited.[713]
- Where bone resection is required, the assessment is based upon both clinical inspection and radiological findings. Intra-operative techniques such as periosteal stripping may guide resection margins.

Bone invasion

The extent to which bone invasion influences survival depends on both the depth of tumour invasion and overall size.[714,715]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Where bone involvement is confined to just cortical erosion, no adverse impact on survival is apparent. In situations where the tumour abuts but does not invade the bone, it is not clear whether incorporating uninvolved bone to help obtain a negative resection margin confers an oncological advantage. However, it remains an important consideration to avoid close or involved margins at the bony interface, thus influencing pathological clearance assessment (no residual tumour (R_0) *vs* microscopic residual tumour (R_1)) and hence adjuvant therapy with consequent morbidity. Assessment of periosteum can also address these issues when tumour abuts bone.

By contrast, medullary bone involvement confers a poor prognosis, with a significantly increased risk of cancer-specific death even after adjustment for tumour size and other covariates. Medullary bone invasion is an independent predictor of distant metastatic disease.[714,715]

A 2018 systematic review and meta-analysis of 15 retrospective cohort studies, including over 1600 individuals,[716] provided evidence for improved local disease control for individuals undergoing segmental mandibulectomy. There was no statistically significant difference in terms of survival when marginal mandibulectomy was compared to segmental mandibulectomy, although there was a weak trend towards improved overall survival for the latter. In cases where medullary invasion of the mandible occurred, segmental mandibulectomy provided better disease-free survival.

Surgery – reconstruction

Oral cavity cancer frequently requires the reconstruction of ablated tissues to provide restoration of form and functional integrity of the oral cavity and its adjacent bony structures. The importance of appropriate reconstruction in this vital area, including the mandible and maxilla, cannot be overstated. There is a plethora of retrospective series reporting technique and outcome of a wide range of reconstructive techniques for the repair of defects following ablation for oral cavity tumours. The literature suffers from a wide range of heterogeneous factors introducing bias, including tumour sites, stages, patient variables, institutional preferences, surgical techniques, study designs, small numbers, lack of clarity for treatment intention and the reporting of different outcome measures.

Reconstructive options, including local flaps, regional pedicled flaps, and, more frequently, soft tissue and composite microvascular free-tissue transfer, are discussed elsewhere in the guidelines (Chapter 7).

Management of neck lymph node metastasis

Clinically node-negative neck

Occult nodal metastases are present in up to 30 per cent of patients with oral cavity SCC. Randomised, controlled trial evidence supports the provision of an elective neck dissection in the clinically N_0 neck, as this confers improved overall and disease-free survival compared with initial surveillance.[717,718] The relevance of using tumour thickness as a determinant for elective neck management is still debated. However, the NICE (NG36) guidance recommends that all patients with T_{1-2} oral SCC be offered surgical management of the neck.[719] In a significant proportion of patients, the neck will be accessed for microvascular reconstruction, and hence the issue of elective neck dissection is relatively minor, with little additional surgical morbidity when the neck is accessed and dissected for vessel preparation.

When undertaking an elective neck dissection for oral cavity SCC, levels I–III should be included. Evidence for the exclusion of level IIb for tumours other than those arising from the oral tongue remains insufficient to recommend a practice change.[720–722]

Sentinel lymph node biopsy has been demonstrated to be a safe oncological technique for staging the clinically N_0 neck in patients with T_{1-2} oral SCC. In addition to defining the presence of metastasis in the sentinel node, the technique presents potential benefits through the staging of both sides of the neck (12.4 per cent of well lateralised oral tumours demonstrate contralateral drainage[723]), in addition to the avoidance of selective neck dissection for those staged pathologically N_0. The sensitivity of sentinel lymph node biopsy is approximately 85 per cent and the negative predictive value is about 95 per cent.

Sentinel lymph node biopsy may be justifiable in terms of clinical utility and cost effectiveness, and NICE guidance (NG36) recommends that a sentinel lymph node biopsy be offered to patients with T_{1-2} oral cancer.[719] However, debate regarding the optimal approach for the clinically N_0 neck in early oral cancer remains.[724,725] There is a lack of evidence for a reduction in morbidity when sentinel lymph node biopsy is compared to elective neck dissection. The Sentinel European Node Trial ('SENT') reported a false-negative rate of 14 per cent of cases,[723] and, as with any nodal recurrence, clinical outcomes following salvage neck dissection were inferior compared with primary, elective neck dissection. These data should be viewed in the context of the neck recurrence rate for elective neck dissection. A recent systematic review and meta-analysis of evidence reported regional recurrence in $T_{1/2}$ patients with a pathologically N_0 neck following elective neck dissection in 7.5 per cent of cases (range, 1.5–14 per cent).[726] Randomised, controlled trials of sentinel lymph node dissection versus elective neck dissection powered to assess comparative survival outcomes are ongoing and capable of guiding future practice.[727]

Where primary tumours abut the midline, consideration should be made for elective surgical treatment of the contralateral neck given the potential for contralateral neck drainage.

For patients who decline elective surgical management of the neck, regular ultrasound surveillance can be considered.

Clinically node-positive neck

Neck dissection at the time of surgery is indicated when there is clinico-radiological evidence of neck metastasis. The extent of neck dissection is determined by the levels and overall neck disease burden. However, at least levels Ia, Ib, IIa, IIb and III should be dissected. In the largest prospective study, of 583 neck dissections, 91 per cent of nodal metastases were at level I–III.[728] Metastasis at nodal station IIb, IV and V was reported at 3.8 per cent, 4.8 per cent and 3.3 per cent, respectively, with no skip metastases at level IV in the absence of metastasis at levels I–III.[728] A systematic review and meta-analysis of retrospective studies comparing selective neck dissection (I–III) with comprehensive neck dissection in oral SCC patients with a clinically node-positive neck suggested comparable oncological outcomes.[729] (See also Chapter 26, on the management of neck metastases.)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Radiotherapy in oral cavity squamous cell cancer

The role of RT in oral SCC is essentially as post-operative adjuvant therapy with or without synchronous chemotherapy. It is not a standard of care for definitive treatment, but may be considered for patients unfit or unwilling to undergo surgery. Radiotherapy can be delivered by external beam RT (Table 5) or brachytherapy.[730–106] The latter requires specialist expertise not widely available in the UK, and is therefore not discussed further. Intensity-modulated RT is the accepted standard of care for patients undergoing primary and adjuvant external beam RT.

Post-operative radiotherapy and chemoradiotherapy

Recommendations

- Assess suitability for radical surgery and post-operative RT or chemoradiotherapy for patients with locally advanced disease before surgery (good practice point (G))
- Post-operative RT with concurrent chemotherapy (chemoradiotherapy) should be offered to eligible patients with involved positive resection margins (≤1 mm) and/or extra-nodal extension (evidence-based recommendation (R))

Combined modality treatment with surgery followed by post-operative RT or chemoradiotherapy should be considered in all patients with locally advanced or high-risk disease. This is discussed in more detail in Chapter 4. The suitability of patients with locally advanced disease to undergo multimodality treatment should be evaluated at the outset, as well as the likelihood of disease control balanced with the functional impact of treatment. This is particularly important in this patient group who often have significant co-morbidities and social issues. Alternatives to radical treatment should be discussed with the patient as part of the informed consent and decision-making process.

The need for post-operative treatment should be confirmed in the MDT meeting after definitive pathology reporting. The presence of high-risk features (extra-nodal extension and/or positive resection margins) are definite indications for RT,[732] with concurrent chemotherapy (chemoradiotherapy) in those eligible.[733,734] Other adverse features for considering adjuvant RT include close margins (1–5 mm), pathologically $T_{3/4}$, node-positive disease, perineural invasion and lymphovascular invasion, and tumours with a non-cohesive invasive front.[147]

Pre-operative imaging, examination reports, intra-operative findings, and the final pathology result should be available to inform treatment volume delineation.

The clinical target volume should include the primary and nodal tumour bed, with a suitable margin to account for microscopic spread,[735] including all pathologically involved nodal levels. The elective clinical target volume should include at-risk uninvolved nodal levels; this will vary according to primary tumour and nodal factors.

Inclusion of the contralateral (undissected) but clinically or radiologically node-negative neck is controversial. Whilst unilateral RT may allow toxicity reduction with sparing of the contralateral mucosa and parotid, it has been shown that recurrences are unlikely to be successfully salvaged in oral cavity SCC.[737] This, along with patient fitness, must be considered when assessing the risk of treating or omitting the contralateral neck. Radiotherapy to the contralateral neck is recommended in cases following surgery to the primary site and ipsilateral neck when any of the following apply: pathological $T_{3/4}$ tumour stage, a primary tumour within 10 mm (or less) of the midline, and ipsilateral nodal metastasis (with extra-nodal extension).[147,735,738–739]

Post-operative RT should start within six to seven weeks post-operatively. Delayed adjuvant RT and prolonged duration of the treatment package is associated with reduced locoregional control and overall survival.[736]

Table 5. External beam radiotherapy dosage

Primary setting
– 70 Gy in 35 fractions over 7 weeks
Adjuvant setting*
– 66 Gy in 33 fractions (high-risk features present)
– 60 Gy in 30 fractions (no high-risk features)[730,731]
– 50–54 Gy (2 Gy/fraction) (low risk of microscopic disease)[108]

*The dosage of 65–66 Gy in 30 fractions over six weeks (with elective dose of 54 Gy in 30 fractions) has been adopted as a primary treatment or adjuvant treatment for high-risk patients in most UK centres or trials.[106]

Primary radiotherapy in oral squamous cell carcinoma

External beam RT is not recommended as the primary curative treatment in oral cavity SCC.[740–743] In selected patients, usually those unwilling to undergo surgery, it may be carefully considered. This may be as a single modality for early-stage disease or utilised with concurrent platinum or cetuximab for locally advanced disease.[744–745] Whilst surgical and non-surgical treatment have not been compared prospectively, retrospective data suggest that disease control is likely inferior with RT.[740–742]

Morbidity is significant and primary RT is therefore not an alternative to surgery, irrespective of patient performance status.

Treatment – lip cancer

Recommendations

- Early-stage lip cancer can be treated by surgical resection or RT (evidence-based recommendation (R))
- The standard of care for advanced lip cancer is primary surgery (R)
- There is no evidence to support elective treatment for cervical lymph nodes when there is no indication of lymph node metastases (R)
- In the absence of clear margins, further surgical excision to achieve this may be preferable to adjuvant RT and should be considered (good practice point (G))

Early-stage lip cancer can be treated by surgery or RT. Prognosis is generally excellent, as patients tend to present early. Locally advanced disease is best treated by surgery. Lymph node metastases are relatively uncommon.

The five-year crude survival rates for surgical treatment are about 85–95 per cent for T_1 to T_2 tumours, dropping to 40–70 per cent for T_3 and T_4 tumours.[746,747] The local recurrence rate is low because of the relative ease of surgical excision and accurate margin assessment. Re-excision following local failure retains a salvage rate of 75–80 per cent.[748]

Early-stage lip cancer ($T_{1/2}$)

Although there is a paucity of comparative data, it is accepted that early-stage cancers can be treated equally well by surgery

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

or RT. However, surgery represents the commoner modality and the simplest treatment pathway, with small lesions being managed in a single stage by simple surgical excision and primary closure. When used, external beam RT using electrons or orthovoltage photons may be used to treat the full lip thickness whilst minimising the dose (and therefore the toxicity) to the oral cavity. The Royal College of Radiologists dose fractionation guidance recommends a variety of doses, including 35 Gy in 5 fractions, 45 Gy in 10 fractions, 50 Gy in 15–20 fractions, 55 Gy in 20 fractions and 60 Gy in 30 fractions.[147] Decisions regarding radiation method and dose depend on the size and depth of the area treated, the radiation tolerance of the tissue and patient fitness, and so are based largely on clinical judgement. For most cancers, 50 Gy in 15 fractions over three weeks using a single anterior field with orthovoltage may be suitable.

Topical and tissue destructive methods of treatment are reserved for non-invasive lesions, and are not recommended for the treatment of invasive carcinomas. Superficial field change lesions affecting the external vermilion of the lip, such as leukoplakia or actinic keratosis, may be managed with a range of techniques. These include carbon dioxide laser ablation and cryotherapy. Larger confluent lesions may be suitable for lip shave and mucosal advancement surgery.

Advanced stage lip cancer ($T_{3/4}$)

It is generally accepted that the standard of care for advanced lip cancer is primary surgery. As is the case for larger T_2 cancers, advanced stage lip cancer requires either local flaps to reconstruct, or, infrequently, free-tissue transfer to restore a circumferential oral seal and adjacent tissue loss. Adjuvant treatment is determined on the basis of histopathological stage and adverse features, as is the case for oral cavity SCC.

Principles of surgery

There is little in the way of agreed consensus as to what surgical margins of clearance are required for lip SCC. This relates to the nature of the lip resting between the oral cavity proper, in which a 5 mm pathological margin is regarded as the minimum for a clear surgical margin, and the surrounding skin (cutaneous SCC), in which, although the aim is 4–6 mm, a 1 mm pathological margin is regarded as adequate. Other relevant factors include the size of the tumour and the fact that lip function can be compromised with larger excisions. In general, for cancers of the wet vermilion that verge into the oral cavity proper, margins as for mucosal SCC should be achieved (5 mm). For other areas of the lip vermilion, a margin of 3 mm is probably adequate, but practice varies.[749]

Small lesions are managed by simple surgical excision and primary closure. There are reports of using Moh's surgery, as there are for small cutaneous SCC elsewhere in the head and neck, but with little data specifically on lip SCC.[750]

Small lower lip lesions are managed by simple surgical excision and primary closure (such as pentagonal wedge excision or 'W'-plasty resection techniques). Small upper lip lesions can be treated in a similar manner to small lower lip defects, but issues of symmetry can affect the aesthetic outcome, especially in younger patients.

Surgery for larger lip lesions requires greater consideration of the functional outcomes of lip reconstruction (including sensation and muscle function). Whatever technique is chosen, the repair should provide sufficient mucosa contiguous to the commissure, to avoid contracture and microstomia. Full thickness flaps (skin, muscle and mucosa) used in tissue advancement or lip-sharing techniques (unilaterally or bilaterally) are useful in this setting. Various eponymous techniques are described. Ultimately, if full thickness repair including innervated orbicularis oris muscle covered with skin and mucosa can be achieved, this typically gives the best outcome. Balanced microstomia can be addressed with lip stretching exercises once healing is complete, and this often gives acceptable results. Extensive defects of the lip may require remote tissue to be imported in order to achieve healing. Cheek flaps or free flaps can provide adequate tissue, but often functional and aesthetic outcomes are poor because of a lack of innervated orbicularis muscle, poor sensory recovery, and/or differences in skin texture and colour.

Management of the neck in lip cancer

Most large series in the literature show that the majority of patients have small lesions without occult cervical metastases.

The primary lymphatic drainage of the lips is to the submental and submandibular cervical lymph nodes. Elective neck dissection is not performed routinely for lip cancers because of the low rates of occult metastasis. However high-risk tumours that are thought to significantly involve the oral mucosa can be treated as higher-risk oral cavity tumours. Tumours that involve the dry vermilion and skin external to this without mucosal involvement may be treated in the way that cutaneous SCCs are (see Chapter 27, on non-melanoma skin cancer); in such cases, elective neck dissection would not typically be undertaken.

The role of sentinel lymph node biopsy in lip cancer is not clearly defined and is not routine treatment at this stage.

The presence of regional metastases at presentation is a poor prognostic indicator.

Clinically node-positive neck

Management of the node-positive neck in lip cancer is broadly consistent with treatment of anterior oral cavity tumours with nodal metastasis (see above). The extent of neck dissection is governed by the size and location of both the primary tumour and secondary lymph node mass(es). Resection of appropriate levels of the neck may be considered on a case by case basis, but central tumours may often require a bilateral neck dissection. There is conflicting evidence as to need for comprehensive neck dissection in the setting of upper anterior neck lymph node metastasis.[751,752] A more selective neck dissection, omitting levels IIb and V in particular, may be reasonable in certain situations.

Post-operative radiotherapy and chemoradiotherapy

Indications for adjuvant treatment are comparable to the remainder of oral cavity SCC. In the absence of clear margins, further surgical excision to achieve this may be preferable to adjuvant RT and should be considered.

Recurrent oral squamous cell carcinoma

Patients with locally recurrent disease should be fully restaged and assessed for consideration of curative treatment. This can include salvage surgery and/or RT. Careful patient selection is essential. (See also Chapter 5.)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Palliative treatment

The population who are eligible or might benefit from palliative treatment is heterogeneous, and as such there is no firm evidence base to recommend a specific regimen. Given the limited survival often reported in this patient group, treatment should be of the shortest possible duration, whilst ensuring effective palliation and minimal side effects.[753]

Potential benefit from treatment must be balanced with toxicity and possible alternatives (e.g. pharmacological interventions) in the context of the patient's anticipated life expectancy.

Patients with adequate performance status who have inoperable, recurrent or metastatic oral cancer may be considered for palliative systemic anticancer treatment (see Chapter 4). Any role of debulking surgery is minimal.

Pending research questions

- Chemotherapy prevention studies – can novel agents or repurposed drugs support the prevention of high-risk lesions (dysplasia) undergoing malignant transformation?
- Combination immunotherapy strategies – how and when should immunotherapy be integrated into curative treatment pathways for locally advanced oral cavity cancer?
- Does the omission of the pathologically node-negative neck from post-operative RT fields reduce toxicity without compromising survival?
- Are smaller surgical margins safe for smaller non-metastatic cancers?[754]

Studies due to report

A direct comparison of elective neck dissection with sentinel lymph node biopsy in early-stage oral cavity cancer (NCT04333537) is being assessed currently in a phase III clinical trial seeking evidence for the equivalence (or otherwise) of the two treatment strategies in terms of survival.

Chapter 18: Oropharyngeal squamous cell carcinoma

Table of Contents

Introduction

Internationally, the incidence of oropharyngeal squamous cell carcinoma (SCC) has been increasing. The most recent UK figures from the Office of National Statistics show that the annual incidence increased from 1029 to 2997 cases between 2000 and 2016, with the rate almost doubling over the last 10 years. Human papillomavirus (HPV) is the proposed driver of the increase in global rates, with a 20.6 per cent rise in worldwide prevalence of HPV-positive oropharyngeal SCC.[755] Human papillomavirus was associated with over 70 per cent of oropharyngeal SCCs by 2009 in both the UK and USA, with little change in the prevalence in non-HPV-related oropharyngeal SCCs.[204]

Presentation and diagnosis

Recommendations

- Record the site, size and fixity of the oropharyngeal primary tumour, and any restrictions in transoral access (before biopsy or tonsillectomy) (good practice point (G))

Patients with oropharyngeal cancers may present with a variety of symptoms. These include: dysphagia, odynophagia, pain in the throat, tongue or referred otalgia, weight loss, and altered speech. Speech changes can include problems with articulation, a 'hot potato' type voice, or, rarely, hoarseness. While some patients may present with symptoms, others will present with an otherwise asymptomatic neck lump and be investigated via the carcinoma of unknown primary pathway (see Chapter 27), with an oropharyngeal primary being discovered during diagnostic investigation.

Oropharyngeal cancer primary sites may be biopsied under local anaesthesia if practical and safe, or under general anaesthesia. If general anaesthesia assessment is performed, the transoral access for the primary site, the fixity of the tumour and the feasibility for resection should be documented. Cervical lymphadenopathy when present should be assessed, and a core or fine needle biopsy performed for diagnosis. Performing this under ultrasound guidance is preferable.[756]

Support from allied health members of the multidisciplinary team (MDT) should be offered to all patients, given the physical and psychosocial effects of cancer, and, in particular, the potential impact on diet and swallowing.[71]

Imaging

Recommendations

Recommendations for pre-treatment imaging in oropharyngeal SCC are shown in Table 1.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Magnetic resonance imaging (MRI) with contrast is optimal for primary tumour staging; it is preferable to computed tomography (CT) as it provides improved soft tissue contrast resolution between tumour, muscle and mucosa. It also allows for the evaluation of: early bone marrow involvement, pterygopalatine fossa extension, prevertebral muscle involvement,[757] retropharyngeal lymph node involvement, the relationship to the internal carotid artery and the perineural spread of the tumour.[758,759] Magnetic resonance imaging can stage the primary site and neck nodes at the same time. Magnetic resonance imaging is also much less degraded by artefacts from dental amalgam when compared to contrast-enhanced CT.

Computed tomography may be required to evaluate invasion of bony structures (e.g. mandible and skull base), or when MRI is contraindicated (e.g. pacemaker).

Ultrasound with or without needle sampling (fine needle aspirate biopsy or core biopsy as appropriate) can provide further information as to the status of indeterminate cervical nodes.[760,761]

Systemic staging is recommended for all patients. Although National Institute for Health and Care Excellence (NICE) guidance states that, in tumour–node stage $T_{1-2}N_0$ disease, systemic staging may be omitted,[756] this is unusual practice and most patients undergo CT of the thorax.

Fluoro-deoxy-glucose (FDG) positron emission tomography (PET)-CT has been shown to provide no significant benefit in the pre-treatment evaluation of staging oropharyngeal SCC, with only a 50 per cent specificity in the node-negative (N_0) neck and similar sensitivity to conventional modalities.[762] It may have some utility in treatment planning, but this has not yet been defined. Current NICE guidelines recommend FDG PET-CT for patients with N_3 nodal stage.[756]

Staging

All tumours should be staged using the *TNM Classification of Malignant Tumours* (eighth edition).[763] There are now separate classifications for the clinical and pathological staging of neck lymph node metastases. The eighth edition also introduced a new classification for p16-positive oropharyngeal cancers (Tables 2–6). P16 immunohistochemistry overexpression is a surrogate marker for HPV infection. As p16 (HPV) positive oropharyngeal SCCs have a favourable prognosis,[764] the staging for these two diseases is distinct.[763]

Pathology

Recommendations

- Testing for HPV should be carried out for all oropharyngeal SCCs (evidence-based recommendation (R))
- Testing for HPV-related disease should be performed by an appropriately accredited laboratory (good practice point (G))
- Surgical specimens should be orientated clearly and details communicated to the pathologist (R)

Table 1. Pre-treatment imaging in oropharyngeal SCC

Staging	Modality
Primary / neck	MRI preferred (CT if contraindicated)
Thorax / systemic	CT of thorax (PET-CT for N_3 disease)

SCC = squamous cell carcinoma; MRI = magnetic resonance imaging; CT = computed tomography; PET = positron emission tomography; N = nodal stage

Table 2. Primary tumour (T) staging for oropharyngeal SCC (p16-negative and p16-positive)*

T stage	p16-negative oropharyngeal SCC	p16-positive oropharyngeal SCC
T_X	Primary tumour cannot be assessed	
Tis	Carcinoma in situ	
T_1	Tumour sized ≤2 cm in greatest dimension	
T_2	Tumour sized >2 cm, but ≤4 cm in greatest dimension	
T_3	Tumour sized >4 cm in greatest dimension or with extension to lingual surface of epiglottis	
T_4 (p16-positive only)		Tumour invades larynx, deep or extrinsic tongue muscles (genioglossus, hyoglossus, palatoglossus & styloglossus), medial pterygoid, hard palate, mandible, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery
T_{4a} (p16-negative)	Tumour invades larynx, deep or extrinsic tongue muscles, medial pterygoid, hard palate, or mandible	
T_{4b} (p16-negative)	Tumour invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx or skull base, or encases carotid artery	

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] SCC = squamous cell carcinoma

Surgical specimens

Regarding surgical specimens, see also Chapter 3, on pathology. When surgery is performed for diagnosis or treatment, evaluation of the specimens can be challenging for the pathologist, especially if a mosaic resection has been performed. Good communication with the surgical team is required to establish the orientation of the specimen and to identify critical margins.

Orientation can be challenging for transoral specimens. Specimens should be orientated, and labelled using a cork board, or sutured to a foam pad or acetate sheet and annotated with labels.[765] The pathologist can then document the specimen with photography and ink the excision margins appropriately.

Intra-operative frozen sections can be used to guide surgery, but this requires appropriate planning and resources.

The definition of close and positive margins is controversial and confounded by difficulties in accurately assessing composite resection specimens. Ultimately, the margin status influences decisions around the provision of further surgery and the use of non-surgical adjuvant treatment, and is best formulated in the context of a head and neck cancer MDT meeting or within a trial protocol.

Human papillomavirus testing

There are numerous methods to test for HPV-related oropharyngeal SCC. P16 immunohistochemistry is a simple,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Nodal (N) staging for p16-negative oropharyngeal SCC*

N stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	
N_0	No regional lymph node metastasis	
N_1	Metastasis in a single ipsilateral lymph node sized ≤3 cm in greatest dimension & with no extra-nodal extension	
N_{2a}	Metastasis in a single ipsilateral lymph node sized <3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node sized <3 cm & with extra-nodal extension; Or metastasis in a single ipsilateral node sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension & with no extra-nodal extension	
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension & with no extra-nodal extension	
N_{3a}	Metastasis in a lymph node sized >6 cm in greatest dimension & with no extra-nodal extension	
N_{3b}	Metastasis in any node(s) with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node sized >3 cm in greatest dimension & with extra-nodal extension; Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, or any with extra-nodal extension; Or metastasis in a single contralateral node of any size & with extra-nodal extension

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] SCC = squamous cell carcinoma

Table 4. Nodal (N) staging for p16-positive oropharyngeal SCC*

N stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	
N_0	No regional lymph node metastasis	
N_1	Unilateral metastasis in lymph node(s) sized ≤6 cm in greatest dimension	Metastasis in 1–4 lymph nodes
N_2	Metastasis in bilateral or contralateral lymph node(s), all sized ≤6 cm in greatest dimension	Metastasis in ≥5 lymph nodes
N_3	Metastasis in lymph node(s) sized >6 cm in greatest dimension	N/A

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] SCC = squamous cell carcinoma; N/A = not applicable

Table 5. Group staging for p16-negative oropharyngeal SCC*

Group stage – p16-negative	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	$T_{1–3}$	N_1	M_0
IVA	$T_{1–3}$	N_2	M_0
	T_{4a}	$N_{0–2}$	M_0
IVB	Any T	N_3	M_0
	T_{4b}	Any N	M_0
IVC	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] SCC = squamous cell carcinoma

Table 6. Group staging for p16-positive oropharyngeal SCC*

Group stage – p16-positive	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	$T_{1–2}$	$N_{0–1}$	M_0
II	$T_{1–2}$	N_2	M_0
	$T_{3–4}$	$N_{0–1}$	M_0
III	$T_{3–4}$	N_2	M_0
IV	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] SCC = squamous cell carcinoma

thoroughly validated surrogate marker for HPV-related oropharyngeal SCC and has a prognostic impact. The most commonly used cut-off for a p16-positive result is strong and diffuse nuclear and cytoplasmic staining in 70 per cent or more of the malignant cells. Human papillomavirus specific tests are directed at the detection of high-risk HPV DNA or RNA by in situ hybridisation or polymerase chain reaction methods.[766] The World Health Organization, American Joint Committee on Cancer, Union for International Cancer Control, International Collaboration on Cancer Reporting and College of American Pathologists recommended p16 immunohistochemistry to infer HPV status for disease classification.[763,766–768] Nevertheless, there is emerging evidence from studies in Europe that p16 testing alone may not be sufficient for accurate prognosis. Specifically, patients with p16-positive, HPV DNA or RNA negative oropharyngeal SCC have a similar poor prognosis to patients with p16-negative disease.[769] An established algorithm using p16 immunohistochemistry followed by HPV-specific testing of p16-positive cases is required for accurate prognostication and for recruitment of patients to interventional clinical trials.[770–772] The HPV testing should be performed in a quality assured laboratory with appropriate accreditation (e.g. International Organization for Standardization accreditation ISO15189:2012).

Human papillomavirus status and impact on management

Recommendations

- Use HPV status to stage and counsel patients regarding prognosis, but not to modify treatment outside of the trial setting (good practice point (G))

The *TNM Classification of Malignant Tumours* (eighth edition) incorporated a different staging system for p16-positive and p16-negative tumours (utilising this as a surrogate marker for HPV) because of their different prognostic outcomes. However, there is currently no evidence to offer treatments

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

of reduced intensity based on HPV status.[756] For example, there should be no difference in management between a patient with p16-positive oropharyngeal SCC with two lymph node metastases (N_1) and a patient with the same, but p16-negative (N_{2b}).

Management of early oropharyngeal cancer ($T_{1-2}N_{0-1}$)

Recommendations

- Offer patients with early oropharyngeal SCC information regarding primary surgical and non-surgical approaches for curative treatment (evidence-based recommendation (R))
- Every MDT should have the facility and expertise to offer radical radiotherapy (RT) (with concurrent chemotherapy) and transoral surgery (R)
- Consider primary non-surgical treatment if adjuvant radiation following transoral surgery is likely to include concurrent chemotherapy. This avoids triple modality treatment. This is particularly the case in patients with HPV-related oropharyngeal SCC who have an excellent prognosis (good practice point (G))
- Open primary surgery is not recommended for early oropharyngeal SCC (G)

There remains considerable ongoing debate regarding the management of early oropharyngeal SCC. Open primary surgery is not recommended; the essential options for treatment are either:

(1) Primary RT (with chemotherapy, if suitable, for tumours with more than one lymph node or a lymph node sized 3 cm or larger (i.e. N_2 using p16-negative classification for all oropharyngeal SCC)); or
(2) Primary transoral surgery and neck dissection with or without post-operative RT or chemoradiotherapy.

In many cases, it is the lymph node status that informs the choice, i.e. whether concurrent chemotherapy would be indicated as part of treatment. For oropharyngeal SCC with no lymph node metastases or limited to a single lymph node sized less than 3 cm, the choice is between single modality treatment with RT or surgery (but possibly with post-operative RT). One key issue with surgery in such circumstances is the determination of a margin status indicating R_0 resection (no residual tumour) and no need for adjuvant treatment. There is growing consensus that 2–3 mm (and possibly less), rather than 5 mm, is appropriate for p16-positive oropharyngeal SCC.[773]

The NICE concluded that transoral surgical resection or primary RT should be offered for $T_{1-2}N_0$ tumours of the oropharynx, with post-operative RT (with or without chemotherapy) if adverse risk factors are identified.[756]

Where patients are suitable for either primary RT or transoral surgery, this should be discussed in an MDT and the current equipoise discussed with the patient. As part of the discussion, the patient should be aware of the possibility of requiring post-operative RT or chemoradiotherapy.

Evidence to date has shown that both primary surgery and RT offer broadly comparable and excellent survival and functional outcomes for patients with early oropharyngeal SCC. A number of trials have been performed (but findings are as yet unreported) or are underway to address the clinical question of how best to treat these tumours, both in terms of oncological effectiveness and treatment effects (particularly swallowing). These trials include direct comparisons between treatment modalities and de-escalation strategies, and are discussed at the end of this chapter.

Management of early oropharyngeal cancer – surgery

Recommendations

- Consider transoral surgery as the first treatment option for patients with a high likelihood of achieving R_0 resection (evidence-based recommendation (R))
- Offer ipsilateral neck dissection (levels II–IV) for patients with well lateralised cancer and clinically N_0 or clinically N_1 neck disease, when the primary tumour is being managed by transoral surgery (R)
- Consider contralateral selective neck dissection for patients with clinical and radiological absence of disease, when the non-lateralised primary tumour is being managed by transoral surgery and ipsilateral neck dissection (good practice point (G))
- Offer ipsilateral feeder vessel ligation for patients undergoing transoral resection of oropharyngeal cancer (R)

Primary site

T_1 and T_2 tumours and selected T_3 tumours may be considered for surgical resection.[774] The aim of surgery is to obtain an R_0 resection (see above regarding margins). Important considerations include access, fixity, palatal extent, laterality and vessel location.

Surgical techniques include transoral robotic surgery, transoral laser microsurgical resection or other endoscopic resections (e.g. monopolar diathermy with endoscope visualisation). No evidence exists to suggest the superiority of any of these techniques. Transoral surgery may involve en bloc resections or sectional (mosaic resections), with or without separate margins.

Post-operative haemorrhage following transoral resection is well recognised, with major or severe haemorrhage reported in 6.7 per cent and 2.6 per cent of cases respectively; 60 per cent of these patients will need to go to the operating theatre for haemostasis.[775] In order to help decrease the incidence of life-threatening bleeding, ligation of the external carotid artery branches (lingual and facial branches) is recommended at the time of neck dissection.[776]

Neck

Neck treatment should cover levels II–IV on the ipsilateral side.[777] Between 10 and 31 per cent of patients who are clinically staged as $T_{1-2}N_0$ will have occult nodal disease.[778] As occult level IB metastasis risk is low, routine dissection of this level is not indicated in clinically N_0 disease. Level I disease is associated with worse outcomes, especially with a higher T or N stage.[779,780]

Contralateral nodal involvement is generally low (up to 4 per cent), with the highest risk when disease is within 1 cm of the midline.[778] Therefore, it may be appropriate to consider contralateral super-selective neck dissection for at-risk tumours if this will alter the overall treatment plan.[777]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Primary and neck surgery can be completed at the same sitting or separated by up to two weeks, with the neck surgery preceding the transoral resection.

Post-operative adjuvant treatment

Recommendations

- Offer patients post-operative RT in the presence of adverse pathological features (close margins, multiple nodes) (evidence-based recommendation (R))
- Offer patients aged under 70 years with positive margins and extra-nodal extension post-operative RT with concurrent chemotherapy (R)

There are no recommendations for adjuvant RT treatment that is specific to oropharyngeal SCC. See Chapter 4 for general considerations. The recommended adjuvant dose is 60 Gy in 30 fractions, with a dose of up to 66 Gy in 33 fractions to high-risk sub-volumes.

Patients with extra-nodal extension or positive resection margins (less than 1 mm), who are aged less than 70 years, should be offered post-operative RT with concurrent chemotherapy, unless part of a trial.[733] No evidence supports altering the adjuvant regimen based on HPV status, and this should only be done within a trial envelope. Preparation for adjuvant treatment (e.g. dental extractions, percutaneous endoscopic gastrostomy placement) can be completed at the time of primary surgery.

Management of early oropharyngeal cancer – non-surgical treatments

Recommendations

- Intensity-modulated RT should be used with the '5 + 5' technique (good practice point (G))
- The dose should be equivalent to 70 Gy (evidence-based recommendation (R))
- When the tumour is not lateralised, the contralateral neck should be treated (G)
- Assessment of the nodal burden should be considered in lateralised tumours when considering omitting contralateral RT (R)

Radical radiotherapy

Recommendations for the treatment of oropharyngeal SCC are provided per the Royal College of Radiologists' 2021 head and neck consensus statement and the European Organisation for Research and Treatment of Cancer 2017 consensus guidelines.[781,782] Intensity-modulated RT should be used ideally with a '5 + 5' technique, as per protocol, but consider larger margins if there is uncertainty regarding the gross tumour volume. Organs at risk for these fields include the spinal cord, brainstem and parotid glands. It is suggested that a dose equivalent to 70 Gy in 35 fractions (typically 65–66 Gy in 30 fractions) is used.[783]

With the aim of reducing toxicity, the high level II lymph nodes (i.e. cranial border of level II defined as where the internal jugular vein crosses the posterior belly of the digastric muscle) should be omitted from the elective target volume in an uninvolved contralateral neck.[784]

It is also possible to consider omitting the contralateral retropharyngeal lymph nodes from the elective target volume and when delivering radical RT, as long as there are no ipsilateral involved retropharyngeal lymph nodes and the gross tumour volume of the primary does not involve the soft palate or posterior pharyngeal wall.[146]

Neck radiotherapy

The contralateral neck can be omitted for well lateralised T_{1-2} SCC of the tonsil with a N_0 neck or with one involved ipsilateral neck node.

'Well lateralised' is defined as a tumour confined to the palatine tonsil, tonsillar fossa or lateral pharyngeal wall, with greater than 10 mm clearance from midline, not involving the base of the tongue or posterior pharyngeal wall, and extending on to the adjacent soft palate by less than 10 mm. Omission can be considered in well lateralised T_{1-2} of the tonsil with ipsilateral nodes but a low nodal burden (i.e. fewer than three nodes, less than 3 cm, only levels II–III).[785,786]

Management of advanced oropharyngeal squamous cell carcinoma (T_{3-4} or N_{2+})

Recommendations

- Offer RT with concurrent chemotherapy with platinum-based chemotherapy to suitable patients with advanced staged disease (good practice point (G))
- Consider tri-modality treatment in select cases, following full discussion of the benefits and drawbacks with patients (G)
- Consider early, rapid nutritional intervention (evidence-based recommendation (R))

Concurrent chemoradiotherapy for advanced disease when indicated can improve survival, and should be the standard of care for patients aged under 70 years with no contraindications. Evidence suggests an overall survival benefit of 4–8 per cent for patients aged under 70 years who are receiving concurrent chemotherapy with radiation.[787] Weekly cisplatin may be considered in patients not suitable for three-weekly cisplatin.[788] Cetuximab as an alternative concurrent chemotherapeutic agent is inferior to cisplatin.[136,789]

Whilst chemoradiotherapy remains the standard of care for advanced oropharyngeal SCC, triple modality treatment may provide a survival benefit in a subset of patients with advanced tonsil cancer.[790] Surgery may have a role in cases when concurrent chemotherapy is contraindicated (i.e. as preferred to RT alone).

Where surgery is offered, this should be with the aim of achieving complete resection at the primary site. Open surgery can be considered for $T_{3/4}$ disease, especially in the presence of bone invasion.

In the presence of advanced neck disease, it is important to assess the likelihood of achieving macroscopic clearance when performing a neck dissection. This is less likely in N_3 disease or where skin resection may be required. The radiological likelihood of extra-nodal extension, especially in patients with HPV-negative disease, should be assessed at the MDT, as this will upstage tumours and will necessitate adjuvant chemoradiotherapy (triple modality treatment) if there is pathological evidence of extra-nodal extension and positive surgical margins.[733]

Tumours in the oropharynx may affect the airway at presentation, and large tumours and subsequent swelling with RT may compromise airway safety. If the risk of airway swelling due to treatment is felt to be significant, it is advisable to offer prophylactic tracheostomy in order to avoid breaks in

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

treatment. An increased duration of nutritional support is likely with advanced tumours, and this should be factored into treatment planning; the prophylactic placement of a feeding tube or a low threshold for triggering reactive nasogastric tube feeding should be considered in this patient group. Patient choice and local availability will influence this decision.

Post-treatment imaging and follow up

Recommendations

- Offer all patients PET-CT at a minimum interval of 12 weeks after primary non-surgical treatment (evidence-based recommendation (R))
- Offer neck dissection to patients with an incomplete lymph node response on PET-CT imaging after primary non-surgical treatment (good practice point (G))
- Consider a neck dissection or further PET-CT scan at 10–12 weeks in patients treated for HPV-positive oropharyngeal SCC with primary non-surgical treatment who have an equivocal response on initial PET-CT (G)

Following non-surgical treatment, FDG PET-CT at a minimum of 12 weeks has been shown to accurately evaluate the response to treatment, and, in the absence of residual structural or metabolic activity, no surgical treatment is needed.[204,756] For HPV-positive patients with equivocal FDG PET-CT findings at 12 weeks, a repeat scan following a further 10–12 weeks can be considered as an alternative to a neck dissection.[791–793] Equivocal FDG PET-CT findings in patients with HPV-negative oropharyngeal SCC are associated with a high specificity for residual disease and will need surgical treatment.[794,795] Post-treatment neck dissection should include at least the nodal level(s) demonstrated on the FDG PET-CT and an adjacent level if possible. Evidence for the extent of neck dissection is absent.

In those patients treated with primary surgery with or without adjuvant therapy, a post-treatment baseline MRI scan at 12 weeks is helpful as a future method of comparing changes.

Ultrasound evaluation with needle sampling can be helpful in the decision-making process for patients showing equivocal residual nodal disease on FDG PET-CT. Diffusion-weighted MRI sequences can help to distinguish recurrent disease from radiation-induced soft tissue changes.[796] Fluoro-deoxy-glucose PET-CT may be a useful adjunct to CT or MRI in inconclusive cases and to rule out distant metastatic disease, particularly if further treatment is planned.

For those patients undergoing non-surgical treatment, there is no evidence that further routine surveillance imaging, besides regular clinical follow up, results in better survival rates for patients who remain asymptomatic after being treated with curative intent and who show a full metabolic and structural response on the post-treatment FDG PET.[797]

Recurrent disease

Recommendations

- All recurrent cases of oropharyngeal SCC should be re-staged (evidence-based recommendation (R))
- The MDT should have pathways to offer all potential treatments for recurrent cases of oropharyngeal SCC (R)

See also Chapter 5, on follow up, surveillance and recurrent disease. Recurrent disease following previous irradiation is challenging. The local stage and extent of recurrence, coupled with the type of treatment given previously, will be important determinants of the treatment options. Complete re-staging of the primary site and systemic body imaging are recommended, as well as assessment of nutritional status, speech and swallowing function.

Surgical resection in those patients previously treated with RT remains an option in a selected group of patients. Surgery is complicated and should be undertaken by an experienced team. Open surgery is more frequently offered for larger tumours, when transoral access is compromised or when vascularised tissue reconstruction is required. Transoral resection can be offered in select patient groups, including those with vascularised tissue reconstruction, with good oncological and functional outcomes.[773]

Other management options apply as for other recurrent cancers, discussed in Chapters 4 and 5, and include: RT for patients previously treated with surgery only; re-irradiation (only in select patients); surgery for isolated lymph node recurrence (Chapter 26); systemic palliative therapy with chemotherapy and/or immunotherapy; and best supportive care.

Ongoing research

It remains unknown whether there is functional benefit from either non-surgical primary treatment or transoral surgery.[798,799] This is especially important in the context of de-intensified radiation regimens offering comparable outcomes.[51]

A number of trials on oropharyngeal cancer are currently actively recruiting in the UK, which will report in the next five years. These include the 'Post-Operative Treatment for HPV-positive Tumours' ('PATHOS') trial, which will report on the impact of lower-dose adjuvant RT in intermediate risk oropharyngeal SCC and the omission of chemotherapy in high-risk oropharyngeal SCC following primary transoral resection. Furthermore, a direct comparison of surgery versus RT for early-stage oropharyngeal SCC will come from the 'Study Assessing The "Best of" Radiotherapy vs the "Best of" Surgery in Patients With Oropharyngeal Carcinoma (Best Of)'. 'A trial of proton beam RT for oropharyngeal cancer' ('TORPEdO') is evaluating whether proton beam therapy can reduce the side effects of non-surgical treatments, whilst the 'Phase III Randomised Controlled Trial Comparing Alternative Regimens for Escalating Treatment of Intermediate and High-risk Oropharyngeal Cancer' ('ComPARE') is investigating standard chemoradiotherapy against dose-escalated chemoradiotherapy or the addition of the programmed death-ligand 1 (PD-L1) inhibitor durvalumab.

Important research questions to be answered

(1) Is p16 immunohistochemistry alone sufficient for prognostication?
(2) Can treatment or surveillance protocols be stratified based on HPV status?
(3) What are oncologically safe transoral surgical margins?
(4) What is the functional and survival profile of transoral surgery and risk-stratified adjuvant treatment versus standard non-surgical treatment?
(5) Does immunotherapy in combination with other agents confer a survival benefit in oropharyngeal SCC?
(6) Would proton beam therapy provide functional or survival benefits over intensity-modulated RT?

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Chapter 19: Nasopharyngeal carcinoma

Table of Contents

Introduction

Nasopharyngeal carcinoma (NPC) has a unique pattern of endemic distribution, with the highest incidences in Southeast and East Asia. Nasopharyngeal carcinoma is non-endemic and rare in Western populations.[801,802]

In non-endemic populations, there is a bimodal peak, with an initial peak in adolescents/young adults and a second peak after 65 years of age.[801,803]

Management of NPC is particularly challenging in non-endemic areas such as the UK. The validity of basing the management of NPC in non-endemic areas upon evidence derived from large endemic trials remains uncertain.

Presentation and diagnosis

Summary recommendations

- Diagnosis should be made by an endoscopic guided biopsy of the nasopharynx (good practice point (G))
- Epstein–Barr virus (EBV) status of lymph node biopsies should be assessed in the investigation of an unknown primary cancer of the head and neck region (evidence-based recommendation (R)). In this scenario, ^{18}F-fluoro-deoxy-glucose (FDG) positron emission tomography (PET) imaging can guide biopsy of the nasopharynx.

Clinical presentation of nasopharyngeal carcinoma (NPC) is usually related either to the extent of primary disease or regional neck lymph node metastases. Because of its highly infiltrative nature, NPC spreads easily in a stepwise fashion via pathways of lower resistance, and via neural pathways and foramina.[804,805] Involvement of the nasal cavity, paranasal sinuses, skull base, cavernous sinus, brain parenchyma or orbit can cause a variety of symptoms. These include unilateral nasal obstruction, epistaxis, deafness (typically unilateral) and cranial nerve palsies (with cranial nerves III, IV, Va,b, VI and XII being most commonly affected). Around three-quarters of patients will have regional lymph node metastases at presentation. The retropharyngeal and level II lymph nodes are commonly involved, and skipped lymph node metastases are uncommon.[801] An endoscopic guided biopsy of the primary should be performed to confirm the diagnosis.

Initial presentation may be with lymphadenopathy, with no evidence of a primary site clinically or radiologically (i.e. an unknown primary; see Chapter 27). Imaging (magnetic resonance imaging (MRI) of the neck or PET-computed tomography (CT)) and/or in situ hybridisation determining EBV status may suggest a nasopharyngeal primary, and endoscopic biopsies of the nasopharyngeal mucosa should then be performed.

Imaging

Table 1 shows a summary of imaging recommendations for nasopharyngeal carcinoma.[806,807]

Summary recommendations

- Magnetic resonance imaging of the skull base and neck is the imaging modality of choice for local staging (good practice point (G))
- Whole-body CT or ^{18}FDG-PET-CT is required for staging (G)
- Magnetic resonance imaging co-registration is recommended for radiotherapy (RT) planning (G)
- ^{18}F-fluoro-deoxy-glucose-PET-CT is the most accurate modality for response assessment (evidence-based recommendation (R))

Accurate mapping of the entirety of perineural spread, the extent of skull base infiltration and the proximity to organs at risk (e.g. optic chiasm) is crucial for RT planning. A close collaborative approach between the radiologist and clinical oncologist is therefore recommended. A rigid co-registration of an MRI acquired within two to three weeks of the planning CT scan improves accuracy of both target volume and organ-at-risk delineation.[805] Although not currently available in many UK centres, the method of ensuring maximum accuracy of co-registration is for the MRI to be performed in the RT treatment position with the immobilisation devices used for treatment.[805,808]

Staging and prognostic markers

Staging

Nasopharyngeal carcinoma has its own nodal (N) staging. This is unchanged in the *TNM Classification of Malignant Tumours* (eighth edition) (Tables 2 and 3).[809]

Other prognostic markers for survival risk stratification

In addition to the tumour–node–metastasis (TNM) stage, other independent prognostic markers are important. Plasma

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Summary of imaging recommendations for nasopharyngeal carcinoma

Staging	Modality	Comment
Primary & neck	Multiparametric MRI with gadolinium enhancement Ultrasound ± FNA to investigate suspicious lymph nodes	MRI provides accurate tumour staging, assessment of perineural spread & evaluation of nodal involvement Contrast-enhanced CT if contraindication or intolerance of MRI (but is inferior) Nasopharynx is source of physiological FDG uptake on ^{18}F-FDG PET-CT which can be asymmetric – local staging preferably by MRI & endoscopy
Distant staging	Whole-body CT; Or ^{18}F-FDG PET-CT[806]	Given potential for disseminated disease at presentation & greater likelihood of hepatic & bone involvement, whole-body imaging is recommended ^{18}F-FDG PET-CT is useful as baseline pre-CRT for subsequent response assessment with ^{18}F-FDG PET-CT. NICE currently recommends ^{18}F-FDG PET-CT for staging of tumour T_4 disease only
Response assessment (3–6 months post treatment)	^{18}F-FDG PET-CT ± MRI	^{18}F-FDG PET-CT is most accurate modality for response assessment[806,807]
Surveillance imaging		Not routinely recommended

MRI = magnetic resonance imaging; FNA = fine needle aspiration; CT = computed tomography; FDG = fluoro-deoxy-glucose; PET = positron emission tomography; CRT = chemoradiotherapy; NICE = National Institute for Health and Care Excellence

Table 2. Tumour (T) and nodal (N) staging for nasopharyngeal carcinoma*

Stage	Description
T stage	
T_1	Tumour confined to nasopharynx, or extends to oropharynx &/or nasal cavity without parapharyngeal involvement
T_2	Tumour with extension to parapharyngeal space, &/or infiltration of medial pterygoid, lateral pterygoid, &/or prevertebral muscles
T_3	Tumour invades bony structures of skull base, cervical vertebrae, pterygoid structures &/or paranasal sinuses
T_4	Tumour with intracranial extension, &/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, &/or infiltration beyond lateral surface of lateral pterygoid muscle
N stage	
N_0	No regional lymph node metastases
N_1	Unilateral metastases, in cervical lymph node(s) &/or unilateral or bilateral metastases in retropharyngeal lymph nodes, sized ≤6 cm in greatest dimension, above caudal border of cricoid cartilage
N_2	Bilateral metastases in cervical lymph node(s), sized ≤6 cm in greatest dimension, above caudal border of cricoid cartilage
N_3	Metastases in cervical lymph node(s), sized >6 cm in dimension, &/or extension below caudal border of cricoid cartilage

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[809]

Table 3. Group staging for nasopharyngeal carcinoma*

Group stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_1	N_1	M_0
	T_2	N_{0-1}	M_0
III	T_{1-2}	N_2	M_0
	T_3	N_{0-2}	M_0
IVA	T_4	N_{0-2}	M_0
	Any T	N_3	M_0
IVB	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[809]

Epstein–Barr virus DNA is associated with non-keratinising nasopharyngeal carcinoma, with higher pre-treatment levels having an inferior prognosis.[802]

Pathology

Based upon the World Health Organization criteria, nasopharyngeal carcinoma is categorised into three subtypes: keratinising; non-keratinising, which includes differentiated and undifferentiated; and a third group of basaloid squamous cell carcinoma. Non-keratinising cancer comprises more than 95 per cent of endemic cases, and there is a strong association with Epstein–Barr virus infection in endemic regions.[801,802] Keratinising cancer is more common in non-endemic regions.[801] Another potential viral aetiological factor is human papillomavirus (HPV).[801,810] In non-endemic areas, HPV appears more frequently in keratinising cancer cases, although is rarely described with an uncertain impact upon prognosis.[811] Epstein–Barr virus and HPV infections are nearly always mutually exclusive.[801]

Treatment of non-metastatic nasopharyngeal carcinoma

Table 4 shows a summary of treatment approaches for non-metastatic (M_0) nasopharyngeal carcinoma (NPC).

Summary recommendations

- Intensity-modulated RT is standard of care (evidence-based recommendation (R))
- Chemoradiotherapy is recommended for stage II (with the exception of T_2N_0), stage III and stage IVa disease (R)
- Induction chemotherapy should be considered for all patients with high-risk locoregionally advanced NPC (R)
- In patients who cannot receive induction chemotherapy, adjuvant chemotherapy should be considered (R)

Radiotherapy

Intensity-modulated RT is the current standard treatment.[807] Randomised, controlled trials have shown that intensity-

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Summary of treatment approaches for non-metastatic (M_0) nasopharyngeal carcinoma

Parameter	TNM stage	Preferred treatment options	Comments
Early localised	$T_{1-2}N_0M_0$	RT	Concurrent chemotherapy may be offered if bulky primary or high EBV DNA copy number
	$T_{1-2}N_1M_0$	CRT (or RT)	Concurrent chemotherapy if risk factors for distant metastases, e.g. lymph node sized >4 cm, high plasma DNA >2000–4000 copies/ml. Usually appropriate for T_2N_1 disease
Locoregionally advanced	T_3N_0	CRT	
	T_3N_1* T_4N_0* T_4N_{1+} Any N_{2-3}	CRT Induction chemotherapy + CRT (GP, TPF & PF are induction chemotherapy options) CRT + adjuvant chemotherapy (PF & capecitabine are options)	Induction chemotherapy not normally considered if patients aged over 70 years. Benefit of induction chemotherapy less certain in non-endemic population

*See main text for comment on induction chemotherapy plus chemoradiotherapy (CRT) and chemoradiotherapy alone for disease stages T_3N_1 and T_4N_0. TNM = tumour–node–metastasis; RT = radiotherapy; EBV = Epstein–Barr virus; GP = gemcitabine, cisplatin; TPF = docetaxel, cisplatin, 5-fluorouracil; PF = cisplatin, 5-fluorouracil

modulated RT improves locoregional control and overall survival, and reduces late toxicity including xerostomia, temporal lobe damage and trismus.[105,812] Local control following intensity-modulated RT for T_3 disease or lower is more than 90 per cent, but is lower for T_4 disease, with reported local control rates of 74–80 per cent.[812] Conventional dose fractionation remains standard, with no established benefit for altered fractionation schedules including modest acceleration,[801,807] although a moderately hypofractionated dose of 68.2 Gy in 30 fractions (2.27 Gy per fraction) can be used for small tumours ($T_{1-2}N_{0-1}$).[807,813] A commonly agreed standard total dose is in the order of 70 Gy in 33–35 fractions or equivalent (2–2.12 Gy per fraction), with 54–60 Gy for at-risk areas.[807,812] Use of a dose of 65 Gy in 30 fractions has also been reported within the UK.[814] There is a clear dose–response relationship; under-dosing of the tumour target (65 Gy or lower) is associated with inferior local control and survival.[815] Significant anatomical changes are common during treatment because of shrinkage of the primary tumour and lymph node disease, along with changes in body contour due to weight loss.[812] Correction of set-up errors and a low threshold for re-planning associated with volume changes during RT are key aspects of treatment delivery.

Primary tumour target volume delineation is a complex process; recent international guidelines are available.[805] Magnetic resonance imaging co-registration is recommended.[807]

Lymph node involvement typically occurs in an orderly fashion, with retropharyngeal and level II being the most commonly involved levels; skip metastases are unusual.[816] Bilateral neck treatment is standard, and traditionally has involved the inclusion of the entire lymph node draining basin including bilateral retropharyngeal lymph nodes down to the lower neck.[816] There is interest in a more selective approach to neck treatment with the possibility of omission of the lower neck volume in the uninvolved side,[807] based on a meta-analysis of nine studies.[817] Elective level Ib irradiation can be omitted in the absence of involvement of the anterior half of the nasal cavity, or if there are level II lymph nodes that are more than 2 cm in size or with evidence of extracapsular spread or bilateral involvement.[805,807,818] In approximately 25 per cent of NPC patients, involved level II lymph nodes are located above the caudal edge of the lateral process of C1 (which is defined as the superior boundary of level II).[819] Lymph node mapping studies[805] have highlighted the need to extend the cranial border to the skull base in order to extend coverage of retropharyngeal lymph nodes, to include the medial retropharyngeal lymph nodes to the caudal edge of C2, and to cover the full posterior triangle including transverse vessels of the neck.

Following induction chemotherapy, international guidelines recommend contouring to include the pre-chemotherapy disease extent,[805,807] whilst respecting tolerances of organs at risk. Recent studies suggest the potential for an intermediate dose to 'resolved' pre-induction induction chemotherapy areas of disease, whilst delivering the full dose to post-chemotherapy residuum.[820,821] These data are useful for some cases of advanced disease following a response to induction chemotherapy, in which it would not be possible to keep organs at risk such as optic pathways within tolerance if treating the pre-chemotherapy extent to full prescription doses.

Proton therapy offers steep dose fall offs beyond target volumes. Dosimetric studies suggest that proton therapy for NPC would deliver lower doses to critical organs at risk, whilst early clinical studies show high rates of locoregional control.[822] It is plausible that proton therapy can result in the reduction of acute toxicities compared to conventional intensity-modulated RT. Proton therapy can be considered for patients aged less than 25 years via the NHS England Proton Beam National Clinical Reference panel.

Role of concurrent chemoradiotherapy

Locally advanced disease (stages III–IVa/b)

Multiple studies in patients with locally advanced (stage III and IVA) NPC have established the use of concurrent chemotherapy as a standard of care,[801] supported by an updated Meta-Analysis of Chemo-therapy in Nasopharynx Carcinoma ('MAC-NPC').[823] The Meta-Analysis does not show that the benefit of concurrent chemotherapy on overall survival is lost with age, although the hazard ratio for progression-free survival is non-significant for patients aged over 60 years.[823] Concurrent cisplatin, either 100 mg/m^2[802] three weekly or 40 mg/m^2[802] weekly, are widely used and a recent randomised phase 3 trial confirms that both regimens harbour comparable efficacy, albeit haematological toxicities and late-onset auditory loss were increased with the weekly regimen.[824] Achieving a cumulative dose of 200 mg/m^2[802] of concurrent cisplatin appears optimal for definitive chemoradiotherapy.[802] For patients with a contra-indication to cisplatin, carboplatin area under the curve

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

based dosing of 5–6 mg/ml/minute may be a suitable alternative.[807,825,826]

Stage II disease

The role of concurrent chemotherapy for stage II NPC is controversial in the intensity-modulated RT era. Stage II disease represents a heterogeneous group, encompassing T_2N_0 and $T_{1/2}N_1$ disease. Local control is high with RT alone, although a pre-intensity-modulated RT randomised trial has demonstrated a survival advantage for concurrent cisplatin with the benefit being mediated via improved distant metastasis-free survival.[827] Meta-analyses based on mainly retrospective studies in the endemic population[828,829] do not suggest a clear benefit of concurrent chemotherapy for stage II disease in the intensity-modulated RT era. Recent consensus guidelines recommend the use of concurrent chemotherapy for $T_{1-2}N_1$, reflecting the higher risk of developing distant metastatic disease in stage 2 disease with nodal involvement.[807]

Role of induction or adjuvant chemotherapy

Given that distant metastases development is a major cause of treatment failure, multiple trials have examined the intensification of systemic therapy with induction chemotherapy or adjuvant chemotherapy.

Induction chemotherapy is an appealing strategy, with high rates of compliance and the potential to eradicate occult metastases early in treatment.[830] Results of recent phase III trials have established induction chemotherapy as a standard of care for locoregionally advanced NPC, with reduced rates of distant failure and improved survival outcomes[831–833] following no demonstrated benefit in a prior study.[834] It should be noted that these trials excluded older patients, and/or patients with $T_{3-4}N_0$ and T_3N_1 NPC, in two of the trials.[831–833] Patients with T_3N_0 disease are lower risk, and the addition of induction chemotherapy would be based on individual discussions of benefits and risks.[807] For patients with T_4N_0 and T_3N_1 disease, induction chemotherapy should be offered, although chemoradiotherapy alone can be considered in selected cases, e.g. a non-bulky and/or single-involved neck node (less than 4 cm), and/or a low Epstein–Barr virus (EBV) DNA copy number titre (where available). Whether these results can be extrapolated to the non-endemic population is unclear. Chemoradiotherapy should start 21–28 days from the 1st day of the final cycle of induction chemotherapy.[807]

The early chemoradiotherapy trials for locoregionally advanced NPC have often included adjuvant chemotherapy with chemoradiotherapy. Whilst the addition of systemic therapy proved to be superior over RT alone, the issue with adjuvant chemotherapy had always been the fact that it is poorly tolerated after an intensive course of chemoradiotherapy.[801] A phase III trial failed to show a benefit of chemoradiotherapy-adjuvant chemotherapy over chemoradiotherapy alone in NPC patients who are at high risk of distant metastatic relapse ($T_{3-4}N_+$ or N_{2-3}).[835] Adjuvant chemotherapy is an approach that has rarely been used in non-teenage/young adult populations in the UK.[836,837] However, the updated network Meta-Analysis of Chemo-therapy in Nasopharynx Carcinoma, which comprised mostly endemic NPC cases, showed that concurrent chemoradiotherapy followed by adjuvant chemotherapy was ranked above chemoradiotherapy alone for the failure-free and overall survival.[838] Cisplatin and 5-fluorouracil is the standard doublet adjuvant chemotherapy regimen; however, two recent randomised, controlled phase III trials showed that adjuvant full dose or metronomic dose capecitabine is an efficacious adjuvant chemotherapy.[839,840]

Teenage and young adult population

Based on randomised trial data, the European Cooperative Study Group for Pediatric Rare Tumors ('EXPeRT') / Paediatric Rare Tumours Network – European Registry ('PARTNER') consensus group recommends treatment of NPC in children and adolescents using: doublet induction chemotherapy with cisplatin and 5-fluoro-uracil, RT doses of 54 Gy in good responders, and the consideration of adjuvant interferon therapy.[841] It is important to note that the paediatric trials overwhelmingly involved non-keratinising, undifferentiated EBV-positive patients. This wide differentiation in practice versus adult management presents a challenge for treatment selection in young adults aged over 16 years. Limited prospective and retrospective data suggest that a dose-attenuated approach is effective in EBV-related disease in the young adult population; however, larger prospective studies are needed in this patient group.[842,843]

Management of recurrent or distant metastatic disease

Table 5 shows the different approaches to the management of recurrent or metastatic disease.

Summary recommendations

- Treatment approaches are individualised for the different recurrence scenarios (good practice point (G))
- Standard of care for first-line palliative systemic therapy is cisplatin plus gemcitabine, with recent trials showing an advantage for this combination with immune checkpoint blockade (evidence-based recommendation (R))
- For patients with *de novo* metastatic disease and a demonstrated complete or partial response to first-line systemic therapy, consider consolidation RT to the primary and regional sites (G)
- For patients with locally recurrent disease, consider salvage surgery for selected superficial T_{1-3} tumours; in unresectable cases, re-irradiation with or without chemotherapy can be considered, if deemed at low risk of severe complications with re-treatment (G)
- Isolated regionally recurrent disease can be managed with neck dissection (G)
- For patients who relapse with oligometastases, consider metastasis-directed therapy with or without systemic chemotherapy (G)

Nasopharyngeal carcinoma presenting with synchronous distant metastases

A national cancer database analysis of 718 patients demonstrated superior survival outcomes for patients treated with chemotherapy and RT to the primary site versus those receiving chemotherapy alone, with the benefit maintained in models of single versus multiple organ distant metastases.[844] The overall survival benefits were seen amongst patients receiving 50 Gy or more. This is supported by a phase III trial that closed early after recruiting 126 patients because of an

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 5. Approaches to management of recurrent or metastatic disease

Disease type	Treatment options	Comments
Synchronous oligometastatic disease	Ablative therapy to oligometastases, chemotherapy & CRT to primary	Consider aggressive multimodality therapy
Synchronous (non-oligometastatic) distant metastases	Chemotherapy & CRT to primary	Survival advantage for addition of CRT to primary
Metachronous oligometastatic disease	Ablative therapy	
Widespread distant metastases	Chemotherapy	Gemcitabine + cisplatin as first-line treatment. Recent trials show benefit of combination with immune checkpoint blockade
Locally recurrent disease without distant metastases	Salvage surgery for recurrent tumour stage $T_{1/2}$ disease ± repeat re-irradiation Re-irradiation ± induction chemotherapy ± concurrent chemotherapy Chemotherapy if not suitable for salvage surgery	
Regionally recurrent disease without distant metastases	Neck dissection ± re-irradiation ± chemotherapy	

CRT = chemoradiotherapy

imbalance of deaths, with a median overall survival for the chemotherapy and RT arm of 40.2 months versus 24.5 months in the chemotherapy alone arm.[845]

Nasopharyngeal carcinoma with oligometastatic disease

Nasopharyngeal carcinoma patients with oligometastatic disease have a considerably better prognosis than those with widespread distant metastases.[846] Patients with lung-only metastasis have a more favourable outlook, whilst liver metastases are associated with inferior survival outcomes.[846] For patients presenting with synchronous oligometastatic disease, aggressive treatment with ablative treatment (e.g. stereotactic RT or metastasectomy) of oligometastases, systemic therapy and consolidation RT to the primary tumour is advocated.[801,846] Longer-term survival is possible for selected patients with metachronous oligometastases following ablative therapy.[847,848]

Palliative systemic therapy for distant metastatic disease

The seminal phase III trial by Zhang *et al.* established cisplatin with gemcitabine as the standard of care.[832] Two other randomised, controlled phase III trials investigated the role of combining the anti-programmed cell death-1 (anti-PD1) antibody; recent results confirmed a further improvement in progression-free survival when compared to cisplatin plus gemcitabine (the 'JUPITER-02' trial, investigating the efficacy and safety of toripalimab injection combined with chemotherapy for nasopharyngeal cancer, reported median progression-free survival of 11.7 months *vs* 8.0 months;[849] the 'CAPTAIN-1st' trial, a phase III study of camrelizumab in combination with chemotherapy in recurrent or metastatic nasopharyngeal carcinoma, reported median progression-free survival of 9.7 months *vs* 6.9 months[850]). Another recent clinical trial from China[851] also reported prolonged progression-free survival with maintenance capecitabine after cisplatin plus gemcitabine (median progression-free survival of 35.2 months *vs* 9.1 months), albeit the results were immature for overall survival. Single-agent chemotherapy with taxanes or capecitabine are appropriate second-line therapies, with response rates of 30–40 per cent.[801]

Local recurrence

Long-term disease control is achievable, and so aggressive treatment is often appropriate, especially for limited local recurrences, although the risk of complications is high. Options include surgery or re-irradiation with or without chemotherapy. Prior treatment including doses to organs at risk, latency from treatment, late toxicity from prior treatment, age, co-morbidity, performance status and extent of recurrence are all key factors.

Open or endoscopic nasopharyngectomy should be considered if it is considered likely that clear margins can be achieved;[852] one series reported five-year post-recurrence survival of 56 per cent following surgery for early stage recurrence.[853] The availability of surgical expertise is critical, and re-irradiation is an alternative.[852] Complications of open surgical approaches are high (over 40 per cent, with risks of trismus, fistula and facial numbness), and endoscopic approaches have been developed.[854,855]

Recent international guidelines for re-irradiation have been published.[852] Re-irradiation is an effective treatment, with a five-year failure-free survival rate of 72 per cent and an overall survival rate of 41 per cent reported in a meta-analysis, although risks of late complications are high, with one-third experiencing fatal toxicity.[856] Re-irradiation is not appropriate for disease that recurs less than one year from treatment indicating radio-resistance. Re-irradiation after surgery is advisable for positive margins and can be considered for close margins.[852] Nonetheless, it must be cautioned that re-irradiation following surgery, especially for recurrent tumours, is linked to substantially increased rates of severe morbidities.[857] Re-irradiation should also be considered for unresectable local recurrence. Based on an extrapolation from the *de novo* trials, consideration can be given to integrating induction chemotherapy with or without concurrent chemotherapy with re-irradiation. The total dose for re-irradiation is recommended to be in the order of 60–66 Gy EQD_2 (equivalent dose

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

in 2 Gy fractions);[852] hyper-fractionation may improve the therapeutic window (ongoing trial NCT02456506).[852] Elective lymph node treatment is not recommended in this scenario.[852] Using a survival risk prediction model, Li and colleagues were able to stratify patients into low- and high-risk groups; the latter was at risk of re-irradiation mortality.[858] For this group, chemotherapy with or without anti-PD1 antibody could be appropriate.[802]

Isolated regional recurrence

Isolated regional lymph node recurrences can be managed with a neck dissection. Selective and comprehensive neck dissections have similar outcomes, with a three-year overall survival rate of 67 per cent; negative prognostic markers include extracapsular spread, recurrent N stage and positive margins.[859]

Follow up

The recommendations for follow up are set out in Chapter 5.

Recommendations

- Response assessment should take place at least 12 weeks post treatment[802] (evidence-based recommendation (R)), including clinical examination, nasoendoscopy and imaging (PET-CT/MRI), with or without Epstein–Barr virus (EBV) DNA titres (if detectable pre-treatment) (good practice point (G))
- Ongoing follow up should include clinical examination with nasendoscopy (G)
- Surveillance imaging is not routinely recommended (G)
- Monitoring for late complications is a key component of follow up (G)

In endemic areas, persistent detection or re-emergence of plasma EBV DNA post treatment has been shown to correspond to an increased likelihood of relapse and a precursor of clinical disease; monitoring of this biomarker may thus have a role in surveillance.[801,860]

Monitoring for late complications of treatment is a key component of follow up (see Chapter 16). Late effects include sensorineural and conductive hearing loss, visual impairment, endocrine (pituitary and thyroid) dysfunction, xerostomia, dysphagia, soft tissue fibrosis, osteoradionecrosis, and neurological complications (e.g. temporal lobe injury, cranial neuropathy, brachial plexus neuropathy).[801,802]

Studies due to report

There is an ongoing phase 3 trial (NCT026330202) comparing concurrent chemoradiotherapy versus RT alone for stage II and $T_3N_0M_0$ disease, as well as an ongoing NRGHN001 trial (NCT02135042) exploring the use of post-RT plasma Epstein–Barr virus DNA to identify subgroups who may benefit from adjuvant chemotherapy.

Research questions

- Establishing the place for proton therapy.
- Incorporating immunotherapy into current treatment paradigms.
- Selecting patients for induction chemotherapy, and determining the optimal induction chemotherapy regimen.

Chapter 20: Hypopharyngeal cancer

Table of Contents

Introduction

Cancers originating in the hypopharynx are relatively rare, accounting for approximately 3 per cent of head and neck cancers in the UK.[861] They are more prevalent in men, and the prognosis is generally worse than cancer in other head and neck sites, with an overall five-year survival rate of around 25 per cent in the UK,[861] increasing to 40 per cent for patients suitable for curative treatment.[862] This is partly due to advanced stage disease at presentation. However, early-stage tumours (T_{1-2}) treated with curative intent have an overall five-year survival of around 60 per cent or more.[863]

The hypopharynx is subdivided into the pyriform sinuses, the posterior pharyngeal wall and the post-cricoid areas, with the majority of cases being located in the pyriform sinuses (60–85 per cent).[862] Lymphatic drainage from the hypopharynx is rich and drains to the jugular as well as retropharyngeal lymph nodes. Over 50 per cent of patients present with metastatic lymphadenopathy.

Many patients have significant co-morbidities. Baseline performance status is an independent prognostic factor for overall survival, and this should be borne in mind when determining management options.

Diagnosis

Recommendations

- Perform endoscopic examination under general anaesthesia for biopsy and to determine the extent of primary tumour (if suitable for anaesthesia) (evidence-based recommendation (R))
- Narrow-band imaging increases the diagnostic potential of endoscopy in the early detection of hypopharyngeal malignant lesions (good practice point (G))
- Transnasal oesophagoscopy can facilitate early evaluation and detection, and allow for biopsies in the clinic (G)

Presenting symptoms and physical examination

Symptoms from hypopharyngeal cancer (HPC) are determined by the size and location of the tumour. These include sore

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

throat, odynophagia, dysphagia, referred otalgia, blood-stained phlegm, airway obstruction and aspiration. However, the most common presentation of HPC is a neck mass, and the incidence of regional metastasis at presentation is 70 per cent, especially in cancers that originate in the pyriform sinuses. This incidence is higher than in any other head and neck location.[864]

Assessment of a patient with HPC should comprise a full head and neck examination, including oral cavity examination, neck palpation and fibre-optic examination of the upper aerodigestive track. Suggestive signs include the presence of a mucosal ulceration, erythematous lesions, vocal fold immobility or pooling of secretions.

Narrow-band imaging increases the diagnostic benefit of endoscopy in the detection of early malignant lesions within the hypopharynx.[865] Laryngopharyngeal evaluation with transnasal oesophagoscopy, including hypopharyngeal biopsies under topical anaesthesia, can be used to help with early evaluation and biopsy, therefore shortening the diagnostic pathway.[866]

Endoscopy and tissue sampling

Examination under general anaesthesia enables tissue biopsy, assessment of the extent of the tumour and determination of the presence of synchronous tumours, which can be found in 10–15 per cent of the patients.[867] Again, narrow-band imaging may help. Photographic documentation of the clinical lesion as well as documentation of transoral access should be included, using the appropriate grading system.

Imaging

Table 1 shows recommendations for pre-treatment imaging in cancers originating in the hypopharynx.

Recommendations

- Positron emission tomography (PET-) computed tomography (CT) is advised in recurrent HPC cases, in advanced disease cases and to determine the inferior extent of the tumour (good practice point (G))

Imaging should be conducted prior to a biopsy wherever possible, to avoid a post-biopsy artefact caused by oedema and subsequent over-staging.

Assessment of the primary tumour extent and size should be performed with magnetic resonance imaging (MRI) pre- and post-gadolinium enhancement and/or with multi-slice intravenous contrast-enhanced CT. Magnetic resonance imaging is recommended for the evaluation of soft-tissue extension, and in specific clinical scenarios such as possible early cartilage invasion. A combination of axial, coronal and sagittal T1-weighted and T2-weighted sequences may be required. A slice thickness of 3 mm is recommended for the assessment of early laryngeal cartilage invasion. A CT scan can be performed at the same time as the CT scan of the chest, to enable full staging of the tumour.

The PET scan is useful to confirm the extent of the primary site, specifically the inferior extent in post-cricoid cancers, in order to detect distant metastatic spread in cases of occult disease and in recurrent tumours.[868] Current National Institute for Health and Care Excellence (NICE) guidelines indicate the use of PET-CT for T_4 cancers of the hypopharynx and nodal stage N_3 cancers, which are most likely to have distant metastases.[869]

As for other upper aerodigestive tract cancers, the NICE guidelines do not mandate systemic imaging for $T_{1-2}N_0$ cancers. However, it is standard practice to stage the thorax via a chest CT (if PET-CT is not indicated) in all patients, as there is a relatively high incidence of second primaries or metastasis at presentation.

Table 1. Recommendations for pre-treatment imaging in cancers originating in the hypopharynx

Staging	Modality
Primary & neck	MRI or CT (MRI preferred)
Thorax/systemic	CT of thorax PET-CT for T4 primary or N3 disease

MRI = magnetic resonance imaging; CT = computed tomography; PET = positron emission tomography; T = tumour stage; N = nodal stage

Staging

The Union for International Cancer Control tumour–node-metastasis (TNM) classification (eighth edition) for HPC is described in Tables 2–5.[763]

Pathology

The vast majority (95 per cent) of HPCs are squamous cell carcinomas (SCCs), with two-thirds of these being keratinising SCC. Other tumour types include lymphoma, sarcoma and adenocarcinoma; these are typically poorly differentiated and aggressive.[867]

Only a small proportion of HPC cases have been associated with human papillomavirus infection,[870] and there is no proven impact on HPC treatment or prognosis as yet.

Pre- and post-treatment speech and swallow rehabilitation

All patients presenting with head and neck cancer should undergo speech and swallowing and dietetic pre-treatment assessment, as discussed in other chapters.

Table 2. Staging of primary tumours in hypopharyngeal cancer

Tumour (T) stage	Description
T_X	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T_1	Tumour limited to 1 hypopharyngeal subsite or sized ≤2 cm in greatest dimension
T_2	Tumour invades >1 subsite of hypopharynx or an adjacent site, or measures >2 cm but not >4 cm in greatest dimension, without fixation of hemi-larynx
T_3	Tumour > 4 cm in greatest dimension, or with fixation of hemi-larynx or extension to oesophageal mucosa
T_{4a}	Moderately advanced local disease Tumour invades thyroid or cricoid cartilage, hyoid bone, thyroid gland, oesophageal muscle, or central compartment soft tissue†
T_{4b}	Very advanced local disease Tumour invades prevertebral fascia, encases carotid artery or involves mediastinal structures

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] †Central compartment soft tissue includes pre-laryngeal strap muscles and subcutaneous fat.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Clinical staging of regional lymph nodes in hypopharyngeal cancer*

Nodal (N) stage	Description
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral node, sized >3 cm but <6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastases in multiple ipsilateral node(s), sized <6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in lymph node, sized > 6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s) & clinically overt extra-nodal extension

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763]

Management of hypopharyngeal cancer

Table 6 shows the treatment options for hypopharyngeal cancer.

Recommendations

- Treat early-stage cancers with single-modality treatment and offer patients all viable options (evidence-based recommendation (R))

Table 4. Pathological staging of regional lymph nodes in hypopharyngeal cancer*

Nodal (N) stage	Description
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral node, sized >3 cm but <6 cm in greatest dimension, & with no extra-nodal extension Or metastasis in a single ipsilateral node, sized ≤3 cm in greatest dimension, & with extra-nodal extension†
N_{2b}	Metastases in multiple ipsilateral node(s), sized <6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastases in bilateral or contralateral lymph node(s), none > 6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized > 6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension† Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, any with extra-nodal extension† Or metastasis in a single contralateral node, of any size, & with extra-nodal extension†

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763] †Indicates upstaging from clinical stage when extra-nodal extension is confirmed.

Table 5. Group staging of hypopharyngeal cancer*

Group stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	$T_{1–3}$	N_1	M_0
IVA	$T_{1–3}$	N_2	M_0
	T_{4a}	$N_{0–2}$	M_0
IVB	Any T	N_3	M_0
	T_{4b}	Any N	M_0
IVC	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763]

- Offer primary concomitant chemoradiotherapy/radiotherapy (RT) or surgery plus (chemo)radiotherapy to patients with locally advanced disease as options for treatment with curative intent (R)
- Consider post-operative RT in patients with adverse pathological risk factors (good practice point (G))
- The addition of chemotherapy (in suitable patients) combined with post-operative RT is recommended in patients with positive margins or extracapsular extension (R)

Early-stage hypopharyngeal cancer $T_{1–2}N_0$

Early-stage HPC should be treated as much as possible with a single-modality treatment (surgery or RT).[871,872] Most patients are treated with RT. There are insufficient data to ascertain the functional and oncological results from primary surgery, and to determine how often this is possible as a single-modality treatment option. However, reported outcomes suggest equipoise with RT in selected patients.[863]

Treatment with RT should consist of intensity-modulated RT or volumetric-modulated arc therapy.[871] The standard primary radical RT fractionation used for head and neck cancer patients in the UK currently varies mainly between 70 Gy in 35 fractions over seven weeks and 65 Gy in 30 fractions over six weeks.[873] Radiotherapy should include neck levels IIa, III and IV. Prophylactic irradiation of retropharyngeal nodes also provides effective regional control.[874]

Surgical management includes open surgical procedures and transoral approaches (transoral laser surgery and transoral robotic surgery). This should be combined with selective neck dissection, bilateral for midline tumours. Transoral approaches are preferred, having less morbidity compared to open surgery, and with a reported laryngeal preservation rate of 70 per cent.[875,876] Complete excision with margins of 5 mm or greater should be the mainstay of treatment. Positive margins should be considered for re-resection or post-operative chemoradiotherapy. Other adverse pathological features, including on neck dissection, may also mandate adjuvant therapy.[109]

Locally advanced cancer (stage III–IV hypopharyngeal cancer)

The options for curative treatment are laryngeal preservation with radical RT with concurrent chemotherapy, or primary surgery with pharyngolaryngectomy.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 6. Treatment of hypopharyngeal cancer

Disease (TNM) stage	First-line treatment	Alternative options	Lymph nodes
$T_{1–2}N_0M_0$	RT or surgery (TLM, transoral surgery, or open pharyngeal surgery + neck dissection)		Treat levels IIa, III & IV, retropharyngeal nodes*, uni/bilaterally
$T_{1–2}N_{1–3}$ or $T_3N_{0–3}$	Concomitant CRT or RT	RT alone Pharyngolaryngectomy ± (chemo)-RT	Treat levels IIa, III & IV, retropharyngeal nodes*, bilaterally
$T_{4a}N_{0–3}$	Pharyngolaryngectomy + (chemo)-RT	Concomitant CRT Induction chemotherapy ± surgery/RT	Treat levels IIa, III & IV, retropharyngeal nodes*, bilaterally
$T_{4b}N_{0–3}$		Concomitant CRT Induction chemotherapy ± RT	

*Applies only to radiotherapy. TNM = tumour–node–metastasis; RT = radiotherapy; TLM = transoral laser microsurgery; CRT = chemoradiotherapy

As for other upper aerodigestive tract cancers, concomitant chemoradiotherapy has greater locoregional control and improved overall survival in comparison with RT alone, but its effect decreases with age over 70 years; RT alone is generally used for patients older than 70 years. Induction chemotherapy is not recommended.

Concomitant chemoradiotherapy has the obvious advantage of organ preservation, with surgery reserved for locally recurrent disease, if appropriate (albeit with increased rates of post-operative morbidity). However, functional status before treatment is a key determinant of functional status after chemoradiotherapy. Pre-treatment extensive invasion of surrounding structures (T_{4a} tumours) and poor laryngeal function are associated with poor functional outcomes. According to Chen *et al.*, in patients with T_{4a} disease, hyoid bone invasion significantly increases the severe complication rate in organ preservation treatment, with overall pharyngeal dysfunction, laryngeal dysfunction and aspiration rates of 36 per cent, 27 per cent and 25 per cent, respectively.[877]

Hence, it is generally recommended that patients with T_{4a} tumours be treated with pharyngolaryngectomy.[877] Reconstruction after pharyngolaryngectomy is discussed in Chapter 7.

