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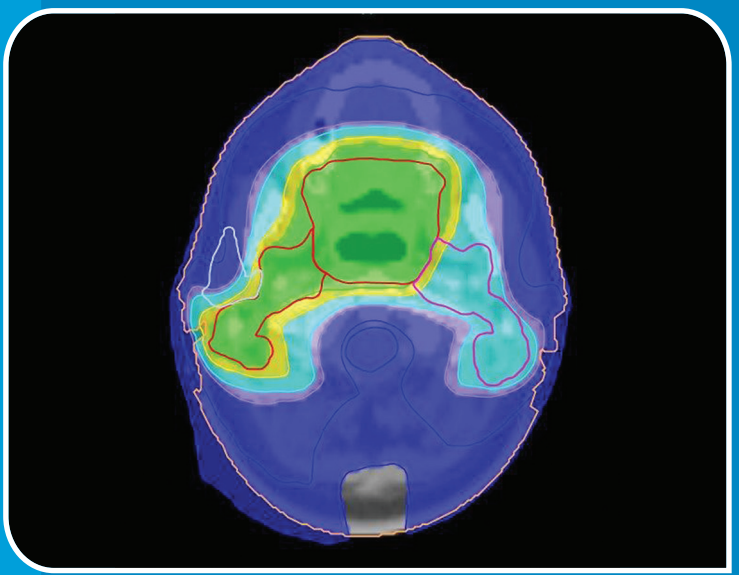
Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines

Edited by Vinidh Paleri and Nick Roland



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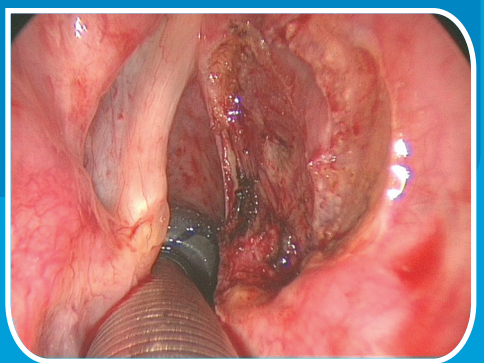

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Head and Neck Cancer:

United Kingdom National Multidisciplinary Guidelines

Edited by:

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FOREWORD

On behalf of the British Association of Endocrine and Thyroid Surgeons, it is a pleasure to endorse this multidisciplinary document. BAETS represents surgeons who have developed particular expertise in thyroid surgery, regardless of the specialty in which they originally trained. The inclusion of thyroid cancer with upper airway cancers is pragmatic because they share some common features clinically at presentation, particularly the presence of a 'lump' in the neck. The most recent British Thyroid Association guidelines for the treatment of thyroid cancer cover the investigation and management of thyroid cancer in depth. BAETS maintains a huge database of outcomes after surgery of the thyroid, both benign and malignant. This satisfies the requirement for surgeons to collect data in line with the requirements of HQIP.

Mark Lansdown BSc, MBBCh, MCh, FRCS
President
British Association of Endocrine and Thyroid Surgeons

The United Kingdom is a major player in clinical and basic science research into head and neck cancer, but trying to compare treatment methods is fraught with difficulty, and therefore evidence for one treatment over another is scarce. Due to the complexity and rarity of head and neck cancer, it has always been very difficult to decide what the best treatment is as there are multiple elements to the management.

In 2011, two brave souls decided that the time was right to pull together the great and the good to produce a UK Multidisciplinary Consensus Guideline for Head and Neck Oncology, in an attempt to establish best practice.

This has been the benchmark document for the management head and neck cancer in the UK on which to base our MDT decisions. It was and continues to be truly multidisciplinary.

Over time, treatments are evaluated, so in light of the advances made in radiotherapy delivery and chemotherapeutic options, as well as new technologies e.g. transoral robotic surgery, the time is right to relook at these guidelines and update them,

The British Association of Head and Neck Oncologists represents the multidisciplinary head and neck community within the UK, so as President, I offer once again the grateful thanks of our association to both the editors and the many contributing authors for their tireless efforts in compiling and publishing this essential set of clinical guidelines.

Michael Fardy FFDRCSI, FDSRCS, FRCS
President
British Association of Head and Neck Oncologists

Guidelines are an essential part of the process of ensuring appropriate treatment is available and provided for patients unfortunate enough to be given a diagnosis of a head and neck malignancy. There is a need to make sure that these guidelines are regularly updated so that our interventions remain up to date and effective, and I am pleased that this has already taken place. As a maxillofacial head and neck surgeon I have seen many changes and improvements, but teamwork, respect and co-operation with colleagues to smooth the patient journey are paramount and have greatly improved. The Liverpool group was lucky enough to have the opportunity to host the European Congress on Head and Neck Oncology in 2014, and demonstrate the high level of team-working in the clinical and research arena. The average head and neck cancer patient has a rocky path to tread, and there is no doubt that such a publication available to all will help them along the way.

Professor James S Brown MD FRCS FDSRCS
President
British Association of Oral and Maxillofacial Surgeons

It is a privilege to write a foreword for this superb document. Once again our head and neck colleagues have demonstrated great collegiality and teamwork to produce an outstanding consensus document. It is also remarkably user friendly and I am sure will provide a superb clinical resource for the benefit of our patients. This approach along with improved

data collection and analysis will help keep British surgery at the forefront of care for many years ahead.

Professor Antony A Narula MA MB BChir FRCS FRCS (Ed)
President
British Association of Otorhinolaryngology-Head & Neck Surgery

It is fascinating to compare these excellent, updated guidelines with the old version. Doing so unfolds a story of true multidisciplinary care leading to improved patient outcomes, where each individual in a team knows that they cannot function without the others, and that everyone has skills and strengths to add to the whole for the benefit of the patient under the team's care. As a result of that multidisciplinary care, the treatment of head and neck cancer has changed very much for the better in the last two decades, and I commend those involved in treating these patients for their dedication. In particular, the head and neck surgeons deserve praise for being first on board the National Flap Register, which is a testament to their desire to continuously improve care and outcomes for this complex and heterogenous patient population. Congratulations to all!

Mr Nigel Mercer FRCS
President, 2015–2016
British Association of Plastic, Reconstructive and Aesthetic Surgeons

The Royal College of Pathologists is delighted to endorse this publication and I would like to take the opportunity to thank the authors and editors for all their hard work, particularly Professor Helliwell and Dr Giles, who contributed the pathology content. Members of all the contributing specialties are to be congratulated on the degree of collaboration and consensus reached and the high quality of the resulting document. The latest version of these comprehensive guidelines will support multidisciplinary teams working in head and neck cancer and help them provide the best possible outcome for patients. Additions since the last edition include recent advances in molecular pathology, particularly the development of molecular evaluation for viral-induced cancers. Such quality-assured pathology guidance provides reassurance to clinical teams that pathology information is based on good evidence and has the confidence of pathologists across the UK. Congratulations on an excellent document, which I'm sure will be welcomed by members of all specialties working in this area.

Suzy Lishman FRCPath
President
The Royal College of Pathologists

On behalf of The Royal College of Radiologists I very much welcome the updating of these important multidisciplinary guidelines for head and neck cancer. They provide a valuable resource for all those across many specialties who are involved in the treatment of patients with head and neck cancer and they should continue to be essential reading. The guidelines cover all aspects of head and neck cancer management, from epidemiology and diagnosis through to treatment and outcomes, and I commend the editors and authors – a number of whom are Fellows of the RCR – for this tremendous body of work. I hope this new edition will continue to encourage and support multidisciplinary working and thereby help to improve patient care and ensure the highest possible standards are achieved and maintained.

Dr Giles Maskell
President
The Royal College of Radiologists

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GUIDELINE

Introduction to the United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer

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Abstract

This is the 5th edition of the UK Multi-Disciplinary Guidelines for Head and Neck Cancer, endorsed by seven national specialty associations involved in head and neck cancer care. Our aim is to provide a document can be used as a ready reference for multidisciplinary teams and a concise easy read for trainees. All evidence based recommendations in this edition are indicated by '(R)' and where the multidisciplinary team of authors consider a recommendation to be based on clinical experience, it is denoted by '(G)' as a good practice point.

It is an enormous privilege and a great pleasure to introduce the 5th edition of the UK Multi-Disciplinary Guidelines for Head and Neck Cancer. Akin to the 4th edition,[1] each aspect of the guideline has been developed by an expert team, often multidisciplinary. An affirmation of the true multidisciplinary nature of these guidelines is the endorsement by seven medical specialty organisations involved in head and neck cancer care in the UK: British Association of Endocrine and Thyroid Surgeons, British Association of Head and Neck Oncologists, British Association of Oral and Maxillofacial Surgeons, British Association of Otorhinolaryngology-Head and Neck Surgery, British Association of Plastic, Reconstructive and Aesthetic Surgeons, The Royal College of Pathologists and The Royal College of Radiologists (Faculty of Clinical Oncology). The guidelines will be of interest across the spectrum of healthcare professionals who look after patients with Head and Neck Cancer.

Our aim was to produce multidisciplinary consensus recommendations on the management of Head and Neck cancer based on the expertise and experience invested within the UK-based international experts and their appraisal of the current evidence. The remit of these guidelines is to provide evidence-based recommendations that will help identify an optimal management strategy. It should be appreciated that the ultimate decision for the management should rest with the multidisciplinary team, which takes into account all clinical data pertaining to the patient and his or her own social circumstances and individual preferences.