In select smaller stage III tumours, partial laryngectomy with partial pharyngectomy might be considered.[878]

Preservation of part or all of the thyroid gland should be the aim in patients undergoing surgery for cancers originating in the hypopharynx, as thyroid invasion is uncommon.[879]

Standard indications for considering post-operative RT apply after surgery, as for other SCCs of the upper aerodigestive tract (see Chapter 4). These include pathologically $T_{3–4}$ tumours, positive margins (≤1 mm), close margins (1–5 mm), perineural or lymphovascular spread, more than one involved lymph node, or extracapsular extension. The radiotherapy dose should be up to 60–66 Gy in 30–33 daily fractions. Concomitant chemoradiotherapy with platinum-based chemotherapy is indicated in the presence of extracapsular extension or positive margins. Post-operative RT should be started within six to seven weeks after surgery (Table 6).[871]

Management of the neck

See also Chapter 26.

Recommendations

- The neck should be treated bilaterally for tumours involving the midline, post-cricoid area, medial wall of the pyriform sinus or posterior pharyngeal wall (evidence-based recommendation (R))
- Clinically node-negative (N_0) neck – levels II to IV should be treated electively (R)
- Clinically node-positive (N_+) neck – levels II(a/b) to V should be treated (R)

For patients with no evidence of cervical lymph node metastases (clinically N_0), elective treatment by selective neck dissection or irradiation of cervical lymph node levels II–IV is recommended.[880] Treatment should be bilateral for tumours involving the midline, post-cricoid area, the medial wall of the pyriform sinus, the posterior pharyngeal wall, the posterior annular region or tumours across the midline.[236,881]

There is no clear evidence regarding the extent of neck dissection for patients undergoing primary surgery with N_+ disease. In addition to levels IIA–IV, neck dissection of levels IIB and V would be recommended, accepting the increased risk of accessory nerve dysfunction. Level I can be spared unless involved radiologically.

Follow up

Locally advanced head and neck cancer carries a high risk of local recurrence (15–40 per cent depending on staging and location) and distant metastasis. Follow up is described in Chapter 5. In patients who have had treatment for HPC, surveillance should include flexible laryngoscopy (if pharyngolaryngectomy has not been performed). Persistent or recurrent pain should be considered as a serious warning sign of recurrent HPC, even if there is no endoscopic evidence of persistent and/or recurrent disease.[868,882] Assessment under general anaesthesia and biopsies are indicated in cases of suspected recurrence after performing a PET-CT. Of patients treated with RT to the larynx, 6–53 per cent will develop hypothyroidism.[883] Therefore, thyroid-stimulating hormone levels should be monitored every 6–12 months. Total laryngectomy alone is also associated with hypothyroidism in 13–48 per cent of cases.[883]

Post-cricoid hypopharyngeal stenosis can occur after organ-preservation strategies for HPC. Its pathogenesis is not well established, although it could be the consequence of chemoradiation-induced mucositis which results in ulceration of the mucosal surface of the post-cricoid region, with subsequent circumferential fibrosis formation which leads to post-cricoid stenosis.[884] Dilatation for this complication or for stenosis following pharyngolaryngectomy may be required in some patients.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Recurrent tumours

The management of recurrent head and neck cancer in general is discussed in Chapter 5. Locoregional recurrence cancers should be restaged with endoscopy under general anaesthesia and MRI (of the neck); for distant metastases and second primary disease, CT of the thorax or (preferably) PET-CT should be conducted.[885,886] The management of isolated recurrence in cervical lymph nodes is discussed in Chapter 26.

With regard to HPC, a small proportion of patients treated initially with chemoradiotherapy or RT may be suitable for salvage surgery. For such individuals, the outcomes are often poor. For example, one series reported a 40 per cent rate of major post-operative complications, with a median overall survival of 17 months and a 5-year survival rate of 30 per cent.[887]

Other options, discussed in Chapter 4, include palliative chemotherapy, immunotherapy, (rarely) re-irradiation and best supportive care.

The complications and toxicities from further surgery, RT and systemic treatments can significantly impact the quality of life of patients with a very low likelihood of cure, even for those undergoing treatment with curative intent. Hence, multidisciplinary team discussion about treatment options, as well as detailed discussion with patients regarding the potential benefits and the risks of treatments, are crucial.

Studies due to report

There are no National Cancer Research Institute phase III/III clinical trials specific to hypopharyngeal cancer. Global trials can be found in: https://clinicaltrials.gov.

Important research questions to be answered

- Refining the choice between primary surgery and organ-preservation RT/chemoradiotherapy in advanced HPC.
- Defining the place of transoral surgery in early HPC.
- Predicting the outcome after salvage pharyngolaryngectomy: identifying patients in whom salvage surgery will not improve survival and who might benefit from immunotherapy despite having potentially resectable disease.

Chapter 21: Laryngeal cancer

Table of Contents

Introduction

This chapter concentrates on squamous cell carcinoma (SCC), which accounts for over 90 per cent of laryngeal cancer cases. Laryngeal SCC is primarily caused by cigarette smoking, although approximately 20 per cent of patients are non-smokers.[888]

For most patients with laryngeal cancer, primary surgery or primary radiotherapy (RT) (with or without chemotherapy) are appropriate treatment options. There is a lack of clinical trial data comparing different treatment modalities for laryngeal SCC, and there have been no significant published clinical trials since the last version of these guidelines. In situations where surgery and RT-based treatments are thought to be equally effective, the decision of which treatment to proceed with is based on the values and perspectives of the individual patient.

Presentation and diagnosis

Laryngeal SCC usually presents with a hoarse voice. Supraglottic laryngeal SCC may present with pain. Symptoms suggestive of more advanced laryngeal SCC include: odynophagia, dysphagia, referred otalgia, palpable lymphadenopathy and stridor.

Out-patient clinical examination must include flexible laryngoscopy. Photographic documentation is good practice for diagnosis, referrals, follow-up surveillance and training.[71] Vocal fold mobility must be documented.

Patients with clinically concerning laryngeal lesions should undergo laryngoscopy under general anaesthesia, which is more frequently performed with an array of angled endoscopes than with the microscope. Narrow-band imaging and similar technologies may improve diagnosis.[889] In addition to an appropriate biopsy, photographic documentation of the lesion should be made in the operating theatre. There should be sufficient anatomical detail, particularly details on transoral access, to allow the treating multidisciplinary team (MDT) to establish appropriate treatment options, especially the option of transoral microsurgery. In patients not fit for general anaesthetic assessment, channelled laryngoscopy may permit biopsy under local anaesthesia.

Recommendations

- Photographic documentation should be available, and be used as a record of out-patient and operative laryngoscopy findings (good practice point (G))
- Vocal fold mobility must be documented at out-patient laryngoscopy (evidence-based recommendation (R))

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Any restriction in transoral access should be documented when performing diagnostic laryngoscopy (R)

Imaging

Table 1 shows recommendations for pre-treatment imaging (note that points 1–3 below correspond with the same numbers in Table 1).[888–889]

(1) Imaging is not necessary for superficial tumour stage T_1 cancers not involving the anterior commissure, unless there is concern regarding lateral extension and paraglottic involvement.

(2) Whilst the probability of distant metastasis is very low so as not to require systemic imaging, there is some uncertainty about the use of thorax computed tomography (CT) for screening for synchronous primary bronchial malignancy, given the similar risk factors and relatively high instance of pulmonary nodules and lung cancer in patients with laryngeal carcinoma.[50] Despite National Institute for Health and Care Excellence guidance to the contrary,[890] mainstream practice follows a pragmatic approach of routinely performing CT of the thorax in patients with laryngeal carcinoma, irrespective of primary stage, with a recent study showing a 9 per cent rate of second primary cancers or distant metastases in patients with $T_{1/2}$ laryngeal SCC who are smokers.[891]

(3) Positron emission tomography (PET)-CT is preferred for nodal stage N_3 disease.[890]

Computed tomography imaging benefits from a short scanning time, wide availability and excellent anatomical resolution. The superior contrast resolution of magnetic resonance imaging (MRI) enables better evaluation of the thyroid cartilage.[892] Magnetic resonance imaging is also superior for assessing tongue base and pre-epiglottic fat invasion.[893]

After RT with or without chemotherapy for advanced disease, post-treatment baseline imaging is recommended, with PET-CT following RT or chemoradiotherapy for stage III/IV disease.

Staging

Laryngeal cancer staging relies heavily on clinical examination findings, including the site of origin, involvement of compartments and determination of vocal fold mobility to assess the tumour. Radiological or pathological staging of early laryngeal cancers often requires clinical information for accurate staging.

The eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control tumour–node–metastasis (TNM) staging[894] made no changes to primary site staging for laryngeal carcinoma (Tables 2–4).

Pathology

Biopsy samples of the larynx are often fragmented and poorly orientated. The use of devices producing thermal artefacts to take purely diagnostic samples is not recommended given the unacceptable level of tissue distortion often associated with small samples. Biopsy material should be entirely processed and examined at multiple levels. Minimum criteria should include confirmation of the type of carcinoma, grade, if SCC, and presence and grade of epithelial dysplasia.

Squamous cell carcinoma is the most common cancer of the larynx (more than 90 per cent of all cases).

A number of morphological variants of SCC have been noted to arise within the larynx: verrucous SCC, basaloid SCC, papillary SCC, spindle cell SCC, adenosquamous carcinoma and lymphoepithelial carcinoma.

These variants are associated with varying difficulties in pathological diagnosis, with reported differences in prognosis, metastatic potential and response rates to different treatment modalities. There is no good evidence for a different treatment approach for these variants and, stage for stage, treatment should be the same as for classical SCC.

Other histological types of malignant disease arising within the larynx include: neuroendocrine carcinoma, minor salivary gland carcinoma (see also Chapter 22), melanoma (see also Chapter 27), and soft tissue tumours such as liposarcoma, granular cell tumour, inflammatory myofibroblastic tumour, chondroma and chondrosarcoma. These are relatively rare. Neuroendocrine and soft tissue tumours should be co-managed with referral to specialised neuroendocrine tumour and sarcoma MDTs respectively.

Table 1. Recommendations for pre-treatment imaging

Staging	Modality
Primary & neck	MRI or CT (1)
Thorax/systemic	CT of thorax (2) PET-CT for N_3 disease (3)

Note that the numbers in parentheses correspond with the same numbers in the main text when referring to Table 1. MRI = magnetic resonance imaging; CT = computed tomography; PET = positron emission tomography; N = nodal stage

Speech and language therapy

Laryngeal cancer and its treatment can profoundly affect voice and swallowing. Hence, the involvement of speech and language therapy in patient management is pivotal. Speech and language therapy in head and neck cancer, including in relation to total laryngectomy, is discussed in detail in Chapter 10. Any consequent effects on nutrition are discussed in Chapter 9.

Recommendations

- All patients with laryngeal SCC should be assessed by a speech therapist before treatment and during rehabilitation (good practice point (G))
- The impact of treatment options on voice quality, swallowing and other areas of function should be discussed with all patients (evidence-based recommendation (R))
- All patients undergoing total laryngectomy should be considered for speech valve rehabilitation (R)

Management of laryngeal dysplasia

Laryngeal dysplasia can be associated with any abnormal mucosal appearance, most commonly leukoplakia or erythroleukoplakia, but also hyperkeratosis, mucosal reddening or simply thickening.

The World Health Organization (WHO) classification system divides laryngeal dysplasia into two categories: low-grade and high-grade dysplasia. Carcinoma in situ is included within high-grade dysplasia, and the WHO 2017 guidelines allow the use of this term if preferred.[65] The risk of malignant transformation is approximately 10 per cent for low-grade dysplasia and 30 per cent for high-grade dysplasia, with a mean time to malignancy of six years.[895] A useful flowchart describing the

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Primary tumour staging for laryngeal cancer*

Tumour (T) stage	Description
Supraglottis	
– T_1	Tumour limited to 1 subsite with normal vocal fold mobility
– T_2	Tumour invades mucosa of >1 adjacent subsite of supraglottis or glottis, or region outside supraglottis (e.g. mucosa of tongue base, vallecular, medial wall of pyriform sinus) without fixation of larynx
– T_3	Tumour limited to larynx with vocal fold fixation, &/or invades any of following: post-cricoid area, pre-epiglottic space, paraglottic space, &/or inner cortex of thyroid cartilage
– T_{4a}	Tumour invades through thyroid cartilage &/or invades tissues beyond larynx, e.g. trachea, soft tissues of neck including deep or extrinsic tongue muscles (genioglossus, hyoglossus, palatoglossus & styloglossus), strap muscles, thyroid, or oesophagus
– T_{4b}	Tumour invades prevertebral space, encases carotid artery or mediastinal structures
Glottis	
– T_1	Tumour limited to vocal fold(s) (may involve anterior or posterior commissure), with normal mobility T_{1a} – tumour limited to 1 vocal fold T_{1b} – tumour involves both vocal folds
– T_2	Tumour extends to supraglottis &/or subglottis, &/or with impaired vocal fold mobility
– T_3	Tumour limited to larynx with vocal fold fixation, &/or invades paraglottic space, &/or with invasion of inner cortex of thyroid cartilage
– T_{4a}	Tumour invades through outer cortex of thyroid cartilage &/or invades tissues beyond larynx, e.g. trachea, soft tissues of neck including deep or extrinsic tongue muscles (genioglossus, hyoglossus, palatoglossus & styloglossus), strap muscles, thyroid, or oesophagus
– T_{4b}	Tumour invades prevertebral space, encases carotid artery or mediastinal structures
Subglottis	
– T_1	Tumour limited to subglottis
– T_2	Tumour extends to vocal fold(s), with normal or impaired mobility
– T_3	Tumour limited to larynx, with vocal fold fixation
– T_{4a}	Tumour invades cricoid or thyroid cartilage, &/or invades tissues beyond larynx, e.g. trachea, soft tissues of neck including extrinsic tongue muscles (genioglossus, hyoglossus, styloglossus & palatoglossus), strap muscles, thyroid, or oesophagus
– T_{4b}	Tumour invades prevertebral space, encases carotid artery or mediastinal structures

*According to the *TNM Classification of Malignant Tumours*, eighth edition.[894]

Table 3. Nodal staging for laryngeal cancer*

Nodal (N) stage	Clinical nodal (cN) staging	Pathological nodal (pN) staging
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized <3 cm, & with extra-nodal extension Or metastasis in a single ipsilateral node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension†	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, any with extra-nodal extension Or metastasis in a single contralateral node of any size & with extra-nodal extension

*According to the *TNM Classification of Malignant Tumours*, eighth edition.[894] †The presence of skin involvement or soft tissue invasion with deep fixation or tethering to underlying muscle or adjacent structures, or clinical signs of nerve involvement, is classified as extra-nodal extension. Midline nodes are considered ipsilateral nodes.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Group staging for laryngeal cancer*

Group stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	T_{1-3}	N_1	M_0
IVA	T_{1-4a}	N_2	M_0
	T_{4a}	N_{0-1}	M_0
IVB	Any T	N_3	M_0
	T_{4b}	Any N	M_0
IVC	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours*, eighth edition.[894]

management of laryngeal dysplasia has been written by Cosway and Paleri.[896]

Recommendations

- Describe laryngeal dysplasia as low or high grade. Avoid the use of other descriptors (e.g. moderate) (evidence-based recommendation (R))
- Treatment of low-grade dysplasia – excisional biopsy, with a minimum of six months' surveillance post-excision biopsy. Patients with continued mucosal abnormalities should remain under surveillance, especially if they continue to smoke[894] (good practice point (G))
- Treatment of high-grade dysplasia (including carcinoma in situ) – definitive treatment required (R). Transoral laser microsurgery is preferred. Follow up as per T_{1a} laryngeal SCC recommendations
- Patients should be offered support in stopping smoking (R)
- Photographic documentation should be used for follow up and surveillance (G)

Narrow-band imaging may assist in follow up and surveillance. Radiotherapy can be used to treat high-grade dysplasia in patients with multiple recurrences, a high anaesthetic risk, wide-field multiple lesions, or poor endoscopic access preventing transoral laser microsurgery, and is associated with roughly equivalently high rates of local control as compared to transoral laser microsurgery.[897]

Early laryngeal cancer ($T_{1-2}N_0M_0$)

Key recommendations

- The options of transoral laser microsurgery or RT should be discussed with every patient (evidence-based recommendation (R))
- Transoral laser microsurgery for T_{1a} glottic tumours is a cost-effective treatment and recommended in National Institute for Health and Care Excellence (NICE) guidance (good practice point (G))
- Single-modality treatment should be the principal aim (R)
- Transoral surgical techniques should not be considered if complete surgical excision of the tumour is in doubt (R)

Table 5 summarises the recommendations for the primary treatment of early-stage cancers.

Early laryngeal SCC comprises T_{1a} glottic laryngeal SCC in 50–60 per cent of cases; 20 per cent of cases are T_2 glottic laryngeal SCC and 12 per cent are supraglottic laryngeal SCC.[898]

Laryngeal SCC staged $T_{1-2}N_0$ should be treated ideally with single-modality therapy using transoral surgical techniques or RT. Transoral surgery requires appropriate expertise and patient selection to achieve clear margins and minimise the requirement for post-operative RT. There are no suitable randomised, controlled trials (RCTs) assessing oncological or functional outcomes between the two treatment modalities.

Glottis

Stage T_{1a} disease

Local and overall survival are similar for both RT and transoral laser microsurgery. For example, a pooled case series showed very similar three-year local control rates for both treatments, of 89 per cent (88.9 per cent for transoral laser surgery and 89.3 per cent for RT).[899] Whilst treatment with initial transoral laser microsurgery may offer superior laryngeal preservation rates,[900] voice outcomes appear broadly similar, with the only RCT published showing a less breathy voice after RT.[366]

Transoral laser microsurgery is a cost-effective strategy to treat T_{1a} glottic laryngeal SCC.[890,901] Difficult transoral access and posterior glottic tumours around the arytenoid preclude straightforward transoral laser microsurgery resection. Radiotherapy is recommended for these tumours.

Stage $T_{1b-2}N_0$ disease

There is much less data for non-T_{1a} glottic laryngeal SCC. Large database analysis and pooled data suggest approximate equivalence in local control and overall survival, with approximate local control rates of around 75 per cent at five years for T_2 tumours. The outcomes for T_{1b} laryngeal SCC are somewhere between this and those for T_{1a} tumours, with little data for this particular subgroup of patients.[899,902–904]

The evidence for a difference in voice outcome is poor but, intuitively, given that transoral laser microsurgery must involve resection of the anterior commissure and/or into the paraglottic space, voice outcomes are expected to be worse for transoral laser microsurgery.

It should be noted that the previous subdivisions of T_{2a} and T_{2b} (reflecting impairment of vocal fold mobility) are not used in the eighth edition of the *TNM Classification of Malignant Tumours*.[894] Outcomes for T_{2b} laryngeal SCC treated with

Table 5. Summary recommendations for primary treatment of early-stage cancers

Disease subsite	Treatment recommendation	Lymph nodes
Glottic $T_{1a}N_0$	TLM or RT	No treatment
Glottic $T_{1b}N_0$	TLM or RT	No treatment
Glottic T_2N_0	TLM or RT	No treatment
Supraglottic T_1N_0	RT or transoral surgery*	Consider bilateral levels IIA, III & IV
Supraglottic T_2N_0	RT or transoral surgery*	Consider bilateral levels IIA, III & IV
Subglottic $T_{1/2}N_0$	RT or TLM	Consider bilateral levels IIA, III & IV

*Transoral laser microsurgery, transoral robotic surgery or transoral endoscopic techniques. T = tumour stage; N = nodal stage; TLM = transoral laser microsurgery; RT = radiotherapy

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

both transoral laser microsurgery or RT are worse than for T_{2a} disease.[905,906] With improved radiology, many T_2 tumours with impaired mobility may be upstaged to T_3 on the basis of paraglottic space invasion. The addition of chemotherapy to primary RT may be considered for these deeply invasive T_2 tumours with impaired vocal fold mobility.

Pathological margins after transoral laser microsurgery

Incompletely excised tumours require further treatment, either additional surgical resection or RT. Patients with involved margins have a significant rate of residual disease at second-look surgery (about 25 per cent).[907] A UK consensus group[908] recommended considering 1 mm clearance to require no further treatment following transoral laser microsurgery, and advocated second-look procedures in instances of confident per-operative microsurgical perception of clearance but with tumour at the histological margin. The use of separate marginal biopsies following the main tumour resection is another popular strategy, in which negative marginal biopsies may constitute adequate surgical clearance.[909]

Recommendations

- Clear margins can be assumed with histological clearance of 1 mm (good practice point (G))
- Further surgery (second-look or wider clearance) is necessary for assumed involved margins (G)

Supraglottis

Transoral techniques and the use of RT have significantly reduced the indications for open partial supraglottic laryngectomy. No high-quality data exist to demonstrate any differences in oncological outcomes between RT and transoral surgical techniques, nor in terms of functional outcomes. Individual patient and tumour characteristics should be considered when deciding between the two modalities. Large database analyses assessing outcomes between RT and surgery include only small numbers of patients treated surgically, very likely highly selected on their tumour characteristics.[910] Elective, bilateral neck treatment is often recommended for supraglottic disease, but with little evidence base for T_1 tumours, although these are unusual.[911] Well lateralised low-volume supraglottic tumours not involving the epiglottis or pre-epiglottic space may be considered for ipsilateral neck treatment alone.

Open partial laryngectomy for early laryngeal squamous cell carcinoma

Open partial laryngectomy for early-stage disease is an alternative treatment to RT or transoral laser microsurgery in cases of difficult transoral access. Open partial laryngectomy may be more suitable for intermediate-stage tumours or those that involve tissues posterior to the vocal process of the arytenoid,[912] as an alternative to RT with or without chemotherapy. Pooled case series data including over 5000 patients showed that open partial laryngectomy can offer local control rates of nearly 90 per cent at two years.[913] However, the functional results are worse in almost all respects, and rehabilitation is challenging. Open partial laryngectomy should only be considered for patients with good pre-treatment swallowing function and appropriate lung function, to allow successful functional rehabilitation, and where there is a good reason not to favour transoral surgery or RT.

Advanced laryngeal cancer

Summary recommendations

- Pre-treatment laryngeal function must be assessed to guide treatment options (evidence-based recommendation (R))
- Patients with T_3 and carefully selected early T_{4a} tumours with preserved pre-treatment laryngeal function should be offered primary RT with or without chemotherapy (R)
- Patients with obstructive tumours and/or impaired laryngeal function, and most T_{4a} cases, should be offered primary total laryngectomy (R)
- Open partial laryngectomy may be appropriate for carefully selected patients (good practice point (G))
- All patients treated with primary surgery should be offered adjuvant RT with or without chemotherapy, other than carefully selected patients with pathologically staged T_3N_0 disease (G)
- Patients with unresectable disease (T_{4b}) may be offered radical RT with or without chemotherapy, a palliative RT regimen, or alternative systemic anti-cancer therapies (G)

The Veterans Affairs trial,[914] and subsequent Radiation Therapy Oncology Group 'RTOG 91-11' trials,[915] showed that advanced laryngeal SCC is a radiosensitive disease, with concurrent chemoradiotherapy leading to high laryngeal preservation and locoregional control than RT alone or with induction chemotherapy followed by RT. No randomised trials have assessed surgery versus RT with or without chemotherapy. Since these trials, clinicians have had to collate experience and observational evidence in order to attempt to define recommendations that improve shared decision-making with individual patients.[916]

Consistent subsequent data have shown that disease-specific and overall survival for T_3 laryngeal SCC are similar when comparing RT or chemoradiotherapy and total laryngectomy.[916,917]

Where there is threatened or actual airway obstruction, a tracheostomy would be necessary before chemoradiotherapy, and there is no functional advantage in preserving the larynx. When there are other forms of laryngeal dysfunction (e.g. aspiration), laryngeal function is similarly already compromised. Pre-treatment chronic aspiration will likely persist after oncologically successful chemoradiotherapy.[918] Hence, patients with T_3 laryngeal SCC with airway obstruction or laryngeal dysfunction should be offered primary surgery with total laryngectomy.

Whilst there is consistent evidence of superior survival for patients with T_{4a} laryngeal SCC treated with surgery compared to chemoradiotherapy, there is limited evidence to suggest that the survival disadvantage associated with primary chemoradiotherapy is either non-existent or at least more limited when the primary disease is low volume with limited cartilage involvement. Hence, in carefully selected patients with low-volume T_{4a} tumours, and with limited cartilage invasion, together with well-preserved function, primary chemoradiotherapy should be considered as a means of laryngeal preservation, with little compromise in local control or survival.[916]

However, for other patients with T_{4a} laryngeal SCC, the standard of care is primary surgery, with consistently reported improved locoregional disease control in particular, and, to a lesser extent, improved overall survival.

Whilst the evidence offers the basis for broad guidelines as above, any guideline cannot capture the nuanced nature of

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

decision-making bearing in mind the impact of laryngectomy, which varies from patient to patient. For example, in a patient who values survival above all else, and who has a large-volume T_3 tumour with lymph node metastases, but is not suitable for chemotherapy, then total laryngectomy with neck dissection and post-operative RT, rather than RT only, may be the preferred option for them. The equipoise in survival between RT or chemoradiotherapy and total laryngectomy for T_3 laryngeal SCC in general may not be applicable to this subgroup.[919] Or, for a patient who might struggle to come to terms with laryngectomy, with a T_{4a} tumour with high-volume or multiple lymphadenopathy, who is fit for chemoradiotherapy, primary chemoradiotherapy may be preferred, as overall survival is poor whatever the initial treatment, as long as pre-treatment function is not overtly compromised.

Table 6 summarises the recommendations for the primary treatment of advanced cancers.

Chemoradiotherapy should be offered to patients who are suitable (see Chapter 4). Total laryngectomy might need to include partial or circumferential pharyngectomy and tissue transfer for reconstruction (see Chapter 7). Adequate pharyngectomy with adequate tumour margins is essential. The overall incidence of thyroid gland invasion is low, and, therefore, thyroidectomy should be reserved for cases considered to be at risk, as opposed to being a routine measure for all total laryngectomies. Advanced laryngeal and hypopharyngeal carcinomas involving the subglottis carry a significantly elevated risk of thyroid gland invasion compared with those that spare this subsite.[920]

Post-operative radiotherapy with or without chemotherapy

All patients should be offered post-operative RT for the recognised pathological indications (see Chapter 4). This will include all patients with T_4 disease. Oncological outcomes may not be improved with post-operative RT for pathologically staged T_3N_0 disease, when considering large database analyses.[921]

Neck metastases in advanced laryngeal squamous cell carcinoma

Patients with $T_{3-4}N_0$ disease should have levels IIA–IV treated electively.[922] For disease involving the supraglottis, and any tumour involving or crossing the midline, bilateral neck treatment is generally recommended. There is no clear evidence regarding the extent of neck dissection for patients undergoing primary surgery with N_+ disease. In addition to levels IIA–IV, neck dissection of levels IIB and V would be recommended, accepting the increased risk of accessory nerve dysfunction. Level I can be spared unless involved radiologically. (See also Chapter 26.)

Open partial laryngectomy for locally advanced laryngeal squamous cell carcinoma

Open partial laryngectomy can be considered for carefully selected T_3 tumours, especially those anteriorly situated in the larynx.[912] Functional outcomes are superior if post-operative RT can be avoided – i.e. with complete tumour resection and by selecting patients with N_0 disease.[916]

Follow up

The recommendations for follow up are set out in Chapter 5. Routine imaging is not required after primary surgery or RT for early-stage ($T_{1-2}N_0$) disease, unless there is clinical concern.

Recommendations

- All patients with a preserved larynx should undergo flexible laryngoscopy at follow-up appointments (evidence-based recommendation (R)), ideally with photographic documentation (good practice point (G))
- Thyroid function should be assessed at least every six months for any patients undergoing neck RT or open laryngeal surgery (R)

Management of complications in laryngeal cancer treatment

Complications of both RT and surgery are not uncommon, especially for advanced laryngeal SCC. These are discussed in Chapter 16.

Recurrent disease

Summary recommendations

- Consider both primary and recurrent disease stage and extent (evidence-based recommendation (R))
- Consider organ preservation for early-stage laryngeal SCC recurrences (R)

Table 6. Summary recommendations for primary treatment of advanced cancers

Disease stage	Generally preferred treatment	Alternative options	Lymph nodes
T_3N_0 or T_3N_+	RT ± chemotherapy	Total laryngectomy ± post-operative RT ± chemotherapy for bulky tumours &/or impaired laryngeal function	N_0: treat levels IIa, III & IV (bilateral if supraglottic) N_+: treat levels IIa, IIb, III & IV (± V & ± I)
$T_{4a}N_0$ or $T_{4a}N_+$	Total laryngectomy + post-operative RT ± chemotherapy	Chemoradiotherapy may be an option for selected patients with low-volume, minimal cartilage invasive disease & preserved laryngeal function	N_0: treat levels IIa, III & IV (bilateral if supraglottic) N_+: treat levels IIa, IIb, III & IV (± V & ± I)
$T_{4b}N_{0/+}M_0$	RT ± chemotherapy (unresectable disease)	Other anti-cancer therapies Best supportive care	Individualised approach depending on treatment aims

T = tumour stage; N = nodal stage; RT = radiotherapy; M = metastasis stage

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Consider vascularised tissue transfer in salvage total laryngectomy, to reduce risks of wound breakdown and fistula (R)

All recurrent tumours must be staged clinically and radiologically, for locoregional and distant disease. Both CT and MRI may be required to stage the primary disease for complex salvage surgical decisions. The management of recurrence in general is discussed in Chapter 5, and non-surgical management options, including systemic therapy, are discussed in Chapter 4.

Patients with early-stage recurrences following previous transoral laser microsurgery may be suitable for further transoral laser microsurgery, RT or open partial laryngectomy, assuming laryngeal function is preserved.

Patients with early-stage disease following previous RT may be suitable for laryngeal preservation surgery (transoral surgery or open partial laryngectomy). Open partial laryngectomy may be preferred for recurrent disease after RT. Transoral laser microsurgery may be appropriate for selected small, accessible, well-defined glottic lesions, but, overall, it is associated with a lower local control rate than open partial laryngectomy.[923,924] Open partial laryngectomy requires suitable pre-treatment swallowing and lung function to aid rehabilitation. Total laryngectomy should be considered if transoral surgery or open partial laryngectomy are not possible.

Advanced stage disease following previous RT should be managed with total laryngectomy if the disease is resectable with no distant metastasis. Very selected patients with recurrent T_3 disease may be suitable for open partial laryngectomy, accepting prolonged rehabilitation.

Vascularised tissue transfer should be considered in salvage total laryngectomy, to reduce risks of wound breakdown and fistula.[925] This may be myofascial as a second layer to the pharyngeal primary repair, or with skin if required in order to allow wider extra-laryngeal surgical clearance margins without causing stricture.

For patients who have had full treatment (i.e. total laryngectomy and RT or chemoradiotherapy, in any order), most will have a very low chance of survival and will be best treated for palliation (see Chapters 4 and 15). Patients with unresectable disease, or those who are unfit to undergo major surgery, may be offered immunotherapy, chemotherapy or re-irradiation (see Chapter 4).

Very occasionally, a patient with, for example, peri-stomal recurrence may be suitable for salvage surgery, usually involving manubriumectomy, mediastinal dissection, pharyngectomy and challenging reconstruction, but this is exceptional in a patient group with very poor overall survival prospects.

The management of lymph nodes in the setting of salvage laryngectomy for local recurrence and management of isolated lymph node recurrence is discussed in Chapter 26.

Studies due to report

'Laryngeal Cancer Cohort' ('LARCH') – an enhanced cohort study of patients with newly diagnosed laryngeal cancer (UK, Health Research Authority).

'Vocal-cord vs. Complete Laryngeal Radiotherapy for Early Glottic Cancer' ('VOCAL'); ClinicalTrials.gov identifier: NCT03759431. This is a phase II trial assessing the non-inferiority of local control achieved with vocal-fold-only RT compared to complete larynx RT in T_1N_0 glottic laryngeal SCC.

There are no National Cancer Research Institute phase III/III clinical trials specific to laryngeal cancer. Other global trials can be found in: https://clinicaltrials.gov.

Important research questions to be answered

(1) Methods to define patient selection for primary treatment (e.g. total laryngectomy or chemoradiotherapy): chemo-selection protocols and improved radiogenomics prognostication.
(2) More evidence for local control, comparing transoral laser microsurgery and RT for early-stage laryngeal SCC, particularly for T_{1b} and T_2 laryngeal SCC.
(3) More evidence for voice outcomes following transoral laser microsurgery and RT for early-stage laryngeal SCC.

Chapter 22: Management of lateral skull base cancer

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

The scope of this chapter pertains to cancers involving the bony lateral skull base and its associated structures. These include primary temporal bone malignancies which usually arise from the external auditory canal or middle ear, and locally advanced skin or parotid malignancies which involve the lateral skull base though direct extension. If treated surgically, similar principles apply to these groups.

Primary temporal bone malignancies are uncommon, and account for less than 1 per cent of all head and neck cancers. The majority of these are squamous cell carcinoma (SCC), accounting for approximately 60–80 per cent of cases.[926] Locally advanced skin cancers can arise from the pinna or peri-auricular skin, and are usually SCC, basal cell carcinoma (BCC), melanomas or skin adnexal tumours. Parotid malignancies with lateral skull base involvement are often high-grade cancers of salivary gland origin, and can also include metastatic SCC to the parotid. Other sites of tumour origin include the infratemporal fossa and temporomandibular joint (TMJ), where a variety of pathologies, including sarcomas, can arise.

This area is therefore highly heterogeneous. In addition, the largest subgroup, primary temporal bone cancer, is a rare cancer, and hence there is relatively poor evidence to inform best practice.

Presentation, investigation and diagnosis

Recommendations

- Consider malignancy in cases of progressive otalgia, otorrhoea, bleeding, hearing loss and/or facial nerve palsy when there are abnormal clinical signs (good practice point (G))
- Skull base osteomyelitis can mimic malignancy;[927] biopsy is essential for diagnosis (G)
- Audiology should be performed in primary temporal bone cancers and for all cases to be treated by temporal bone surgery (G)
- Imaging for temporal bone cancers should include both magnetic resonance imaging (MRI) and computed tomography (CT) scanning (G)

Presentation

Clinical presentation will depend on the site of origin and stage of tumour.

Primary temporal bone malignancies of the external auditory canal or middle ear often present with unilateral symptoms of pain, otorrhoea, bleeding and hearing loss,[927] and with facial nerve palsy in advanced cases. Examination may reveal a lesion which can be polypoidal or exophytic. External auditory canal and middle-ear tumours can also arise as a result of chronic inflammation or infection.[928] Both the symptoms and signs of this rare malignancy can therefore be similar to chronic external and middle-ear inflammation, often resulting in a late diagnosis. In many cases, it is the degree or persistence of pain that raises the possibility of malignancy.

Skin cancers will usually be visible as irregular, ulcerated lesions, with advanced cases demonstrating the fixation and invasion of underlying structures. Advanced parotid cancers are often palpable, with a parotid gland mass, which may involve the skin or TMJ. Deep lobe origin or extension is common, with the possible involvement of pterygoid musculature and the mandibular ramus. Facial palsy can be a presenting sign, but in many cases nerve function may be preserved till late, even in cases of tumour encasement of the nerve.

Tumours of the infratemporal fossa may be asymptomatic until significant tumour progression, at which stage symptoms can include (hemifacial) pain, trismus and lower cranial nerve dysfunction. Clinical examination may show fullness in the zygomatic region and loss of sensation in the V3 (mandibular nerve) distribution.

Diagnosis

Diagnosis is usually made through histological assessment of a biopsy specimen. This is generally straightforward to undertake in visible skin or external auditory canal tumours. Middle-ear cancers may require transtympanic or transmastoid biopsy. Image-guided fine needle aspiration cytology or core biopsy is possible in most parotid or infratemporal fossa tumours.

Histological or cytological confirmation of malignancy is important, as other benign or inflammatory conditions, such as skull base osteomyelitis, may be part of the differential diagnosis.

Audiology

Pure tone audiometry may show conductive hearing loss with or without sensorineural loss in primary temporal bone cancers. It will also provide information to predict post-operative hearing problems and rehabilitation options.

Imaging

Table 1 summarises the pre-treatment imaging recommendations.

Cross-sectional imaging provides valuable information on tumour stage, extent and surgical resectability.

Both CT and MRI with contrast are used for assessment of the primary tumour. High-resolution CT is essential for bone assessment of temporal bone erosion, skull base foramina, middle-ear ossicles, mandible and TMJ. Magnetic resonance imaging is helpful for soft tissue, including the dura and brain, masticator space and parotid gland, and in differentiating fluid from the tumour, particularly within the mastoid air cells.

In cases where primary surgery is planned, and there is close proximity of the tumour to the internal carotid artery, which may require sacrifice, then a pre-operative balloon occlusion test with or without embolisation can be considered.

Staging and pathology

Staging

Recommendations

- Use modified Pittsburgh staging for primary temporal bone cancers[930] (good practice point (G))

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Pre-treatment imaging recommendations

Staging	Modality
Primary	CT & MRI
Neck	CT or MRI
Thorax	CT or PET-CT*

*Positron emission tomography computed tomography (PET-CT) is preferred in high-grade non-squamous cell carcinoma primary and/or nodal stage N_3 neck disease. CT = computed tomography; MRI = magnetic resonance imaging

- Use the applicable site of origin (based on Union for International Cancer Control ('UICC') *TNM Classification of Malignant Tumours*, eighth edition[763]) for non-primary temporal bone lateral skull base malignancies (G)

The American Joint Committee on Cancer ('AJCC')/Union for International Cancer Control tumour–node–metastasis (TNM) staging does not include a specific cancer staging system for lateral skull base or temporal bone malignancies. However, certain sites of origin can fit into the *TNM Classification of Malignant Tumours*, eighth edition.[763] These sites are: skin carcinoma of the head and neck (for external auditory canal, pinna and peri-auricular skin), the major salivary gland for parotid cancers, tumours of bone and soft tissue for sarcomas, and head and neck malignant melanoma. These are described in the relevant chapters of these guidelines.

The modified Pittsburgh staging system,[929] described for cancer arising from the external auditory canal, is often used for other primary temporal bone cancers and can be used for cutaneous cancers as well. It provides an intuitive staging system and good prognostication, and is also helpful for clinical decision-making and surgical planning.[930] This is therefore the recommended staging system for primary temporal bone malignancies.

Recent studies have shown a number of additional factors that are important in prognostication; these include: dural involvement, histological grade of tumour and route of spread. With regard to the latter, tumour stage T_4 cancers on the basis of anterior spread have a much better prognosis than T_4 on the basis of spread in other directions.[931,932] There is an argument for revising the T_4 classification. Clinicians should be aware of this, as the former group of T_4 patients have a better prognosis.

Neck and distant metastatic disease are assessed using the standard American Joint Committee on Cancer/Union for International Cancer Control *TNM Classification of Malignant Tumours* (eighth edition) classification for head and neck cancers (Tables 2–4).[763]

Pathology

The main pathologies can be considered by site of origin. Table 5 shows the main pathologies affecting the lateral skull base.

Treatment

Recommendations

- Primary surgery is generally accepted as the standard of care in suitable patients (evidence-based recommendation (R))
- Surgery will usually entail at least a lateral temporal bone resection, with consideration of adjacent structures (good practice point (G))

Table 2. Modified Pittsburg primary tumour staging[929]

Tumour (T) stage	Description
T_1	Tumour limited to EAC, without bony erosion or evidence of soft tissue involvement
T_2	Tumour with limited EAC bone erosion (not full thickness), with limited (<0.5 cm) soft tissue involvement
T_3	Tumour eroding osseous EAC (full thickness), with limited (<0.5 cm) soft tissue involvement, or tumour involving middle ear, mastoid or both
T_4	Tumour eroding cochlea, petrous apex, medial wall of middle ear, carotid canal or jugular foramen of dura; or with extensive soft tissue involvement (>0.5 cm), such as TMJ or stylomastoid foramen involvement; or with evidence of facial paresis

EAC = external auditory canal; TMJ = temporomandibular joint

- The parotid and neck regional lymph nodes should be treated electively in most cases of cutaneous SCC and T_{3-4} primary temporal bone SCC (R)
- Post-operatively radiotherapy (RT) as intensity-modulated RT is the standard of care in T_{2-4} cancers (G)
- Surgery should be avoided in advanced cases with dural and/or carotid artery involvement, as the prognosis is very poor and the likelihood of surgical morbidity is high (G)

General principles

Primary surgery is the mainstay of treatment for most lateral skull base cancers.

The decision for surgery is dependent on the extent of tumour and the ability to achieve an appropriate oncological resection. Patient factors and co-morbidities must also be weighed into the decision-making process. Cases should be referred for management to designated supra-regional head and neck or skull base oncology multidisciplinary teams (MDTs) with expertise in managing such cases.

Primary RT or chemoradiotherapy may be used as an approach in selected cases where surgery is not appropriate or acceptable. Palliative RT and/or chemotherapy may also have a role for symptom control or in cases with distant metastatic disease.

Surgical management and considerations are described below. Similar approaches for surgery, post-operative management and rehabilitation may be required for primary temporal bone malignancies and advanced parotid or skin cancers.

Primary temporal bone cancers

It is generally accepted that primary temporal bone cancers, arising from the external auditory canal or middle ear, are best treated with surgery followed by adjuvant post-operative RT.[927,932] However, there is very little evidence comparing different modalities of treatment.

Survival in early-stage T_{1-2} disease is good with primary surgery and post-operative RT if necessary. Data show a five-year disease-free survival rate of 67–100 per cent and a disease-specific survival rate of 92–100 per cent. Most surgery entails a lateral temporal bone resection with little resultant major morbidity.[933]

Locally advanced tumours, treated with primary surgery and post-operative RT, have lower survival with T_{3-4} disease,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Nodal staging*

Nodal (N) stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension Or metastasis in a single ipsilateral node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, any with extra-nodal extension Or metastasis in a single contralateral node, of any size, & with extra-nodal extension

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763]

Table 4. Metastasis staging*

Metastasis (M) stage	Description
Clinically M_0	No distant metastasis
Clinically M_1	Distant metastasis
Pathologically M_1	Distant metastasis, microscopically confirmed

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[763]

Table 5. Main pathologies affecting lateral skull base

Site of origin	Malignant pathology
Primary temporal bone	EAC or middle ear: SCC, BCC, skin adnexal Advanced cutaneous: SCC, BCC, melanoma, skin adnexal
Advanced cutaneous	SCC, BCC, melanoma, skin adnexal
Advanced parotid	Adenocarcinoma, adenoid cystic, metastatic SCC
Infratemporal fossa or TMJ	Chondrosarcoma, osteosarcoma, chordoma

EAC = external auditory canal; SCC = squamous cell carcinoma; BCC = basal cell carcinoma; TMJ = temporomandibular joint

with a disease-free survival rate of 41–59 per cent and a disease-specific survival rate of 48–65 per cent. However, rates have been improving with time, indicating that advances in treatment have impacted positively in this group.[930,934,935] Most data, for patients treated with curative intent, arise from patients who have been treated with primary surgery. However, more limited data from patients with T_{3-4} cancers treated with primary chemoradiotherapy show near equivalent survival.[933,936,937]

Involvement of the dura confers a worse prognosis. One group reported five-year disease-specific survival rate of 37 per cent in 14 patients with brain involvement.[927] However, this has not been reported by others, e.g. a 0 per cent disease-specific survival rate with dural involvement in nine patients was reported by one group[931] and 0 per cent rate in nine patients by another.[934]

Encasement of the petrous internal carotid artery (ICA) is a poor prognostic sign, and surgery for such cases will almost always cause highly morbid neurological functional loss with a very poor chance of survival.[927] Ferrari *et al.* reported a small series of 10 patients with ICA resection, with a 10 per cent peri-operative mortality rate and a 25 per cent major neuromorbidity rate of the survivors, with a mean overall survival of 27 months.[938]

There is varying evidence as to the prognostic impact of facial nerve involvement, with some series showing worse outcomes and others showing no significance.[939–941]

As in other head and neck cancers, the presence of nodal disease has a significant impact on disease-specific and overall survival (by about 40–50 per cent),[930,932] as do positive surgical margins.[934]

The route of spread for advanced cancer is highly prognostic, with a much better prognosis for advanced cancers that are T_4 on the basis of anterior spread (to the parotid gland and/or pre-auricular tissue or skin) than T_4 on the basis of spread in other directions (55 per cent *vs* 16 per cent five-year disease-specific survival rate in 21 patients).[931]

Surgery will usually require at least a lateral temporal bone resection, with advanced-stage tumours requiring an extended temporal bone resection. Adequate surgery is required to achieve optimal prognosis; this should be performed en bloc when possible, to maximise the chance of margin control. Surgery, other than for palliation, should not be performed without a high chance of complete microscopic resection.

Stage T_1 tumours

In selected superficial cases, a sleeve resection may be considered. This may be appropriate, for example, for an early-stage superficial BCC involving the cartilaginous external auditory

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

canal. Otherwise, a lateral temporal bone resection is required to achieve adequate margins.

Stage T_2 tumours

A lateral temporal bone resection is recommended as a minimum for all T_2 cases. The specific details of surgery are outside the scope of this chapter, but it involves en bloc resection of the external auditory canal and tympanic membrane lateral to the facial nerve and stapes.

Stage T_3 tumours

For T_3 tumours not extending medial to the tympanic membrane, a lateral temporal bone resection may be sufficient. Evidence from pathological specimens shows that tumours eroding the anterior bony external auditory canal should also undergo TMJ resection. If there is middle-ear involvement, an extended temporal bone resection should be performed.

Stage T_4 tumours – extended temporal bone resection

The term extended temporal bone resection encompasses various types of temporal bone resection, with described terminology including subtotal, near total and total temporal bone resection.

The essential elements of extended temporal bone resection are: (1) facial nerve sacrifice; (2) posterior and middle craniotomy; (3) labyrinthectomy; (4) transection of the internal auditory canal; (5) resection of the petrous tip; (6) exposure of the intra-petrous portion of the carotid; and (7) total parotidectomy.

Additional options include: craniectomy (squamous temporal bone; sphenoid wing, posterior fossa); mandibulectomy; parapharyngeal or infratemporal fossa resection; extension to the jugular foramen; lower cranial nerve sacrifice; ICA; dura; and brain.

Table 6 summarises the surgical management of primary temporal bone cancer.

Advanced skin and parotid gland malignancy

Locally advanced cutaneous or parotid malignancy may also necessitate lateral temporal bone resection as part of the resection, in cases where the tumour abuts or locally erodes into the temporal bone. Tumour extension up to or through the stylomastoid foramen may also occur, with or without facial palsy.

In this setting, lateral temporal bone resection can enable complete tumour resection, and allow improved access to gain better margins and to allow proximal dissection of the facial neve in the temporal bone for grafting. This approach has shown improved locoregional control in cases of locally advanced parotid and cutaneous malignancies.[942–945]

Table 6. Surgical management of primary temporal bone cancer

Primary tumour (T) stage*	Surgical requirement
T_1	Sleeve resection (superficial cancers confined to cartilaginous EAM) or lateral temporal bone resection
T_2	Lateral temporal bone resection
T_3	Lateral or extended temporal bone resection
T_4	Extended temporal bone resection

*Modified Pittsburgh classification.[929] EAM = external auditory meatus

Management of additional structures

Facial nerve

In cases of pre-existing facial palsy, the involved portion of the intra-temporal and extra-temporal facial nerve will require resection, ideally with frozen section control.

Facial nerve sacrifice may also be required when the nerve is functioning normally pre-operatively, if there is tumour encasement of the nerve, extension through the stylomastoid foramen, or where preservation would compromise successful tumour extirpation.

Temporomandibular joint

The TMJ is in close proximity to the external auditory canal and parotid, and consideration should be given to it as part of operative planning. Resection of the TMJ is not required routinely in every lateral temporal bone resection and does contribute to post-operative morbidity.[927,946] Where there is anterior external auditory canal bony canal erosion, microscopic tumour involvement of the TMJ is significantly more likely.[947] A selective approach is therefore advised, with TMJ resection more likely to be required in advanced tumours and those with anterior extension.

Dura or brain

Cases with dura involvement can be operated upon, in highly select cases, with dura resection. Gross brain parenchymal invasion has a low likelihood of curative outcomes, and, in this setting, a primary surgical approach is not recommended.

Mandible

Adjacent bony structures include the mandibular ramus and zygomatic arch. Partial or complete resection of these structures may be necessary to achieve appropriate margins or access.

Parotid gland

The parotid gland may also be involved through direct tumour invasion. In cases of parotid involvement through direct invasion, parotidectomy should be undertaken, guided by the degree of local extension. Parotidectomy may also be carried out as part of surgical access for a complete en bloc resection, or for possible micrometastatic lymph node disease (see below).

Internal carotid artery

Limited disease at the ICA in an otherwise resectable tumour could, in select cases, warrant consideration of ICA sacrifice. Pre-operative balloon occlusion testing should be undertaken and, if there is a high likelihood of sacrifice, occlusion of the artery with coiling can be performed.

Management of regional lymph nodes

The parotid gland and cervical lymph nodes are the regional nodal basins in primary temporal bone and cutaneous malignancies.

Clinically staged node-negative (N_0) disease

For primary temporal bone cancers, routine elective treatment of the parotid and neck in $T_{1–2}$ SCC is not necessary, with

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

occult metastasis rates of 0 and 7 per cent respectively.[948] However, most patients with T_{1-2} primary temporal bone SCC will receive surgical treatment, and elective treatment of these nodal basins may be undertaken for surgical access requirements or can be considered part of adjuvant post-operative RT, factoring in histopathology. Elective treatment of the parotid and neck is recommended in T_{3-4} primary temporal bone SCC, with occult metastasis rates of around 20 per cent,[948] in keeping with generally accepted practice.

Elective treatment should be undertaken in the majority of cutaneous SCC cases requiring lateral temporal bone resection.[949]

If elective treatment of the node-negative neck and parotid is planned, this would usually be undertaken as part of the primary surgery, with dissection of nodal levels 2(a/b) and 3 as well as a superficial parotidectomy.

Clinically staged node-positive (N_+) metastatic disease

In the setting of clinical-radiological evidence of nodal metastatic disease to the parotid or neck, both parotidectomy[950] and neck dissection should be performed, the extent of which is dependent on the burden of disease. This should at least involve a superficial parotidectomy, and dissection of nodal levels to typically include 1b, 2, 3, 4 and 5a. Dissection of the deep lobe of the parotid is more controversial in the context of facial nerve preservation and the absence of deep lobe involvement.

Radiotherapy and chemoradiotherapy

Radiotherapy is usually given in the adjuvant post-operative setting. Most T_{2-4} primary temporal bone cancers and locally advanced malignant parotid tumours show improved survival rates with adjuvant RT. Selected T_1 tumours with clear resection margins may be managed with surgery alone.[951]

Highly conformed intensity-modulated RT is the standard of care to reduce the dose to normal structures, including the adjacent inner ear and oral cavity, and to reduce the volume of bone treated to a high dose. Post-operative doses used for head and neck cancer are 60 Gy in 30 fractions for moderate-risk disease and 66 Gy in 33 fractions for high-risk disease.

Synchronous post-operative treatment with cisplatin can be considered for high-risk SCC, e.g. involved surgical margins (see Chapter 4).

Primary RT or chemoradiotherapy may be used as an approach in selected cases as an alternative to surgery, with similar outcome data for advanced disease.[933,936,937] The use of induction pre-operative chemoradiation therapy has also been reported to help obtain surgical tumour-free margins in advanced disease,[937] but is not in common practice.

Inoperable tumours

In cases where surgery is not undertaken, definitive or palliative treatment can be given. The choice is dependent on the rationale for not undertaking surgery, the extent of tumour, and patient age and co-morbidities.

Advanced disease at presentation may make the tumour either technically inoperable or render the chance of cure very low with factors such as gross brain invasion, cavernous sinus involvement or carotid encasement. It may therefore be deemed that the benefit of surgery is outweighed by the poor prognosis and attendant morbidity. In an otherwise fit patient, definitive RT or chemoradiotherapy using intensity-modulated RT may be considered. Long-term durable results, albeit with lower success, can be seen with this approach.[937]

Palliative RT can be given for the control of local symptoms such as pain and fungating disease. Palliative systemic treatment can also be considered for reasons of local control and to manage distant metastatic disease.

Reconstruction and rehabilitation following surgery

Recommendations

- The anterolateral thigh free flap offers excellent reconstruction for lateral skull base defects (good practice point (G))
- Facial nerve rehabilitation should be initiated at primary surgery (G)
- Osseo-integrated bone-anchored hearing aids (BAHAs) can be considered for hearing rehabilitation (G)
- Selected condylar defects may be left unreconstructed with minor occlusal disturbance (G)

There are a number of important considerations in reconstruction and rehabilitation following lateral skull base surgery. One or more of the following areas may require addressing:

- Management of any dural defect
- Filling of the volume defect and coverage of skin defects
- Management of pinna defects
- Facial nerve management and rehabilitation
- Hearing and balance rehabilitation
- Management of cranial nerve or neurological deficits
- Temporomandibular joint loss or dysfunction

Dura, tissue volume and skin

Dural defects are normally repaired with non-vascularised tissue such as autologous fascia lata grafts, pericardial xenografts, or synthetic materials.

Volume and skin defects are determined by the extent of surgery. For smaller skin defects without much volume loss, options include a radial forearm free flap, cervicofacial rotation flap, temporalis flap and supraclavicular artery island flap. These can be used to reconstruct small skin or auricle defects with modest volume loss.[952,953]

For most defects after temporal bone resection, the anterolateral thigh free flap offers optimal reconstruction, providing bulk (variable by the inclusion of the vastus lateralis) and enough skin for most defects (which can be reduced by de-epithelialisation if the pinna is not resected).[952,953] It is reliable, has the requisite tissue and is associated with minimal donor site morbidity. It allows vascularised fascia lata to be used for static facial suspension or the lateral cutaneous femoral nerve for either sensory innervation of the flap or an interpositional facial nerve graft. Also, the accessible donor site allows for concomitant flap harvest and tumour ablation. Alternative flaps include the latissimus dorsi, rectus abdominis or deep inferior epigastric artery perforator, radial forearm, medial sural artery, and lateral arm flaps.

In a vessel-depleted neck or in a patient unsuitable for microvascular surgery, a lower trapezius muscle island flap or supraclavicular artery island flap (if the transverse cervical vessels are intact), or a superior trapezius flap (when a radical neck dissection has been performed), can be used. The use of a pectoralis major or deltopectoral flap is suboptimal as the

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

lateral skull base is at or beyond the limits of rotation in many cases.

Facial function

In cases in which facial nerve sacrifice is necessary, one or more of the steps described below should be considered. It should be borne in mind that the best time to perform many of these interventions is at the time of tumour resection, as virtually every patient in this group will go on to have post-operative RT. Patients will require detailed pre- and post-operative counselling for the functional and cosmetic sequelae resulting from a facial nerve palsy.

For cases with pre-operative facial function, a cable graft to intra-parotid branches can be performed if: (a) there is enough proven tumour-free proximal facial nerve (otherwise a facial-hypoglossal anastomosis can be considered); and (b) the peripheral branches can be identified (this may be difficult when a radical en bloc parotidectomy with overlying skin is performed). Useful donor nerves include the greater auricular nerve, sural nerve or lateral cutaneous nerve of the thigh (easily available if harvesting an anterolateral thigh free flap). Free flaps give the option of skin, muscle, and fat or fascia for dead space filling, as well as vascularised nerves to bridge any facial nerve defect. Commonly used chimeric free flap options include the anterolateral thigh or latissimus dorsi free flaps. Such vascularised nerve conduits may take time to function. Buddying the buccal branch or zygomatic branches onto the nerve to the masseter provides more rapid reanimation and neuromuscular end plate function. This allows time for the vascularised nerve conduit to work.

Other options, and for cases with pre-operative facial palsy, include static procedures such as a fascia lata sling for oral commissure or cheek suspension, or dynamic procedures such as lengthened temporalis myoplasty (e.g. Labbé type I or II), if the deep temporal nerve and artery are preserved. Oculoplastic interventions (e.g. upper lid weight, canthoplasty) can be performed at the time of tumour resection or later on. Immediate on-table options include a lateral tarsal strip procedure or lateral tarsorrhaphy.

Hearing

Ipsilateral total or total conductive hearing deficit is an inevitable outcome of temporal bone resection. Pre-operative audiological assessment of the contralateral ear will identify patients with a pre-existing deficit. This may be corrected or improved with appropriate aiding in either the pre- or post-operative period. Total conductive hearing loss can be rehabilitated through an osseo-integrated BAHA. Total hearing loss can be rehabilitated through either a BAHA or a bilateral contralateral routing of signals aid.

Balance

Post-operative vertigo is expected if there is resection of a functioning labyrinth. If vestibular compensation is protracted and incomplete, referral for vestibular rehabilitation services should be considered.

Lower cranial nerves

In addition to VIIth cranial nerve (facial nerve) issues, all lower cranial nerves essential for swallowing and voice (IXth, Xth and XIIth cranial nerves) are at risk of injury or sacrifice during surgery for advanced tumours. Care of the patient in this situation must include close involvement of speech and language therapists. Interventions include: either pre- or post-operative percutaneous gastrostomy; a nasogastric tube; or a tracheostomy if aspirating on saliva. Later interventions include vocal fold medialisation and cricopharyngeal myotomy.

Temporomandibular joint

It is feasible to leave selected condylar resections unreconstructed, accepting minor dental occlusal disturbance. Where mandibular reconstruction is required, a composite microvascular flap such as a chimeric thoracodorsal artery perforator, scapula osteomusculocutaneous or deep superior epigastric artery with costochondral junction flap can restore a large mandibular and lateral skull defect.

Follow up

Given the numerous considerations of rehabilitation, follow up should ideally be in an MDT clinic setting. Post-treatment imaging and surveillance will include an initial post-treatment scan approximately 12 weeks after the completion of definitive treatment, which will act as a baseline scan. Magnetic resonance imaging after surgery, with or without positron emission tomography (PET)-CT, is most useful in this regard. As most tumour recurrences are not detectable by clinical examination, especially if a free flap has been used, six-monthly MRI scans for the first year and annual MRI scans until year five are recommended.

Recurrent local disease

When only limited primary surgery (less than lateral temporal bone resection) has been previously performed, surgery based on the principles described above is appropriate.

Local recurrence after comprehensive treatment may be aggressive and is associated with a poor prognosis. In the majority of cases, recurrences in this setting are inoperable. Longer survival can be achieved through palliative treatment than through surgery.[954] Consideration may be given to re-irradiation if there is a sufficient time interval from prior RT. Palliative options can also be considered (see Chapter 4).

Other lateral skull base cancers

There is large variability in both the histology and anatomical origin of these tumours. They may arise from the contents of the infratemporal fossa, temporal bone or adjacent structures. They include sarcomas, malignant neurogenic tumours and paragangliomas. This heterogeneity makes it difficult to be generalisable in terms of guidelines. Similar principles of management as described in this chapter will usually however apply, with surgery being the mainstay of treatment, involving oncological resection of the primary tumour, followed by adjuvant RT.

The skillset required to deal with such cases is highly specialised, requiring surgeons who have expertise in various forms of surgical access and resection of the infratemporal fossa, with joint neurosurgery input when necessary. Referrals should be made to designated supra-regional head

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

and neck or skull base oncology MDTs with experience in managing these cases.

Studies due to report

Current evidence is based on retrospective case series and expert opinion. No randomised, controlled trials exist or are likely to, given the low incidence of cases.

Cemiplimab, an anti-programmed cell death 1 immune checkpoint inhibitor, has shown promise in the treatment of non-resectable advanced cutaneous SCC.[955] It is currently being investigated in a phase 2 clinical trial in a neo-adjuvant setting prior to surgery.[955]

Vismodegib is an inhibitor of the hedgehog signalling pathway, and is under investigation in locally advanced BCCs, where given pre-operatively it may allow for downstaging of the extent of surgery.[956]

Important research questions

The role of proton therapy in a pre- or post-operative adjuvant setting is also of interest given the close anatomical proximity of the lateral skull base to critical functionally significant structures.

Evidence comparing different modalities of primary treatment would be desirable, but may be unachievable in this rare tumour group.

Chapter 23: Nasal/paranasal sinus and anterior skull base cancer

Table of Contents

Introduction

Paranasal sinus and skull base malignancies are a rare and heterogeneous group of diseases representing less than 5 per cent of all head and neck cancers. The incidence of these cancers is just less than 1 in 100 000 people per year, peaking between the ages of 50 and 60 years.[957] Arising within a relatively small anatomical area, these rare tumours comprise a variety of histological types. The typical presentation is with locally advanced stage disease, and subsequent treatment is complicated by the proximity of critical anatomical structures. Clinical practice is based on low-quality evidence, with wide variation across the UK.[958]

Presentation and diagnosis

The propensity for sinonasal malignancy to present at a locally advanced stage reflects both the innocuous symptoms of early-stage disease and the difficulty of endonasal examination in the community. Unilateral nasal symptoms should raise suspicion. Localised disease may present with epistaxis, nasal obstruction and hyposmia. Advanced disease, with adjacent structural involvement, may result in corresponding functional symptoms affecting the: orbit (diplopia, proptosis); pre-masseteric space, pterygopalatine or infratemporal fossa (trismus, facial pain, facial sensory change); anterior cranial fossa (headaches, anosmia); palate (intraoral mass, loose dentition, malocclusion); and lacrimal apparatus (epiphora).

Occupational risk factors include exposure to wood and leather dust for intestinal-type adenocarcinoma. Nickel or chromium, organic solvents, and construction and textile site environments are mainly risk factors for squamous cell carcinoma (SCC).[959] A full ENT, head and neck, and cranial nerve examination must be supplemented by nasendoscopy. Biopsy can be performed in the clinic or in an operating theatre setting.[958]

Imaging prior to biopsy should be carried out before general anaesthetic biopsy. However, a small out-patient biopsy from a non-vascular mass will not interfere with subsequent imaging and can expedite diagnosis. Biopsy, which is usually performed by a referring surgeon, should not take the form of a debulking, as this can make surgical planning more difficult, and may lead to an underappreciation of tumour extent (even if full pre-biopsy imaging is performed).

After diagnosis, in addition to standard head and neck multidisciplinary team (MDT) discussion with its core members, input from rhinology and skull base, neurosurgery, and oculoplastic surgery departments may be required. Additional MDT input will be required for sarcomas and may be necessary for neuroendocrine carcinomas.

Recommendations

- Sinonasal malignancy is a rare but complex disease that should be managed by a specialist MDT that includes anterior skull base expertise and oculoplastic input as necessary (evidence-based recommendation (R))
- History and examination should focus not only on the nasal cavity and paranasal sinuses, but also any potentially involved adjacent structures (good practice point (G))
- Biopsy should not take the form of macroscopic tumour debulking prior to referral to the appropriate MDT (G)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Imaging

The role of imaging is to define staging, help plan the surgical approach and enable planning of subsequent radiotherapy (RT) treatment volumes.

Table 1 shows the recommendations for different imaging modalities.[960]

Pathology

Sinonasal tumours are histologically very diverse, and arise from surface epithelium or underlying seromucinous glands. Tumour types should be categorised according to the World Health Organization classification of head and neck tumours (fifth edition, 2022), which has several changes for sinonasal tract cancers.[961] The commonest types are shown in Table 2.[960,962]

Correct diagnosis of these lesions is critical, but often poses significant pathological difficulties because of overlapping features, with up to 30 per cent of alterations reported from second opinions at centres of excellence.[963] This is further complicated by a number of new disease entities being recognised on genetic and phenotypic testing, including NUT carcinomas, SW1/SNF (switch/sucrose non-fermentable) complex deficient sinonasal carcinoma and human papillomavirus (HPV)-related multi-phenotypic sinonasal carcinoma. To date, these have largely been of histopathological interest. Whilst any differences in the clinical behaviours are now being recognised in these rare subtypes, the principles of treatment remain the same as for other sinonasal carcinomas, which are fairly uniform, with the exception of increasingly used induction chemotherapy for sinonasal undifferentiated carcinoma.

Staging

AJCC/UICC tumour–node–metastasis staging

The eighth edition of the American Joint Committee on Cancer ('AJCC') / Union for International Cancer Control ('UICC') *TNM Classification of Malignant Tumours* made no changes to primary site staging for paranasal sinus tumours (Tables 3–5).[964] Pathology is a major determinant for both disease behaviour and prognosis, and, as such, the tumour–node–metastasis (TNM) system is often a less useful clinical guide for management in this tumour site. Furthermore, primary sites of the frontal and sphenoid sinus are not covered. Historical classifications such as Ohngren's line,[965] predicting a poor prognosis for tumours located postero-superiorly to a line connecting the angle of the mandible to the medial canthus, retain clinical relevance.

The final TNM stage is used to categorise patients into prognostic disease stage groups, with five-year overall survival rates for different stages as follows: stage I (63 per cent), stage II (61 per cent), stage III (50 per cent) and stage IV (35 per cent).[966] However, histopathological subtype specific data are likely to be more clinically relevant than staging.

A variety of different staging systems are used in practice for specific tumour types.

Table 1. Recommendations for different imaging modalities

Staging	Modality
Primary (sinuses or anterior skull base)	CT & MRI* ± X-ray OPG
Regional neck	CT or MRI
Distant	CT or PET-CT†

*A combination of computed tomography (CT) and magnetic resonance imaging (MRI) of the sinuses and neck including the skull base is generally required for complete staging before treatment. Computed tomography is superior for delineation of bony and skull base erosion. Magnetic resonance imaging is superior for assessing soft tissue involvement (orbit, dura and brain parenchyma), perineural tumour spread, and differentiation of tumour from inflammation and secretions. †Positron emission tomography (PET)-CT can be considered for high-grade disease, or when there is significant nodal disease. Melanoma staging requires whole-body CT (or PET-CT) and brain imaging to identify occult tumours.[960]
OPG = orthopantomogram

Olfactory neuroblastoma

Staging classification of olfactory neuroblastoma was first proposed by Kadish *et al.* in 1976,[967] and modified by Morita and colleagues in 1993[968] to include four stages (Table 6). This staging is also sometimes used for other tumour histological types.

In variable clinical use, this and other complimentary alternative systems help guide treatment and surgical approaches, but are poor predictors of survival. Disease-grade stratification with pathological Hyams grading is complementary to radiological staging and independently associated with prognosis.[961]

Sinonasal malignant melanoma

The American Joint Committee on Cancer / Union for International Cancer Control staging system for mucosal melanoma of the head and neck is the most commonly used in clinical practice and is described in Chapter 29.

Nasal vestibule cancer

Often amalgamated within skin classifications, the nasal vestibule is a rare subsite and hence there is a lack of consensus about which staging system is most appropriate to use. However, Wang's classification (Table 7) is popular as it contains the most clinically relevant criteria.[969]

Treatment

General principles

Recommendations

- The heterogeneity of tumour histological types, and the extent and nature of invasion, together with a poor evidence base means that MDT discussion is nuanced to the individual patient (good practice point (G))
- Sinonasal cancer management should take place in high-volume centres with appropriate histopathological, oncological, surgical, oculoplastic and reconstructive expertise (G)
- Most operable tumours are treated by primary surgery with post-operative RT or chemoradiotherapy (G)
- Tumours classified as 'T1' nasal vestibule cancers according to Wang[969] should be treated by single-modality treatment, either RT or surgery (evidence-based recommendation (R))

Although many studies have shown improved survival over the last two to three decades, the overall prognosis remains poor, with five-year overall survival rates of around 40–50 per cent.[970] Achieving local tumour control is challenging because of the close proximity of critical anatomical structures.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Pathological summary of sinonasal tumours

Histology	Comments	Sub-categorisation
Common variants		
– Sinonasal SCC	Most common (>50% of cases, especially in maxillary sinus) Can arise from malignant transformation within inverted papilloma	Can be keratinising or non-keratinising, with same rarer subtypes found in other H&N SCCs, e.g. spindle cell, basaloid, adenosquamous variants Subset of non-keratinising SCC is HPV-related & has better prognosis[962]
– Sinonasal adenocarcinoma	10–20% of sinonasal malignancies[960]	Salivary (variable grade)
		Non-salivary Intestinal-type adenocarcinoma Non-intestinal (variable grade)
– Sinonasal tumours with neuroendocrine differentiation		Neuroectodermal origin Olfactory neuroblastoma
		Epithelial origin Sinonasal endocrine carcinoma
Other carcinoma variants		
– Sinonasal undifferentiated carcinoma	Diagnosis of exclusion	
– NUT carcinoma	Poor prognosis	
– SW1/SNF complex deficient sinonasal carcinoma	Poor prognosis	Most common subtype is SMARCB-1 deficient carcinoma
– Sinonasal lymphoepithelial carcinoma	Similar to nasopharyngeal carcinoma but in nasal cavity or sinuses Strongly associated with EBV	
– Teratocarcinoma	High-grade mixed epithelial, mesenchymal & neuroectodermal malignancy	
– HPV-related multi-phenotypic sinonasal carcinoma	Can be confused with adenoid cystic carcinoma, but with high-risk HPV transcripts Favourable prognosis	
– Minor salivary gland carcinomas		As for salivary gland carcinomas arising elsewhere, commonest sinonasal histology is adenoid cystic carcinoma (two-thirds of cases)
– Sarcomas	<10% soft tissue sarcomas	Diverse histological types, including Ewing & Ewing like sarcoma, bi-phenotypic sinonasal sarcoma, & undifferentiated pleomorphic sarcoma
– Mucosal melanoma	See Chapter 29 (70% of H&N mucosal melanomas affect nasal cavity)	

SCC = squamous cell carcinoma; H&N = head and neck; HPV = human papillomavirus; SW1/SNF = switch/sucrose non-fermentable; EBV = Epstein–Barr virus

Local recurrence dominates failures (and hence a low threshold for post-operative RT), and isolated distant metastases are only seen in about 5 per cent of cases.[971]

As for many rare cancer sites, there are no phase III trial data to direct therapy. Surgery is generally accepted to be the mainstay of treatment for operable tumours in suitable patients, with most cases also having post-operative RT, with or without chemotherapy. Single-modality surgical treatment is possible in selected T_1 ethmoidal, or T_1 and limited T_2 (infrastructure or middle meatal extension) maxillary sinus cancers, if clear pathological margins can be confidently demonstrated in the absence of unfavourable histopathological features. Primary (chemo)radiotherapy can be considered for inoperable disease. Induction chemotherapy is variably but increasingly used for sinonasal undifferentiated carcinoma (discussed below). Cross-specialty involvement is crucial in these complex cases; where possible, sinonasal cancer management should take place in high-volume centres, with appropriate histopathological, oncological, surgical and reconstructive expertise.

The input and possible refinement of chemotherapy (neo-adjuvant, adjuvant or palliative) by a neuroendocrine MDT may be necessary for sinonasal neuroendocrine carcinomas of epithelial origin. Sarcomas should be discussed within a sarcoma MDT in conjunction with the head and neck MDT. Most patients with chondrosarcomas have primary surgery followed by adjuvant therapy. Other sinonasal sarcoma treatment is more nuanced in terms of the exact sequence and nature of multimodality treatment.

Nasal vestibule cancers are generally SCC, relatively rare, and behave more like cutaneous SCC. Hence, the evidence base for best treatment is poor. Generally, there is equipoise between surgery or RT for disease classified as 'T1' by Wang,[969] and possibly for limited 'T2' disease.[972] The choice may depend on the confidence of surgical resection achieving clear margins and the prospects of satisfactory reconstruction. For other larger tumours, multimodality treatment may be recommended, but that may depend on the radicality of surgery (e.g. where total rhinectomy is performed for $T_{2/3}$ tumours with clear margins and no other adverse features, nasal vestibule cancer could be treated using surgery alone).

Inverted papilloma is a benign tumour with a significant risk of malignant transformation. It is most commonly staged based on local extent using the Krouse staging system.[973]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 3. Primary tumour staging*

Tumour (T) stage by primary tumour site	Description
Maxillary sinus	
– T_X	Primary tumour cannot be assessed
– Tis	Carcinoma in situ
– T_1	Tumour limited to maxillary sinus mucosa, with no erosion or destruction of bone
– T_2	Tumour causing bone erosion or destruction, including extension into the hard palate or middle nasal meatus, except extension to posterior wall of maxillary sinus & pterygoid plates
– T_3	Tumour invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
– T_{4a}	Moderately advanced local disease – tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
– T_{4b}	Very advanced local disease – tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus
Nasal cavity & ethmoid sinus	
– T_X	Primary tumour cannot be assessed
– Tis	Carcinoma in situ
– T_1	Tumour restricted to any 1 subsite, with or without bony invasion
– T_2	Tumour invading 2 subsites in a single region or extending to involve an adjacent region within naso-ethmoidal complex, with or without bony invasion
– T_3	Tumour extends to invade medial wall or floor of orbit, maxillary sinus, palate, or cribriform plate
– T_{4a}	Moderately advanced local disease – tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
– T_{4b}	Very advanced local disease – tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[964]

Table 4. Nodal staging*

Nodal (N) stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension Or metastasis in a single ipsilateral node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension Or metastasis in multiple ipsilateral, contralateral, or bilateral nodes, any with extra-nodal extension Or metastasis in a single contralateral node, of any size, & with extra-nodal extension

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[964]

Contrary to previous opinion, these tumours are generally not HPV driven with no evidence of high-risk HPV transcripts. It is locally aggressive, with recurrence rate estimates of up to 14 per cent and potential malignancy transformation risk of up to 8 per cent.[974] Treatment usually involves endoscopic resection, with subperiosteal clearance at the tumour insertion point of

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 5. Group staging*

Group stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	T_{1-3}	N_1	M_0
IVA	T_{1-4a}	N_2	M_0
	T_{4a}	N_{0-1}	M_0
IVB	Any T	N_3	M_0
	T_{4b}	Any N	M_0
IVC	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[964]

Table 6. Kadish *et al*. staging of esthesioneuroblastoma[967,968]

Kadish stage	Description
A	Tumour confined to nasal cavity
B	Involvement of nasal cavity & paranasal sinuses
C	Extension beyond paranasal sinuses
D	Regional or distant metastases

Table 7. Wang's staging of nasal vestibule carcinoma[969]

Wang stage	Description
T1	Superficial lesion limited to nasal vestibule
T2	Lesion extended to adjacent structures (upper nasal septum, upper lip, philtrum, skin of nose, nasolabial fold), but not fixed to underlying bone
T3	Lesion further extended (hard palate, buccogingival sulcus, large portion of upper lip, upper nasal septum, turbinate &/or adjacent paranasal sinuses), fixed with deep muscle & bone involvement

particular importance in order to minimise the risk of recurrence.[975] When SCC is found histologically, management should be appropriate for this malignant diagnosis.

Surgery

A full description of surgical techniques is out of the scope of these guidelines; however, it is important that clinicians managing this condition are aware of the different options to best approach this disease. A number of different algorithms have been published to help inform surgical decision-making. We present one example, adapted from Naunheim *et al*.,[976] as an example guide for approaching this disease (Figure 1).

Craniofacial resection has long been held as the historical 'gold standard' method for ensuring adequate removal of anterior skull base tumours. However, endoscopic resection, facilitated by technological advances, has been shown to have equivalent long-term outcomes with less morbidity.[977] This has addressed potential criticisms of endoscopic piecemeal resections. Even in open surgery, a true en bloc resection is rarely achieved because of tumour and anatomical factors.

This body of evidence now supports a treatment paradigm that focuses on negative surgical margins rather than the method of resection or choice of surgical approach.[978] The surgical options available, tailored to a patient's needs, can be viewed as different combinations of facial and cranial access (Table 8), together with additional access approaches (e.g. lateral).

Post-operative histopathology should be reported to include at least core items, as for other head and neck cancers, and should be discussed within the MDT meeting. Surgical–pathological correlation is vital to understand resection margins. This is challenging for sinonasal cancers because of the anatomical complexity and the typical piecemeal nature of resection. Reliance on multiple margin specimens or biopsies is common, but there needs to be a high degree of confidence if a decision to not offer post-operative RT is based on the assumption of adequately clear margins.

Recommendations

- Involvement of an MDT with the correct cross-specialty skill mix is critical to devise an appropriate surgical plan, including, where necessary, input from restorative dentistry and prosthetics, neurosurgery, rhinology, and oculoplastic surgery (evidence-based recommendation (R))
- The surgical approach selected should maximise the chance of achieving an R_0 microscopically margin-negative resection (no residual tumour) (R)
- Surgical–pathological correlation discussed within an MDT meeting is vital to understand the completeness of excision (R)

Management of the eye

It is accepted that intraconal invasion, demonstrated clinically by visual loss, restriction of ocular mobility or globe infiltration, or by cross-sectional imaging, mandates exenteration. However, eye preservation in the presence of periorbita or even focal extraconal fat involvement remains controversial. Case series have reported high rates of orbital preservation and function.[979,980] However, published data are considerably heterogeneous,[981] and a nuanced approach based on experience and individual patient circumstances is required. It should also be considered that most patients who have surgery near to or within the orbit will undergo post-operative RT, and hence will experience the combined effects of both treatments. When there is orbital involvement and eye preservation is aimed for, oculoplastic surgery input is ideal.

Detailed long-term data on radiation-induced orbital effects are lacking. Up to 83 per cent of patients suffer post-treatment complications at five years.[982] De-intensification strategies related to eye preservation should therefore be adopted, ideally within a prospective clinical trial context.

Recommendations

- Orbital exenteration should be performed for intraconal invasion of sinonasal malignancy (evidence-based recommendation (R))
- Further prospective research is required for a histologically driven approach to eye conservation surgery (good practice point (G))

Radiotherapy and chemotherapy

Nasal vestibule cancers staged as T_1 can be treated with RT as a single-modality treatment.[983,984]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

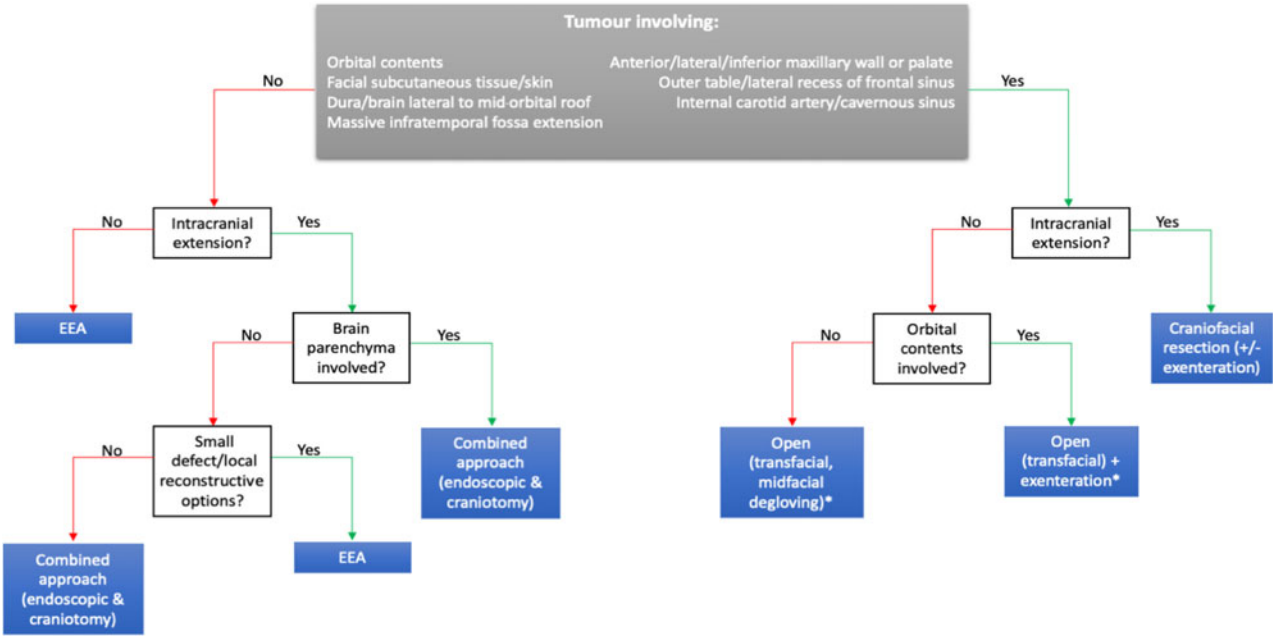


Figure 1. Flowchart for surgical approach to sinonasal or anterior skull base malignancy, adapted from Naunheim *et al.*[976] *Endoscopic assistance can be utilised in open approaches to: assess disease intra-operatively, perform targeted incisions (septum, lamina papyracea and skull base, pterygopalatine fossa) and facilitate repair. EEA = endoscopic endonasal approach

For other sinonasal cancers, definitive (chemo)radiotherapy can be considered for inoperable disease (approximately 20 per cent of patients) or in those who choose to avoid surgery.