In contrast to the 4th edition, we have migrated away from the Scottish Intercollegiate Guidelines Network (SIGN) grading of recommendations. In 2013, SIGN abandoned its ABCD grading method[2] as it became evident that not all research would fit within the constraints of this system. Scottish Intercollegiate Guidelines Network has since adopted the system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[3] Having studied the GRADE methodology in detail, we concluded that a guideline such as this, generated by a multidisciplinary group of practising clinicians, simply did not possess the resources and the time to use the GRADE methodology. Similar to some of the more recent SIGN guidelines, all evidence-based recommendations in this edition come without a grade attached, indicated by '(R)' and where the multidisciplinary team of authors consider a recommendation to be based on clinical experience, it is denoted as a good practice point '(G)'.

The 5th edition will again provide a robust clinical document, which can be used as a ready reference. and a concise easy read for trainees and all involved in Head and Neck cancer care. In conjunction with the upper aerodigestive tract cancer guidelines published recently by the National Institute for Health and Care Excellence,[4] the recommendations across these two publications should improve the care provided to this complex disease. The tremendous amount of work put in by the authors is being recognised by individually indexed publications; however, we would recommend that readers use this supplement in the Journal of Laryngology and Otology as a single document owing to the cross-referencing within it. We are confident that the publication of the 5th edition as a

journal supplement will enhance readership and facilitate greater dissemination across the Head and Neck community.

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2 Scottish Intercollegiate Guidelines Network (SIGN). Methodological principles. http://www.sign.ac.uk/methodology/index.html (accessed 15 October 2015)
3 Grading of Recommendations Assessment, Development and Evaluation Working Group. http://www.gradeworkinggroup.org/ (accessed 15 October 2015)
4 National Institute for Health and Care Excellence. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. London: National Institute for Health and Care Excellence, 2016. https://www.nice.org.uk/guidance/ng36 (accessed 27 April 2016)

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GUIDELINE

Organisation and provision of head and neck cancer surgical services in the United Kingdom: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the surgical specialty associations involved in the care of head and neck cancer patients in the UK. This paper summarises the current state of play in the organisation and provision of head and neck cancer surgical services in the UK.

Introduction

The quality and availability of care for patients with head and neck cancer has improved immeasurably over the past 30 years. Improved training, application of evidence-based practice, multi-disciplinary working, improved surgical and radiation techniques, chemotherapy, public health education, subspecialisation and in particular the National Institute for Health and Care Excellence (NICE) Improving Outcomes guidelines,[1] the previous editions of the Multidisciplinary Head and Neck Cancer guidelines[2] and peer review have all played their part. Despite this, the availability of some treatment options and survival outcomes in the UK still seem to lag behind other Western countries. Further improvement is required but the financial constraints in the National Health Service (NHS), highlighted over recent months, could overwhelm us and consequently could affect progress in developing clinical services for the foreseeable future.

Since the inception of the NHS, healthcare spending in the UK has increased 4 per cent per year. In 1960, it was less than 5 per cent of gross domestic product (GDP), 50 years on it is now about 10 per cent of GDP. Current estimates suggest that within 10 years, unchecked healthcare spending will outstrip economic growth and is not sustainable, and by 2050 spending would increase to over 20 per cent of GDP.[3] The Five Year Forward View, published in October 2014,[4] describes ways in which the NHS intends to tackle the exponential rises in the cost of NHS services.

Commissioning healthcare services

England

Commissioning of healthcare in all its aspects underwent a total organisational restructuring based upon recommendations in the Health and Social Care Act 2012.[5] This is the fifth major reorganisation of the NHS structure since 2000. Primary Care Trusts and Strategic Health Authorities were disbanded and replaced with 211 Clinical Commissioning Groups (CCGs) made up of local GPs covering populations of over 250 000 under the umbrella of The NHS Commissioning Board, which became NHS England and began functioning on 1st April 2013. Clinical Commissioning Groups do not commission GP or specialised services as these are directly commissioned.[6] Some services have been designated as 'specialised' and based upon principles laid out in the Carter Report and the Department of Health white paper 'Equity and excellence: liberating the NHS'.[7] In addition, a structure for prescribing and identifying these services is now in place.

NHS England became responsible for directly commissioned services (including specialised services) in April 2013 (Scotland and Wales have their own commissioning structures). This structure is currently under review and many of the designated specialised services may have commissioning devolved to the CCGs. The NHS England website defines specialised services as those provided in relatively few hospitals, accessed by comparatively small numbers of patients but with catchment populations of usually more than 1 million. These services tend to be located in specialised hospital trusts that can recruit a team of staff with the appropriate expertise and enable them to develop their skills. Specialised services account for approximately 14 per cent of the total NHS budget, about £13.8 billion per annum. The commissioning of specialised services is a prescribed direct commissioning responsibility of NHS England. The manual for prescribed specialised services 2013/2014 identifies 143 services.[8]

A description of the new structure for commissioning specialised services is given in detail on the NHS England website. Commissioning has been devolved to six programmes of care (POC) each with its own team of commissioners:

- internal medicine
- cancer
- blood and infection
- mental health
- trauma
- women and children.

The national Cancer and Blood POC covers the prescribed specialised services in infection, cancer, immunity and haematology. This relates to both specialised and highly specialised prescribed services, and includes both surgical and medical services. There are 74 specialist services within the POC, and these are clustered into Clinical Reference Groups (CRGs) to support the national work in these areas. The Cancer Programme of Care covers some of the prescribed specialised and highly specialised services. Complex head and neck is one of 17 specialised services in the Cancer and Blood Programme. These service-specific CRGs also work with other CRGs where key service interfaces and interdependencies between CRG areas occur. A public consultation to amalgamate CRGs is currently underway; the impact for head and neck surgery will be the creation of a super CRG that includes all of cancer surgery.

The CRG for a specific specialty will advise the designated commissioners on service standards and requirements, and will complete designated tasks requested by the commissioners. Each CRG consists of a chair and members (up to 15) consisting of representatives from the 12 Clinical Senates, relevant professional organisations and patient groups. England has been divided into 12 Clinical Senates similar (but not identical) geographically to the new Cancer Networks providing members for the different CRGs. More information is available on the NHS England website (http://www.england.nhs.uk/ourwork/part-rel/cs/)

The Complex Head and Neck Clinical Reference Group (HNCRG) covers complex benign and malignant head and neck services and refers to a group of very different tumours, including oral (mouth, lip and oral cavity), larynx, pharynx, thyroid and salivary glands tumours amongst others. It may become the responsibility of the CRGs to advise specialised commissioners and NHS England on ways to improve efficiency and reduce costs without affecting quality or provision of care. An example is the NHS England policy on Transoral Robotic Surgery that has been developed under the aegis of the CRG which is undergoing public consultation at the time of this paper going to press. The apparent poor comparisons with other European cancer outcome audits and a wide national variation in provision of services and outcomes have become powerful drivers for political intervention and change. Thus, over the past 10 years many providers in England have moved towards some forms of centralisation model in response to the National Institute for Health and Care Excellence (NICE) improving outcomes guidance (IOG) for head and neck cancers, although this is not universal.

Potentially, the HNCRG can have a great deal of influence on the future structure of services nationally by setting clear standards to the commissioners who control the funding. To influence this process, readers to contact their respective senate representative. More information about CRGs is available from the NHS England website. http://www.england.nhs.uk/ourwork/commissioning/spec-services/npc-crg/

Scotland

The NHS in Scotland is a devolved service run by the Scottish government out of parliament in Edinburgh. It is delivered by 14 Regional Health Boards that cover the disparate geography of Scotland. The Scottish NHS budget is approximately £11.9 billion (2013–2014 budget).

Head and neck cancer services are delivered by the three major Cancer Networks within Scotland: North of Scotland cancer network (NOSCAN), South of Scotland (SCAN) and West of Scotland (WOSCAN).

These cancer networks work closely together to provide a full and comprehensive head and neck cancer service to the estimated 5.5 million population in Scotland which is spread across a wide range of geographic areas from dense urban to remote and rural sites. Over 1100 new cases of head and neck cancer are diagnosed in Scotland per year.

In Scotland, commissioning groups have not been introduced in the same way as in England and the delivery of the NHS in Scotland still follows the traditional NHS method of GP referral to the local secondary care centre with 'urgent suspicion of cancer' referral guidelines published by NHS Scotland in place. This sets the standard of 62 days from referral to treatment for cancer cases (http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/programme_resources/scottish_referral_guidelines.aspx).

Quality improvement processes are in place in Scotland including the introduction of quality performance indicators (QPIs) to set the standards for cancer care within all cancer groups including head and neck cancer. The QPIs have been developed collaboratively with the three Regional Cancer Networks (NOSCAN, SCAN, WOSCAN), Information Services Division and Healthcare Improvement Scotland. The Scottish Government has asked Healthcare Improvement Scotland to provide performance assurance against cancer QPIs and to publish their findings on a three yearly basis (http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis.aspx).

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The NHS funding constraints may make it necessary to review the role of the currently designated cancer centres in Scotland in the future.

Wales

The NHS England has identified head and neck surgery as a speciality requiring specific funding arrangements. The organisation and provision must be based in centres covering a large population with an adequate workload. Over the past 10 years many providers have moved towards some forms of centralisation model in response to the NICE IOG, although this is not universal.

All seven health boards in Wales offer head and neck cancer services, irrespective of numbers; despite an extensive review in 2009 attempting to rationalise services, this has never happened. The existing regional service provision and local geographical and population factors will of course impact on practical arrangements, but trusts will be expected to justify the service structure with robust data. As yet it is not clear if the CRG recommendations, when they are published, will be accepted in Wales and how they will be enforced. It is clear that there will be no increase in funding and only measures which reduce or stabilise costs are likely to be adopted. Head and neck cancer surgical service providers should review their service provision as and when new guidance is published, but no statutory authority exists to enforce these guidelines.

Cost of head and neck cancer care

Head and neck cancer is expensive to manage. In the USA, it has been suggested that it is the most expensive cancer to treat and patients rarely return to a productive life, with estimated costs of $96 000–$150 000 for multimodality treatment (surgery, chemotherapy and/or radiotherapy).

The UK head and neck surgical services initially developed within ENT and Oral and Maxillofacial (OMF) departments without the introduction of funding and were bundled in with other routine non-oncologic surgical procedures and paid for through local commissioning. Devolvement of services, centralisation and specialisation mean this model cannot continue. Cost estimates for surgery with reconstruction range in the UK and Europe from £25 000 to £30 000 and it is unclear in many units exactly how much of the true cost is reimbursed by current tariffs based on the health resource group codes. We need to be able to quantify the financial impact of CRG advice regarding changes to clinical practice and in order to do this, more clear and more reliable coding and costing is required to understand the viability of services in the future and to monitor the financial effects of change.

Caseload and service provision

It is generally accepted, with some evidence, that patients requiring complex surgical and oncological treatments have better outcomes and the service is more efficient when carried out in larger centres with specialist surgeons and oncologists. It has already been shown that there is a huge variation nationally in basic measures such as in-hospital mortality and complications which are unacceptable and a major factor in driving change.

The NICE guidance defines a minimum of 100 new cases per year to be a credible provider. The previous edition of the Multidisciplinary Head and Neck Cancer guidelines suggested a higher number, over 250, to generate enough operative cases to develop and maintain skills, provide a suitable training and research environment and allow a sufficient number of qualified surgeons to provide adequate 24 hour, 7 days a week services.

When the 4th edition of these guidelines were published in 2011,[2] there were 33 cancer networks, with 69 multidisciplinary teams (MDTs) and 79 hospital providers. The 2012 Data for Head and Neck Oncology audit reported 28 MDTs in England, 2 in Wales with 64 service providers for 8272 new cases. Of these providers, 14 reported fewer than 50 new cases per year and a further 11, fewer than 100 new cases. The other units mostly report 150–180 cases, with six providers reporting more than 200 cases per year. There is some under reporting in these numbers due to failure to identify a provider, but the picture is clear. There are units providing head and neck services with relatively low numbers. Trusts and individual surgeons should be examining the sustainability of such service provision outside larger centres. While geographical and public transport issues exist, the CRG agrees with the NICE recommendations for Head and Neck Centres to serve populations of over a million or more. Within England, the CRG's view is that cancer centres should have a case load of at least 250 cases per year, using a regional hub and spoke structure, with centralised surgery and peripheral clinic and support services. Currently, NHS England, in conjunction with National Cancer Intelligence Network, is undertaking an audit of current cancer service provision in England; thus no recommendations will be forthcoming until the audit and the restructuring of the CRG is complete.

Sir Bruce Keogh announced on 16th November 2014 the findings of a forum on provision of a 24 hour, 7 days a week health service, which will filter through to head and neck services eventually (http://www.nhsiq.nhs.uk/improvement-programmes/acute-care/seven-day-services.aspx) and such reorganisation will help with the planned 7-day health service.

Keys to the successful management of HNC are the specialist nursing, speech and language, dietetics and social support that these patients require. Easy and ready access locally is essential. To counterbalance the move to concentrate specialist surgery (radiotherapy is by its nature centralised already) local provision of centrally guided support units and visiting consultant clinics should mitigate some of the patient concerns about distance from the surgical unit.

Surgical numbers

Individual surgeon reporting is not a concept that is useful or valid in determining outcomes in head and neck surgical practice. However, better outcome

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measures are on the way and accurate data collection and publication from providers will be required to justify funding, allow comparison with other centres and highlight problems more quickly. Data collection is still poor and undervalued by many hospital managers trying to trim budgets, but the value of accurate validated data cannot be underestimated and it should not be left to busy clinicians to coordinate or enter data but to properly trained and motivated data managers.

Surgeons' operative numbers is always a thorny question. The peer review process for thyroid surgery adopted the British Association of Endocrine and Thyroid Surgeons guideline of at least 20 thyroidectomies per year as one of its markers and this is likely to be expanded to some of the more common head and neck procedures; examples include neck dissection, oral cancer resection, laryngectomy and free flap reconstruction. There is no real evidence base to determine how many particular procedures should be recommended, but less than five major procedures per year at a centre is not sustainable and a service review is mandatory. Unusual procedures such as craniofacial resection will be restricted even further to a small number of nationally recognised centres.

Funding

As part of the Five Year Forward View, the commissioning of specialised services will assess the opportunities for co-commissioning across all specialised services in order to maximise all service elements associated with the patients' pathway and the provision of services to meet the needs of patients. The national service specifications and other commissioning products will provide a framework through which specialised services can be defined to ensure that services are delivered to national standards.

At the time of writing it is not clear what, if any, changes will occur that could affect the commissioning of complex head and neck cancer surgery. At present the commissioning of these services sits within the remit of specialised commissioning, directly commissioned by NHS England. The remaining services are funded by CCGs.

At the start of the specialised commissioning process in 2013, it was clearly stated that the commissioning of these services would be placed in the hands of specialised commissioners, giving the opportunity to ensure that the service delivered was in accordance with the published service specification to ensure equity of access to high-quality services across the country and to aid the smoothing out variations in outcomes noted in cancer audits. There was also a clear belief that this would also drive a more efficient use of funds by providers, potentially a cost reduction through larger services leading to a critical mass of patients supported by an appropriate and cost-effective infrastructure improving the quality and cost-effectiveness in line with the NICE IOG.

Wholesale restructuring of regional services is rarely achievable without cost. This will not be easy and it seems to have stalled the process. Also, such changes are often unwelcome in larger more sparsely populated geographical areas, although evidence would suggest that it is clinicians and providers who provide the most resistance; patients when questioned more often express a desire to go to the expert centre.

Summary

Complex head and neck surgery has been commissioned as a specialised service by NHS England. The organisation and provision must be based in centres covering a large population with an adequate workload. Over the past 10 years many providers have moved towards some form of centralisation model in response to the NICE IOG, although this is not universal. This is the driver for the work of the CRG, which intends to undertake an audit of the current head and neck services to explore whether the configuration in place meets national IOG requirements and that there is a consistent picture of delivering good outcomes to patients. The view of the CRG is that more centralisation is required.

The existing regional service provision and local geographical and population factors will of course impact on practical arrangements, but trusts will be expected to justify the service structure with robust data. As yet it is not clear if the CRG recommendations will be accepted and how they will be enforced. It is clear that there will be no increase in funding and only measures which reduce or stabilise costs are likely to be adopted. Head and neck cancer surgical service providers should consider their current service provision and assess and consider the potential impact of changes to future guidelines.

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GUIDELINE

Aetiology and risk factors for head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It discusses the aetiology and risk factors for head and neck cancer and the recommended interventions appropriate for each risk factor.

Recommendations

- Recent evidence synthesis from National Institute for Health and Care Excellence suggests that the following brief interventions for smoking cessation work should be used:
  - Ask smokers how interested they are in quitting (R)
  - If they want to stop, refer them to an intensive support service such as National Health Service Stop Smoking Services (R)
  - If they are unwilling or unable to accept a referral, offer a stop smoking aid, e.g. pharmacotherapy. (R)
- Brief interventions are effective for hazardous and harmful drinking. (R)
- Specialist interventions are effective in people with alcohol dependence. (R)
- Most people with alcohol dependence can undergo medically assisted withdrawal safely at home, after risk assessment. (R)
- Management of leukoplakia is not informed by high-level evidence but consensus supports targeted use of biopsy and histopathological assessment. (R)
- The management of biopsy proven dysplastic lesions favours:
  - advice to reduce known environmental carcinogens such as tobacco and alcohol (R)
  - surgical excision when the size of the lesions and the patient's function allows (R)
  - long-term surveillance. (R)
- Fanconi anaemia patients should:
  - be followed up in a multidisciplinary specialist Fanconi anaemia clinic (G)
  - have quarterly screening for head and neck squamous cell carcinoma and an aggressive biopsy policy (G)
  - receive prophylactic vaccination against high risk human papilloma virus (G)
  - receive treatment for head and neck squamous cell carcinoma with surgery alone where possible. (G)

Introduction

The major risk factors for head and neck cancer in the UK are tobacco smoking and alcohol consumption and withdrawal of these environmental carcinogens remains the focus for primary and secondary prevention. Additionally the role of human papilloma virus (HPV) is being increasingly recognised, but as the natural history and transmission of oral and oropharyngeal HPV infection are incompletely understood, the opportunities for reducing this risk are not yet clear. Some patients have recognised local or systemic pre-malignant conditions which are also discussed.