There is very little data comparing definitive RT with surgery. The studies that have been published suggest comparable outcomes for SCC,[985] despite treatment selection bias. Salvage surgery is possible after definitive RT for residual disease (similar to laryngectomy after initial RT for T_3 laryngeal cancer, for example), although this is an uncommon treatment strategy, with little outcome data. For sinonasal undifferentiated carcinoma, definitive RT may be given after a significant response to induction chemotherapy avoiding surgery.[986]

Radiotherapy dose–volume coverage is complex because of the proximity of critical structures including the eye, optic pathway, base of skull, brainstem and brain. There is potential for severe late radiation toxicities, including ocular, auditory, olfactory, endocrine, sinus or neurocognitive dysfunction.[987] The use of intensity-modulated RT is the standard of care, whilst observational data from non-comparative studies suggest proton beam therapy may improve survival and late toxicity outcomes.[124,988]

Table 8. Summary of combinations of surgical approaches to paranasal sinuses and adjacent structures

Nasal access	Skull base access	± Additional access
Endoscopic	None required	None required
Mid-facial degloving & medial maxillectomy	Endoscopic	Lateral sub-temporal
Lateral rhinotomy & medial maxillectomy	Sub-cranial	Orbito-zygomatic approach
Via facial defect – orbital exenteration or rhinectomy	Via craniotomy	Transorbital
Via maxillectomy	Via craniectomy	

For post-operative RT, doses of 60–66 Gy in 30–33 fractions of 2.0 Gy, or equivalent, are used. For definitive RT, a dose of 70 Gy in 35 fractions of 2.0 Gy, or equivalent, is used. For post-operative volumes, the gross tumour volume refers to the macroscopic tumour prior to surgery (and, where used, the pre-chemotherapy tumour volume), based on pre-treatment magnetic resonance imaging (MRI) and computed tomography (CT) scans. The high-dose clinical target volume includes a 1 cm expansion from gross tumour volume edited for natural fascial, air and bone boundaries, and the lower-dose clinical target volume includes the surgical bed or resection cavity, surgical clips, and the ipsilateral sinonasal compartment of the involved sinuses. For definitive RT volumes, the gross tumour volume refers to the macroscopic tumour (where used, the pre-chemotherapy tumour volume). The high-dose clinical target volume includes a 0.5 cm expansion from the gross tumour volume, edited for natural fascial, air and bone boundaries, and the lower-dose clinical target volume includes a 1 cm expansion from the gross tumour volume and the ipsilateral sinonasal compartment of the involved sinus(es).

The basis for the use of concurrent chemotherapy is extrapolated from head and neck pharyngeal SCCs.[733,989] For sinonasal SCCs (and select other high-grade pathologies), concurrent cisplatin chemotherapy may be used in the definitive setting, and post-operatively, where there are less than 1 mm surgical margins or pathological extra-capsular extension of the nodes.

The role of cisplatin-based induction chemotherapy for locally advanced inoperable sinonasal SCC or high-grade pathologies remains to be established. It may be used where the tumour is in close proximity to critical organs, predominantly for a down-staging effect prior to definitive surgery or chemoradiotherapy.[990] For sinonasal undifferentiated carcinomas, there is often a significant response to induction chemotherapy, and treatment selection based on this response has been published in large series, with chemotherapy responders receiving RT without surgery.[986] A histology-driven approach

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

of induction chemotherapy followed by response-based treatment selection is an important area of current research.

Recommendations

- Most patients treated by primary surgery undergo post-operative RT (good practice point (G))
- The indications for concurrent chemotherapy are extrapolated from head and neck SCC in general (G)
- Induction chemotherapy should be considered for sinonasal undifferentiated carcinoma (G)

Management of the neck

Lymphatics directed to the upper jugular, perifacial and retropharyngeal nodes comprise the main drainage pathways, with levels I and II being the most commonly involved regions. Overall, less than 10 per cent of patients present with regional disease,[991] although nodal recurrence – which is highly dependent on histology and site – can occur in up to 33 per cent of patients. Table 9 indicates the major risk factors, with increasing cumulative incidence of nodal disease.[991]

Clinico-radiological nodal metastases are treated as for other head and neck cancers, by neck dissection for those having primary surgery, with or without post-operative (chemo) radiotherapy.

Elective treatment of the clinically node-negative neck, however, should be carefully considered depending on the risk factors involved. When an open surgical approach with free flap reconstruction is planned, elective neck dissection should be performed in conjunction with vessel exposure. Otherwise, elective neck irradiation for the above high-risk features should be considered, with the retropharyngeal and lower jugular (level IV) nodes included in the clinical target volume.[146] This approach has been shown to decrease the regional relapse rate to 5–10 per cent.[992,993]

The highest level of evidence for elective neck management in sinonasal undifferentiated carcinoma comes from a recent meta-analysis with a positive nodal rate at presentation of 16 per cent, with 26.9 per cent regional failure at two years,[994] advocating elective neck treatment with irradiation or neck dissection in locally advanced disease.

The role of elective neck treatment in other histological subtypes is more uncertain, but would appear to be unnecessary in low-grade pathologies.[995–997]

Recommendations

- Therapeutic neck treatment when there are clinical-radiological nodal metastases follows that for head and neck cancer in general, namely surgery (with or without post-operative (chemo)radiotherapy) or primary (chemo) radiotherapy (evidence-based recommendation (R))
- Elective neck treatment (generally bilateral) for the clinically staged node-negative (N_0) neck with irradiation or neck dissection is recommended for $T_{3/4}$ SCC and sinonasal undifferentiated carcinoma (R)
- There is insufficient evidence to support recommendations in other sinonasal subtypes, although elective neck treatment in high-grade tumours should be considered to reduce regional failure (good practice point (G))

Table 9. Risk factors for positive nodal disease

Maxillary sinus, especially with posterior wall invasion
Advanced tumour (T) stage
Primary tumour sized >4 cm
SCC or sinonasal undifferentiated carcinoma histology

SCC = squamous cell carcinoma

Reconstruction and rehabilitation

The aims of reconstruction serve two primary purposes, namely functional (separation of the intracranial cavity and sinonasal airspace; separation of the mouth, and nose or sinuses; creation of a barrier between sinonasal airspace and skin; orbital support), and aesthetic (addressing skin loss, facial contour deformity).

Although there is the potential for refinements later in the treatment pathway, reconstruction should be addressed at primary surgical planning and prior to adjuvant RT.

There are further details on maxilla and mid-facial reconstruction in Chapter 7 (on reconstructive considerations) and Chapter 13 (on restorative dentistry), which discuss extra-oral and oral prosthetics. Anterior skull base defects for reconstruction can be divided into four broad categories.

Skull base only (bone with or without dural defect)

There are a variety of choices for closure, ranging from non-vascularised fat or a fascial graft (inlay and/or onlay), often in conjunction with fibrin glue, or a multilayer closure with local nasoseptal flaps (after limited endoscopic resections) or a pericranial flap (after a bicoronal flap) if available.

Skull base plus facial defects and/or orbital exenteration

Local skin flap options are limited in volume to close the dead space, and local muscle options (e.g. temporoparietal flaps) are limited in reach to the central area. These can, however, be combined with osseo-integration for facial prostheses in patients not suitable for microvascular free flaps. Otherwise, the optimal approach is microvascular free tissue transfer, providing well-vascularised tissue with a suitable volume for dead space filling as well as skin for cutaneous reconstruction.

Skull base plus lower maxillary or palate defects

For large volume defects that result in communication from the oral cavity to the skull base (see Chapter 7), composite free tissue transfer is generally required. There should be enough tissue transfer to safely close off any skull base defect. Soft-tissue-only reconstructions will obturate the operative site, but tend to descend and retract with gravity, causing mid-facial ptosis, speech and swallowing issues as well as aesthetic concerns.

Frontal sinus and frontal bone reconstruction

If the inner table is resected, the sinus can be cranialised. If an open sub-cranial approach is used, the outer table is re-plated with the upper nasal bones. This can occasionally break down after RT (usually as a late effect). If ablation of both tables is necessary, the resulting through and through defect requires reconstruction. Soft tissue only at this site retracts and potentially descends. Osseous free flaps can be used for such defects with associated soft tissue, to protect pedicles from

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

aerodigestive tract secretions, close dural defects and fill any local dead space. Autogenous calvarial grafts or synthetic cranioplasty materials (titanium, polyetheretherketone ('PEEK') and so on) can be employed, but their non-vascularised nature may be complicated within irradiated fields.

Recommendations

- Early involvement of reconstructive and prosthetic specialists is vital to achieve optimal functional and cosmetic outcomes (evidence-based recommendation (R))

Follow up

Follow up should be guided by local and standard head and neck practice (Chapter 5). Support for those patients with functional and aesthetic defects is essential. Some patients will have on-going prosthetic intervention (intra-oral and extra-oral). In patients with orbital preservation, treatment effects are common, which can include epiphora, the effects of changes in globe position, and radiation-induced retinal and optic nerve damage and cataracts. Hence, ophthalmology input is required for this patient group.

Imaging by MRI of the primary site three to four months after treatment completion is standard practice for establishing a baseline for future comparison, as anatomy will usually be altered through treatment.[998] The positron emission tomography (PET)-CT will often be performed within three to four months of definitive radiation or systemic therapy, for assessment of treatment response and to identify any residual tumour.

It is worth noting that hypermetabolism following sinonasal malignancy treatment can be prolonged.[999] Additional re-imaging should be considered depending on baseline imaging findings, concerning signs or symptoms, risk of recurrence, and ease of clinical surveillance (e.g. after reconstruction when endoscopy is not reliable or possible). In most cases, imaging is an important component of surveillance.

Recommendations

- Baseline imaging by MRI of the primary site should be conducted around three to four months post-treatment, to allow for future comparison (evidence-based recommendation (R))
- Tumour surveillance is both clinical and radiological (R)

Recurrent tumours

Recommendations

- Many locally recurrent tumours are incurable. Careful selection for salvage surgery is recommended on the basis of prognosis and morbidity of salvage surgery (good practice point (G))

Most recurrences of sinonasal cancer after treatment are local. Local recurrences are prognostic for poor overall survival.[988] Surgery usually provides the only feasible treatment option. Recurrences should be assessed on a case-by-case basis. Tumours of high-risk histological subtype or grade (most types except lower grade salivary cancers and low-grade olfactory neuroblastomas), and/or with orbital and skull base involvement, have a very poor prognosis. Occasionally, limited additional surgery is appropriate. Local recurrences limited to the ethmoid sinus region have a better prognosis.[1000] Local recurrences of intestinal-type adenocarcinoma tumours are frequently localised, which may in part reflect the multifocality of this tumour, and many are suitable for endoscopic resection.[1001] Otherwise, radical salvage surgery involves significant morbidity, and clear margins are difficult to achieve.

There is a lack of evidence for immune-based targeted therapies in sinonasal malignancy. Despite programmed death-ligand 1 (PD-L1) positivity not appearing to have prognostic value, its use is likely to be extrapolated from other head and neck subsite protocols.

Studies due to report

'Docetaxel, Cisplatin and Fluorouracil in Treating Patients With Previously Untreated Stage II-IV Nasal Cavity and Paranasal Sinus Cancer' – a phase II trial of induction chemotherapy (docetaxel, cisplatin and fluorouracil) in patients with previously untreated stage II–IV nasal cavity and/or paranasal sinus cancer. Location: MD Anderson Cancer Center, Texas, USA.

'Prospective Sinonasal Cancer Multi-institution Study' – a multi-institution prospective study of patients with sinonasal malignancies, to study disease course, treatment outcomes and patient quality of life. Location: Mayo Clinic in Rochester, New York, USA.

'Intensity-Modulated or Proton Radiation Therapy for Sinonasal Malignancy' – a prospective, non-randomised, phase II study comparing local control and the toxicity profile of proton beam therapy and conventional intensity-modulated RT in advanced sinonasal malignancy. Location: Massachusetts General Hospital, Boston, USA.

Research questions

Is there a role for induction chemotherapy for specific sinonasal malignancies in addition to sinonasal undifferentiated carcinoma, e.g. for chemo-selection or as a pre-surgical organ preservation approach?

Is there a genomic or transcriptomic profile that will further help risk-stratify patients or predict treatment response? This will require a collaborative national or international sample collection given the disease rarity.

What is the role of charged particle therapy as a primary and adjuvant treatment modality compared to standard intensity-modulated RT in a phase III, prospective randomised, controlled trial?

Chapter 24: Salivary gland cancer

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

Malignant salivary gland tumours contribute to about 5 per cent of head and neck cancers, with an incidence of 8–13 per one million per year.[1002] Their relative rarity, diverse histopathology and heterogeneity of clinical behaviour mean that there are limited trial data from which to develop evidence-based management recommendations.

Tumour grade is an important factor to consider, as it relates to prognosis and treatment. As a general principle, surgery forms the mainstay of treatment. Adjuvant radiotherapy (RT) should also be considered for the majority of malignant salivary tumours (except small, low-grade tumours).

Presentation and diagnosis

Presentation

In general, malignant salivary gland tumours present either as painless, mobile lumps, or with an enlarging, painful, fixed mass, with or without facial palsy and regional lymph node spread. It is notable that most salivary gland malignancies present without signs of malignancy, i.e. without skin involvement, facial nerve weakness, short history, rapid growth, pain and/or paraesthesia, regional lymphadenopathy. These clinical features occur only in 25–35 per cent of parotid carcinomas.[1003] Therefore, all salivary gland masses must be carefully investigated to establish whether they are benign or malignant.

Table 1 describes data from three large UK series.[1004–1006] Although, overall, tumours are more common in the parotid; those that are malignant have a higher proportion in the submandibular, sublingual and minor salivary glands.[1007,1008]

Table 1. Site and malignancy rate in salivary gland tumours

Location	% of all salivary tumours	% malignant
Parotid	64–85	20–25
Submandibular gland	8–12	35–45
Sublingual gland	<2	75–90
Minor gland	9–25	50–60

Diagnosis

Recommendations

- Ultrasound-guided fine needle aspiration cytology (FNAC) or core biopsy are recommended for all salivary gland tumours (evidence-based recommendation (R))
- Both FNAC and core biopsy should be available (R)
- Magnetic resonance imaging (MRI) is the preferred axial imaging modality (good practice point (G))

Patients should be assessed in a rapid access clinic by appropriate clinicians with access to ultrasound and cytopathology (see Chapter 2). Every effort should be made to determine whether the tumour is benign or malignant before proceeding to surgical treatment. However, definitive exclusion of malignancy may only be possible following histological evaluation of the entirely excised tumour in some cases.

Fine needle aspiration cytology and core biopsy

Fine needle aspiration cytology and/or core biopsy should be considered in all salivary gland tumours. Fine needle aspiration cytology is less invasive, and can provide a diagnosis of neoplasia and may differentiate benign from malignant. The large number of salivary gland tumour entities, the morphological complexity and heterogeneity within a single neoplasm, the metaplastic changes and the absence of tumour architecture in cytology specimens limit the accuracy of FNAC. Fine needle aspiration cytology has a sensitivity of 67–98 per cent, a specificity of 82–100 per cent and accuracy of 81–99 per cent.[1009–1011] The current and most widely accepted reporting system for salivary gland cytopathology is the Milan system (Table 2).[1012]

Core biopsy in general is more helpful to assess tumour morphology and establish the type of tumour. A meta-analysis of ultrasound-guided core biopsies, mostly using 18–20 gauge spring-loaded needles, reported a pooled sensitivity of 94 per cent and a specificity of 98 per cent.[1013]

Occasionally, excision may be required for definitive tumour characterisation, but only if all efforts to establish a diagnosis fail. Similarly, open biopsy should be avoided if possible, given the risk of tumour seeding and spillage, but it has a role in fungating tumours.

Minor salivary gland tumour biopsies may be taken by skin punch or incision biopsy.

Frozen section

The indications of frozen sections for intra-operative diagnosis are highly limited and its routine use is discouraged. Occasionally, however, intra-operative frozen section may be considered in cases where attempts at cytological diagnosis have failed on at least two occasions, and may help to stratify the risk of malignancy and extent of surgery in such cases.[1014,1015]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Milan system for reporting salivary gland cytopathology

Diagnostic category	Description	Management
I	Non-diagnostic	Clinical & radiological correlation; repeat FNA
II	Non-neoplastic	Clinical follow up & radiological correlation
III	Atypia of undetermined significance	Repeat FNA or surgery
IV A	Benign neoplasm	Surgery or clinical follow up
IV B	Salivary gland neoplasm of uncertain malignant potential	Surgery
V	Suspicion of malignancy	Surgery
VI	Malignant	Surgery

FNA = fine needle aspiration

Table 3. Tumour staging for major salivary gland tumours*

Tumour (T) stage	Description
– T_X	Primary tumour cannot be assessed
– T_0	No evidence of primary tumour
– T_1	Tumour sized ≤2 cm in greatest dimension, without extra-parenchymal extension
– T_2	Tumour sized >2 cm but ≤4 cm in greatest dimension, without extra-parenchymal extension
– T_3	Tumour sized >4 cm &/or with extra-parenchymal extension†
– T_{4a}	Tumour invades skin, mandible, ear canal &/or facial nerve
– T_{4b}	Tumour invades skull base &/or pterygoid plates, &/or encases carotid artery

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[1016]
†Extra-parenchymal extension refers to clinical or macroscopic evidence of soft tissue invasion; microscopic evidence alone does not constitute extra-parenchymal extension for classification purposes.

Imaging

Ultrasound imaging is a key part of the initial assessment of major salivary gland tumours, assisting with staging and tissue sampling. Ultrasound should be used to guide needle aspiration or core biopsy in nearly all major salivary gland tumours, and may assist with the assessment of regional adenopathy.

When malignancy is suspected or confirmed, contrast MRI is the preferred axial imaging modality, although computed tomography (CT) is an alternative and can characterise bone invasion in locally advanced tumours. For tumours that are thought to be malignant, CT scanning of the thorax, or positron emission tomography (PET)-CT, are used to assess for distant metastases.

Carcinomas of minor salivary glands are imaged as tumours of the lip and oral cavity.

Recommendations

Recommendations for different imaging modalities:

- Primary major salivary gland – MRI with or without CT
- Regional neck – MRI or CT
- Distant – CT or PET-CT (the latter can be considered for high-grade disease or when there is significant nodal disease)

Staging

The eighth edition of the *TNM Classification of Malignant Tumours* staging system for salivary gland primary tumours is unchanged from the seventh edition (Tables 3–5).[1016] Carcinomas of minor salivary glands are staged according to tumours of the lip and oral cavity.

Pathology, classification and tumour biology

Recommendations

- All treatment centres should have access to diagnostic molecular testing (good practice point (G))
- Consider pathology review when initial biopsy or surgery conducted outside of the treatment centre (G)

Salivary gland tumours are a heterogeneous group. Detailed description of salivary gland tumour pathology is beyond the scope of this guideline. New tumour subtypes have been identified, largely based on molecular alterations, rearrangements and fusions, leading to the existence of a new 'molecular gold standard'. The World Health Organization (WHO) 2022 classification of head and neck tumours incorporates some new entities (Table 6).[1017] The classification contains a category 'Salivary carcinoma not otherwise specified (NOS) and emerging entities', which includes some poorly differentiated carcinomas and oncocytic carcinomas.

Histological grading of salivary gland carcinomas can serve as an independent predictor of biological behaviour, prognosis and outcome, which may help optimise therapy. A positive correlation between histological grade and clinical stage has been consistently identified.[1018,1019]

Examples of salivary gland neoplasms that are typically low-grade include acinic cell carcinoma, basal cell adenocarcinoma, epithelial-myoepithelial carcinoma, secretory carcinoma and clear cell carcinoma. Myoepithelial carcinoma is typically of intermediate grade. Salivary duct carcinoma, lymphoepithelial carcinoma, small cell and large cell neuroendocrine carcinoma, large cell undifferentiated carcinoma, primary squamous cell carcinoma, and carcinosarcoma are typically high-grade. Some tumours, such as mucoepidermoid carcinoma, adenoid cystic carcinoma, intraductal carcinoma, carcinoma ex pleomorphic adenoma and adenocarcinoma not otherwise specified, can show variable grades.

A solid and highly infiltrative growth pattern can also be a feature of high-grade transformation in otherwise typically low-grade salivary gland malignancies.

Treatment

Recommendations

- Wide local excision achieving clear margins is the principle surgical operation for most submandibular gland cancers (evidence-based recommendation (R))
- Total parotidectomy with preservation of facial nerve function is the principle of treatment for most parotid cancers (R)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Nodal staging for major salivary gland tumours*

Nodal (N) stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node, sized >3 cm but not more than 6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized >3 cm but not more than 6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, any with extra-nodal extension Or metastasis in a single contralateral node of any size & with extra-nodal extension

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[1016]

Table 5. Group staging for major salivary gland tumours*

Group stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	T_{1-3}	N_1	M_0
IVA	T_{1-4a}	N_2	M_0
	T_{4a}	N_{0-1}	M_0
IVB	Any T	N_3	M_0
	T_{4b}	Any N	M_0
IVC	Any T	Any N	M_1

*According to the *TNM Classification of Malignant Tumours* (eighth edition).[1016]

Table 6. WHO classification of salivary gland tumours (2022)[1017]

Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Acinic cell carcinoma
Secretory carcinoma
Microsecretory adenocarcinoma
Polymorphous adenocarcinoma
Hyalinising clear cell carcinoma
Basal cell adenocarcinoma
Intraductal carcinoma
Salivary duct carcinoma
Myoepithelial carcinoma
Epithelial-myoepithelial carcinoma
Mucinous adenocarcinoma
Sclerosing microcystic adenocarcinoma
Carcinoma ex pleomorphic adenoma
Carcinosarcoma of salivary glands
Sebaceous adenocarcinoma
Lymphoepithelial carcinoma
Squamous cell carcinoma
Sialoblastoma

WHO = World Health Organization

- In general, if facial nerve function is normal pre-operatively, and is not involved or encased by the tumour, the facial nerve function should preserved (good practice point (G))
- Resection of facial nerve branches should be undertaken where there is pre-operative and/or intra-operative evidence of nerve invasion by the cancer (R)
- Clinically staged node-positive (N_+) neck – neck dissection should be performed (R)
- Clinically staged node-negative (N_0) neck – high or intermediate or indeterminate grade disease – selective neck dissection should be performed as elective treatment (R)
- Clinically staged N_0 neck – low-grade tumours – elective selective neck dissection should be considered (G)
- The standard indications for post-operative RT (see Chapter 4) apply to salivary gland cancers (R)
- Additional considerations specific to salivary gland cancers include all stage 3/4 tumours, high-grade cancers and adenoid cystic carcinoma (G)

Surgery

Surgery is the treatment of choice for resectable salivary gland cancers. As with all cancers, it is important to achieve clear resection margins.[1007,1020] Whilst head and neck malignancies are typically resected with a margin of up to 1 cm in order to achieve a 5 mm pathological margin (where anatomical and functional considerations permit), in salivary gland cancers,

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

the optimal resection margin has not been established in a randomised study, and close margins may not necessarily adversely affect the oncological outcome.[1021] Attaining an uninvolved closest resection margin is balanced against the need for the preservation of function and cosmesis and preservation of the facial nerve. A close resection margin, therefore, is not uncommon.

Submandibular gland

Wide excision is appropriate for tumours confined to the gland, combined with neck dissection. Some argue in favour of a wider resection for adenoid cystic carcinoma, but even with radical surgery it is frequently difficult to obtain adequate surgical margins.[1022] It should be noted that the advice for radical surgery in submandibular gland malignancy is at variance with recommendations for the preservation of the uninvolved facial nerve in parotid malignancy. However, it is generally accepted that high-grade tumours should be treated aggressively, involving excision of the gland with wider resection margins and with the resection of involved nerves if necessary. Large infiltrative tumours with bony involvement are treated with composite resection of the tumour, adjacent soft tissue cuff and segmental mandibulectomy.

Parotid gland

Surgery is the treatment of choice for malignant parotid tumours, with the extent of surgery tailored to the individual tumour. In general, a conservative total parotidectomy with preservation of facial nerve function is the principle of treatment for most lesions, except for small, low-grade malignancies which may be treated by a partial or superficial parotidectomy.

The facial nerve is a critical structure that limits the margin of resection in parotid malignancies. If there is a facial nerve palsy pre-operatively, the facial nerve should be resected, with frozen section evaluation of surgical margins to ensure adequate clearance.

If there is a plane of dissection between the functioning nerve and tumour, the surgeon should undertake facial nerve preservation. If it is evident that the facial nerve is invaded or encased by a confirmed cancer, the involved trunk or branches should be resected to optimise local tumour control. Where facial nerve resection forms part of a planned resection of parotid carcinoma, the ablative procedure should be accompanied by planned reconstructive procedures including nerve grafting and/or slings. The eye should be protected and assessed for any procedures at a later date.

It should be noted that resection of the uninvolved facial nerve in adenoid cystic carcinoma has been shown not to affect local control.[1023]

Inadvertent injury to the facial nerve should be repaired as soon as possible, ideally at the time of tumour resection. Direct microsurgical repair without tension, or a cable nerve graft, offer the best chance of recovery. Facial re-animation techniques may be considered if specialist input is available.

More extensive parotidectomy should be undertaken in locally advanced cancers invading extra-parotid structures (e.g. lateral skull base – see Chapter 25).

Minor salivary glands

Tumours of the minor salivary glands have been reported to have a worse oncological outcome compared to parotid and submandibular gland malignancies.[1024] The outcome is worse for occult sites such as the nasal cavity, nasopharynx, larynx and trachea.

Most cases are treated in a similar way to squamous cell carcinoma, with en bloc resection, with the depth of excision compatible to treatment of squamous cell carcinoma, to ensure adequate resection margins. Significant defects are reconstructed as appropriate with local or free flaps.

Neck metastases

Clinically node-positive (N_+) disease

Patients with confirmed neck metastases should have a therapeutic neck dissection. The levels of neck dissection will be influenced by the primary tumour site and stage, histological subtype and grade.

For a parotid primary tumour, the neck dissection should include at least levels IIA, III and IV,[1025] and consideration should be given to the dissection of adjacent uninvolved levels.

For submandibular gland primary tumours, the neck dissection should include at least levels Ia, IIa and III. Again, consideration should be given to the dissection of adjacent uninvolved levels.

Clinically node-negative (N_0) disease

The evidence base for the management of a clinically N_0 neck is poor. The frequent lack of knowledge of the histological subtype and grade pre-operatively is a complicating factor in deciding on the appropriate management.[1026] Clinical staging underestimates the rates of regional lymph node metastases, with the rate of occult lymph node spread being 23 per cent in elective neck dissections in one pooled analysis[1027,1028] and 34 per cent for high-grade cancers in another.[1029] Elective neck dissection should be performed in the presence of adverse features, a high-grade and an advanced stage.[1030]

Neck dissection should include levels Ia, IIa, IIb and III for parotid primary tumours, and levels I, IIa and III for submandibular gland primary tumours.[1025]

In low-grade tumours, with clinically staged N_0 necks, the same elective neck dissection should be considered in most cases, but the decision-making may be more nuanced, e.g. with more selective (less extensive) elective neck dissections.

When a malignant diagnosis is not known or suspected before or at surgery, the clinically staged N_0 neck may be addressed by RT and/or re-operative neck dissection, but any elective reoperation should not delay RT.

Post-operative radiotherapy

Adjuvant RT improves survival in patients with early- and advanced-stage salivary gland cancers, according to an analysis of 8580 patients from the US National Cancer Database, whilst concurrent chemotherapy did not improve outcome.[1031]

The decision for RT should be made after discussion at the specialist multidisciplinary team (MDT) meeting. The standard indications for post-operative RT (see Chapter 4) apply to salivary gland cancers. Additional considerations specific to salivary gland cancers include all stage 3/4 tumours, high-grade cancers and adenoid cystic carcinoma.

Hence, adjuvant RT is recommended in cases including:

- High-grade tumours
- Advanced-stage tumours (stage 3/4 tumours)
- Involved resection margins (R1–2, microscopic or macroscopic residual tumour)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Perineural invasion
- Lymphovascular invasion
- Extra-nodal extension
- Following revision resection
- Adenoid cystic carcinoma

Radiotherapy is not required for small, low-grade tumours that have been completely excised.

Recurrent malignant parotid gland tumours

This situation requires careful evaluation of the patient with repeat imaging and a review of the histology from the initial excision. Treatment will usually require more radical surgery, with sacrifice of the facial nerve and overlying skin if there is any suspicion of involvement by the tumour. Radical resections of the skull base have not to date shown convincing evidence of improved survival. Where an R0 resection (no residual tumour) is considered not achievable, surgery should not be attempted. Chemotherapy, RT and drug trials should be considered for palliation.

Post-treatment surveillance

Patients should be followed up for at least five years, in keeping with MDT protocols. In salivary gland malignancies with adverse features, the survival curves tend to begin to plateau towards 10 years rather than 5 years, and follow up should be considered for longer. Ultrasound may be a useful supplement to clinical follow up. Baseline CT, MRI or PET-CT imaging at three months may be useful for comparison if there is a suspicion of recurrent disease at a later stage.

There is no consensus regarding chest imaging as part of follow up for cancers that have a predilection for distant metastases to the lungs (e.g. adenoid cystic carcinoma). There are ongoing trial therapies for metastatic salivary tumours and, whilst their efficacy is as yet not proven, detection of distant metastases.

Benign tumours

When treatment is considered, surgery is the treatment of choice. For benign tumours of the submandibular gland, the gland should be excised in a supracapsular plane. A wide dissection of local tissues is not required.

For benign parotid tumours, resection of the tumour should be performed without breach of the tumour capsule and with preservation of the facial nerve. There is no consensus within the literature as to the extent of resection. Procedures include: formal superficial parotidectomy, partial parotidectomy and extra-capsular dissection. The extent of surgery is largely determined by the location and size of the tumour, and by the preference of the operating surgeon. There is a trend towards reducing the extent of the resection with the proviso of preserving the tumour capsule and facial nerve function. The facial nerve is often in close proximity to the tumour, thereby not infrequently leading to close margins on final histology assessment. It is important to avoid tumour rupture, by careful dissection.

Tumour spillage carries with it an increased rate of tumour recurrence over a prolonged period.[1032] Tumour spillage may be frank and noted at the time of surgery, or more commonly noted on the final histology report. If tumour spillage has been noted, consideration should be given to long-term follow up, and the case should be discussed in the MDT meeting as there is a potential role for RT in a select few cases. Radiotherapy is generally not indicated for the majority of cases of tumour spillage and is generally not recommended in younger patients because of the risk of radiation-induced tumours.

Recurrent benign tumours require careful investigation, including ultrasound with fine needle aspiration (FNA) and MRI imaging. Treatment is usually surgical excision of the recurrent tumour with preservation of facial nerve function, to include resection of all recurrent nodules. In some cases, surgical excision of isolated tumour nodules may suffice. Recurrence is often multifocal, and re-recurrence is therefore common given the challenges of excising all of the recurrent nodules. Therefore, adjuvant RT should be considered for such cases in the MDT meeting.

Additional considerations regarding specific tumour histological types

Commoner histological types

Mucoepidermoid carcinoma

- Most common major salivary gland tumour (4–9 per cent) (including in children), with over 90 per cent occurring in the parotid gland.
- These tumours have a variable grade.
- Histopathological division into low, intermediate and high grades correlates somewhat with prognosis; although low-grade tumours can on occasion metastasise to cervical lymph nodes. Five-year survival rates vary between 86 per cent for low-grade and 22 per cent for high-grade tumours.
- Treatment guidelines vary according to grade.

Adenoid cystic carcinoma

- Accounts for 25 per cent of malignant salivary gland tumours – all major glands and minor glands.
- Slow, pervasive growth and a high incidence of perineural infiltration which can cause pain.
- Predilection for distant pulmonary metastases.
- Variable histological appearance. It can be difficult to correlate with clinical behaviour, although, in general, tubular and cribriform patterns are associated with a better prognosis than solid pattern tumours. Tumours with NOTCH1 mutation have a poorer prognosis than tumours with MYB or MYB1 and/or NFIB translocations.[1033]
- Szanto *et al.*[1034] and Perzin *et al.*[1035] described a commonly used grading scheme: grade 1 – predominantly tubular, no solid component; grade 2 – predominantly cribriform, less than 30 per cent solid component; and grade 3 – solid component of more than 30 per cent.
- Only 20 per cent of patients with pulmonary metastases survive more than five years.
- Stage I and II cancers may be cured, although the survival curve never flattens, even after 20 years. Long-term follow up is recommended because there is a high late recurrence rate. Stage III and IV disease is associated with a poor prognosis, with low survival rates at 10 years.
- There are insufficient data to clarify whether pulmonary metastectomy (and therefore chest imaging surveillance) is beneficial in some patients.

Acinic cell carcinoma

- Around 3 per cent of parotid tumours

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

- Usually low grade
- Can be multifocal in origin and occasionally bilateral
- Survival rates of 90 per cent at 5 years and 55 per cent at 20 years
- Lymph node metastases occur in approximately 10 per cent of cases
- Treatment is in keeping with grade and size of tumour

Adenocarcinoma not otherwise specified

- This uncommon tumour is most frequently (90 per cent) found in the parotid gland.
- It has a variable grade; histological appearance varies between low-grade, well-differentiated papillary or mucinous patterns, to high-grade, undifferentiated lesions.
- The incidence of distant metastases is 40 per cent for high-grade tumours, and is directly related to survival rates (five-year survival rate of 75 per cent for low-grade tumours and 19 per cent for high-grade tumours).
- Treatment is usually as for high-grade salivary cancer, unless proven low-grade and small.

Carcinoma ex pleomorphic adenoma

- Carcinoma ex pleomorphic adenoma is a broad category of carcinomas of the salivary glands that often pose a diagnostic challenge to clinicians and pathologists.
- Carcinoma ex pleomorphic adenoma are carcinomas with histological, molecular or historic evidence of arising in or from a primary or recurrent pleomorphic adenoma.
- These tumours are classified as in situ carcinomas, non-invasive or intracapsular, and minimally invasive (less than 4–6 mm) or invasive. The extent of invasion is an important prognostic factor; the clinical behaviour of non-invasive tumours is similar to that of pleomorphic adenoma with a good prognosis, whilst tumours extending more than 6 mm have been shown to have a poor prognosis.
- Different patterns of malignant change can occur in carcinoma ex pleomorphic adenoma, with the other types being a carcinosarcoma and metastasising pleomorphic adenoma. The malignant component is most often salivary duct carcinoma, but can also be adenocarcinoma not otherwise specified, adenoid cystic or mucoepidermoid carcinoma.
- The remainder are probably not a homogeneous group of tumours, and may occur *de novo* rather than following a malignant generation of pleomorphic adenoma.
- Locoregional recurrence is considered to be an important prognostic factor with a poor prognosis after detection of recurrence. The reported survival rate at 5 years is 30–40 per cent, dropping to 20 per cent at 15 years.

Squamous cell carcinoma

- Squamous cell carcinoma affecting the parotid gland is a rare primary tumour, and is usually one or more regional lymph node metastases from a current or previous cutaneous squamous cell carcinoma of the scalp or face including the nasal cavity and ear canal.
- It tends to occur in older adults (seventh and eighth decades of life).
- It is associated with poor prognosis and should be treated in a similar fashion to high-grade cancers.
- The five-year disease-specific survival rate is about 25 per cent, with high rates of distant metastasis.

New malignant tumour entities and recent modification of terminology

Secretory carcinoma

Formerly known as mammary analogue secretory carcinoma, this salivary gland adenocarcinoma is characterised by *ETV6* gene rearrangement and is composed of intercalated duct-type cells; 70 per cent of the tumours have been described in the parotid gland, followed by 20 per cent in the minor salivary glands of the oral cavity and 8 per cent in the submandibular gland.

Most cases of secretory carcinoma are low-grade, and present as a slow-growing, painless, well-demarcated mass with a possible cystic component. Up to 25 per cent of cases can develop lymph node metastasis. Lymphovascular and perineural invasion are uncommon. Architectural patterns within the tumour can vary and are similar to acinic cell carcinomas. Distant metastases and tumour-related deaths are rare, except in rare cases with high-grade transformation.

Microsecretory adenocarcinoma

These tumours were previously reported as a low-grade variant of adenocarcinoma not otherwise specified. Given the small number of cases identified as microsecretory adenocarcinoma, data on prognosis and overall survival are currently limited.

Sclerosing microcystic adenocarcinoma

Sclerosing microcystic adenocarcinoma has also been described. It resembles microcystic adnexal carcinoma of the skin, showing an infiltrative duct forming tumour and syringoma-like formations. Most cases occur in the oral cavity. This is classed as a low-grade variant of adenocarcinoma not otherwise specified spectrum.

Intraductal carcinoma

This refers to a malignant salivary gland tumour where all salivary proliferations are entirely or predominantly intraductal in location. This entity was previously known as low-grade salivary duct carcinoma and low-grade cribriform cystadenocarcinoma. It is predominantly seen in the parotid gland. Subtypes include: intercalated duct-type and oncocytic, both of which are rarely associated with invasion; apocrine type, which can show low- or high-grade cytomorphology; and mixed intercalated duct-apocrine tumour.

Intraductal carcinoma without invasion has an excellent prognosis following complete surgical excision, requiring no adjuvant therapy. Apocrine intraductal carcinoma with invasion has a poorer prognosis. A diagnosis of intraductal carcinoma on a core biopsy means that the tumour needs to be excised with caution, and the clinician should be made aware of the possibility that an invasive component could be present in the excision specimen.

Polymorphous adenocarcinoma

Previously named polymorphous low-grade adenocarcinoma, this is a malignant tumour. It is usually low-grade, but some – known as cribriform adenocarcinoma of the salivary gland – have behaved more like high-grade tumours. Cribriform adenocarcinoma may be considered an emerging new tumour entity. It demonstrates a predilection for the tongue base, and has an up to 65 per cent risk of nodal metastases.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Future research

Clinical trials in the management of salivary carcinoma are a particular challenge because these cancers are rare. Working towards meaningful trials in this area, the establishment of tumour registries on a prospective basis would provide a foundation for future trial design. This would provide accurate observational data and allow outcome comparison, and hence facilitate the development of research questions and trial design for this rare and diverse tumour group. Widespread collaboration – an increasing trend in head and neck surgical research in the UK – will be necessary to provide these processes and data.

Chapter 25: Management of thyroid cancer

Table of Contents

Introduction

Thyroid cancer is an uncommon malignancy, with an incidence in the UK of approximately 8 per 100 000 women and 3 per 100 000 men.[1036] Evidence suggests an increasing incidence due to increased rates of detection; however, the survival rates remain static. Thyroid nodules are common, with 50–70 per cent of the general population showing ultrasound evidence of nodules.

The long-term prognosis for differentiated thyroid cancer, which includes papillary and follicular subtypes, is excellent, with a survival rate for adults of over 90 per cent at 10 years' follow up.[1037] However, up to 20 per cent of patients develop locoregional recurrence requiring further treatment, and 5 per cent go on to develop distant metastases. Recent improvements in the understanding of biology have led to a move away from aggressive treatment of differentiated cancers, based on appropriate initial and subsequent dynamic risk stratification associated with the response to initial therapy.

Medullary and anaplastic thyroid cancers are rare and more aggressive. A structured approach to the assessment and management of these conditions is essential to optimise outcomes for these patients. The main types of thyroid cancer are summarised in Table 1.[1038]

The primary treatment of most thyroid carcinomas is surgical, with radio-iodine therapy for many patients after total thyroidectomy. Advancements in targeted therapies now offers hope to even those with recurrent, radio-iodine resistant disease, and anaplastic cancers.

There have been several detailed guidelines published on the diagnosis and management of thyroid cancer.[1039] Three key ones are the guidelines for thyroid cancer management (2014) by the British Thyroid Association,[1040] the revised American Thyroid Association Management Guidelines (2016)[1041] and, most recently, the National Institute for Health and Care Excellence (NICE) Guideline NG230 (2022).[1042] Given differences in presentation, pathophysiology and outcomes, separate guidelines exist for children with differentiated thyroid cancer.[1043]

Clinical presentation and referral

Patients generally present with a thyroid lump or mass, or lymph node metastasis. Many cancers are also detected as incidental findings on imaging performed for unrelated reasons.

Clinical features associated with an increased risk of malignancy in individuals with a thyroid nodule (and which should be referred urgently as suspected cancer) include:

- Stridor
- Presentation at the extremes of age (less than 18 years or 70 years or more)
- Rapid growth over a period of weeks
- Fixation to adjacent structures
- Voice change due to vocal fold paralysis
- Associated lymphadenopathy
- History of neck or upper body irradiation
- Strong family history of thyroid cancer

As the majority of thyroid nodules are benign, in the absence of the above 'red flags', urgent (suspected cancer) referral is not indicated.

Assessment

Recommendations

- Ultrasound scanning of the thyroid and cervical lymph nodes is mandated in the investigation of thyroid nodules and masses (evidence-based recommendation (R))

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Pathological characteristics of thyroid cancer[1038]

Cancer type	Proportion of thyroid malignancy (%)	Predominant pattern of metastasis	More aggressive variants
Papillary carcinoma	70	Lymph node (a small proportion develop late systemic disease)	Tall cell variant Columnar cell variant Diffuse sclerosing variant Hobnail cell variant
Follicular carcinoma	15	Systemic	Widely invasive follicular thyroid cancer
Hürthle cell carcinoma	5	Systemic	
Poorly differentiated carcinoma	<5	Lymph node & systemic	
Anaplastic carcinoma	<5	Locally aggressive, lymph nodes, systemic	
Medullary carcinoma	<5	Lymph node & systemic	

- Thyroid nodules should be classified using a recognised system such as the European Thyroid Association Thyroid Imaging Reporting And Data Systems (EU-TIRADS) or by ultrasound 'U' grading (R)
- Fine needle aspiration cytology should be carried out under ultrasound guidance (R)
- Fine needle aspiration cytology should be performed for all nodules with potentially suspicious ultrasound features (EU-TIRADS score of 4 or more; or 'U' grades of U3–U5) and for patients with risk factors for malignancy (R)
- Cytological analysis and categorisation should be reported according to the current Royal College of Pathologists guidance (R)
- Ultrasound assessment of cervical nodes should be performed in fine needle aspiration cytology (FNAC)-proven cancer (R)
- Contrast-enhanced cross-sectional imaging should be carried out in suspected cases of retrosternal extension, when there are bulky lateral nodal metastases or when there is suspicion of locally invasive disease (good practice point (G))
- For patients with Thy 3f or Thy 4 FNAC, a diagnostic hemithyroidectomy at least is recommended (R)

The key elements of investigation are as follows, not all of which may apply to any given patient:

- Palpation of the neck including assessment of potential retrosternal extension.
- Fibre-optic laryngoscopy if there is airway compromise or voice change (and pre-operative laryngoscopy if surgery is indicated – best practice).
- Blood tests: thyroid-stimulating hormone (TSH); autoantibody status if thyroiditis is suspected and/or to assist with indeterminate FNAC; calcitonin – only in suspected cases of medullary thyroid cancer (e.g. family history, or after imaging or cytology); and bone profile including vitamin D (if surgery is contemplated).
- Ultrasound of the neck.
- Fine needle aspiration cytology under ultrasound guidance depending on ultrasound findings (see below).
- Computed tomography (CT) scan of the neck and thorax if retrosternal extension is suspected, or for selected cases of confirmed or suspected cancer (see below).

Ultrasound and fine needle aspiration cytology of thyroid nodules

The crucial diagnostic investigations for a thyroid nodule or mass are ultrasound and, when indicated, FNAC, under ultrasound guidance for optimal accuracy.[1044] The 2014 British Thyroid Association guidelines for thyroid cancer management recommend the U grading system.[1040] However, the 2022 NICE guidance simply recommends using an established system for grading ultrasound appearance.[1042] Ultrasound imaging should include assessment of cervical lymph nodes.

A description of the 'U' grading system can be found in the 2014 British Thyroid Association guidelines.[1040] The EU-TIRADS classification system is described by Russ *et al.*[1045] Nodules graded as U2 or with an EU-TIRADS score of less than 4 can be considered benign and do not require FNAC in the absence of risk factors (i.e. family history, radiation exposure, fluoro-deoxy-glucose (FDG) avidity for incidental nodules, symptoms (e.g. growth) or signs (e.g. vocal fold palsy)). Such patients do not require further management for suspected or possible thyroid cancer.

Further management is then determined largely by cytopathology, which should be reported using the Royal College of Pathologists' thyroid classification (Table 2).[1046] When a repeat sample is required, the 2022 NICE guidelines advocate core needle biopsy as an alternative to repeat FNAC, particularly for Thy 3a lesions.[1042] These guidelines also advocate considering further investigation of Thy 2 nodules (by repeat ultrasound scan, with or without core needle biopsy or FNAC) before discharge, although this is not widely adopted presently.

Fine needle aspiration cytology should also be carried out on any abnormal lymph nodes.

Thy 1 and Thy 2 can be further classified into Thy 1c and Thy 2c for cystic lesions. In a pure or simple cyst on ultrasound, a Thy 1c cytology may be considered definitive.

Immunohistochemistry on FNAC material and/or core biopsy may be helpful for confirmation of the type of suspected malignancy in the thyroid or in a lateral neck lymph node, particularly if metastasis to the thyroid is considered, or if there is suspicion of de-differentiated disease, anaplastic thyroid carcinoma or lymphoma. In some very limited circumstances, *BRAF V600E* molecular testing of FNAC or core biopsy material may be useful, to confirm a diagnosis of carcinoma on pre-operative FNAC or needle core biopsy. More extensive molecular testing of cytologically indeterminate

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Cytopathology classification of thyroid nodules

Thy classification	Description	Risk of malignancy (%)[1046]	Management options
1	Non-diagnostic	12	CNB or repeat FNAC
2	Non-neoplastic	5	Consider repeat ultrasound scan, ± CNB or repeat FNAC Discharge patient
3a	Neoplasm possible – atypia	27.5	CNB or repeat FNAC If 2nd FNAC or CNB indicates Thy 3a, consider hemithyroidectomy
3f	Possible follicular neoplasm	31	Hemithyroidectomy
4	Suspicion of malignancy	79	MDT discussion of surgery: hemithyroidectomy or definitive treatment, as below
5	Malignant	98	MDT discussion & staging; further investigations where indicated Definitive thyroid cancer surgery (hemi- or total thyroidectomy) with neck dissection where indicated

CNB = core needle biopsy; FNAC = fine needle aspiration cytology; MDT = multidisciplinary team

thyroid nodules (e.g. Afirma®, Veracyte® or ThyroSeq®), although utilised overseas, has not become standard practice in the UK. Other proposed strategies for risk stratification include utilising the presence of nuclear atypia or ultrasound characteristics.

Computed tomography / axial imaging

Computed tomography of the neck and thorax should be carried out in cases with suspected retrosternal extension, tracheal compression or invasion. It can be considered for complete systemic staging and the evaluation of mediastinal disease for $T_{3–4}$ tumours, for tumours with aggressive features, and in cases with bulky or multiple cervical lymph node metastases, with NICE guidance stating it can be considered for N_1 disease.

Borderline neoplasms of the thyroid gland

A non-invasive follicular thyroid neoplasm with papillary-like nuclei, a follicular tumour of uncertain malignant potential and a well-differentiated tumour of uncertain malignant potential[1047] cannot be reliably diagnosed pre-operatively, although a non-invasive follicular thyroid neoplasm with papillary-like nuclei may be suspected by ultrasound or FNAC findings. These lesions require meticulous pathological assessment, typically after diagnostic hemithyroidectomy. *BRAF V600E* mutation assessment may be helpful, as a non-invasive follicular thyroid neoplasm with papillary-like nuclei does not show *BRAF V600E* mutation. The UK incidence of a non-invasive follicular thyroid neoplasm with papillary-like nuclei is low (estimated as below 5 per cent of all newly diagnosed malignant thyroid lesions).[1048] These lesions are not regarded as malignant and need no further management after hemithyroidectomy. The need for and extent of follow up or surveillance varies and is not evidence-based.

Staging

The tumour, nodes and metastases (*AJCC Cancer Staging Manual*, eighth edition) staging system[87] (Tables 3–6)[1049,1050] is used to stage thyroid cancers; this should be used in all cases prior to treatment, and may change based on intra-operative findings or the post-operative pathology. Post-operatively, 'R' is used to describe the adequacy of surgical margins (R1, microscopic residual disease; R2, macroscopic residual disease), although interpretation of this requires communication between pathologist and surgeon. The main changes in the eighth edition of the *AJCC Cancer Staging Manual* centre on downstaging more patients into lower stages than reflect their better prognosis. This includes the selection of age cut-off criterion to 55 years rather than 45 years.

Table 3. Tumour staging for differentiated and medullary thyroid cancer with relationship to overall disease stage*

Tumour (T) stage	T criteria†
T_X	Primary tumour cannot be assessed
T_0	No evidence of primary tumour
T_1	Tumour ≤2 cm
T_{1a}	Tumour ≤1 cm
T_{1b}	Tumour >1 cm but ≤2 cm
T_2	Tumour >2 cm but ≤4 cm
T_3	Tumour >4 cm limited to thyroid, or gross extra-thyroidal extension involving straps only
T_{3a}	Tumour >4 cm limited to thyroid
T_{3b}	Tumour has gross extra-thyroidal extension involving strap muscles only
T_4	Gross extra-thyroidal extension into major neck structures
T_{4a}	Gross extra-thyroidal extension into soft tissues, larynx, trachea, oesophagus or recurrent nerve
T_{4b}	Gross extra-thyroidal extension into prevertebral fascia, carotid artery or mediastinal vessels

*According to the *AJCC Cancer Staging Manual* (eighth edition).[87] †All may be solitary ('s') or multifocal ('m') – the largest tumour determines the classification

Thyroid surgery

Surgeons performing operations for confirmed or suspected thyroid cancer should be core members of the thyroid cancer multidisciplinary team (MDT) and should perform a minimum of 20 thyroidectomies per year.[1051] Complex surgery and lymph node surgery should be undertaken by nominated surgeons in the team with specific training in, and experience of, thyroid oncology.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 4. Nodal staging for differentiated and medullary thyroid cancer with relationship to overall disease stage*

Nodal (N) stage	N criteria
N_X	Regional nodes cannot be assessed
N_0	No evidence of regional metastases
N_1	Metastases to regional lymph nodes
N_{1a}	Metastases to levels VI–VII (unilateral or bilateral)
N_{1b}	Metastases to lateral neck nodes (unilateral or bilateral) or retropharyngeal lymph nodes

*According to the *AJCC Cancer Staging Manual* (eighth edition).[87]

Table 5. Metastasis staging for differentiated and medullary thyroid cancer with relationship to overall disease stage*

Metastasis (M) stage	M criteria
M_0	No distant metastases
M_1	Distant metastases

*According to the *AJCC Cancer Staging Manual* (eighth edition).[87]

Management of differentiated thyroid carcinoma

Microcarcinomas (T_{1a})

Microcarcinomas are differentiated thyroid carcinomas sized less than 10 mm in maximum dimension and are predominantly papillary carcinomas. When a microcarcinoma is found after thyroid lobectomy, if it is a solitary focus, and there are no high-risk features (e.g. multifocal disease, aggressive histological variant, family history), no further treatment is required. No follow up is required. When there are higher-risk features (or abnormalities in the contralateral lobe on ultrasonography), completion thyroidectomy can be considered. Management after completion thyroidectomy is the same as for papillary thyroid carcinoma, as described below.

For cases that are diagnosed through FNAC, active surveillance of these extremely low-risk tumours may be appropriate, with groups in Japan[1052] and the USA[1053] showing that this is safe in selected patients, with only around one-third of patients demonstrating progression during 10–20 years of follow up. At present, this has not been widely adopted in the UK, except for in high-risk surgical patients.

Initial thyroid surgery for papillary thyroid cancer

A strategy for the surgical treatment of papillary thyroid cancer is detailed in Table 7. All cases should be discussed preoperatively at the thyroid cancer MDT. Previous recommendations considered all patients suitable for total thyroidectomy to render them able to receive radioactive iodine. However, a recognition that only a select group of patients with aggressive disease will benefit from radioactive iodine has resulted in an increased percentage of patients being considered for less than total thyroidectomy (i.e. thyroid lobectomy).

Although rates of lymph node occult disease are relatively high, few patients ever develop clinically evident metastases. Prophylactic lateral neck dissection for a clinically staged node-negative (N_0) neck is not indicated. Most clinicians now only consider a prophylactic central neck dissection if there is extensive local disease (tumour stage $T_{3/4}$) or lateral nodal disease (N_{1b}).

Radical locoregional surgery should be considered to provide long-term locoregional disease control in the metastasis stage M_1 setting and to facilitate radio-iodine ablation of distant metastatic disease.

Initial surgery for follicular thyroid cancer and Hürthle cell cancer

The majority of patients undergoing surgery for follicular thyroid cancer will be undiagnosed at the time of the initial surgery (typically Thy 3f cytology). Frozen section histology cannot reliably differentiate benign follicular lesions from follicular thyroid cancer, and is not recommended. After diagnostic hemithyroidectomy, MDT discussion will inform whether completion thyroidectomy is indicated to facilitate radioactive iodine ablation.

Table 6. Group staging for differentiated and medullary thyroid cancer with relationship to overall disease stage*

Age group	Distant metastases?	Gross ETE?	Structures involved with gross ETE	Tumour (T) category	Node (N) category	Stage	Expected 10-year DSS (%)[1049]	10-year CSS (%)[1050]
<55 years	No	Yes or no	Any or none	Any	Any	I	98–100	99.6
	Yes	Yes or no	Any or none	Any	Any	II	85–95	97.1
≥55 years	No	No	None	≤4 cm ($T_{1/2}$)	N_0/N_x	I	98–100	99.6
					N_{1a}/N_{1b}	II	85–95	97.1
	No	No	None	>4 cm (T_{3a})	N_{0-1b}	II	85–95	97.1
	No	Yes	Only strap (T_{3b})	Any	Any	II	85–95	97.1
	No	Yes	Advanced ETE (T_{4a})	Any	Any	III	60–70	93.5
	No	Yes	Very advanced (T_{4b})	Any	Any	IVA	<50	64.4
	Yes	Yes or no	Any or none	Any	Any	IVB	<50	64.4

*According to the *AJCC Cancer Staging Manual* (eighth edition).[87] ETE = extra-thyroidal extension; DSS = disease-specific survival rate; CSS = cancer-specific survival rate

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 7. Surgical options for papillary thyroid cancer in patients fit for treatment

Disease (TNM) stage	Management
– T_{1a} N_0	Hemithyroidectomy or surveillance
– $T_{1b–2}N_0$ (assumed M_0) – $T_{3a}N_0M_0$ (at discretion of MDT) – And: • Unilobular disease; & • No adverse histopathological findings (multifocal, angioinvasion, aggressive subtypes etc.)	Hemithyroidectomy, or total or completion thyroidectomy (patient preference)
– Any tumour with higher-risk histopathology findings – $T_{3–4}N_0$ – Any T, N_1 – Any T, any N, M_1	Total or completion thyroidectomy, ± neck dissection

TNM = tumour–node–metastasis; MDT = multidisciplinary team

Prophylactic level VI dissection is not indicated, with low rates of occult disease in follicular thyroid cancer.

An operative strategy for surgical treatment of follicular cancer is outlined in Table 8.

Although data are conflicting, Hürthle cell cancers (follicular oncocytic) can be more aggressive, and many centres would generally treat these by total (or completion) thyroidectomy and radioactive iodine, although hemithyroidectomy can be considered in selected cases, along the same principles outlined in Table 8. Patients with tumours that exceed 4 cm but who show no signs of aggressive disease (pathologically staged T_{3a}) have traditionally been offered total or completion thyroidectomy and radioactive iodine, but, if histologically non-aggressive, selected cases may be managed without the need for completion thyroidectomy and routine ablation.

Completion thyroidectomy

Many cases of differentiated thyroid cancer are diagnosed after initial hemithyroidectomy; when total thyroidectomy is recommended, as described above, completion surgery is necessary. In patients at higher risk of morbidity, e.g. with recurrent laryngeal nerve palsy before or after initial surgery, the benefits of completion surgery need to be weighed up against the risks.

Table 8. Surgical options for follicular thyroid cancer in patients fit for treatment

Disease (TNM) stage	Management
– T_1 & T_2, N_0 (assumed M_0) – And: • Minimally capsular invasion • Minimal vascular invasion (at discretion of MDT) • Unilobular disease, & • No adverse histopathological findings, & – $T_{3a}N_0M_0$ (at discretion of MDT)	Hemithyroidectomy,* or total or completion thyroidectomy (patient preference)
– Any tumour with higher-risk histopathology findings (gross capsular invasion, vascular invasion, Hürthle cell) (at discretion of MDT) – $T_{3–4}N_0$ – Any T, N_1 – Any T, any N, M_1	Total or completion thyroidectomy, ± neck dissection

TNM = tumour–node–metastasis; MDT = multidisciplinary team

Management of lymph nodes in differentiated thyroid cancer

Prophylactic level VI lymph node dissection is associated with a higher incidence of recurrent laryngeal nerve damage and long-term permanent hypoparathyroidism.[1054] It is therefore not routinely recommended, but it may be indicated in individuals with high-risk tumours.

Ipsilateral prophylactic central neck dissection is often recommended in patients with known involved lateral nodes. Therapeutic central neck dissection is recommended when the presence of lymph node metastasis is confirmed (usually as a per-operative finding).

Clinically involved lateral cervical lymph nodes should be managed by selective neck dissection (of at least levels IIa–Vb). Involvement of level I and Va nodes is rare in differentiated thyroid cancer and should only be dissected if involved. Prophylactic lateral compartment neck dissection for node-negative patients is not recommended.

Recommendations

- Total thyroidectomy is recommended for most patients with tumours greater than 4 cm in diameter, or tumours of any size with any of the following characteristics: multifocal disease, bilateral disease, extra-thyroidal spread (pathologically staged T_{3b} and T_{4a} disease), familial disease, and those with clinically or radiologically involved nodes and/or distant metastases (evidence-based recommendation (R))
- Subtotal thyroidectomy should not be used in the management of thyroid cancer (good practice point (G))
- Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of locoregionally advanced disease (R)
- Patients with metastases in the lateral compartment should undergo therapeutic lateral compartment neck dissection, usually with ipsilateral central compartment neck dissection (R)

Locally advanced disease with extra-thyroidal spread

Where possible, locally advanced disease should be resected. Preservation of recurrent laryngeal nerves should be attempted in almost all cases, particularly where pre-operative function is preserved.[1055,1056] For minimal involvement, organs should be preserved with 'shave procedures' where appropriate. Extensive resection of the trachea, larynx and oesophagus should be considered if potentially curative.[1057] Where disease is unresectable, or after R2 resection (macroscopic residual disease) of such cases, external beam radiotherapy, radioactive iodine, and systemic therapies such as tyrosine kinase inhibitors should be considered.

Post-operative management

After total thyroidectomy for differentiated thyroid cancer, patients should be commenced on TSH-suppressive (aiming for TSH of less than 0.1) doses of levothyroxine (approximately 2 µg/kg). Radio-iodine ablation is not required for low-risk patients; in such patients, TSH should be maintained in the low normal range.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Calcium and parathyroid hormone (PTH) levels should be routinely checked within 24 hours, and hypocalcaemia should be treated and monitored appropriately according to local guidelines.

Based on the British Association of Endocrine and Thyroid Surgeons' position statement from 2010,[1058] post-operative laryngoscopy is required as a key quality performance indicator and should be mandatory. As an alternative, a normal signal from intra-operative nerve monitoring at the end of the operation can be used as a surrogate marker of intact recurrent laryngeal nerve function in patients without post-operative voice changes.

Persistent voice dysfunction should be investigated, with referral to a specialised practitioner for assessment and speech therapy. Patients with long-term hypocalcaemia (hypoparathyroidism) should have their calcium, vitamin D and PTH levels regularly monitored, either in association with an endocrinologist or with their general practitioner.

Thyroglobulin levels should be checked no earlier than six weeks after surgery. Achieving unmeasurable thyroglobulin levels after total thyroidectomy for early disease could become a quality control parameter, but this is yet to be introduced into routine clinical practice.

Post-operative radio-iodine (iodine-131) ablation and external beam radiotherapy in differentiated thyroid cancer

All patients with thyroid cancer should be clinically re-staged in the MDT meeting and scored using one of the clinicopathological scoring systems (e.g. American Thyroid Association Management Guidelines[1041]). This will aid planned follow up, and help identify high-risk patients and those who would benefit from radio-iodine therapy (Table 9).

Randomised trials have shown that in low- and intermediate-risk differentiated thyroid cancer ablation patients, success and five-year recurrence rates with a lower dose of radioactive iodine ablation (1.1 GBq) are non-inferior to the previous standard dose of radioactive iodine ablation (3.7 GBq).[1059]

Patients should be prepared for iodine-131 (I131) by having a low-iodine diet for one to two weeks prior to treatment. Recombinant human TSH therapy prior to I131 is preferable to thyroid hormone withdrawal, and is preferred by patients as it avoids periods of hypothyroidism.

Pregnancy and breast feeding should be excluded prior to giving I131. A post-ablation whole body scan, should be performed after I131 when residual activity levels permit satisfactory imaging. Practically, this is generally 1–10 days following treatment. Following I131, TSH should be suppressed to less than 0.1 mIU/l (approximately 2 μg/kg).

Adjuvant external beam radiotherapy should only be considered in individual cases where there remains gross disease following surgery and I131.

Between 9 and 12 months following I131 for low-risk differentiated thyroid cancer, patients should undergo dynamic risk stratification (Table 10). Patients are then categorised as having either an excellent response, an indeterminate response or an incomplete biochemical or structural response.[1060] The extent of TSH suppression is then accordingly modified.

Table 9. Indications for radioactive iodine ablation following total thyroidectomy or differentiated thyroid cancer

Recommendation	Clinical details
Definite ablation*	T_{3-4}
	N_1
	M_1
	Widespread angioinvasion
	Unfavourable histology (tall cell, diffuse sclerosing)
No ablation	Microcarcinoma
	Low risk – tumour sized <4 cm (staged $T_{1-2}N_0M_0$)

*Consider 3.7 GBq (rather than 1.1 GBq) for tumour–node–metastasis (TNM) stage $T_4N_{1b}M_1$ or aggressive subtypes.

Post-treatment follow up and surveillance

Thyroglobulin monitoring is most effective following total thyroidectomy with or without I131, and is an important modality in detecting persistent or recurrent disease. Physicians should be aware that thyroglobulin estimations vary according to the assay method. The presence of anti-thyroglobulin antibodies (in up to 30 per cent of cases) renders thyroglobulin levels unreliable. In this situation, serial anti-thyroglobulin antibody levels can be used cautiously as a surrogate tumour marker, along with ultrasound or other imaging.

Patients should have their thyroglobulin levels checked at 6–12 monthly intervals. Thyroglobulin evaluation is most effective following TSH stimulation, either by direct recombinant human TSH stimulation or by withdrawal of thyroid hormone replacement. However, super-sensitive modern assays may avoid the need for stimulation. There is no clear consensus as to when, how often and in which patients these more sensitive methods of thyroglobulin monitoring are required (i.e. when standard non-supressed thyroglobulin is normal).

A rise in thyroglobulin on serial monitoring may be suggestive of recurrent or residual disease, and needs further evaluation with imaging in the first instance.

A risk-adapted approach to follow up is recommended. For patients treated with surgery only without radioactive iodine ablation, those with T_{1a} tumours can be offered discharge. For other surgically treated low-risk patients, ultrasound at 6–12 months and then annual follow up for 5 years can be offered (ultrasound and thyroglobulin in patients who have had total thyroidectomy).

For other patients who have had post-operative radioactive iodine ablation, there is no formalised standard of care to determine thyroid cancer follow up in terms of length of follow up and intensity (e.g. the repetition of dynamic risk stratification). A suggested guide appears in the 2022 NICE guidelines (Table 11).[1042]

Recommendations

- A risk-adapted approach to follow up for differentiated thyroid cancer is recommended (good practice point (G))
- Follow up should be based on serum thyroglobulin, thyroglobulin antibody and TSH levels, with an ultrasound scan where indicated (evidence-based recommendation (R))

Management of recurrent differentiated thyroid cancer

Recurrence in differentiated thyroid cancer is a complex subject; it can be local, regional, distant or solely biochemical

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 10. Post-treatment dynamic risk stratification and TSH suppression targets[1041]

Parameter	Excellent response	Indeterminate response	Incomplete response
Post-treatment dynamic risk stratification*	Low risk	Intermediate risk	High risk
Post-treatment TSH suppression†	0.3–2.0 mIU/l	0.1–0.5 mIU/l with longitudinal reassessment	<0.1 mIU/l with longitudinal reassessment
Criteria	All the following:	Any of the following:	Any of the following:
	– Suppressed & stimulated Tg <1 lg/l‡	– Suppressed Tg <1 lg/l‡	– Suppressed Tg ≥1 g/l or stimulated Tg ≥10 lg/l‡
	– No evidence of disease on imaging	– Non-specific changes on imaging	– Rising Tg
			– Disease identified on imaging

*After 12 months of treatment for differentiated thyroid cancer. †Thyroid-stimulating hormone (TSH) suppression targets for patients treated with complete resection, total thyroidectomy and radioactive iodine ablation. ‡Assumes the absence of interference in the thyroglobulin assay. Tg = thyroglobulin

Table 11. Risk-stratified follow up following total thyroidectomy with radioactive iodine ablation*

Risk group	Follow up
Low risk on DRS, & no biochemical or imaging evidence of recurrence	– At least annual follow – Ultrasound & Tg testing – 2–5 years
Medium risk – Tg 0.2–1 mcg/l or – Stimulated Tg 1–10 mcg/l	– At least annual follow – Ultrasound & Tg testing – 5–10 years
High risk – Tg >1 mcg/l or – Stimulated Tg >10 mcg/l	– At least annual follow – Ultrasound & Tg testing – 10+ years

*Adapted from National Institute for Health and Care Excellence guidelines.[1042] DRS = dynamic risk stratification; Tg = thyroglobulin

(thyroglobulin). A rise in thyroglobulin is now the most common mode of presentation. When this occurs, neck ultrasound is the first investigation, with or without FNAC of any identifiable recurrence. If this shows recurrence, axial neck imaging may be considered for lesions in proximity to central neck structures.

If there is no evidence of a recurrence in the neck, CT of the thorax or FDG positron emission tomography (PET)-CT can be considered.

The aim of treatment for locoregional recurrence is to surgically clear all macroscopic disease, if possible weighing up the benefits and risks. Small-volume recurrent lymph nodes that are distant from vital structures may be monitored in the first instance. In the setting of residual disease after surgery for recurrence, for unresectable locoregional disease or for distant metastases, further radio-iodine therapy can be given, and the prognosis can still be favourable as long as the tumour remains radioactive iodine avid.

A small percentage of recurrent disease will become de-differentiated and refractory to radioactive iodine, at which point the 10-year survival can drop significantly. In these cases, local treatment with external beam radiotherapy, including newer forms (e.g. stereotactic radiotherapy, surgery for bone disease, embolisation, radio frequency ablation, alcohol injection, vertebroplasty and so on), may be considered for local control and palliation of symptoms.

In specialist units, selected patients with progressive symptomatic metastatic disease that is refractory to radioactive iodine are treated with kinase inhibitors such sorafenib, lenvatinib, larotrectinib and entrectinib within clinical trials if appropriate. These drugs can offer benefit in progression-free survival not overall survival, but patients need monitoring for side effects and deterioration in quality of life.[1061,1062]

Recommendations

- Patients with iodine-refractory disease should be referred to a centre with experience of managing these patients within clinical trials (good practice point (G))

Medullary thyroid cancer

Diagnosis and assessment

Medullary thyroid cancer is rare (approximately 1–3 per cent of all thyroid cancer cases).[1063] The same investigations as for any patient with a thyroid mass are required. Fine needle aspiration cytology may be diagnostic or suspicious for medullary thyroid cancer, and ultrasound imaging may also show features associated with medullary thyroid cancer. When medullary thyroid cancer is suspected or confirmed, serum calcitonin and carcinoembryonic antigen should be measured. This can assist with diagnosis when medullary thyroid cancer is suspected and measurements show a pre-treatment baseline level. Calcitonin levels are also predictive of the disease load or extent, and prognosis. In addition to an ultrasound scan of the neck, CT or magnetic resonance imaging (MRI) may be indicated, to guide the extent of surgical resection at initial surgery. Calcitonin gene product can cause systemic symptoms. Enquiry about symptoms such as flushing, diarrhoea or irritable bowel symptoms should be made.

All cases should be referred for surgical treatment to a regional designated cancer centre of the Thyroid Cancer Network. Twenty-five per cent of medullary thyroid cancer cases are familial (MEN2A, MEN2B and familial non-MEN medullary thyroid cancer). A family history must be ascertained, as should urinary or serum metanephrine levels to exclude phaeochromocytoma, and PTH and calcium levels to exclude hyperparathyroidism. If a phaeochromocytoma is diagnosed, adrenalectomy should be performed prior to offering thyroid surgery for medullary thyroid cancer.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Staging

The tumour–node–metastasis (TNM) staging for medullary thyroid cancer follows the same criteria as for differentiated thyroid cancer (Table 12); however, the stage grouping differs.

Treatment

All patients with medullary thyroid cancer should undergo:

- Total thyroidectomy and central compartment node clearance (level VI). This should be performed even in the presence of disseminated metastases to aim for disease control in the central neck.

Lateral neck lymph nodes (clinically staged node-positive (N_+)):

- Patients with clinically involved lateral compartment nodes should have a therapeutic lateral neck dissection (levels IIa–Vb) to eradicate regional disease on that side.

Lateral neck lymph nodes (clinically staged N_0):

- Prophylactic ipsilateral lateral neck dissection (levels IIa–Vb) should be considered in patients with involved ipsilateral central neck nodes and in those with high calcitonin levels, although exact cut-offs are debatable.
- Prophylactic contralateral lateral neck dissection may even be considered in the presence of ipsilateral N_{1b} disease and calcitonin levels over 200 pg/ml. It may also be considered in cases where a biochemical cure is not achieved after total thyroidectomy and ipsilateral neck surgery.

Mediastinal disease:

- Intra-thoracic disease should be resected, and, when below the level of the brachiocephalic vein, be resected via sternotomy or using robotic surgery where feasible.

Post-operatively, patients with medullary thyroid cancer should aim to have TSH levels in the normal range (i.e. no need for suppression).

Post-operative radiotherapy:

- Patients with macroscopic residual disease, gross extrathyroidal extension or extensive lymph node metastases should be considered for external beam radiation.

Table 12. Disease staging for medullary thyroid carcinoma

Stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
Stage I	T_{1a}, T_{1b}	N_0	M_0
Stage II	T_2, T_3	N_0	M_0
Stage III	T_1, T_2, T_3	N_{1a}	M_0
Stage IVA	T_1, T_2, T_3	N_{1b}	M_0
	T_{4a}	Any N	M_0
Stage IVB	T_{4b}	Any N	M_0
Stage IVC	Any T	Any N	M_1

Calcitonin and carcinoembryonic antigen should be measured at two to six weeks and at three to six months after the operation to determine the exact nadir. Those patients with persistent elevation of calcitonin should have further radiological assessment to determine disease persistence. Computed tomography, MRI, ultrasound, selective arteriography, I131-metaiodobenzylguanidine, FDG-PET, indium-111 (In111)-octreotide and DOTA-TATE PET/CT may all be useful in identifying the source of raised calcitonin, but their use in patients with calcitonin levels of less than 400–500 pg/ml is unlikely to identify metastases.

Genetic assessment

Genetic assessment for all patients, including germline RET proto-oncogene mutational analysis, should be performed after surgery, once diagnosis is established, even in the absence of a familial history.

Prophylactic thyroidectomy should be offered to RET-positive family members following specialist counselling by the cancer genetics team. The timing and extent of surgery are dependent on genotype (codon mutation), the calcitonin level and age at detection of RET positivity.

Lifelong follow up is recommended for all patients with medullary thyroid cancer. Screening should include calcitonin and carcinoembryonic antigen. Rising calcitonin levels should trigger investigations to identify potentially treatable metastatic disease.

Patients with recurrent medullary thyroid cancer present a complex problem; they should be managed by teams with experience of such cases, and with access to the full spectrum of surgical and non-surgical approaches that this cohort requires. The primary aim should always be to control locoregional disease.

Calcitonin and carcinoembryonic antigen doubling times are helpful markers of disease aggressiveness and prognosis. A calcitonin doubling time exceeding 6 months is associated with 5-year and 10-year survival rates in excess of 90 per cent and 35 per cent, respectively; shorter doubling times predict markedly worse survival.

In patients with a significant tumour burden and those who are symptomatic of progressive metastatic disease, multikinase inhibitor therapy should be considered. There are two drugs licensed for use in progressive locally advanced and/or metastatic medullary thyroid cancer: vandetanib[1064] and cabozantinib.[1065] Both these drugs were shown to improve progression-free survival over placebo. As with multikinase inhibitors in iodine-refractory thyroid cancer, these drugs have potentially significant side effects, and patients should be managed within a specialist unit. Recent promising data for the specific RET inhibitors selpercatinib[1066] and pralsetinib[1066] may lead to the licensing and availability of these drugs as a treatment option for patients with tumours harbouring a somatic RET mutation, or those patients with a germline RET mutation.

Supportive care may provide significant symptomatic relief for patients with advanced medullary thyroid cancer. For example, analgesia, anti-diarrheal medication, bisphosphonate or denosumab infusions for extensive bone involvement can all be useful. Patients with isolated metastases or those with differential progression should be considered for locally ablative treatment modalities such as surgical resection, external beam radiotherapy including stereotactic body radiation therapy, radiofrequency ablation, or embolisation.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Recommendations

- All patients with suspected or proven medullary thyroid cancer should have assessments of: serum calcitonin and carcinoembryonic antigen levels, catecholamine and normetanephrine urine estimation (or plasma-free normetanephrine estimation) at 24 hours, serum calcium levels, and PTH levels (evidence-based recommendation (R))
- Routine ultrasound should be performed in all cases, and CT is advised in the presence of advanced local or any nodal disease, to guide the extent of surgery (R)
- All patients with proven medullary thyroid cancer measuring over 5 mm should undergo total thyroidectomy and central compartment neck dissection (R)
- Patients with lateral nodal involvement should undergo selective neck dissection (IIa–Vb) (R)
- All patients with proven medullary thyroid cancer should have genetic screening for germline RET mutation (R)
- All patients with sporadic medullary thyroid cancer should have their histopathology examined for a somatic RET mutation (R)
- Prophylactic thyroidectomy should be offered to RET-positive family members (R)
- Neither FDG-PET/CT nor F-DOPA (fluorodopa) PET/CT is recommended to detect the presence of distant metastases at presentation (good practice point (G))
- Patients with locally advanced or metastatic disease that is progressing and/or symptomatic should be considered for entry into clinical trials, for locally ablative palliative treatments or for systemic targeted therapy (G)

Anaplastic thyroid cancer

The prognosis of patients with anaplastic thyroid cancer is poor, and all patients are considered stage IV at presentation (Table 13).[1067]

Many patients present with a history of a rapidly enlarging thyroid mass in a long-standing goitre. As soon as a diagnosis of anaplastic thyroid cancer is considered, investigations should be expedited to enable treatment initiation within days not weeks. Core biopsy is preferable to FNAC in achieving a diagnosis if possible, as it will help differentiate anaplastic thyroid cancer from thyroid lymphoma, which can present in a similar manner. Tissue should be sent for urgent immunohistochemistry for BRAF *V600E*, and next-generation sequencing for BRAF *V600E* mutation and NTRK, ALK and RET fusions.

If anaplastic thyroid cancer is considered resectable, patients should undergo total thyroidectomy, and be considered for post-operative radiation with or without chemotherapy on an individual case basis. Unfortunately, many patients will present with extremely advanced disease, a poor performance status and extremely limited life expectancy. Such patients require a swift diagnosis and best supportive care. In this situation, tracheostomy should be avoided as it is unlikely to result in a meaningful improvement in overall quality of life.

Select patients who present with advanced disease and who retain a good performance status may be eligible for targeted therapies.

Up to 45 per cent of anaplastic thyroid cancer patients will harbour a BRAF V600E mutation; the combination of a BRAF inhibitor (dabrafenib) and a MEK inhibitor (trametinib) has shown encouraging activity, with a response rate of 61 per cent, partial response rate of 67 per cent and complete response rate of 44 per cent in 23 patients, with 64 per cent maintaining a response for six months or more.[1068] These data were presented to the Food and Drug Administration, which led to the approval of this drug combination for this specific group of patients in the USA. It is currently being evaluated in the UK.

In suitable patients, NTRK or RET fusion anaplastic thyroid cancer patients with stage IVC disease, a TRK inhibitor (either larotrectinib or entrectinib) or RET inhibitor (selpercatinib or pralsetinib), preferably inside a clinical trial, if available, may be considered.

In stage IVC anaplastic thyroid cancer, patients with high programmed death-ligand 1 (PD-L1) expression, checkpoint (PD-L1, programmed death-1 (PD1)) inhibitors can be considered in the context of a clinical trial.

In patients without a druggable target or appropriate clinical trial, best supportive care should be pursued, which may include palliative external beam radiotherapy. Cytotoxic chemotherapy has poor response rates, but may be considered in the palliative setting where there are no targeted therapy options and the patient retains a good performance status.

Table 13. Disease staging for anaplastic thyroid cancer

Stage IV subtype*	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
Stage IVA	T_1, T_2, T_{3a}	N_0	M_0
Stage IVB	T_1, T_2, T_{3a}	N_1	M_0
	T_{3b}, T_{4a}, T_{4b}	Any N	M_0
Stage IVC	Any T	Any N	M_1

*All are considered stage IV

Recommendations

- Initial assessment should focus on identifying the small proportion of patients with localised disease and a good performance status, who may benefit from surgical resection and other adjuvant therapies (good practice point (G))
- Investigations should be expedited to enable the initiation of a treatment plan within days (G)
- The surgical intent, when appropriate, should be gross tumour resection and not merely an attempt at debulking (G)
- Pathology should be sent for molecular profiling, specifically for BRAF V600E mutation, NTRK, ALK and RET fusions (G)
- Targeted therapies should be considered if druggable genomic alteration is present (G)
- If no targeted therapy is appropriate, the patient should be given best supportive care, with consideration of palliative radiotherapy for symptomatic relief (G)

Studies due to report

'IoN' trial[1069] – this national multicentre randomised, controlled trial has been designed to address the question of whether the omission of radioactive iodine is non-inferior to its use in low to intermediate risk differentiated thyroid cancer.

'HoT' trial[1070] – a UK national multicentre randomised, controlled trial designed to address the question of whether

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

lobectomy is non-inferior to total thyroidectomy in selected cases of low-risk differentiated thyroid cancer.

The 'NIFTy' trial[1071] – this trial seeks to evaluate the role of near-infrared fluorescent imaging in reducing the rate of parathyroid gland injury in thyroid surgery, which may help minimise hypoparathyroidism in patients treated for thyroid cancer.

'Thy3000' – a national observational study of the epidemiology and initial management pathway of thyroid nodules. This is a retrospective study of 3000 thyroid nodules in the UK that hopes to increase the understanding of epidemiology of thyroid nodules and the nature of practice across the UK.

Important research questions to be answered

The excellent outcomes associated with differentiated thyroid cancer have made it a challenging subject to study. Large patient numbers and long follow-up periods are required to perform definitive randomised, controlled trials. Therefore, many subjects remain unresolved, including: the extent of surgery and adjuvant therapy required for lower-risk differentiated thyroid cancer, and the duration and frequency of follow up required and how this is influenced by initial treatments (lobectomy *vs* total thyroidectomy and radioactive iodine ablation, for example).

Although great strides have been made in recent times in terms of treatment for de-differentiated thyroid cancers such as anaplastic thyroid cancers and radio-iodine refractory recurrent cancers, outcomes remain poor. Further work to optimise outcomes in these high-risk groups is required.

The application of risk-stratification strategies for indeterminate cytology (Thy 3) also requires consideration. Such strategies include molecular testing, the presence of nuclear atypia and ultrasound characteristics.

Research in medullary thyroid cancer is limited by the rarity of the disease. The extent of initial treatment including the need for lateral neck dissection, the role of calcitonin in determining initial management, and the targeted treatment of progressive recurrent or distant disease are all important topics for the future.