Smoking

Smoking is an independent risk factor for head and neck cancer.[1] Patients who continue to smoke during radiotherapy are more likely to develop osteoradionecrosis and to require hospitalisation during treatment. Continued smoking through radiotherapy was thought to have an adverse effect on local control (hazard ratio 1.5) and survival (hazard ratio 1.7), but more recent evidence would suggest baseline smoking status is more important.[2] Smoking cessation before surgery is desirable to reduce the risk of anaesthetic related complications and improve wound healing, particularly after reconstructive surgery.[3,4]

Quitting tobacco smoking for a short period of time (one to four years) results in a head and neck cancer risk reduction of about 30 per cent compared with current smoking, reduces the risk of laryngeal cancer by 60 per cent after 10–15 years and after 20 years

can reduce the risk of developing oral cavity cancer to the level of a never smoker.[5]

Recommendations

- **Recent evidence from NICE suggests that the following brief interventions for smoking cessation work should be used:**
  - **Ask smokers how interested they are in quitting (R)**
  - **If they want to stop, refer them to an intensive support service such as NHS Stop Smoking Services (R)**
  - **If they are unwilling or unable to accept a referral, offer a stop smoking aid, e.g. pharmacotherapy (R)**

Alcohol

Alcohol is the other major independent risk factor for head and neck cancer. Patients who continue to drink heavily after treatment for head and neck cancer have a significantly worse quality of life[6] and continued drinking has a negative impact on survival (hazard ratio 1.28).[7,8] The beneficial effects of quitting alcohol, on the risk of developing head and neck cancer, are only observed after more than 20 years, when the level of risk reaches that of non-drinkers.[5]

Cessation of alcohol on admission for surgery can present a significant problem in heavy drinkers. A review in the British Medical Journal suggests that we should screen all patients for excessive alcohol consumption with a validated questionnaire such as Fast Alcohol Screening Test.[9]

Recommendations

- **Brief interventions are effective for hazardous and harmful drinking (R)**
- **Specialist interventions are effective in people with alcohol dependence (R)**
- **Most people with alcohol dependence can undergo medically assisted withdrawal safely at home, after risk assessment (R)**

Human papilloma virus

Human papilloma virus -16 is an increasingly relevant causative agent in oropharyngeal and oral squamous cell carcinoma (SCC), however doubt remains in other sites and for other HPV subtypes. Combined data from recently published (2006–2009) studies shows that 55 per cent of 654 oropharyngeal SCC cases were HPV-16 positive.[10] The prevalence of HPV-16 chronic infection in oropharyngeal mucosa of the general population is currently unclear. Without a clinically identifiable premalignant lesion, any future (primary or secondary) screening approach would rely on molecular biomarkers. Oral HPV infection increases with numbers of recent oral sex partners and isolated cases of transmission of HPV-16 between partners leading to the possible 'transmission' of cancer have been reported.[11] Evidence seems currently insufficient to counsel avoidance of specific sexual activities, over and above guidance that informs the prevention of other sexually transmitted diseases. It is awaited with interest as to whether the current programme of vaccination against high risk HPV (strains 16 and 18) offered to 12–13-year-old girls will in the future reduce the incidence of head and neck squamous cell carcinoma (HNSCC).

Premalignant lesions

Leukoplakia and erythroplakia are common premalignant lesions; however, most HNSCC cases have no history of such antecedent lesions. Biopsy-proven epithelial dysplasia is demonstrated in 25 per cent of biopsies of leukoplakia but most erythroplakia; however, HPV-16 is very rarely a factor in these conditions. The significant clinical predictors of malignant transformation in oral dysplastic lesions are non-smoking status, sub-site (e.g., high risk in lateral tongue and low risk in floor of mouth), non-homogeneous appearance, size of lesion greater than 200 mm and higher histological grade (severe *vs* mild/moderate). A recent systematic review of oral dysplasia (992 patients) showed malignant transformation in 12.1 per cent after mean 4.3 years following biopsy.[12] Severity of dysplasia predicted for malignant transformation ($p = 0.008$). Lesions that were not excised demonstrated considerably higher transformation rate than those that were excised ($p = 0.003$).[13] A binary histological grading into the high and low risks has been suggested based on good predictive power that has been independently verified in other series. A systematic review of laryngeal dysplastic lesions (942 patients) showed transformation in 14 per cent after a mean interval of 5.8 years, again severity of dysplasia correlated with risk of transformation.[14]

Importantly, these data only reflect patients already referred for a specialist opinion and with biopsy-proven dysplasia. In population-based studies of oral leukoplakia without histological inclusion criteria the risks are much lower; 40–50 per cent regress spontaneously and less than 1 per cent transform.[15,16] There is insufficient evidence to justify screening in the general population to prevent oral cancer.[17]

The premalignant potential of oral lichen planus (OLP) is controversial; however, rigorously conducted retrospective series have confirmed the risk in classic inflammatory OLP with histological confirmation is low, at about 1 per cent. Oral lichenoid lesions which harbour features of OLP, but also epithelial dysplasia do present a modest risk for malignant transformation, and in some series this subset reflect the only cancer

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cases arising, interestingly with a predisposition to lateral tongue. Proliferative verrucous leukoplakia is a rare condition presenting with exophytic widespread progressive leukoplakia, somewhat refractory to intervention and with very high (50–80 per cent) transformation rates and hence, poor overall prognosis.

Recommendations

- **Management of leukoplakia is not informed by high-level evidence, but consensus supports targeted use of biopsy and histopathological assessment (R)**
- **The management of biopsy proven dysplastic lesions favours:**
  - **advice to reduce known environmental carcinogens such as tobacco and alcohol (R)**
  - **surgical excision when the size of the lesions and the patient's function allows (R)**
  - **long-term surveillance (R)**

Premalignant conditions

Inherited

Inherited conditions with increased risk of HNSCC include Fanconi anaemia (FA), ataxia telangiectasia, Bloom's syndrome and Li–Fraumeni syndrome. Fanconi anaemia has a very high risk of developing HNSCC (particularly oropharyngeal squamous cell carcinoma), most notably after haematopoietic stem cell transplantation.[18] Recent evidence suggests a possibility that HPV may be implicated in FA-related oropharyngeal squamous cell carcinoma.[19] Fanconi anaemia patients do not tolerate cisplatin and have severe toxicity with radiotherapy. Life expectancy has improved so that the population at risk for HNSCC is greater. Head and neck squamous cell carcinoma can occur early in patients as young as 11 years old. Further guidance is available from http://www.fanconianaemia.nhs.uk

Recommendation

- **Fanconi anaemia patients should:**
  - **be followed up in a multidisciplinary specialist FA clinic (G)**
  - **have quarterly screening for HNSCC and an aggressive biopsy policy (G)**
  - **receive prophylactic vaccination against high risk HPV (G)**
  - **receive treatment for HNSCC with surgery alone where possible**

Acquired immunodeficiency

Patients who are immunosuppressed due to poor nutrition, advanced age, immunosuppressive therapy after transplant or acquired immunodeficiency syndrome (AIDS) are at greater risk of developing malignancy. The most commonly reported AIDS-related neoplasms of the head and neck region include Kaposi's sarcoma and non-Hodgkin's lymphoma. There is also an increased risk of oropharyngeal squamous cell carcinoma. Although HPV-related HNSCC has been seen in immunosuppressed patients, further clinical studies are needed to determine the safety and effectiveness of HPV vaccines in this setting.

Key points

- Smoking is an independent risk factor for head and neck cancer, is associated with post treatment complications and has an adverse effect on oncological outcomes
- Alcohol is an independent risk factor for head and neck cancer and continued drinking has a negative impact on survival
- High risk human papilloma viruses (HPV 16 and 18) are recognised causative agents for oropharyngeal squamous cell carcinoma
- Malignant transformation of oral dysplasia and laryngeal dysplasia occurs in 12 per cent (mean 4.3 years) and in 14 percent (mean 5.8 years) respectively.

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GUIDELINE

Pre-treatment clinical assessment in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. This paper provides recommendations on the pre-treatment clinical assessment of patients presenting with head and neck cancer.

Recommendations

- Comorbidity data should be collected as it is important in the analysis of survival, quality of life and functional outcomes after treatment as well as for comparing results of different treatment regimens and different centres. (R)
- Patients with hypertension of over 180/110 or associated target organ damage, should have antihypertensive medication started pre-operatively as per British Hypertension Society guidelines. (R)
- Rapidly correcting pre-operative hypertension with beta blockade appears to cause higher mortality due to stroke and hypotension and should not be used. (R)
- Patients with poorly controlled or unstable ischaemic heart disease should be referred for cardiology assessment pre-operatively. (G)
- Patients within one year of drug eluting stents should be discussed with the cardiologist who was responsible for their percutaneous coronary intervention pre-operatively with regard to cessation of antiplatelet medication due to risk of stent thrombosis. (G)
- Patients with multiple recent stents should be managed in a centre with access to interventional cardiology. (G)
- Surgery after myocardial infarction should be delayed if possible to reduce mortality risk. (R)
- Patients with critical aortic stenosis (AS) should be considered for pre-operative intervention. (G)
- Clopidogrel should be discontinued 7 days pre-operatively; warfarin should be discontinued 5 days pre-operatively. (R)
- Patients with thromboembolic disease or artificial heart valves require heparin therapy to bridge peri-operative warfarin cessation, this should start 2 days after last warfarin dose. (R)
- Cardiac drugs other than angotensin-converting enzyme inhibitors and angiotensin II antagonists should be continued including on the day of surgery. (R)
- Angotensin-converting enzyme inhibitors and angiotensin II antagonists should be withheld on the day of surgery unless they are for the treatment of heart failure. (R)
- Post-operative care in a critical care area should be considered for patients with heart failure or significant diastolic dysfunction. (R)
- Patients with respiratory disease should have their peri-operative respiratory failure risk assessed and critical care booked accordingly. (G)
- Patients with severe lung disease should be assessed for right heart disease pre-operatively. (G)
- Patients with pulmonary hypertension and right heart failure will be at extraordinarily high risk and should have the need for surgery re-evaluated. (G)
- Perioperative glucose readings should be kept within 4–12 mmol/l. (R)
- Patients with a high HbA1C facing urgent surgery should have their diabetes management assessed by a diabetes specialist. (G)
- Insulin-dependent diabetic patients must not omit insulin for more than one missed meal and will therefore require an insulin replacement regime. (R)
- Patients taking more than 5 mg of prednisolone daily should have steroid replacement in the peri-operative period. (R)

- Consider proton pump therapy for patients taking steroids in the peri-operative phase if they fit higher risk criteria. (R)
- Surgery within three months of stroke carries high risk of further stroke and should be delayed if possible. (R)
- Patients with rheumatoid arthritis should have flexion/extension views assessed by a senior radiologist pre-operatively. (R)
- Patients at risk of post-operative cognitive dysfunction and delirium should be highlighted at pre-operative assessment. (G)
- Patients with Parkinson's disease (PD) must have enteral access so drugs can be given intra-operatively. Liaison with a specialist in PD is essential. (R)
- Intravenous iron should be considered for anaemia in the urgent head and neck cancer patient. (G)
- Preoperative blood transfusion should be avoided where possible. (R)
- Where pre-operative transfusion is essential it should be completed 24–48 hours pre-operatively. (R)
- An accurate alcohol intake assessment should be completed for all patients. (G)
- Patients considered to have a high level of alcohol dependency should be considered for active in-patient withdrawal at least 48 hours pre-operatively in liaison with relevant specialists. (R)
- Parenteral B vitamins should be given routinely on admission to alcohol-dependent patients. (R)
- Smoking cessation, commenced preferably six weeks before surgery, decreases the incidence of post-operative complications. (R)
- Antibiotics are necessary for clean-contaminated head and neck surgery, but unnecessary for clean surgery. (R)
- Antibiotics should be administered up to 60 minutes before skin incision, as close to the time of incision as possible. (R)
- Antibiotic regimes longer than 24 hours have no additional benefit in clean-contaminated head and neck surgery. (R)
- Repeat intra-operative antibiotic dosing should be considered for longer surgeries or where there is major blood loss. (R)
- Local antibiotic policies should be developed and adhered to due to local resistance patterns. (G)
- Individual assessment for venous thromboembolism (VTE) risk and bleeding risk should occur on admission and be reassessed throughout the patients' stay. (G)
- Mechanical prophylaxis for VTE is recommended for all patients with one or more risk factors for VTE. (R)
- Patients with additional risk factors of VTE and low bleeding risk should have low molecular weight heparin at prophylactic dose or unfractionated heparin if they have severe renal impairment. (R)

Introduction

This section deals with the topics of patient assessment and optimisation prior to treatment for head and neck cancer (HNC). The importance of collaborative teamwork, structured pre-operative assessment, grading and analysing comorbidity, and prophylaxis against infection and venous thromboembolism (VTE) are summarised in the section below.

Comorbidity: outcomes and data collection

The presence of illnesses unrelated to the tumour significantly affects prognosis in HNC patients, and is contributed to by tobacco, alcohol and substance misuse. The Adult Comorbidity Evaluation 27 (ACE 27) and the Charlson Index are the most commonly used indices to quantify comorbidity.

The National Cancer Intelligence Network (NCIN) recommends that collection of an ACE 27 comorbidity score be mandated for all adult cancer patients. This facilitates surgical oncology research with the objective of improving cancer care through improved patient counselling and treatment planning. Information should be extracted from notes rather than relying on self-reporting.

Comorbidity scoring captures the impact of co-existing diseases, but not the disease of interest.[1,2] Performance status assesses the effect of all illnesses on the patients' functional ability. Performance status is not a reliable substitute for comorbidity status as a prognostic measure, as they can each independently lead to poor tolerance of treatment. There is good evidence that integrating comorbidity with staging systems produces better prognostic instruments. The development of 'prognostigrams' relating to tumour–node–metastasis (TNM) stage, comorbidity and performance status require the accurate collection of these variables in large numbers as suggested by NCIN.

The effects of increased pre-treatment comorbid burden include:

- Adverse impact on short-term mortality of patients with newly diagnosed head and neck squamous cell carcinoma (HNSCC)
- Reduced overall survival in HNSCC and possible predictor for distant metastases
- Adverse influence on disease-specific survival, probably due to the advanced stage at presentation and the likelihood of such patients undergoing less aggressive treatment i.e. treatment selection
- Higher incidence of and more severe complications
- Adverse impact on quality of life (QoL)
- Adverse impact on functional outcomes
- Increased cost of treatment.

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The relationship between performance status and survival is much less well-defined.

Recommendation

- **Comorbidity data should be collected as it is important in the analysis of survival, QoL and functional outcomes after treatment as well as for comparing results of different treatment regimens and different centres. (R)**

Pre-operative assessment

A good pre-operative assessment system will provide an appropriately informed, consented and prepared patient on the day of surgery, avoiding late cancellation and preventable risk. It is imperative that referral for pre-operative assessment takes place as early as possible within the patient pathway.

Measures of the effectiveness of a pre-operative assessment service should be regularly audited. These include:

- Avoiding delay in listing and admission for surgery
- Avoiding unnecessary or duplicate investigations
- High proportion of same day admissions for surgery
- No cancellations as a result of inadequate investigation or workup
- Length of hospital stay.

The role of the anaesthetist in pre-operative assessment includes:

- Identification of the difficult airway
- Risk stratification and discussion
- Optimisation of comorbidities within the limited timeframe prior to surgery
- Formulation of a plan for peri-operative care with appropriate allocation to critical care resources.

Guidance for the use of pre-operative testing is available from National Institute for Health and Care Excellence (NICE), The Clinical Audit and Practice Advisory Group of ENT UK and the British Association of Day Surgery and Royal College of Anaesthetists.[3,4] Individual department guidelines should be developed, including the use of general and dynamic testing.

There should be a clinical lead in each anaesthetic department for pre-operative assessment and for head and neck anaesthesia with established links to related specialities.

Identification of the difficult airway

In head and neck practice, the surgeon and anaesthetist have an important role in identifying the difficult airway (Box I).

BOX I
RISK FACTORS FOR A DIFFICULT INTUBATION INCLUDE

- Previous difficult intubation
- Mallampati grade III or IV
- Thyromental distance <6 cm
- Reduced mouth opening, inter-dental distance <3 cm
- Reduced neck extension
- Presence of retrognathia
- Poor dentition
- Obstructive laryngeal tumours
- Tongue base tumours
- Hypopharyngeal lesions
- Previous head and neck surgery or radiotherapy

A collaborative approach and communication greatly reduces the risk associated with a difficult airway. Suspected cases should be discussed between surgeon and anaesthetist prior to the day of surgery ideally with nasolaryngoscopy and scans to aid decision making. Airway assessment is imperfect in predicting problems and an airway strategy that encompasses emergency options should be formulated for both induction and the end of surgery. This strategy must be communicated clearly to the entire team working in theatre on the day and human factors considered.

Risk stratification and optimisation of comorbidities

Assessment of risk. In recent years, there has been an increasing focus on risk prediction in patients undergoing major surgical procedures. In terms of risk stratification, head and neck surgery is classed as intermediate-risk surgery.

The POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) score is a useful aid to predicting morbidity but despite being a well-validated tool, it has not demonstrated effective prediction of mortality in head and neck surgery.

The extensively validated Revised (Lee) Cardiac Risk Index (Box II) is a six point index score derived from patients over the age of 49; it is used to assess the risk of major cardiac event associated with non-cardiac surgery. This and other scoring systems were predominantly validated in the general and vascular surgical populations, but evidence suggests that it is a useful predictor of cardiovascular morbidity peri-operatively in head and neck surgery, particularly when combined with age over 70 as an additional variable.

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BOX II
REVISED (LEE) CARDIAC RISK INDEX VARIABLES

- History of IHD
- History of congestive heart failure
- Cerebrovascular disease (stroke or transient ischaemic attack)
- Diabetes requiring insulin use
- Chronic kidney disease (Creatinine > 2.0 mg/dl or 177 μmol/l)
- High-risk surgery – intra-peritoneal, intra-thoracic and suprainguinal vascular

Predicted risk of major cardiac event:
0 variables = 0.4 per cent risk
1 variable = 0.9 per cent risk
2 variables = 6.6 per cent risk
3 or more variables = 11 per cent risk

The assessment of dynamic function or aerobic fitness is extremely important to aid quantification of risk and allocation of critical care resources. Simple subjective methods include the estimate of metabolic equivalents (METs), where one MET equates to the oxygen consumption of a 70 kg man at rest, four METs equate to walking up one flight of stairs; failure to achieve this is associated with increased risk. Dynamic testing of functional capacity may include the use of shuttle walk testing, 6 minutes walk testing, treadmill cardiac testing and cardiopulmonary exercise testing (CPET).