Chapter 26: Management of neck metastases in head and neck cancer

Table of Contents

Introduction

Most head and neck cancers have a propensity to metastasise to regional lymph nodes. The presence, site and size of metastatic neck disease are important prognostic factors in head and neck squamous cell cancer (SCC) (generally, survival in non-human papillomavirus (HPV) associated head and neck SCC decreases by up to 50 per cent with lymph node metastasis, and by the same again with extra-nodal extension). Cancers can present with lymph node metastases. Investigation and treatment of macroscopic and microscopic lymph node disease is applicable to all head and neck cancer sites, and can be treated surgically or non-surgically.

Consequently, the management of lymph node metastases features throughout these guidelines. The assessment of lymph node disease through radiology and cytopathology is covered in Chapter 2 (on clinical assessment and diagnosis). Radiotherapy (RT) and chemoradiotherapy treatment for neck disease is covered in Chapter 4 (on non-surgical oncology). Investigation and management of patients presenting with SCC with unknown primary is discussed in Chapter 27. The management of primary site-specific lymph node disease, both for clinically negative and positive disease, is discussed in each site-specific chapter.

This chapter will pull these areas together, and expand on areas of neck metastatic disease not covered elsewhere.

Assessment of metastatic lymph node disease

For primary diagnosis of cancer

See Chapter 2. Investigations for diagnosis and staging are summarised in Figure 1. For malignant disease other than SCC, further investigations will depend on cytopathology or histopathology. Positron emission tomography computed tomography (PET-CT) should be organised as soon as carcinoma with unknown primary is suspected.

For staging of head and neck cancer

Recommendations

- Magnetic resonance imaging (MRI) or computed tomography (CT) should be used for the clinical staging of neck metastases (evidence-based recommendation (R))
- Positron emission tomography CT should be used in nodal stage N_3 disease, and to evaluate the response to chemoradiotherapy (in addition to other indications specific to the primary disease or histology type) (R)
- Positron emission tomography CT should be considered in recurrent disease with lymph node metastases (good practice point (G))

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

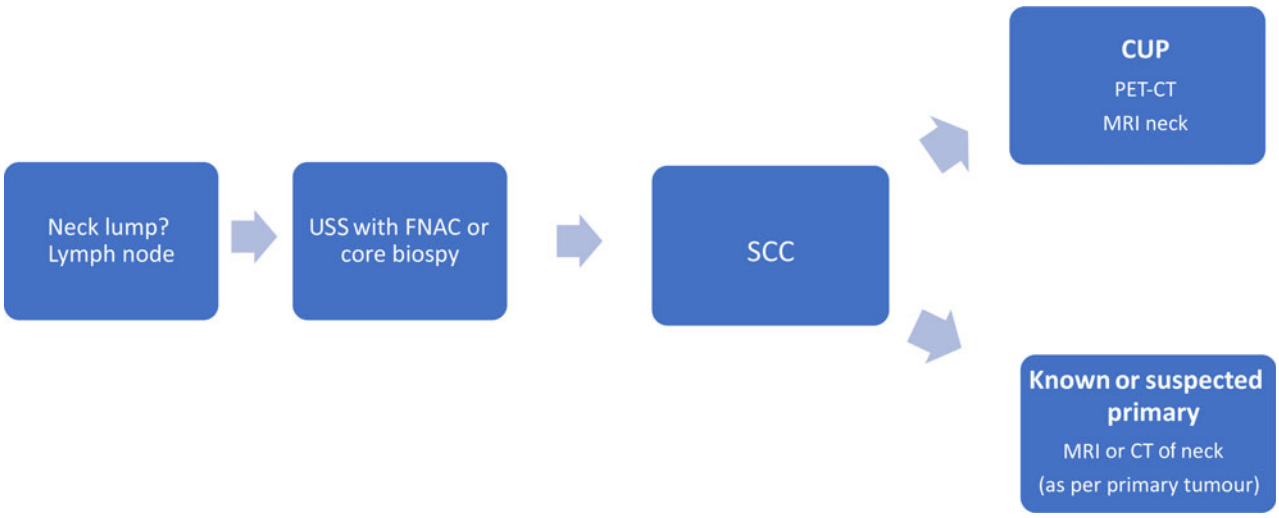


Figure 1. Diagnosis and staging for suspected lymph node metastatic disease. USS = ultrasound scan; FNAC = fine needle aspiration cytology; SCC = squamous cell carcinoma; CUP = carcinoma with unknown primary; PET-CT = positron emission tomography computed tomography; MRI = magnetic resonance imaging; CT = computed tomography

Appropriate staging of neck disease may have been performed as part of the assessment (see above). The choice of cross-sectional imaging (CT and/or MRI) depends upon the imaging preference for primary tumour staging. Computed tomography and MRI show a similar performance in the nodal staging of head and neck SCC.[1072] The presence of regional nodes has been shown to be the strongest independent predictor for distant metastases,[1073] and, as mentioned above, PET-CT is recommended in N_3 stage disease.[1074] For this and other standard indications (e.g. tumour stage T_4 disease of the hypopharynx or nasopharynx, carcinoma with unknown primary, stage 3 melanoma, and other circumstances with high chance of distant metastasis), PET-CT may increase the accuracy of nodal staging, in addition to MRI or CT, in the setting of a clinically node-negative neck.[1075] Positron emission tomography CT is used to detect persistent disease after chemoradiotherapy and often in suspected recurrent disease (see relevant sections in this chapter).

Lymph node levels

The levels and sublevels of the neck were described by Robbins *et al.* in 2002, updated in 2008, together with an anatomical description for each one (see Figure 2).[1076]

Additional regional lymph node sites

The incidence of retropharyngeal lymph node metastases in head and neck SCC is 4–44 per cent, with the highest incidence in nasopharyngeal cancer where the retropharyngeal lymph nodes are the first echelon nodes. In oropharyngeal SCC, the incidence of retropharyngeal lymph nodes is greater in tumours involving the posterior wall, soft palate and contralateral neck. Retropharyngeal lymph node metastases are associated with a poorer prognosis and impact upon therapeutic management.[1077] Positron emission tomography CT in combination with CT and MRI improves overall accuracy in detecting metastatic retropharyngeal lymph nodes, and is recommended in equivocal cases.[1078]

Intra-parotid lymph nodes may be first echelon nodes in cutaneous head and neck cancers and temporal bone SCC, and can occasionally be involved when there is cervical lymph node metastasis from mucosal head and neck SCC.[1079]

Buccal, retroauricular and occipital lymph nodes may be involved in cutaneous cancers.

Staging

There were three main areas of change to regional lymph node staging in the eighth edition of the *AJCC Cancer Staging Manual*.[87]

Extra-nodal extension

The presence of extra-nodal extension is a poor prognostic factor. All HPV-negative tumours from any subsite (excluding nasopharyngeal carcinoma) incorporate extra-nodal extension in the nodal staging. For clinical staging, extra-nodal extension should be unequivocal, because the sensitivity of early radiological extra-nodal extension (e.g. indistinct nodal margin) is modest.[1080]

If there is evidence of pathological extra-nodal extension in a single node sized 3 cm or less, this is upstaged to N_{2a}, and in all other instances to N_{3b}. Pathological extra-nodal extension may be further subdivided into minor or major categories if the metastasis has extended less than 2 mm or more than 2 mm beyond the lymph node capsule respectively, although this subdivision is for documentation purposes only.[87]

P16-positive squamous cell carcinoma

In addition, a different staging is adopted for p16-positive oropharyngeal and SCC with unknown primary, based on the better prognosis of HPV-associated oropharyngeal SCC.

It should also be noted that there are differences in the clinico-radiological staging of HPV-related neck disease, and pathological (but post neck dissection only) staging. This is based on the prognostic implications of a neck dissection having been carried out.

Different staging remains in place for the thyroid, nasopharynx and melanoma. The staging for these can be found in the relevant chapters. The main staging (for p16-negative and p16-positive disease) is shown in Tables 1 and 2.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

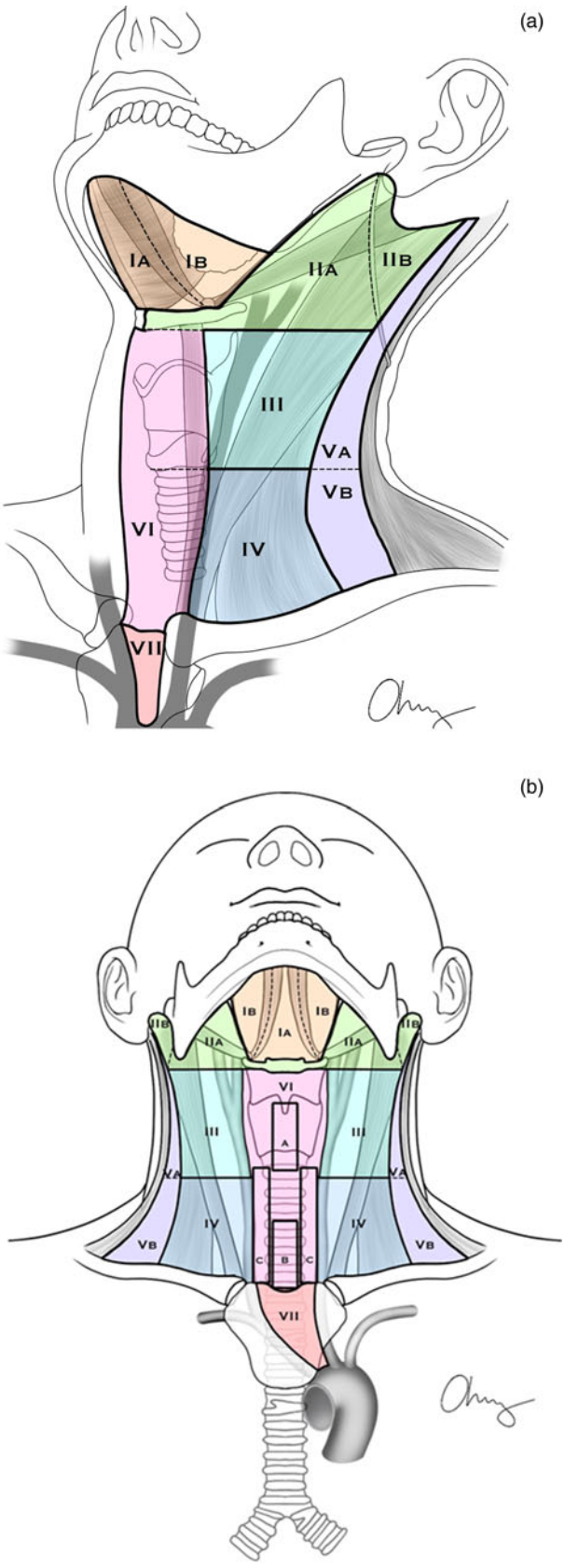


Figure 2. The levels and sublevels of the neck. (a) The anterior or medial border of levels III and IV is formed by the lateral border of the sternohyoid muscle. Key anatomical landmarks dividing levels II, III and IV are the inferior border of the hyoid bone and the inferior border of the cricoid cartilage. (b) The central compartment is further divided in thyroid cancer into (1) pre-laryngeal, (2) pre-tracheal and (3) para-tracheal, with the inferior border of the central compartment defined as the innominate artery on the right and the corresponding axial plane on the left, as inferior lymphatic drainage is contiguous with the anterior superior mediastinum.

Nasopharynx

In order to ensure clearer delineation and concordance with imaging, the caudal border of cricoid cartilage is used to define lymph node metastases in low neck levels IV and Vb, requiring upstaging to N_3 disease. Nodal masses larger than 6 cm are also classed as N_3, with removal of the prior separate N_{3a} and N_{3b} group classification. Nodal stage N_3 is seated in the prognostic stage grouping of IVA, rather than IVB.

Classification of neck dissection

Recommendations

- Neck dissection should be classified according to levels or sublevels dissected and the non-lymphatic structures removed, with or without additional nodal groups being dissected (evidence-based recommendation (R))
- There should be an agreed local protocol for neck dissection specimen orientation, to facilitate accurate pathological lymph node staging (good practice point (G))

Historic neck dissection classification can be misleading. The American Academy of Otolaryngology and Head and Neck classification, described in 1991 and updated in 2002, still contains the terms 'radical' and 'modified radical' neck dissection.[1076] These terms imply the dissection of all levels of the neck. In fact, a full dissection of all levels and sublevels is unusual.

The classification for the commonly surgically removed cervical lymph node groups in the neck is well established and commonly understood.[1076] It is recommended that any type of neck dissection is denoted by 'ND', followed by node level or sublevel and non-lymphatic structures removed.[1081] The classification of neck dissection is as shown in Table 3.

There is a lack of clear guidance on distinguishing neck dissection levels for residual or persistent disease after initial RT or chemoradiotherapy from truly recurrent disease. The definition of the latter varies within reports, ranging from six months to two years after primary treatment. This is in contrast to the pathological distinction, in which the 'y' prefix indicates those cases that are performed following initial multimodality therapy (neoadjuvant chemotherapy and/or RT). The commonest clinical scenario for neck dissection for residual or persistent disease is when it follows routine surveillance PET-CT, or there is MRI evidence of persistent disease, typically three months after primary chemoradiotherapy. In this setting, neck dissection should be considered as part of the primary multimodality treatment.

There is no consensus regarding a minimum nodal yield from an untreated neck. A minimum nodal yield of 18 lymph nodes is supported by the prognostic therapeutic effect of neck dissection.[1082] The tumour–node–metastasis (TNM) stage refers to 10 and 20 nodes for 'selective' and 'radical' neck dissections, respectively. The yield from a previously irradiated neck would be expected to be smaller.

In order to facilitate accurate pathological lymph node staging, and to plan post-operative RT volumes and dose, there should be an agreed local protocol for neck dissection specimen orientation. The options are to divide according to neck levels in the operating theatre and send in separate containers, or the orientation on a suitable base and labelling of neck levels with an indelible marking pen.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 1. Main head and neck cancer nodal (N) staging (including a p16-negative unknown primary and oropharynx)*

Nodal (N) stage	Clinical N stage (cN)	Pathological N stage (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node, sized >3 cm but not more than 6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized <3 cm, & with extra-nodal extension Or metastasis in a single ipsilateral node, sized >3 cm but not more than 6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, any with extra-nodal extension Or metastasis in a single contralateral node of any size, & with extra-nodal extension

*According to the *AJCC Cancer Staging Manual* (eighth edition).[87]

Table 2. Nodal (N) staging for a p16-positive unknown primary (SCC with unknown primary) and oropharynx*

Nodal (N) stage	Clinical N stage (cN)	Pathological N stage (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Unilateral metastasis in lymph node(s), sized ≤6 cm in greatest dimension	Metastasis in 1–4 lymph nodes
N_2	Metastasis in bilateral or contralateral lymph node(s), all sized ≤6 cm in greatest dimension	Metastasis in ≥5 lymph nodes
N_3	Metastasis in lymph node(s), sized >6 cm in greatest dimension	n/a

*According to the *AJCC Cancer Staging Manual* (eighth edition).[87] SCC = squamous cell carcinoma; n/a = not applicable

Table 3. Classification of neck dissection

Levels or sublevels dissected	Non-lymphatic structures removed	Additional nodal groups dissected*
Ia, Ib, IIa, IIb, III, IV, Va, Vb, VI, VII	Major nerves or branches of VIIth, IXth–XIIth cranial nerves, sympathetic chain	Parotid
	Major blood vessels (i.e. IJV, carotid)	Buccal
	Muscle (i.e. sternocleidomastoid)	Retroauricular
	Submandibular gland	Occipital
	Overlying skin	Retropharyngeal

*As defined in the *AJCC Cancer Staging Manual* (eighth edition).[87] IJV = internal jugular vein

Treatment of clinically staged node-negative neck

Recommendations

- Elective neck treatment should be offered if the risk of occult metastasis is greater than 20 per cent (evidence-based recommendation (R))
- Surgery and RT are equally effective (R)
- Elective treatment should be given by the same modality used for the primary tumour (R)
- Sentinel node biopsy should be considered for oral cavity SCC (good practice point (G))

A proportion of patients staged as clinically staged node-negative (N_0) will have occult metastases. These are not detectable on clinical or radiological assessment, and they include micro-metastases (defined strictly as less than 2 mm). The two strategies in this group are to treat electively, or to observe and then treat, any neck recurrence in the proportion that develop subsequent metastasis. It is now generally accepted that elective neck treatment, rather than observation, should be considered when the risk of occult (undetectable) metastasis is greater than 20 per cent.[1083]

This is essentially an historic threshold figure. Given the lower morbidity of modern RT techniques and selective neck dissection surgical techniques, there is an argument that the cut-off value could be lower (e.g. 15 per cent). In their landmark clinical trial, D'Cruz *et al.* showed a survival benefit in elective neck dissection (*vs* initial surveillance) for N_0 oral

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

SCC.[717] However, the pathological metastasis rate was just under 30 per cent in this patient group.

The following are the basic principles that underpin treatment for the clinically node-negative neck:

- If the risk of occult metastasis is greater than 20 per cent, elective neck treatment should be offered. This effectively applies to all mucosal head and neck SCC, with the exception of a $T_{1/2}$ glottic larynx and $T_{1/2}$ sinonasal and lip SCC.
- For non-SCC head and neck cancers, the requirement for elective neck treatment is more nuanced and dependent on histological type. In general, low-grade or low-stage cancers may not need elective neck treatment.
- Surgery and RT are thought to be equally effective.[1084] Radiotherapy treats retropharyngeal lymph nodes; surgery generally does not.
- Elective treatment should be given by the same modality used for the primary tumour.
- The same principle applies to the contralateral neck – i.e. elective treatment if the chance of occult metastasis is significant.
- For midline tumours, both sides of the neck need to be considered.

The levels or sublevels of the neck that are at risk are determined by the site of the primary tumour. The choice of levels to be treated is explained in the relevant chapters of these guidelines. Surgical dissection of level IIb is associated with higher rates of shoulder dysfunction.[1085] There is a high level of evidence to support the omission of level IIb dissection in laryngeal, hypopharyngeal and $T_{1/2}$ oropharynx primary cancer sites, in cases with no intra-operative findings suggestive of metastatic lymph nodes elsewhere in the neck.[1086,1087] The evidence for the omission of level IIb is less convincing for clinically staged N_0 oropharyngeal primary cancers with more advanced primary tumours ($T_{3/4}$).[1087] Whilst oral cancers have higher rates of occult metastases than other mucosal primary sites, the rate of occult IIb metastases in clinically staged N_0 necks is very low (1 per cent in a meta-analysis of 937 patients), which suggests that level IIb dissection can be omitted in this group also.[1088]

For oral cavity cancers in particular, sentinel node biopsy is an alternative to elective neck treatment (see Chapter 17).

Table 4 summarises the neck levels that should be detected for each primary cancer site.

Treatment of clinically staged node-positive neck

Recommendations

- The initial modality used should be the same as for the primary cancer (evidence-based recommendation (R))
- Radiotherapy surgery can be used as a single modality treatment for a single lymph node metastasis sized less than 3 cm (R)
- After neck dissection for SCC, RT or chemoradiotherapy should be considered for patients with adverse pathological features and/or N_{2+} disease (R)
- After neck dissection for SCC, chemoradiotherapy should be considered for eligible patients with extra-nodal extension and a high chance of residual disease (R)
- When primary chemoradiotherapy or RT is used for cancers with node-positive (N_+) neck disease, evaluation of response by PET-CT scan is recommended at three to four months post-treatment (R)
- After post-chemoradiotherapy PET-CT, patients with an incomplete nodal response should be considered for neck dissection (R). (Note that the extent of neck dissection is variable)
- After post-chemoradiotherapy PET-CT, patients with N_{1-2} HPV-positive cancers and an initial equivocal nodal response should be offered another PET-CT scan in a further three months (R)

A clinically staged N_+ neck requires treatment, alongside treatment of the primary cancer.

The modality used is generally the same as for the primary cancer which, in turn, is determined by both the primary and neck staging. When RT is the primary treatment modality, the international consensus guidelines for delineating nodal levels in the neck and selecting lymph node target volume for intensity-modulated RT and volumetric modulated arc therapy, are recommended.[146]

The historic principle was that 'comprehensive' treatment (equating to all lymph node levels) was required for the N_+ neck. However, contemporary practice has moved towards a more selective approach when appropriate.

Generally, the greater the burden of neck disease, the more comprehensive the neck treatment should be. Treatment is also dependent on the site of the primary tumour and clearly the levels shown to be involved on imaging. The nodal groups treated for a small single N_1 lymph node metastasis might not differ greatly from those for a N_0 neck of the same primary cancer. On the other hand, advanced neck disease (N_3), or

Table 4. Neck level treatment for a clinically node-negative (N_0) neck according to primary tumour site

	Neck level								
Primary tumour site	Ia	Ib	IIa	IIb	III	IV	Va	Vb	VI
Oral cavity	X	X	X	±	X	±	0	0	0
Oropharynx	0	0	X	±	X	X	0	0	0
Larynx (not glottic T_{1-2})	0	0	X	0	X	X	0	0	± (subglottic or transglottic X)
Hypopharynx	0	0	X	0	X	X	0	0	X
Parotid gland*	0	±	X	X	X	0	0	0	0
Submandibular gland*	X	X	X	X	X	0	0	0	0

*High-grade histology or tumour (T) stage $T_{3/4}$. 'X' = treatment recommended, evidence-based and/or generally accepted practice; '±' = consider treatment / variable treatment practice; '0' = treatment not necessary

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

multiple level involvement in an $N_{2b/c}$ neck, if treated surgically, will generally require dissection of all levels and selected non-lymphatic structures.

Therefore, the choice of lymph node levels is nuanced, and it is almost impossible to arrive at an evidence-based guideline specifying which levels need to be treated and which do not. The described lymph node levels for clinically staged N_0 disease (Table 4) can be taken as a minimal or starting point when considering which levels require treatment. Furthermore, image-guided RT utilising fluoro-deoxy-glucose (FDG)-PET/CT based nodal target volume can be used to tailor the dose prescription to different areas of the neck.[1089] This has been shown to improve the regional control of disease and survival compared to CT, and supports future potential target volume transformation in therapeutic and elective neck treatment by RT.

For non-surgical primary treatment, synchronous chemoradiotherapy should be given for all suitable patients.[109]

The following principles apply, however:

- The initial modality used is generally the same as for the primary cancer
- Radiotherapy or surgery can be used as a single modality treatment for single nodal disease sized less than 3 cm without adverse pathological features*
- The minimum neck levels or sublevels to be treated are as for clinically staged N_0 disease relevant to the primary site, as well as any level with radiological suspicion of lymph node metastasis (careful pre-operative imaging is essential)
- Radiotherapy or chemoradiotherapy can follow primary surgery, and can be tailored to pathological staging and other histopathological features (see below)
- Surgery can follow primary RT or chemoradiotherapy when there is evidence of possible residual disease (see below)

*Note that this is not the same as clinically staged N_1, which, for HPV-positive oropharyngeal SCC, can include multiple nodes measuring up to 6 cm.

Primary neck dissection when the primary tumour is to be treated with RT or chemoradiotherapy, even in cases of resectable N_3 disease, is not routinely recommended, but should be considered on a case-by-case basis.[1090,1091] One indication may be cases where there is skin ulceration and possible haemorrhage risk.

The definition of resectable N_3 disease may vary. Relative contraindications include skull base erosion by metastatic neck disease, prevertebral fascia invasion, and gross carotid involvement. These cases can technically be resected, but will have a low likelihood of cure. In patients with very advanced, bordering unresectable nodal disease, RT or chemoradiotherapy (possibly induction chemotherapy) may be better initial options.[1084,1092]

Adjuvant treatment after neck dissection

When neck dissection is performed, and there is proven lymph node metastasis, post-operative RT or chemoradiotherapy can be considered. Much of the evidence around the indication for post-operative RT is extrapolated from the oral cavity.[1084] The addition of chemotherapy in the presence of extra-nodal extension and/or involved surgical margins is associated with improved locoregional control and overall survival, based on randomised, controlled trials from the European Organisation for Research and Treatment of Cancer trial 'EORTC 22931' and Radiation Therapy Oncology Group trial 'RTOG 9501' (but not controlled for HPV-positive oropharyngeal SCC).[733]

The indications are summarised below, which include primary tumour considerations.

- Pathologically staged N_1 without adverse features* – no adjuvant treatment required
- Pathologically staged N_1 with adverse features – post-operative RT or chemoradiotherapy
- Pathologically staged $N_{2/3}$ – post-operative RT or chemoradiotherapy

*Adverse features include positive margin(s) at the primary site and extra-nodal extension, and may include advanced T stage (pathologically staged T_{3-4}), involved nodes in levels IV and Vb, lymphovascular invasion, perineural invasion and a high grade (non-SCC histological tumour types).

For patients aged less than 70 years and fit for chemotherapy, chemoradiotherapy should be considered. The strongest indications are when there is likely to be residual disease after surgery, extra-nodal extension spread,[733] and high nodal burden (e.g. multiple lymph nodes or N_3 disease).

Neck dissection for suspected persistent lymph node (only) disease after primary chemoradiotherapy or radiotherapy

When primary chemoradiotherapy or RT is used for cancers with N_+ neck disease (most commonly for oropharyngeal SCC), post-treatment surgery may be required for suspected persistent neck disease. Such cases should be discussed in a multidisciplinary team (MDT) meeting.

There is no role for a planned neck dissection in all patients following primary chemoradiotherapy. The PET-Neck trial compared PET–CT-guided active surveillance with planned neck dissection for neck disease staged N_2 or N_3 treated by chemoradiotherapy, and showed that neck dissection as indicated by post-treatment PET-CT led to fewer neck dissections with no detrimental effect on survival.[51] The PET-Neck trial had only a small proportion of N_3 tumours (6 per cent). However, retrospective N_3 stage cohort studies support a PET-CT-guided neck dissection strategy.[1093] In N_3 disease, the commonest pattern of failure is distant metastases (17–44 per cent), and there is conflicting evidence regarding the benefit of induction chemotherapy on the impact of distant failure and resultant overall survival.[1092]

The PET-Neck trial established the standard of care of a PET-CT scan at 12 weeks following chemoradiotherapy. The categorisation of responses as complete, equivocal and incomplete is recommended. There is no consensus regarding the optimum qualitative interpretive criteria (e.g. Neck Imaging Reporting and Data Systems ('NI-RADS'), Hopkins, and Deauville criteria) in post-treatment PET-CT in head and neck SCC, but the use of scoring systems that minimise indeterminate scores, whilst delivering a high negative predictive value, is recommended.[1094] Comparison to the pre-treatment PET-CT avidity also may help. When there is evidence of an incomplete response, a neck dissection is required, the extent of which may vary. There is an increasing trend to perform a more selective neck dissection in patients who have completed standard chemoradiotherapy schedules and who have isolated, single-level disease on post-treatment PET-CT imaging.[1095] However, the extent of pre-

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

treatment neck disease may also be factored into the decision-making, as well as the fact that the post-chemoradiotherapy neck dissection may be the last opportunity for curative neck surgery.

When there is an equivocal response (e.g. mild or no FDG avidity in enlarged nodes, or mild avidity in normal or borderline-sized nodes), there is variance in consequent management. In HPV-positive tumours (the majority in this group), involution continues beyond 12 weeks (especially for cystic nodules). Over 85 per cent of this group with an initial equivocal response do not go on to develop lymph node recurrence. A second-look interval PET-CT at a further three months showed that over 70 per cent of cases convert to a radiological complete response, with no subsequent regional failure.[163,1096]

Ultrasound with fine needle aspiration cytology in the assessment of disease response cannot be relied upon in isolation.[1097] Other potential strategies in this situation that require more evaluation include diffusion-weighted imaging MRI,[1098] or the use of circulating biomarkers such as tumour DNA or HPV antigens to detect disease persistence.[1099]

Currently, a therapeutic neck dissection is generally recommended in advanced N_3 HPV-positive or HPV-negative SCC with an equivocal response, because there is little evidence to modify the standard of care with a second, delayed PET-CT scan.

Treatment of contralateral lymph nodes in lateralised primary cancers

Recommendations

- There is no need for contralateral elective neck treatment for lateralised $T_{1/2}$ cancers with limited or no ipsilateral neck metastases (N_0 or single lymph node sized 3 cm or less) (evidence-based recommendation (R))

The contralateral neck should in general be treated according to the same principles as described above, which deal with the ipsilateral neck (or both sides for midline tumours).

Not irradiating the contralateral neck spares treatment effects, and is supported by low contralateral isolated nodal recurrence rates.[1100,1101] Much of the evidence has focused on oropharyngeal SCC. The evidence supports the fact that contralateral neck irradiation is not indicated for lateralised T_1 or T_2 oropharyngeal cancers staged as N_0 or with a single ipsilateral lymph node sized less than 3 cm (i.e. N_1, seventh edition of the TNM classification and staging system). The contralateral regional failure rate with ipsilateral neck (only) treatment is low (1 per cent or less).[1102] There is growing evidence that this also applies to cases with multiple ipsilateral lymph nodes (i.e. N_{2b}, seventh edition of the TNM classification and staging system) with low isolated contralateral neck recurrence (around 3 per cent).[1103] However, practice varies, and MDT discussion is recommended in such cases, especially when there is a high burden of ipsilateral neck disease and more advanced primary cancers.

The use of lymphatic mapping with single-photon emission computed tomography ('SPECT')-CT and/or sentinel lymph node biopsy in order to guide neck treatment, including the contralateral neck, may assist with this issue (see the Studies due to report section below).

Recurrent disease

Isolated lymph node recurrent disease

Recommendations

- Salvage neck dissection with curative intent should be offered for recurrent neck disease deemed to be operable (good practice point (G))

When isolated nodal recurrence is found, a PET-CT scan is recommended, to help delineate the recurrence and to assess for local and distant disease. Patients with isolated nodal recurrence that is thought to be resectable with clear margins should be considered for salvage neck dissection, as it provides the best chance of regional control. The reported overall survival outcome for isolated nodal recurrence treated with salvage neck dissection varies from 25 per cent to 56 per cent.[1104,1105] Favourable prognostic factors for survival include p16-positive SCC, complete margins, no extra-nodal extension, low-volume disease, no previous neck treatment and a disease-free interval of greater than six months.[1106] Current evidence suggests regional recurrence occurs generally in the previously treated involved neck levels, regardless of whether the initial modality was surgery or (chemo)radiotherapy. Limited evidence exists regarding the optimal extent of salvage neck dissection in isolated nodal recurrence, with low rates of occult metastases reported in levels I and V.

For unresectable disease or resectable disease resulting in significant morbidity, re-irradiation may be considered in carefully selected patients using high precision conformal RT (intensity-modulated RT, volumetric modulated arc therapy) and novel (stereotactic ablative RT) techniques to reduce severe toxicity.[1107]

The combination of chemoradiotherapy and then secondary neck dissection adds to the risk of severe late toxicity (chronic laryngeal or pharyngeal toxicity grade of more than 3, organ dysfunction, or death).[1108]

Treatment of clinically staged node-negative neck with primary tumour recurrence

Most evidence in this area is from salvage laryngectomy, the commonest salvage surgery scenario. Here, the incidence of occult metastases is low, around 10–15 per cent. Neck dissection in the whole patient group does not improve overall survival, although it does improve locoregional control.[1109,1110]

However, the risk of occult metastases is higher in patients with initial N_+ disease, a previously untreated neck, advanced $T_{3/4}$ primary disease or higher risk subsites for occult metastases (e.g. hypopharynx, supraglottis).[1109,1111] Hence, ipsilateral neck dissection should at least be considered in these circumstances, and may be associated with improved survival.

A concern in the setting of salvage laryngectomy is whether neck dissection increases the risk of pharyngocutaneous fistula, with some supporting evidence for this.

In the setting of salvage surgery for non-laryngeal or non-hypopharyngeal cancers, there are less data, but the principle appears to be broadly similar with generally low rates of occult metastases (around 10 per cent) and no survival advantage as a result of neck dissection.[1111] However, in many cases, the neck will be accessed for microvascular reconstruction, and neck dissection of levels 2–3 adds little morbidity when microvascular access for free-flap reconstruction is required.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Studies due to report

'Post-operative Adjuvant Treatment for HPV-positive Tumours (PATHOS)' (ClinicalTrials.gov Identifier: NCT02215265). This study further investigates the significance of extra-nodal extension and omission of chemotherapy for HPV-positive SCC, and the outcomes of ipsilateral neck irradiation for well-lateralised oropharyngeal cancer tumours.

'Comparing Sentinel Lymph Node (SLN) Biopsy With Standard Neck Dissection for Patients With Early-Stage Oral Cavity Cancer' (NRG Oncology study identification number: HN006). A phase II and subsequent planned phase III non-inferiority trial of 5 per cent absolute difference in two-year disease-free survival.

'Lymph Drainage Mapping for Tailoring Elective Nodal Irradiation in Head and Neck Cancer (SUSPECT-2)' (ClinicalTrials.gov Identifier: NCT03968679). A single-centre prospective trial of single-photon emission computed tomography CT-guided elective nodal irradiation.

'SPECT-CT Guided ELEctive Contralateral Neck Treatment in Lateralized Oropharyngeal Cancer (SELECT)' (Canadian Cancer Trials Group study identification number: CCTG-HN11). A phase III randomised, controlled trial.

'Lymphatic Mapping Of Oropharyngeal Cancer (LOOC)' (ClinicalTrials.gov Identifier: NCT04498221). A phase II multicentre study to validate the use of sentinel node biopsy.

Research questions

(1) What is the prognostic significance of extra-nodal extension in HPV-related oropharyngeal cancer?
(2) What is/are the ideal radiological modality/modalities for detecting pre-treatment nodal extra-nodal extension?
(3) What are the indications for dose reduction in the surgically staged neck for HPV-related and unrelated head and neck SCC?
(4) What are the indications for dose reduction in the clinically staged neck for HPV-related and unrelated head and neck SCC?
(5) Does sentinel node guided neck treatment offer functional advantages over sentinel node dissection?

Chapter 27: Management of head and neck squamous cell carcinoma of unknown primary

Table of Contents

Introduction

Producing and interpreting guidelines for the management of head and neck squamous cell carcinoma (SCC) of unknown primary is inherently challenging. Firstly, there is a paucity of robust contemporary evidence on the topic. Many historic studies predate our understanding of the role of human papillomavirus (HPV) in head and neck cancer,[226] and, with the incidence of HPV-related disease rising,[205] management recommendations must necessarily be updated to be most effective at improving patient care. Secondly, the understanding and definition of what is considered an 'unknown primary' evolves during the diagnostic pathway. During this process, clinical examination, imaging investigations and surgical biopsies all may identify a primary disease. As a result, direct inter-study comparisons or meta-analysis are complicated by incongruent cohort definitions and eligibility criteria. Thirdly, true unknown primary disease is not common, and so establishing both a substantial evidence base and reasonable clinical experience regarding its management can be challenging, particularly in single-centre settings.

Despite these limitations, many organisations have produced guidelines covering the management of head and neck SCC of unknown primary, using a variety of methodologies.[1112–871] The present guidelines were produced following a multi-stage meta-consensus initiative that was developed specifically for this work. This incorporated a National Audit of Practice, a National Consensus Day and a National Delphi Exercise. Through this process, novel data were generated, the most up to date published and unpublished studies were considered, and draft statements were generated before being scrutinised by representatives from all UK head and neck multidisciplinary teams (MDTs) to produce these final recommendations. The full outline of this methodology has been published separately.[1114]

These guidelines follow the patient journey from presentation with unknown primary disease to post-treatment surveillance. Recommendations are included as statements at the beginning of each section, followed by further guidance and commentary to add context. National Institute for Health and Care Excellence (NICE) phraseology has been used when generating the statements, to reflect the strength of evidence and level of certainty in the benefit of the intervention for each recommendation presented.[1115] The terms 'offer', 'perform', 'refer' and 'include' reflect confidence in a strong patient benefit. Where the evidence offers less certainty in a clear benefit, the term 'consider' is used.

These guidelines do not describe the management of non-SCC disease of unknown primary origin.

An illustration of the patient pathway related to proposed minimum required interventions is shown in Figure 1.

Investigations before diagnostic surgery

Recommendations

- Offer all patients with clinically suspected head and neck SCC of unknown primary ultrasound-guided sampling as a first-line investigation to diagnose cervical metastasis of SCC, which must include p16 and/or HPV subtyping and ancillary tests (evidence-based recommendation (R))
- Do not offer open biopsy to patients with a neck lump as a first-line investigation to diagnose cervical metastasis (R)
- Offer all patients with clinical suspicion of head and neck SCC of unknown primary concurrent magnetic resonance imaging (MRI) and positron emission tomography

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

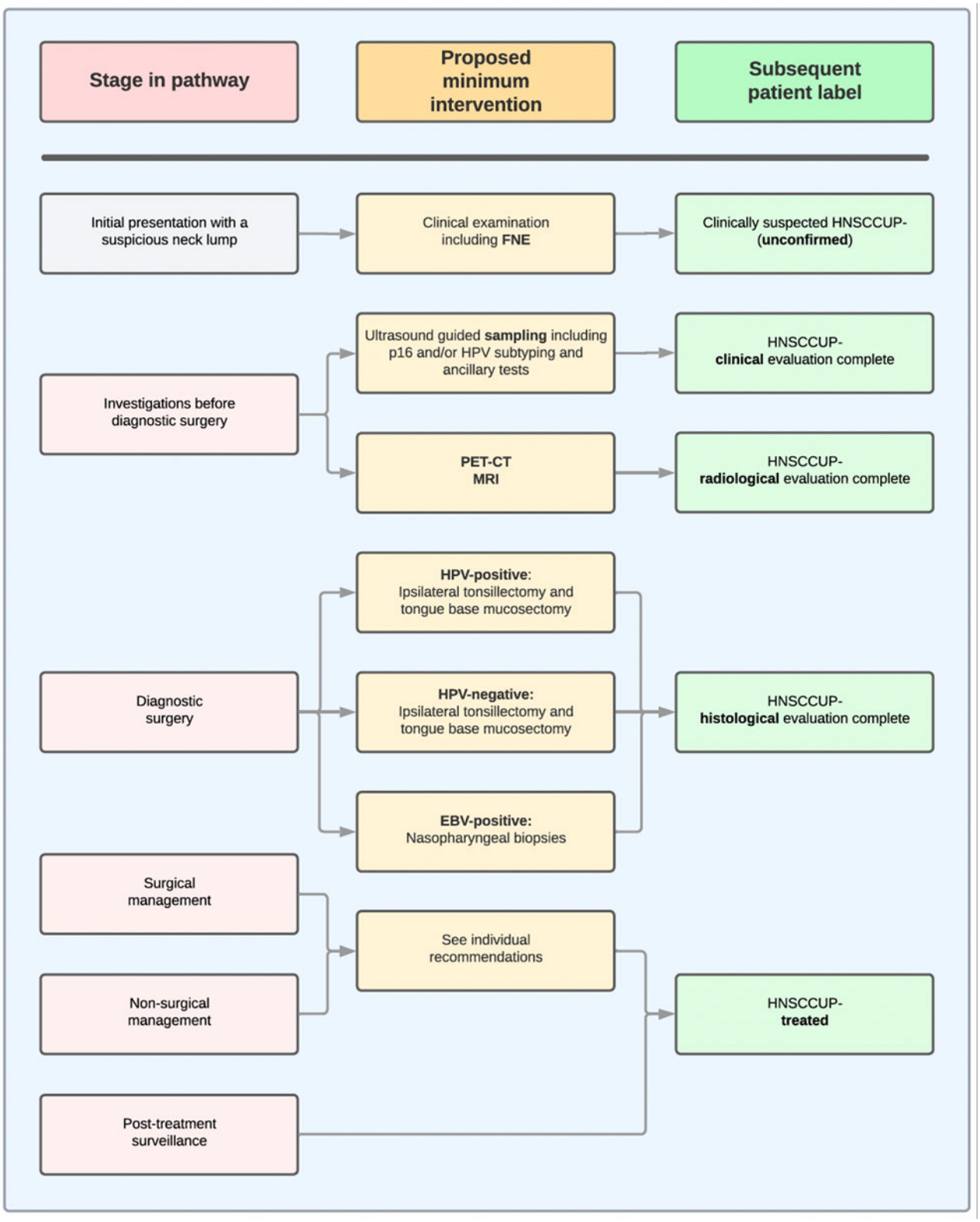


Figure 1. Illustration of the patient pathway, related to proposed minimum required intervention patient labels for these groups (each stage assumes the primary site remains unknown). FNE = flexible nasendoscopy; HNSCCUP = head and neck squamous cell carcinoma of unknown primary; HPV = human papillomavirus; PET-CT = positron emission tomography computed tomography; MRI = magnetic resonance imaging; EBV = Epstein–Barr virus

computed tomography (PET-CT) scanning as first-line cross-sectional imaging investigations (R)

- Consider image-enhancement technology (including narrow-band imaging) as an adjunct to white-light endoscopy in the examination of all patients with clinically suspected head and neck SCC of unknown primary (good practice point (G))
- Refer all patients with clinically suspected pathologically confirmed head and neck SCC of unknown primary to a core member of the head and neck MDT for further investigations (R)

All patients presenting with a neck mass will need a comprehensive history taking, and clinical examination including flexible nasendoscopy (FNE). Alongside FNE, there is good evidence that virtual chromoendoscopy (e.g. narrow-band imaging) can aid the recognition of otherwise occult mucosal

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

lesions, though it is acknowledged that not all UK centres have access to this technology.[1116]

All patients will require cytological or cytopathological confirmation of cancer. Subtyping of HPV is important for the effective management of all clinically suspected head and neck SCC of unknown primary patients; if this is not available on fine needle aspiration cytology then core biopsy should be performed. This is particularly important for patients in whom no primary site is identified by the end of the diagnostic pathway and who do not undergo neck dissection, as they will have no other tissue on which to perform HPV and Epstein–Barr virus analysis. Ultrasound guidance increases the diagnostic accuracy of the biopsy.[1117] Open biopsy is not felt to be an appropriate alternative to ultrasound-guided core biopsy.

Patients presenting with clinically suspected head and neck SCC of unknown primary often experience long diagnostic pathways before starting definitive treatment, with a significant amount of time on the pathway spent awaiting imaging investigations, PET-CT in particular. Current NICE guidance is to consider a PET-CT scan for patients with confirmed metastatic disease in whom no primary is evident on clinical examination.[1074] Immediately following cytological or cytopathological confirmation of metastatic disease, concurrent MRI and PET-CT, requested as first-line cross-sectional imaging, would allow synchronous interpretation, cover staging of the chest, and expedite progression to diagnostic surgery in search of a primary site.

Timely referral to a head and neck MDT is deemed essential to ensure appropriate oversight of the diagnostic pathway, as well as subsequent treatment.[1118]

Diagnostic surgery

Recommendations

- Perform all radiological investigations that aim to identify the primary site prior to discussion at the head and neck MDT and before diagnostic surgery (evidence-based recommendation (R))
- Offer nasopharyngeal biopsies when the cervical node sampling reveals Epstein–Barr virus positive metastasis (R)
- Do not offer biopsies of clinically and radiologically normal upper aerodigestive tract mucosa. This excludes tonsillectomy or tongue base mucosectomy (R)
- Offer ipsilateral tonsillectomy (rather than incisional biopsy) in all patients (R)
- Consider ipsilateral tongue base mucosectomy in all patients (good practice point (G))
- Consider contralateral tonsillectomy (rather than incisional biopsy) in all patients (G)
- Consider contralateral tongue base mucosectomy in all patients (G)
- Perform tongue base mucosectomy using one of the following transoral techniques, when indicated: endoscopic, microscopic or robot-assisted (G)

Strategies for obtaining oropharyngeal biopsies remain contentious. In 2016, NICE guidance included offering surgery to identify the unknown primary.[1074] However, as with all surgery, these procedures are associated with their own morbidities and complications; if offered to the patient, each element should be clinically justifiable, and the patient fully informed of the risks and benefits.[1119,1120]

Ipsilateral tonsillectomy is widely accepted as being diagnostically beneficial. However, the detection rate of primary disease from a contralateral tonsillectomy is lower. Consequently, the marginal benefit from removing the contralateral tonsil for diagnostic purposes, as well as the advantage of a symmetrical oropharynx being easier to monitor for future disease, must be weighed against the additional morbidity from the procedure.[1121]

Removal of the lingual tonsillar tissue (also known as tongue base mucosectomy) as a diagnostic procedure in search of a primary tumour has become more prevalent. This is, in part, due to the advent of robotic technology, although other transoral techniques are available and have proved efficacious. Tongue base mucosectomy has been reported to increase the identification of the primary tumour.[1122,1123] There remains debate about the extent of tongue base mucosectomy (whether it should be unilateral or bilateral) as well as the timing of the procedure (whether it should be performed at the same time as palatine tonsillectomy or only following negative histology from palatine tonsillectomy); both factors will affect the apparent detection rate. Practice regarding the extent of oropharyngeal clearance is influenced by concerns of pharyngeal stenosis, though a rate of symptomatic narrowing has not been established in any large-scale cohorts.

Surgical management

Unless otherwise specified, patients with head and neck SCC of unknown primary referred to in this section are assumed to have undergone an adequate diagnostic investigation, as per their MDT, and are due to commence treatment for head and neck SCC of unknown primary.

Recommendations

- Consider ipsilateral tonsillectomy and tongue base mucosectomy, and ipsilateral neck dissection in both HPV-negative and HPV-positive head and neck SCC of unknown primary in cases with a single involved node sized 3 cm or less with no radiological extra-nodal extension (good practice point (G))
- Consider neck dissection prior to treatment in patients with HPV-negative head and neck SCC of unknown primary undergoing radical radiotherapy with advanced disease who are unsuitable for concomitant chemotherapy (G)
- Consider neck dissection prior to radiotherapy, with or without chemotherapy, in HPV-negative head and neck SCC of unknown primary patients with nodal stage N_3 neck disease (G)

Single modality surgery may be considered as appropriate treatment for patients undergoing ipsilateral surgery to the oropharynx and the neck with a single involved node measuring 3 cm or less with no radiological extra-nodal extension. Clearance of the contralateral tonsil and/or tongue base may help reassure the MDT that the putative primary sites have been adequately addressed to manage the risk of primary emergence.

Concomitant chemotherapy has been shown to have a significant benefit in patients with HPV-negative disease, which is more commonly associated with an aggressive course.[1124] If concomitant chemotherapy is not felt to be suitable then primary surgery should be considered in these patients, to ensure dual modality therapy is delivered. An alternative is

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

to perform surgery after radiotherapy, depending on PET-CT imaging findings.

In HPV-negative head and neck SCC of unknown primary patients with N_3 disease, primary neck dissection should be considered before radiotherapy, regardless of the patients' suitability for chemotherapy, owing to their poorer survival outcomes.[1124]

Some MDTs currently advocate a limited 'staging' neck dissection of the clinically negative contralateral neck, with the intention being to show the contralateral neck is histologically disease-free and so to spare this volume from subsequent radiotherapy. However, there is currently a lack of evidence in the literature to support this strategy and so it is not recommended (or opposed) by these guidelines.

Non-surgical management

Unless otherwise specified, patients with head and neck SCC of unknown primary in this section are assumed to have undergone an adequate diagnostic investigation, as per their MDT, and are due to commence treatment for head and neck SCC of unknown primary.

Recommendations

- Consider omitting adjuvant radiotherapy after an ipsilateral neck dissection where there is a single involved node sized 3 cm or less with no extra-nodal extension (good practice point (G))
- Offer adjuvant radiotherapy, with or without chemotherapy, to the ipsilateral neck after an ipsilateral neck dissection where there is a single involved node sized greater than 3 cm, or there are multiple involved nodes, or there is extra-nodal extension (evidence-based recommendation (R))
- Consider adjuvant radiotherapy with or without chemotherapy to the bilateral neck after an ipsilateral neck dissection where there are multiple involved nodes or there is pathological extra-nodal extension (G)
- Consider radiotherapy, with or without chemotherapy, to the bilateral neck if there are multiple involved ipsilateral nodes or there is radiological extra-nodal extension (G)
- Consider including the ipsilateral oropharynx in the treated volume when giving radiotherapy to the neck for unilateral HPV-positive head and neck SCC of unknown primary (G)
- Consider including possible mucosal primary sites when giving radiotherapy to the neck for unilateral HPV-negative head and neck SCC of unknown primary. Decide possible sites based on the pattern of nodal involvement, clinicopathological features and risk factors (e.g. smoking) (G)
- Offer 50 Gy in 2 Gy fractions or equivalent (e.g. 54 Gy in 30 fractions or 56 Gy in 35 fractions) as the radiotherapy dose for possible mucosal primary sites when they are intentionally included in the target volume (R)
- Offer concomitant cisplatin chemotherapy with adjuvant radiotherapy if there is pathological extra-nodal extension and the patient is suitable to receive cisplatin (R)
- Offer concomitant cisplatin chemotherapy with primary radiotherapy if there are multiple involved nodes or radiological extra-nodal extension and the patient is deemed fit to receive cisplatin (R)
- Include the ipsilateral retropharyngeal and retrostyloid nodes in the elective target volume when giving radiotherapy to the ipsilateral neck where level II is involved (R)

Adjuvant radiotherapy to the ipsilateral neck in more advanced head and neck SCC of unknown primary disease is essential.[1125] Contralateral radiation should be considered in the case of extra-nodal extension or where multiple nodes are involved. For the majority of head and neck SCC of unknown primary disease patients who present with level II involvement, retropharyngeal and retrostyloid nodes should be included in the elective target volume.

There is insufficient evidence to support or oppose ipsilateral radiation to the oropharynx in all unilateral HPV-positive head and neck SCC of unknown primaries, or indeed to any putative mucosal sites in HPV-negative disease. Where radiotherapy is given for HPV-negative head and neck SCC of unknown primary disease, the mucosal sites should be chosen based on the pattern of nodal involvement and any other relevant clinicopathological features. In all cases where radiotherapy is given to mucosal target volumes, these guidelines advocate the use of a prophylactic dose, not as high as used in adjuvant or radical dosing regimens, though it is accepted this is based on consensus opinion rather than any high-level evidence. The omission of radiation to putative mucosal sites may be considered under MDT supervision, but assumes an adequate diagnostic investigation and appropriate clinico-radiological surveillance.

Post-treatment surveillance

Recommendations

- Consider adding regular cross-sectional imaging to the regular clinical examination for post-treatment surveillance of patients treated with surgery as a single modality, following bilateral tonsillectomy and tongue base mucosectomy and pathologically staged N_1 disease with no extra-nodal extension (good practice point (G))
- Follow up is discussed in a separate chapter, but, because of the nature of unknown primary disease and the effects of treatment on imaging, baseline cross-sectional imaging is recommended, and surveillance imaging should be considered for those who have received single modality surgical treatment, in particular (G)

National audit data have suggested that locoregional control rates may be lower in patients treated by surgery alone. As such, this group has been highlighted for regular imaging surveillance, for primary emergence, in addition to regular clinical review. It is possible that the addition of radiation directed at the neck may give enough dose to putative mucosal sites to treat any occult primary disease that is not clinically, radiologically or histologically evident by the time some patients commence definitive treatment for their head and neck SCC of unknown primary.

Limitations

A complete outline of the methodology used to develop these guidelines is published elsewhere, which outlines the initiative used to generate these consensus recommendations.[1126] The following limitations are highlighted here as particularly relevant to the process. Firstly, attendance at the Consensus Day was self-selecting, giving the potential for disproportionate representation of individual stakeholder groups during the generation of the draft consensus statements. Secondly, during the Delphi exercise, the MDT contact was asked to record the

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

consensus view of their team. However, the true level of consultation with each MDT was not recorded and may have varied. Responses may, therefore, have been biased towards those who engaged in the process locally, and specifically towards ENT team members who were the contact specialty for this exercise. Finally, our Delphi exercise used a binary response to register support either for or against each statement under consideration. As such, there may have been an underrepresentation of clinical oncology input. This methodology is unable to present the strength of opinion from individual units, and could be seen to misrepresent the views of a minority of respondents who may have had strong opposition to the statement as presented, compared to a majority who felt only weakly in favour.

Acknowledgements. This work was only possible due to contributions of the individuals listed in Appendix 2.

Chapter 28: Non-melanoma skin cancer

Table of Contents

Introduction

Non-melanoma skin cancer is the most common type of malignancy in the Caucasian population and is four times more common than any other cancer in the UK.[1127] One in four men and one in six women will develop a non-melanoma skin cancer in their lifetime.[1128] Mortality from non-melanoma skin cancer is rare, but tends to be from local or regional disease. Distant metastasis is rare with the exception of Merkel cell carcinoma. The majority of non-melanoma skin cancers can be cured by adequate initial surgical management. High-risk and complex non-melanoma skin cancer may be challenging to manage, and must be carried out through a skin cancer multidisciplinary team (MDT).

The majority of non-melanoma skin cancers occur in the skin of the head and neck. However, their clinical behaviours do not mirror that of head and neck mucosal malignancies. In order to optimise management and outcomes, all non-melanoma skin cancers (with the exception of specifically defined low-risk basal cell carcinoma (BCC)) should be managed by core members of a skin cancer MDT.

This chapter will describe the recommendations for the investigation and management of non-melanoma skin cancer, drawing on guidelines produced by the British Association of Dermatologists. These are recommended reading, as they are accepted as the national guidelines for the management of non-melanoma skin cancer and are mandated by the National Institute for Health and Care Excellence (NICE).[1129,1130]

Pathology

The majority of non-melanoma skin cancers are keratinocyte cancers, of which approximately 80 per cent are BCCs. Of the remaining non-melanoma skin cancers, the majority are cutaneous squamous cell carcinomas (SCCs), with a very small number of rare tumours such as Merkel cell carcinoma and adnexal tumours.

Premalignant lesions such as actinic keratosis or Bowen's disease (in situ cutaneous SCC) can undergo malignant transformation to non-melanoma skin cancer. The risk of a single actinic keratosis transforming to SCC is low (around 1 per cent on 10 years). However, patients with actinic keratosis are five times more likely to develop a skin cancer compared to matched controls, with the greatest risk for cutaneous SCC.[1131] Around 3–5 per cent of proven Bowen's disease transforms to cutaneous SCC, higher in high-risk populations such as the immunosuppressed.[1132]

Epidemiology and aetiology

The UK annual incidence of non-melanoma skin cancer is around 210 000 cases per year, with at least a 5 per cent annual increase observed from 2013 to 2015.[1131] Non-melanoma skin cancer is more common in men, with a mean age of onset in the eighth decade of life. The majority of patients with non-melanoma skin cancer are Caucasian. The major aetiological factors for non-melanoma skin cancer are fair skin type and chronic exposure to sunlight, and indoor tanning or other types of ionising radiation. Genetic syndromes are associated with the risk of non-melanoma skin cancer, such as Gorlin syndrome (BCC), Muir–Torre syndrome which is a phenotypic variant of Lynch syndrome (characterised by keratoacanthomas and sebaceous tumours, but also with an increased risk of cutaneous SCCs), and xeroderma pigmentosa (melanoma and non-melanoma skin cancer).[1133] Immunosuppression is also a significant risk factor. Human papilloma virus infection (beta types), particularly in the immunosuppressed, is also an important aetiological factor in cutaneous SCC.[1134]

Previous non-melanoma skin cancer is a noteworthy risk factor, with over 40 per cent of patients with BCC and 37 per cent of patients with cutaneous SCC developing further non-melanoma skin cancer. For Merkel cell carcinoma, there is association with ultraviolet (UV) exposure, increasing age and immunosuppression. There is now growing

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

evidence that for some Merkel cell carcinomas, a major aetiological factor is infection with Merkel cell polyomavirus,[1135] though in Australasia the main factor may be UV exposure.[1136,1137]

Presentation, diagnosis and multidisciplinary team management

Recommendations

- Measure and record suspected skin cancers (evidence-based recommendation (R))
- Photograph suspected skin cancers before biopsy or excision (R)
- Royal College of Pathology minimum dataset should be used to report all non-melanoma skin cancer pathology (R)
- Cross-sectional imaging should be arranged to assess fixed and/or locally advanced cancers (good practice point (G))
- All head and neck non-melanoma skin cancer (except specifically defined, completely excised low-risk BCC) should be discussed at a skin MDT meeting (R)

Initial patient assessment should include history-taking, a full skin examination, and measurement and photographs of the lesion. For a majority of non-melanoma skin cancer patients, an excisional biopsy will be both diagnostic and therapeutic, planned with a margin likely to completely excise the lesion. It is important where possible to plan a surgical margin that will result in a 1 mm or more histological margin.

Where this is not possible, if there is diagnostic doubt or if the extent of treatment is significant (such as for very large lesions or those invading adjacent structures), and when radiotherapy is being considered as the primary treatment, a diagnostic biopsy may be more appropriate.

Imaging requirements are discussed under the relevant tumour management sections. However, cross-sectional imaging should be undertaken for all primary tumours where deeper tissue involvement is suspected.

In order to optimise management and outcomes, all non-melanoma skin cancers except low-risk BCC cancers should be managed by core members of a skin cancer MDT. This may occur after diagnosis for advanced, rare or metastatic disease, and/or after initial surgery, as well as for recurrent disease.

The following cases do not routinely require MDT discussion in the absence of any other high-risk factors:

- Diagnostics biopsies of BCC
- Diagnostic biopsies of cutaneous SCC
- Completely excised BCC with 1 mm or more histological clearance at all surgical margins following excision with curative intent
- Completely excised low-risk pathologically staged T_1 cutaneous SCC in a low-risk patient (these patients can be tabled for inclusion in cancer registries where that is the local mechanism)

All other cases should be discussed and managed under the auspices of a skin cancer MDT. There may be regional variation in the organisation and set up of different levels of skin MDTs. In some parts of the UK, two levels of skin cancer MDT are recognised: local hospital skin cancer MDTs and regional specialist skin cancer MDTs. The British Association of Dermatology have set levels of care to match the complexity of case needs with varying level of clinical expertise (Figure 1), with some variance according to local or regional expertise.

The importance of specialist pathologists, radiologists, dermatologists, surgeons, clinical oncologists and specialist nurses working together to achieve the best, highest quality outcomes for patients is paramount.

Other specialist input, such as discussion in the head and neck, skull base and/or neuro-oncology MDTs, and collaboration in care, may be required in some cases.

All patients should receive education in self-surveillance and self-examination, UV exposure protection, and vitamin D supplementation.

Staging

The eighth edition of the *AJCC Cancer Staging Manual* has also clarified the classification for cutaneous SCC of the lip, by defining SCC of the dry vermillion as a cutaneous cancer that as such needs to be managed in line with cutaneous SCC guidance.[1138]

There is separate staging for cutaneous SCC of the eyelid and for Merkel cell carcinoma.

Tables 1–3 show the tumour–node–metastasis (TNM) staging for non-melanoma skin cancer (according to the *AJCC Cancer Staging Manual*, eighth edition[1138]).

Management of basal cell carcinoma

Recommendations

- Consider standard surgical excision with a 4–5 mm peripheral margin as the first-line treatment for adults with low-risk BCC (good practice point (G))
- Offer standard surgical excision with immediate reconstruction for adults with BCC with a high-risk factor if the BCC has well defined margins (evidence-based recommendation (R))
- Offer standard surgical excision and delayed reconstruction or Mohs surgery for high-risk or high-risk site BCC with poorly defined margins (R)
- Consider radiotherapy for the treatment of adults with BCC where a patient is unsuitable for, or declines, surgical treatment (R)
- Discuss incompletely excised or complex BCCs within a skin MDT meeting (R)

Basal cell carcinoma is slow-growing and locally invasive, but very rarely metastasises. Although there are many subtypes of BCC, the majority of BCCs can be diagnosed clinically by experienced clinicians with good lighting, skin stretch and dermoscopy.

The British Association of Dermatologists guidelines on the management of BCC have adopted the Royal College of Pathologists dataset for reporting BCCs.[1130] They have combined this with guidelines from NICE, the National Comprehensive Cancer Network[1139] and the Union for International Cancer Control / American Joint Committee on Cancer *AJCC Cancer Staging Manual* (eighth edition)[1138] to produce the criteria for high- and low-risk BCCs (Figure 2). A summary of BCC management is shown in Figure 3.

Low-risk basal cell carcinomas

Low-risk BCCs of the head and neck should be referred to the hospital setting for management by the local hospital skin cancer or specialist skin cancer MDTs.[1140]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Care level	Person or team	Case mix / procedure
1	Any GP in the community	– Benign lesions – Actinic keratoses – Precancerous – SCC in situ or Bowen's disease
2	Listed community skin cancer clinicians associated with a named MDT (LSMDT or SSMDT acting as 'local' LSMDT)	– Low-risk BCC
3	LSMDT, hospital staff core team member (may be core member of SSMDT acting as 'local' LSMDT), without mandatory individual case review by MDT	– High-risk BCC – SCC } Other than categories below
4	LSMDT, hospital staff core team member(s), with mandatory individual case review by LSMDT (may be the SSMDT & its core members acting as 'local' LSMDT)	– High-risk BCC } Recurrent or with positive excision margins – SCC – Malignant melanoma – new, single primary, adult, non-metastatic, not for approved trial entry, up to & including stage IIa (must fulfil all these criteria) – Radiotherapy if attendance by clinical oncologist at LSMDT – Lesion where diagnosis is uncertain but may be malignant – Incompatible clinical & histological findings
5	SSMDT hospital staff core team member(s), with mandatory individual case review by SSMDT (may have been previously reviewed by LSMDT or rapidly referred without prior review). For some cases – only 1 agreed SSMDT, if more than 1 in the Network Cases to be dealt with by only 1 agreed SSMDT per Network, if more than 1 in the Network: – Cutaneous lymphoma – Kaposi's sarcoma	– Selected BCCs & SCCs needing plastic or reconstructive surgery by SSMDT core member (as per Network clinical guidelines) – Radiotherapy (as per Network clinical guidelines). If not, discussed & treated by LSMDT clinical oncology core team member – Metastatic SCC on presentation or newly metastatic – Malignant melanoma – stage IIb or more; or aged <19 years, or metastatic on presentation, or newly metastatic, or recurrent, or for approved trial entry, or positive excision margins – Any cases for approved trial entry

Figure 1. Levels of care for skin cancer multidisciplinary teams. The Improving Outcomes Guidance, either explicitly or by implication, effectively specifies six levels of care, differing in the degree of specialisation, case mix, and the procedures and service consolidation needed, as demonstrated in the table. GP = general practitioner; SCC = squamous cell carcinoma; MDT = multidisciplinary team; LSMDT = local hospital skin cancer multidisciplinary team; SSMDT = specialist skin cancer multidisciplinary team; BCC = basal cell carcinoma; SCG = Specialised Commissioning Group

Whilst destructive techniques such as cryotherapy, curettage and cautery, and photodynamic therapy may safely be used by appropriately trained clinicians in specific circumstances, standard surgical excision remains the mainstay of treatment for low-risk BCCs, using at least a 4 mm peripheral margin.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

	– Cutaneous sarcoma above superficial fascia. (Below fascia, refer to sarcoma MDT) Note: there should be agreed working arrangements with site-specialised MDTs for SCC of head & neck, & sarcoma, & mucosal malignant melanoma	– Any cases for adjuvant therapy (as per Network clinical guidelines) – Histology opinion from SSMDT core pathology team member – Mohs surgery – Skin cancer in immunocompromised patients including organ transplant recipients – Skin cancer in genetically predisposed patients including Gorlin syndrome
6	– Supranetwork team. Selected Networks only. Agreed with SCGs – Clinician responsible for named facilities for photopheresis (very small numbers of patients). Agreed with SCGs	– T-cell cutaneous lymphoma: total body surface electron beam therapy – T-cell cutaneous lymphoma. Photopheresis

Figure 1. (Continued)

High-risk basal cell carcinomas

The treatment options are primary surgery, Mohs surgery, radiotherapy or no treatment. Surgery should aim to achieve at least a 5 mm peripheral clearance margin. Mohs micrographic surgery may also be considered, particularly for poorly defined cancers. Radiotherapy may be used in the treatment of primary BCC in patients who are unwilling or unsuitable for surgery, or who have a preference for radiotherapy. Radiotherapy may be of particular benefit in cosmetically sensitive areas. Radiotherapy is contraindicated in previously irradiated areas, in patients with genetic conditions predisposing to BCC (e.g. Gorlin syndrome), and in cases where there is bone or cartilage invasion. Surgery is generally preferred in younger patients, but there may be occasions where, on the balance of risks and benefits, radiotherapy is used.

For recurrent or incompletely excised BCCs, Mohs surgery, standard excision with delayed reconstruction or radiotherapy should be considered following discussion at a specialist skin cancer MDT meeting.

Table 1. Tumour staging for non-melanoma skin cancer*

Tumour (T) stage	Primary tumour criteria
T_X	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T_1	Tumour sized ≤2 cm in greatest dimension
T_2	Tumour sized >2 cm to ≤4 cm in greatest dimension
T_3	Tumour sized >4 cm in greatest dimension, or minor bone erosion, or perineural invasion (of named nerve) or deep invasion†
T_{4a}	Tumour with gross cortical bone or marrow invasion
T_{4b}	Tumour with skull base or axial skeleton invasion, including foraminal involvement &/or vertebral foramen involvement to epidural space

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138] †Beyond subcutaneous fat or more than 6 mm from the granular layer of adjacent normal epidermis

Advanced BCCs – those invading multiple structures, in complex and functionally and cosmetically important areas, with large numbers of co-existing tumours, which are multiply recurrent, a high-risk subtype or require extensive treatment – should be discussed in a specialist skin cancer MDT meeting and treatment carefully planned. The patient's performance status and frailty, and their preferences, should be considered when planning treatment, and it must be accepted that, for some patients, not treating the BCC may be the best option.

Other treatment options may be suitable for patients with complex or advanced disease who are not suitable for standard surgical management or radiotherapy, such as electrochemotherapy, which is NICE-approved in appropriate cases.[1141] The use of these modalities must be discussed at a specialist skin cancer MDT meeting. Vismodegib, a hedgehog pathway inhibitor was introduced for use in patients with Gorlin syndrome and unresectable BCCs, but in 2017 approval for vismodegib was withdrawn by NICE. However, it is now available via the National Health Service (NHS) England Cancer Drugs Fund for use in Gorlin syndrome patients where there are six or more BCCs or in a non-Gorlin syndrome patient with more than six non-locally advanced BCCs, and in non-metastatic BCC cases where surgical treatment would be very disfiguring.[1142]

Patients with a single adequately treated BCC do not require routine follow up and can be discharged with appropriate advice. Patients require follow up if the tumour is at a high risk of recurrence (e.g. after inadequate initial treatment) or there is a high risk of further BCC development (multiple previous BCCs, Gorlin syndrome or immunosuppression).

Cutaneous squamous cell carcinoma

Recommendations

- Request ultrasound with or without fine needle aspiration cytology (FNAC) for clinically suspected lymph node

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Nodal staging for non-melanoma skin cancer*

Nodal (N) stage	Clinical N stage (cN)	Pathological N stage (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized ≤3 cm in greatest dimension, & with no extra-nodal extension
N_{2a}	Metastasis in a single ipsilateral lymph node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a single ipsilateral lymph node, sized <3 cm & with extra-nodal extension Or metastasis in a single ipsilateral node, sized >3 cm but not >6 cm in greatest dimension, & with no extra-nodal extension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in multiple ipsilateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in bilateral or contralateral lymph node(s), none sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3a}	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension	Metastasis in a lymph node, sized >6 cm in greatest dimension, & with no extra-nodal extension
N_{3b}	Metastasis in any node(s), with clinically overt extra-nodal extension	Metastasis in a single ipsilateral node, sized >3 cm in greatest dimension, & with extra-nodal extension Or metastasis in multiple ipsilateral, contralateral or bilateral nodes, any with extra-nodal extension Or metastasis in a single contralateral node, of any size, & with extra-nodal extension

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138]

metastases for non-melanoma skin cancers (evidence-based recommendation (R))
- Request axial imaging for $T_{3–4}$ cancers and include regional nodal basins (good practice point (G))
- Offer standard surgical excision as the first-line option to patients with cutaneous SCC, with peripheral surgical margins based on risk stratification (R)
- Lesions should be excised to the next clear surgical plane; in the scalp, resection should include galea (R)
- Discuss all cutaneous SCC cases, except pathologically staged T_1 tumours excised with 1 mm or greater margin, at skin cancer MDT meetings (R)
- Consider a less than 1 mm histological margin in cutaneous SCC as a close margin, and consider wider excision or adjuvant radiotherapy (R)
- Offer adjuvant radiotherapy to patients with pathologically staged T_3 cutaneous SCC with significant perineural invasion involving one or more nerves of greater than 0.1 mm in diameter, or involving a nerve beyond the dermis or a named nerve (R)

Table 3. Group staging for non-melanoma skin cancer*

Group stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
II	T_2	N_0	M_0
III	T_3	N_0	M_0
	$T_{1–3}$	N_1	M_0
IVA	$T_{1–3}$	$N_{2–3}$	M_0
	T_4	Any N	M_0
IVB	Any T	Any N	M_1

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138]

- Offer parotidectomy and neck dissection to patients with nodal metastasis and no evidence of systemic disease (R)
- Offer adjuvant radiotherapy following nodal dissection for patients with higher than N_1 disease or high-risk pathological features (R)
- Consider immunotherapy for patients with locally and/or regionally advanced disease that is not suitable for surgery or radiotherapy, or those patients with systemic metastases (R)

Suspected cutaneous SCC should be managed by clinicians who are core members of a skin cancer MDT. The British Association of Dermatologists published guidelines on the management of patients with cutaneous SCC in October 2020.[1129] These divide cutaneous SCC into low-, high- and very high-risk status, by integrating clinical, pathological, TNM and margin criteria (Figure 4).

In cases where there is diagnostic uncertainty or complex treatment is required, diagnostic biopsy should be undertaken before definitive treatment.

Imaging for cutaneous squamous cell carcinoma

Cancers staged $T_{3–4}$ need assessment of local extension with appropriate axial imaging (magnetic resonance imaging (MRI) and/or computed tomography (CT)). The regional nodes should be included in this imaging. Magnetic resonance imaging can highlight pathologically involved cranial (or less commonly peripheral) nerves, and should be carried out if there is clinical evidence of nerve involvement (dysaesthesia, formication, motor nerve palsy or severe neuralgic pain).

Lymph node assessment (by ultrasound scan and FNAC) should be conducted if there is evidence of possible lymph node metastasis, but can be considered for high-risk lesions without clinical evidence, such as greater than stage T_2 lip SCC. Patients with regional metastatic disease should undergo CT of the thorax or positron emission tomography (PET)-CT when indicated.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

	Low risk	High risk[a]
Clinical criteria		
Location and size	Area L[b] ≤ 20 mm (maximum clinical diameter) Area M[c] ≤ 10 mm (maximum clinical diameter)	Area L[b] > 20 mm (maximum clinical diameter) Area M[c] > 10 mm (maximum clinical diameter) Area H[d]
Borders	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior radiotherapy	No	Yes
Pathological criteria		
BCC and stage		
Growth pattern	Nodular or superficial	Infiltrative (infiltrating, morphoeic, micronodular)
Differentiation: basosquamous	Absent	Present (with or without lymphovascular invasion)
Level of invasion	Dermis, subcutaneous fat	Beyond subcutaneous fat
Depth (thickness)	≤ 6 mm	> 6 mm
Perineural invasion[e]	Absent	Present
Pathological TNM stage	pT1 ≤ 20 mm (maximum diameter)	pT2 > 20 mm but ≤ 40 mm (maximum diameter) pT3 > 40 mm (maximum diameter), or upstaged[f] pT1 or pT2, or minor bone invasion pT4 major bone invasion
Margins		
Histological margins	Not involved (≥ 1 mm)	Involved (0 mm) or histologically close (< 1 mm)

TNM, Tumour–Nodes–Metastasis. [a]One or more criteria equals high risk, unless stated differently in the summary of the recommendations, or in an explanatory note. [b]Area L = trunk and extremities **but excluding** hands, nail units, genitals, pretibia, ankles and feet. [c]Area M (see Figure 1) = cheeks, forehead, scalp, neck and pretibia. [d]Area H (see Figure 1) = 'mask areas' of face [central face, eyebrows, periorbital, nose, lips (cutaneous and vermilion), chin, mandible, preauricular, postauricular, temple, ears]; genital areas; hands, nail units, ankles and feet, but **excluding the eyelid**. For tumours < 6 mm in size without other high-risk features, standard surgical excision may be considered if a ≥ 4 mm clinical surgical margin can be obtained without significant anatomical or functional distortions. [e]A named nerve or a diameter ≥ 0·1 mm or beyond the dermis. [f]T1 and T2 can be upstaged to T3 by the presence of one or more high-risk clinical or pathological factors comprising specifically defined perineural invasion or deep invasion representing either a tumour thickness or depth > 6 mm and/or invasion beyond or further than the subcutaneous fat.

Figure 2. Criteria for low- and high-risk basal cell carcinoma (BCC).

Surgery for cutaneous squamous cell carcinoma

For the majority of patients, standard surgical excision will provide adequate treatment. Excision should be undertaken by appropriately trained clinicians, under bright light and magnification or dermoscopy. Peripheral margins should be:

- At least 4 mm for low-risk lesions
- At least 6 mm for high-risk lesions
- At least 10 mm for very high-risk lesions

Where tumours are mobile, the deep margin of excision should be at the next anatomically clear plane. On the scalp, at least the galea should be excised with the specimen. The aim should be to achieve clear surgical margins; this may require extensive resection with fascia, muscle, bone and other structures, which may have significant aesthetic and functional ramifications. Where perineural involvement is clinically or radiologically apparent, surgical resection of an involved nerve should be included in the primary treatment if feasible. Where possible, histologically clear margins should be confirmed prior to complex reconstruction. Clearly, in the head and neck this may not always be possible, as some defects will require immediate reconstruction (e.g. in skull base resection or where one or more major vessel(s) are exposed).

Non-surgical options for cutaneous squamous cell carcinoma

Where surgical excision is not feasible, or is likely to result in a poor functional or aesthetic outcome, or where the patient's preference is to avoid surgery, radiotherapy may be considered.

Locally advanced cutaneous SCC in particular requires careful consideration, as surgical excision (with or without adjuvant radiotherapy) may not be the best treatment modality. Locally advanced cutaneous SCCs can be defined as: tumours with symptomatic or radiological evidence of perineurial spread, pathologically staged T_4 tumours, tumours

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

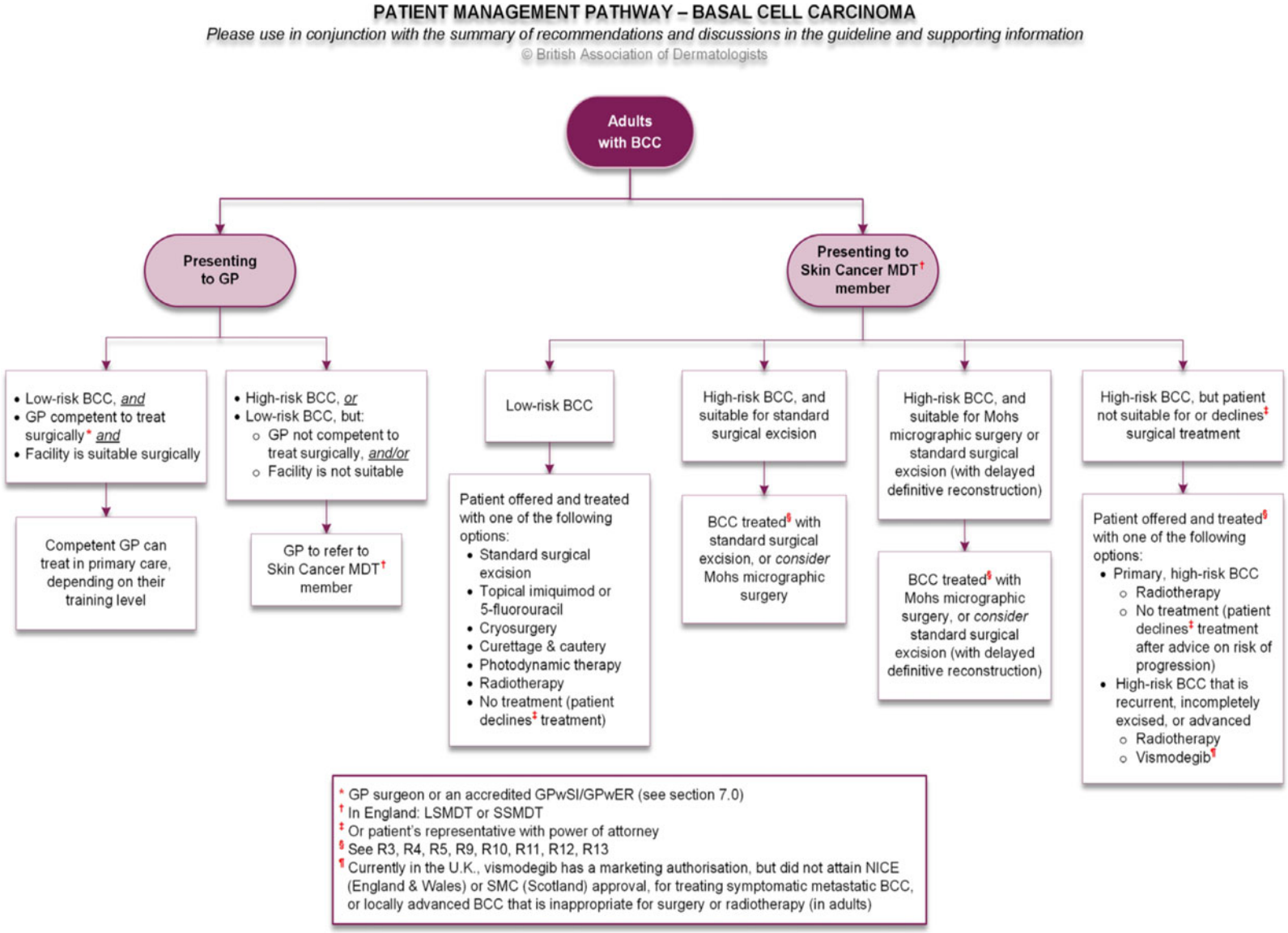


Figure 3. Management of basal cell carcinoma (BCC). GP = general practitioner; MDT = multidisciplinary team; GPwSI = general practitioner with a special interest; GPwER = general practitioner with an extended role; LSMDT = local hospital skin cancer multidisciplinary team; SSMDT = specialist skin cancer multidisciplinary team; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium

	Low risk	High risk	Very high risk
Tumour Factors	Tumour diameter ≤ 20 mm (= pT1) Tumour thickness ≤ 4 mm Invasion into dermis No perineural invasion Well differentiated or moderately differentiated histology No lymphovascular invasion (ALL ABOVE FACTORS SHOULD APPLY to denote a low-risk tumour)	Diameter > 20 – 40 mm (= pT2) Thickness > 4 mm – 6 mm Invasion into subcutaneous fat Perineural invasion present – dermal only; nerve diameter < 0.1 mm Poorly differentiated histology Lymphovascular invasion Tumour site ear or lip Tumour arising within scar or area of chronic inflammation (ANY SINGLE FACTOR denotes a high-risk tumour)	Diameter > 40 mm (= pT3) Thickness > 6 mm Invasion beyond subcutaneous fat Any bone invasion Perineural invasion present in named nerve; nerve ≥ 0.1 mm; or nerve beyond dermis High-grade histological subtype – adenosquamous, desmoplastic, spindle/ sarcomatoid/metaplastic In transit metastasis (ANY SINGLE FACTOR denotes a very high-risk tumour)
Margin status	Clear pathology margins in all dimensions (≥ 1 mm)	One or more involved or close (< 1 mm) pathology margin in a pT1 tumour.	One or more involved or close (< 1 mm) pathology margin in a high-risk tumour
Patient Factors	Immune-competent	Iatrogenic immunosuppression or biological therapies; frailty and/or comorbidities likely to cause some degree of immune compromise; HIV infection stabilized on HAART	AS FOR HIGH-RISK especially: solid organ transplant recipients; haematological malignancies such as chronic lymphocytic leukaemia or myelofibrosis; other significant immunosuppression
Referral to MDT *(Scotland has no LSMDT/ SSMDT division)*	LSMDT discussion not needed	LSMDT discussion of patients with close or involved pathology margins; if margins are not involved other factors alone may not require LSMDT discussion unless more than one factor pertains. Patient factors increase risk, but do not mandate LSMDT discussion in absence of tumour risk factors.	SSMDT discussion should be considered for all patients with very high-risk tumours except those which require straightforward standard surgical excision. A referral to or opinion from an appropriate site-specific MDT may be required to ensure the best management.
Follow-up	Follow-up in secondary care not needed after single post-treatment appointment, where appropriate. Full skin check, examination of regional lymph node basin, discussion of diagnosis and patient education, this may take place before the histological diagnosis. Patient education about sun protection and skin surveillance is advised. Patients and their GPs should be informed of the risk of further cSCCs. There is a 40% risk of a further keratinocyte cancer within 5 years. If this is suspected, refer via the 2-week wait pathway.	4-monthly for 12 months (+ 6-monthly for the second year) especially if several risk factors apply. Full skin check, examination of regional lymph node basin,* discussion of diagnosis and patient education. Advise patient education about sun protection and skin surveillance. Patients with more than one prior keratinocyte carcinomas have a 80% risk of a further keratinocyte cancer within 5 years.	4-monthly for 2 years and 6-monthly for a third year. Full skin check, examination of regional lymph node basin,* discussion of diagnosis and patient education. Advise patient education about sun protection and skin surveillance. Patients with more than one prior keratinocyte carcinomas have a 80% risk of a further keratinocyte cancer within 5 years.