CPET is currently the most reliable and objective assessment of functional capacity; the anaerobic threshold and peak oxygen consumption are proven to be well correlated with morbidity and mortality in the peri-operative period in major surgery; its application to head and neck surgery is still being evaluated.

The following sections will concentrate on identification of significant comorbidities and therapies which require specific pre-operative management, using a system-based approach.

Cardiovascular system. Between 40 and 50 per cent of patients will have cardiovascular disease.[5] All patients over 55 years and those with diabetes or other cardiac risk should have an electrocardiogram (ECG) as a minimum pre-operative investigation.

Hypertension. Hypertension is the commonest cardiovascular comorbidity. There is evidence that hypertension with target organ damage is associated with a small increased incidence of major cardiovascular events.

The diagnosis of hypertension should be made in primary care. A patient with a blood pressure of greater than 180/110 mm Hg has severe hypertension and should not proceed to non-urgent surgery until the blood pressure is controlled to below 160/100. Patients with more moderate hypertension with associated target organ damage are also at higher risk. Where surgery must proceed patients should be made aware of the increased risk. Patients with hypertension demonstrate a more labile haemodynamic response to induction, airway instrumentation, surgical stimulus and post-operative pain. The practice of rapidly correcting pre-operative hypertension with beta blockade appears to cause higher mortality due to stroke and hypotension as per the PeriOperative ISchaemic Evaluation (POISE) study.

Patients with hypertension pre-operatively should be managed by their primary care doctor with introduction of antihypertensive agents as per the British Hypertension Society (BHS) guidelines.[6]

Ischaemic heart disease. Patients with poorly controlled ischaemic heart disease (IHD) should be referred for cardiology assessment. There is no evidence that pre-operative percutaneous coronary intervention (PCI) improves outcome, peri-operative nor long term, in patients with stable coronary artery disease; however, it is justifiable when it is likely to improve the patient's long-term prognosis, such as due to the presence of left main stem stenosis, three-vessel disease or left ventricular (LV) dysfunction. Referral to a cardiologist for patients with recent unstable coronary symptoms should precede surgery. If PCI is performed prior to major surgery bare metal stents are preferred, as these require only four to six weeks of dual antiplatelet therapy, which otherwise markedly increases peri-operative bleeding. Patients with poorly controlled IHD (including recent myocardial infarction (MI)) or who have had recent intervention should undergo surgery in a centre with access to interventional cardiology.

Cardiac investigations. Echocardiography is indicated in the situations shown in Box III.[7]

BOX III
INDICATIONS FOR ECHOCARDIOGRAM

- Documented IHD with reduced functional capacity unexplained by other musculoskeletal disease
- Dyspnoea without obvious non-cardiac cause (e.g. METs < 4 or METs < 7 and dyspnoea with normal PFTs)
- Murmur or history of murmur PLUS symptoms suggestive of valve disease or abnormal ECG
- Known significant valve disease with change of symptoms or no echo within two years
- New atrial fibrillation
- New left bundle branch block or left ventricular hypertrophy on ECG
- Suspected cardiomyopathy
- Lung disease with suspicion of cardiac involvement (cor pulmonale)
- Known or suspected pulmonary hypertension

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Dobutamine stress echocardiography can provide a useful dynamic assessment if IHD is suspected and CPET is not possible. Patients with severe valvular disease have an increased risk of surgery. Aortic stenosis can progress rapidly in the elderly population, and those with critical aortic stenosis may need to be considered for pre-operative intervention.

Arrhythmias and pacing. Atrial fibrillation and other arrhythmias are frequently found at pre-operative assessment; these may be known or new. Management should focus on the rate control, appropriate anticoagulation and identification of associated risks such as structural heart disease or indication for pre-operative pacing.

Cardiac pacemakers should have a recent battery and threshold check within one year. Patients with implantable defibrillators require organisation with a cardiology technician so that they can be deactivated in the anaesthetic room and external pads placed; this is due to the risk of inappropriate discharge due to anaesthetic drugs (suxamethonium) or movement. In both cases, theatre alerts should be placed to remind staff about diathermy risk and bipolar used.

Cardiac and anticoagulant drugs. Clopidogrel should normally be discontinued 7 days pre-operatively; aspirin should be continued without interruption. Patients taking warfarin for uncomplicated atrial fibrillation can discontinue it 5 days pre-operatively, restarting post-operatively when enteral function returns and the risk of bleeding is low. Patients with thromboembolic disease or artificial heart valves require heparin therapy to bridge peri-operative warfarin cessation. This will normally be with therapeutic dose low molecular weight heparin (LMWH) and can be managed in the community either with self-injection or district nurse involvement. Last dose should be 24 hours before the start of surgery. Patients with severe renal impairment will require adjusted dosing or occasionally unfractionated heparin infusion. LMWH or heparin infusion will need to be continued post-operatively until the INR is within the therapeutic range.

Newer oral anticoagulants (e.g. Dabigatran and Apixaban) have variable elimination times depending on renal and liver function; these are non-reversible agents and if there are no locally agreed policies, advice should be sought from a haematologist.

There is increasing evidence that statin therapy should be continued without interruption to prevent peri-operative coronary syndromes due to its plaque stabilising properties.

Provision should be made for enteral administration of cardiac drugs as early as possible post-operatively, and patients should continue the majority of these medicines up to admission. Angotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists are a source of debate; the majority of anaesthetists will choose to omit these drugs on the morning of surgery, particularly if it is purely for hypertension control.

Recommendations

- **Patients with hypertension of >180/110 or associated target organ damage, should have antihypertensive medication started pre-operatively as per BHS guidelines (R)**
- **Rapidly correcting pre-operative hypertension with beta blockade appears to cause higher mortality due to stroke and hypotension and should not be used (R)**
- **Patients with poorly controlled or unstable IHD should be referred for cardiology assessment pre-operatively (G)**
- **Patients within one year of drug eluting stents should be discussed with the cardiologist who was responsible for their PCI pre-operatively with regard to cessation of antiplatelet medication due to risk of stent thrombosis (G)**
- **Patients with multiple recent stents should be managed in a centre with access to interventional cardiology (G)**
- **Surgery after MI should be delayed if possible to reduce mortality risk (R)**
- **Patients with critical AS should be considered for pre-operative intervention (G)**
- **Clopidogrel should be discontinued 7 days pre-operatively; warfarin should be discontinued 5 days pre-operatively (R)**
- **Patients with thromboembolic disease or artificial heart valves require heparin therapy to bridge peri-operative warfarin cessation; this should start 2 days after last warfarin dose (R)**
- **Cardiac drugs other than ACE inhibitors and angiotensin II antagonists should be continued including on the day of surgery (R)**
- **Angotensin-converting enzyme inhibitors and angiotensin II antagonists should be withheld on the day of surgery unless they are for the treatment of heart failure (R)**
- **Post-operative care in a critical care area should be considered for patients with heart failure or significant diastolic dysfunction (R)**

Heart failure and diastolic dysfunction. Heart failure is a considerably greater peri-operative risk factor than angina or previous MI alone. New or poorly controlled heart failure should be referred to cardiology for optimisation, with early commencement and uptitration of an ACE inhibitor, unless contraindicated, whilst that assessment is pending.

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Heart failure carries a 50 per cent four-year mortality from diagnosis if the underlying cause cannot be treated; 50 per cent of patients with severe heart failure (symptomatic and frequent presentations) will die within one year.

Post-operative care in a critical care area should be considered for patients with heart failure or significant diastolic dysfunction.

Right heart failure carries a very high peri-operative risk, much more than LV failure, and there is little available treatment. Right heart failure associated with pulmonary hypertension carries extraordinary risk and is discussed in the respiratory section.

Respiratory system. Significant respiratory disease occurs in 20–30 per cent of patients and respiratory morbidity is the most frequent medical complication of major surgery and cause of intensive care unit stay. Preoperative respiratory disease should be optimised wherever possible and right heart disease and pulmonary hypertension considered in those with significant hypoxia (oxygen saturations <93 per cent) or exercise limitation.

Respiratory investigations. Chest radiographs are not required routinely from a fitness perspective; the functional capacity of the patient is paramount here. Cardiopulmonary exercise testing may be useful to assess dynamic function and can demonstrate whether respiratory disease is the main contributing factor to generalised debility.

Intensive care must be planned for patients with significant pulmonary hypertension.

Lung disease should be quantified with spirometry and in severe cases arterial blood gas sampling. An FEV1 of less than 25 per cent predicted poses a markedly increased risk of post-operative ventilatory support, especially when accompanied by hypoxia, hypercarbia or cor pulmonale. The risk of respiratory mortality alone may outweigh any benefit from major surgery. The following actions will optimise a patient's condition for surgery:

- Optimise bronchodilator therapy
- Trial of steroid responsiveness in moderate and severe disease
- Smoking cessation
- Peri-operative nebuliser therapy
- Treatment of inter-current chest infection, possibly delaying surgery
- Sputum sampling to enable 'best guess' treatment of chest infection.

Patients with significant hypoxia (oxygen saturations greater than 93 per cent) arterial blood gas estimation should be performed to look for CO_2 retention. Such patients should be considered for an echocardiogram.