Figure 4. Criteria for risk stratification in cutaneous squamous cell carcinoma (cSCC). pT = pathological tumour stage; HIV = human immunodeficiency virus; HAART = highly active anti-retroviral therapy; MDT = multidisciplinary team; LSMDT = local hospital skin cancer multidisciplinary team; SSMDT = specialist skin cancer multidisciplinary team; GP = general practitioner

requiring complex or extensive resection deep to subcutaneous fat, and tumours with two or more local recurrences. These cases, and those in which surgery may not be preferred or possible, should be discussed in the specialist skin cancer MDT meeting and the patients seen in a multidisciplinary clinic to ensure the best treatment modalities are selected. Although not explicitly included in the definition, patient factors such as frailty or medical co-morbidities may require a similar approach.

Post-operative management and adjuvant therapy

Non-recurrent isolated pathologically staged T_1 cutaneous SCCs with at least 1 mm histological clearance at all margins, in an immunocompetent patient, do not require skin cancer MDT discussion, and the patient can be discharged. Other cutaneous SCC cases should be discussed at the MDT meeting. Patients with one or more clear but close margin may be suitable for observation if the tumour and patient are low risk. For patients with higher risk factors or tumours, and/or one or more close (less than 1 mm) or involved margin, further treatment should be considered and discussed with the patient. This may involve further surgery, including the use of Mohs surgery where appropriate, or adjuvant radiotherapy. An individually tailored approach is required for the immunosuppressed patient, and these patients will require regular surveillance for the long term. Patients with pathologically staged T_{3-4} tumours with histologically significant perineural invasion or other high-risk features will require specialist skin cancer MDT discussion regarding the possibility of adjuvant radiotherapy.[1129,1139]

Regional lymph node metastasis in cutaneous squamous cell carcinoma

Lymph node metastases may rarely be present at the time of diagnosis or occur later. The UK frequency of metastatic cutaneous SCC has been shown to be 1.1 per cent for women and 2.4 per cent for men.[1143] Other studies have shown higher rates of up to 6.7 per cent, but these may be in preselected higher-risk patients being treated in secondary care.[1144]

The mean age of metastatic cutaneous SCC diagnosis is 80 years, and metastases mostly present within 2 years of the primary cutaneous SCC. Risk factors for developing metastatic disease are age over 80 years, being male, immunosuppression and deprivation. Tumours on the ear and lip are also at higher risk of metastasis. This patient group are often older adults, frail and have multiple co-morbidities, and may be challenging to manage.

Survival rates with metastatic cutaneous SCC are poor, with a three-year survival rate of 46 per cent in men and 29 per cent in women, though these data pre-date the emerging role of immune checkpoint inhibition in metastatic cutaneous SCC.[1143] These poor outcomes may reflect the fact that cutaneous SCC is a disease of the older adult. The management of complex metastatic disease is often complicated by multiple co-morbidities and frailty.

Neck dissection and lymphadenectomy

Nodal spread is unpredictable, and varies from the well demonstrated patterns of spread from mucosal aero digestive tract malignancies. The parotid is the most common site of metastasis, followed by level 2.

The evidence for patterns of nodal spread in cutaneous SCC is based in part on sentinel node mapping both for melanoma[1145] and from cutaneous SCC patients who have undergone neck dissection.[1146]

Each individual case should be managed on its own merits, but, in general:

- Clinically or radiologically suspected lymph node metastases should be included in therapeutic lymphadenectomy
- If the parotid gland alone is involved but no other lymph nodes on clinical or radiological assessment, parotidectomy and dissection of levels 1–3 should be carried out
- Parotidectomy should be included in a therapeutic lymphadenectomy
- For the clinically staged N_+ neck in posterior tumours, levels 2–5 should be dissected; level 1 can be omitted if uninvolved
- For the clinically staged N_+ neck in anterior tumours, levels 1–4 should be dissected; level 5 can be omitted if uninvolved

As lymphatic drainage of the skin is initially via the superficial system, removing these draining nodes as well as the deep system seems prudent, and would include the superficial pre-auricular, post-auricular and occipital nodes for primaries draining via those regions.

Post-operative radiotherapy for lymph node metastases

Albeit without good evidence, the general consensus is that patients with pathologically staged N_1 disease without extracapsular spread may be spared radiotherapy. For other cases, there is overwhelming evidence that the best outcomes are achieved with the dual-modality treatment of surgical resection and adjuvant radiotherapy.[1147,1148]

Immunotherapy

Immunotherapy is effective in palliation, with growing evidence to indicate that long-term cure is achievable. Though rarely fatal, non-melanoma skin cancer is responsible for a great deal of functional morbidity, disfigurement and healthcare costs.

Probably the most significant recent development in the management of cutaneous SCC is the introduction of immunotherapy in the form of cemiplimab. Platinum-based chemotherapy is rarely used, because it is frequently toxic, especially in a frail older adult population, and both overall response rate and duration of response are very poor. Based on the 'EMPOWER' (Eliminating Medications Through Patient Ownership of End Results) trial and real world Systemic Anti-Cancer Therapy ('SACT') data, cemiplimab offers a well-tolerated, effective treatment for locally advanced or metastatic cutaneous SCC. Whilst there is not a direct comparison, survival and quality of life are likely to be improved with cemiplimab over palliative chemotherapy[955] or best supportive care in the treatment of patients with locally advanced or metastatic cutaneous SCC where curative surgical treatment or radiotherapy is not deemed appropriate or feasible. Cemiplimab is funded on the NHS through the Cancer Drugs Fund.[1149] There is early phase II evidence to support the role of neoadjuvant cemiplimab, and further studies are being undertaken; however, currently this is not supported by NICE or the Cancer Drugs Fund.[1150] Decisions regarding the use of immunotherapy must be made in a specialist skin cancer MDT meeting with one or more oncologists in attendance.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Follow up

All patients with cutaneous SCC should be offered a key worker (e.g. a clinical nurse specialist). They should all have a skin and nodal examination after diagnosis (as well as before), and be educated on self-examination and surveillance, and given advice about UV light protection and vitamin D supplementation.

Patients with low-risk, completely excised cutaneous SCC without a previous history of skin malignancy may be discharged at the first follow-up appointment, but other cutaneous SCC patients will require follow up. Patients with high-risk cutaneous SCC should be offered follow-up appointments every 4 months for 12 months, then every 6 months for at least 12 months. Patients with very high-risk cutaneous SCC should be offered follow-up appointments every 4 months for 24 months, then every 6 months for at least 12 months. Patients with a significant risk factor such as immunosuppression should be offered lifelong follow up.

Merkel cell cancer

Recommendations

- Discuss all cases of Merkel cell carcinoma at the specialist skin MDT meeting (evidence-based recommendation (R))
- Wide local excision of Merkel cell carcinoma should be performed with a 1–2 cm margin down to fascia (R)
- Offer sentinel node biopsy to patients who are staged N_0 and M_0 (node and metastasis negative) at presentation, at the time of wide local excision (R)
- Offer patients adjuvant radiotherapy to the primary tumour site and involved lymph node basins (R)
- Consider immunotherapy for patients with locally advanced or metastatic disease (R)

Merkel cell cancer is a rare cutaneous neuroendocrine tumour. It occurs predominantly in the Caucasian population, and is commonly found on the head and neck (42.6 per cent). There is growing evidence to support an association with infection with Merkel cell polyomavirus. Despite the name of the tumour, there is still discussion in the literature as to the cell of origin, with Merkel cells (mechanoreceptor cells), dermal and epidermal stem cells, and lymphoid progenitor cells all postulated. The extent of disease at presentation (local, nodal and distant) is predictive of five-year survival, and this has been incorporated into the *AJCC Cancer Staging Manual* (eighth edition)[1138] Merkel cell carcinoma staging (Tables 4–8).

Initial assessment of patients with Merkel cell carcinoma should include thorough history-taking and examination, including evaluation of the primary site for satellite lesions, dermal seeding and palpable lymphadenopathy. Macroscopic and microscopic nodal involvement is common, and cross-sectional imaging (CT and/or MRI) should be carried out.

The management of Merkel cell carcinoma can be complex, and must be planned and discussed in a specialist skin cancer MDT meeting, and the treatment carried out by core members.

Treatment of the primary tumour is usually surgical with wide local excision, aiming to achieve clear primary lesion surgical margins, followed in most cases by adjuvant radiotherapy. A 1–2 cm margin down to fascia is recommended. Sentinel node biopsy is indicated for patients with a histologically proven primary Merkel cell carcinoma, who are staged N_0M_0 at presentation, after discussion in a specialist skin cancer MDT meeting. Merkel cell carcinoma is very radiosensitive, and adjuvant radiotherapy is recommended for most primary tumours and for lymph node metastasis. For patients with local advanced disease or metastatic disease, immunotherapy (avelumab) can be highly effective, with a reported objective response rate of 62.1 per cent.[1151]

Guidelines for follow up of Merkel cell carcinoma vary, but the National Comprehensive Cancer Network guidelines recommend complete skin and nodal examination every 3–6 months for 3 years, then every 6–12 months thereafter.[1152]

Table 4. Tumour staging for Merkel cell cancer*

Tumour (T) stage	Primary tumour criteria
T_X	Primary tumour cannot be assessed
Tis	Carcinoma in situ
T_1	Tumour ≤2 cm in greatest dimension
T_2	Tumour >2 cm to ≤5 cm in greatest dimension
T_3	Tumour >5 cm in greatest dimension
T_4	Tumour invades deep extra dermal structures

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138]

Table 5. Nodal staging for Merkel cell cancer*

Nodal (N) stage	Clinical N (cN)	Pathological N (pN)
N_X	Regional lymph node cannot be assessed	Regional lymph node cannot be assessed
N_0	No regional lymph node metastasis	No regional lymph node metastasis
N_1	Regional lymph node metastasis	Regional lymph node metastasis Pathologically staged N_{1a} (sn), detected on sentinel node biopsy Pathologically staged N_{1a} microscopic metastasis after neck dissection Pathologically staged N_{1b} macroscopic metastasis
N_2	In-transit metastasis† without regional lymph node metastasis	In-transit metastasis† without regional lymph node metastasis
N_3	In-transit metastasis† with regional lymph node metastasis	In-transit metastasis† with regional lymph node metastasis

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138] †In-transit metastasis: discontinuous tumour distinct from the primary lesion, and located either between it and regional lymph node or distal to the primary lesion.

Table 6. Metastasis staging for Merkel cell cancer*

Metastasis (M) stage	M criteria
M_0	No distant metastasis
M_{1a}	Distant metastasis in skin, subcutaneous tissue or non-regional lymph nodes
M_{1b}	Distant metastasis in lung
M_{1c}	Distant metastasis in other sites

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 7. Clinical group staging for Merkel cell cancer*

Group stage – clinical	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
IIA	$T_{2–3}$	N_0	M_0
IIB	T_4	N_0	M_0
III	Any T	$N_{1–3}$	M_0
IV	Any T	Any N	M_1

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138]

Table 8. Pathological group staging for Merkel cell cancer*

Group stage – pathological	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
0	Tis	N_0	M_0
I	T_1	N_0	M_0
IIA	$T_{2–3}$	N_0	M_0
IIB	T_4	N_0	M_0
IIIA	T_0	N_{1b}	M_0
	$T_{1–4}$	N_{1a}, N_{1a} (sn)†	
IIIB	Any T	N_{1b}–N_3	M_0
IV	Any T	Any N	M_1

*According to the *AJCC Cancer Staging Manual* (eighth edition).[1138] †Detected on sentinel node biopsy

Non-melanoma skin cancer of the eyelids

Non-melanoma skin cancer of the eyelids warrants special mention as it has its own *AJCC Cancer Staging Manual* (eighth edition)[1138] staging system, and its own very specific anatomical and reconstructive constraints. There is also variation of the types of non-melanoma skin cancer that present on the eyelids compared to other parts of the body. These tumours should be managed through the specialist skin cancer MDT by clinicians appropriately trained in occuloplastic techniques and skin cancer management.

Studies due to report

'Rational treatment selection for Merkel Cell Carcinoma' – this is a trial comparing radiotherapy with surgery for Merkel cell carcinoma (in: https://doi.org/10.1186/ISRCTN16290169).

Cemiplimab, an anti-programmed cell death 1 immune checkpoint inhibitor, has shown promise in the treatment of non-resectable advanced cutaneous SCC. It is currently being investigated in a phase 2 clinical trial in a neo-adjuvant setting prior to surgery.[955]

Pre-operative vismodegib has been investigated for down-staging the extent of surgery.[956]

Important research questions

Randomised, controlled trials comparing standard surgical re-excision of high-risk BCC excised with close (less than 1 mm) or involved histological margins versus Mohs micrographic surgery, radiotherapy or no treatment.

Randomised, controlled trials comparing standard surgical excision versus Mohs micrographic surgery for high-risk BCC.

Investigation of the role of sentinel node biopsy in cutaneous SCC.

There is some evidence that immunotherapy may serve as an effective treatment for advanced BCC. Investigation of the role of immunotherapy in advanced BCC may be important, given the limitations of use on the hedgehog pathway inhibitors.

Chapter 29: Head and neck mucosal melanoma

Table of Contents

Introduction

Head and neck mucosal melanomas are rare, accounting for only 1–4 per cent of all melanomas,[1153] and are an aggressive subtype of melanocytic malignancies, with a very poor prognosis. They are neural crest-derived malignancies, thought to arise from errors in melanocyte migration to the mucosa of the upper aerodigestive tract during fetal development.[1154] They most commonly arise in the nasal cavity and paranasal sinuses (80 per cent), followed by the oral cavity, pharynx and larynx (in decreasing order of frequency).[1155] The incidence of head and neck mucosal melanoma has remained stable.[1156] There are, however, no clear modifiable risk factors for head and neck mucosal melanoma. Their aetiology is still poorly understood.[1157,1158]

Because of their rarity, there is little evidence to guide management, and consequently few evidence-based clinical guidelines. Five-year survival rates remain very low at 20–28 per cent, with little improvement in modern times.[1155,1159,1160]

Presentation and diagnosis

Clinical presentation is dependent on the subsite of the lesion. The most common presenting symptoms for sinonasal head and neck mucosal melanoma are nasal obstruction and unilateral epistaxis, seen in combination in up to 95 per cent of patients.[1155,1161,1162]

These, and other sinonasal symptoms, are also common presentations of benign sinonasal disease, which may explain why it has been reported that sinonasal head and neck

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

mucosal melanoma has a longer duration of symptoms prior to diagnosis (6.7 months) when compared to oral cavity head and neck mucosal melanoma (3.1 months).[1163] Patients with oral cavity head and neck mucosal melanoma are often diagnosed by dental practitioners due to pain, bleeding, ulceration, ill-fitting dentures or the identification of incidental pigmented lesions, and present earlier (3.1 months) when compared to patients with sinonasal head and neck mucosal melanoma (6.7 months).[1163,1164] More rarely, head and neck mucosal melanoma can present in the oropharynx or larynx, and these cases present in a similar manner to squamous cell carcinoma (SCC) in those sites.[1165]

Within the nasal cavity, the lateral nasal wall and septum are the most common subsites.[1166] The overwhelming majority of oral cavity head and neck mucosal melanomas arise in the upper maxillary alveolar ridge and hard palate.[1167] It is worth noting that up to 30 per cent of oral head and neck mucosal melanomas are amelanotic.[1163] On top of this, they can vary in their macroscopic appearance, being described as red or white, as well as characteristic dark brown.[1168]

Patient evaluation is performed according to the primary site, as for other upper aerodigestive tract SCCs. Biopsy can be carried out under general or local anaesthetic, depending on the nature of the disease and the patients' co-morbidities. Attempts at excisional biopsy may compromise further surgical treatment, hence incisional biopsy or sampling is advised. At the time of biopsy, it is important to make an assessment of resectability, and mapping biopsies of adjacent areas may be useful to determine the extent of disease.

Table 1. TNM classification of head and neck mucosal melanoma*

Staging	Description
Tumour (T) stage	
– T_X	Primary tumour not identified or not assessed
– T_3	Tumours limited to mucosa & immediately underlying soft tissue, regardless of thickness or greatest dimension, e.g. polypoid nasal disease, pigmented or non-pigmented lesions of oral cavity, pharynx or larynx
– T_{4a}	Moderately advanced disease: tumour invades soft tissue, cartilage, bone or overlying skin
– T_{4b}	Very advanced disease: tumour invades any of the following deeper structures: brain, dura, skull base, lower cranial nerves (IXth, Xth, XIth, XIIth), masticator space, carotid artery, prevertebral space or mediastinal structures
Nodal (N) stage	
– N_0	No regional metastases
– N_1	Regional lymph node metastasis/metastases present
Metastasis (M) stage	
– Clinically staged M_0	No distant metastases
– Clinically staged M_1	Distant metastases present
– Pathologically staged M_1	Distant metastases pathologically confirmed

*According to the *TNM Classification of Malignant Tumours*[1169]

Imaging

Imaging is the same as for other cancers arising from the affected site (see Chapter 17 on oral cavity cancer and Chapter 23 on sinonasal cancer). However, to stage potential regional and distant metastatic sites, contrast-enhanced computed tomography (CT) of the neck, chest, thorax, abdomen and pelvis (or positron emission tomography (PET)-CT), and contrast-enhanced magnetic resonance imaging of the brain, are recommended.

Recommendations

- Patients with head and neck mucosal melanoma present with symptoms dependent on the mucosal site of origin. Some lesions may be amelanocytic, particularly in the oral cavity (evidence-based recommendation (R))
- At the time of biopsies, an assessment of resectability should be made, and mapping biopsies of adjacent areas may help make this assessment (good practice point (G))
- Systemic imaging including brain imaging is recommended (R)

Staging

It is important to note that there is no early stage head and neck mucosal melanoma. All disease is classified as stage III or IV. Clinicians should use the most recent Union for International Cancer Control ('UICC') *TNM Classification of Malignant Tumours*, eighth edition (2017) (Tables 1 and 2).[1169]

Pathology

The diagnostic pathology specimen should be reviewed by pathologists with relevant expertise, usually supplemented by molecular pathology reports. It is worth noting that neither tumour thickness (Breslow depth) nor depth of invasion (Clark's level) inform prognosis, and, therefore, these do not need to be documented. It is recommended that molecular analysis for BRAF V600 and KIT mutations is performed routinely, at the time of first diagnosis, in line with both local and national genomic guidelines and pathways, as it may offer patients treatment options in both adjuvant and metastatic settings. Both genes encode for growth kinase proteins that can be targeted by specific therapies. Over time, it is possible that other mutations may be identified which may represent clinically relevant actionable therapeutic targets.

Recommendations

- There is no early stage head and neck mucosal melanoma, which reflects the aggressive nature of the disease (evidence-based recommendation (R))
- Molecular analysis for all known current targetable mutations (currently BRAF and KIT) should be undertaken (R)
- Unlike in cutaneous melanoma, depth of invasion or tumour thickness do not inform prognosis (R)

Treatment

Localised tumours (stage III disease)

Primary surgery

Surgery with the aim of achieving clear margins is still the standard of care and first-line management option for localised tumours. There are no datasets to use for relative indications or contraindications for surgery, however several series

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Disease staging of head and neck mucosal melanoma*

Disease stage	TNM staging
III	$T_3N_0M_0$
IVA	$T_{4a}N_0M_0$
	$T_{3-4a}N_1M_0$
IVB	T_{4b}, any N, M_0
IVC	Any T, any N, M_1

*According to the *TNM Classification of Malignant Tumours*.[1169] TNM = tumour–node–metastasis

demonstrate improved disease-free survival and overall survival where negative margins can be achieved (R0 resection).[1170,1171]

In the context of head and neck mucosal melanoma of the paranasal sinuses, historically it was thought that the only method to achieve an R0 resection was by radical transfacial resections with subsequent reconstruction. However, some series report that an endoscopic approach gives comparable disease-free survival and overall survival to open approaches.[1172] These findings need to be interpreted in the context of the selection bias that results from smaller lesions being amenable to endoscopic resection. The anatomical constraints of the paranasal sinuses and proximity of vital anatomical structures make achieving 5 mm margins impossible in many patients. Equally, en bloc resection may not be possible, and therefore a mosaic approach with marginal biopsies is a widely accepted endoscopic technique.[1173] With regard to oral cavity, oropharyngeal, hypopharyngeal and laryngeal head and neck mucosal melanoma, traditional surgical techniques used for the resection of upper aerodigestive tract cancers are accepted as the 'gold standard'.

Multidisciplinary teams (MDTs) need to weigh the morbidity of surgery with the likelihood of achieving clear margins. Surgery that is thought to carry unacceptable morbidity or have a significant negative impact on a patient's quality of life is clearly contraindicated. What is deemed unacceptable morbidity is patient-specific, and these decisions must be made with the patient at the centre of the process. It may be necessary to involve a local skull base MDT in specific cases.

Post-operative radiotherapy

There is a lack of good evidence to support the routine use of post-operative radiotherapy with respect to improvement in disease-free survival or overall survival. At the time of writing, there are four relevant meta-analyses available in the literature. Three demonstrated no improvement in overall survival, but did demonstrate improvements in locoregional control.[1174–1176] The final meta-analysis did demonstrate a significant improvement for three-year overall survival and a mild improvement for five-year overall survival.[1177] The MDTs may still wish to consider post-operative intensity-modulated radiotherapy in tumours with traditional features that denote a high chance of recurrence, such as close or positive margins, stage T_4 tumours, sinonasal tumours and/or multifocal tumours. It is essential to inform patients that this treatment would expose them to toxicities associated with radiotherapy, with uncertain benefits in overall survival.

Role of neck dissection and sentinel lymph node biopsy in the node-negative neck

In cutaneous melanoma, regional lymph node disease is a significant factor in predicting prognosis as well as treatment modality. However, there is no evidence that, in head and neck mucosal melanoma cases, treatment of regional lymph nodes in the clinical and radiological node-negative (N_0) setting or in known regional lymph node metastases has any impact on disease-free survival or overall survival.[1178,1179] One series from Wu *et al.* demonstrated a slight improvement in five-year overall survival in patients undergoing selective neck dissection versus observation (18 per cent *vs* 4 per cent, $p = 0.001$).[1180] However, this series was limited to 67 patients with nodular oral cavity head and neck mucosal melanoma, and it is not clear how patients were selected for selective neck dissection or observation. Other series available did not report any benefit in disease-free survival or overall survival. Therefore, in the recently published UK guidelines commissioned by Melanoma Focus, it is recommended to only consider surgery to regional lymph nodes in the context where the detection of occult metastatic disease would make a patient eligible for adjuvant systemic treatment (standard of care or clinical trial).[1181] In the context of oral cavity head and neck mucosal melanoma, it is easier to perform sentinel lymph node biopsy given the easy accessibility of the primary site for injection and first-echelon nodes. This is more difficult in head and neck mucosal melanoma of the paranasal sinuses and therefore a selective neck dissection can be considered as an alternative.

Recommendations

- Surgical resection achieving clear margins gives the best chance of cure. It is vital to weigh the likelihood of achieving clear margins with the morbidity and impact on quality of life of any proposed surgery (evidence-based recommendation (R))
- In sinonasal head and neck mucosal melanoma, endoscopic approaches should be used where possible (good practice point (G))
- There is no evidence to support the use of selective neck dissection or sentinel lymph node biopsy in the N_0 neck, and these are only advised in the context of upstaging a patient to make them eligible for adjuvant therapy or a clinical trial (G)
- There is no evidence to support the use of post-operative radiotherapy in terms of improved overall survival or disease-free survival. However, post-operative radiotherapy may help with regional control, and MDTs may still wish to consider its use in select patients with adverse pathological features (G)

More advanced tumours (stage IV disease)

Unfortunately, the prognosis for patients with unresectable tumours or metastatic disease is extremely poor (median overall survival of 9.1 months from diagnosis). Immune checkpoint inhibitors such as anti-programmed death 1 (anti-PD-1) (e.g. nivolumab or pembrolizumab) and T-lymphocyte-associated protein 4 (anti-CTLA-4) inhibitors (e.g. ipilimumab) (either in combination or monotherapy) are now considered the standard of care in metastatic melanoma in the UK.[1181] As with any immunotherapy, the risk of adverse events, particularly in those with co-morbidities, is significant. As outlined earlier, tumourogenic mutations such as BRAF V600 and KIT are targets for additional systemic therapies, which can be considered in the context of failure on immunotherapy or first-line management where urgent symptomatic benefit is required.[1181] The BRAF V600 mutation is less common in mucosal melanoma (3–

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

15 per cent) compared to cutaneous melanoma (50 per cent).[1182,1183] The KIT alteration is identified in 7–17 per cent of mucosal melanomas.[1184,1185] Objective response rates in mucosal melanoma in single-agent immunotherapy have been quoted as 23–25 per cent and 37.1 per cent in combination treatment, which is less than in cutaneous melanoma (40.9 per cent and 60.4 per cent respectively for single and combination immunotherapy).[1186] It is not fully understood why mucosal melanoma is less responsive to immunotherapy. In addition to the differences in targetable mutations detailed above, fewer patients with mucosal melanoma have high levels of programmed death-ligand 1 (PD-L1) expression (21 per cent *vs* 35 per cent).[1186] These factors in combination probably explain the difference in objective response rates noted.

In patients where immunotherapy is felt to be contraindicated because of pre-existing auto-immune conditions, immunosuppression or other co-morbidities, cytotoxic chemotherapy can be considered. Prior to the advent of the immunotherapies outlined above, dacarbazine had been the standard of care for metastatic melanoma, and there is ongoing research investigating the use of this in combination with immunotherapy.[1187] In addition, radiotherapy with palliative intent can be considered in select cases where it is thought it would offer symptomatic benefit.

Recommendations

- Combination immunotherapy should be offered as a first-line management option to patients with a good performance status and who are willing to accept the risk of adverse events (evidence-based recommendation (R))
- Monotherapy should be offered to patients considered insufficiently fit or those who find the risks of combination therapy unacceptable (good practice point (G))
- BRAF or KIT targeted agents can be offered to those with appropriate mutations as a first-line management option if urgent symptomatic relief is desired or in the context of failure on immunotherapy (G)
- Chemotherapy and radiotherapy with palliative intent are other treatment modalities that can be considered in select cases (G)

Follow up

Table 3 outlines the follow-up schedule currently advocated in the UK.

Table 3. Follow-up schedule currently advocated in the UK

Year	Actions
Year 1	6–8 weekly clinical examination* to identify locoregional disease
	3 monthly imaging† to identify systemic disease
	6 monthly brain imaging‡
Year 2–3	3 monthly clinical examination to identify locoregional disease
	6 monthly imaging to identify systemic disease
	6 monthly brain imaging
Year 4–5	6 monthly clinical examination to identify locoregional disease
	12 monthly imaging to identify systemic disease
	12 monthly brain imaging
Year 5+	Consider annual review or open access

*Clinical examination should include examination of the upper aerodigestive tract, supplemented by flexible nasendoscopic examination and palpation of the neck. †Imaging should include cross-sectional imaging of the upper aerodigestive tract, neck, chest, abdomen and pelvis (centres with access to magnetic resonance imaging (MRI) may wish to use MRI to image the neck and paranasal sinuses in combination with computed tomography (CT) for the chest, abdomen and pelvis; otherwise, CT can be used alone). ‡Cross-sectional imaging of the brain refers to MRI or CT (with MRI being preferable in centres with access; otherwise, CT is acceptable).

Recurrence

Head and neck mucosal melanoma unfortunately has the tendency to recur distally as part of the natural history of the disease. In these circumstances, the treatment options are limited to immunotherapy and chemotherapy. Salvage surgery is rarely indicated in the recurrent setting. If salvage surgery were to be undertaken, it should be under the same paradigm as primary surgery, addressing the question of whether surgery is likely to achieve clear margins with acceptable morbidity. Palliative debulking surgery could be considered in, for example, an obstructing sinonasal tumour.

Studies due to report

(1) 'Neoadjuvant Treatment Associated With Maintenance Therapy by Anti-PD1 Immunotherapy in Patients With Resectable Head and Neck Melanoma (IMMUQ)' (ClinicalTrials.gov Identifier: NCT03313206).
(2) 'Mucosal Melanoma of Head and Neck in Intensity-modulated Radiotherapy Era'. A prospective phase II study in patients with mucosal melanoma of the head and neck in the intensity-modulated radiotherapy era (ClinicalTrials.gov Identifier: NCT03138642).

Research questions

- Is there a role for adjuvant or neoadjuvant immunotherapy in patients undergoing surgical resection for head and neck mucosal melanoma?
- What other targetable genetic mutations are there that are specific to head and neck mucosal melanoma?

Chapter 30: Paraganglioma of the head and neck

Table of Contents

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Introduction

Paragangliomas are rare neuroendocrine neoplasms that arise from neural crest derivatives close to sympathetic ganglia. Paraganglioma supersedes the old term, glomus tumour. Paragangliomas of the head and neck arise from parasympathetic glomus cells in close association with the glossopharyngeal and vagus nerves. Paragangliomas also arise along the aorta, and phaeochromocytoma in the adrenal glands.

Paraganglioma of the head and neck was classified by the World Health Organization according to the site of origin as:

- Carotid body
- Jugulotympanic
- Vagal
- Laryngeal
- Miscellaneous

The larynx, nose, paranasal sinuses, parotid gland, pharynx, sympathetic trunk, thyroid and trachea are very rare sites for head and neck paraganglioma.

The population incidence of head and neck paraganglioma is about 1:30 000, accounting for 3 per cent of all paragangliomas. Women are affected more than men. A familial tendency is seen in about 40 per cent of paragangliomas, more than any other tumour in adults.[1188]

It is thought that only about 5 per cent of head and neck paragangliomas are malignant. Malignant paragangliomas are not defined histologically, but through evidence of regional lymph node spread or distant metastases in non-endocrine tissue. Therefore, paragangliomas are classified as primary and metastatic hereafter.[1189] Metastatic paragangliomas must be distinguished from multifocal primary disease.[1189]

Under 5 per cent of head and neck paragangliomas secrete catecholamines, usually noradrenaline.

Surveillance, surgery, and radiotherapy including stereotactic radiotherapy should be considered in each case. Published evidence is mainly retrospective. Paragangliomas are best managed at specialist centres.

Presentation and diagnosis

Recommendations

- Examination should include: flexible nasopharyngolaryngoscopy, cranial nerve function assessment and otoscopy (evidence-based recommendation (R))
- Magnetic resonance imaging (MRI) is mandated in suspected head and neck paraganglioma cases (R)
- All patients should have a plasma metanephrines test at the time of diagnosis, and all patients with raised metanephrine levels should be referred to endocrinology (R)
- All patients should be offered genetic testing (R)

Paragangliomas of the neck can present to several clinical specialties with a neck mass (70 per cent), hoarseness (17 per cent) or dysphagia (11 per cent), or based on incidental imaging findings (13 per cent).[1190] Rarely, head and neck paragangliomas are vasoactive, and present with agitation, flushing, hypertension and palpitations. Paragangliomas of the temporal bone usually present with hearing loss or pulsatile tinnitus, but may also present with cranial nerve palsy. Head and neck paraganglioma should be considered in the differential diagnosis of a neck mass.

Clinical examination should include flexible nasopharyngolaryngoscopy, cranial nerve function assessment, otoscopy and auscultation for bruit. Audiometry should be performed for temporal bone paragangliomas.

Head and neck paraganglioma may be suspected at ultrasound imaging. The diagnosis is made using contrast-MRI (see Imaging section below). Fine needle aspiration cytology is not usually necessary.

The secretion of metanephrines may cause labile hypertension, and correlates with a poorer prognosis. All patients with head and neck paraganglioma should be tested for metanephrines, either in plasma or urine, following local protocols. When testing in urine, it is important to consider possible inaccuracies in 24-hour urine collection. All patients with raised metanephrine levels should be referred to endocrinology services.

All patients should be offered genetic testing with clinical genetics or endocrinology services.

Imaging

Recommendations

- All patients should undergo contrast-MRI scanning of the head and neck (evidence-based recommendation (R))
- In jugular and tympanic paragangliomas, patients should also undergo computed tomography (CT) of the temporal bone with fine cuts (R)
- All patients should undergo whole-body imaging to examine for multifocal paragangliomas, phaeochromocytoma and distant metastases (R)
- Patients should undergo MRI (of the thorax, abdomen and pelvis)
- Ga-68-Dotatate positron emission tomography (PET)-CT can be considered instead of MRI for whole-body imaging (good practice point (G))
- Metastatic and functional head and neck paragangliomas are staged using the *TNM Classification of Malignant Tumours* (eighth edition) for phaeochromocytoma[1191] (G)

Contrast-MRI of the head and neck is the preferred mode of imaging to diagnose and assess the extent of a head and neck paraganglioma. High-resolution CT imaging of the base of the skull is also necessary in jugular and tympanic paragangliomas.

Of patients, 10–15 per cent have synchronous multifocal, functional or metastatic paragangliomas. Therefore, all

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

patients should have radiological screening with whole-body MRI of the thorax, abdomen and pelvis, as well as the head and neck. Whole-body MRI is preferable to whole-body CT, because whole-body CT adds a significant dose of ionising radiation. Ga-68-Dotatate PET-CT is more accurate in detecting paragangliomas than other forms of functional imaging,[1192] and therefore might be the preferred means of detecting metastatic or multifocal paragangliomas.

Staging

Metastatic and functional head and neck paragangliomas are staged using the Union for International Cancer Control / American Joint Committee on Cancer *TNM Classification of Malignant Tumours* (eighth edition) for phaeochromocytoma, as below.[1191]

Primary tumour (T):

- T_1: phaeochromocytoma sized less than 5 cm
- T_2: functional (sympathetic) paragangliomas of any size, or phaeochromocytoma sized 5 cm or greater
- T_3: local extension to surrounding organs

Regional lymph node (N):

- N_0: no regional lymph node metastasis
- N_1: regional lymph node metastasis

Distant metastasis (M):

- M_0: no distant metastasis
- M_{1a}: metastasis to bone only
- M_{1b}: metastasis to distant lymph nodes, liver or lung
- M_{1c}: metastasis to bone and multiple other sites

The tumour–node–metastasis (TNM) prognostic staging groups are given in Table 1. No histology grading system is established.

Carotid body paragangliomas were classified by Shamblin *et al.* (1971) into three groups assigned intra-operatively,[1193] so the utility of the classification for planning surgery is very limited:

- Group 1: tumours resectable without significant trauma to the vessel wall or tumour capsule
- Group 2: tumours partially surround the vessel wall and are more adherent to adventitia
- Group 3: tumours have an intimate and adherent relationship to the entire circumference of the carotid bifurcation

Modifications to the Shamblin classification have been proposed in order to reflect the risks of neurological and vascular injury from carotid body paraganglioma surgery, such as subgroups 3a (complete carotid encasement) and 3b (infiltration of the carotid wall irrespective of tumour size).[1194] More recently, Mehanna *et al.* reported and validated a classification system based on the highest anatomical landmark reached by the upper surface of carotid body paraganglioma.[1195]

The British Society of Otology guideline group supported the use of the Fisch classification of temporal bone paragangliomas with some caveats:[1196]

- A: Mesotympanic
- B: Tympanomastoid

Table 1. TNM prognostic staging

Disease stage	Tumour (T) stage	Nodal (N) stage	Metastasis (M) stage
Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III	T_{1-2}	N_1	M_0
	T_3	N_{0-1}	M_0
Stage IV	T_{1-3}	N_{0-1}	M_1

- C: Carotid canal involvement: (1) limited; (2) vertical portion; (3) horizontal portion; and (4) extension to foramen lacerum with or without cavernous sinus thrombosis
- D: Intracranial extension: (1) extradural; and (2) intradural

Type A and most type B are tympanic paragangliomas because they arise from the tympanic plexus. Large tympanic paragangliomas may involve the jugular bulb and are thus jugulotympanic. Small jugular paragangliomas may extend superiorly without carotid artery involvement and are thus type B. There may not be stepwise progression through classes.[1196]

Genetics

About 40 per cent of paragangliomas are caused by pathogenic variants of cancer predisposition genes, especially succinate dehydrogenase (SDH) genes. The probability of a genetic aetiology is increased by a family history, younger age and tumour multifocality.

All patients with a diagnosis of head and neck paraganglioma should be offered genetic testing; there is no maximum age limit for testing.[1197] The referral for genetic testing should be made to clinical genetics or subspecialist endocrinology services, and be concurrent with other investigations. The timing of testing depends on the management of the presenting lesion, patient choice and family circumstances. If treatment does not need to be urgent, management can sometimes wait until the results of germline testing become available, which in the UK may be three months. Patients should undergo germline testing prior to discharge from head and neck or skull base services.

In the UK, 11 genes are screened for pathogenic variants (R223 analysis) (Table 2). Variants that are pathogenic, or likely to be pathogenic, are considered to be actionable, whereas variants of unknown significance are not actionable and should not be used for testing the patient's family. Reassessment is undertaken three to five years later in case a variant of unknown significance has become actionable.

After a pathogenic, or likely pathogenic, variant has been identified in an individual, predictive genetic testing may be offered to unaffected individuals in the family.

In relatives identified as having one of the more pathogenic variants, surveillance is recommended, typically with annual plasma metanephrines tests from the age of 8 years, whole-body MRI every 3 years from age 15 years, and abdominal ultrasound in the years between MRI scans.[1196] There are separate surveillance protocols for individuals with pathogenic variants of *NF1* and *VHL*. In asymptomatic individuals with a maternally-inherited *SDHC* variant, surveillance is not currently recommended.

The following description is limited to genes in which pathogenic variants are commonly identified in individuals with head and neck paraganglioma.

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Table 2. Genes screened in the UK*

Gene	Inheritance	Phenotype	H&N paraganglioma	Frequency
RET	AD	Multiple endocrine neoplasia type 2 – medullary thyroid carcinoma, phaeochromocytoma & hyperparathyroidism	Rare	– 50% patients develop phaeochromocytoma – 5% patients with phaeochromocytoma
VHL	AD	Cerebellar & spinal haemangioblastoma, retinal angioma, phaeochromocytoma, renal cell carcinoma	Rare	– Penetrance varies with mutation, up to about 20% individuals with VHL – 5–10% patients with paraganglioma or phaeochromocytoma
SDHB	AD	Phaeochromocytoma & paraganglioma. Higher rate of metastasis. Have been associated with renal tumours	Common	– Penetrance about 20–30% – 10–15% patients with paraganglioma or phaeochromocytoma
SDHD	AD (parent-of-origin effect)	Phaeochromocytoma & paraganglioma. Higher rate of H&N paraganglioma. Usually not metastatic, frequently multiple. Only develop tumours if inherited from father	Common	– Penetrance up to 40–75% – 5–10% patients with phaeochromocytoma or paraganglioma
SDHC	AD	Phaeochromocytoma & paraganglioma. Mainly H&N paraganglioma	Common	– Penetrance 8–10% – Rare
SDHA	AD	Phaeochromocytoma & paraganglioma. All locations described	Rare	– Recent estimates at about 2% – Accounts for <1% inherited paraganglioma
SDHAF2	AD (parent-of-origin effect)	Head & neck paraganglioma. Only develop tumours if inherited from father	More common	– Penetrance unclear – Rare
MAX	AD (parent-of-origin effect)	Phaeochromocytoma & paraganglioma. Metastatic cases have been described. Only develop tumours if inherited from father	Rare	– Penetrance unknown – <1% patients with phaeochromocytoma
TMEM127	AD	Phaeochromocytoma often bilateral & multicentric. Metastasis rare. Paraganglioma has been described	Rare	– Penetrance unclear – 1–2% patients with phaeochromocytoma
FH	AD	Usually associated with leiomyomatosis & renal carcinoma. Recent association with phaeochromocytoma described	Rare	– Penetrance unknown – Very rarely found

*According to the National Test Directory, October 2021.[1197] (*MEN1* is also included in the R223 analysis.) H&N = head and neck; AD = autosomal dominant; VHL = Von Hippel–Lindau syndrome

SDHD

Pathogenic variants in *SDHD* are the most common germline variant in head and neck paraganglioma. The tumours are rarely metastatic but frequently bilateral. The majority of patients have head and neck paraganglioma, though phaeochromocytoma can occur. The penetrance is estimated at 80–90 per cent by 50 years of age.[1198]

SDHD mutations are inherited in autosomal dominant fashion, but the phenotype demonstrates parent-of-origin effect, with tumour development only if the germline mutation is inherited by the paternal line. With rare exception, the overwhelming majority of carriers of maternally-transmitted *SDHD* mutations remain tumour-free.[1199]

SDHB

Pathogenic variants in *SDHB* are more likely to cause phaeochromocytoma and extra-adrenal functioning tumours than head and neck paraganglioma. *SDHB* pathogenic variants are the most common, accounting for up to 40 per cent of families with familial paraganglioma syndrome. The mean age of diagnosis is about 30 years.

Earlier estimates of the penetrance of *SDHB* pathogenic variants were about 50 per cent, but genetic testing in families indicated the penetrance is 20–30 per cent.[1200] There is a higher rate of metastatic disease associated with tumours in individuals who have an *SDHB* pathogenic variant.[1201] *SDHB* pathogenic variants have also been associated with: renal cell carcinoma (often with sarcomatoid features), thyroid malignancies and wild-type gastrointestinal stromal tumours.

SDHC

SDHC pathogenic variants are identified less commonly than variants in the other SDHx genes. A UK-wide series of *SDHC* cases demonstrated that 65 per cent presented with head and neck paraganglioma.[1202] Around 20 per cent of head and neck paragangliomas and 30 per cent of phaeochromocytomas were metastatic. As with the other genes, penetrance is difficult to estimate. In the UK series, the cumulative risk in probands was 94 per cent by the age of 60 years, and 16 per cent in non-probands.

Surveillance and treatment

The rarity, complexity and potential sequelae of head and neck paragangliomas necessitates early referral to specialist centres, to ensure higher case volumes and robust, personalised care.

A diverse range of specialists is involved. The choices of management are: (1) surveillance, (2) surgery, and (3)

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

radiotherapy alone or in combination. The natural history of head and neck paraganglioma is long, and there is a paucity of prospective data to support the optimal choice of management.

Recommendations

- Patients with head and neck paraganglioma should be referred early to a specialist centre with a regional multidisciplinary team (MDT) (desirable (D))
- Surveillance with serial imaging is often appropriate (good practice point (G))
- Active treatment may be by surgery or radiation, alone or in combination (evidence-based recommendation (R))
- Early treatment is appropriate for primary and metastatic tumours causing symptoms, tympanic paragangliomas, functional tumours, and rapid growth (R)
- Stereotactic radiotherapy is optimal first-line radiotherapy treatment for intracranial tumours sized less than 3 cm (R)
- Carotid body paragangliomas sized less than 4 cm, especially if inferior to the level of the hyoid bone, and tympanic paragangliomas classified as Fisch A and B have low risks of post-operative cranial nerve impairment and are most suited to surgical resection if appropriate (G)
- Non-functional and non-metastatic vagal paragangliomas are best managed through surveillance or radiotherapy (G)
- Patients with cranial nerve palsies should receive MDT input from speech and language therapy and dietetics services; liaison with specialist facial nerve palsy and laryngology teams may be needed (essential (E))
- If surgery is offered for jugulotympanic paragangliomas, subtotal resection with or without adjuvant radiotherapy should be considered, to minimise cranial nerve deficit (G)
- Vascular surgery expertise should be involved if there is a chance of carotid artery reconstruction being required or atherosclerosis, and to facilitate sharing of expertise (E)
- Functional tumours should be treated with surgery (R)
- Pre-operative endocrinology input and alpha-adrenoreceptor antagonist therapy are required before surgery for functional head and neck paragangliomas (E)
- Potentially functional non-head and neck paragangliomas should be removed prior to surgery for head and neck paraganglioma, to avoid the risk of hypertensive crisis (E)

General principles of management

Surveillance

Surveillance is an appropriate option for head and neck paragangliomas that are benign, solitary, stable, non-functional, asymptomatic and non-tympanic. In head and neck paragangliomas under surveillance, more than half remain static in size over a five-year period according to a retrospective study of 109 patients and 258 tumours.[1203] Among the tumours that grew (44 per cent), the maximum dimension increased by an average of 2.7 mm per year in jugulotympanic paragangliomas, 6.4 mm per year in carotid body paragangliomas, and 11 mm per year in vagal paragangliomas. These data provide a point of comparison when assessing the rate of growth and considering the offer of treatment for head and neck paragangliomas under observation.

By using surveillance in appropriate head and neck paraganglioma cases, the potential complications of treatment may be postponed or avoided. Hence, management has become more conservative. In a series of 103 patients at Memorial Sloan Kettering Cancer Center, the use of surveillance increased from 5 to 36 per cent in new head and neck paraganglioma cases, while surgery reduced from 95 to 55 per cent, and radiation therapy alone increased from 0 to 9 per cent in the initial management of 103 patients between 1986 and 2017.[1190] Six of the 14 patients (43 per cent) under observation were subsequently treated by surgery and/or radiation.

Radiotherapy

Radiotherapy may be used alone or in combination with surgery in head and neck paraganglioma. Radiotherapy alters the kinetics of the tumour but does not usually result in disappearance. Local control rates for head and neck paraganglioma are over 90 per cent with radiotherapy.[1204–1206]

Traditionally, external beam radiotherapy has been used mostly in unresectable head and neck paraganglioma cases to stop or limit tumour growth. Symptomatic improvement was achieved in more than 70 per cent of cases in a review of 34 published series.[1204] The typical dose is 45 Gy over five weeks.[1207]

In jugular and vagal paragangliomas, major complications of external beam radiotherapy occurred in 12 per cent of patients (57 out of 461) at systematic review, including osteoradionecrosis, cranial neuropathy, brain necrosis, deafness and mortality.[1205] The risk of a second malignancy is an ongoing concern from external beam radiotherapy (0.28 per cent).[1208,1209] Smaller, more precise treatment volumes achieved by integrating three-dimensional imaging (CT, MRI or PET-CT) may decrease complications in surrounding tissue.

Stereotactic radiotherapy is the most precise form of therapeutic radiation. It incurs a low rate of side effects without compromising local tumour control. The risk of a second malignancy is estimated at less than 0.001 per cent.[1210]

Stereotactic doses of 12–15 Gy, or hypofractionation with 21 Gy in three fractions, or 25 Gy in five fractions, are typical.[1207] Intracranial tumours measuring less than 3 cm are the best candidates for stereotactic approaches, whereas larger tumours or those with extracranial spread are better suited to external beam radiotherapy.[1207]

In functional head and neck paragangliomas, the published evidence does not support radiotherapy over surgical resection because of the delay in reducing catecholamine secretion.

Surgery

The goals of surgery are complete surgical resection and the preservation of important anatomical structures. However, subtotal resection with adjuvant radiotherapy may be preferred in some temporal bone paragangliomas. Any co-existing functional paragangliomas outside the head and neck should be removed prior to surgery for head and neck paraganglioma, to avoid the risk of hypertensive crisis.

Carotid body and vagal paragangliomas are usually approached transcervically. Jugulotympanic paragangliomas are usually approached transtemporally. Local tumour control rates are about 85–95 per cent.

Post-operative cranial neuropathy is common in larger tumours and vagal paragangliomas. The lower cranial nerves (VIIth–XIIth) are at risk from injury with surgery for associated head and neck paraganglioma, causing permanent disability. The site and size of head and neck paragangliomas are the main risk factors. Vagus nerve palsy can be expected as a consequence of any surgical excision of a vagal paraganglioma (including attempted nerve-sparing surgery); this

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

causes aspiration, hoarseness and the need for long-term gastrostomy tube feeding. Horner's syndrome – enophthalmos, ptosis, miosis and anhidrosis – may occur and cause cosmetic embarrassment.

The involvement of allied health professionals, and speech and language therapy and dietetics services is essential, and liaison with specialist facial nerve palsy and laryngology teams may also be needed.

Surgery is preferred for smaller head and neck paragangliomas as single-modality treatment when the risk of complications is low (e.g. tympanic and smaller carotid body tumours) and for secreting tumours. In other cases, the decision-making is more complex and nuanced.

Pre-operative embolisation of head and neck paragangliomas is generally considered safe.[1211,1212] Aeta-analysis of 1326 patients with carotid body tumours identified that pre-operative embolisation was associated with significantly lower intra-operative blood loss and reduced length of surgery. However, there were no differences in the rates of cranial nerve injury, stroke, transient ischaemic attack or length of stay.[1213] In another meta-analysis, pre-operative embolisation did not reduce the rate of re-operation for haematoma.[1214] Hence, pre-operative embolisation should be considered, but the evidence does not support this as a didactic recommendation.

Regarding vascular investigation and management of vascular injury, if a tumour encases the carotid artery and the aim of surgery is total excision, a balloon occlusion study of cerebral blood flow may indicate whether resection might cause stroke, but the accuracy is limited. When carotid artery resection is inevitable, pre-operative coiling is an option in patients with a normal balloon occlusion test finding. Pre-operative stenting has also been shown in small series to benefit carotid artery integrity. In a small series of Shamblin grade II–III tumours, stenting preserved carotid artery integrity.[1215] Carotid artery integrity should be preserved where possible.

In all cases where there is a risk of carotid injury, a vascular surgeon should be present or immediately available. Shamblin grade II–III carotid paragangliomas are more likely to require vascular reconstruction, where primary repair, patch graft or reverse saphenous vein graft may be reasonable options, though there are increased rates of haemorrhage, cranial neuropathy, stroke and mortality.[1216–1218] In order to facilitate the sharing of expertise, joint working on carotid body tumours may be beneficial.

Functional (secretory) tumours are rare and only account for 3–5 per cent of head and neck paragangliomas.[1219] Surgical excision should be undertaken when possible. These patients require MDT management with endocrinology and anaesthesia inputs, for pre-operative optimisation and planning.

The objectives are to achieve pre-operative normalisation of heart rate, blood pressure and fluid balance. Alpha-adrenoceptor antagonists are the mainstay of treatment. Phenoxybenzamine is considered first-line treatment and should be commenced at least one to two weeks before surgery. Intra-operative continuous blood pressure monitoring, alpha and beta blockade, and careful fluid balance can all minimise the risk of significant intra- and post-operative complications including hypotension.[1220]

Management of more common head and neck paraganglioma

Carotid body paraganglioma

Surveillance, surgery or radiotherapy are options for most tumours.

Surgery offers a high chance of long-term local cure, with cure rates of around 95 per cent.[1196,1221,1222] In carotid body paragangliomas, the risk of hypoglossal and vagus nerve injury depends on size: 15 per cent risk for those sized less than 4 cm and 40 per cent risk for those over 4 cm.[1196] A systematic review reported a post-operative weighted cranial neuropathy rate of 20 per cent temporarily and 11 per cent permanently.[1214] The hypoglossal and vagus nerves are at greatest risk and equally affected. The 30-day post-operative risk of stroke is 4 per cent and the 30-day mortality rate is less than 1 per cent. Using the Mehanna classification, the risk of complications from surgery for small carotid body paragangliomas that extend to the hyoid bone is about 3 per cent, whereas in tumours that extend to the mandibular angle the risk is 21 per cent, and for even larger tumours, 44–70 per cent.[1195]

Adjuvant radiotherapy may be considered after subtotal resection or for metastatic cases.

Hence, surgery for carotid body paragangliomas may be attractive for small tumours and non-genetic cases. Compared to the main alternatives of surveillance or radiotherapy, surgery offers closure for the patient. Radiotherapy gives similarly excellent local control but no closure, with a residual lesion to monitor. For larger tumours, the decision-making is more complex, and the risks and benefits of surveillance, surgery and radiotherapy should be considered.

Jugulotympanic paraganglioma

Tympanic paragangliomas should be surgically resected with hearing preservation. For tumours extending to the jugular bulb, management is as for jugular paragangliomas.[1196]

For jugular paragangliomas, surveillance, surgery or radiotherapy are options for most tumours. With local control from radiotherapy equal to that from surgery, radiotherapy, with less morbidity, is the mainstay of treatment.[1196,1223]

Surgery should be considered for secretory tumours, and for tumours causing troublesome local symptoms, as an alternative to radiotherapy for growing tumours and for growth after radiotherapy. The lower cranial nerves are at risk. Total resection may be appropriate in some cases, such as when the tumour does not involve the jugular foramen. Otherwise, to minimise the risk of cranial nerve damage, subtotal resection with or without adjuvant radiotherapy is the preferred management method.[1224]

As with carotid body paragangliomas, the risk of cranial neuropathy increases with tumour size (about 10 per cent for Fisch class C and 40–80 per cent for Fisch class D tumours).[1219,1225] Hearing loss is another complication. In Fisch class C/D tumours, cochlear preservation facilitates hearing rehabilitation. In a meta-analysis of 1048 patients, risks included meningitis in 33 per cent, cerebrospinal fluid (CSF) leak in 10 per cent, severe aspiration pneumonia in 7 per cent and stroke in 2 per cent. The risk of major complications was 28 per cent and the risk of post-operative mortality was 2 per cent.[1205] Free-flap reconstruction may reduce CSF leak and improve cosmesis; two-stage resection may also reduce CSF leak.[1196]

Meta-analysis showed a five-year control rate after surgery of about 85 per cent.[1205] Recurrence may be salvaged by radiotherapy or re-operation, or observation may be appropriate. The risk of tumour progression is increased with subtotal resection, but there is some evidence that if more than 80 per cent of the tumour is excised regrowth may be less likely to occur.[1224]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

Vagal paraganglioma

Most patients with vagal paragangliomas are minimally symptomatic. Surveillance is often initially appropriate. Surgery should be avoided in vagal paragangliomas if other management options are available. Surgery for vagal paragangliomas will usually cause at least vagal nerve palsy, and consequent severe impairments in articulation, voice and swallowing, with possible long-term gastrostomy tube dependence. In patients with vagal nerve dysfunction pre-operatively, surgery causes further worsening of function. In a systematic review of 226 vagal paragangliomas, tumour control was obtained in 98 per cent of complete resections and in 93 per cent of all resections, while the vagus nerve was functionally preserved in only 11 patients (5 per cent).[1205] The published evidence from radiotherapy treatment is limited, but in the University of Florida experience of head and neck paragangliomas treated with radiotherapy over 35 years, local control in 17 patients was 100 per cent.[1223]

Metastatic head and neck paraganglioma

Recommendations

- All patients should be discussed and managed at a specialist centre by a head and neck cancer and/or skull base MDT with oncological input, and/or a paraganglioma MDT with oncological input (essential (E))

There is a small subset of extra-adrenal paragangliomas with a propensity for regional lymph node spread and distant metastasis. All paragangliomas have malignant potential; therefore, they are not classified as benign or malignant, but as primary and metastatic.[1189] Metastasis must be distinguished from multifocal primary disease.[1189] Distant metastases occur mainly to bone, lung and liver.[1207,1226,1227]

There is a high rate of metastasis (30–70 per cent) in the familial syndrome associated with *SDHB* mutation.[1206] The greater risk of aggressive disease and metastasis with *SDHB* mutation may lower the threshold for offering surgery. Mutations including *SDHA*, *TMEM127* and *VHL* are also higher risk. The occurrence of metastasis depends on the site of origin: orbital and laryngeal paragangliomas are very rare, but have a 25 per cent risk of metastasis.[1207,1226,1227] The occurrence of metastasis is less than 19 per cent for vagal paragangliomas, 5 per cent for jugulotympanic paragangliomas and 3 per cent for carotid body paragangliomas.[1206]

Metastasis is confirmed by the presence of tumours in lymph nodes or distant metastasis to non-endocrine tissues.[1207,1226,1227] Hence, malignancy is established by whole-body imaging, with whole-body MRI and/or Ga-68-Dotatate PET-CT.[1192]

Local and regional tumour control are best achieved by surgical resection and adjuvant radiotherapy. The five-year survival rate is 50–80 per cent for patients with regional lymph node spread, but only 11 per cent for those with distant metastases.[1228] The disease can relapse up to 20 years after first treatment.[1207,1226,1227]

Chemotherapy, with cyclophosphamide, vincristine and dacarbazine, is considered the standard of care in advanced metastatic paragangliomas. Response rates to chemotherapy of 33–41 per cent have been reported, with a biochemical response of 54 per cent.[1229,1230] Some patients with distant metastases may be candidates for peptide receptor radionuclide therapy with iodine-123-metaiodobenzylguanidine (123I-MIBG) for example, on which there are limited data on efficacy.[1231] Bone marrow and renal toxicities are potential side effects. Temozolomide may show a response in SDHB-associated metastatic paragangliomas.[1232]

Table 3. Follow-up guidelines for sporadic head and neck paraganglioma

Management	Follow up
Surveillance or radiotherapy	Contrast-MRI at 6 months, then annually
	If stable, contrast-MRI can be increased to 2-yearly for 6 years then 3-yearly (surveillance may be stopped in older adult patients with stable tumours)
	Plasma metanephrines test – if initial test results normal, endocrinology follow up is not required
Surgery	As above, but discharge from follow up is reasonable after total resection & no evidence of recurrence at 5 years

MRI = magnetic resonance imaging

Table 4. Follow-up guidelines for genetic head and neck paraganglioma (life-long follow up)

Assessment	Description
Head & neck imaging	Contrast-MRI at 6 months, then annually
	If stable, can be increased to 2-yearly for 6 years then 3-yearly
Body imaging (to screen for phaeochromocytoma & renal cell carcinoma)	Annual renal ultrasound (in years in between whole-body MRI)
	MRI of thorax, abdomen, pelvis every 3 years
Plasma metanephrines test	Annually (non-functional tumours can start to secrete)
	If levels raised, MRI of thorax, pelvis, abdomen required

MRI = magnetic resonance imaging

Follow up

Recommendations

- Most patients should have specialist long-term follow up including serial MRI scans (good practice point (G))
- At five years, patients with definitively treated, isolated, sporadic, and benign head and neck paraganglioma may be discharged from follow up (G)
- Patients, and any relatives, with relevant gene variants should have life-long specialist follow up, including annual plasma metanephrines testing and whole-body imaging (evidence-based recommendation (R))

The nature and duration of surveillance for head and neck paraganglioma depends on genetic status and treatment; this is summarised in Tables 3 and 4, adapted from the British Skull Base Society consensus guidelines (2020).[1196] Patients

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

should have a review in the clinic to assess for clinical progression and cranial neuropathy, in addition to radiological and biochemical follow up. At five years, sporadic cases treated with total surgical resection can be discharged from follow up, depending on individual circumstances.

Patients with complications of disease and therapy, such as cranial nerve palsy and hearing loss, should have follow up tailored to their needs in a head and neck cancer or skull base MDT clinic.

Studies due to report

No phase III trials were identified.

Important research questions to be answered

The data on the long-term outcome of surveillance for head and neck paragangliomas remain limited, together with identification of predictive factors.

More information is required on the true frequency of metastasis in head and neck paraganglioma and on survival outcomes.

The published evidence on radiotherapy for vagal paraganglioma treatment is limited.

It is not clear whether genetic mutation status should alter management in unifocal head and neck paraganglioma cases (e.g. whether there should be a lower threshold for offering surgery to *SDHB* mutation cases with a greater chance of aggressive disease and metastasis).

Appendices

Appendix 1. List of reviewers

David Allin, Andrew Barber, Andrea Beech, Zac Cole-Healy, Richard Gan, Kate Garcez, Jarrod Homer, Hiro Ishii, Chris Jennings, Jemy Jose, Shane Lester, Navin Mani, Emma Molena, Elizabeth Neslon, Eugene Omakobia, Vin Paleri, Susannah Penney, Paul Pracy, Costa Repanos, Sajid Sainuddin, Mantegh Sethi, Ricard Simo, Maria Smith, Sanjai Sood, Frank Stafford, Selvam Thavaraj, Hugh Wheatley, Mark Wilke, Stuart Winter, Billy Wong.

Appendix 2. Management of head and neck squamous cell carcinoma of unknown primary (Chapter 27) – initiative collaborators

Syed Ahsan, Basil Al Omari, Arvind Arya, Panagiotis Asimakopoulos, Zaid Awad, Nigel Beasley, Kirsty Beaton, Sandeep Berry, Conor Bowe, Alex Bowen, Grainne Brady, Malcolm Buchanan, Dawn Carnell, Preetha Chengot, Peter Clarke, Andrew Coatesworth, James Constable, Oliver Dale, Charles Daultrey, Katharine Davies, Cameron Davies-Husband, John de Almeida, Sian Dobbs, Mouli Doddi, Olly Donnelly, Brian Fish, Liam Flood, Montey Garg, Ajith George, Andrew Harris, Chris Hogan, Christopher Holsinger, Jarrod Homer, Robert Hone, David Howe, Jonathan P Hughes, Kate Hulse, Andrew Husband, Shahid Iqbal, Hiro Ishii, Zsuzsanna Iyizoba-Ebozue, Macolm Jackson, Sharan Jayaram, Jean-Pierre Jeannon, Chris Jennings, Jemy Jose, Noemi Kelemen, Shivun Khosla, Emma King, B Nirmal Kumar, Rohit Kumar, Shane Lester, Peter Lion, Zi Wei Liu, Gitta Madani, Jaiganesh Manickavasagam, Marcos Martinez Del Pero, Oliver McLaren, Kris Milinis, George Mochloulis, Jennifer Montgomery, James Moor, Iain Nixon, Enyi Ofo, James O'Hara, Oladejo Olaleye, Nashreen Oozeer, Nimesh Patel, Claire Paterson, Jo Patterson, Imran Petkar, Vinod Prabhu, Paul Pracy, Mark Puvanendran, Costa Repanos, Max Robinson, Bindy Sahota, Ann Sandison, Mehmet Sen, Ketan Shah, Neil Sharma, Somiah Siddiq, Ricard Simo, Salil Sood, Dev Srinivasan, Paul Stimpson, Mrinal Supriya, Arun Takhar, Taran Tatla, Racheal Thomas, Anna Thompson, Paul Tierney, Athena Togo, Tommi Tornari, Ben Tudor-Green, Kishan Ubayasiri, Ramzan Ullah, Navdeep Upile, Jagdeep Virk, David Walker, Giles Warner, Hugh Wheatley, Mark Wilkie, Richard Williams, Andrew Williamson, Christina Wilson, Stuart Winter.

References

1 National Institute for Clinical Excellence. *Guidance on Cancer Services: Improving Outcomes in Head and Neck Cancers – The Manual*. London: NICE, 2004

2 Cancer Research UK. Head and neck cancers incidence statistics. In: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/incidence#ref- [15 February 2023]

3 Bergamini C, Locati L, Bossi P, Granata R, Alfieri S, Resteghini C *et al.* Does a multidisciplinary team approach in a tertiary referral centre impact on the initial management of head and neck cancer? *Oral Oncol* 2016;**54**:54–7

4 Brunner M, Gore SM, Read RL, Alexander A, Mehta A, Elliot M *et al.* Head and neck multidisciplinary team meetings: effect on patient management. *Head Neck* 2015;**37**:1046–50

5 Kelly SL, Jackson JE, Hickey BE, Szallasi FG, Bond CA. Multidisciplinary clinic care improves adherence to best practice in head and neck cancer. *Am J Otolaryngol* 2013;**34**:57–60

6 Loevner LA, Sonners AI, Schulman BJ, Slawek K, Weber RS, Rosenthal DI *et al.* Reinterpretation of cross-sectional images in patients with head and neck cancer in the setting of a multidisciplinary cancer center. *AJNR Am J Neuroradiol* 2002;**23**:1622–6

7 Starmer H, Sanguineti G, Marur S, Gourin CG. Multidisciplinary head and neck cancer clinic and adherence with speech pathology. *Laryngoscope* 2011;**121**:2131–5

8 Wheless SA, McKinney KA, Zanation AM. A prospective study of the clinical impact of a multidisciplinary head and neck tumor board. *Otolaryngol Head Neck Surg* 2010;**143**:650–4

9 Shang C, Feng L, Gu Y, Hong H, Hong L, Hou J. Impact of multidisciplinary team management on the survival rate of head and neck cancer patients: a cohort study meta-analysis. *Front Oncol* 2021;**11**:630906

10 CancerData. Radiotherapy Data Set. In: https://www.cancerdata.nhs.uk/radiotherapy [15 February 2023]

11 Royal College of Radiologists. *Clinical Oncology: UK Workforce Census 2020 Report*. London: Royal College of Radiologists, 2021

12 NHS England. Service Specification for External Beam Radiotherapy (Adults) (NHS England Ref: 170091S). In: https://www.england.nhs.uk/wp-content/uploads/2019/01/External-Beam-Radiotherapy-Services-Delivered-as-Part-of-a-Radiotherapy-Network-Adults.pdf [15 February 2023]

13 Eskander A, Irish J, Groome PA, Freeman J, Gullane P, Gilbert R *et al.* Volume-outcome relationships for head and neck cancer surgery in a universal health care system. *Laryngoscope* 2014;**124**:2081–8

14 Eskander A, Monteiro E, Irish J, Gullane P, Gilbert R, de Almeida J *et al.* Adherence to guideline-recommended process measures for squamous cell carcinoma of the head and neck in Ontario: impact of surgeon and hospital volume. *Head Neck* 2016;**38**(suppl 1):E1987–92

15 Gourin CG, Forastiere AA, Sanguineti G, Koch WM, Marur S, Bristow RE. Impact of surgeon and hospital volume on short-term outcomes and cost of laryngeal cancer surgical care. *Laryngoscope* 2011;**121**:85–90

16 Gourin CG, Stewart CM, Frick KD, Fakhry C, Pitman KT, Eisele DW *et al.* Association of hospital volume with laryngectomy outcomes in patients with larynx cancer. *JAMA Otolaryngol Head Neck Surg* 2019;**145**:62–70

17 Robertson AG, Robertson C, Soutar DS, Burns H, Hole D, McCarron P. Treatment of oral cancer: the need for defined protocols and specialist centres. Variations in the treatment of oral cancer. *Clin Oncol (R Coll Radiol)* 2001;**13**:409–15

18 Torabi SJ, Benchetrit L, Kuo Yu P, Cheraghlou S, Savoca EL, Tate JP *et al.* Prognostic case volume thresholds in patients with head and neck squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg* 2019;**145**:708–15

19 Morton M. *Oral and Maxillofacial Surgery: GIRFT Programme National Specialty Report*. London: Getting It Right First Time, 2018. In: https://gettingitrightfirsttime.co.uk/wp-content/uploads/2018/11/OMFS-Report-Nov18-F_Layout-1-FINAL.pdf [15 February 2023]

20 Nouraei SA, Middleton SE, Hudovsky A, Branford OA, Lau C, Clarke PM *et al.* Role of reconstructive surgery in the management of head and neck cancer: a national outcomes analysis of 11,841 reconstructions. *J Plast Reconstr Aesthet Surg* 2015;**68**:469–78

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

21 CancerData. In: https://www.cancerdata.nhs.uk [17 February 2023]
22 National Cancer Registration and Analysis Service. Routes to Diagnosis. In: http://www.ncin.org.uk/publications/routes_to_diagnosis [17 February 2023]
23 Seoane J, Takkouche B, Varela-Centelles P, Tomás I, Seoane-Romero JM. Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis. *Clin Otolaryngol* 2012;**37**:99–106
24 National Institute for Health and Care Excellence. In: *Suspected Cancer: Recognition and Referral. NICE Guideline [NG12]*. London: NICE, 2015;24
25 Gao C, Qin C, Freeman S, Oskooee N, Hughes J. Two week wait referral criteria – heading in the right direction? *J Laryngol Otol* 2019;**133**:704–12
26 Tikka T, Pracy P, Paleri V. Refining the head and neck cancer referral guidelines: a two-centre analysis of 4715 referrals. *Clin Otolaryngol* 2016;**41**:66–75
27 Tikka T, Kavanagh K, Lowit A, Jiafeng P, Burns H, Nixon IJ *et al*. Head and neck cancer risk calculator (HaNC-RC)-V.2. Adjustments and addition of symptoms and social history factors. *Clin Otolaryngol* 2020;**45**:380–8
28 Hardman JC, Tikka T, Paleri V. Remote triage incorporating symptom-based risk stratification for suspected head and neck cancer referrals: a prospective population-based study. *Cancer* 2021;**127**:4177–89
29 NHS. NHS Long term plan. In: https://www.longtermplan.nhs.uk/ [17 February 2023]
30 van Schaik JE, Halmos GB, Witjes MJH, Plaat BEC. An overview of the current clinical status of optical imaging in head and neck cancer with a focus on narrow band imaging and fluorescence optical imaging. *Oral Oncol* 2021;**121**:105504
31 Abou-Nader L, Wilson JA, Paleri V. Transnasal oesophagoscopy: diagnostic and management outcomes in a prospective cohort of 257 consecutive cases and practice implications. *Clin Otolaryngol* 2014;**39**:108–13
32 Howe TE, Khurram SA, Hunter K, Martin LH, Fry AM. Accuracy of staging of oral squamous cell carcinoma of the tongue: should incisional biopsy be done before or after magnetic resonance imaging? *Br J Oral Maxillofac Surg* 2017;**55**:298–9
33 Schutte HW, Takes RP, Slootweg PJ, Arts M, Honings J, van den Hoogen FJA, *et al*. Digital video laryngoscopy and flexible endoscopic biopsies as an alternative diagnostic workup in laryngopharyngeal cancer: a prospective clinical study. *Ann Otol Rhinol Laryngol* 2018;**127**:770–6
34 Cozens NJA. A radiologist's perspective of the value of ultrasound-guided fine needle aspiration cytology in the assessment of head and neck lesions. *Cytopathology* 2021;**32**:394–6
35 Breeze J, Poller DN, Gibson D, Tilley EA, Cooke L, Soar E *et al*. Rapid on-site assessment of specimens by biomedical scientists improves the quality of head and neck fine needle aspiration cytology. *Cytopathology* 2014;**25**:316–21
36 Douville NJ, Bradford CR. Comparison of ultrasound-guided core biopsy versus fine-needle aspiration biopsy in the evaluation of salivary gland lesions. *Head Neck* 2013;**35**:1657–61
37 Goldenberg D, Begum S, Westra WH, Khan Z, Sciubba J, Pai SI *et al*. Cystic lymph node metastasis in patients with head and neck cancer: an HPV-associated phenomenon. *Head Neck* 2008;**30**:898–903
38 Royal College of Radiologists. *Recommendations for Cross-Sectional Imaging in Cancer Management*: *Imaging in the Evaluation of Cancer*, 2nd edn. London: Royal College of Radiologists, 2014
39 Batuwitage BT, Hanlon R, Charters P. Imaging in head and neck cancers. *BJA Educ* 2021;**21**:2–9
40 Bartz BH, Case IC, Srinivasan A, Mukherji SK. Delayed MDCT imaging results in increased enhancement in patients with head and neck neoplasms. *J Comput Assist Tomogr* 2006;**30**:972–4
41 Touska P, Connor SEJ. New and advanced magnetic resonance imaging diagnostic imaging techniques in the evaluation of cranial nerves and the skull base. *Neuroimaging Clin N Am* 2021;**31**:665–84
42 Richards PS, Peacock TE. The role of ultrasound in the detection of cervical lymph node metastases in clinically N0 squamous cell carcinoma of the head and neck. *Cancer Imaging* 2007;**7**:167–78
43 Marchi F, Filauro M, Iandelli A, Carobbio ALC, Mazzola F, Santori G *et al*. Magnetic resonance vs. intraoral ultrasonography in the preoperative assessment of oral squamous cell carcinoma: a systematic review and meta-analysis. *Front Oncol* 2019;**9**:1571
44 Rusthoven KE, Koshy M, Paulino AC. The role of fluorodeoxyglucose positron emission tomography in cervical lymph node metastases from an unknown primary tumor. *Cancer* 2004;**101**:2641–9
45 Xu G, Li J, Zuo X, Li C. Comparison of whole body positron emission tomography (PET)/PET-computed tomography and conventional anatomic imaging for detecting distant malignancies in patients with head and neck cancer: a meta-analysis. *Laryngoscope* 2012;**122**:1974–8
46 National Institute for Health and Care Excellence. *Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and Over. NICE Guideline [NG36]*. London: NICE, 2016
47 Chen J, Hagiwara M, Givi B, Schmidt B, Liu C, Chen Q *et al*. Assessment of metastatic lymph nodes in head and neck squamous cell carcinomas using simultaneous (18)F-FDG-PET and MRI. *Sci Rep* 2020;**10**:20764
48 Mukherji SK, Bradford CR. Controversies: is there a role for positron-emission tomographic CT in the initial staging of head and neck squamous cell carcinoma? *Am J Neuroradiol* 2006;**27**:243–5
49 Ferlito A, Shaha AR, Silver CE, Rinaldo A, Mondin V. Incidence and sites of distant metastases from head and neck cancer. *ORL J Otorhinolaryngol Relat Spec* 2001;**63**:202–7
50 Piersiala K, Akst LM, Hillel AT, Best SR. CT lung screening in patients with laryngeal cancer. *Sci Rep* 2020;**10**:4676
51 Mehanna H, Wong WL, McConkey CC, Rahman JK, Robinson M, Hartley AG *et al*. PET-CT surveillance versus neck dissection in advanced head and neck cancer. *N Engl J Med* 2016;**374**:1444–54
52 de Bree R, van der Putten L, van Tinteren H, Wedman J, Oyen WJ, Janssen LM *et al*. Effectiveness of an (18)F-FDG-PET based strategy to optimize the diagnostic trajectory of suspected recurrent laryngeal carcinoma after radiotherapy: the RELAPS multicenter randomized trial. *Radiother Oncol* 2016;**118**:251–6
53 Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 8th edn. Hoboken, NJ: Wiley Blackwell, 2016
54 Tanjak P, Suktitipat B, Vorasan N, Juengwiwattanakitti P, Thiengtrong B, Songjang C *et al*. Risks and cancer associations of metachronous and synchronous multiple primary cancers: a 25-year retrospective study. *BMC Cancer* 2021;**21**:1045
55 Coca-Pelaz A, Rodrigo JP, Suárez C, Nixon IJ, Mäkitie A, Sanabria A *et al*. The risk of second primary tumors in head and neck cancer: a systematic review. *Head Neck* 2020;**42**:456–66
56 Kuhlin B, Kramer B, Nefas V, Rotter N, Aderhold C. Indicators for secondary carcinoma in head and neck cancer patients following curative therapy: a retrospective clinical study. *Mol Clin Oncol* 2020;**12**:403–10
57 McGarey PO Jr, O'Rourke AK, Owen SR, Shonka DC Jr, Reibel JF, Levine PA *et al*. Rigid esophagoscopy for head and neck cancer staging and the incidence of synchronous esophageal malignant neoplasms. *JAMA Otolaryngol Head Neck Surg* 2016;**142**:40–5
58 Head and Neck National Optimal Pathway In: https://collaborative.nhs.wales/networks/wales-cancer-network/wcn-documents/clinician-hub/csg-pathways-and-associated-documents/h-n-nop-mucosal-pdf/ [2 March 2022]
59 Royal College of Pathologists. Dataset for histopathology reporting of mucosal malignancies of the larynx. In: https://www.rcpath.org/asset/0D6C0512-E285-40FD-B8A9EE31B13887DE/ [25 February 2023]
60 Royal College of Pathologists. Dataset for histopathology reporting of mucosal malignancies of the nasal cavities and paranasal sinuses. In: https://www.rcpath.org/uploads/assets/011ca2d9-65a2-4512-b9127043a73c0a40/Dataset-for-histopathology-reporting-of-mucosal-malignancies-of-the-nasal-cavities-and-paranasal-sinuses.pdf [1 July 2021]
61 Royal College of Pathologists. Dataset for histopathology reporting of mucosal malignancies of the oral cavity. In: https://www.rcpath.org/uploads/assets/c4a9faf7-393a-4ba8-9532f719d8cdff3b/Dataset-for-histopathology-reporting-of-mucosal-malignancies-of-the-oral-cavity.pdf [1 July 2021]
62 Royal College of Pathologists. Dataset for histopathology reporting of mucosal malignancies of the pharynx. In: https://www.rcpath.org/asset/6201BEF5%2D79DF%2D4107%2DBA6A42833377457F/ [1 July 2021]
63 Royal College of Pathologists. Dataset for histopathology reporting of nodal excisions and neck dissection specimens associated with head and neck carcinomas. In: https://www.rcpath.org/uploads/assets/2babb476-472b-4008-997c6a1074fddb23/ataset-for-histopathology-reporting-of-nodal-excisions-and-neck-dissection-specimens-associated-with-head-and-neck-carcinomas.pdf [1 July 2021]
64 Royal College of Pathologists. Dataset for histopathology reporting of salivary gland neoplasms. In: https://www.rcpath.org/uploads/assets/3d46a973-a5fd-49f5-87dc074b90a69b72/Dataset-for-histopathology-reporting-of-salivary-gland-neoplasms.pdf [1 July 2021]
65 El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, eds. *WHO Classification of Head and Neck Tumours*, 4th edn. Lyon: IARC Press, 2017

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

66 International Collaboration on Cancer Reporting. Datasets: Head and Neck. In: http://www.iccr-cancer.org/datasets/published-datasets/head-neck [1 June 2021]
67 UKAS. Laboratory Accreditation. In: https://www.ukas.com/accreditation/standards/laboratory-accreditation/ [25 February 2023]
68 NHS England. Cancer Alliances - improving care locally. In: https://www.england.nhs.uk/cancer/cancer-alliances-improving-care-locally/ [25 February 2023]
69 NHS England. Pathology quality assurance dashboard, 2nd edn. 2019. In: https://www.england.nhs.uk/wp-content/uploads/2020/08/Pathology_quality_assurance_dashboard_PQAD.pdf [25 February 2023]
70 British Society for Oral and Maxillofacial Pathology. National Head & Neck Histopathology EQA Scheme. In: https://www.bsomp.org.uk/eqa [1 July 2021]
71 Schache A, Kerawala C, Ahmed O, Brennan PA, Cook F, Garrett M *et al.* British Association of Head and Neck Oncologists (BAHNO) standards 2020. *J Oral Pathol Med* 2021;**50**:262–73
72 Royal College of Pathologists. Dataset for thyroid cancer histopathology reports. In: https://www.rcpath.org/uploads/assets/f9998652-9f19-47e5-8c8fa4cae8fda6bd/g098_thyroid_dataset_feb14.pdf [1 July 2021]
73 Royal College of Pathologists. Guidance on the reporting of thyroid cytology specimens. In: https://www.rcpath.org/uploads/assets/7d693ce4-0091-4621-97f79e2a0d1034d6/g089_guidance_on_reporting_of_thyroid_cytology_specimens.pdf [1 July 2021]
74 Kain JJ, Birkeland AC, Udayakumar N, Morlandt AB, Stevens TM, Carroll WR *et al.* Surgical margins in oral cavity squamous cell carcinoma: current practices and future directions. *Laryngoscope* 2020;**130**:128–38
75 Simo R, Morgan P, Jeannon JP, Odell E, Harrison J, Almeida B *et al.* Integrated media presentation in multidisciplinary head and neck oncology meetings. *Eur Arch Otorhinolaryngol* 2009;**266**:261–5
76 Woolgar JA, Triantafyllou A. Lymph node metastases in head and neck malignancies: assessment in practice and prognostic importance. *Diagn Histopathol* 2010;**16**:265–75
77 Varley I, Howe TE, Hunter K, Smith AT. Errors in interpretation of neck levels in postoperative pathological specimens. *Br J Oral Maxillofac Surg* 2017;**55**:302–4
78 National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. In: https://www.nice.org.uk/guidance/NG36/chapter/Recommendations#treatment-of-early-stage-disease [1 May 2018]
79 Bernadt CT, Collins BT. Fine-needle aspiration biopsy of HPV-related squamous cell carcinoma of the head and neck: current ancillary testing methods for determining HPV status. *Diagn Cytopathol* 2017;**45**:221–9
80 Cree IA, Deans Z, Ligtenberg MJ, Normanno N, Edsjo A, Rouleau E *et al.* Guidance for laboratories performing molecular pathology for cancer patients. *J Clin Pathol* 2014;**67**:923–31
81 NHS England. National Genomic Test Directory. In: https://www.england.nhs.uk/publication/national-genomic-test-directories/ [1 February 2022]
82 NHS Scotland Laboratory Genetic Services. In: https://www.nss.nhs.scot/publications/scottish-molecular-pathology-test-directory/ [1 February 2022]
83 National Institute for Health and Care Excellence. Pembrolizumab for untreated metastatic or unresectable recurrent head and neck squamous cell carcinoma. In: https://www.nice.org.uk/guidance/TA661/chapter/1-Recommendations [25 February 2023]
84 National Institute for Health and Care Excellence. Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy. In: https://www.nice.org.uk/guidance/TA490/chapter/1-Recommendations [25 February 2023]
85 Crosta S, Boldorini R, Bono F, Brambilla V, Dainese E, Fusco N *et al.* PD-L1 testing and squamous cell carcinoma of the head and neck: a multicenter study on the diagnostic reproducibility of different protocols. *Cancers* (*Basel*) 2021;**13**:292
86 Lewis JS Jr. Morphologic diversity in human papillomavirus-related oropharyngeal squamous cell carcinoma: catch me if you can! *Mod Pathol* 2017;**30**:S44–53
87 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK *et al.*, eds. *AJCC Cancer Staging Manual*, 8th edn. New York: Springer, 2017
88 Odell E, Baumhoer D, Carlos R, Hunter KD, Mosqueda-Taylor A, Richardson M *et al. Malignant Odontogenic Tumours. Histopathology Reporting Guide*. Sydney: International Collaboration on Cancer Reporting, 2018
89 Thompson LDR, Gupta R, Sandison A, Wenig BM. *Ear and Temporal Bone Tumours. Histopathology Reporting Guide*. Sydney: International Collaboration on Cancer Reporting, 2018
90 Thompson LDR, Franchi A, Helliwell T, Müller S, Williams M. *Mucosal Melanomas of the Head and Neck. Histopathology Reporting Guide*. Sydney: International Collaboration on Cancer Reporting, 2018
91 Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*, 8th edn. Chichester: John Wiley & Sons, 2016
92 Sobin LH, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours (UICC International Union Against Cancer)*, 7th edn. Hoboken, NJ: Wiley-Blackwell, 2009
93 de Juan J, Garcia J, Lopez M, Orus C, Esteller E, Quer M *et al.* Inclusion of extracapsular spread in the pTNM classification system: a proposal for patients with head and neck carcinoma. *JAMA Otolaryngol Head Neck Surg* 2013;**139**:483–8
94 van den Brekel MW, Lodder WL, Stel HV, Bloemena E, Leemans CR, van der Waal I. Observer variation in the histopathologic assessment of extranodal tumor spread in lymph node metastases in the neck. *Head Neck* 2012;**34**:840–5
95 Lewis JS Jr, Tarabishy Y, Luo J, Mani H, Bishop JA, Leon ME *et al.* Inter- and intra-observer variability in the classification of extracapsular extension in p16 positive oropharyngeal squamous cell carcinoma nodal metastases. *Oral Oncol* 2015;**51**:985–90
96 Kujan O, Khattab A, Oliver RJ, Roberts SA, Thakker N, Sloan P. Why oral histopathology suffers inter-observer variability on grading oral epithelial dysplasia: an attempt to understand the sources of variation. *Oral Oncol* 2007;**43**:224–31
97 Ranganathan K, Kavitha L, Sharada P, Bavle RM, Rao RS, Pattanshetty SM *et al.* Intra-observer and inter-observer variability in two grading systems for oral epithelial dysplasia: a multi-centre study in India. *J Oral Pathol Med* 2020;**49**:948–55
98 Speight PM, Abram TJ, Floriano PN, James R, Vick J, Thornhill MH *et al.* Interobserver agreement in dysplasia grading: toward an enhanced gold standard for clinical pathology trials. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;**120**:474–82.e2
99 Royal College of Pathologists. Tissue pathways for diagnostic cytopathology. In: https://www.rcpath.org/uploads/assets/b328ab3d-f574-40f1-8717c32ccfc4f7d8/G086-Tissue-pathways-for-diagnostic-cytopathology.pdf [1 July 2021]
100 Moberly AC, Vural E, Nahas B, Bergeson TR, Kokoska MS. Ultrasound-guided needle aspiration: impact of immediate cytologic review. *Laryngoscope* 2010;**120**:1979–84
101 Schmidt RL, Witt BL, Lopez-Calderon LE, Layfield LJ. The influence of rapid onsite evaluation on the adequacy rate of fine-needle aspiration cytology: a systematic review and meta-analysis. *Am J Clin Pathol* 2013;**139**:300–8
102 Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**:e7586
103 Kendall TJ, Robinson M, Brierley DJ, Lim SJ, O'Connor DJ, Shaaban AM *et al.* Guidelines for cellular and molecular pathology content in clinical trial protocols: the SPIRIT-Path extension. *Lancet Oncol* 2021;**22**:e435–45
104 100,000 Genomes Project. In: https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/ [1 July 2018]
105 Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. *Oral Oncol* 2015;**51**:1041–6
106 Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C *et al.* Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011;**12**:127–36
107 Royal College of Radiologists. *On Target 2: Updated Guidance for Image-Guided Radiotherapy*. London: Royal College of Radiologists, 2021
108 Royal College of Radiologists. *Radiotherapy Dose Fractionation*, 3rd edn. London: Royal College of Radiologists, 2019
109 Lacas B, Carmel A, Landais C, Wong SJ, Licitra L, Tobias JS *et al.* Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. *Radiother Oncol* 2021;**156**:281–93
110 Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M *et al.* Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol* 2017;**18**:1221–37

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

111 Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K *et al*. Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. *Int J Radiat Oncol Biol Phys* 2000;**47**:13–47

112 Smith J, Nastasi D, Tso R, Vangaveti V, Renison B, Chilkuri M. The effects of continued smoking in head and neck cancer patients treated with radiotherapy: a systematic review and meta-analysis. *Radiother Oncol* 2019;**135**:51–7

113 Royal College of Radiologists. *Timely Delivery of Radical Radiotherapy: Guidelines for the Management of Unscheduled Treatment Interruptions*, 4th edn. London: Royal College of Radiologists, 2021

114 Waldram R, Taylor AE, Whittam S, Iyizoba-Ebozue Z, Murray L, Frood R *et al*. Evaluation of locoregional recurrence patterns following adjuvant (chemo)radiotherapy for oral cavity carcinoma. *Clin Oncol* (*R Coll Radiol*) 2020;**32**:228–37

115 Tree AC, Khoo VS, Eeles RA, Ahmed M, Dearnaley DP, Hawkins MA *et al*. Stereotactic body radiotherapy for oligometastases. *Lancet Oncol* 2013;**14**:e28–37

116 Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;**393**:2051–8

117 Xiang M, Chang DT, Pollom EL. Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy. *Cancer* 2020;**126**:3560–8

118 Newhauser WD, Zhang R. The physics of proton therapy. *Phys Med Biol* 2015;**60**:R155–209

119 Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS *et al*. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys* 2002;**53**:407–21

120 Gunn GB, Blanchard P, Garden AS, Zhu XR, Fuller CD, Mohamed AS *et al*. Clinical outcomes and patterns of disease recurrence after intensity modulated proton therapy for oropharyngeal squamous carcinoma. *Int J Radiat Oncol Biol Phys* 2016;**95**:360–7

121 Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M *et al*. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - a case matched analysis. *Radiother Oncol* 2016;**120**:48–55

122 Li X, Kitpanit S, Lee A, Mah D, Sine K, Sherman EJ *et al*. Toxicity profiles and survival outcomes among patients with nonmetastatic nasopharyngeal carcinoma treated with intensity-modulated proton therapy vs intensity-modulated radiation therapy. *JAMA Netw Open* 2021;**4**:e2113205

123 Holliday EB, Garden AS, Rosenthal DI, Fuller CD, Morrison WH, Gunn GB *et al*. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. *Int J Part Ther* 2015;**2**:19–28

124 Patel SH, Wang Z, Wong WW, Murad MH, Buckey CR, Mohammed K *et al*. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. *Lancet Oncol* 2014;**15**:1027–38

125 Price J, Hall E, West C, Thomson D. TORPEdO - a phase III trial of intensity-modulated proton beam therapy versus intensity-modulated radiotherapy for multi-toxicity reduction in oropharyngeal cancer. *Clin Oncol* (*R Coll Radiol*) 2020;**32**:84–8

126 Burnet NG, Mackay RI, Smith E, Chadwick AL, Whitfield GA, Thomson DJ *et al*. Proton beam therapy: perspectives on the National Health Service England clinical service and research programme. *Br J Radiol* 2020;**93**:20190873

127 Boeckman HJ, Trego KS, Turchi JJ. Cisplatin sensitizes cancer cells to ionizing radiation via inhibition of nonhomologous end joining. *Mol Cancer Res* 2005;**3**:277–85

128 Winquist E, Oliver T, Gilbert R. Postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck: a systematic review with meta-analysis. *Head Neck* 2007;**29**:38–46

129 Dauzier E, Lacas B, Blanchard P, Le QT, Simon C, Wolf G *et al*. Role of chemotherapy in 5000 patients with head and neck cancer treated by curative surgery: a subgroup analysis of the meta-analysis of chemotherapy in head and neck cancer. *Oral Oncol* 2019;**95**:106–14

130 Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V *et al*. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oncologist* 2017;**22**:1056–66

131 Szturz P, Wouters K, Kiyota N, Tahara M, Prabhash K, Noronha V *et al*. Altered fractionation radiotherapy combined with concurrent low-dose or high-dose cisplatin in head and neck cancer: a systematic review of literature and meta-analysis. *Oral Oncol* 2018;**76**:52–60

132 Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A *et al*. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. *J Clin Oncol* 2018;**36**:1064–72

133 Helfenstein S, Riesterer O, Meier UR, Papachristofilou A, Kasenda B, Pless M *et al*. 3-weekly or weekly cisplatin concurrently with radiotherapy for patients with squamous cell carcinoma of the head and neck - a multicentre, retrospective analysis. *Radiat Oncol* 2019;**14**:32

134 Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK *et al*. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;**11**:21–8

135 Gebre-Medhin M, Brun E, Engström P, Haugen Cange H, Hammarstedt-Nordenvall L, Reizenstein J *et al*. ARTSCAN III: a randomized phase III study comparing chemoradiotherapy with cisplatin versus cetuximab in patients with locoregionally advanced head and neck squamous cell cancer. *J Clin Oncol* 2021;**39**:38–47

136 Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T *et al*. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019;**393**:51–60

137 Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S *et al*. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;**359**:1116–27

138 Ferrari D, Fiore J, Codecà C, Di Maria G, Bozzoni S, Bordin V *et al*. A phase II study of carboplatin and paclitaxel for recurrent or metastatic head and neck cancer. *Anticancer Drugs* 2009;**20**:185–90

139 Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F *et al*. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;**25**:2171–7

140 Guardiola E, Peyrade F, Chaigneau L, Cupissol D, Tchiknavorian X, Bompas E *et al*. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. *Eur J Cancer* 2004;**40**:2071–6

141 Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr *et al*. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019;**394**:1915–28

142 Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ *et al*. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 2019;**393**:156–67

143 Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L *et al*. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;**375**:1856–67

144 Grégoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA *et al*. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014;**110**:172–81

145 Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A *et al*. Delineation of the primary tumour clinical target volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. *Radiother Oncol* 2018;**126**:3–24

146 Biau J, Lapeyre M, Troussier I, Budach W, Giralt J, Grau C *et al*. Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 update. *Radiother Oncol* 2019;**134**:1–9

147 Royal College of Radiologists. *Head and Neck Cancer - RCR Consensus Statements*. London: Royal College of Radiologists, 2022

148 Pagh A, Grau C, Overgaard J. Failure pattern and salvage treatment after radical treatment of head and neck cancer. *Acta Oncol* 2016;**55**:625–32

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

149 Morris LG, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. *J Clin Oncol* 2011;**29**:739–46

150 Integrate (UK ENT Trainee Research Network). Post-treatment head and neck cancer care: national audit and analysis of current practice in the United Kingdom. *Clin Otolaryngol* 2021;**46**:284–94

151 Tan HK, Giger R, Auperin A, Bourhis J, Janot F, Temam S. Salvage surgery after concomitant chemoradiation in head and neck squamous cell carcinomas - stratification for postsalvage survival. *Head Neck* 2010;**32**:139–47

152 Chang JH, Wu CC, Yuan KS, Wu ATH, Wu SY. Locoregionally recurrent head and neck squamous cell carcinoma: incidence, survival, prognostic factors, and treatment outcomes. *Oncotarget* 2017;**8**:55600–12

153 Mabanta SR, Mendenhall WM, Stringer SP, Cassisi NJ. Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. *Head Neck* 1999;**21**:591–4

154 Kothari P, Trinidade A, Hewitt RJD, Singh A, O'Flynn P. The follow-up of patients with head and neck cancer: an analysis of 1,039 patients. *Eur Arch Otorhinolaryngol* 2011;**268**:1191–200

155 Hanemaaijer SH, Fazzi M, Steenbakkers R, Dorgelo B, van der Vegt B, Witjes MJH *et al.* (18) F-FDG PET/CT for response evaluation of regional lymph nodes in 97 head and neck squamous cell carcinoma patients: differences in the predictive value of residual disease after radiotherapy and chemoradiotherapy. *Clin Otolaryngol* 2020;**45**:805–10

156 Slevin F, Subesinghe M, Ramasamy S, Sen M, Scarsbrook AF, Prestwich RJ. Assessment of outcomes with delayed (18)F-FDG PET-CT response assessment in head and neck squamous cell carcinoma. *Br J Radiol* 2015;**88**:20140592

157 Ho AS, Tsao GJ, Chen FW, Shen T, Kaplan MJ, Colevas AD *et al.* Impact of positron emission tomography/computed tomography surveillance at 12 and 24 months for detecting head and neck cancer recurrence. *Cancer* 2013;**119**:1349–56

158 Girelli L, Locati L, Galeone C, Scanagatta P, Duranti L, Licitra L *et al.* Lung metastasectomy in adenoid cystic cancer: is it worth it? *Oral Oncol* 2017;**65**:114–18

159 Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953;**6**:963–8

160 Do KA, Johnson MM, Doherty DA, Lee JJ, Wu XF, Dong Q *et al.* Second primary tumors in patients with upper aerodigestive tract cancers: joint effects of smoking and alcohol (United States). *Cancer Causes Control* 2003;**14**:131–8

161 Gilbert DC, Wakeham K, Langley RE, Vale CL. Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis. *Br J Cancer* 2019;**120**:256–68

162 Cramer JD, Grauer J, Sukari A, Nagasaka M. Incidence of second primary lung cancer after low-dose computed tomography vs chest radiography screening in survivors of head and neck cancer: a secondary analysis of a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg* 2021;**147**:1071–8

163 Prestwich RJD, Arunsingh M, Zhong J, Dyker KE, Vaidyanathan S, Scarsbrook AF. Second-look PET-CT following an initial incomplete PET-CT response to (chemo)radiotherapy for head and neck squamous cell carcinoma. *Eur Radiol* 2020;**30**:1212–20

164 Sheikhbahaei S, Taghipour M, Ahmad R, Fakhry C, Kiess AP, Chung CH *et al.* Diagnostic accuracy of follow-up FDG PET or PET/CT in patients with head and neck cancer after definitive treatment: a systematic review and meta-analysis. *AJR Am J Roentgenol* 2015;**205**:629–39

165 Semple CJ, Dunwoody L, George Kernohan W, McCaughan E, Sullivan K. Changes and challenges to patients' lifestyle patterns following treatment for head and neck cancer. *J Adv Nurs* 2008;**63**:85–93

166 Aggarwal P, Goepfert RP, Garden AS, Garg N, Zaveri JS, Du XL *et al.* Risk and clinical risk factors associated with late lower cranial neuropathy in long-term oropharyngeal squamous cell carcinoma survivors. *JAMA Otolaryngol Head Neck Surg* 2021;**147**:469–78

167 Ghazali N, Cadwallader E, Lowe D, Humphris G, Ozakinci G, Rogers SN. Fear of recurrence among head and neck cancer survivors: longitudinal trends. *Psychooncology* 2013;**22**:807–13

168 Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE *et al.* Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol* 2018;**4**:173–82

169 Sinard RJ, Tobin EJ, Mazzaferri EL, Hodgson SE, Young DC, Kunz AL *et al.* Hypothyroidism after treatment for nonthyroid head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2000;**126**:652–7

170 van der Meulen IC, May AM, de Leeuw JR, Koole R, Oosterom M, Hordijk GJ *et al.* Long-term effect of a nurse-led psychosocial intervention on health-related quality of life in patients with head and neck cancer: a randomised controlled trial. *Br J Cancer* 2014;**110**:593–601

171 Lewis RA, Neal RD, Hendry M, France B, Williams NH, Russell D *et al.* Patients' and healthcare professionals' views of cancer follow-up: systematic review. *Br J Gen Pract* 2009;**59**:e248–59

172 Lorenc A, Wells M, Fulton-Lieuw T, Nankivell P, Mehanna H, Jepson M *et al.* Clinicians' views of patient-initiated follow-up in head and neck cancer: a qualitative study to inform the PETNECK2 trial. *Clin Oncol* (*R Coll Radiol*) 2022;**34**:230–40

173 de Oliveira Faria S, Hurwitz G, Kim J, Liberty J, Orchard K, Liu G *et al.* Identifying patient-reported outcome measures (PROMs) for routine surveillance of physical and emotional symptoms in head and neck cancer populations: a systematic review. *J Clin Med* 2021;**10**:4162

174 Huang SH, Perez-Ordonez B, Weinreb I, Hope A, Massey C, Waldron JN *et al.* Natural course of distant metastases following radiotherapy or chemoradiotherapy in HPV-related oropharyngeal cancer. *Oral Oncol* 2013;**49**:79–85

175 Kaka AS, Zhao S, Ozer E, Agrawal A, Kang S, Rocco J *et al.* Comparison of clinical outcomes following head and neck surgery among patients who contract to abstain from alcohol vs patients who abuse alcohol. *JAMA Otolaryngol Head Neck Surg* 2017;**143**:1181–6

176 Ailianou A, Mundada P, De Perrot T, Pusztaszieri M, Poletti PA, Becker M. MRI with DWI for the detection of posttreatment head and neck squamous cell carcinoma: why morphologic MRI criteria matter. *AJNR Am J Neuroradiol* 2018;**39**:748–55

177 Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? *Laryngoscope* 2000;**110**(3 Pt 2 suppl 93):1–18

178 Putten L, Bree R, Doornaert PA, Buter J, Eerenstein SE, Rietveld DH *et al.* Salvage surgery in post-chemoradiation laryngeal and hypopharyngeal carcinoma: outcome and review. *Acta Otorhinolaryngol Ital* 2015;**35**:162–72

179 Kim J, Kim S, Albergotti WG, Choi PA, Kaplan DJ, Abberbock S *et al.* Selection of ideal candidates for surgical salvage of head and neck squamous cell carcinoma: effect of the Charlson-Age Comorbidity Index and oncologic characteristics on 1-year survival and hospital course. *JAMA Otolaryngol Head Neck Surg* 2015;**141**:1059–65

180 Tam S, Araslanova R, Low TH, Warner A, Yoo J, Fung K *et al.* Estimating survival after salvage surgery for recurrent oral cavity cancer. *JAMA Otolaryngol Head Neck Surg* 2017;**143**:685–90

181 Mucke T, Wagenpfeil S, Kesting MR, Holzle F, Wolff KD. Recurrence interval affects survival after local relapse of oral cancer. *Oral Oncol* 2009;**45**:687–91

182 Borsetto D, Higginson JA, Aslam A, Al-Qamachi L, Dhanda J, Marioni G *et al.* Factors affecting prognosis in locoregional recurrence of oral squamous cell carcinoma. *J Oral Pathol Med* 2019;**48**:206–13

183 Okano W, Hayashi R, Matsuura K, Shinozaki T, Tomioka T. Extent of salvage neck dissection following chemoradiation for locally advanced head and neck cancer. *Head Neck* 2021;**43**:413–18

184 Robbins KT, Doweck I, Samant S, Vieira F. Effectiveness of superselective and selective neck dissection for advanced nodal metastases after chemoradiation. *Arch Otolaryngol Head Neck Surg* 2005;**131**:965–9

185 Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;**13**:8–10

186 Vengaloor Thomas T, Packianathan S, Bhanat E, Albert A, Abraham A, Gordy X *et al.* Oligometastatic head and neck cancer: comprehensive review. *Head Neck* 2020;**42**:2194–201

187 Lustig RA, Vogl TJ, Fromm D, Cuenca R, Alex Hsi R, D'Cruz AK *et al.* A multicenter phase I safety study of intratumoral photoactivation of talaporfin sodium in patients with refractory solid tumors. *Cancer* 2003;**98**:1767–71

188 Tan IB, Dolivet G, Ceruse P, Vander Poorten V, Roest G, Rauschning W. Temoporfin-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study. *Head Neck* 2010;**32**:1597–604

189 Strojan P, Groselj A, Sersa G, Plaschke CC, Vermorken JB, Nuyts S *et al.* Electrochemotherapy in mucosal cancer of the head and neck: a systematic review. *Cancers* (*Basel*) 2021;**13**:1254

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

190 Kanatas A, Coffey D, Spellman J, Twigg J, Lowe D, Rogers SN. Follow-up arrangements in head and neck cancer clinics during the COVID-19 pandemic: results from two tertiary UK head and neck cancer centres. *Ann R Coll Surg Engl* 2021. Epub 2021 Dec 23

191 Taneja A, Su'a B, Hill AG. Efficacy of patient-initiated follow-up clinics in secondary care: a systematic review. *Intern Med J* 2014;**44**:1156–60

192 Shah K, Te Marvelde L, Collins M, De Abreu Lourenco R, D'Costa I, Coleman A *et al*. Safety and cost analysis of an (18)FDG-PET-CT response based follow-up strategy for head and neck cancers treated with primary radiation or chemoradiation. *Oral Oncol* 2015;**51**:529–35

193 Tanaka H, Takemoto N, Horie M, Takai E, Fukusumi T, Suzuki M *et al*. Circulating tumor HPV DNA complements PET-CT in guiding management after radiotherapy in HPV-related squamous cell carcinoma of the head and neck. *Int J Cancer* 2021;**148**:995–1005

194 National Institute for Health and Care Excellence. *Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and Over*. London: NICE, 2016

195 Sanderson RJ, Ironside JAD. Squamous cell carcinomas of the head and neck. *BMJ* 2002;**325**:822–7

196 International Statistical Classification of Diseases and Related Health Problems 10th Revision. In: https://icd.who.int/browse10/2019/en#/ [9 August 2021]

197 Conway DI, Purkayastha M, Chestnutt IG. The changing epidemiology of oral cancer: definitions, trends, and risk factors. *Br Dent J* 2018;**225**:867–73

198 Kaste L, Dolecek TA, Zavras AI. Head and neck cancer epidemiology and health services research. In: Radosevich JA, ed. *Head & Neck Cancer: Current Perspectives, Advances, and Challenges*. Dordrecht: Springer, 2013;37–71

199 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209–49

200 Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. *Nat Rev Dis Primers* 2020;**6**:92

201 Bravi F, Lee YA, Hashibe M, Boffetta P, Conway DI, Ferraroni M *et al*. Lessons learned from the INHANCE Consortium: an overview of recent results on head and neck cancer. *Oral Dis* 2021;**27**:73–93

202 Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F *et al*. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. *CA Cancer J Clin* 2017;**67**:51–64

203 Cheong SC, Vatanasapt P, Yi-Hsin Y, Zain RB, Kerr AR, Johnson NW. Oral cancer in South East Asia: current status and future directions. *Transl Res Oral Oncol* 2017;**2**

204 Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V *et al*. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. *Head Neck* 2013;**35**:747–55

205 Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. *J Clin Oncol* 2015;**33**:3235–42

206 Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017;**3**:524–48

207 Miranda-Filho A, Bray F. Global patterns and trends in cancers of the lip, tongue and mouth. *Oral Oncol* 2020;**102**:104551

208 Bosetti C, Carioli G, Santucci C, Bertuccio P, Gallus S, Garavello W *et al*. Global trends in oral and pharyngeal cancer incidence and mortality. *Int J Cancer* 2020;**147**:1040–9

209 Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. *Oral Oncol* 2009;**45**:309–16

210 Louie KS, Mehanna H, Sasieni P. Trends in head and neck cancers in England from 1995 to 2011 and projections up to 2025. *Oral Oncol* 2015;**51**:341–8

211 Purkayastha M, McMahon AD, Gibson J, Conway DI. Trends of oral cavity, oropharyngeal and laryngeal cancer incidence in Scotland (1975-2012) - a socioeconomic perspective. *Oral Oncol* 2016;**61**:70–5

212 Cancer incidence by deprivation. In: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/incidence#heading-Four [17 May 2022]

213 National Cancer Registration and Analysis Service CancerData. Stage at Diagnosis. In: https://www.cancerdata.nhs.uk/stage_at_diagnosis [9 August 2021]

214 Brierley J, Asamura, H, van Eycken E, Rous B. *TNM Atlas*, 7th edn. Hoboken: Wiley-Blackwell, 2021

215 Cancer Research UK (CRUK). Head and neck cancers mortality statistics. In: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/mortality [29 July 2021]

216 Du E, Mazul AL, Farquhar D, Brennan P, Anantharaman D, Abedi-Ardekani B *et al*. Long-term survival in head and neck cancer: impact of site, stage, smoking, and human papillomavirus status. *Laryngoscope* 2019;**129**:2506–13

217 International Agency for Research on Cancer (IARC). Head and neck cancer in South America and Europe HEADSpAcE translational studies. In: https://headspace.iarc.fr/ [9 August 2021]

218 Ness AR, Waylen A, Hurley K, Jeffreys M, Penfold C, Pring M *et al*. Establishing a large prospective clinical cohort in people with head and neck cancer as a biomedical resource: Head and Neck 5000. *BMC Cancer* 2014;**14**:973

219 Ingarfield K, McMahon AD, Hurley K, Toms S, Pring M, Thomas SJ *et al*. Inequality in survival of people with head and neck cancer: Head and Neck 5000 cohort study. *Head Neck* 2021;**43**:1252–70

220 Conway DI, Hashibe M, Boffetta P, Wunsch-Filho V, Muscat J, La Vecchia C *et al*. Enhancing epidemiologic research on head and neck cancer: INHANCE - The International Head and Neck Cancer Epidemiology Consortium. *Oral Oncol* 2009;**45**:743–6

221 The International Head and Neck Cancer Epidemiology (INHANCE) Consortium. About Us. In: https://www.inhance.utah.edu/ [9 August 2021]

222 Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C *et al*. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidem Biomar* 2009;**18**:541–50

223 Gormley M, Dudding T, Sanderson E, Martin RM, Thomas S, Tyrrell J *et al*. A multivariable Mendelian randomization analysis investigating smoking and alcohol consumption in oral and oropharyngeal cancer. *Nat Commun* 2020;**11**:6071

224 Hobbs CG, Sterne JA, Bailey M, Heyderman RS, Birchall MA, Thomas SJ. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. *Clin Otolaryngol* 2006;**31**:259–66

225 Anantharaman D, Muller DC, Lagiou P, Ahrens W, Holcátová I, Merletti F *et al*. Combined effects of smoking and HPV16 in oropharyngeal cancer. *Int J Epidemiol* 2016;**45**:752–61

226 Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF *et al*. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;**363**:24–35

227 Vukovic V, Stojanovic J, Vecchioni A, Pastorino R, Boccia S. Systematic review and meta-analysis of SNPs from genome-wide association studies of head and neck cancer. *Otolaryngol Head Neck Surg* 2018;**159**:615–24

228 Lesseur C, Diergaarde B, Olshan AF, Wunsch V, Ness AR, Liu G *et al*. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nat Genet* 2016;**48**:1544–50

229 Chalmers RL, Rahman KM, Young S, Kennedy M, Endersby S, Adams JR *et al*. The medial sural artery perforator flap in intra-oral reconstruction: a Northeast experience. *J Plast Reconstr Aesthet Surg* 2016;**69**:687–93

230 Green R, Rahman KM, Owen S, Paleri V, Adams J, Ahmed OA *et al*. The superficial circumflex iliac artery perforator flap in intra-oral reconstruction. *J Plast Reconstr Aesthet Surg* 2013;**66**:1683–7

231 Brown JS, Barry C, Ho M, Shaw R. A new classification for mandibular defects after oncological resection. *Lancet Oncol* 2016;**17**:e23–30

232 Brown JS, Shaw RJ. Reconstruction of the maxilla and midface: introducing a new classification. *Lancet Oncol* 2010;**11**:1001–8

233 Meccariello G, Montevecchi F, Sgarzani R, De Vito A, D'Agostino G, Gobbi R *et al*. The reconstructive options for oropharyngeal defects in the transoral robotic surgery framework. *Oral Oncol* 2017;**66**:108–11

234 Marijić B, Grasl S, Grasl MC, Faisal M, Erovic BM, Janik S. Do salivary bypass tubes reduce the risk of pharyngocutaneous fistula after laryngopharyngectomy--a systematic review and meta-analysis. *Cancers (Basel)* 2021;**13**:2827

235 Patel RS, Goldstein DP, Brown D, Irish J, Gullane PJ, Gilbert RW. Circumferential pharyngeal reconstruction: history, critical analysis of techniques, and current therapeutic recommendations. *Head Neck* 2010;**32**:109–20

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

236 Viñals JMV, Rodrigues TAG, Lopez CC, Payro JMS, Porté JAP, Sildenikova DP *et al.* Outcomes of gastro-omental free flap reconstruction for salvage laryngopharyngectomy for pharyngeal and laryngeal cancer after concurrent chemoradiotherapy. *Ann Plast Surg* 2017;**79**:e20–4

237 Patel RS, Makitie AA, Goldstein DP, Gullane PJ, Brown D, Irish J *et al.* Morbidity and functional outcomes following gastro-omental free flap reconstruction of circumferential pharyngeal defects. *Head Neck* 2009;**31**:655–63

238 Butskiy O, Rahmanian R, White RA, Durham S, Anderson DW, Prisman E. Revisiting the gastric pull-up for pharyngoesophageal reconstruction: a systematic review and meta-analysis of mortality and morbidity. *J Surg Oncol* 2016;**114**:907–14

239 Paleri V, Drinnan M, van den Brekel MW, Hinni ML, Bradley PJ, Wolf GT *et al.* Vascularized tissue to reduce fistula following salvage total laryngectomy: a systematic review. *Laryngoscope* 2014;**124**:1848–53

240 Walia A, Lee JJ, Jackson RS, Hardi AC, Bollig CA, Graboyes EM *et al.* Management of flap failure after head and neck reconstruction: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2022;**167**:224–35

241 Pohlenz P, Klatt J, Schön G, Blessmann M, Li L, Schmelzle R. Microvascular free flaps in head and neck surgery: complications and outcome of 1000 flaps. *Int J Oral Maxillofac Surg* 2012;**41**:739–43

242 Han ZF, Guo LL, Liu LB, Li Q, Zhou J, Wei AZ *et al.* A comparison of the Cook-Swartz Doppler with conventional clinical methods for free flap monitoring: a systematic review and a meta-analysis. *Int J Surg* 2016;**32**:109–15

243 Zoccali G, Molina A, Farhadi J. Is long-term post-operative monitoring of microsurgical flaps still necessary? *J Plast Reconstr Aesthet Surg* 2017;**70**:996–1000

244 Macmillan Cancer Support. Principles and guidance for prehabilitation within the management and support of people with cancer. In: https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1532-10061/prehabilitation-for-people-with-cancer-tcm9-353994?_ga=2.237589184.1911031931.1614596514-809671574.1614596514 [29 July 2021]

245 Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil* 2013;**92**:715–27

246 Langius JA, van Dijk AM, Doornaert P, Kruizenga HM, Langendijk JA, Leemans CR *et al.* More than 10% weight loss in head and neck cancer patients during radiotherapy is independently associated with deterioration in quality of life. *Nutr Cancer* 2013;**65**:76–83

247 Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;**26**:3770–6

248 Jager-Wittenaar H, Dijkstra PU, Dijkstra G, Bijzet J, Langendijk JA, van der Laan B *et al.* High prevalence of cachexia in newly diagnosed head and neck cancer patients: an exploratory study. *Nutrition* 2017;**35**:114–18

249 Findlay M, White K, Lai M, Luo D, Bauer JD. The association between computed tomography-defined sarcopenia and outcomes in adult patients undergoing radiotherapy of curative intent for head and neck cancer: a systematic review. *J Acad Nutr Diet* 2020;**120**:1330–47.e8

250 Office for National Statistics. Adult smoking habits in the UK: 2019. In: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2019 [29 July 2021]

251 Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H *et al.* HPV-related oropharyngeal cancer in the United Kingdom: an evolution in understanding of disease etiology. *Cancer Res* 2016;**76**:6598–606

252 Boereboom C, Doleman B, Lund JN, Williams JP. Systematic review of pre-operative exercise in colorectal cancer patients. *Tech Coloproctol* 2016;**20**:81–9

253 Faithfull S, Turner L, Poole K, Joy M, Manders R, Weprin J *et al.* Prehabilitation for adults diagnosed with cancer: a systematic review of long-term physical function, nutrition and patient-reported outcomes. *Eur J Cancer Care* (*Engl*) 2019;**28**:e13023

254 Forbes CC, Swan F, Greenley SL, Lind M, Johnson MJ. Physical activity and nutrition interventions for older adults with cancer: a systematic review. *J Cancer Surviv* 2020;**14**:689–711

255 Singh F, Newton RU, Galvao DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol* 2013;**22**:92–104

256 Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N *et al.* Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. *Gastroenterology* 2018;**155**:391–410.e4

257 Britton B, Baker AL, Wolfenden L, Wratten C, Bauer J, Beck AK *et al.* Eating As Treatment (EAT): a stepped-wedge, randomized controlled trial of a health behavior change intervention provided by dietitians to improve nutrition in patients with head and neck cancer undergoing radiation therapy (TROG 12.03). *Int J Radiat Oncol Biol Phys* 2019;**103**:353–62

258 Bye A, Sandmael JA, Stene GB, Thorsen L, Balstad TR, Solheim TS *et al.* Exercise and nutrition interventions in patients with head and neck cancer during curative treatment: a systematic review and meta-analysis. *Nutrients* 2020;**12**:3233

259 Moore J, Scoggins CR, Philips P, Egger M, Tennant P, Little J *et al.* Implementation of prehabilitation for major abdominal surgery and head and neck surgery: a simplified seven-day protocol. *J Gastrointest Surg* 2021;**25**:2076–82

260 Grimmett C, Bradbury K, Dalton SO, Fecher-Jones I, Hoedjes M, Varkonyi-Sepp J *et al.* The role of behavioral science in personalized multimodal prehabilitation in cancer. *Front Psychol* 2021;**12**:634223

261 Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F *et al.* ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;**36**:11–48

262 Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A *et al.* Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology* 2014;**121**:937–47

263 Capozzi LC, Nishimura KC, McNeely ML, Lau H, Culos-Reed SN. The impact of physical activity on health-related fitness and quality of life for patients with head and neck cancer: a systematic review. *Br J Sports Med* 2016;**50**:325–38

264 Starmer HM, Yang W, Gourin CG, Kumar R, Jones B, McNutt T *et al.* One-year swallowing outcomes in patients treated with prophylactic gabapentin during radiation-based treatment for oropharyngeal cancer. *Dysphagia* 2017;**32**:437–42

265 Melnyk M, Casey RG, Black P, Koupparis AJ. Enhanced recovery after surgery (ERAS) protocols: time to change practice? *Can Urol Assoc J* 2011;**5**:342–8

266 Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N; Zurich Fast Track Study Group. A fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology* 2009;**136**:842–7

267 Watson LJ, Ewers C. Enhanced recovery after head and neck cancer surgery: a review of current literature. *Curr Opin Otolaryngol Head Neck Surg* 2020;**28**:161–4

268 Seven H, Calis AB, Turgut S. A randomized controlled trial of early oral feeding in laryngectomized patients. *Laryngoscope* 2003;**113**:1076–9

269 Bannister M, Ah-See KW. Enhanced recovery programmes in head and neck surgery: systematic review. *J Laryngol Otol* 2015;**129**:416–20

270 Aires FT, Dedivitis RA, Petrarolha SM, Bernardo WM, Cernea CR, Brandao LG. Early oral feeding after total laryngectomy: a systematic review. *Head Neck* 2015;**37**:1532–5

271 Prasad KC, Sreedharan S, Dannana NK, Prasad SC, Chandra S. Early oral feeds in laryngectomized patients. *Ann Otol Rhinol Laryngol* 2006;**115**:433–8

272 Brookes JT, Seikaly H, Diamond C, Mechor B, Harris JR. Prospective randomized trial comparing the effect of early suturing of tracheostomy sites on postoperative patient swallowing and rehabilitation. *J Otolaryngol* 2006;**35**:77–82

273 Dort JC, Farwell DG, Findlay M, Huber GF, Kerr P, Shea-Budgell MA *et al.* Optimal perioperative care in major head and neck cancer surgery with free flap reconstruction: a consensus review and recommendations from the enhanced recovery after surgery society. *JAMA Otolaryngol Head Neck Surg* 2017;**143**:292–303

274 Bianchini C, Pelucchi S, Pastore A, Feo CV, Ciorba A. Enhanced recovery after surgery (ERAS) strategies: possible advantages also for head and neck surgery patients? *Eur Arch Otorhinolaryngol* 2014;**271**:439–43

275 Yueh B, Weaver EM, Bradley EH, Krumholz HM, Heagerty P, Conley A *et al.* A critical evaluation of critical pathways in head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2003;**129**:89–95

276 Farwell DG, Reilly DF, Weymuller EA Jr, Greenberg DL, Staiger TO, Futran NA. Predictors of perioperative complications in head and neck patients. *Arch Otolaryngol Head Neck Surg* 2002;**128**:505–11

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

277 Worrall DM, Tanella A, DeMaria S Jr, Miles BA. Anesthesia and enhanced recovery after head and neck surgery. *Otolaryngol Clin North Am* 2019;**52**:1095–114
278 ClinicalTrials.gov. A Comprehensive Approach to Head and Neck Cancer Prehabilitation. ClinicalTrials.gov Identifier: NCT04617678. In: https://clinicaltrials.gov/ct2/show/NCT04617678 [29 July 2021]
279 National Cancer Research Institute. Research Priorities. In: https://www.ncri.org.uk/groups/living-with-beyond-cancer-group/research-priorities/ [24 June 2021]
280 Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME. Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. *Head Neck* 2005;**27**:659–68
281 Hébuterne X, Lemarié E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. *JPEN J Parenter Enteral Nutr* 2014;**38**:196–204
282 Brown T, Ross L, Jones L, Hughes B, Banks M. Nutrition outcomes following implementation of validated swallowing and nutrition guidelines for patients with head and neck cancer. *Support Care Cancer* 2014;**22**:2381–91
283 The NHS Long Term Plan. In: https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/ [16 March 2023]
284 Melnychuk M, Vindrola-Padros C, Aitchison M, Clarke CS, Fulop NJ, Levermore C *et al*. Centralising specialist cancer surgery services in England: survey of factors that matter to patients and carers and health professionals. *BMC Cancer* 2018;**18**:226
285 Ho YW, Yeh KY, Hsueh SW, Hung CY, Lu CH, Tsang NM *et al*. Impact of early nutrition counseling in head and neck cancer patients with normal nutritional status. *Support Care Cancer* 2021;**29**:2777–85
286 Findlay M, Brown C, De Abreu Lourenço R, White K, Bauer J. Sarcopenia and myosteatosis in patients undergoing curative radiotherapy for head and neck cancer: impact on survival, treatment completion, hospital admission and cost. *J Hum Nutr Diet* 2020;**33**:811–21
287 Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H *et al*. ESPEN practical guideline: clinical nutrition in cancer. *Clin Nutr* 2021;**40**:2898–913
288 National Collaborating Centre for Acute Care. *Nutrition Support for Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition*. London: National Collaborating Centre for Acute Care, 2006
289 Müller-Richter U, Betz C, Hartmann S, Brands RC. Nutrition management for head and neck cancer patients improves clinical outcome and survival. *Nutr Res* 2017;**48**:1–8
290 Gourin CG, Couch ME, Johnson JT. Effect of weight loss on short-term outcomes and costs of care after head and neck cancer surgery. *Ann Otol Rhinol Laryngol* 2014;**123**:101–10
291 Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T *et al*. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. *J Cachexia Sarcopenia Muscle* 2019;**10**:207–17
292 Ni J, Zhang L. Cancer cachexia: definition, staging, and emerging treatments. *Cancer Manag Res* 2020;**12**:5597–605
293 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F *et al*. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010;**39**:412–23
294 Mendes NP, Barros TA, Rosa COB, Franceschini SDCC. Nutritional screening tools used and validated for cancer patients: a systematic review. *Nutr Cancer* 2019;**71**:898–907
295 Findlay M, Rankin NM, Shaw T, White K, Boyer M, Milross C *et al*. Best evidence to best practice: implementing an innovative model of nutrition care for patients with head and neck cancer improves outcomes. *Nutrients* 2020;**12**:1465
296 Talwar B, Findlay M. When is the optimal time for placing a gastrostomy in patients undergoing treatment for head and neck cancer? *Curr Opin Support Palliat Care* 2012;**6**:41–53
297 British Dietetic Association. *Model and Process for Nutrition and Dietetic Practice*. Birmingham: British Dietetic Association, 2006
298 Parr K, Johnson F, Langley N, Richardson P. Improving patient pathways in head and neck cancer at a UK cancer centre. Results of a dietetic pretreatment project (DPP). *Clin Nutr ESPEN* 2020;**35**:250
299 Loewen I, Jeffery CC, Rieger J, Constantinescu G. Prehabilitation in head and neck cancer patients: a literature review. *J Otolaryngol Head Neck Surg* 2021;**50**:2
300 McCurdy B, Nejatinamini S, Debenham BJ, Álvarez-Camacho M, Kubrak C, Wismer WV *et al*. Meeting minimum ESPEN energy recommendations is not enough to maintain muscle mass in head and neck cancer patients. *Nutrients* 2019;**11**:2743
301 Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P *et al*. ESPEN guidelines on enteral nutrition: surgery including organ transplantation. *Clin Nutr* 2006;**25**:224–44
302 Todorovic VE, Mafrici B, eds. *A Pocket Guide to Clinical Nutrition*, 5th edn. Birmingham: British Dietetic Association, 2018
303 da Silva JSV, Seres DS, Sabino K, Adams SC, Berdahl GJ, Citty SW *et al*. ASPEN Consensus Recommendations for Refeeding Syndrome. *Nutr Clin Pract* 2020;**35**:178–95
304 Williams GF, White H, Sen M, Prestwich RJD. Patients' experience of enteral feeding following (chemo) radiotherapy for head and neck cancer: a qualitative study. *Clin Nutr* 2019;**38**:1382–9
305 Brown TE, Banks MD, Hughes BGM, Lin CY, Kenny LM, Bauer JD. Comparison of nutritional and clinical outcomes in patients with head and neck cancer undergoing chemoradiotherapy utilizing prophylactic versus reactive nutrition support approaches. *J Acad Nutr Diet* 2018;**118**:627–36
306 Madhoun MF. Prophylactic PEG placement in head and neck cancer: how many feeding tubes are unused (and unnecessary)? *World J Gastroenterol* 2011;**17**:1004–8
307 Axelsson L, Silander E, Nyman J, Bove M, Johansson L, Hammerlid E. Effect of prophylactic percutaneous endoscopic gastrostomy tube on swallowing in advanced head and neck cancer: a randomized controlled study: effect of prophylactic percutaneous endoscopic gastrostomy on swallowing. *Head Neck* 2017;**39**:908–15
308 Strijbos D, Keszthelyi D, Bogie RMM, Gilissen LPL, Lacko M, Hoeijmakers JGJ *et al*. A systematic review and meta-analysis on outcomes and complications of percutaneous endoscopic versus radiologic gastrostomy for enteral feeding. *J Clin Gastroenterol* 2018;**52**:753–64
309 National Patient Safety Agency. *Patient Safety Alert NPSA/2011/PSA002: Reducing the Harm caused by Misplaced Nasogastric Feeding Tubes in Adults, Children and Infants*. London: National Patient Safety Agency, 2011
310 Espeli V, Vergotte S, Dietrich P-Y, Pichard C, Siano M. Prolonged versus short-duration use of nasogastric tubes in patients with head and neck cancer during radiotherapy alone or combined chemoradiotherapy. *Nutr Cancer* 2018;**70**:1069–74
311 McCloskey P, Duffy C, Brown K, Irwin A, Faloon SJ. To improve nutrition of head and neck (H&N) cancer patients receiving radical radiotherapy (RT) in an outpatient setting by establishing a nasogastric (NG) feeding service to reduce lengthy inpatient stays and improve patient outcomes. *Clin Oncol* 2019;**31**(suppl 1):e7
312 Hazzard E, Gulliver S, Walton K, McMahon A-T, Milosavljevic M, Tapsell L. The patient experience of having a feeding tube during treatment for head and neck cancer: a systematic literature review. *Clin Nutr ESPEN* 2019;**33**:66–85
313 Nugent B, Lewis S, O'Sullivan JM. Enteral feeding methods for nutritional management in patients with head and neck cancers being treated with radiotherapy and/or chemotherapy. *Cochrane Database Syst Rev* 2013;**2013**:CD007904
314 McClelland S, Andrews JZ, Chaudhry H, Teckie S, Goenka A. Prophylactic versus reactive gastrostomy tube placement in advanced head and neck cancer treated with definitive chemoradiotherapy: a systematic review. *Oral Oncol* 2018;**87**:77–81
315 Brown TE, Spurgin A-L, Ross L, Tripcony L, Keller J, Hughes BGM *et al*. Validated swallowing and nutrition guidelines for patients with head and neck cancer: identification of high-risk patients for proactive gastrostomy. *Head Neck* 2013;**35**:1385–91
316 Brown TE, Getliffe V, Banks MD, Hughes BGM, Lin CY, Kenny LM *et al*. Validation of an updated evidence-based protocol for proactive gastrostomy tube insertion in patients with head and neck cancer. *Eur J Clin Nutr* 2016;**70**:574–81
317 National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. In: https://www.nice.org.uk/guidance/ng36 [16 March 2023]
318 Stableforth WD, Thomas S, Lewis SJ. A systematic review of the role of immunonutrition in patients undergoing surgery for head and neck cancer. *Int J Oral Maxillofac Surg* 2009;**38**:103–10
319 Bilku D, Dennison A, Hall T, Metcalfe M, Garcea G. Role of preoperative carbohydrate loading: a systematic review. *Ann R Coll Surg Engl* 2014;**96**:15–22

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

320 Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S *et al.* ESPEN guideline: clinical nutrition in surgery. *Clin Nutr* 2017;**36**:623–50

321 McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C *et al.* Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016;**40**:159–211

322 Kerawala CJ, Riva F, Paleri V. The impact of early oral feeding following head and neck free flap reconstruction on complications and length of stay. *Oral Oncol* 2021;**113**:105094

323 Brook I. Late side effects of radiation treatment for head and neck cancer. *Radiat Oncol J* 2020;**38**:84–92

324 Vlooswijk CP, van Rooij PHE, Kruize JC, Schuring HA, Al-Mamgani A, de Roos NM. Dietary counselling and nutritional support in oropharyngeal cancer patients treated with radiotherapy: persistent weight loss during 1-year follow-ups. *Eur J Clin Nutr* 2016;**70**:54–9

325 Crowder SL, Douglas KG, Yanina Pepino M, Sarma KP, Arthur AE. Nutrition impact symptoms and associated outcomes in post-chemoradiotherapy head and neck cancer survivors: a systematic review. *J Cancer Surviv* 2018;**12**:479–94

326 Crowder SL, Najam N, Sarma KP, Fiese BH, Arthur AE. Head and neck cancer survivors' experiences with chronic nutrition impact symptom burden after radiation: a qualitative study. *J Acad Nutr Diet* 2020;**120**:1643–53

327 Goldstein NE, Genden E, Morrison RS. Palliative care for patients with head and neck cancer: "I would like a quick return to a normal lifestyle". *JAMA* 2008;**299**:1818–25

328 Sciubba J. End-of-life care in the head and neck cancer patient. *Oral Dis* 2016;**22**:740–4

329 Howes N, Atkinson C, Thomas S, Lewis SJ. Immunonutrition for patients undergoing surgery for head and neck cancer. *Cochrane Database Syst Rev* 2018;**8**:CD010954

330 Yu K, Zheng X, Wang G, Liu M, Li Y, Yu P *et al.* Immunonutrition vs standard nutrition for cancer patients: a systematic review and meta-analysis (part 1). *JPEN J Parenter Enteral Nutr* 2020;**44**:742–67

331 Lyra MMF, Meira JEC, Guedes GDS, Bueno NB. Immunonutrition in head and neck cancer: systematic review and metanalysis of its clinical and nutritional effects. *Clin Nutr ESPEN* 2021;**41**:30–41

332 Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M *et al.* Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer – a case matched analysis. *Radiother Oncol* 2016;**120**:48–55

333 Royal College of Physicians. *Outpatients: The Future – Adding Value Through Sustainability*. London: RCP, 2018

334 NHS England. Supplementary prescribing by dietitians. In: https://www.england.nhs.uk/ahp/med-project/dietitians/ [16 March 2023]

335 Aapro M, Bossi P, Dasari A, Fallowfield L, Gascón P, Geller M *et al.* Digital health for optimal supportive care in oncology: benefits, limits, and future perspectives. *Support Care Cancer* 2020;**28**:4589–612

336 Pfeifer M, Keeney C, Bumpous J, Schapmire T, Studts J, Myers J *et al.* Impact of a telehealth intervention on quality of life and symptom distress in patients with head and neck cancer. *J Community Support Oncol* 2015;**13**:14–21

337 Wilson JA, Carding PN, Patterson JM. Dysphagia after nonsurgical head and neck cancer treatment: patients' perspectives. *Otolaryngol Head Neck Surg* 2011;**145**:767–71

338 Dziewas R, Beck AM, Clave P, Hamdy S, Heppner HJ, Langmore SE *et al.* Recognizing the importance of dysphagia: stumbling blocks and stepping stones in the twenty-first century. *Dysphagia* 2017;**32**:78–82

339 Hutcheson KA, Lewin JS, Barringer DA, Lisec A, Gunn GB, Moore MW *et al.* Late dysphagia after radiotherapy-based treatment of head and neck cancer. *Cancer* 2012;**118**:5793–9

340 Hutcheson KA, Yuk MM, Holsinger FC, Gunn GB, Lewin JS. Late radiation-associated dysphagia with lower cranial neuropathy in long-term oropharyngeal cancer survivors: video case reports. *Head Neck* 2015;**37**:E56–62

341 Allen J, Greene M, Sabido I, Stretton M, Miles A. Economic costs of dysphagia among hospitalized patients. *Laryngoscope* 2020;**130**:974–9

342 Martino R, Ringash J, Durkin L, Greco E, Huang SH, Xu W *et al.* Feasibility of assessing patient health benefits and incurred costs resulting from early dysphagia intervention during and immediately after chemoradiotherapy for head-and-neck cancer. *Curr Oncol* 2017;**24**:e466–76

343 VanderMolen L, VanRossum M, Burkhead L, Smeele L, Rasch C, Hilgers F. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. *Dysphagia* 2011;**26**:155–70

344 Russi EG, Corvò R, Merlotti A, Alterio D, Franco P, Pergolizzi S *et al.* Swallowing dysfunction in head and neck cancer patients treated by radiotherapy: review and recommendations of the supportive task group of the Italian Association of Radiation Oncology. *Cancer Treat Rev* 2012;**38**:1033–49

345 Patterson JM, McColl E, Carding PN, Hildreth AJ, Kelly C, Wilson JA. Swallowing in the first year after chemoradiotherapy for head and neck cancer: clinician- and patient-reported outcomes. *Head Neck* 2014;**36**:352–8

346 Robbins J, Levine R, Wood J, Roecker E, Luschei E. Age effects on lingual pressure generation as a risk factor for dysphagia. *Gerontol A Biol Sci Med Sci* 1995;**50**:M257–62

347 Govender R, Smith CH, Barratt H, Gardner B, Taylor SA. SIP SMART: a parallel group randomised feasibility trial of a tailored pre-treatment swallowing intervention package compared with usual care for patients with head and neck cancer. *BMC Cancer* 2020;**20**:360

348 Patterson JM, Brady GC, Roe JWG. Research into the prevention and rehabilitation of dysphagia in head and neck cancer: a UK perspective. *Curr Opin Otolaryngol Head Neck Surg* 2016;**24**:208–14

349 Dawson C, Pracy P, Patterson J, Paleri V. Rehabilitation following open partial laryngeal surgery: key issues and recommendations from the UK evidence based meeting on laryngeal cancer. *J Laryngol Otol* 2019;**133**:177–82

350 Perry A, Lee SH, Cotton S, Kennedy C. Therapeutic exercises for affecting post-treatment swallowing in people treated for advanced-stage head and neck cancers. *Cochrane Database Syst Rev* 2016;**2016**:CD011112

351 Greco E, Simic T, Ringash J, Tomlinson G, Inamoto Y, Martino R. Dysphagia treatment for patients with head and neck cancer undergoing radiation therapy: a meta-analysis review. *Int J Radiat Oncol Biol Phys* 2018;**101**:421–44

352 Starmer HM, Ayoub N, Byward C, Kizner J, Le Q, Hara W *et al.* The impact of developing a speech and swallow rehab program: improving patient satisfaction and multidisciplinary care. *Laryngoscope* 2017;**127**:2578–81

353 Hutcheson KA, Bhayani MK, Beadle BM, Gold KA, Shinn EH, Lai SY *et al.* Eat and exercise during radiotherapy or chemoradiotherapy for pharyngeal cancers: use it or lose it. *JAMA Otolaryngol Head Neck Surg* 2013;**139**:1127–34

354 Occomore L, Knight Z. A weekly speech and language therapy service for head and neck radiotherapy patients during treatment: maximizing accessibility and efficiency. *J Community Support Oncol* 2015;**13**:248–55

355 Malandraki GA, Hutcheson KA. Intensive therapies for dysphagia: implementation of the intensive dysphagia rehabilitation and the MD Anderson swallowing boot camp approaches. *Perspect ASHA Spec Interest Groups* 2018;**3**:133–45

356 Mashhour K, Abdelkader R, Abdelkader L, El Hadary S, Hashem W. Swallowing exercises: will they really help head and neck cancer patients? *Asian Pac J Cancer Prev* 2018;**19**:797–801

357 Kraaijenga SA, van der Molen L, Stuiver MM, Teertstra HJ, Hilgers FJ, van den Brekel MW. Effects of strengthening exercises on swallowing musculature and function in senior healthy subjects: a prospective effectiveness and feasibility study. *Dysphagia* 2015;**30**:392–403

358 Van Daele DJ, Langmore SE, Krisciunas GP, Lazarus CL, Pauloski BR, McCulloch TM *et al.* The impact of time after radiation treatment on dysphagia in patients with head and neck cancer enrolled in a swallowing therapy program. *Head Neck* 2019;**41**:606–14

359 Pauloski BR. Rehabilitation of dysphagia following head and neck cancer. *Phys Med Rehabil Clin N Am* 2008;**19**:889–928

360 Logemann JA, Pauloski BR, Rademaker AW, Colangelo LA. Super-supraglottic swallow in irradiated head and neck cancer patients. *Head Neck* 1997;**19**:535–40

361 Clark HM, Shelton N. Training effects of the effortful swallow under three exercise conditions. *Dysphagia* 2014;**29**:553–63

362 Hutcheson KA, Hammer MJ, Rosen SP, Jones CA, McCulloch TM. Expiratory muscle strength training evaluated with simultaneous high-resolution manometry and electromyography. *Laryngoscope* 2017;**127**:797–804

363 Patterson JM, McColl E, Carding PN, Wilson JA. Swallowing beyond six years post (chemo)radiotherapy for head and neck cancer; a cohort study. *Oral Oncol* 2018;**83**:53–8

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

364 Radhakrishna N, Yamini BK, Kadam AS, Shivashankar N, Vishwanathan C, Javarappa R. Acoustic analysis of voice in nonlaryngeal head and neck cancer patients post chemoradiotherapy. *J Cancer Res Ther* 2017;**13**:113–17

365 Lazarus CL. Effects of chemoradiotherapy on voice and swallowing. *Curr Opin Otolaryngol Head Neck Surg* 2009;**17**:172–8

366 Aaltonen LM, Rautiainen N, Sellman J, Saarilahti K, Mäkitie A, Rihkanen H *et al*. Voice quality after treatment of early vocal cord cancer: a randomized trial comparing laser surgery with radiation therapy. *Int J Radiat Oncol Biol Phys* 2014;**90**:255–60

367 Verdolini-Marston K, Burke MK, Lessac A, Glaze L, Caldwell E. Preliminary study of two methods of treatment for laryngeal nodules. *J Voice* 1995;**9**:74–85

368 Stemple JC, Lee L, D'Amico B, Pickup B. Efficacy of vocal function exercises as a method of improving voice production. *J Voice* 1994;**8**:271–8

369 Sharpe G, Camoes Costa V, Doubé W, Sita J, McCarthy C, Carding P. Communication changes with laryngectomy and impact on quality of life: a review. *Qual Life Res* 2019;**28**:863–77

370 Coffey MM, Tolley N, Howard D, Drinnan M, Hickson M. An investigation of the post-laryngectomy swallow using videofluoroscopy and fiberoptic endoscopic evaluation of swallowing (FEES). *Dysphagia* 2018;**33**:369–79

371 Lee MT, Govender R, Roy PJ, Vaz F, Hilari K. Factors affecting swallowing outcomes after total laryngectomy: participant self-report using the swallowing outcomes after laryngectomy questionnaire. *Head Neck* 2020;**42**:1963–9

372 Macri GF, Bogaardt H, Parrilla C, Minni A, D'Alatri L, de Vincentiis M *et al*. Patients' experiences with HMEs and attachments after total laryngectomy. *Clin Otolaryngol* 2016;**41**:652–9

373 Longobardi Y, Parrilla C, Di Cintio G, De Corso E, Marenda ME, Mari G *et al*. Olfactory perception rehabilitation after total laryngectomy (OPRAT): proposal of a new protocol based on training of sensory perception skills. *Eur Arch Otorhinolaryngol* 2020;**277**:2095–105

374 van Sluis KE, Kornman AF, van der Molen L, van den Brekel MWM, Yaron G. Women's perspective on life after total laryngectomy: a qualitative study. *Int J Lang Commun Disord* 2020;**55**:188–99

375 Patterson JM. Late effects of organ preservation treatment on swallowing and voice; presentation, assessment, and screening. *Front Oncol* 2019;**9**:401

376 Dong Y, Ridge JA, Li T, Lango MN, Churilla TM, Bauman JR *et al*. Long-term toxicities in 10-year survivors of radiation treatment for head and neck cancer. *Oral Oncol* 2017;**71**:122–8

377 Davies-Husband C, Murphy J, Kelly C, Drinnan M, Paleri V. Extreme long-term voice outcomes after concurrent chemoradiotherapy for advanced non-laryngeal head and neck cancer: eight-year post-treatment analysis. *Clin Otolaryngol* 2018;**43**:1494–9

378 Aylward A, Abdelaziz S, Hunt JP, Buchmann LO, Cannon RB, Lloyd S *et al*. Rates of dysphagia-related diagnoses in long-term survivors of head and neck cancers. *Otolaryngol Head Neck Surg* 2019;**161**:643–51

379 Clunie GM, Kinshuck AJ, Sandhu GS, Roe JWG. Voice and swallowing outcomes for adults undergoing reconstructive surgery for laryngotracheal stenosis. *Curr Opin Otolaryngol Head Neck Surg* 2017;**25**:195–9

380 Cocks H, Ah-See K, Capel M, Taylor P. Palliative and supportive care in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**(S2):S198–207

381 Mayland CR, Ho QM, Doughty HC, Rogers SN, Peddinti P, Chada P *et al*. The palliative care needs and experiences of people with advanced head and neck cancer: a scoping review. *Palliat Med* 2021;**35**:27–44

382 Hirano M. *Clinical Examination of Voice*. New York: Springer Verlag, 1981

383 List MA, D'Antonio LL, Cella DF, Siston A, Mumby P, Haraf D *et al*. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. *Cancer* 1996;**77**:2294–301

384 Bours GJJW, Speyer R, Lemmens J, Limburg M, De Wit R. Bedside screening tests vs. videofluoroscopy or fibreoptic endoscopic evaluation of swallowing to detect dysphagia in patients with neurological disorders. *J Adv Nurs* 2009;**65**:477–93

385 Rinkel RN, Verdonck-de Leeuw IM, van Reij EJ, Aaronson NK, Leemans CR. Speech Handicap Index in patients with oral and pharyngeal cancer: better understanding of patients' complaints. *Head Neck* 2008;**30**:868–74

386 Jacobson BH, Johnson A, Grywalski C, Silbergleit A, Jacobson G, Benninger MS *et al*. The Voice Handicap Index (VHI). *Am J Speech Lang Pathol* 1997;**6**:66–70

387 Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J *et al*. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson Dysphagia Inventory. *Arch Otolaryngol Head Neck Surg* 2001;**127**:870–6

388 Govender R, Lee MT, Davies TC, Twinn CE, Katsoulis KL, Payten CL *et al*. Development and preliminary validation of a patient-reported outcome measure for swallowing after total laryngectomy (SOAL questionnaire). *Clin Otolaryngol* 2012;**37**:452–9

389 Govender R, Lee MT, Drinnan M, Davies T, Twinn C, Hilari K. Psychometric evaluation of the Swallowing Outcomes After Laryngectomy (SOAL) patient-reported outcome measure. *Head Neck* 2016;**38**(suppl 1):E1639–45

390 Crary MA, Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Arch Phys Med Rehabil* 2005;**86**:1516–20

391 Enderby P, John A, Petheram B. *Therapy Outcome Measures for Rehabilitation Professionals: Speech and Language Therapy, Physiotherapy, Occupational Therapy*. Chichester: Wiley, 2006

392 Hurren A, Miller N, Carding P. Perceptual assessment of tracheoesophageal voice quality with the SToPS: the development of a reliable and valid tool. *J Voice* 2019;**33**:465–72

393 Rosenbek JC, Robbins JA, Roecker EB, Coyle JL, Wood JL. A penetration-aspiration scale. *Dysphagia* 1996;**11**:93–8

394 Hutcheson KA, Barrow MP, Barringer DA, Knott JK, Lin HY, Weber RS *et al*. Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): scale development and validation. *Cancer* 2017;**123**:62–70

395 Miles A, Hunting A, McFarlane M, Caddy D, Scott S. Predictive value of the New Zealand Secretion Scale (NZSS) for pneumonia. *Dysphagia* 2018;**33**:115–22

396 Miles A, Hunting A. Development, intra- and inter-rater reliability of the New Zealand Secretion Scale (NZSS). *Int J Speech Lang Pathol* 2019;**21**:377–84

397 Neubauer PD, Rademaker AW, Leder SB. The Yale Pharyngeal Residue Severity Rating Scale: an anatomically defined and image-based tool. *Dysphagia* 2015;**30**:521–8

398 Starmer HM, Drinnan M, Bhabra M, Watson LJ, Patterson J. Development and reliability of the revised Patterson Edema Scale. *Clin Otolaryngol* 2021;**46**:752–7

399 Petkar I, Bhide S, Newbold K, Harrington K, Nutting C. Dysphagia-optimised intensity-modulated radiotherapy techniques in pharyngeal cancers: is anyone going to swallow it? *Clin Oncol* 2017;**29**:e110–18

400 Owadally W, Hurt C, Timmins H, Parsons E, Townsend S, Patterson J *et al*. PATHOS: a phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for human papillomavirus (HPV) positive oropharyngeal cancer. *BMC Cancer* 2015;**15**:602

401 Patterson JM, Govender R, Roe J, Clunie G, Murphy J, Brady G *et al*. COVID-19 and ENT SLT services, workforce and research in the UK: a discussion paper. *Int J Lang Commun Disord* 2020;**55**:806–17

402 DAHNO. *National Head and Neck Cancer Audit. Tenth Annual Report*. Leeds: Health and Social Care Information Centre, 2014

403 Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer* 2013;**132**:1133–45

404 Deschler DG, Richmon JD, Khariwala SS, Ferris RL, Wang MB. The "new" head and neck cancer patient - young, nonsmoker, nondrinker, and HPV positive: evaluation. *Otolaryngol Head Neck Surg* 2014;**151**:375–80

405 National Cancer Intelligence Unit. Profile of Head and Neck Cancers in England: Incidence, Mortality and Survival, 2010. In: www.ncin.org.uk/ [15 November 2020]

406 Cappiello J, Piazza C, Giudice M, De Maria G, Nicolai P. Shoulder disability after different selective neck dissections (levels II-IV versus levels II-V): a comparative study. *Laryngoscope* 2005;**115**:259–63

407 Cheng PT, Hao SP, Lin YH, Yeh AR. Objective comparison of shoulder dysfunction after three neck dissection techniques. *Ann Otol Rhinol Laryngol* 2000;**109**(8 Pt 1):761–6

408 Rogers SN, Ferlito A, Pellitteri PK, Shaha AR, Rinaldo A. Quality of life following neck dissections. *Acta Otolaryngol* 2004;**124**:231–6

409 Shone GR, Yardley MP. An audit into the incidence of handicap after unilateral radical neck dissection. *J Laryngol Otol* 1991;**105**:760–2

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

410 Chan JY, Wong ST, Chan RC, Wei WI. Shoulder dysfunction after selective neck dissection in recurrent nasopharyngeal carcinoma. *Otolaryngol Head Neck Surg* 2015;**153**:379–84

411 Guru K, Manoor UK, Supe SS. A comprehensive review of head and neck cancer rehabilitation: physical therapy perspectives. *Indian J Palliat Care* 2012;**18**:87–97

412 Chaplin JM, Morton RP. A prospective, longitudinal study of pain in head and neck cancer patients. *Head Neck* 1999;**21**:531–7

413 Roerink SHPP, Coolen L, Schenning ME, Husson O, Smit JWA, Marres HA *et al.* High prevalence of self-reported shoulder complaints after thyroid carcinoma surgery. *Head Neck* 2017;**39**:260–8

414 Robinson M, Ward L, Mehanna H, Paleri V, Winter SC. Provision of physiotherapy rehabilitation following neck dissection in the UK. *J Laryngol Otol* 2018;**132**:624–7

415 National Institute for Health Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE guideline [NG36]. In: https://www.nice.org.uk/guidance/ng36 [15 November 2020]

416 Waterland JL, McCourt O, Edbrooke L, Granger CL, Ismail H, Riedel B *et al.* Efficacy of prehabilitation including exercise on postoperative outcomes following abdominal cancer surgery: a systematic review and meta-analysis. *Front Surg* 2021;**8**:628848

417 Gane EM, Michaleff ZA, Cottrell MA, McPhail SM, Hatton AL, Panizza BJ *et al.* Prevalence, incidence, and risk factors for shoulder and neck dysfunction after neck dissection: a systematic review. *Eur J Surg Oncol* 2017;**43**:1199–218

418 Thomas G, Tahir MR, Bongers BC, Kallen VL, Slooter GD, van Meeteren NL. Prehabilitation before major intra-abdominal cancer surgery: a systematic review of randomised controlled trials. *Eur J Anaesthesiol* 2019;**36**:933–45

419 Steegmann J, Bartella AK, Kloss-Brandstatter A, Kamal M, Holzle F, Lethaus B. A randomized clinical trial on the efficacy of a patient-adapted autonomous exercise regime for patients with head and neck cancer. *J Craniomaxillofac Surg* 2020;**48**:187–92

420 Takamura Y, Miyauchi A, Tomoda C, Uruno T, Ito Y, Miya A *et al.* Stretching exercises to reduce symptoms of postoperative neck discomfort after thyroid surgery: prospective randomized study. *World J Surg* 2005;**29**:775–9

421 Lauchlan DT, McCaul JA, McCarron T. Neck dissection and the clinical appearance of post-operative shoulder disability: the post-operative role of physiotherapy. *Eur J Cancer Care* (*Engl*) 2008;**17**:542–8

422 McNeely ML, Parliament M, Courneya KS, Seikaly H, Jha N, Scrimger R *et al.* A pilot study of a randomized controlled trial to evaluate the effects of progressive resistance exercise training on shoulder dysfunction caused by spinal accessory neurapraxia/neurectomy in head and neck cancer survivors. *Head Neck* 2004;**26**:518–30

423 McNeely ML, Parliament MB, Seikaly H, Jha N, Magee DJ, Haykowsky MJ *et al.* Effect of exercise on upper extremity pain and dysfunction in head and neck cancer survivors: a randomized controlled trial. *Cancer* 2008;**113**:214–22

424 McNeely ML, Parliament MB, Seikaly H, Jha N, Magee DJ, Haykowsky MJ *et al.* Sustainability of outcomes after a randomized crossover trial of resistance exercise for shoulder dysfunction in survivors of head and neck cancer. *Physiother Can* 2015;**67**:85–93

425 McGarvey AC, Hoffman GR, Osmotherly PG, Chiarelli PE. Maximizing shoulder function after accessory nerve injury and neck dissection surgery: a multicenter randomized controlled trial. *Head Neck* 2015;**37**:1022–31

426 Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A *et al.* The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**:570–9

427 Su TL, Chen AN, Leong CP, Huang YC, Chiang CW, Chen IH *et al.* The effect of home-based program and outpatient physical therapy in patients with head and neck cancer: a randomized, controlled trial. *Oral Oncol* 2017;**74**:130–4

428 Thomas A, D'Silva C, Mohandas L, Pais SMJ, Samuel SR. Effect of muscle energy techniques v/s active range of motion exercises on shoulder function post modified radical neck dissection in patients with head and neck cancer – a randomized clinical trial. *Asian Pac J Cancer Prev* 2020;**21**:2389–93

429 Pfister DG, Cassileth BR, Deng GE, Yeung KS, Lee JS, Garrity D *et al.* Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. *J Clin Oncol* 2010;**28**:2565–70

430 Jansen F, Eerenstein SEJ, Cnossen IC, Lissenberg-Witte BI, de Bree R, Doornaert P *et al.* Effectiveness of a guided self-help exercise program tailored to patients treated with total laryngectomy: results of a multi-center randomized controlled trial. *Oral Oncol* 2020;**103**:104586

431 Jansen F, Coupe VMH, Eerenstein SEJ, Cnossen IC, van Uden-Kraan CF, de Bree R *et al.* Cost-utility and cost-effectiveness of a guided self-help head and neck exercise program for patients treated with total laryngectomy: results of a multi-center randomized controlled trial. *Oral Oncol* 2021;**117**:105306

432 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76

433 Adair M, Murphy B, Yarlagadda S, Deng J, Dietrich MS, Ridner SH. Feasibility and preliminary efficacy of tailored yoga in survivors of head and neck cancer: a pilot study. *Integr Cancer Ther* 2018;**17**:774–84

434 Chen YH, Lin CR, Liang WA, Huang CY. Motor control integrated into muscle strengthening exercises has more effects on scapular muscle activities and joint range of motion before initiation of radiotherapy in oral cancer survivors with neck dissection: a randomized controlled trial. *PloS One* 2020;**15**:e0237133

435 Gallyer V, Smith TO, Fordham B, Dutton S, Chester-Jones M, Lamb SE *et al.* Getting Recovery Right After Neck Dissection (GRRAND-F): mixed-methods feasibility study to design a pragmatic randomised controlled trial protocol. *BMJ Open* 2021;**11**:e045741

436 Gilbert AW, Jones J, Stokes M, May CR. Factors that influence patient preferences for virtual consultations in an orthopaedic rehabilitation setting: a qualitative study. *BMJ Open* 2021;**11**:e041038

437 Dempsey L, Orr S, Lane S, Scott A. The clinical nurse specialist's role in head and neck cancer care: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**:S212–15

438 NHS stop smoking services help you quit. In: https://www.nhs.uk/live-well/quit-smoking/nhs-stop-smoking-services-help-you-quit/ [22 March 2023]

439 Throat Cancer Foundation. In: https://www.throatcancerfoundation.org/ [22 March 2023]

440 National Association of Laryngectomee Clubs. In: https://www.laryngectomy.org.uk/ [22 March 2023]

441 The Swallows In: https://www.theswallows.org.uk/ [22 March 2023]

442 Butterfly Thyroid Cancer Trust. In: http://www.butterfly.org.uk/ [22 March 2023]

443 National Institute for Healthcare and Excellence. *Guidance on Cancer Services – Improving Outcomes in Head and Neck Cancers – The Manual*. London: NICE, 2004

444 Iftikhar A, Islam M, Shepherd S, Jones S, Ellis I. Cancer and stress: does it make a difference to the patient when these two challenges collide? *Cancers* (*Basel*) 2021;**13**:163

445 Davidson A, Williams J. Factors affecting quality of life in patients experiencing facial disfigurement due to surgery for head and neck cancer. *Br J Nurs* 2019;**28**:180–4

446 Dawson C, Roe J, Starmer H, Brady G, Nund R, Coffey M *et al.* Patient advocacy in head and neck cancer: realities, challenges and the role of the multi-disciplinary team. *Clin Otolaryngol* 2020;**45**:437–44

447 Robson W. Supporting patients at every stage of living with head and neck cancers. *Nursing Times*, 11 November 2019

448 Macmillan Cancer Support. Principles and guidance for prehabilitation within the management and support of people with cancer. In: https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1532-10061/prehabilitation-for-people-with-cancer-tcm9-353994 [22 March 2023]

449 Dawson C, Adams J, Fenlon D. The experiences of people who receive swallow therapy after surgical treatment of head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2019;**128**:456–63

450 Holistic Needs Assessments. In: https://www.macmillan.org.uk/healthcare-professionals/innovation-in-cancer-care/holistic-needs-assessment [1 August 2021]

451 Muzumder S, Srikantia N, Udayashankar AH, Kainthaje PB, John Sebastian MG. Burden of acute toxicities in head-and-neck radiation therapy: a single-institutional experience. *South Asian J Cancer* 2019;**8**:120–3

452 Gunn L, Gilbert J, Nenclares P, Soliman H, Newbold K, Bhide S *et al.* Taste dysfunction following radiotherapy to the head and neck: a systematic review. *Radiother Oncol* 2021;**157**:130–40

453 Cocks H, Ah-See K, Capel M, Taylor P. Palliative and supportive care in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**:S198–207

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

454 Nayak SG, Pai MS, George LS. Self concept of head and neck cancer patients–a systematic review. *Int J Sci Res* 2015;**4**(2)
455 Windon MJ, D'Souza G, Faraji F, Troy T, Koch WM, Gourin CG *et al.* Priorities, concerns, and regret among patients with head and neck cancer. *Cancer* 2019;**125**:1281–9
456 Lin BM, Starmer HM, Gourin CG. The relationship between depressive symptoms, quality of life, and swallowing function in head and neck cancer patients 1 year after definitive therapy. *Laryngoscope* 2012;**122**:1518–25
457 Yilmaz M, Yener M, Yollu U, Akil F, Haciyev Y, Yargic I *et al.* Depression, self-esteem and sexual function in laryngeal cancer patients. *Clin Otolaryngol* 2015;**40**:349–54
458 Henry M, Ho A, Lambert SD, Carnevale FA, Greenfield B, MacDonald C *et al.* Looking beyond disfigurement: the experience of patients with head and neck cancer. *J Palliat Care* 2014;**30**:5–15
459 Rogers SN, Allmark C, Bekiroglu F, Edwards RT, Fabbroni G, Flavel R *et al.* Improving quality of life through the routine use of the Patient Concerns Inventory for head and neck cancer patients: main results of a cluster preference randomised controlled trial. *Eur Arch Otorhinolaryngol* 2021;**278**:3435–49
460 Lexomboon D, Karlsson P, Adolfsson J, Ekbom A, Naimi-Akbar A, Bahmanyar S *et al.* Consumption and direct costs of dental care for patients with head and neck cancer: a 16-year cohort study. *Plos One* 2017;**12**:e0182877
461 Royal College of Surgeons of England, British Society for Disability and Oral Health. The Oral Management of Oncology Patients Requiring Radiotherapy, Chemotherapy and / or Bone Marrow Transplantation, 2018. In: https://www.rcseng.ac.uk/-/media/files/rcs/fds/publications/rcs-oncology-guideline-update--v36.pdf [24 March 2023]
462 National Institute for Healthcare and Excellence. *Improving Outcomes in Head and Neck Cancers*. London: NICE, 2004
463 British Association of Head and Neck Oncologists. BAHNO Standards. In: https://bahno.org.uk/clinicians_area/publications.aspx [2 March 2022]
464 NHS England, NHS Improvement. Commissioning Standard for Restorative Dentistry, 2019. In: https://www.england.nhs.uk/wp-content/uploads/2019/07/commissioning-standard-for-restorative-dentistry-v1.pdf [1 July 2021]
465 Predicting and Managing Oral and Dental Complications of Surgical and Non-Surgical Treatment for Head and Neck Cancer. A Clinical Guideline. In: https://www.restdent.org.uk/uploads/RD-UK%20H%20and%20N%20guideline.pdf [1 July 2021]
466 Levine JP, Bae JS, Soares M, Brecht LE, Saadeh PB, Ceradini DJ *et al.* Jaw in a day: total maxillofacial reconstruction using digital technology. *Plast Reconstr Surg* 2013;**131**:1386–91
467 Witjes MJH, Schepers RH, Kraeima J. Impact of 3D virtual planning on reconstruction of mandibular and maxillary surgical defects in head and neck oncology. *Curr Opin Otolaryngol Head Neck Surg* 2018;**26**:108–14
468 Rodby KA, Turin S, Jacobs RJ, Cruz JF, Hassid VJ, Kolokythas A *et al.* Advances in oncologic head and neck reconstruction: systematic review and future considerations of virtual surgical planning and computer aided design/computer aided modeling. *J Plast Reconstr Aesthet Surg* 2014;**67**:1171–85
469 Schubert O, Schweiger J, Stimmelmayr M, Nold E, Guth JF. Digital implant planning and guided implant surgery - workflow and reliability. *Br Dent J* 2019;**226**:101–8
470 Rogers SN, McNally D, Mahmoud M, Chan M, Humphris GM. Psychologic response of the edentulous patient after primary surgery for oral cancer: a cross-sectional study. *J Prosthet Dent* 1999;**82**:317–21
471 Patel J, Antov H, Nixon P. Implant-supported oral rehabilitation in oncology patients: a retrospective cohort study. *Br J Oral Maxillofac Surg* 2020;**58**:1003–7
472 Alberga JM, Vosselman N, Korfage A, Delli K, Witjes MJH, Raghoebar GM *et al.* What is the optimal timing for implant placement in oral cancer patients? A scoping literature review. *Oral Dis* 2021;**27**:94–110
473 dos Santos DM, de Caxias FP, Bitencourt SB, Turcio KH, Pesqueira AA, Goiato MC. Oral rehabilitation of patients after maxillectomy. A systematic review. *Br J Oral Maxillofac Surg* 2018;**56**:256–66
474 Sharaf MY, Ibrahim SI, Eskander AE, Shaker AF. Prosthetic versus surgical rehabilitation in patients with maxillary defect regarding the quality of life: systematic review. *Oral Maxillofac Surg* 2018;**22**:1–11
475 Buurman DJM, Speksnijder CM, de Groot RJ, Kessler P, Rieger JM. Mastication in maxillectomy patients: a comparison between reconstructed maxillae and implant supported obturators: a cross-sectional study. *J Oral Rehabil* 2020;**47**:1171–7
476 Buurman DJM, Speksnijder CM, Engelen BHBT, Kessler P. Masticatory performance and oral health-related quality of life in edentulous maxillectomy patients: a cross-sectional study to compare implant-supported obturators and conventional obturators. *Clin Oral Implants Res* 2020;**31**:405–16
477 King E, Abbott C, Dovgalski L, Owens J. Orofacial rehabilitation with zygomatic implants: CAD-CAM bar and magnets for patients with nasal cancer after rhinectomy and partial maxillectomy. *J Prosthet Dent* 2017;**117**:806–10
478 Branemark P. *The Zygomatic Fixture: Clinical Procedures*. Gothenburg: Nobel Biocare, 1998
479 Hackett S, El-Wazani B, Butterworth C. Zygomatic implant-based rehabilitation for patients with maxillary and mid-facial oncology defects: a review. *Oral Dis* 2021;**27**:27–41
480 Pellegrino G, Basile F, Relics D, Ferri A, Grande F, Tarsitano A *et al.* Computer-aided rehabilitation supported by zygomatic implants: a cohort study comparing atrophic with oncologic patients after five years of follow-up. *J Clin Med* 2020;**9**:3254
481 Ramezanzade S, Yates J, Tuminelli FJ, Keyhan SO, Yousefi P, Lopez-Lopez J. Zygomatic implants placed in atrophic maxilla: an overview of current systematic reviews and meta-analysis. *Maxillofac Plast Reconstr Surg* 2021;**43**:1
482 Rogers SN, Alvear A, Anesi A, Babin E, Balik A, Batstone M *et al.* Variations in concerns reported on the Patient Concerns Inventory in patients with head and neck cancer from different health settings across the world. *Head Neck* 2020;**42**:498–512
483 Rogers SN, Barber B. Using PROMs to guide patients and practitioners through the head and neck cancer journey. *Patient Relat Outcome Meas* 2017;**8**:133–42
484 Korfage A, Schoen PJ, Raghoebar GM, Roodenburg JLN, Vissink A, Reintsema H. Benefits of dental implants installed during ablative tumour surgery in oral cancer patients: a prospective 5-year clinical trial. *Clin Oral Implants Res* 2010;**21**:971–9
485 Dholam KP, Gurav SV. Dental implants in irradiated jaws: a literature review. *J Cancer Res Ther* 2012;**8**:S85–93
486 Javed F, Al-Hezaimi K, Al-Rasheed A, Almas K, Romanos GE. Implant survival rate after oral cancer therapy: a review. *Oral Oncol* 2010;**46**:854–9
487 In 't Veld M, Schulten EAJM, Leusink FKJ. Immediate dental implant placement and restoration in the edentulous mandible in head and neck cancer patients: a systematic review and meta-analysis. *Curr Opin Otolaryngol Head Neck Surg* 2021;**29**:126–37
488 Barber AJ, Butterworth CJ, Rogers SN. Systematic review of primary osseointegrated dental implants in head and neck oncology. *Br J Oral Maxillofac Surg* 2011;**49**:29–36
489 Zhang L, Ding Q, Liu C, Sun Y, Xie Q, Zhou Y. Survival, function, and complications of oral implants placed in bone flaps in jaw rehabilitation: a systematic review. *Int J Prosthodont* 2016;**29**:115–25
490 Chrcanovic BR, Albrektsson T, Wennerberg A. Dental implants in irradiated versus nonirradiated patients: a meta-analysis. *Head Neck* 2016;**38**:448–81
491 Claudy MP, Quevedo Miguens SA, Celeste RK, Parente RC, Gonzalez Hernandez PA, da Silva AN Jr. Time interval after radiotherapy and dental implant failure: systematic review of observational studies and meta-analysis. *Clin Implant Dent Relat Res* 2015;**17**:402–11
492 Schiegnitz E, Al-Nawas B, Kaemmerer PW, Grotz KA. Oral rehabilitation with dental implants in irradiated patients: a meta-analysis on implant survival. *Clin Oral Investig* 2014;**18**:687–98
493 Nobrega AS, Santiago JF Jr, de Faria Almeida DA, dos Santos DM, Pellizzer EP, Goiato MC. Irradiated patients and survival rate of dental implants: a systematic review and meta-analysis. *J Prosthet Dent* 2016;**116**:858–66
494 Shugaa-Addin B, Al-Shamiri H-M, Al-Maweri S, Tarakji B. The effect of radiotherapy on survival of dental implants in head and neck cancer patients. *J Clin Exp Dent* 2016;**8**:e194–200
495 Zen Filho EV, Tolentino E de S, Silva Santos PS. Viability of dental implants in head and neck irradiated patients: a systematic review. *Head Neck* 2016;**38**:E2229–40
496 Ettl T, Junold N, Zeman F, Hautmann M, Hahnel S, Kolbeck C *et al.* Implant survival or implant success? Evaluation of implant-based prosthetic rehabilitation in head and neck cancer patients--a prospective observational study. *Clin Oral Investig* 2020;**24**:3039–47
497 Nooh N. Dental implant survival in irradiated oral cancer patients: a systematic review of the literature. *Int J Oral Maxillofac Implants* 2013;**28**:1233–42