Obstructive sleep apnoea. It is useful to know the degree of obstructive sleep apnoea (OSA) pre-operatively to allow post-operative care planning and to consider the need to exclude pulmonary hypertension and right heart failure, which may occur if there has been an extended period of untreated OSA. Mask fitting should be optimised and any change to anatomy that could compromise use of the mask should be considered and managed appropriately. Patients with proven or suspected OSA and no continuous positive airway pressure (e.g. not tolerated), will require critical care for at least the first post-operative night.

Recommendations

- **Patients with respiratory disease should have their peri-operative respiratory failure risk assessed and critical care booked accordingly (G)**
- **Patients with severe lung disease should be assessed for right heart disease pre-operatively (G)**
- **Patients with pulmonary hypertension and right heart failure will be at extraordinarily high risk and should have the need for surgery re-evaluated (G)**

Endocrine system

Diabetes. Poor glycaemic control is associated with increased wound infections, post-operative morbidity, intensive care requirements and hospital mortality. Peri-operative glucose readings should be kept within the target range of 6–10 mmol/l or the acceptable range of 4–12 mmol/l in order to reduce risk. HbA1C is a useful indicator of diabetic control within the preceding three months and patients with an HbA1C greater than 69 should be considered as higher risk of peri-operative poor glucose control. If time allows, these patients should be referred to a diabetes specialist as important changes can be made to glucose control within two to three weeks of surgery.

Clear and accessible peri-operative diabetes guidelines should be available in every hospital; National Health Service (NHS) guidelines are available for the management of adults with diabetes undergoing surgery.[8] Insulin-dependent diabetic patients must not omit insulin for more than one missed meal and will therefore require an insulin replacement regime, such as a variable rate intra-venous insulin infusion (VRIII) or a glucose potassium insulin infusion (GKI) for major surgery. Many of the longer acting insulins regimes should be continued at reduced dose alongside the insulin replacement regime. Oral hypoglycaemic agents should be omitted on the day of surgery and restarted when normal diet is resumed. Many of these patients will also require a VRIII or GKI. This can still be managed with day of surgery admission in the well-controlled diabetic patient, provided that sufficient protocols are in place.

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Many patients with HNC will have an adjusted diet post-operatively and input from diabetic specialists is important to successfully manage medication requirements.

Steroids. Steroid replacement is essential for those with adrenal suppression from primary or secondary causes to prevent potentially fatal adrenal crises; 60 per cent of patients taking 5 mg of prednisolone daily fail a short Synacthen test and are therefore at risk of relative post-operative adrenal failure. Guidelines agreed and awaiting publication by the AAGBI and agreed by the Clinical Advisory Panel to the Addison's Disease Self-Help Group, recommend the use of peri-operative steroid cover for all patients taking more than 5 mg prednisolone daily, or the equivalent doses of hydrocortisone 20 mg or dexamethasone 1 mg. Patients using inhaled, intra-nasal or topical steroids may also be at risk. Hydrocortisone is only therapeutic for 2–3 hours after intra-venous bolus, so the more traditional QDS bolusing can leave patients sub-therapeutic for several hours before the next dose.

The recommended steroid replacement regime is as follows: 100 mg IM hydrocortisone at induction followed 4 hours later by 200 mg by intra-venous infusion over 24 hours; this may be commenced intra-operatively. This infusion should be continued until oral steroids can be used. Oral dosing should be doubled for at least 48 hours for major surgery and then rapidly tapered back to normal dosing. If intra-venous infusion is impossible, a secondary option is IM 50 mg hydrocortisone QDS.

National Institute for Health and Care Excellence guidelines regarding oral corticosteroids note a higher risk of gastrointestinal bleeding and dyspepsia if steroid use is associated with advanced cancer, older age, concomitant non-steroidal anti-inflammatory medications or anticoagulants, previous gastrointestinal ulcer, bleed or perforation. These patients should be considered for proton pump therapy.

Recommendations

- **Peri-operative glucose readings should be kept within 4–12 mmol/l (R)**
- **Patients with a high HbA1C facing urgent surgery should have their diabetes management assessed by a diabetes specialist (G)**
- **Insulin-dependent diabetic patients must not omit insulin for more than one missed meal and will therefore require an insulin replacement regime (R)**
- **Patients taking more than 5 mg of prednisolone daily should have steroid replacement in the peri-operative period (R)**
- **Consider proton pump therapy for patients taking steroids in the peri-operative phase if they fit higher risk criteria (R)**

Neurological system

Stroke. Peri-operative stroke occurs in approximately 1 in 1000 patients with no prior history of stroke. The comparative odds ratios increase markedly in the presence of prior stroke.[9]

Where surgery cannot be delayed, attention must be paid to cardiovascular stability with avoidance of significant hypotension and head positioning to avoid compression or distortion of the neck vessels, which may impede cerebral perfusion pressure. Carotid dopplers are appropriate for stroke within 12 months.

Rheumatoid arthritis related neck instability. Patients with rheumatoid arthritis are at risk of atlanto-axial subluxation and subsequent cord injury and extreme caution should be used at intubation and head positioning.[10] There are no clear guidelines on the use of cervical spine radiographs pre-operatively. Symptoms suggesting a higher risk of atlanto-axial instability include hesitation on neck movement, pain on movement radiating to the occiput, paraesthesia to the shoulder blades on head movement, or sensory loss in the hands. Up to 20 per cent of patients with rheumatoid arthritis can demonstrate abnormalities on radiographs and in view of the movement often required at surgery for head and neck disease it is advisable that these patients should have cervical spine stability assessed radiologically. Flexion and extension views of the cervical spine are required and should be interpreted by a senior radiologist.

Recommendations

- **Surgery within three months of stroke carries high risk of further stroke and should be delayed if possible (R)**
- **Patients with rheumatoid arthritis should have flexion/extension views assessed by a senior radiologist pre-operatively (R)**
- **Patients at risk of POCD and delirium should be highlighted at pre-operative assessment (G)**
- **Patients with Parkinson's disease (PD) must have enteral access so drugs can be given intra-operatively. Liaison with a specialist in PD is essential (R)**

Post-operative cognitive dysfunction (POCD) and post-operative delirium. Post-operative cognitive dysfunction is new cognitive impairment arising after a surgical procedure, which may be permanent. The incidence of POCD in non cardiac surgery is in the region of 20 per cent at one week and 10 per cent at three months, rising with age. The incidence of delirium (temporary acute confusional state) is higher.

Every effort should be made to highlight these risk factors at pre-operative assessment so the anaesthetic and post-operative care can be tailored accordingly (Box IV). This may include the use of short acting

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anaesthetic agents, close monitoring for infection and ensuring adequate pain relief; but also includes ensuring the patient has all necessary aids such as for hearing and sight.

BOX IV
RISK FACTORS FOR POCD OR DELIRIUM INCLUDE

- Age > 70
- Preoperative cognitive impairment or dementia
- Depression
- Preoperative alcohol misuse
- Visual impairment
- Renal dysfunction
- Tobacco use
- Previous delirium

Haematological system. The commonest haematological abnormality is anaemia, usually due to iron deficiency. It is essential that haematinic evaluation is completed to look for the specific deficiency, which may be associated with nutritional failure. A source of iron deficiency anaemia should be always sought (occult malignancy, ulcer disease).

Treatment should be based on the active replacement of the haematinics, whether B_{12}, folate or iron. Iron replacement can be oral or intravenous; oral therapy will only be effective if absorption is likely and there is at least six weeks before surgery. Intravenous iron is increasingly used and can cause a meaningful rise in haemoglobin levels within two to three weeks. Erythropoietin should be considered on advice from a haematologist or nephrologist for patients with anaemia due to renal disease or anaemia related to chronic disease.

Recommendations

- **Intravenous iron should be considered for anaemia in the urgent HNC patient (G)**
- **Preoperative blood transfusion should be avoided where possible (R)**
- **Where pre-operative transfusion is essential it should be completed 24–48 hours pre-operatively (R)**

Preoperative transfusion should be avoided wherever possible and considered on a case by case basis rather than a target haemoglobin level. There is no evidence to support a cut off transfusion point and there is significant risk independently associated with peri-operative blood transfusion. Where pre-operative transfusion cannot be avoided, it should be completed at least 24–48 hours pre-operatively in order to allow time for regeneration of 2,3-diphosphoglycerate in stored red cells, which ensures optimum oxygen delivery by the haemoglobin.

Alcohol and smoking

Alcohol misuse. There is an increased rate of high alcohol intake in patients with HNCs. General post-operative complication rates are approximately 50 per cent higher for patients who drink 5–6 units of alcohol per day compared with those who drink 0–3 units. If untreated, 6 per cent of alcohol-dependent patients will develop clinically relevant symptoms of withdrawal, and up to 10 per cent of these will experience delirium tremens. Acute alcohol withdrawal in the context of major surgery can cause significant morbidity and a peri-operative mortality of up to 10 per cent.

An accurate alcohol assessment should include details of intake and level of dependency as well as impact on general health. Alcohol withdrawal should be considered in any patient who has hazardous drinking levels defined as more than 5 units per day for men, 3 units per day for women. Information about appropriate alcohol counselling and support should be provided to patients considered at risk.