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

498 Shaw RJ, Butterworth CJ, Silcocks P, Tesfaye BT, Bickerstaff M, Jackson R *et al.* HOPON (hyperbaric oxygen for the prevention of osteoradionecrosis): a randomized controlled trial of hyperbaric oxygen to prevent osteoradionecrosis of the irradiated mandible after dentoalveolar surgery. *Int J Radiat Oncol Biol Phys* 2019;**104**:530–9

499 Koudougou C, Bertin H, Lecaplain B, Badran Z, Longis J, Corre P *et al.* Postimplantation radiation therapy in head and neck cancer patients: literature review. *Head Neck* 2020;**42**:794–802

500 Negreiros WA, Teixeira RR, Peixoto RF, Regis RR. The challenge of managing oral maxillofacial rehabilitation with quality and cost-benefit. *J Prosthet Dent* 2022;**127**:508–14

501 Hong CHL, Hu S, Haverman T, Stokman M, Napeñas JJ, Braber JB *et al.* A systematic review of dental disease management in cancer patients. *Support Care Cancer* 2018;**26**:155–74

502 Vartanian JG, Rogers SN, Kowalski LP. How to evaluate and assess quality of life issues in head and neck cancer patients. *Curr Opin Oncol* 2017;**29**:159–65

503 Rogers SN, Semple C, Babb M, Humphris G. Quality of life considerations in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**:S49–52

504 Beech N, Robinson S, Porceddu S, Batstone M. Dental management of patients irradiated for head and neck cancer. *Aust Dent J* 2014;**59**:20–8

505 Wells M, Cunningham M, Lang H, Swartzman S, Philp J, Taylor L *et al.* Distress, concerns and unmet needs in survivors of head and neck cancer: a cross-sectional survey. *Eur J Cancer Care* (*Engl*) 2015;**24**:748–60

506 van Huizen LS, Dijkstra PU, van der Laan B, Reintsema H, Ahaus KTB, Bijl HP *et al.* Multidisciplinary first-day consultation accelerates diagnostic procedures and throughput times of patients in a head-and-neck cancer care pathway, a mixed method study. *BMC Health Serv Res* 2018;**18**:820

507 Schoonbeek RC, de Vries J, Bras L, Plaat BEC, van Dijk BAC, Halmos GB. Determinants of delay in the head and neck oncology care pathway: the next step in value-based health care. *Eur J Cancer Care* (*Engl*) 2021;**30**: e13419

508 Lang H, France E, Williams B, Humphris G, Wells M. The psychological experience of living with head and neck cancer: a systematic review and meta-synthesis. *Psychooncology* 2013;**22**:2648–63

509 Van Beek FE, Wijnhoven LMA, Holtmaat K, Custers JAE, Prins JB, Verdonck-de Leeuw IM *et al.* Psychological problems among cancer patients in relation to healthcare and societal costs: a systematic review. *Psychooncology* 2021;**30**:1801–35

510 Hammerlid E, Ahlner-Elmqvist M, Bjordal K, Biörklund A, Evensen J, Boysen M *et al.* A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. *Br J Cancer* 1999;**80**:766–74

511 Badr H, Carmack CL, Diefenbach MA. Psychosocial interventions for patients and caregivers in the age of new communication technologies: opportunities and challenges in cancer care. *J Health Commun* 2015;**20**:328–42

512 Back AL, Arnold RM, Baile WF, Fryer-Edwards KA, Alexander SC, Barley GE *et al.* Efficacy of communication skills training for giving bad news and discussing transitions to palliative care. *Arch Intern Med* 2007;**167**:453–60

513 Newton JT. Reactions to cancer: communicating with patients, family and carers. *Oral Oncol* 2010;**46**:442–4

514 Austin CA, Mohottige D, Sudore RL, Smith AK, Hanson LC. Tools to promote shared decision making in serious illness: a systematic review. *JAMA Intern Med* 2015;**175**:1213–21

515 Grimmett C, Heneka N, Chambers S. Psychological interventions prior to cancer surgery: a review of reviews. *Curr Anesthesiol Rep* 2022;**12**:78–87

516 Chen SC, Lai YH, Liao CT, Chang JT, Lin CC. Unmet information needs and preferences in newly diagnosed and surgically treated oral cavity cancer patients. *Oral Oncol* 2009;**45**:946–52

517 Humphris GM, Ozakinci G. Psychological responses and support needs of patients following head and neck cancer. *Int J Surg* 2006;**4**:37–44

518 Llewellyn CD, McGurk M, Weinman J. How satisfied are head and neck cancer (HNC) patients with the information they receive pre-treatment? Results from the Satisfaction with Cancer Information Profile (SCIP). *Oral Oncol* 2006;**42**:726–34

519 Ethunandan M, Rennie A, Hoffman G, Morey PJ, Brennan PA. Quality of dying in head and neck cancer patients: a retrospective analysis of potential indicators of care. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;**100**:147–52

520 Mitchell AJ. Pooled results from 38 analyses of the accuracy of distress thermometer and other ultra-short methods of detecting cancer-related mood disorders. *J Clin Oncol* 2007;**25**:4670–81

521 Semple CJ, Dunwoody L, Kernohan WG, McCaughan E. Development and evaluation of a problem-focused psychosocial intervention for patients with head and neck cancer. *Support Care Cancer* 2009;**17**:379–88

522 Hodges LJ, Humphris GM. Fear of recurrence and psychological distress in head and neck cancer patients and their carers. *Psychooncology* 2009;**18**:841–8

523 Hagedoorn M, Molleman E. Facial disfigurement in patients with head and neck cancer: the role of social self-efficacy. *Health Psychol* 2006;**25**:643–7

524 Rogers SN, Scott B, Lowe D, Ozakinci G, Humphris GM. Fear of recurrence following head and neck cancer in the outpatient clinic. *Eur Arch Otorhinolaryngol* 2010;**267**:1943–9

525 Williams JTW, Pearce A, Smith A. A systematic review of fear of cancer recurrence related healthcare use and intervention cost-effectiveness. *Psychooncology* 2021;**30**:1185–95

526 Groß SE, Nitzsche A, Gloede TD, Ansmann L, Street R, Pfaff H *et al.* The initial clinical interview--can it reduce cancer patients' fear? *Support Care Cancer* 2015;**23**:977–84

527 Casswell G, Gough K, Drosdowsky A, Bressel M, Coleman A, Shrestha S *et al.* Fear of cancer recurrence in survivors of human papillomavirus-associated oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2021;**111**:890–9

528 Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S *et al.* Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. *J Cancer Surviv* 2013;**7**:300–22

529 Lim E, Humphris G. The relationship between fears of cancer recurrence and patient age: a systematic review and meta-analysis. *Cancer Rep* (*Hoboken*) 2020;**3**:e1235

530 Pang C, Humphris G. The relationship between fears of cancer recurrence and patient gender: a systematic review and meta-analysis. *Front Psychol* 2021;**12**:640866

531 Rogers SN, Monssen C, Humphris GM, Lowe D, Kanatas A. Which head and neck cancer patients are most at risk of high levels of fear of cancer recurrence. *Front Psychol* 2021;**12**:671366

532 Deuning-Smit E, Custers JAE, Miroševič Š, Takes RP, Jansen F, Langendijk JA *et al.* Prospective longitudinal study on fear of cancer recurrence in patients newly diagnosed with head and neck cancer: course, trajectories, and associated factors. *Head Neck* 2022;**44**:914–25

533 Ozakinci G, Swash B, Humphris G, Rogers SN, Hulbert-Williams NJ. Fear of cancer recurrence in oral and oropharyngeal cancer patients: an investigation of the clinical encounter. *Eur J Cancer Care* (*Engl*) 2018;**27**: e12785

534 Butow P, Lebel S, Shaw J, Humphris G. Editorial: uncertainty, anxiety, and fear of cancer recurrence. *Front Psychol* 2021;**12**:811602

535 Tauber NM, O'Toole MS, Dinkel A, Galica J, Humphris G, Lebel S *et al.* Effect of psychological intervention on fear of cancer recurrence: a systematic review and meta-analysis. *J Clin Oncol* 2019;**37**:2899–915

536 Humphris GM, Watson E, Sharpe M, Ozakinci G. Unidimensional scales for fears of cancer recurrence and their psychometric properties: the FCR4 and FCR7. *Health Qual Life Outcomes* 2018;**16**:30

537 Dermody SM, Shuman AG. Psychosocial implications of COVID-19 on head and neck cancer. *Curr Oncol* 2022;**29**:1062–8

538 Gremore TM, Brockstein B, Porter LS, Brenner S, Benfield T, Baucom DH *et al.* Couple-based communication intervention for head and neck cancer: a randomized pilot trial. *Support Care Cancer* 2021;**29**:3267–75

539 Badr H, Yeung C, Lewis MA, Milbury K, Redd WH. An observational study of social control, mood, and self-efficacy in couples during treatment for head and neck cancer. *Psychol Health* 2015;**30**:783–802

540 Davidson J, Malloch M, Humphris G. A single-session intervention (the Mini-AFTERc) for fear of cancer recurrence: a feasibility study. *Psychooncology* 2018;**27**:2668–70

541 Yang Y, Zhang H, Li Y, Liu Z, Liu S, Li X *et al.* The effectiveness of computer-assisted cognitive behavioral therapy (cCBT) for psychological outcomes in patients with laryngectomy: randomized controlled trial. *J Affect Disord* 2022;**300**:59–65

542 Sciubba JJ. End of life considerations in the head and neck cancer patient. *Oral Oncol* 2009;**45**:431–4

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

543 Gibson C, O'Connor M, White R, Baxi S, Halkett G. Burnout or fade away; experiences of health professionals caring for patients with head and neck cancer. *Eur J Oncol Nurs* 2021;**50**:101881
544 Brenner MJ, Hickson GB, Boothman RC, Rushton CH, Bradford CR. Honesty and transparency, indispensable to the clinical mission-part III: how leaders can prevent burnout, foster wellness and recovery, and instill resilience. *Otolaryngol Clin North Am* 2022;**55**:83–103
545 Alabi RO, Hietanen P, Elmusrati M, Youssef O, Almangush A, Mäkitie AA. Mitigating burnout in an oncological unit: a scoping review. *Front Public Health* 2021;**9**:677915
546 World Health Organization. Palliative Care. In: https://www.who.int/news-room/fact-sheets/detail/palliative-care [27 March 2023]
547 Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM *et al.* Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2017;**35**:96–112
548 Ullgren H, Kirkpatrick L, Kilpelainen S, Sharp L. Working in silos? - Head & neck cancer patients during and after treatment with or without early palliative care referral. *Eur J Oncol Nurs* 2017;**26**:56–62
549 Quill TE, Abernethy AP. Generalist plus specialist palliative care--creating a more sustainable model. *N Engl J Med* 2013;**368**:1173–5
550 Hui D, Mori M, Watanabe SM, Caraceni A, Strasser F, Saarto T *et al.* Referral criteria for outpatient specialty palliative cancer care: an international consensus. *Lancet Oncol* 2016;**17**:e552–9
551 Meijuan Yang G, Kanesvaran R, Hui-Shan Neo S, Chung Pheng Yee A, Block SD, Bun Cheung Y. Pilot study of a palliative care and medical oncology co-rounding model for advanced cancer inpatients in a tertiary hospital in Singapore. *J Palliat Med* 2018;**21**:95–8
552 Lin C, Kang SY, Donermeyer S, Teknos TN, Wells-Di Gregorio SM. Supportive care needs of patients with head and neck cancer referred to palliative medicine. *Otolaryngol Head Neck Surg* 2020;**163**:356–63
553 North AS, Carson L, Sharp L, Patterson J, Hamilton DW. The unmet needs of patients with advanced incurable head and neck cancer and their carers: a systematic review and meta-ethnography of qualitative data. *Eur J Cancer Care* (*Engl*) 2021;**30**:e13474
554 Hoesseini A, Offerman MPJ, van de Wall-Neecke BJ, Sewnaik A, Wieringa MH, Baatenburg de Jong RJ. Physicians' clinical prediction of survival in head and neck cancer patients in the palliative phase. *BMC Palliat Care* 2020;**19**:176
555 Wilcock A, Howard P, Charlesworth S. *Palliative Care Formulary*. London: Pharmaceutical Press, 2020
556 Joint Formulary Committee. *British National Formulary*. London: BMJ Group and Pharmaceutical Press. In: http://www.medicinescomplete.com [28 March 2023]
557 Chua KS, Reddy SK, Lee MC, Patt RB. Pain and loss of function in head and neck cancer survivors. *J Pain Symptom Manage* 1999;**18**:193–202
558 World Health Organization. *Cancer Pain Relief*, 2nd edn. Geneva: World Health Organization, 1996
559 Fallon M, Dierberger K, Leng M, Hall PS, Allende S, Sabar R *et al.* An international, open-label, randomised trial comparing a two-step approach versus the standard three-step approach of the WHO analgesic ladder in patients with cancer. *Ann Oncol* 2022;**33**:1296–303
560 Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N *et al.* Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012;**13**:e58–68
561 Hui D, Bruera E. A personalized approach to assessing and managing pain in patients with cancer. *J Clin Oncol* 2014;**32**:1640–6
562 George B, Minello C, Allano G, Maindet C, Burnod A, Lemaire A. Opioids in cancer-related pain: current situation and outlook. *Support Care Cancer* 2019;**27**:3105–18
563 Hanks GW, Conno F, Cherny N, Hanna M, Kalso E, McQuay HJ *et al.* Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;**84**:587–93
564 GOV.UK. Drugs and driving: the law. In: https://www.gov.uk/drug-driving-law [28 March 2023]
565 Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. *Am J Hosp Palliat Care* 2012;**29**:177–82
566 National Institute for Health and Excellence. Neuropathic Pain in Adults: Pharmacological Management in Non-Specialist Settings, Clinical Guideline [CG173]. In: https://www.nice.org.uk/guidance/cg173 [28 March 2023]
567 Saunders DP, Rouleau T, Cheng K, Yarom N, Kandwal A, Joy J *et al.* Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer* 2020;**28**:2473–84
568 National Institute for Health and Care Excellence. Palliative care – nausea and vomiting. In: https://cks.nice.org.uk/topics/palliative-care-nausea-vomiting/ [28 March 2023]
569 Leach C. Nausea and vomiting in palliative care. *Clin Med* (*Lond*) 2019;**19**:299–301
570 Sheffield Teaching Hospitals NHS Foundation Trust. The Adult Sheffield Palliative Care Formulary. In: http://nww.sth.nhs.uk/STHcontDocs/STH_CGP/PalliativeCare/SheffieldPalliativeCareFormulary.pdf [28 March 2023]
571 Smyth J, ed. *The NEWT Guidelines*, 3rd edn. Wrexham: Betsi Cadwaladr University Local Health Board (Eastern Division), 2015
572 Larkin PJ, Cherny NI, La Carpia D, Guglielmo M, Ostgathe C, Scotte F *et al.* Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* 2018;**29**(suppl 4): iv111–25
573 Muller-Lissner S, Bassotti G, Coffin B, Drewes AM, Breivik H, Eisenberg E *et al.* Opioid-induced constipation and bowel dysfunction: a clinical guideline. *Pain Med* 2017;**18**:1837–63
574 Prichard D, Norton C, Bharucha AE. Management of opioid-induced constipation. *Br J Nurs* 2016;**25**:S4–5,S8–11
575 Bomeli SR, Desai SC, Johnson JT, Walvekar RR. Management of salivary flow in head and neck cancer patients--a systematic review. *Oral Oncol* 2008;**44**:1000–8
576 National Institute for Health and Care Excellence. Palliative care – Secretions. In: https://cks.nice.org.uk/topics/palliative-care-secretions/ [28 March 2023]
577 National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease. In: https://cks.nice.org.uk/topics/chronic-obstructive-pulmonary-disease/ [28 March 2023]
578 McGeachan AJ, McDermott CJ. Management of oral secretions in neurological disease. *Pract Neurol* 2017;**17**:96–103
579 National Institute for Health and Care Excellence. Palliative care – cough. In: https://cks.nice.org.uk/topics/palliative-care-cough/ [28 March 2023]
580 Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev* 2008;(1):CD005177
581 Mayland CR, Ingarfield K, Rogers SN, Dey P, Thomas S, Waylen A *et al.* Disease trajectories, place and mode of death in people with head and neck cancer: findings from the 'Head and Neck 5000' population-based prospective clinical cohort study. *Palliat Med* 2020;**34**:639–50
582 Harris DG, Noble SI. Management of terminal hemorrhage in patients with advanced cancer: a systematic literature review. *J Pain Symptom Manage* 2009;**38**:913–27
583 Hardy J, Haywood A, Rickett K, Sallnow L, Good P. Practice review: evidence-based quality use of corticosteroids in the palliative care of patients with advanced cancer. *Palliat Med* 2021;**35**:461–72
584 Rietjens JAC, Sudore RL, Connolly M, van Delden JJ, Drickamer MA, Droger M *et al.* Definition and recommendations for advance care planning: an international consensus supported by the European Association for Palliative Care. *Lancet Oncol* 2017;**18**:e543–51
585 Vukkadala N, Fardeen T, Ramchandran K, Divi V. End-of-life practice patterns in head and neck cancer. *Laryngoscope* 2021;**131**:1769–73
586 Paladino J, Koritsanszky L, Nisotel L, Neville BA, Miller K, Sanders J *et al.* Patient and clinician experience of a serious illness conversation guide in oncology: a descriptive analysis. *Cancer Med* 2020;**9**:4550–60
587 Childers JW, Back AL, Tulsky JA, Arnold RM. REMAP: a framework for goals of care conversations. *J Oncol Pract* 2017;**13**:e844–50
588 Parsons HA, de la Cruz MJ, Zhukovsky DS, Hui D, Delgado-Guay MO, Akitoye AE *et al.* Characteristics of patients who refuse do-not-resuscitate orders upon admission to an acute palliative care unit in a comprehensive cancer center. *Cancer* 2010;**116**:3061–70
589 Field RA, Fritz Z, Baker A, Grove A, Perkins GD. Systematic review of interventions to improve appropriate use and outcomes associated with do-not-attempt-cardiopulmonary-resuscitation decisions. *Resuscitation* 2014;**85**:1418–31
590 National Institute for Health and Care Excellence. Care of dying adults in the last days of life, NICE Guideline [NG31]. In: https://www.nice.org.uk/guidance/ng31 [28 March 2023]
591 Orrevall Y. Nutritional support at the end of life. *Nutrition* 2015;**31**:615–16

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

592 Leadership Alliance for the Care of Dying People. One Chance to Get it Right, 2014. In: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/323188/One_chance_to_get_it_right.pdf [28 March 2023]
593 Haun MW, Estel S, Rucker G, Friederich HC, Villalobos M, Thomas M *et al.* Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev* 2017;**6**:CD011129
594 Davis MP, Temel JS, Balboni T, Glare P. A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. *Ann Palliat Med* 2015;**4**:99–121
595 Patil VM, Singhai P, Noronha V, Bhattacharjee A, Deodhar J, Salins N *et al.* Effect of early palliative care on quality of life of advanced head and neck cancer patients: a phase III trial. *J Natl Cancer Inst* 2021;**113**:1228–37
596 National End of Life Intelligence Network. *Head and Neck Cancers in England: Who Dies from Them and Where Do They Die?* London: Public Health England, 2014
597 Higginson IJ. Research challenges in palliative and end of life care. *BMJ Support Palliat Care* 2016;**6**:2–4
598 Mayland C, Payne S. Editorial. *Palliat Med* 2018;**32**:1286–7
599 Delaney SW, Shi H, Shokrani A, Sinha UK. Management of chyle leak after head and neck surgery: review of current treatment strategies. *Int J Otolaryngol* 2017;**2017**:8362874
600 Brennan PA, Blythe JN, Herd MK, Habib A, Anand R. The contemporary management of chyle leak following cervical thoracic duct damage. *Br J Oral Maxillofac Surg* 2012;**50**:197–201
601 de Gier HH, Balm AJ, Bruning PF, Gregor RT, Hilgers FJ. Systematic approach to the treatment of chylous leakage after neck dissection. *Head Neck* 1996;**18**:347–51
602 Erisen L, Coskun H, Basut O. Objective and early diagnosis of chylous fistula in the postoperative period. *Otolaryngol Head Neck Surg* 2002;**126**:172–5
603 Rodgers GK, Johnson JT, Petruzzelli GJ, Warty VS, Wagner RL. Lipid and volume analysis of neck drainage in patients undergoing neck dissection. *Am J Otolaryngol* 1992;**13**:306–9
604 Campisi CC, Boccardo F, Piazza C, Campisi C. Evolution of chylous fistula management after neck dissection. *Curr Opin Otolaryngol Head Neck Surg* 2013;**21**:150–6
605 Talwar B, Donnelly R, Skelly R, Donaldson M. Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**(S2):S32–40
606 Magoo S, Bhate K, Santhosh Kumar SN, Kakodkar P, Gajul M, Mastud S. Effect of octreotide in stopping post surgical chyle leak in neck dissection--a systematic review. *J Oral Biol Craniofac Res* 2022;**12**:737–41
607 Wilkerson PM, Haque A, Pitkin L, Soon Y. Thoracoscopic ligation of the thoracic duct complex in the treatment for high-volume chyle leak following modified radical neck dissection: safe, feasible, but underutilised. *Clin Otolaryngol* 2014;**39**:73–4
608 Harris M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. *Br J Oral Maxillofac Surg* 1992;**30**:313–18
609 Frankart AJ, Frankart MJ, Cervenka B, Tang AL, Krishnan DG, Takiar V. Osteoradionecrosis: exposing the evidence not the bone. *Int J Radiat Oncol Biol Phys* 2021;**109**:1206–18
610 Shaw R, Tesfaye B, Bickerstaff M, Silcocks P, Butterworth C. Refining the definition of mandibular osteoradionecrosis in clinical trials: the cancer research UK HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis). *Oral Oncol* 2017;**64**:73–7
611 Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K *et al.* Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. *Head Neck* 2003;**25**:181–6
612 Rice N, Polyzois I, Ekanayake K, Omer O, Stassen LF. The management of osteoradionecrosis of the jaws--a review. *Surgeon* 2015;**13**:101–9
613 Delanian S, Chatel C, Porcher R, Depondt J, Lefaix JL. Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase II trial. *Int J Radiat Oncol Biol Phys* 2011;**80**:832–9
614 Kolokythas A, Rasmussen JT, Reardon J, Feng C. Management of osteoradionecrosis of the jaws with pentoxifylline-tocopherol: a systematic review of the literature and meta-analysis. *Int J Oral Maxillofac Surg* 2019;**48**:173–80
615 Marx RE, Johnson RP, Kline SN. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc* 1985;**111**:49–54
616 Annane D, Depondt J, Aubert P, Villart M, Gehanno P, Gajdos P *et al.* Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. *J Clin Oncol* 2004;**22**:4893–900
617 Clinical Trial Results: Hyperbaric oxygen treatment of mandibular osteoradionecrosis. A randomized clinical trial. In: https://www.clinicaltrialsregister.eu/ctr-search/trial/2007-007842-36/results [22 March 2021]
618 Bettoni J, Olivetto M, Duisit J, Caula A, Bitar G, Lengele B *et al.* Treatment of mandibular osteoradionecrosis by periosteal free flaps. *Br J Oral Maxillofac Surg* 2019;**57**:550–6
619 Lee M, Chin RY, Eslick GD, Sritharan N, Paramaesvaran S. Outcomes of microvascular free flap reconstruction for mandibular osteoradionecrosis: a systematic review. *J Craniomaxillofac Surg* 2015;**43**:2026–33
620 Dijkstra PU, Huisman PM, Roodenburg JL. Criteria for trismus in head and neck oncology. *Int J Oral Maxillofac Surg* 2006;**35**:337–42
621 Scott B, Butterworth C, Lowe D, Rogers SN. Factors associated with restricted mouth opening and its relationship to health-related quality of life in patients attending a maxillofacial oncology clinic. *Oral Oncol* 2008;**44**:430–8
622 Abboud WA, Hassin-Baer S, Alon EE, Gluck I, Dobriyan A, Amit U *et al.* Restricted mouth opening in head and neck cancer: etiology, prevention, and treatment. *JCO Oncol Pract* 2020;**16**:643–53
623 Kamstra JI, van Leeuwen M, Roodenburg JL, Dijkstra PU. Exercise therapy for trismus secondary to head and neck cancer: a systematic review. *Head Neck* 2017;**39**:160–9
624 Bensadoun RJ, Riesenbeck D, Lockhart PB, Elting LS, Spijkervet FK, Brennan MT *et al.* A systematic review of trismus induced by cancer therapies in head and neck cancer patients. *Support Care Cancer* 2010;**18**:1033–8
625 Lee R, Yeo ST, Rogers SN, Caress AL, Molassiotis A, Ryder D *et al.* Randomised feasibility study to compare the use of Therabite((R)) with wooden spatulas to relieve and prevent trismus in patients with cancer of the head and neck. *Br J Oral Maxillofac Surg* 2018;**56**:283–91
626 Skoretz SA, Anger N, Wellman L, Takai O, Empey A. A systematic review of tracheostomy modifications and swallowing in adults. *Dysphagia* 2020;**35**:935–47
627 Bertolini R, Meyenberger C, Putora PM, Albrecht F, Broglie MA, Stoeckli SJ *et al.* Endoscopic dilation of complete oesophageal obstructions with a combined antegrade-retrograde rendezvous technique. *World J Gastroenterol* 2016;**22**:2366–72
628 Moss WJ, Pang J, Orosco RK, Weissbrod PA, Brumund KT, Weisman RA *et al.* Esophageal dilation in head and neck cancer patients: a systematic review and meta-analysis. *Laryngoscope* 2018;**128**:111–17
629 Chapuy CI, Annino DJ, Tishler RB, Haddad RI, Snavely A, Goguen LA. Success of endoscopic pharyngoesophageal dilation after head and neck cancer treatment. *Laryngoscope* 2013;**123**:3066–73
630 Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF *et al.* Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;**31**:845–52
631 Hutcheson KA, Alvarez CP, Barringer DA, Kupferman ME, Lapine PR, Lewin JS. Outcomes of elective total laryngectomy for laryngopharyngeal dysfunction in disease-free head and neck cancer survivors. *Otolaryngol Head Neck Surg* 2012;**146**:585–90
632 Dawe N, Patterson J, Hamilton D, Hartley C. Targeted use of endoscopic CO2 laser cricopharyngeal myotomy for improving swallowing function following head and neck cancer treatment. *J Laryngol Otol* 2014;**128**:1105–10
633 Ku PKM, Vlantis AC, Cho RHW, Yeung ZWC, Ho OYM, Hui TSC *et al.* Tubed supraglottic laryngeal closure to treat chronic aspiration after radiotherapy for head and neck cancer. *Laryngoscope* 2021;**131**:E1234–43
634 Epstein JB, Thariat J, Bensadoun RJ, Barasch A, Murphy BA, Kolnick L *et al.* Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. *CA Cancer J Clin* 2012;**62**:400–22
635 Burlage FR, Coppes RP, Meertens H, Stokman MA, Vissink A. Parotid and submandibular/sublingual salivary flow during high dose radiotherapy. *Radiother Oncol* 2001;**61**:271–4
636 Nagler RM. The enigmatic mechanism of irradiation-induced damage to the major salivary glands. *Oral Dis* 2002;**8**:141–6

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

637 Konings AWT, Coppes RP, Vissink A. On the mechanism of salivary gland radiosensitivity. *Int J Radiat Oncol Biol Phys* 2005;**62**:1187–94
638 Jensen SB, Mouridsen HT, Reibel J, Brünner N, Nauntofte B. Adjuvant chemotherapy in breast cancer patients induces temporary salivary gland hypofunction. *Oral Oncol* 2008;**44**:162–73
639 Wijers OB, Levendag PC, Braaksma MMJ, Boonzaaijer M, Visch LL, Schmitz PIM. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck* 2002;**24**:737–47
640 Porter SR, Fedele S, Habbab KM. Xerostomia in head and neck malignancy. *Oral Oncol* 2010;**46**:460–3
641 van der Laan HP, Van den Bosch L, Schuit E, Steenbakkers RJHM, van der Schaaf A, Langendijk JA. Impact of radiation-induced toxicities on quality of life of patients treated for head and neck cancer. *Radiother Oncol* 2021;**160**:47–53
642 Mercadante V, Al Hamad A, Lodi G, Porter S, Fedele S. Interventions for the management of radiotherapy-induced xerostomia and hyposalivation: a systematic review and meta-analysis. *Oral Oncol* 2017;**66**:64–74
643 Senahayake F, Piggott K, Hamilton-Miller JMT. A pilot study of Salix SST (saliva-stimulating lozenges) in post-irradiation xerostomia. *Curr Med Res Opin* 1998;**14**:155–9
644 Jensdottir T, Nauntofte B, Buchwald C, Hansen HS, Bardow A. Effects of sucking acidic candies on saliva in unilaterally irradiated pharyngeal cancer patients. *Oral Oncol* 2006;**42**:317–22
645 Jensen SB, Vissink A, Limesand KH, Reyland ME. Salivary gland hypofunction and xerostomia in head and neck radiation patients. *J Natl Cancer Inst Monogr* 2019;**2019**:lgz016
646 LeVeque FG, Montgomery M, Potter D, Zimmer MB, Rieke JW, Steiger BW *et al.* A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *J Clin Oncol* 1993;**11**:1124–31
647 Cheng CQ, Xu H, Liu L, Wang RN, Liu YT, Li J *et al.* Efficacy and safety of pilocarpine for radiation-induced xerostomia in patients with head and neck cancer: a systematic review and meta-analysis. *J Am Dent Assoc* 2016;**147**:236–43
648 Simcock R, Fallowfield L, Monson K, Solis-Trapala I, Parlour L, Langridge C *et al.* ARIX: a randomised trial of acupuncture v oral care sessions in patients with chronic xerostomia following treatment of head and neck cancer. *Ann Oncol* 2013;**24**:776–83
649 Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;**6**:15–24
650 Li LX, Tian G, He J. The standardization of acupuncture treatment for radiation-induced xerostomia: a literature review. *Chin J Integr Med* 2016;**22**:549–54
651 Assy Z, Brand HS. A systematic review of the effects of acupuncture on xerostomia and hyposalivation. *BMC Complement Altern Med* 2018;**18**:57
652 Ni X, Tian T, Chen D, Liu L, Li X, Li F *et al.* Acupuncture for radiation-induced xerostomia in cancer patients: a systematic review and meta-analysis. *Integr Cancer Ther* 2020;**19**:1534735420980825
653 Salimi F, Saavedra F, Andrews B, FitzGerald J, Winter SC. Trans-cutaneous electrical nerve stimulation to treat dry mouth (xerostomia) following radiotherapy for head and neck cancer. A systematic review. *Ann Med Surg* (*Lond*) 2021;**63**:102146
654 Nouraei SAR, Allen J, Kaddour H, Middleton SE, Aylin P, Darzi A *et al.* Vocal palsy increases the risk of lower respiratory tract infection in low-risk, low-morbidity patients undergoing thyroidectomy for benign disease: a big data analysis. *Clin Otolaryngol* 2017;**42**:1259–66
655 Alghonaim Y, Roskies M, Kost K, Young J. Evaluating the timing of injection laryngoplasty for vocal fold paralysis in an attempt to avoid future type 1 thyroplasty. *J Otolaryngol Head Neck Surg* 2013;**42**:24
656 Friedman AD, Burns JA, Heaton JT, Zeitels SM. Early versus late injection medialization for unilateral vocal cord paralysis. *Laryngoscope* 2010;**120**:2042–6
657 Vila PM, Bhatt NK, Paniello RC. Early-injection laryngoplasty may lower risk of thyroplasty: a systematic review and meta-analysis. *Laryngoscope* 2018;**128**:935–40
658 Snyder SK, Angelos P, Carty SE, Doherty GM, Howe JR, Lee JA *et al.* Injection of bulking agents for laryngoplasty. *Surgery* 2018;**163**:6–8
659 Fancello V, Nouraei SAR, Heathcote KJ. Role of reinnervation in the management of recurrent laryngeal nerve injury: current state and advances. *Curr Opin Otolaryngol Head Neck Surg* 2017;**25**:480–5
660 Blackshaw H, Carding P, Jepson M, Mat Baki M, Ambler G, Schilder A *et al.* Does laryngeal reinnervation or type I thyroplasty give better voice results for patients with unilateral vocal fold paralysis (VOCALIST): study protocol for a feasibility randomised controlled trial. *BMJ Open* 2017;**7**:e016871
661 Lin Z, Yang Z, He B, Wang D, Gao X, Tam SY *et al.* Pattern of radiation-induced thyroid gland changes in nasopharyngeal carcinoma patients in 48 months after radiotherapy. *PLoS One* 2018;**13**:e0200310
662 Jereczek-Fossa BA, Alterio D, Jassem J, Gibelli B, Tradati N, Orecchia R. Radiotherapy-induced thyroid disorders. *Cancer Treat Rev* 2004;**30**:369–84
663 Feen Ronjom M. Radiation-induced hypothyroidism after treatment of head and neck cancer. *Dan Med J* 2016;**63**:B5213
664 National Institute for Health and Care Excellence. Hypothyroidism: Subclinical hypothyroidism (non-pregnant). In: https://cks.nice.org.uk/topics/hypothyroidism/management/subclinical-hypothyroidism-non-pregnant/ [1 January 2022]
665 Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. *Drugs* 2012;**72**:17–33
666 Wass J, Owen K. *Oxford Handbook of Endocrinology and Diabetes*, 3rd edn. Oxford: Oxford University Press, 2014
667 British Thyroid Foundation. Your guide to hypothyroidism. In: https://www.btf-thyroid.org/hypothyroidism-leaflet [20 September 2021]
668 Dalton DS, Cruickshanks KJ, Klein BEK, Klein R, Wiley TL, Nondahl DM. The impact of hearing loss on quality of life in older adults. *Gerontologist* 2003;**43**:661–8
669 Basch E, Reeve BB, Mitchell SA, Clauser SB, Minasian LM, Dueck AC *et al.* Development of the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Natl Cancer Inst* 2014;**106**:dju244
670 Frisina RD, Wheeler HE, Fossa SD, Kerns SL, Fung C, Sesso HD *et al.* Comprehensive audiometric analysis of hearing impairment and tinnitus after cisplatin-based chemotherapy in survivors of adult-onset cancer. *J Clin Oncol* 2016;**34**:2712–20
671 Vermorken JB, Kapteijn TS, Hart AAM, Pinedo HM. Ototoxicity of cis-diamminedichloroplatinum (II): influence of dose, schedule and mode of administration. *Eur J Cancer Clin Oncol* 1983;**19**:53–8
672 Moroso MJ, Blair RL. A review of cis-platinum ototoxicity. *J Otolaryngol* 1983;**12**:365–9
673 Foreword. *J Laryngol Otol* 2016;**130**(S2):S1–2
674 Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. *Ann Oncol* 1998;**9**:13–21
675 Guan J, Li Q, Zhang Y, Xiao N, Chen M, Zhang Y *et al.* A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). *Oncotarget* 2016;**7**:7110–19
676 Moretti JA. Sensori-neural hearing loss following radiotherapy to the nasopharynx. *Laryngoscope* 1976;**86**:598–602
677 Young Y-H, Cheng P-W, Ko J-Y. A 10-year longitudinal study of tubal function in patients with nasopharyngeal carcinoma after irradiation. *Arch Otolaryngol Head Neck Surg* 1997;**123**:945–8
678 Anteunis LJC, Wanders SL, Hendriks JJT, Langendijk JA, Manni JJ, de Jong JMA. A prospective longitudinal study on radiation-induced hearing loss. *Am J Surg* 1994;**168**:408–11
679 Chen WC, Liao CT, Tsai HC, Yeh JY, Wang CC, Tang SG *et al.* Radiation-induced hearing impairment in patients treated for malignant parotid tumor. *Ann Otol Rhinol Laryngol* 1999;**108**:1159–64
680 van der Putten L, de Bree R, Plukker JT, Langendijk JA, Smits C, Burlage FR *et al.* Permanent unilateral hearing loss after radiotherapy for parotid gland tumors. *Head Neck* 2006;**28**:902–8
681 Lamaj E, Vu E, van Timmeren JE, Leonardi C, Marc L, Pytko I *et al.* Cochlea sparing optimized radiotherapy for nasopharyngeal carcinoma. *Radiat Oncol* 2021;**16**:64
682 Theunissen EAR, Zuur CL, Jóźwiak K, Lopez-Yurda M, Hauptmann M, Rasch CRN *et al.* Prediction of hearing loss due to cisplatin chemoradiotherapy. *JAMA Otolaryngol Head Neck Surg* 2015;**141**:810–15
683 Zuur CL, Simis YJ, Lamers EA, Hart AA, Dreschler WA, Balm AJ *et al.* Risk factors for hearing loss in patients treated with intensity-modulated radiotherapy for head-and-neck tumors. *Int J Radiat Oncol Biol Phys* 2009;**74**:490–6
684 Mujica–Mota M, Waissbluth S, Daniel SJ. Characteristics of radiation-induced sensorineural hearing loss in head and neck cancer: a systematic review. *Head Neck* 2013;**35**:1662–8
685 Sham JST, Wei WI, Lau SK, Yau CC, Choy D. Serous otitis media: an opportunity for early recognition of nasopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 1992;**118**:794–7

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

686 Wei WI, Engzell UCG, Lam KH, Lau SK. The efficacy of myringotomy and ventilation tube insertion in middle-ear effusions in patients with nasopharyngeal carcinoma. *Laryngoscope* 1987;**97**:1295–8
687 Young YH, Sheen TS. Preservation of tubal function in patients with nasopharyngeal carcinoma, post-irradiation. *Acta Otolaryngol* 1998;**118**:280–3
688 Tsang RK, Kwong DL, Ho AC, To VS, Ho WK, Wei WI. Long-term hearing results and otological complications of nasopharyngeal carcinoma patients: comparison between treatment with conventional two-dimensional radiotherapy and intensity-modulated radiotherapy. *ORL J Otorhinolaryngol Relat Spec* 2012;**74**:228–33
689 Hsin CH, Chen TH, Young YH, Liu WS. Comparison of otologic complications between intensity-modulated and two-dimensional radiotherapies in nasopharyngeal carcinoma patients. *Otolaryngol Head Neck Surg* 2010;**143**:662–8
690 Hsin CH, Tseng HC, Lin HP, Chen TH. Post-irradiation otitis media, rhinosinusitis, and their interrelationship in nasopharyngeal carcinoma patients treated by IMRT. *Eur Arch Otorhinolaryngol* 2016;**273**:471–7
691 Skinner DW, Van Hasselt CA. A study of the complications of grommet insertion for secretory otitis media in the presence of nasopharyngeal carcinoma. *Clin Otolaryngol Allied Sci* 1991;**16**:480–2
692 Chen CY, Young YH, Hsu WC, Hsu MM. Failure of grommet insertion in post-irradiation otitis media with effusion. *Ann Otol Rhinol Laryngol* 2001;**110**:746–8
693 Charusripan P, Khattiyawittayakun L. The effectiveness of myringotomy and ventilation tube insertion versus observation in post-radiation otitis media with effusion. *Eur Arch Otorhinolaryngol* 2017;**274**:3283–90
694 Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1996;**122**:143–8
695 Niemensivu R, Saarilahti K, Ylikoski J, Aarnisalo A, Mäkitie AA. Hearing and tinnitus in head and neck cancer patients after chemoradiotherapy. *Eur Arch Otorhinolaryngol* 2016;**273**:2509–14
696 Office for National Statistics. Cancer registration statistics, England: 2017. In: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017 [8 April 2023]
697 Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. *Head Neck* 2009;**31**:1600–9
698 Burr AR, Harari PM, Ko HC, Chen S, Yu M, Baschnagel AM *et al.* HPV impacts survival of stage IVC non-oropharyngeal HNSCC cancer patients. *Otorhinolaryngol Head Neck Surg* 2018;**3**:10
699 Ko HC, Harari PM, Sacotte RM, Chen S, Wieland AM, Yu M *et al.* Prognostic implications of human papillomavirus status for patients with non-oropharyngeal head and neck squamous cell carcinomas. *J Cancer Res Clin Oncol* 2017;**143**:2341–50
700 Chung CH, Zhang Q, Kong CS, Harris J, Fertig EJ, Harari PM *et al.* p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. *J Clin Oncol* 2014;**32**:3930–8
701 Lingen MW, Xiao W, Schmitt A, Jiang B, Pickard R, Kreinbrink P *et al.* Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. *Oral Oncol* 2013;**49**:1–8
702 Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. *Cancer* 2009;**115**:1489–97
703 Rethman MP, Carpenter W, Cohen EE, Epstein J, Evans CA, Flaitz CM *et al.* Evidence-based clinical recommendations regarding screening for oral squamous cell carcinomas. *J Am Dent Assoc* 2010;**141**:509–20
704 Wolff KD, Follmann M, Nast A. The diagnosis and treatment of oral cavity cancer. *Dtsch Arztebl Int* 2012;**109**:829–35
705 Duprez F, Berwouts D, De Neve W, Bonte K, Boterberg T, Deron P *et al.* Distant metastases in head and neck cancer. *Head Neck* 2017;**39**:1733–43
706 National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. In: http://www.nice.org.uk/guidance/ng36 [8 April 2023]
707 Montero PH, Yu C, Palmer FL, Patel PD, Ganly I, Shah JP *et al.* Nomograms for preoperative prediction of prognosis in patients with oral cavity squamous cell carcinoma. *Cancer* 2014;**120**:214–21
708 Ganly I, Goldstein D, Carlson DL, Patel SG, O'Sullivan B, Lee N *et al.* Long-term regional control and survival in patients with "low-risk," early stage oral tongue cancer managed by partial glossectomy and neck dissection without postoperative radiation: the importance of tumor thickness. *Cancer* 2013;**119**:1168–76
709 Zhang H, Dziegielewski PT, Biron VL, Szudek J, Al-Qahatani KH, O'Connell DA *et al.* Survival outcomes of patients with advanced oral cavity squamous cell carcinoma treated with multimodal therapy: a multi-institutional analysis. *J Otolaryngol Head Neck Surg* 2013;**42**:30
710 Yan F, Reddy PD, Nguyen SA, Chi AC, Neville BW, Day TA. Grading systems of oral cavity pre-malignancy: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol* 2020;**277**:2967–76
711 Ranganathan K, Kavitha L. Oral epithelial dysplasia: classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol* 2019;**23**:19–27
712 Gerber S, Gengler C, Gratz KW, Kruse AL. The impact of frozen sections on final surgical margins in squamous cell carcinoma of the oral cavity and lips: a retrospective analysis over an 11 years period. *Head Neck Oncol* 2011;**3**:56
713 McCaul JA, Cymerman JA, Hislop S, McConkey C, McMahon J, Mehanna H *et al.* LIHNCS - Lugol's iodine in head and neck cancer surgery: a multicentre, randomised controlled trial assessing the effectiveness of Lugol's iodine to assist excision of moderate dysplasia, severe dysplasia and carcinoma in situ at mucosal resection margins of oral and oropharyngeal squamous cell carcinoma: study protocol for a randomised controlled trial. *Trials* 2013;**14**:310
714 Ebrahimi A, Murali R, Gao K, Elliott MS, Clark JR. The prognostic and staging implications of bone invasion in oral squamous cell carcinoma. *Cancer* 2011;**117**:4460–7
715 Fried D, Mullins B, Weissler M, Shores C, Zanation A, Hackman T *et al.* Prognostic significance of bone invasion for oral cavity squamous cell carcinoma considered T1/T2 by American Joint Committee on Cancer size criteria. *Head Neck* 2014;**36**:776–81
716 Gou L, Yang W, Qiao X, Ye L, Yan K, Li L *et al.* Marginal or segmental mandibulectomy: treatment modality selection for oral cancer: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg* 2018;**47**:1–10
717 D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R *et al.* Elective versus therapeutic neck dissection in node-negative oral cancer. *N Engl J Med* 2015;**373**:521–9
718 Hutchison IL, Ridout F, Cheung SMY, Shah N, Hardee P, Surwald C *et al.* Nationwide randomised trial evaluating elective neck dissection for early stage oral cancer (SEND study) with meta-analysis and concurrent real-world cohort. *Br J Cancer* 2019;**121**:827–36
719 National Institute for Health and Care Excellence. Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and Over. [A] Evidence reviews for treatment of advanced disease. In: https://www.nice.org.uk/guidance/ng36/evidence/a-evidence-reviews-for-treatment-of-advanced-disease-pdf-4847703517 [16 April 2023]
720 Lea J, Bachar G, Sawka AM, Lakra DC, Gilbert RW, Irish JC *et al.* Metastases to level IIb in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. *Head Neck* 2010;**32**:184–90
721 Kou Y, Zhao T, Huang S, Liu J, Duan W, Wang Y *et al.* Cervical level IIb metastases in squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. *Onco Targets Ther* 2017;**10**:4475–83
722 Pandey M, Karthikeyan S, Joshi D, Kumar M, Shukla M. Results of a randomized controlled trial of level IIb preserving neck dissection in clinically node-negative squamous carcinoma of the oral cavity. *World J Surg Oncol* 2018;**16**:219
723 Schilling C, Stoeckli SJ, Haerle SK, Broglie MA, Huber GF, Sorensen JA *et al.* Sentinel European Node Trial (SENT): 3-year results of sentinel node biopsy in oral cancer. *Eur J Cancer* 2015;**51**:2777–84
724 McGurk M, Chegini S, Schilling C, Lai SY. What is the optimum operative approach for the N0 neck in patients with early mouth cancer - a review of current status. *Br J Oral Maxillofac Surg* 2022;**60**:864–7
725 Vassiliou LV, Acero J, Gulati A, Holzle F, Hutchison IL, Prabhu S *et al.* Management of the clinically N0 neck in early-stage oral squamous cell carcinoma (OSCC). An EACMFS position paper. *J Craniomaxillofac Surg* 2020;**48**:711–18
726 Chegini S, Schilling C, Walgama ES, Yu KM, Thankappan K, Iyer S *et al.* Neck failure following pathologically node-negative neck dissection (pN0) in oral squamous cell carcinoma: a systematic review and meta-analysis. *Br J Oral Maxillofac Surg* 2021;**59**:1157–65
727 Schilling C, Stoeckli SJ, Vigili MG, de Bree R, Lai SY, Alvarez J *et al.* Surgical consensus guidelines on sentinel node biopsy (SNB) in patients with oral cancer. *Head Neck* 2019;**41**:2655–64

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

728 Pantvaidya GH, Pal P, Vaidya AD, Pai PS, D'Cruz AK. Prospective study of 583 neck dissections in oral cancers: implications for clinical practice. *Head Neck* 2014;**36**:1503–7

729 Liang L, Zhang T, Kong Q, Liang J, Liao G. A meta-analysis on selective versus comprehensive neck dissection in oral squamous cell carcinoma patients with clinically node-positive neck. *Oral Oncol* 2015;**51**:1076–81

730 Langendijk JA, Ferlito A, Takes RP, Rodrigo JP, Suarez C, Strojan P *et al.* Postoperative strategies after primary surgery for squamous cell carcinoma of the head and neck. *Oral Oncol* 2010;**46**:577–85

731 Expert Panel on Radiation Oncology-Head and Neck; Salama JK, Saba N, Quon H, Garg MK, Lawson J *et al.* ACR appropriateness criteria® adjuvant therapy for resected squamous cell carcinoma of the head and neck. *Oral Oncol* 2011;**47**:554–9

732 Huang DT, Johnson CR, Schmidt-Ullrich R, Grimes M. Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: a comparative study. *Int J Radiat Oncol Biol Phys* 1992;**23**:737–42

733 Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A *et al.* Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). *Head Neck* 2005;**27**:843–50

734 Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB *et al.* Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2012;**84**:1198–205

735 Metcalfe E, Aspin L, Speight R, Ermis E, Ramasamy S, Cardale K *et al.* Postoperative (chemo)radiotherapy for oral cavity squamous cell carcinomas: outcomes and patterns of failure. *Clin Oncol* (*R Coll Radiol*) 2017;**29**:51–9

736 Rosenthal DI, Liu L, Lee JH, Vapiwala N, Chalian AA, Weinstein GS *et al.* Importance of the treatment package time in surgery and postoperative radiation therapy for squamous carcinoma of the head and neck. *Head Neck* 2002;**24**:115–26

737 Kowalski LP. Results of salvage treatment of the neck in patients with oral cancer. *Arch Otolaryngol Head Neck Surg* 2002;**128**:58–62

738 Chan AK, Huang SH, Le LW, Yu E, Dawson LA, Kim JJ *et al.* Postoperative intensity-modulated radiotherapy following surgery for oral cavity squamous cell carcinoma: patterns of failure. *Oral Oncol* 2013;**49**:255–60

739 Kao YS, Hsu Y. Adjuvant contralateral neck irradiation for oral cavity cancer - a systematic review and meta-analysis. *Am J Otolaryngol* 2021;**42**:102885

740 Ellis MA, Graboyes EM, Wahlquist AE, Neskey DM, Kaczmar JM, Schopper HK *et al.* Primary surgery vs radiotherapy for early stage oral cavity cancer. *Otolaryngol Head Neck Surg* 2018;**158**:649–59

741 Graillon N, Iocca O, Carey RM, Benjamin K, Cannady SB, Hartner L *et al.* What has the National Cancer Database taught us about oral cavity squamous cell carcinoma? *Int J Oral Maxillofac Surg* 2022;**51**:10–17

742 Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY *et al.* Definitive radiotherapy or surgery for early oral squamous cell carcinoma in old and very old patients: a propensity-score-matched, nationwide, population-based cohort study. *Radiother Oncol* 2020;**151**:214–21

743 Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY *et al.* Definitive intensity-modulated radiotherapy or surgery for early oral cavity squamous cell carcinoma: propensity-score-matched, nationwide, population-based cohort study. *Head Neck* 2021;**43**:1142–52

744 Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;**354**:567–78

745 Pignon JP, le Maitre A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;**92**:4–14

746 Ozturk K, Gode S, Erdogan U, Akyildiz S, Apaydin F. Squamous cell carcinoma of the lip: survival analysis with long-term follow-up. *Eur Arch Otorhinolaryngol* 2015;**272**:3545–50

747 Biasoli ER, Valente VB, Mantovan B, Collado FU, Neto SC, Sundefeld ML *et al.* Lip cancer: a clinicopathological study and treatment outcomes in a 25-year experience. *J Oral Maxillofac Surg* 2016;**74**:1360–7

748 Zitsch RP 3rd, Park CW, Renner GJ, Rea JL. Outcome analysis for lip carcinoma. *Otolaryngol Head Neck Surg* 1995;**113**:589–96

749 de Visscher JG, Gooris PJ, Vermey A, Roodenburg JL. Surgical margins for resection of squamous cell carcinoma of the lower lip. *Int J Oral Maxillofac Surg* 2002;**31**:154–7

750 Hunt WTN, Earp E, Brown AC, Veitch D, Wernham AGH. A review of Mohs micrographic surgery for skin cancer. Part 3: squamous cell carcinoma. *Clin Exp Dermatol* 2022;**47**:1765–73

751 Veness MJ. Treatment recommendations in patients diagnosed with high-risk cutaneous squamous cell carcinoma. *Australas Radiol* 2005;**49**:365–76

752 Ebrahimi A, Moncrieff MD, Clark JR, Shannon KF, Gao K, Milross CG *et al.* Predicting the pattern of regional metastases from cutaneous squamous cell carcinoma of the head and neck based on location of the primary. *Head Neck* 2010;**32**:1288–94

753 Shahid Iqbal M, Kelly C, Kovarik J, Goranov B, Shaikh G, Morgan D *et al.* Palliative radiotherapy for locally advanced non-metastatic head and neck cancer: a systematic review. *Radiother Oncol* 2018;**126**:558–67

754 Brennan PA, Dylgjeri F, Coletta RD, Arakeri G, Goodson AM. Surgical tumour margins and their significance in oral squamous cell carcinoma. *J Oral Pathol Med* 2022;**51**:311–14

755 Stein AP, Saha S, Kraninger JL, Swick AD, Yu M, Lambert PF *et al.* Prevalence of human papillomavirus in oropharyngeal cancer: a systematic review. *Cancer J* 2015;**21**:138–46

756 National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE guideline [NG36]. In: https://www.nice.org.uk/guidance/ng36 [14 August 2022]

757 Hsu WC, Loevner LA, Karpati R, Ahmed T, Mong A, Battineni ML *et al.* Accuracy of magnetic resonance imaging in predicting absence of fixation of head and neck cancer to the prevertebral space. *Head Neck* 2005;**27**:95–100

758 Kato H, Kanematsu M, Watanabe H, Mizuta K, Aoki M. Metastatic retropharyngeal lymph nodes: comparison of CT and MR imaging for diagnostic accuracy. *Eur J Radiol* 2014;**83**:1157–62

759 Baulch J, Gandhi M, Sommerville J, Panizza B. 3T MRI evaluation of large nerve perineural spread of head and neck cancers. *J Med Imaging Radiat Oncol* 2015;**59**:578–85

760 Lewis-Jones H, Colley S, Gibson D. Imaging in head and neck cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**(S2):S28–31

761 Olliff J, Richards P, Connor S, Wong W, Beale T, Madani G. Head and neck cancers. In: Nicholson T, ed. *Recommendations for Cross-Sectional Imaging in Cancer Management*, 2nd edn. London: Royal College of Radiologists, 2014

762 Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JP. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. *J Natl Cancer Inst* 2008;**100**:712–20

763 Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 8th edn. Oxford: Wiley Blackwell, 2016

764 El-Naggar AK, Chan JKC, Takata T, Grandis JR, Slootweg PJ. The fourth edition of the head and neck World Health Organization blue book: editors' perspectives. *Hum Pathol* 2017;**66**:10–12

765 Winter SC, Corbridge R, Shah K, Millard P, Cox GJ. Orientation and labelling: use of an acetate sheet to label tumour resection specimens. *Ann R Coll Surg Engl* 2003;**85**:62–3

766 Lewis JS Jr, Beadle B, Bishop JA, Chernock RD, Colasacco C, Lacchetti C *et al.* Human papillomavirus testing in head and neck carcinomas: guideline from the College of American Pathologists. *Arch Pathol Lab Med* 2018;**142**:559–97

767 Lewis JS Jr, Adelstein DJ, Agaimy A, Carlson DL, Faquin WC, Helliwell T *et al.* Data set for the reporting of carcinomas of the nasopharynx and oropharynx: explanations and recommendations of the guidelines from the International Collaboration on Cancer Reporting. *Arch Pathol Lab Med* 2019;**143**:447–51

768 De Virgilio A, Costantino A, Mercante G, Pellini R, Ferreli F, Malvezzi L *et al.* Transoral robotic surgery and intensity-modulated radiotherapy in the treatment of the oropharyngeal carcinoma: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol* 2021;**278**:1321–35

769 Nauta IH, Rietbergen MM, van Bokhoven A, Bloemena E, Lissenberg-Witte BI, Heideman DAM *et al.* Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. *Ann Oncol* 2018;**29**:1273–9

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

770 Craig SG, Anderson LA, Schache AG, Moran M, Graham L, Currie K *et al.* Recommendations for determining HPV status in patients with oropharyngeal cancers under TNM8 guidelines: a two-tier approach. *Br J Cancer* 2019;**120**:827–33

771 Sathasivam HP, Santambrogio A, Andoniadou CL, Robinson M, Thavaraj S. Prognostic utility of HPV specific testing in addition to p16 immunohistochemistry in oropharyngeal squamous cell carcinoma. *Ann Oncol* 2018;**29**:2144–5

772 Craig SG, Anderson LA, Moran M, Graham L, Currie K, Rooney K *et al.* Comparison of molecular assays for HPV testing in oropharyngeal squamous cell carcinomas: a population-based study in Northern Ireland. *Cancer Epidemiol Biomarkers Prev* 2020;**29**:31–8

773 Warner L, O'Hara JT, Lin DJ, Oozeer N, Fox H, Meikle D *et al.* Transoral robotic surgery and neck dissection alone for head and neck squamous cell carcinoma: influence of resection margins on oncological outcomes. *Oral Oncol* 2022;**130**:105909

774 Holsinger FC, McWhorter AJ, Ménard M, Garcia D, Laccourreye O. Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: I. technique, complications, and functional results. *Arch Otolaryngol Head Neck Surg* 2005;**131**:583–91

775 Sharbel DD, Abkemeier M, Sullivan J, Zimmerman Z, Albergotti WG, Duvvuri U *et al.* Transcervical arterial ligation for prevention of postoperative hemorrhage in transoral oropharyngectomy: systematic review and meta-analysis. *Head Neck* 2021;**43**:334–44

776 Stokes W, Ramadan J, Lawson G, Ferris FRL, Holsinger FC, Turner MT. Bleeding complications after transoral robotic surgery: a meta-analysis and systematic review. *Laryngoscope* 2021;**131**:95–105

777 Stanford-Moore GB, Ochoa E, Larson A, Han M, Hoppe K, Ryan WR. Patterns of nodal metastases and predictors of occult disease in HPV-associated oropharynx cancer. *Otolaryngol Head Neck Surg* 2021;**164**:624–30

778 Smith AW, Gallitto M, Lehrer EJ, Wasserman I, Gupta V, Sharma S *et al.* Redefining risk of contralateral cervical nodal disease in early stage oropharyngeal cancer in the human papillomavirus era. *Head Neck* 2021;**43**:1409–14

779 Lee NCJ, Kelly JR, Park HS, Yarbrough WG, Burtness BA, Husain ZA. The risk of level IB nodal involvement in oropharynx cancer: guidance for submandibular gland sparing irradiation. *Pract Radiat Oncol* 2017;**7**:e317–21

780 Xiao R, Ward MC, Yang K, Adelstein DJ, Koyfman SA, Prendes BL *et al.* The prognostic impact of level I lymph node involvement in oropharyngeal squamous cell carcinoma. *Head Neck* 2019;**41**:3895–905

781 Royal College of Radiologists. Head and neck cancer - RCR consensus statements. In: https://www.rcr.ac.uk/publication/head-and-neck-cancer-rcr-consensus-statements [16 April 2023]

782 Gregoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A *et al.* Delineation of the primary tumour clinical target volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines. *Radiother Oncol* 2018;**126**:3–24

783 Royal College of Radiologists. Radiotherapy dose fractionation, third edition. In: https://www.rcr.ac.uk/publication/radiotherapy-dose-fractionation-third-edition [20 December 2021]

784 Spencer CR, Gay HA, Haughey BH, Nussenbaum B, Adkins DR, Wildes TM *et al.* Eliminating radiotherapy to the contralateral retropharyngeal and high level II lymph nodes in head and neck squamous cell carcinoma is safe and improves quality of life. *Cancer* 2014;**120**:3994–4002

785 Sher DJ, Adelstein DJ, Bajaj GK, Brizel DM, Cohen EEW, Halthore A *et al.* Radiation therapy for oropharyngeal squamous cell carcinoma: executive summary of an ASTRO Evidence-Based Clinical Practice Guideline. *Pract Radiat Oncol* 2017;**7**:246–53

786 Al-Mamgani A, van Werkhoven E, Navran A, Karakullukcu B, Hamming-Vrieze O, Machiels M *et al.* Contralateral regional recurrence after elective unilateral neck irradiation in oropharyngeal carcinoma: a literature-based critical review. *Cancer Treat Rev* 2017;**59**:102–8

787 Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J *et al.* Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. *Radiother Oncol* 2011;**100**:33–40

788 Bauml JM, Vinnakota R, Anna Park YH, Bates SE, Fojo T, Aggarwal C *et al.* Cisplatin every 3 weeks versus weekly with definitive concurrent radiotherapy for squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 2019;**111**:490–7

789 Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ *et al.* Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019;**393**:40–50

790 Roden DF, Schreiber D, Givi B. Triple-modality treatment in patients with advanced stage tonsil cancer. *Cancer* 2017;**123**:3269–76

791 Zhou S, Rulach R, Hendry F, Stobo D, James A, Dempsey MF *et al.* Positron emission tomography-computed tomography surveillance after (chemo)radiotherapy in advanced head and neck squamous cell cancer: beyond the PET-NECK protocol. *Clin Oncol* (*R Coll Radiol*) 2020;**32**:665–73

792 Iovoli AJ, Farrugia MK, Ma SJ, Chan JM, Markiewicz MR, McSpadden R *et al.* Role of repeat PET/CT imaging in head and neck cancer following initial incomplete PET/CT response to chemoradiation. *Cancers* (*Basel*) 2021;**13**:1461

793 Liu HY, Milne R, Lock G, Panizza BJ, Bernard A, Foote M *et al.* Utility of a repeat PET/CT scan in HPV-associated oropharyngeal cancer following incomplete nodal response from (chemo)radiotherapy. *Oral Oncol* 2019;**88**:153–9

794 Bird T, Barrington S, Thavaraj S, Jeannon JP, Lyons A, Oakley R *et al.* (18) F-FDG PET/CT to assess response and guide risk-stratified follow-up after chemoradiotherapy for oropharyngeal squamous cell carcinoma. *Eur J Nucl Med Mol Imaging* 2016;**43**:1239–47

795 de Ridder M, Gouw ZAR, Navran A, Hamming-Vrieze O, Jasperse B, van den Brekel MWM *et al.* FDG-PET/CT improves detection of residual disease and reduces the need for examination under anaesthesia in oropharyngeal cancer patients treated with (chemo-)radiation. *Eur Arch Otorhinolaryngol* 2019;**276**:1447–55

796 Vandecaveye V, De Keyzer F, Nuyts S, Deraedt K, Dirix P, Hamaekers P *et al.* Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. *Int J Radiat Oncol Biol Phys* 2007;**67**:960–71

797 Wang SJ. Surveillance radiologic imaging after treatment of oropharyngeal cancer: a review. *World J Surg Oncol* 2015;**13**:94

798 Dawe N, Patterson J, O'Hara J. Functional swallowing outcomes following treatment for oropharyngeal carcinoma: a systematic review of the evidence comparing trans-oral surgery versus non-surgical management. *Clin Otolaryngol* 2016;**41**:371–85

799 Nichols AC, Theurer J, Prisman E, Read N, Berthelet E, Tran E *et al.* Randomized trial of radiotherapy versus transoral robotic surgery for oropharyngeal squamous cell carcinoma: long-term results of the ORATOR trial. *J Clin Oncol* 2022;**40**:866–75

800 Yom SS, Torres-Saavedra P, Caudell JJ, Waldron JN, Gillison ML, Xia P *et al.* Reduced-dose radiation therapy for HPV-associated oropharyngeal carcinoma (NRG Oncology HN002). *J Clin Oncol* 2021;**39**:956–65

801 Chua MLK, Wee JTS, Hui EP, Chan ATC. Nasopharyngeal carcinoma. *Lancet* 2016;**387**:1012–24

802 Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet* 2019;**394**:64–80

803 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424

804 Dubrulle F, Souillard R, Hermans R. Extension patterns of nasopharyngeal carcinoma. *Eur Radiol* 2007;**17**:2622–30

805 Lee AW, Ng WT, Pan JJ, Poh SS, Ahn YC, AlHussain H *et al.* International guideline for the delineation of the clinical target volumes (CTV) for nasopharyngeal carcinoma. *Radiother Oncol* 2018;**126**:25–36

806 Royal College of Radiologists; Royal College of Physicians of London; Royal College of Physicians and Surgeons of Glasgow; Royal College of Physicians of Edinburgh; British Nuclear Medicine Society; Administration of Radioactive Substances Advisory Committee. Evidence-based indications for the use of PET-CT in the United Kingdom 2016. *Clin Radiol* 2016;**71**:e171–88

807 Chen YP, Ismaila N, Chua MLK, Colevas AD, Haddad R, Huang SH *et al.* Chemotherapy in combination with radiotherapy for definitive-intent treatment of stage II-IVA nasopharyngeal carcinoma: CSCO and ASCO Guideline. *J Clin Oncol* 2021;**39**:840–59

808 Prestwich RJ, Sykes J, Carey B, Sen M, Dyker KE, Scarsbrook AF. Improving target definition for head and neck radiotherapy: a place for

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

magnetic resonance imaging and 18-fluoride fluorodeoxyglucose positron emission tomography? *Clin Oncol* (*R Coll Radiol*) 2012;**24**:577–89
809 Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 8th edn. Oxford: Wiley Blackwell, 2017
810 Chan YH, Lo CM, Lau HY, Lam TH. Vertically transmitted nasopharyngeal infection of the human papillomavirus: does it play an aetiological role in nasopharyngeal cancer? *Oral Oncol* 2014;**50**:326–9
811 Huang WB, Chan JYW, Liu DL. Human papillomavirus and World Health Organization type III nasopharyngeal carcinoma: multicenter study from an endemic area in Southern China. *Cancer* 2018;**124**:530–6
812 Lee AW, Ma BB, Ng WT, Chan AT. Management of nasopharyngeal carcinoma: current practice and future perspective. *J Clin Oncol* 2015;**33**:3356–64
813 Miao J, Di M, Chen B, Wang L, Cao Y, Xiao W *et al*. A prospective 10-year observational study of reduction of radiation therapy clinical target volume and dose in early-stage nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2020;**107**:672–82
814 Miah AB, Bhide SA, Del Rosario L, Matthews J, Nicol R, Tanay MA *et al*. Induction chemotherapy followed by chemo-intensity-modulated radiotherapy for locally advanced nasopharyngeal cancer. *Clin Oncol* (*R Coll Radiol*) 2016;**28**:e61–7
815 Ng WT, Lee MC, Chang AT, Chan OS, Chan LL, Cheung FY *et al*. The impact of dosimetric inadequacy on treatment outcome of nasopharyngeal carcinoma with IMRT. *Oral Oncol* 2014;**50**:506–12
816 Ho FC, Tham IW, Earnest A, Lee KM, Lu JJ. Patterns of regional lymph node metastasis of nasopharyngeal carcinoma: a meta-analysis of clinical evidence. *BMC Cancer* 2012;**12**:98
817 Huang CL, Xu C, Zhang Y, Zhou GQ, Mao YP, Liu Q *et al*. Feasibility of ipsilateral lower neck sparing irradiation for unilateral or bilateral neck node-negative nasopharyngeal carcinoma: systemic review and meta-analysis of 2,521 patients. *Radiat Oncol* 2018;**13**:141
818 Ou X, Miao Y, Wang X, Ding J, He X, Hu C. The feasibility analysis of omission of elective irradiation to level IB lymph nodes in low-risk nasopharyngeal carcinoma based on the 2013 updated consensus guideline for neck nodal levels. *Radiat Oncol* 2017;**12**:137
819 Gregoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA *et al*. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. *Radiother Oncol* 2014;**110**:172–81
820 Zhao C, Miao JJ, Hua YJ, Wang L, Han F, Lu LX *et al*. Locoregional control and mild late toxicity after reducing target volumes and radiation doses in patients with locoregionally advanced nasopharyngeal carcinoma treated with induction chemotherapy (IC) followed by concurrent chemoradiotherapy: 10-year results of a phase 2 study. *Int J Radiat Oncol Biol Phys* 2019;**104**:836–44
821 Yang H, Chen X, Lin S, Rong J, Yang M, Wen Q *et al*. Treatment outcomes after reduction of the target volume of intensity-modulated radiotherapy following induction chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a prospective, multi-center, randomized clinical trial. *Radiother Oncol* 2018;**126**:37–42
822 Leeman JE, Romesser PB, Zhou Y, McBride S, Riaz N, Sherman E *et al*. Proton therapy for head and neck cancer: expanding the therapeutic window. *Lancet Oncol* 2017;**18**:e254–65
823 Blanchard P, Lee A, Marguet S, Leclercq J, Ng WT, Ma J *et al*. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. *Lancet Oncol* 2015;**16**:645–55
824 Xia WX, Lv X, Liang H, Liu GY, Sun R, Zeng Q *et al*. A randomized controlled trial comparing two different schedules for cisplatin treatment in patients with locoregionally advanced nasopharyngeal cancer. *Clin Cancer Res* 2021;**27**:4186–94
825 Huang PY, Cao KJ, Guo X, Mo HY, Guo L, Xiang YQ *et al*. A randomized trial of induction chemotherapy plus concurrent chemoradiotherapy versus induction chemotherapy plus radiotherapy for locoregionally advanced nasopharyngeal carcinoma. *Oral Oncol* 2012;**48**:1038–44
826 Chitapanarux I, Lorvidhaya V, Kamnerdsupaphon P, Sumitsawan Y, Tharavichitkul E, Sukthomya V *et al*. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *Eur J Cancer* 2007;**43**:1399–406
827 Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY *et al*. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. *J Natl Cancer Inst* 2011;**103**:1761–70
828 Liu F, Jin T, Liu L, Xiang Z, Yan R, Yang H. The role of concurrent chemotherapy for stage II nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: a systematic review and meta-analysis. *PLoS One* 2018;**13**:e0194733
829 Xu C, Zhang LH, Chen YP, Liu X, Zhou GQ, Lin AH *et al*. Chemoradiotherapy versus radiotherapy alone in stage II nasopharyngeal carcinoma: a systemic review and meta-analysis of 2138 patients. *J Cancer* 2017;**8**:287–97
830 Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J *et al*. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet* 2016;**388**:1883–92
831 Yang Q, Cao SM, Guo L, Hua YJ, Huang PY, Zhang XL *et al*. Induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: long-term results of a phase III multicentre randomised controlled trial. *Eur J Cancer* 2019;**119**:87–96
832 Zhang Y, Chen L, Hu GQ, Zhang N, Zhu XD, Yang KY *et al*. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med* 2019;**381**:1124–35
833 Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY *et al*. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol* 2016;**17**:1509–20
834 Tan T, Lim WT, Fong KW, Cheah SL, Soong YL, Ang MK *et al*. Concurrent chemo-radiation with or without induction gemcitabine, Carboplatin, and Paclitaxel: a randomized, phase 2/3 trial in locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2015;**91**:952–60
835 Chen L, Hu CS, Chen XZ, Hu GQ, Cheng ZB, Sun Y *et al*. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2012;**13**:163–71
836 Slevin F, Pan S, Mistry H, Sen M, Foran B, Slevin N *et al*. A multicentre UK study of outcomes of nasopharyngeal carcinoma treated with intensity-modulated radiotherapy +/- chemotherapy. *Clin Oncol* (*R Coll Radiol*) 2020;**32**:238–49
837 Petkar I, Bhide S, Newbold K, Harrington K, Nutting C. Practice patterns for the radical treatment of nasopharyngeal cancer by head and neck oncologists in the United Kingdom. *Br J Radiol* 2018;**91**:20170590
838 Petit C, Lee AWM, Carmel A, Ng WT, Ma J, Chan ATC *et al*. Network meta-analysis of chemotherapy in nasopharyngeal carcinoma (MAC-NPC): an update on 8221 patients. *J Clin Oncol* 2021;**38**(15 suppl):6523
839 Chen YP, Liu X, Zhou Q, Yang KY, Jin F, Zhu XD *et al*. Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: a multicentre, open-label, parallel-group, randomised, controlled, phase 3 trial. *Lancet* 2021;**398**:303–13
840 Miao J, Wang L, Tan SH, Li J, Yi J, Zhang Y *et al*. Adjuvant capecitabine in locoregionally advanced nasopharyngeal carcinoma: a multicenter randomized controlled phase III trial. *J Clin Oncol* 2021;**39**:6005
841 Ben-Ami T, Kontny U, Surun A, Brecht IB, Almaraz RL, Dragomir M *et al*. Nasopharyngeal carcinoma in children and adolescents: the EXPeRT/PARTNER diagnostic and therapeutic recommendations. *Pediatr Blood Cancer* 2021;**68**(suppl 4):e29018
842 Claude L, Jouglar E, Duverge L, Orbach D. Update in pediatric nasopharyngeal undifferentiated carcinoma. *Br J Radiol* 2019;**92**:20190107
843 Uezono H, Indelicato DJ, Rotondo RL, Sandler ES, Katzenstein HM, Dagan R *et al*. Proton therapy following induction chemotherapy for pediatric and adolescent nasopharyngeal carcinoma. *Pediatr Blood Cancer* 2019;**66**:e27990
844 Rusthoven CG, Lanning RM, Jones BL, Amini A, Koshy M, Sher DJ *et al*. Metastatic nasopharyngeal carcinoma: patterns of care and survival for patients receiving chemotherapy with and without local radiotherapy. *Radiother Oncol* 2017;**124**:139–46
845 You R, Liu YP, Huang PY, Zou X, Sun R, He YX *et al*. Efficacy and safety of locoregional radiotherapy with chemotherapy vs chemotherapy alone in de novo metastatic nasopharyngeal carcinoma: a multicenter phase 3 randomized clinical trial. *JAMA Oncol* 2020;**6**:1345–52
846 Tian YH, Zou WH, Xiao WW, Zeng L, Yuan X, Bai L *et al*. Oligometastases in AJCC stage IVc nasopharyngeal carcinoma: a subset with better overall survival. *Head Neck* 2016;**38**:1152–7
847 Bates JE, De Leo AN, Morris CG, Amdur RJ, Dagan R. Oligometastatic squamous cell carcinoma of the head and neck treated with stereotactic

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

body ablative radiotherapy: single-institution outcomes. *Head Neck* 2019;**41**:2309–14
848 Pan CC, Wu PH, Yu JR, Li W, Huang ZL, Wang JP *et al.* Comparative survival analysis in patients with pulmonary metastases from nasopharyngeal carcinoma treated with radiofrequency ablation. *Eur J Radiol* 2012;**81**:e473–7
849 Xu R, Mai H, Chen Q, Chen D, Hu C, Yang K *et al.* JUPITER-02: randomised, double-blind, phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first line treatment for recurrent of metastatic nasopharyngeal carcinoma (NPC). *J Clin Oncol* 2021;**39**(18 suppl):LBA2
850 Yang Y, Qu S, Li J, Hu C, Xu M, Li W *et al.* Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2021;**22**:1162–74
851 Liu G, Li W, Wang D, Liang H, Lv X, Ye Y *et al.* Capecitabine maintenance therapy after induction chemotherapy in newly diagnosed metastatic nasopharyngeal carcinoma: an open-label, randomized, controlled, phase trial. *J Clin Oncol* 2021;**39**:6044
852 Ng WT, Soong YL, Chan Ahn Y, AlHussain H, Choi HCW, Corry J *et al.* International recommendations on re-irradiation by intensity-modulated radiotherapy for locally recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2021;**110**:682–95
853 Ng WT, Wong ECY, Cheung AKW, Chow JCH, Poon DMC, Lai JWY *et al.* Patterns of care and treatment outcomes for local recurrence of NPC after definite IMRT--a study by the HKNPCSG. *Head Neck* 2019;**41**:3661–9
854 Chen MY, Wang SL, Zhu YL, Shen GP, Qiu F, Luo DH *et al.* Use of a posterior pedicle nasal septum and floor mucoperiosteum flap to resurface the nasopharynx after endoscopic nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Head Neck* 2012;**34**:1383–8
855 Zou X, Han F, Ma WJ, Deng MQ, Jiang R, Guo L *et al.* Salvage endoscopic nasopharyngectomy and intensity-modulated radiotherapy versus conventional radiotherapy in treating locally recurrent nasopharyngeal carcinoma. *Head Neck* 2015;**37**:1108–15
856 Leong YH, Soon YY, Lee KM, Wong LC, Tham IWK, Ho FCH. Long-term outcomes after reirradiation in nasopharyngeal carcinoma with intensity-modulated radiotherapy: a meta-analysis. *Head Neck* 2018;**40**:622–31
857 Maghami E, Koyfman SA, Weiss J. Personalizing postoperative treatment of head and neck cancers. *Am Soc Clin Oncol Educ Book* 2018;**38**:515–22
858 Li YQ, Tian YM, Tan SH, Liu MZ, Kusumawidjaja G, Ong EHW *et al.* Prognostic model for stratification of radioresistant nasopharynx carcinoma to curative salvage radiotherapy. *J Clin Oncol* 2018;**36**:891–9
859 Liu YP, Li H, You R, Li JB, Liu XK, Yang AK *et al.* Surgery for isolated regional failure in nasopharyngeal carcinoma after radiation: selective or comprehensive neck dissection. *Laryngoscope* 2019;**129**:387–95
860 Zhou GQ, Wu CF, Deng B, Gao TS, Lv JW, Lin L *et al.* An optimal post-treatment surveillance strategy for cancer survivors based on an individualized risk-based approach. *Nat Commun* 2020;**11**:3872
861 Head and neck cancers incidence statistics. In: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers/incidence#heading-Three [18 October 2022]
862 Newman JR, Connolly TM, Illing EA, Kilgore ML, Locher JL, Carroll WR. Survival trends in hypopharyngeal cancer: a population-based review. *Laryngoscope* 2015;**125**:624–9
863 Kim D, Kim N, Koh S, Chung MK, Son YI, Oh D *et al.* Oncological and functional outcomes of larynx-preserving surgery for hypopharyngeal cancer: a comparison with definitive radiation-based treatment. *Cancer Res Treat* 2022;**54**:84–95
864 Spector GJ. Distant metastases from laryngeal and hypopharyngeal cancer. *ORL J Otorhinolaryngol Relat Spec* 2001;**63**:224–8
865 Waclawek M, Milonski J, Olszewski J. Comparative evaluation of the diagnostic value of biopsy and NBI endoscopy in patients with cancer of the hypopharynx and larynx. *Otolaryngol Pol* 2019;**73**:12–17
866 Schimberg AS, Wellenstein DJ, van den Broek EM, Honings J, van den Hoogen FJA, Marres HAM *et al.* Office-based vs. operating room-performed laryngopharyngeal surgery: a review of cost differences. *Eur Arch Otorhinolaryngol* 2019;**276**:2963–73
867 Hoffman HT, Karnell LH, Shah JP, Ariyan S, Brown GS, Fee WE *et al.* Hypopharyngeal cancer patient care evaluation. *Laryngoscope* 1997;**107**:1005–17
868 Simo R, Rovira A, Townley W. Salvage treatment options after failed primary treatment of hypopharyngeal cancer. *Adv Otorhinolaryngol* 2019;**83**:135–47
869 Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. In: https://www.nice.org.uk/guidance/NG36/chapter/Recommendations#treatment-of-early-stage-disease [15 May 2018]
870 Eckel HE, Bradley PJ. Treatment options for hypopharyngeal cancer. *Adv Otorhinolaryngol* 2019;**83**:47–53
871 Machiels JP, Rene Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V *et al.* Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;**31**:1462–75
872 Garneau JC, Bakst RL, Miles BA. Hypopharyngeal cancer: a state of the art review. *Oral Oncol* 2018;**86**:244–50
873 Vasiliadou I, Noble D, Hartley A, Moleron R, Sanghera P, Urbano TG *et al.* A multi-centre survey reveals variations in the standard treatments and treatment modifications for head and neck cancer patients during Covid-19 pandemic. *Clin Transl Radiat Oncol* 2021;**30**:50–9
874 Nguyen NP, Vock J, Vinh-Hung V, Almeida F, Ewell L, Betz M *et al.* Effectiveness of prophylactic retropharyngeal lymph node irradiation in patients with locally advanced head and neck cancer. *BMC Cancer* 2012;**12**:253
875 Imanishi Y, Ozawa H, Sakamoto K, Fujii R, Shigetomi S, Habu N *et al.* Clinical outcomes of transoral videolaryngoscopic surgery for hypopharyngeal and supraglottic cancer. *BMC Cancer* 2017;**17**:445
876 Wei WI. The dilemma of treating hypopharyngeal carcinoma: more or less: Hayes Martin Lecture. *Arch Otolaryngol Head Neck Surg* 2002;**128**:229–32
877 Chen LY, Huang CC, Tsou YA, Bau DT, Tsai MH. Prognostic factor of severe complications in patients with hypopharyngeal cancer with primary concurrent chemoradiotherapy. *Anticancer Res* 2015;**35**:1735–41
878 Laccourreye O, Ishoo E, de Mones E, Garcia D, Kania R, Hans S. Supracricoid hemilaryngopharyngectomy in patients with invasive squamous cell carcinoma of the pyriform sinus. Part I: technique, complications, and long-term functional outcome. *Ann Otol Rhinol Laryngol* 2005;**114**:25–34
879 Elliott M, Odell E, Tysome J, Connor S, Siddiqui A, Jeannon J *et al.* Role of thyroidectomy in advanced laryngeal and pharyngolaryngeal carcinoma. *Otolarygol Head and Neck Surg* 2010;**142**:851–5
880 Schmitz S, Machiels JP, Weynand B, Gregoire V, Hamoir M. Results of selective neck dissection in the primary management of head and neck squamous cell carcinoma. *Eur Arch Otorhinolaryngol* 2009;**266**:437–43
881 Johnson JT, Bacon GW, Myers EN, Wagner RL. Medial vs lateral wall pyriform sinus carcinoma: implications for management of regional lymphatics. *Head Neck* 1994;**16**:401–5
882 Scharpf J, Karnell LH, Christensen AJ, Funk GF. The role of pain in head and neck cancer recurrence and survivorship. *Arch Otolaryngol Head Neck Surg* 2009;**135**:789–94
883 Brunet A, Tornari C, Ezebuiro A, Kennedy R, Connor SEJ, Oakley R *et al.* Role of thyroidectomy in recurrent laryngeal carcinoma. *Otolaryngol Head Neck Surg* 2022;**166**:894–900
884 Sullivan CA, Jaklitsch MT, Haddad R, Goguen LA, Gagne A, Wirth LJ *et al.* Endoscopic management of hypopharyngeal stenosis after organ sparing therapy for head and neck cancer. *Laryngoscope* 2004;**114**:1924–31
885 Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol* 2008;**33**:210–22
886 Ul-Hassan F, Simo R, Guerrero-Urbano T, Oakley R, Jeannon JP, Cook GJ. Can (18)F-FDG PET/CT reliably assess response to primary treatment of head and neck cancer? *Clin Nucl Med* 2013;**38**:263–5
887 Zhang Y, Huang Z, Xu M, Liu J, Li Z, An C *et al.* Complications and oncological outcomes after salvage surgery for recurrent and residual hypopharyngeal squamous cell carcinoma: a retrospective cohort study. *Ann Transl Med* 2022;**10**:525
888 Shoffel-Havakuk H, O'Dell K, Johns MM 3rd, Reder L, Popova M, Halperin D, *et al.* The rising rate of nonsmokers among laryngeal carcinoma patients: are we facing a new disease? *Laryngoscope* 2020;**130**:E108–15
889 Stanikova L, Walderova R, Jancatova D, Formanek M, Zelenik K, Kominek P. Comparison of narrow band imaging and the Storz Professional Image Enhancement System for detection of laryngeal

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

and hypopharyngeal pathologies. *Eur Arch Otorhinolaryngol* 2018;**275**:1819–25
890 National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE Guideline [NG36]. In: https://www.nice.org.uk/guidance/ng36 [27 April 2023]
891 Chew S, Cosway B, Hamilton D. Rate of significant radiological findings in early laryngeal cancers: our experience with 137 patients. *Clin Otolaryngol* 2021;**46**:861–3
892 Becker M, Zbären P, Casselman JW, Kohler R, Dulguerov P, Becker CD. Neoplastic invasion of laryngeal cartilage: reassessment of criteria for diagnosis at MR imaging. *Radiology* 2008;**249**:551–9
893 Olliff J, Richards P, Connor S, Wong WL, Beale T, Madani G. Head and neck cancers. In: Nicholson T, ed. *Recommendations for Cross-Sectional Imaging in Cancer Management*, 2nd edn. London: Royal College of Radiologists, 2014
894 Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*, 8th edn. Oxford: Wiley Blackwell, 2016
895 Weller MD, Nankivell PC, McConkey C, Paleri V, Mehanna HM. The risk and interval to malignancy of patients with laryngeal dysplasia; a systematic review of case series and meta-analysis. *Clin Otolaryngol* 2010;**35**:364–72
896 Cosway B, Paleri V. Laryngeal dysplasia: an evidence-based flowchart to guide management and follow up. *J Laryngol Otol* 2015;**129**:598–9
897 Eckel HE, Simo R, Quer M, Odell E, Paleri V, Klussmann JP *et al.* European Laryngological Society position paper on laryngeal dysplasia. Part II: diagnosis, treatment, and follow-up. *Eur Arch Otorhinolaryngol* 2021;**278**:1723–32
898 Health and Social Care Information Centre. *National Head and Neck Cancer Audit 2014 (DAHNO 10th Annual Report)*. London: *Healthcare* Quality Improvement Partnership, 2015
899 O'Hara J, Markey A, Homer JJ. Transoral laser surgery versus radiotherapy for tumour stage 1a or 1b glottic squamous cell carcinoma: systematic review of local control outcomes. *J Laryngol Otol* 2013;**127**:732–8
900 Abdurehim Y, Hua Z, Yasin Y, Xukurhan A, Imam I, Yuqin F. Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer. *Head Neck* 2012;**34**:23–33
901 Prettyjohns M, Winter S, Kerawala C, Paleri V, Robinson M, Bhide S *et al.* Transoral laser microsurgery versus radiation therapy in the management of T1 and T2 laryngeal glottic carcinoma: which modality is cost-effective within the UK? *Clin Otolaryngol* 2017;**42**:404–15
902 Zhan C, Yang X, Song X, Yan L. Radiotherapy vs surgery for T1-2N0M0 laryngeal squamous cell carcinoma: a population-based and propensity score matching study. *Cancer Med* 2018;**7**:2837–47
903 Taylor SM, Kerr P, Fung K, Aneeshkumar MK, Wilke D, Jiang Y *et al.* Treatment of T1b glottic SCC: laser vs. radiation--a Canadian multicenter study. *J Otolaryngol Head Neck Surg* 2013;**42**:22
904 Warner L, Lee K, Homer JJ. Transoral laser microsurgery versus radiotherapy for T2 glottic squamous cell carcinoma: a systematic review of local control outcomes. *Clin Otolaryngol* 2017;**42**:629–36
905 Canis M, Martin A, Ihler F, Wolff HA, Kron M, Matthias C *et al.* Transoral laser microsurgery in treatment of pT2 and pT3 glottic laryngeal squamous cell carcinoma - results of 391 patients. *Head Neck* 2014;**36**:859–66
906 Dixon LM, Douglas CM, Shaukat SI, Garcez K, Lee LW, Sykes AJ *et al.* Conventional fractionation should not be the standard of care for T2 glottic cancer. *Radiat Oncol* 2017;**12**:178
907 To K, Qureishi A, Mortimore S, De M. The role of primary transoral laser microsurgery in laryngeal cancer: a retrospective study. *Clin Otolaryngol* 2015;**40**:449–55
908 Bradley PJ, Mackenzie K, Wight R, Pracy P, Paleri V. Consensus statement on management in the UK: transoral laser assisted microsurgical resection of early glottic cancer. *Clin Otolaryngol* 2009;**34**:367–73
909 Wilkie MD, Lightbody KA, Lythgoe D, Tandon S, Lancaster J, Jones TM. Transoral laser microsurgery for early and moderately advanced laryngeal cancers: outcomes from a single centralised United Kingdom centre. *Eur Arch Otorhinolaryngol* 2015;**272**:695–704
910 Megwalu UC, Panossian H. Survival outcomes in early stage laryngeal cancer. *Anticancer Res* 2016;**36**:2903–7
911 Arshad H, Jayaprakash V, Gupta V, Cohan DM, Ambujakshan D, Rigual NR *et al.* Survival differences between organ preservation surgery and definitive radiotherapy in early supraglottic squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2014;**150**:237–44
912 Succo G, Crosetti E, Bertolin A, Piazza C, Molteni G, Cirillo S *et al.* Treatment for T3 to T4a laryngeal cancer by open partial horizontal laryngectomies: prognostic impact of different pathologic tumor subcategories. *Head Neck* 2018;**40**:1897–908
913 Thomas L, Drinnan M, Natesh B, Mehanna H, Jones T, Paleri V. Open conservation partial laryngectomy for laryngeal cancer: a systematic review of English language literature. *Cancer Treat Rev* 2012;**38**:203–11
914 Department of Veterans Affairs Laryngeal Cancer Study Group; Wolf GT, Fisher SG, Hong WK, Hillman R, Spaulding M *et al.* Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;**324**:1685–90
915 Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W *et al.* Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;**349**:2091–8
916 Forastiere AA, Ismaila N, Lewin JS, Nathan CA, Adelstein DJ, Eisbruch A *et al.* Use of larynx-preservation strategies in the treatment of laryngeal cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncolog* 2018;**36**:1143–69
917 Patel SA, Qureshi MM, Dyer MA, Jalisi S, Grillone G, Truong MT. Comparing surgical and nonsurgical larynx-preserving treatments with total laryngectomy for locally advanced laryngeal cancer. *Cancer* 2019;**125**:3367–77
918 Eskander A, Blakaj DM, Dziegielewski PT. Decision making in advanced larynx cancer: an evidenced based review. *Oral Oncol* 2018;**86**:195–9
919 Dziegielewski PT, Reschly WJ, Morris CG, DeJesus RD, Silver N, Boyce BJ *et al.* Tumor volume as a predictor of survival in T3 glottic carcinoma: a novel approach to patient selection. *Oral Oncol* 2018;**79**:47–54
920 Kumar R, Drinnan M, Robinson M, Meikle D, Stafford F, Welch A *et al.* Thyroid gland invasion in total laryngectomy and total laryngopharyngectomy: a systematic review and meta-analysis of the English literature. *Clin Otolaryngol* 2013;**38**:372–8
921 Cervenka BP, Rao S, Farwell DG, Bewley AF. Efficacy of laryngectomy alone for treatment of locally advanced laryngeal cancer: a stage- and subsite-specific survival analysis. *Clin Otolaryngol* 2018;**43**:544–52
922 O'Hara J, Simo R, McQueen A, Andi K, Lester S, Giddings C *et al.* Management of metastatic neck disease--summary of the 11th Evidence Based Management Day. *Clin Otolaryngol* 2014;**39**:3–5
923 Ramakrishnan Y, Drinnan M, Kwong FN, Grant DG, Mehanna H, Jones T *et al.* Oncologic outcomes of transoral laser microsurgery for radiorecurrent laryngeal carcinoma: a systematic review and meta-analysis of English-language literature. *Head Neck* 2014;**36**:280–5
924 Paleri V, Thomas L, Basavaiah N, Drinnan M, Mehanna H, Jones T. Oncologic outcomes of open conservation laryngectomy for radiorecurrent laryngeal carcinoma: a systematic review and meta-analysis of English-language literature. *Cancer* 2011;**117**:2668–76
925 Paleri V, Drinnan M, van den Brekel MWM, Hinni ML, Bradley PJ, Wolf GT *et al.* Vascularized tissue to reduce fistula following salvage total laryngectomy: a systematic review. *Laryngoscope* 2014;**124**:1848–53
926 Gidley PW, DeMonte F. Temporal bone malignancies. *Neurosurg Clin N Am* 2013;**24**:97–110
927 Masterson L, Rouhani M, Donnelly NP, Tysome JR, Patel P, Jefferies SJ *et al.* Squamous cell carcinoma of the temporal bone: clinical outcomes from radical surgery and postoperative radiotherapy. *Otol Neurotol* 2014;**35**:501–8
928 Allanson BM, Low TH, Clark JR, Gupta R. Squamous cell carcinoma of the external auditory canal and temporal bone: an update. *Head Neck Pathol* 2018;**12**:407–18
929 Moody SA, Hirsch BE, Myers EN. Squamous cell carcinoma of the external auditory canal: an evaluation of a staging system. *Am J Otol* 2000;**21**:582–8
930 Nabuurs CH, Kievit W, Labbé N, Leemans CR, Smit C, van den Brekel MWM *et al.* Evaluation of the modified Pittsburgh classification for predicting the disease-free survival outcome of squamous cell carcinoma of the external auditory canal. *Head Neck* 2020;**42**:3609–22
931 Zanoletti E, Franz L, Cazzador D, Franchella S, Calvanese L, Nicolai P *et al.* Temporal bone carcinoma: novel prognostic score based on clinical and histological features. *Head Neck* 2020;**42**:3693–701
932 Zanoletti E, Marioni G, Stritoni P, Lionello M, Giacomelli L, Martini A *et al.* Temporal bone squamous cell carcinoma: analyzing prognosis with univariate and multivariate models. *Laryngoscope* 2014;**124**:1192–8
933 Morita S, Homma A, Nakamaru Y, Sakashita T, Hatakeyama H, Kano S *et al.* The outcomes of surgery and chemoradiotherapy for temporal bone cancer. *Otol Neurotol* 2016;**37**:1174–82

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

934 Bacciu A, Clemente IA, Piccirillo E, Ferrari S, Sanna M. Guidelines for treating temporal bone carcinoma based on long-term outcomes. *Otol Neurotol* 2013;**34**:898–907

935 Lovin BD, Gidley PW. Squamous cell carcinoma of the temporal bone: a current review. *Laryngoscope Investig Otolaryngol* 2019;**4**:684–92

936 Shinomiya H, Hasegawa S, Yamashita D, Ejima Y, Kenji Y, Otsuki N *et al.* Concomitant chemoradiotherapy for advanced squamous cell carcinoma of the temporal bone. *Head Neck* 2016;**38**(suppl 1):E949–53

937 Takenaka Y, Cho H, Nakahara S, Yamamoto Y, Yasui T, Inohara H. Chemoradiation therapy for squamous cell carcinoma of the external auditory canal: a meta-analysis. *Head Neck* 2015;**37**:1073–80

938 Ferrari M, Zanoletti E, Taboni S, Cazzador D, Tealdo G, Schreiber A *et al.* Resection of the internal carotid artery in selected patients affected by cancer of the skull base. *Head Neck* 2022;**44**:1030–42

939 Cristalli G, Manciocco V, Pichi B, Marucci L, Arcangeli G, Telera S *et al.* Treatment and outcome of advanced external auditory canal and middle ear squamous cell carcinoma. *J Craniofac Surg* 2009;**20**:816–21

940 Leong SC, Youssef A, Lesser TH. Squamous cell carcinoma of the temporal bone: outcomes of radical surgery and postoperative radiotherapy. *Laryngoscope* 2013;**123**:2442–8

941 Xie B, Zhang T, Dai C. Survival outcomes of patients with temporal bone squamous cell carcinoma with different invasion patterns. *Head Neck* 2015;**37**:188–96

942 Mehra S, Morris LG, Shah J, Bilsky M, Selesnick S, Kraus DH. Outcomes of temporal bone resection for locally advanced parotid cancer. *Skull Base* 2011;**21**:389–96

943 Martin JR, Filip P, Thorpe EJ, Leonetti JP. Treatment of locally advanced parotid malignancies with parotidectomy and temporal bone resection. *Am J Otolaryngol* 2017;**38**:380–2

944 Essig GF, Kitipornchai L, Adams F, Zarate D, Gandhi M, Porceddu S *et al.* Lateral temporal bone resection in advanced cutaneous squamous cell carcinoma: report of 35 patients. *J Neurol Surg B Skull Base* 2013;**74**:54–9

945 Shao A, Wong DK, McIvor NP, Mylnarek AM, Chaplin JM, Izzard ME *et al.* Parotid metastatic disease from cutaneous squamous cell carcinoma: prognostic role of facial nerve sacrifice, lateral temporal bone resection, immune status and P-stage. *Head Neck* 2014;**36**:545–50

946 de Casso C, Kwhaja S, Davies S, Al-Ani Z, Saeed SR, Homer JJ. Effect of temporal bone resection on temporomandibular joint function: a quality of life study. *Otolaryngol Head Neck Surg* 2010;**142**:85–9

947 Hosokawa S, Mizuta K, Takahashi G, Okamura J, Takizawa Y, Hosokawa K *et al.* Surgical approach for treatment of carcinoma of the anterior wall of the external auditory canal. *Otol Neurotol* 2012;**33**:450–4

948 Borsetto D, Vijendren A, Franchin G, Donnelly N, Axon P, Smith M *et al.* Prevalence of occult nodal metastases in squamous cell carcinoma of the temporal bone: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol* 2022;**279**:5573–81

949 Wilkie MD, Lancaster J, Roland NJ, Jones TM. Elective management of regional nodal basins in cutaneous squamous cell carcinoma of the head and neck: controversies and contemporary perspectives. *Oral Oncol* 2021;**120**:105432

950 Xie B, Wang M, Zhang S, Liu Y. Parotidectomy in the management of squamous cell carcinoma of the external auditory canal. *Eur Arch Otorhinolaryngol* 2021;**278**:1355–64

951 Kunst H, Lavieille JP, Marres H. Squamous cell carcinoma of the temporal bone: results and management. *Otol Neurotol* 2008;**29**:549–52

952 Rosenthal EL, King T, McGrew BM, Carroll W, Magnuson JS, Wax MK. Evolution of a paradigm for free tissue transfer reconstruction of lateral temporal bone defects. *Head Neck* 2008;**30**:589–94

953 Hanasono MM, Silva AK, Yu P, Skoracki RJ, Sturgis EM, Gidley PW. Comprehensive management of temporal bone defects after oncologic resection. *Laryngoscope* 2012;**122**:2663–9

954 Zanoletti E, Marioni G, Franchella S, Lovato A, Giacomelli L, Martini A *et al.* Recurrent squamous cell carcinoma of the temporal bone: critical analysis of cases with a poor prognosis. *Am J Otolaryngol* 2015;**36**:352–5

955 Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD *et al.* PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med* 2018;**379**:341–51

956 Bertrand N, Guerreschi P, Basset-Seguin N, Saiag P, Dupuy A, Dalac-Rat S *et al.* Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: first results of a multicenter, open-label, phase 2 trial (VISMONEO study): neoadjuvant vismodegib in locally advanced basal cell carcinoma. *EClinicalMedicine* 2021;**35**:100844

957 Dutta R, Dubal PM, Svider PF, Liu JK, Baredes S, Eloy JA. Sinonasal malignancies: a population-based analysis of site-specific incidence and survival. *Laryngoscope* 2015;**125**:2491–7

958 Iyizoba-Ebozue Z, Fleming JC, Prestwich RJD, Thomson DJ. Management of sinonasal cancers: survey of UK practice and literature overview. *Eur J Surg Oncol* 2022;**48**:32–43

959 Binazzi A, Ferrante P, Marinaccio A. Occupational exposure and sinonasal cancer: a systematic review and meta-analysis. *BMC Cancer* 2015;**15**:49

960 Gilain L, Houette A, Montalban A, Mom T, Saroul N. Mucosal melanoma of the nasal cavity and paranasal sinuses. *Eur Ann Otorhinolaryngol Head Neck Dis* 2014;**131**:365–9

961 Thompson LDR, Bishop JA. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Nasal Cavity, Paranasal Sinuses and Skull Base. *Head Neck Pathol* 2022;**16**:1–18

962 Sharma A, Tang AL, Takiar V, Wise-Draper TM, Langevin SM. Human papillomavirus and survival of sinonasal squamous cell carcinoma patients: a systematic review and meta-analysis. *Cancers* (*Basel*) 2021;**13**:3677

963 Bell D, Hanna EY, Weber RS, DeMonte F, Triantafyllou A, Lewis JS Jr *et al.* Neuroendocrine neoplasms of the sinonasal region. *Head Neck* 2016;**38**(suppl 1):E2259–66

964 Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 8th edn. Chichester: John Wiley & Sons, 2016

965 Ohngren G. Malignant disease of the upper jaw: (section of laryngology and section of otology). *Proc R Soc Med* 1936;**29**:1497–514

966 Quan H, Yan L, Zhang H, Zou L, Yuan W, Wang S. Development and validation of a nomogram for prognosis of sinonasal squamous cell carcinoma. *Int Forum Allergy Rhinol* 2019;**9**:1030–40

967 Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. *Cancer* 1976;**37**:1571–6

968 Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. *Neurosurg* 1993;**32**:706–14; discussion 14–15

969 Wang CC. Treatment of carcinoma of the nasal vestibule by irradiation. *Cancer* 1976;**38**:100–6

970 Slevin F, Pan S, Mistry H, Denholm M, Shor D, Oong Z *et al.* A multicentre UK study of outcomes for locally advanced sinonasal squamous cell carcinoma treated with adjuvant or definitive intensity-modulated radiotherapy. *Clin Oncol* (*R Coll Radiol*) 2021;**33**:e450–61

971 Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001;**92**:3012–29

972 Agger A, von Buchwald C, Madsen AR, Yde J, Lesnikova I, Christensen CB *et al.* Squamous cell carcinoma of the nasal vestibule 1993-2002: a nationwide retrospective study from DAHANCA. *Head Neck* 2009;**31**:1593–9

973 Krouse JH. Development of a staging system for inverted papilloma. *Laryngoscope* 2000;**110**:965–8

974 Long C, Jabarin B, Harvey A, Ham J, Javer A, Janjua A *et al.* Clinical evidence based review and systematic scientific review in the identification of malignant transformation of inverted papilloma. *J Otolaryngol Head Neck Surg* 2020;**49**:25

975 Lisan Q, Laccourreye O, Bonfils P. Sinonasal inverted papilloma: from diagnosis to treatment. *Eur Ann Otorhinolaryngol Head Neck Dis* 2016;**133**:337–41

976 Naunheim MR, Goyal N, Dedmon MM, Chambers KJ, Sedaghat AR, Bleier BS *et al.* An algorithm for surgical approach to the anterior skull base. *J Neurol Surg B Skull Base* 2016;**77**:364–70

977 Nicolai P, Castelnuovo P, Lombardi D, Battaglia P, Bignami M, Pianta L *et al.* Role of endoscopic surgery in the management of selected malignant epithelial neoplasms of the naso-ethmoidal complex. *Head Neck* 2007;**29**:1075–82

978 Torabi SJ, Spock T, Cardoso B, Chao J, Morse E, Manes RP *et al.* Margins in sinonasal squamous cell carcinoma: predictors, outcomes, and the endoscopic approach. *Laryngoscope* 2020;**130**:E388–96

979 Iannetti G, Valentini V, Rinna C, Ventucci E, Marianetti TM. Ethmoido-orbital tumors: our experience. *J Craniofac Surg* 2005;**16**:1085–91

980 Muscatello L, Fortunato S, Seccia V, Marchetti M, Lenzi R. The implications of orbital invasion in sinonasal tract malignancies. *Orbit* 2016;**35**:278–84

981 Reyes C, Mason E, Solares CA, Bush C, Carrau R. To preserve or not to preserve the orbit in paranasal sinus neoplasms: a meta-analysis. *J Neurol Surg B Skull Base* 2015;**76**:122–8

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

982 Kamrava M, Lamb J, McCannel TA. Ocular complications of radiotherapy. In: Singh AD, Damato B, eds. *Clinical Ophthalmic Oncology: Basic Principles and Diagnostic Techniques*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2014;99–111

983 Jeannon JP, Riddle PJ, Irish J, O'Sullivan B, Brown DH, Gullane P. Prognostic indicators in carcinoma of the nasal vestibule. *Clin Otolaryngol* 2007;**32**:19–23

984 Filtenborg MV, Lilja-Fischer JK, Sharma MB, Primdahl H, Kjems J, Plaschke CC *et al*. Nasal vestibule squamous cell carcinoma: a population-based cohort study from DAHANCA. *Acta Oncol* 2022;**61**:127–33

985 Duru Birgi S, Teo M, Dyker KE, Sen M, Prestwich RJ. Definitive and adjuvant radiotherapy for sinonasal squamous cell carcinomas: a single institutional experience. *Radiat Oncol* 2015;**10**:190

986 Amit M, Abdelmeguid AS, Watcherporn T, Takahashi H, Tam S, Bell D *et al*. Induction chemotherapy response as a guide for treatment optimization in sinonasal undifferentiated carcinoma. *J Clin Oncol* 2019;**37**:504–12

987 Patel J, Chitguppi C, Vimawala S, Epps G, Fastenberg J, Evans J *et al*. Treatment-related morbidity in patients treated for sinonasal malignancy. *Int Forum Allergy Rhinol* 2020;**10**:526–32

988 Dagan R, Bryant C, Li Z, Yeung D, Justice J, Dzieglewiski P *et al*. Outcomes of sinonasal cancer treated with proton therapy. *Int J Radiat Oncol Biol Phys* 2016;**95**:377–85

989 Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol* 2009;**92**:4–14

990 Khoury T, Jang D, Carrau R, Ready N, Barak I, Hachem RA. Role of induction chemotherapy in sinonasal malignancies: a systematic review. *Int Forum Allergy Rhinol* 2019;**9**:212–19

991 Sangal NR, Lee YJ, Brady JS, Patel TD, Eloy JA, Baredes S *et al*. The role of elective neck dissection in the treatment of maxillary sinus squamous cell carcinoma. *Laryngoscope* 2018;**128**:1835–41

992 Paré A, Blanchard P, Rosellini S, Aupérin A, Gorphe P, Casiraghi O *et al*. Outcomes of multimodal management for sinonasal squamous cell carcinoma. *J Craniomaxillofac Surg* 2017;**45**:1124–32

993 Jeremic B, Nguyen-Tan PF, Bamberg M. Elective neck irradiation in locally advanced squamous cell carcinoma of the maxillary sinus: a review. *J Cancer Res Clin Oncol* 2002;**128**:235–8

994 Morand GB, Anderegg N, Vital D, Ikenberg K, Huber GF, Soyka MB *et al*. Outcome by treatment modality in sinonasal undifferentiated carcinoma (SNUC): a case-series, systematic review and meta-analysis. *Oral Oncol* 2017;**75**:28–34

995 de Gabory L, Maunoury A, Maurice-Tison S, Merza Abdulkhaleq H, Darrouzet V, Bébéar JP *et al*. Long-term single-center results of management of ethmoid adenocarcinoma: 95 patients over 28 years. *Ann Surg Oncol* 2010;**17**:1127–34

996 Lund VJ, Stammberger H, Nicolai P, Castelnuovo P, Beal T, Beham A *et al*. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. *Rhinol Suppl* 2010;**22**:1–143

997 Shay A, Ganti A, Raman A, Kuhar HN, Auger SR, Eggerstedt M *et al*. Survival in low-grade and high-grade sinonasal adenocarcinoma: a national cancer database analysis. *Laryngoscope* 2020;**130**:E1–10

998 Byrd JK, Clair JM, El-Sayed I. AHNS Series: do you know your guidelines? Principles for treatment of cancer of the paranasal sinuses: a review of the National Comprehensive Cancer Network guidelines. *Head Neck* 2018;**40**:1889–96

999 Schwartz JS, Brooks SG, Stubbs V, Ghosh A, Tajudeen BA, Khalili S *et al*. Temporal patterns of (18) F-fluorodeoxyglucose positron emission tomography/computed tomography sinonasal uptake after treatment of sinonasal malignancy. *Int Forum Allergy Rhinol* 2016;**6**:1301–7

1000 Kaplan DJ, Kim JH, Wang E, Snyderman C. Prognostic indicators for salvage surgery of recurrent sinonasal malignancy. *Otolaryngol Head Neck Surg* 2016;**154**:104–12

1001 Camp S, Van Gerven L, Poorten VV, Nuyts S, Hermans R, Hauben E *et al*. Long-term follow-up of 123 patients with adenocarcinoma of the sinonasal tract treated with endoscopic resection and postoperative radiation therapy. *Head Neck* 2016;**38**:294–300

1002 McGurk M, Renehan A. *Controversies in the Management of Salivary Gland Disease*. Oxford: Oxford University Press, 2001

1003 Wong DS. Signs and symptoms of malignant parotid tumours: an objective assessment. *J R Coll Surg Edinb* 2001;**46**:91–5

1004 Jones AV, Craig GT, Speight PM, Franklin CD. The range and demographics of salivary gland tumours diagnosed in a UK population. *Oral Oncol* 2008;**44**:407–17

1005 Munir N, Bradley PJ. Diagnosis and management of neoplastic lesions of the submandibular triangle. *Oral Oncol* 2008;**44**:251–60

1006 Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*, 3rd edn, vol 9. Lyon: IARC Press, 2005

1007 Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. *Head Neck Surg* 1986;**8**:177–84

1008 Alsanie I, Rajab S, Cottom H, Adegun O, Agarwal R, Jay A *et al*. Distribution and frequency of salivary gland tumours: an international multicenter study. *Head Neck Pathol* 2022;**16**:1043–54

1009 Jeong WJ, Park SJ, Cha W, Sung MW, Kim KH, Ahn SH. Fine needle aspiration of parotid tumors: diagnostic utility from a clinical perspective. *J Oral Maxillofac Surg* 2013;**71**:1278–82

1010 Diaz KP, Gerhard R, Domingues RB, Martins LL, Prado Ribeiro AC, Lopes MA *et al*. High diagnostic accuracy and reproducibility of fine-needle aspiration cytology for diagnosing salivary gland tumors: cytohistologic correlation in 182 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014;**118**:226–35

1011 Feinstein AJ, Alonso J, Yang SE, St John M. Diagnostic accuracy of fine-needle aspiration for parotid and submandibular gland lesions. *Otolaryngol Head Neck Surg* 2016;**155**:431–6

1012 Rossi ED, Baloch Z, Pusztaszeri M, Faquin WC. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC): an ASC-IAC-sponsored system for reporting salivary gland fine-needle aspiration. *J Am Soc Cytopathol* 2018;**7**:111–18

1013 Kim HJ, Kim JS. Ultrasound-guided core needle biopsy in salivary glands: a meta-analysis. *Laryngoscope* 2018;**128**:118–25

1014 Olsen KD, Moore EJ, Lewis JE. Frozen section pathology for decision making in parotid surgery. *JAMA Otolaryngol Head Neck Surg* 2013;**139**:1275–8

1015 Choy KCC, Bundele MM, Fu EW, Li H, Gan JYJ, Rao NCL *et al*. Risk stratification of parotid neoplasms based on intraoperative frozen section and preoperative fine needle aspiration cytology. *Eur Arch Otorhinolaryngol* 2022;**279**:2117–31

1016 Brierley JG, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumours*, 8th edn. Toronto: Wiley Blackwell, 2017

1017 Skálová A, Hyrcza MD, Leivo I. Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. *Head Neck Pathol* 2022;**16**:40–53

1018 Seethala RR. An update on grading of salivary gland carcinomas. *Head Neck Pathol* 2009;**3**:69–77

1019 Seethala RR. Histologic grading and prognostic biomarkers in salivary gland carcinomas. *Adv Anat Pathol* 2011;**18**:29–45

1020 Morse E, Fujiwara RJT, Judson B, Prasad ML, Mehra S. Positive surgical margins in parotid malignancies: institutional variation and survival association. *Laryngoscope* 2019;**129**:129–37

1021 Malik A, Devabalan Y, Bernstein J, Awad Z, Gujral D, Partridge S *et al*. Malignant salivary gland tumours: single-centre experience of 108 patients. *Clin Otolaryngol* 2021;**46**:1310–14

1022 Garden AS, Weber RS, Morrison WH, Ang KK, Peters LJ. The influence of positive margins and nerve invasion in adenoid cystic carcinoma of the head and neck treated with surgery and radiation. *Int J Radiat Oncol Biol Phys* 1995;**32**:619–26

1023 Iseli TA, Karnell LH, Preston TW, Graham SM, Funk GF, Buatti JM *et al*. Facial nerve sacrifice and radiotherapy in parotid adenoid cystic carcinoma. *Laryngoscope* 2008;**118**:1781–6

1024 Dos Santos ES, Rodrigues-Fernandes CI, Speight PM, Khurram SA, Alsanie I, Costa Normando AG *et al*. Impact of tumor site on the prognosis of salivary gland neoplasms: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2021;**162**:103352

1025 Ali S, Palmer FL, DiLorenzo M, Shah JP, Patel SG, Ganly I. Treatment of the neck in carcinoma of the parotid gland. *Ann Surg Oncol* 2014;**21**:3042–8

1026 Erovic BM, Shah MD, Bruch G, Johnston M, Kim J, O'Sullivan B *et al*. Outcome analysis of 215 patients with parotid gland tumors: a retrospective cohort analysis. *J Otolaryngol Head Neck Surg* 2015;**44**:43

1027 Valstar MH, van den Brekel MW, Smeele LE. Interpretation of treatment outcome in the clinically node-negative neck in primary parotid carcinoma: a systematic review of the literature. *Head Neck* 2010;**32**:1402–11

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

1028 Xiao CC, Zhan KY, White-Gilbertson SJ, Day TA. Predictors of nodal metastasis in parotid malignancies: a national cancer data base study of 22,653 patients. *Otolaryngol Head Neck Surg* 2016;**154**:121–30
1029 Westergaard-Nielsen M, Rosenberg T, Gerke O, Dyrvig AK, Godballe C, Bjorndal K. Elective neck dissection in patients with salivary gland carcinoma: a systematic review and meta-analysis. *J Oral Pathol Med* 2020;**49**:606–16
1030 Jinnin T, Kawata R, Higashino M, Nishikawa S, Terada T, Haginomori SI. Patterns of lymph node metastasis and the management of neck dissection for parotid carcinomas: a single-institute experience. *Int J Clin Oncol* 2019;**24**:624–31
1031 Cheraghlou S, Kuo P, Mehra S, Agogo GO, Bhatia A, Husain ZA *et al.* Adjuvant therapy in major salivary gland cancers: analysis of 8580 patients in the National Cancer Database. *Head Neck* 2018;**40**:1343–55
1032 Park GC, Cho KJ, Kang J, Roh JL, Choi SH, Kim SY *et al.* Relationship between histopathology of pleomorphic adenoma in the parotid gland and recurrence after superficial parotidectomy. *J Surg Oncol* 2012;**106**:942–6
1033 Miller LE, Au V, Mokhtari TE, Goss D, Faden DL, Varvares MA. A contemporary review of molecular therapeutic targets for adenoid cystic carcinoma. *Cancers* (*Basel*) 2022;**14**:992
1034 Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. *Cancer* 1984;**54**:1062–9
1035 Perzin KH, Gullane P, Clairmont AC. Adenoid cystic carcinomas arising in salivary glands: a correlation of histologic features and clinical course. *Cancer* 1978;**42**:265–82
1036 Li M, Dal Maso L, Vaccarella S. Global trends in thyroid cancer incidence and the impact of overdiagnosis. *Lancet Diabetes Endocrinol* 2020;**8**:468–70
1037 Craig WL, Smart L, Fielding S, Ramsay C, Krukowski ZH. Long term outcomes of simple clinical risk stratification in management of differentiated thyroid cancer. *Surgeon* 2018;**16**:283–91
1038 Scoazec JY, Couvelard A, Reseau T. Classification of pancreatic neuroendocrine tumours: changes made in the 2017 WHO classification of tumours of endocrine organs and perspectives for the future [in French]. *Ann Pathol* 2017;**37**:444–56
1039 Mitchell AL, Gandhi A, Scott-Coombes D, Perros P. Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**:S150–60
1040 Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G *et al.* Guidelines for the management of thyroid cancer. *Clin Endocrinol* (*Oxf*) 2014;**81**(suppl 1):1–122
1041 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE *et al.* 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;**26**:1–133
1042 NICE. Thyroid cancer: assessment and management: NICE guideline [NG230]. In: https://www.nice.org.uk/guidance/ng230 [18 May 2023]
1043 Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM *et al.* Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2015;**25**:716–59
1044 Yeh MW, Bauer AJ, Bernet VA, Ferris RL, Loevner LA, Mandel SJ *et al.* American Thyroid Association statement on preoperative imaging for thyroid cancer surgery. *Thyroid* 2015;**25**:3–14
1045 Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: the EU-TIRADS. *Eur Thyroid J* 2017;**6**:225–37
1046 Poller DN, Bongiovanni M, Trimboli P. Risk of malignancy in the various categories of the UK Royal College of Pathologists Thy terminology for thyroid FNA cytology: a systematic review and meta-analysis. *Cancer Cytopathol* 2020;**128**:36–42
1047 Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LD *et al.* Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol* 2016;**2**:1023–9
1048 Johnson S, Stephenson TJ, Poller DN. *NIFTP addendum to the RCPath Dataset for Thyroid Cancer Histopathology Reports*. London: Royal College of Pathologists, 2016
1049 Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): what changed and why? *Thyroid* 2017;**27**:751–6
1050 Yang F, Zhong Q, Huang Z, Lian M, Fang J. Survival in papillary thyroid microcarcinoma: a comparative analysis between the 7th and 8th versions of the AJCC/UICC staging system based on the SEER database. *Front Endocrinol* (*Lausanne*) 2019;**10**:10
1051 Chadwick D, Kinsman R, Walton P. *The British Association of Endocrine and Thyroid Surgeons Fifth National Audit Report*. Henley-on-Thames: Dendrite Clinical Systems, 2017;196
1052 Ito Y, Miyauchi A, Inoue H, Fukushima M, Kihara M, Higashiyama T *et al.* An observational trial for papillary thyroid microcarcinoma in Japanese patients. *World J Surg* 2010;**34**:28–35
1053 Tuttle RM, Fagin JA, Minkowitz G, Wong RJ, Roman B, Patel S *et al.* Natural history and tumor volume kinetics of papillary thyroid cancers during active surveillance. *JAMA Otolaryngol Head Neck Surg* 2017;**143**:1015–20
1054 Salem FA, Bergenfelz A, Nordenstrom E, Almquist M. Central lymph node dissection and permanent hypoparathyroidism after total thyroidectomy for papillary thyroid cancer: population-based study. *Br J Surg* 2021;**108**:684–90
1055 Shindo ML, Caruana SM, Kandil E, McCaffrey JC, Orloff LA, Porterfield JR *et al.* Management of invasive well-differentiated thyroid cancer: an American Head and Neck Society consensus statement. AHNS consensus statement. *Head Neck* 2014;**36**:1379–90
1056 Fundakowski CE, Hales NW, Agrawal N, Barczynski M, Camacho PM, Hartl DM *et al.* Surgical management of the recurrent laryngeal nerve in thyroidectomy: American Head and Neck Society Consensus Statement. *Head Neck* 2018;**40**:663–75
1057 Wang LY, Nixon IJ, Patel SG, Palmer FL, Tuttle RM, Shaha A *et al.* Operative management of locally advanced, differentiated thyroid cancer. *Surgery* 2016;**160**:738–46
1058 Palazzo F; BAETS. Pre and Post Operative Laryngoscopy in Thyroid and Parathyroid Surgery British Association of Endocrine and Thyroid Surgeons Consensus 2010. In: : https://www.baets.org.uk/wp-content/uploads/2020/09/Vocal-cord-check-consenus-document-2010.pdf [18 May 2023]
1059 Dehbi HM, Mallick U, Wadsley J, Newbold K, Harmer C, Hackshaw A. Recurrence after low-dose radioiodine ablation and recombinant human thyroid-stimulating hormone for differentiated thyroid cancer (HiLo): long-term results of an open-label, non-inferiority randomised controlled trial. *Lancet Diabetes Endocrinol* 2019;**7**:44–51
1060 Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M *et al.* Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid* 2010;**20**:1341–9
1061 Urken ML, Milas M, Randolph GW, Tufano R, Bergman D, Bernet V *et al.* Management of recurrent and persistent metastatic lymph nodes in well-differentiated thyroid cancer: a multifactorial decision-making guide for the Thyroid Cancer Care Collaborative. *Head Neck* 2015;**37**:605–14
1062 Scharpf J, Tuttle M, Wong R, Ridge D, Smith R, Hartl D *et al.* Comprehensive management of recurrent thyroid cancer: an American Head and Neck Society consensus statement: AHNS consensus statement. *Head Neck* 2016;**38**:1862–9
1063 Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. *Pediatrics* 2018;**142**:e20183062
1064 Wells SA Jr, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M *et al.* Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;**30**:134–41
1065 Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH *et al.* Cabozantinib in progressive medullary thyroid cancer. *J Clin Oncol* 2013;**31**:3639–46
1066 Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J *et al.* Efficacy of selpercatinib in RET-altered thyroid cancers. *N Engl J Med* 2020;**383**:825–35
1067 Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ Jr *et al.* 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. *Thyroid* 2021;**31**:337–86
1068 Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC *et al.* Dabrafenib and trametinib treatment in patients with locally

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. *J Clin Oncol* 2018;**36**:7–13
1069 Mallick U, Harmer C, Hackshaw A, Moss L, Io NTMG. Iodine or Not (IoN) for low-risk differentiated thyroid cancer: the next UK National Cancer Research Network randomised trial following HiLo. *Clin Oncol* (*R Coll Radiol*) 2012;**24**:159–61
1070 Hemithyroidectomy or Total-Thyroidectomy in 'low-risk' thyroid cancers (HoT trial). In: https://fundingawards.nihr.ac.uk/award/NIHR128699 [18 May 2023]
1071 Near Infrared Fluorescence (NIRF) Imaging to prevent Post-surgical Hypoparathyroidism (PoSH) after Thyroid Surgery (NIFTy) –preparatory qualitative work prior to a phase II/III pragmatic, multicentre randomised controlled trial. In: https://njl-admin.nihr.ac.uk/document/download/2033129 [18 May 2023]
1072 Sun J, Li B, Li CJ, Li Y, Su F, Gao QH *et al*. Computed tomography versus magnetic resonance imaging for diagnosing cervical lymph node metastasis of head and neck cancer: a systematic review and meta-analysis. *Onco Targets Ther* 2015;**8**:1291–313
1073 van der Kamp MF, Muntinghe FOW, Iepsma RS, Plaat BEC, van der Laan B, Algassab A *et al*. Predictors for distant metastasis in head and neck cancer, with emphasis on age. *Eur Arch Otorhinolaryngol* 2021;**278**:181–90
1074 National Institute for Health and Care Excellence. *Cancer of the Upper Aerodigestive Tract: Assessment and Management in People Aged 16 and Over (NG36)*. London: NICE, 2016
1075 Lowe VJ, Duan F, Subramaniam RM, Sicks JD, Romanoff J, Bartel T *et al*. Multicenter trial of [(18)F]fluorodeoxyglucose positron emission tomography/computed tomography staging of head and neck cancer and negative predictive value and surgical impact in the N0 neck: results from ACRIN 6685. *J Clin Oncol* 2019;**37**:1704–12
1076 Robbins KT, Shaha AR, Medina JE, Califano JA, Wolf GT, Ferlito A *et al*. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg* 2008;**134**:536–8
1077 Iyizoba-Ebozue Z, Murray LJ, Arunsingh M, Dyker KE, Vaidyanathan S, Scarsbrook AF *et al*. Retropharyngeal lymph node involvement in oropharyngeal carcinoma: impact upon risk of distant metastases and survival outcomes. *Cancers* (*Basel*) 2019;**12**:83
1078 Kim JH, Choi KY, Lee SH, Lee DJ, Park BJ, Yoon DY *et al*. The value of CT, MRI, and PET-CT in detecting retropharyngeal lymph node metastasis of head and neck squamous cell carcinoma. *BMC Med Imaging* 2020;**20**:88
1079 Batsakis JG. Pathology consultation. Parotid gland and its lymph nodes as metastatic sites. *Ann Otol Rhinol Laryngol* 1983;**92**:209–10
1080 Park SI, Guenette JP, Suh CH, Hanna GJ, Chung SR, Baek JH *et al*. The diagnostic performance of CT and MRI for detecting extranodal extension in patients with head and neck squamous cell carcinoma: a systematic review and diagnostic meta-analysis. *Eur Radiol* 2021;**31**:2048–61
1081 Ferlito A, Robbins KT, Shah JP, Medina JE, Silver CE, Al-Tamimi S *et al*. Proposal for a rational classification of neck dissections. *Head Neck* 2011;**33**:445–50
1082 Divi V, Harris J, Harari PM, Cooper JS, McHugh J, Bell D *et al*. Establishing quality indicators for neck dissection: correlating the number of lymph nodes with oncologic outcomes (NRG Oncology RTOG 9501 and RTOG 0234). *Cancer* 2016;**122**:3464–71
1083 Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage N0 neck. *Arch Otolaryngol Head Neck Surg* 1994;**120**:699–702
1084 Koyfman SA, Ismaila N, Crook D, D'Cruz A, Rodriguez CP, Sher DJ *et al*. Management of the neck in squamous cell carcinoma of the oral cavity and oropharynx: ASCO Clinical Practice Guideline. *J Clin Oncol* 2019;**37**:1753–74
1085 Dziegielewski PT, McNeely ML, Ashworth N, O'Connell DA, Barber B, Courneya KS *et al*. 2b or not 2b? Shoulder function after level 2b neck dissection: a double-blind randomized controlled clinical trial. *Cancer* 2020;**126**:1492–501
1086 Gross BC, Olsen SM, Lewis JE, Kasperbauer JL, Moore EJ, Olsen KD *et al*. Level IIB lymph node metastasis in laryngeal and hypopharyngeal squamous cell carcinoma: single-institution case series and review of the literature. *Laryngoscope* 2013;**123**:3032–6
1087 Gross BC, Olsen SM, Lewis JE, Kasperbauer JL, Moore EJ, Olsen KD *et al*. Level IIB lymph node metastasis in oropharyngeal squamous cell carcinoma. *Laryngoscope* 2013;**123**:2700–5
1088 Ferreli F, Festa BM, Costantino A, Malvezzi L, Colombo G, Spriano G *et al*. Prevalence of occult level 2b nodal metastases in cN0 squamous cell carcinoma of the oral cavity: a systematic review and meta-analysis. *Oral Oncol* 2021;**122**:105540
1089 van den Bosch S, Doornaert PAH, Dijkema T, Zwijnenburg EM, Verhoef LCG, Hoeben BAW *et al*. (18)F-FDG-PET/CT-based treatment planning for definitive (chemo)radiotherapy in patients with head and neck squamous cell carcinoma improves regional control and survival. *Radiother Oncol* 2020;**142**:107–14
1090 Carsuzaa F, Gorphe P, Vergez S, Malard O, Fakhry N, Righini C *et al*. Consensus on resectability in N3 head and neck squamous cell carcinomas: GETTEC recommendations. *Oral Oncol* 2020;**106**:104733
1091 Boros A, Blanchard P, Dade A, Gorphe P, Breuskin I, Even C *et al*. Outcomes in N3 head and neck squamous cell carcinoma and role of upfront neck dissection. *Laryngoscope* 2021;**131**:E846–50
1092 Du C, Blanchard P, Even C, Boros A, Gorphe P, Breuskin I *et al*. Induction chemotherapy followed by radiotherapy for N3 head and neck squamous cell carcinoma. *Head Neck* 2020;**42**:426–33
1093 Adams G, Porceddu SV, Pryor DI, Panizza B, Foote M, Rowan A *et al*. Outcomes after primary chemoradiotherapy for N3 (>6 cm) head and neck squamous cell carcinoma after an FDG-PET--guided neck management policy. *Head Neck* 2014;**36**:1200–6
1094 Zhong J, Sundersingh M, Dyker K, Currie S, Vaidyanathan S, Prestwich R, *et al*. Post-treatment FDG PET-CT in head and neck carcinoma: comparative analysis of 4 qualitative interpretative criteria in a large patient cohort. *Sci Rep* 2020;**10**:4086
1095 Robbins KT, Shannon K, Vieira F. Superselective neck dissection after chemoradiation: feasibility based on clinical and pathologic comparisons. *Arch Otolaryngol Head Neck Surg* 2007;**133**:486–9
1096 Zhou S, Chan C, Rulach R, Dyab H, Hendry F, Maxfield C *et al*. Long term survival in patients with human papillomavirus-positive oropharyngeal cancer and equivocal response on 12-week PET-CT is not compromised by the omission of neck dissection. *Oral Oncol* 2022;**128**:105870
1097 Costantino A, Mercante G, D'Ascoli E, Ferreli F, Di Tommaso L, Franzese C *et al*. Accuracy of fine-needle aspiration cytology in detecting cervical node metastasis after radiotherapy: systematic review and meta-analysis. *Head Neck* 2021;**43**:987–96
1098 Schouten CS, de Graaf P, Alberts FM, Hoekstra OS, Comans EF, Bloemena E *et al*. Response evaluation after chemoradiotherapy for advanced nodal disease in head and neck cancer using diffusion-weighted MRI and 18F-FDG-PET-CT. *Oral Oncol* 2015;**51**:541–7
1099 Lee JY, Garcia-Murillas I, Cutts RJ, De Castro DG, Grove L, Hurley T *et al*. Predicting response to radical (chemo)radiotherapy with circulating HPV DNA in locally advanced head and neck squamous carcinoma. *Br J Cancer* 2017;**117**:876–83
1100 de Veij Mestdagh PD, Walraven I, Vogel WV, Schreuder WH, van Werkhoven E, Carbaat C *et al*. SPECT/CT-guided elective nodal irradiation for head and neck cancer is oncologically safe and less toxic: a potentially practice-changing approach. *Radiother Oncol* 2020;**147**:56–63
1101 McDowell L, Casswell G, Bressel M, Gough K, Drosdowsky A, Coleman A *et al*. Patient-reported quality of life and toxicity in unilateral and bilateral radiotherapy for early-stage human papillomavirus associated tonsillar carcinoma. *Clin Transl Radiat Oncol* 2020;**21**:85–90
1102 Al-Mamgani A, van Rooij P, Fransen D, Levendag P. Unilateral neck irradiation for well-lateralized oropharyngeal cancer. *Radiother Oncol* 2013;**106**:69–73
1103 Taku N, Chronowski G, Brandon Gunn G, Morrison WH, Gross ND, Moreno AC *et al*. Unilateral radiation therapy for tonsillar cancer: treatment outcomes in the era of human papillomavirus, positron-emission tomography, and intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2022;**113**:1054–62
1104 Giger R, Fink R, Dematté M, Visini M, Elicin O, Anschuetz L. Outcome of salvage therapy in isolated regional recurrence in head and neck squamous cell carcinoma. *Laryngoscope* 2021;**131**:67–72
1105 Lindegaard AM, von Buchwald C, Rasmussen JH, Specht L, Vogelius IR, Zamani M *et al*. Outcome in patients with isolated regional recurrence after primary radiotherapy for head and neck cancer. *Head Neck* 2020;**42**:3161–70
1106 Chung EJ, Lee SH, Baek SH, Bae WJ, Chang YJ, Rho YS. Clinical outcome and prognostic factors after salvage surgery for isolated regional squamous cell carcinoma recurrences. *Head Neck* 2015;**37**:1612–17
1107 Chopra S, Gupta T, Agarwal JP, Budrukkar A, Ghosh-Laskar S, Dinshaw K. Re-irradiation in the management of isolated neck recurrences: current status and recommendations. *Radiother Oncol* 2006;**81**:1–8

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

1108 Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS *et al*. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol* 2008;**26**:3582–9
1109 Lin DJ, Lam A, Warner L, Paleri V. Elective neck dissection in patients with radio-recurrent and radio-residual squamous cell carcinoma of the larynx undergoing salvage total laryngectomy: systematic review and meta-analysis. *Head Neck* 2019;**41**:4026–35
1110 Davies-Husband CR, Drinnan M, King E. Elective neck dissection for salvage total laryngectomy: a systematic review, meta-analysis and "decision-to-treat" approach. *Clin Otolaryngol* 2020;**45**:558–73
1111 Mazerolle P, Gorphe P, Vairel B, Dupret-Bories A, Temam S, Chaltiel L *et al*. Management of the irradiated N0-neck during salvage pharyngolaryngeal surgery. *Eur J Surg Oncol* 2020;**46**:1059–65
1112 Mackenzie K, Watson M, Jankowska P, Bhide S, Simo R. Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol* 2016;**130**:S170–5
1113 Maghami E, Ismaila N, Alvarez A, Chernock R, Duvvuri U, Geiger J *et al*. Diagnosis and management of squamous cell carcinoma of unknown primary in the head and neck: ASCO guideline. *J Clin Oncol* 2020;**38**:2570–96
1114 INTEGRATE (The UK ENT Trainee Research Network). HNSCCUP Audit 2021: National Audit of the Management of Head & Neck Squamous Cell Carcinoma of Unknown Primary. In: https://entintegrate.co.uk/hnsccup [22 May 2023]
1115 National Institute for Health and Care Excellence. *Developing NICE Guidelines: The Manual [PMG20]*. London: NICE, 2020
1116 Di Maio P, Iocca O, De Virgilio A, Giudice M, Pellini R, D'Ascanio L *et al*. Narrow band imaging in head and neck unknown primary carcinoma: a systematic review and meta-analysis. *Laryngoscope* 2020;**130**:1692–700
1117 Robitschek J, Straub M, Wirtz E, Klem C, Sniezek J. Diagnostic efficacy of surgeon-performed ultrasound-guided fine needle aspiration: a randomized controlled trial. *Otolaryngol Head Neck Surg* 2010;**142**:306–9
1118 Licitra L, Keilholz U, Tahara M, Lin JC, Chomette P, Ceruse P *et al*. Evaluation of the benefit and use of multidisciplinary teams in the treatment of head and neck cancer. *Oral Oncol* 2016;**59**:73–9
1119 de Almeida JR. Role of transoral robotic surgery in the work-up of the unknown primary. *Otolaryngol Clin North Am* 2020;**53**:965–80
1120 Ozbay I, Yumusakhuylu AC, Sethia R, Wei L, Old M, Agrawal A *et al*. One-year quality of life and functional outcomes of transoral robotic surgery for carcinoma of unknown primary. *Head Neck* 2017;**39**:1596–602
1121 Pothier DD, Nankivell PC, Matthee W, Hunasaghatta S. The NPTA may have underestimated tonsillectomy complications: a case note review of data submitted by two hospitals. *Clin Otolaryngol* 2007;**32**:414–16
1122 Farooq S, Khandavilli S, Dretzke J, Moore D, Nankivell PC, Sharma N *et al*. Transoral tongue base mucosectomy for the identification of the primary site in the work-up of cancers of unknown origin: systematic review and meta-analysis. *Oral Oncol* 2019;**91**:97–106
1123 Winter SC, Ofo E, Meikle D, Silva P, Fraser L, O'Hara J *et al*. Trans-oral robotic assisted tongue base mucosectomy for investigation of cancer of unknown primary in the head and neck region. The UK experience. *Clin Otolaryngol* 2017;**42**:1247–51
1124 Cheraghlou S, Torabi SJ, Husain ZA, Otremba MD, Osborn HA, Mehra S *et al*. HPV status in unknown primary head and neck cancer: prognosis and treatment outcomes. *Laryngoscope* 2019;**129**:684–91
1125 Frank SJ, Rosenthal DI, Petsuksiri J, Ang KK, Morrison WH, Weber RS *et al*. Intensity-modulated radiotherapy for cervical node squamous cell carcinoma metastases from unknown head-and-neck primary site: M. D. Anderson Cancer Center outcomes and patterns of failure. *Int J Radiat Oncol Biol Phys* 2010;**78**:1005–10
1126 Hardman JC, Harrington K, Roques T, Sood S, Jose J, Lester S *et al*. Methodology for the development of National Multidisciplinary Management Recommendations using a multi-stage meta-consensus initiative. *BMC Med Res Methodol* 2022;**22**:189
1127 Office of National Statistics. *Cancer Registration Statistics, England*. London: ONS, 2015
1128 Kwiatkowska M, Ahmed S, Ardern-Jones M, Bhatti L, Bleiker T, Gavin A *et al*. A summary of the updated report on the incidence and epidemiological trends of keratinocyte cancers in the UK 2013–2018. *Br J Dermatol* 2022;**186**:367–9
1129 Keohane S, Botting J, Budny P, Dolan O, Fife K, Harwood C *et al*. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020. *Br J Dermatol* 2021;**184**:401–14
1130 Nasr I, McGrath E, Harwood C, Botting J, Buckley P, Budny P *et al*. British Association of Dermatologists guidelines for the management of adults with basal cell carcinoma 2021. *Br J Dermatol* 2021;**185**:899–920
1131 Guorgis G, Anderson CD, Lyth J, Falk M. Actinic keratosis diagnosis and increased risk of developing skin cancer: a 10-year cohort study of 17,651 patients in Sweden. *Acta Derm Venereol* 2020;**100**:adv00128
1132 Cox N, Eedy D, Morton C; Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists. Guidelines for management of Bowen's disease: 2006 update. *Br J Dermatol* 2007;**156**:11–21
1133 Sowter P, Santibanez-Koref M, Jackson MS, Borthwick GM, Burn J, Rajan N *et al*. Response to 'Cutaneous squamous cell carcinoma is associated with Lynch syndrome: widening the spectrum of Lynch syndrome-associated tumours'. *Br J Dermatol* 2022;**186**:913–14
1134 Tampa M, Mitran CI, Mitran MI, Nicolae I, Dumitru A, Matei C *et al*. The role of beta HPV types and HPV-associated inflammatory processes in cutaneous squamous cell carcinoma. *J Immunol Res* 2020;**2020**:5701639
1135 Spurgeon ME, Lambert PF. Merkel cell polyomavirus: a newly discovered human virus with oncogenic potential. *Virology* 2013;**435**:118–30
1136 Garneski KM, Warcola AH, Feng Q, Kiviat N, Leonard JH, Nghiem P. Merkel cell polyomavirus is more frequently present in North American than Australian Merkel cell carcinoma tumors. *J Invest Dermatol* 2009;**129**:246–8
1137 Goh G, Walradt T, Markarov V, Blom A, Riaz N, Doumani R *et al*. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. *Oncotarget* 2016;**7**:3403–15
1138 Califano JA, Lydiatt WM, Nehal KS, O'Sullivan B, Schmults C, Seethala RR. Cutaneous squamous cell carcinoma of the head and neck. In: Amin ME, Edge SB, Green FL, Byrd DR, Brookland RK, Washington MK *et al*., ed. *AJCC Cancer Staging Manual*. New York: Springer, 2017;171–81
1139 National Comprehensive Cancer Network. *NCCN Guidelines for Patients: Basal Cell Skin Cancer*. Plymouth Meeting, PA: NCCN, 2022
1140 National Institute for Health and Care Excellence. Improving outcomes for people with skin tumours including melanoma (update): The management of low-risk basal cell carcinomas in the community. In: https://www.nice.org.uk/guidance/csg8/evidence/2010-update-the-management-of-lowrisk-basal-cell-carcinomas-in-the-community-updated-recommendations-and-evidence-on-this-topic-only-pdf-7022614429 [24 May 2023]
1141 National Institute for Health and Care Excellence. Electrochemotherapy for primary basal cell carcinoma and primary squamous cell carcinoma (IPG 478). In: https://www.nice.org.uk/guidance/ipg478/resources/electrochemotherapy-for-primary-basal-cell-carcinoma-and-primary-squamous-cell-carcinoma-1899869938127557 [24 May 2023]
1142 National Cancer Drugs Fund List. In: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/ [24 May 2023]
1143 Venables ZC, Autier P, Nijsten T, Wong KF, Langan SM, Rous B *et al*. Nationwide incidence of metastatic cutaneous squamous cell carcinoma in England. *JAMA Dermatol* 2019;**155**:298–306
1144 Khan K, Mykula R, Kerstein R, Rabey N, Bragg T, Crick A *et al*. A 5-year follow-up study of 633 cutaneous SCC excisions: rates of local recurrence and lymph node metastasis. *J Plast Reconstr Aesthet Surg* 2018;**71**:1153–8
1145 Brennan C, Kelemen N, Matteucci P. Continuing to establish the relationship between anatomical location of cutaneous head and neck melanoma primaries and locoregional sites of metastasis: a consideration of a new anatomical site, drainage to multiple and non-adjacent neck levels, and the impact on the selectivity of neck dissection. *J Plast Reconstr Aesthet Surg* 2021;**74**:3443–76
1146 Vauterin TJ, Veness MJ, Morgan GJ, Poulsen MG, O'Brien CJ. Patterns of lymph node spread of cutaneous squamous cell carcinoma of the head and neck. *Head Neck* 2006;**28**:785–91
1147 Veness MJ, Porceddu S, Palme CE, Morgan GJ. Cutaneous head and neck squamous cell carcinoma metastatic to parotid and cervical lymph nodes. *Head Neck* 2007;**29**:621–31
1148 Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM *et al*. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol* 2018;**36**:1275–83
1149 National Institute for Health and Care Excellence. Cemiplimab for treating metastatic or locally advanced cutaneous squamous cell carcinoma [TA592]. In: https://www.nice.org.uk/guidance/ta592 [24 May 2023]
1150 Gross N, Ferrarotto R, Nagarajan P, Bell D, El-Naggar A, Johnson J *et al.* Phase II study of neoadjuvant cemiplimab prior to surgery in patients with stage III/IV (M0) cutaneous squamous cell carcinoma of the head and neck (CSCC-HN). *Ann Oncol* 2019;**30**:v910
1151 Yusuf MB, McKenzie G, Rattani A, Tennant P, Bumpous J, Miller D *et al.* Merkel cell carcinoma of the head and neck: epidemiology, pathogenesis, current state of treatment and future directions. *Cancers* (*Basel*) 2021;**13**:3506
1152 Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R *et al.* Merkel Cell Carcinoma, Version 1.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2018;**16**:742–74
1153 López F, Rodrigo JP, Cardesa A, Triantafyllou A, Devaney KO, Mendenhall WM *et al.* Update on primary head and neck mucosal melanoma. *Head Neck* 2016;**38**:147–55
1154 Tyrrell H, Payne M. Combatting mucosal melanoma: recent advances and future perspectives. *Melanoma Manag* 2018;**5**:MMT11
1155 Ascierto PA, Accorona R, Botti G, Farina D, Fossati P, Gatta G *et al.* Mucosal melanoma of the head and neck. *Crit Rev Oncol Hematol* 2017;**112**:136–52
1156 Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. *J Am Acad Dermatol* 2007;**56**:828–34
1157 Holmstrom M, Lund VJ. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. *Br J Ind Med* 1991;**48**:9–11
1158 Reuter VE, Woodruff JM. Melanoma of the larynx. *Laryngoscope* 1986;**96**:389–93
1159 Bachar G, Loh KS, O'Sullivan B, Goldstein D, Wood S, Brown D *et al.* Mucosal melanomas of the head and neck: the Princess Margaret Hospital experience. *Head Neck* 2008;**30**:1325–31
1160 Paleri V, Kerawala C, Winter S, Robinson M, Jarrom D, Prettyjohns M *et al.* Upper aerodigestive tract cancer: summary of the National Institute for Health and Care Excellence guidelines for England and Wales. *Clin Otolaryngol* 2017;**42**:3–10
1161 Crawford RI, Tron VA, Ma R, Rivers JK. Sinonasal malignant melanoma--a clinicopathologic analysis of 18 cases. *Melanoma Res* 1995;**5**:261–5
1162 Letievant JC, Poupart M, Ambrun A, Colin C, Pignat JC. Single-center retrospective series of fourteen patients with mucosal melanoma of the nasal cavity and paranasal sinuses. *Eur Ann Otorhinolaryngol Head Neck Dis* 2016;**133**:387–91
1163 McLean N, Tighiouart M, Muller S. Primary mucosal melanoma of the head and neck. Comparison of clinical presentation and histopathologic features of oral and sinonasal melanoma. *Oral Oncol* 2008;**44**:1039–46
1164 Guevara-Canales JO, Gutiérrez-Morales MM, Sacsaquispe-Contreras SJ, Sánchez-Lihón J, Morales-Vadillo R. Malignant melanoma of the oral cavity. Review of the literature and experience in a Peruvian Population. *Med Oral Patol Oral Cir Bucal* 2012;**17**:e206–11
1165 Wenig BM. Laryngeal mucosal malignant melanoma. A clinicopathologic, immunohistochemical, and ultrastructural study of four patients and a review of the literature. *Cancer* 1995;**75**:1568–77
1166 Moreno MA, Roberts DB, Kupferman ME, DeMonte F, El-Naggar AK, Williams M *et al.* Mucosal melanoma of the nose and paranasal sinuses, a contemporary experience from the M. D. Anderson Cancer Center. *Cancer* 2010;**116**:2215–23
1167 Meleti M, Leemans CR, Mooi WJ, Vescovi P, van der Waal I. Oral malignant melanoma: a review of the literature. *Oral Oncol* 2007;**43**:116–21
1168 Yde SS, Sjoegren P, Heje M, Stolle LB. Mucosal melanoma: a literature review. *Curr Oncol Rep* 2018;**20**:28
1169 Brierley JG, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours*. Toronto: Wiley Blackwell, 2017
1170 Konuthula N, Khan MN, Parasher A, Del Signore A, Genden EM, Govindaraj S *et al.* The presentation and outcomes of mucosal melanoma in 695 patients. *Int Forum Allergy Rhinol* 2017;**7**:99–105
1171 Heppt MV, Roesch A, Weide B, Gutzmer R, Meier F, Loquai C *et al.* Prognostic factors and treatment outcomes in 444 patients with mucosal melanoma. *Eur J Cancer* 2017;**81**:36–44
1172 Sayed Z, Migliacci JC, Cracchiolo JR, Barker CA, Lee NY, McBride SM *et al.* Association of surgical approach and margin status with oncologic outcomes following gross total resection for sinonasal melanoma. *JAMA Otolaryngol Head Neck Surg* 2017;**143**:1220–7
1173 Amit M, Na'ara S, Hanna EY. Contemporary treatment approaches to sinonasal mucosal melanoma. *Curr Oncol Rep* 2018;**20**:10
1174 Li W, Yu Y, Wang H, Yan A, Jiang X. Evaluation of the prognostic impact of postoperative adjuvant radiotherapy on head and neck mucosal melanoma: a meta-analysis. *BMC Cancer* 2015;**15**:758
1175 Jarrom D, Paleri V, Kerawala C, Roques T, Bhide S, Newman L *et al.* Mucosal melanoma of the upper airways tract mucosal melanoma: a systematic review with meta-analyses of treatment. *Head Neck* 2017;**39**:819–25
1176 Wushou A, Hou J, Zhao Y-J, Miao X-C. Postoperative adjuvant radiotherapy improves loco-regional recurrence of head and neck mucosal melanoma. *J Craniomaxillofac Surg* 2015;**43**:553–8
1177 Hu R, Yang BB. Surgery alone versus post-operative radiotherapy for sinonasal malignant melanoma: a meta-analysis. *J Laryngol Otol* 2018;**132**:1051–60
1178 Amit M, Tam S, Abdelmeguid AS, Roberts DB, Raza SM, Su SY *et al.* Approaches to regional lymph node metastasis in patients with head and neck mucosal melanoma. *Cancer* 2018;**124**:514–20
1179 Oldenburg MS, Price DL. The utility of sentinel node biopsy for sinonasal melanoma. *J Neurol Surg B Skull Base* 2017;**78**:425–9
1180 Wu Y, Zhong Y, Li C, Song H, Guo W, Ren G. Neck dissection for oral mucosal melanoma: caution of nodular lesion. *Oral Oncol* 2014;**50**:319–24
1181 Nenclares P, Ap Dafydd D, Bagwan I, Begg D, Kerawala C, King E *et al.* Head and neck mucosal melanoma: the United Kingdom national guidelines. *Eur J Cancer* 2020;**138**:11–18
1182 Griffin M, Scotto D, Josephs DH, Mele S, Crescioli S, Bax HJ *et al.* BRAF inhibitors: resistance and the promise of combination treatments for melanoma. *Oncotarget* 2017;**8**:78174–92
1183 Karoulia Z, Gavathiotis E, Poulikakos PI. New perspectives for targeting RAF kinase in human cancer. *Nat Rev Cancer* 2017;**17**:676–91
1184 Öztürk Sari Ş, Yilmaz İ, Taşkin O, Narli G, Şen F, Çomoğlu Ş *et al.* BRAF, NRAS, KIT, TERT, GNAQ/GNA11 mutation profile analysis of head and neck mucosal melanomas: a study of 42 cases. *Pathology* 2017;**49**:55–61
1185 Lyu J, Wu Y, Li C, Wang R, Song H, Ren G *et al.* Mutation scanning of BRAF, NRAS, KIT, and GNAQ/GNA11 in oral mucosal melanoma: a study of 57 cases. *J Oral Pathol Med* 2016;**45**:295–301
1186 D'Angelo SP, Larkin J, Sosman JA, Lebbé C, Brady B, Neyns B *et al.* Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. *J Clin Oncol* 2017;**35**:226–35
1187 Apetoh L, Ladoire S, Coukos G, Ghiringhelli F. Combining immunotherapy and anticancer agents: the right path to achieve cancer cure? *Ann Oncol* 2015;**26**:1813–23
1188 Williams MD, Tischler AS. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Paragangliomas. *Head Neck Pathol* 2017;**11**:88–95
1189 Asa SL, La Rosa S, Mete O. *The Spectrum of Neuroendocrine Neoplasia: A Practical Approach to Diagnosis, Classification and Therapy*. Sham: Springer, 2021
1190 Valero C, Ganly I, Shah JP. Head and neck paragangliomas: 30-year experience. *Head Neck* 2020;**42**:2486–95
1191 Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, 8th edn. Hoboken, NJ: Wiley Blackwell, 2016
1192 Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of (68) Ga-DOTA-conjugated somatostatin receptor-targeting peptide PET in detection of pheochromocytoma and paraganglioma: a systematic review and metaanalysis. *J Nucl Med* 2019;**60**:369–76
1193 Shamblin WR, ReMine WH, Sheps SG, Harrison EG Jr. Carotid body tumor (chemodectoma). Clinicopathologic analysis of ninety cases. *Am J Surg* 1971;**122**:732–9
1194 Luna-Ortiz K, Rascon-Ortiz M, Villavicencio-Valencia V, Herrera-Gomez A. Does Shamblin's classification predict postoperative morbidity in carotid body tumors? A proposal to modify Shamblin's classification. *Eur Arch Otorhinolaryngol* 2006;**263**:171–5
1195 Mehanna H, Mistry P, Golusinski P, Di Maio P, Nankivell P, Snider F *et al.* Development and validation of an improved classification and risk stratification system for carotid body tumors: multinational collaborative cohort study. *Head Neck* 2021;**43**:3448–58
1196 Lloyd S, Obholzer R, Tysome J. British Skull Base Society Clinical Consensus Document on Management of Head and Neck Paragangliomas. *Otolaryngol Head Neck Surg* 2020;**163**:400–9
1197 NHS England. National Genomic Test Directory. In: https://www.england.nhs.uk/publication/national-genomic-test-directories/ [26 May 2023]

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press

1198 Ricketts CJ, Forman JR, Rattenberry E, Bradshaw N, Lalloo F, Izatt L *et al.* Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. *Hum Mutat* 2010;**31**:41–51
1199 Bayley JP, Oldenburg RA, Nuk J, Hoekstra AS, van der Meer CA, Korpershoek E *et al.* Paraganglioma and pheochromocytoma upon maternal transmission of SDHD mutations. *BMC Med Genet* 2014;**15**:111
1200 Andrews KA, Ascher DB, Pires DEV, Barnes DR, Vialard L, Casey RT *et al.* Tumour risks and genotype-phenotype correlations associated with germline variants in succinate dehydrogenase subunit genes SDHB, SDHC and SDHD. *J Med Genet* 2018;**55**:384–94
1201 Burnichon N, Rohmer V, Amar L, Herman P, Leboulleux S, Darrouzet V *et al.* The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. *J Clin Endocrinol Metab* 2009;**94**:2817–27
1202 Williams ST, Chatzikyriakou P, Carroll PV, McGowan BM, Velusamy A, White G *et al.* SDHC phaeochromocytoma and paraganglioma: a UK-wide case series. *Clin Endocrinol* (*Oxf*) 2022;**96**:499–512
1203 Jansen TTG, Timmers H, Marres HAM, Kunst HPM. Feasibility of a wait-and-scan period as initial management strategy for head and neck paraganglioma. *Head Neck* 2017;**39**:2088–94
1204 Lieberson RE, Adler JR, Soltys SG, Choi C, Gibbs IC, Chang SD. Stereotactic radiosurgery as the primary treatment for new and recurrent paragangliomas: is open surgical resection still the treatment of choice? *World Neurosurg* 2012;**77**:745–61
1205 Suárez C, Rodrigo JP, Bödeker CC, Llorente JL, Silver CE, Jansen JC *et al.* Jugular and vagal paragangliomas: systematic study of management with surgery and radiotherapy. *Head Neck* 2013;**35**:1195–204
1206 Suárez C, Rodrigo JP, Mendenhall WM, Hamoir M, Silver CE, Grégoire V *et al.* Carotid body paragangliomas: a systematic study on management with surgery and radiotherapy. *Eur Arch Otorhinolaryngol* 2014;**271**:23–34
1207 Persky MS, Hu KS. Paragangliomas of the head and neck. In: Harrison LB, Hong WK, Sessions RB, eds. *Head and Neck Cancer: A Multi-disciplinary Approach*, 3rd edn. Philadelphia: Lippincott Williams & Wilkins, 2009;655–87
1208 Lalwani AK, Jackler RK, Gutin PH. Lethal fibrosarcoma complicating radiation therapy for benign glomus jugulare tumor. *Am J Otol* 1993;**14**:398–402
1209 Springate SC, Weichselbaum RR. Radiation or surgery for chemodectoma of the temporal bone: a review of local control and complications. *Head Neck* 1990;**12**:303–7
1210 Muracciole X, Régis J. Radiosurgery and carcinogenesis risk. *Prog Neurol Surg* 2008;**21**:207–13
1211 White JB, Link MJ, Cloft HJ. Endovascular embolization of paragangliomas: a safe adjuvant to treatment. *J Vasc Interv Neurol* 2008;**1**:37–41
1212 Helal A, Vakharia K, Brinjikji W, Carlson ML, Driscoll CL, Van Gompel JJ *et al.* Preoperative embolization of jugular paraganglioma tumors using particles is safe and effective. *Interv Neuroradiol* 2022;**28**:145–51
1213 Texakalidis P, Charisis N, Giannopoulos S, Xenos D, Rangel-Castilla L, Tassiopoulos AK *et al.* Role of preoperative embolization in carotid body tumor surgery: a systematic review and meta-analysis. *World Neurosurg* 2019;**129**:503–13.e2
1214 Robertson V, Poli F, Hobson B, Saratzis A, Ross Naylor A. A systematic review and meta-analysis of the presentation and surgical management of patients with carotid body tumours. *Eur J Vasc Endovasc Surg* 2019;**57**:477–86
1215 Prasad SC, Laus M, Al-Ghamdi S, Vashishth A, Piazza P, Sanna M. Update in the classification and the role of intra-arterial stenting in the management of carotid body paragangliomas. *Head Neck* 2019;**41**:1379–86
1216 Smith JJ, Passman MA, Dattilo JB, Guzman RJ, Naslund TC, Netterville JL. Carotid body tumor resection: does the need for vascular reconstruction worsen outcome? *Ann Vasc Surg* 2006;**20**:435–9
1217 Sevil FC. Management and outcomes of vascular reconstruction in carotid body tumor resection: retrospective analysis of 60 cases. *Eur Arch Otorhinolaryngol* 2020;**277**:2299–306
1218 Vogel TR, Mousa AY, Dombrovskiy VY, Haser PB, Graham AM. Carotid body tumor surgery: management and outcomes in the nation. *Vasc Endovascular Surg* 2009;**43**:457–61
1219 Cass ND, Schopper MA, Lubin JA, Fishbein L, Gubbels SP. The changing paradigm of head and neck paragangliomas: what every otolaryngologist needs to know. *Ann Otol Rhinol Laryngol* 2020;**129**:1135–43
1220 Challis BG, Casey RT, Simpson HL, Gurnell M. Is there an optimal preoperative management strategy for phaeochromocytoma/paraganglioma? *Clin Endocrinol* (*Oxf*) 2017;**86**:163–7
1221 Kotelis D, Rizos T, Geisbüsch P, Attigah N, Ringleb P, Hacke W *et al.* Late outcome after surgical management of carotid body tumors from a 20-year single-center experience. *Langenbecks Arch Surg* 2009;**394**:339–44
1222 Chen Y, Li Y, Liu J, Yang L. The clinical characteristics and outcomes of carotid body tumors in Chinese patients: a STROBE-compliant observational study. *Medicine* (*Baltimore*) 2020;**99**:e18824
1223 Hinerman RW, Amdur RJ, Morris CG, Kirwan J, Mendenhall WM. Definitive radiotherapy in the management of paragangliomas arising in the head and neck: a 35-year experience. *Head Neck* 2008;**30**:1431–8
1224 Wanna GB, Sweeney AD, Carlson ML, Latuska RF, Rivas A, Bennett ML *et al.* Subtotal resection for management of large jugular paragangliomas with functional lower cranial nerves. *Otolaryngol Head Neck Surg* 2014;**151**:991–5
1225 Wanna GB, Sweeney AD, Haynes DS, Carlson ML. Contemporary management of jugular paragangliomas. *Otolaryngol Clin North Am* 2015;**48**:331–41
1226 Hu K, Persky MS. The multidisciplinary management of paragangliomas of the head and neck, Part 2. *Oncology* (*Williston Park*) 2003;**17**:1143–53; discussion 54, 58, 61
1227 Hu K, Persky MS. Multidisciplinary management of paragangliomas of the head and neck, Part 1. *Oncology* (*Williston Park*) 2003;**17**:983–93
1228 Pacheco-Ojeda L. Malignant carotid body tumors: report of three cases. *Ann Otol Rhinol Laryngol* 2001;**110**:36–40
1229 Ayala-Ramirez M, Feng L, Habra MA, Rich T, Dickson PV, Perrier N *et al.* Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. *Cancer* 2012;**118**:2804–12
1230 Niemeijer ND, Alblas G, van Hulsteijn LT, Dekkers OM, Corssmit EP. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol* (*Oxf*) 2014;**81**:642–51
1231 Kong G, Grozinsky-Glasberg S, Hofman MS, Callahan J, Meirovitz A, Maimon O *et al.* Efficacy of peptide receptor radionuclide therapy for functional metastatic paraganglioma and pheochromocytoma. *J Clin Endocrinol Metab* 2017;**102**:3278–87
1232 Hadoux J, Favier J, Scoazec JY, Leboulleux S, Al Ghuzlan A, Caramella C *et al.* SDHB mutations are associated with response to temozolomide in patients with metastatic pheochromocytoma or paraganglioma. *Int J Cancer* 2014;**135**:2711–20

https://doi.org/10.1017/S0022215123001615 Published online by Cambridge University Press