Identification of alcohol dependency at pre-operative assessment enables further investigation for associated conditions. It also allows planning for pre-operative detoxification, prophylactic intervention, and a higher level of vigilance during admission for the early signs of alcohol withdrawal.

Patients considered to have a high level of dependency should be considered for active in-patient withdrawal at least 48 hours pre-operatively in liaison with relevant specialists.

Thiamine deficiency is common in patients with alcohol dependency and oral absorption can be poor. Parenteral B vitamins (Pabrinex) should be used before surgery to prevent Wernicke–Korsakoff syndrome in those patients with high levels of alcohol intake.

Tobacco use. Smoking tobacco before diagnosis in patients with HNC has a negative correlation with survival. A significant proportion of patients attending cancer diagnostic clinics are smokers. Continued tobacco use in the period leading up to surgery is associated with higher morbidity and mortality in general. Smokers have a considerably increased risk of both intra-operative and post-operative complications, including a 3 to 6-fold increase of peri-operative pulmonary complications. Patients requiring flap reconstructions have higher flap failure rates and greater wound infection rates. Continued smoking during radiotherapy treatment increases complications in patients with laryngopharyngeal cancer and increases the risk of treatment failure. Smoking shortens overall survival and increases both the risk of recurrence and of developing a second primary tumour.

Ideally patients should be supported to stop smoking from the time of their initial clinic visit. Stopping for

24–48 hours pre-operatively normalises the amount of carbon monoxide in the blood, which may be as high as 15 per cent in smokers, allowing better oxygen carrying capacity of the blood to the heart and surgical wounds. Stopping for four to six weeks will allow the immune system recovery. Stopping for six to eight weeks allows recovery of respiratory tract cilia function. Nicotine withdrawal should be treated both pre- and post-operatively.

The UK Government has set up a comprehensive NHS Stop Smoking Service and a range of products and interventions are available. Many trusts now use the successful Stop Before Your Op campaign.

Recommendations

- **An accurate alcohol intake assessment should be completed for all patients (G)**
- **Patients considered to have a high level of alcohol dependency should be considered for active in-patient withdrawal at least 48 hours pre-operatively in liaison with relevant specialists (R)**
- **Parenteral B vitamins should be given routinely on admission to alcohol-dependent patients (R)**
- **Smoking cessation, commenced preferably six weeks before surgery, decreases the incidence of post-operative complications (R)**

Nutritional failure

Nutritional failure impacts negatively on mortality, infection and wound healing. Detailed nutritional assessment and support should be instituted pre-operatively for all patients facing major head and neck surgery as a matter of routine. Dietician-led nutritional support intervention should be provided to any at-risk patients as part of their multidisciplinary management.

Antibiotic prophylaxis

The rationale for considering surgical antibiotic prophylaxis is based on reducing major morbidity, reducing patient length of stay, reducing hospital costs and decreasing overall consumption of antibiotics. Antibiotic use is not without risk and careful adherence to local antibiotic policies is essential to account for local resistance patterns.

Risk factors affecting the incidence of surgical site infection can be both patient and operation associated. Head and neck cancer patients who smoke, are obese (over 20 per cent of ideal body weight), diabetic and immunosuppressed, and have advanced disease or require free flap reconstruction have the greatest risk of surgical wound infection. Operative factors include duration of surgery, antimicrobial prophylaxis and surgical technique (haemostasis, appropriate use of drains, tissue handling and wound closure). The risks of infection can be minimised by:

- Day of surgery admission where possible
- Advising patients to shower or bathe on the day before or the day of surgery
- Methycillin-resistant *Staphylococcus aureus* screening and use of topical agents to reduce carriage if required
- Use of antibiotic prophylaxis, where indicated
- Aseptic surgical technique and careful tissue handling
- Minimising post-operative stay.

The Scottish Intercollegiate Guidelines Network has published a review of the role of antibiotic prophylaxis in surgery, updated in April 2014. Whilst the guidelines are for surgery in general, the search criteria and conclusions include evidence and specific conclusions for head and neck surgery. It must be remembered that antibiotic use is not without risk and reducing inappropriate prescribing is one of the aims of rationalising surgical antibiotic prophylaxis.

In the setting of clean head and neck surgery for benign disease, antibiotic prophylaxis is not recommended. For surgery with malignant disease that is clean (e.g. neck dissection) antibiotic prophylaxis can be considered. For contaminated and clean-contaminated surgery antibiotic prophylaxis is recommended. In this setting, a single dose of antibiotic with a long enough half-life to achieve activity throughout the operation is recommended. The duration of prophylactic antibiotics should not be more than 24 hours. The choice of antibiotic should ensure broad-spectrum cover for aerobic and anaerobic organisms.

Recommendations

- **Antibiotics are necessary for clean-contaminated head and neck surgery, but unnecessary for clean surgery (R)**
- **Antibiotics should be administered up to 60 minutes before skin incision, as close to the time of incision as possible (R)**
- **Antibiotic regimes longer than 24 hours have no additional benefit in clean-contaminated head and neck surgery (R)**
- **Repeat intra-operative antibiotic dosing should be considered for longer surgeries or where there is major blood loss (R)**
- **Local antibiotic policies should be developed and adhered to due to local resistance patterns (G)**

The timing of the administration of prophylactic antibiotics is important. Intravenous antibiotic should be given up to 60 minutes before the skin is incised.

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There is some evidence which suggests this dose should be as close to incision as possible. Repeat dosing should be considered when the operation is significantly longer than the half-life of the antibiotic given. In the event of major intra-operative blood loss (>1500 ml), additional prophylactic antibiotic dosage should be considered after fluid replacement to maintain serum concentrations.

Thromboembolic disease prophylaxis

The stated incidence of clinically significant venous thromboembolism (VTE) varies from 0 to 13 per cent in HNC operations.[11] Variation may relate to extent of surgery, and non-pharmacological mechanical interventions, with most series showing an incidence of less than 1 per cent. Early mobilisation and adequate hydration status are essential therapeutic interventions.

Current NICE guidance on VTE and Scottish Intercollegiate Guidelines Network guidelines cover all surgical patients without specific reference to head and neck cases. Individual assessment for risk of VTE and bleeding should occur on admission and be repeated at least every 48 hours throughout admission.

All patients with one or more of the risk factors (Box V) should receive mechanical prophylaxis from admission (anti-embolism stockings to knee or thigh, or foot impulse devices or intermittent pneumatic compression devices) unless contraindicated. Do not offer anti-embolism stockings to patients with cardiac failure, peripheral arterial disease or neuropathy or local tissue damage. Patients should be encouraged to mobilise and remain well hydrated.

BOX V
RISK FACTORS FOR VENOUS THROMBOEMBOLISM INCLUDE

- Advancing age >60 years
- Obesity – BMI > 30 kg/m^2
- Varicose veins
- Family history of VTE
- Thrombophilias
- Presence of cancer or other thrombotic states
- Significant medical comorbidities including heart disease
- Oestrogen containing drugs including hormone replacement therapy or tamoxifen
- Immobility
- Anaesthetic and surgical time >90 minutes

If the surgical procedure is associated with a low risk of major bleeding and taking into account individual risk factors, prophylactic LMWH, or unfractionated heparin for those with severe renal impairment, may be added until mobility is restored. From the risk factors detailed above it can be seen that the majority of head and neck patients are likely to be appropriate for combined pharmacological and mechanical prophylaxis regimes.

Recommendations

- **Individual assessment for VTE risk and bleeding risk should occur on admission and be reassessed throughout the patient's stay (G)**
- **Mechanical prophylaxis for VTE is recommended for all patients with one or more risk factors for VTE (R)**
- **Patients with additional risk factors of VTE and low bleeding risk should have LMWH at prophylactic dose or unfractionated heparin if they have severe renal impairment (R)**

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GUIDELINE

Anaesthesia for head and neck surgery: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. The anaesthetic considerations for head and neck cancer surgery are especially challenging given the high burden of concurrent comorbidity in this patient group and the need to share the airway with the surgical team. This paper provides recommendations on the anaesthetic considerations during surgery for head and neck cancer.

Recommendations

- All theatre staff should participate in the World Health Organization checklist process. (R)
- Post-operative airway management should be guided by local protocols. (R)
- Patients admitted to post-operative care units with tracheal tubes in place should be monitored with continuous capnography. Removal for tracheal tubes is the responsibility of the anaesthetist. (R)
- Anaesthetists should formally hand over care to an appropriately trained practitioner in the post-operative or intensive care unit. (G)
- Intensive care unit staff looking after post-operative tracheostomies must be clear about which patients are not suitable for bag-mask ventilation and/or oral intubation in the event of emergencies. (R)

Introduction

The anaesthetic and surgical team need to have a clear understanding about their respective roles in managing the 'shared airway'. This will vary with the surgery and the anaesthetist's requirement to avoid airway compromise by way of gas exchange or soiling. A guaranteed airway from pre-operative ward care through to safe discharge must be considered as an essential duty of care for any institution undertaking surgery of this nature.

Pre-operative assessment

Comorbidity and pre-operative assessment are considered elsewhere in the guidelines.[1] Because of the 'superficial' nature of head and neck surgery, patients are less likely to be considered 'unfit' relative to those presenting for body cavity cancer surgery. One must be aware that this group of patients are prone to sepsis and multi-organ failure needing intensive care support. Such issues should be anticipated and discussed with the patient and relatives as part of the consent for surgery. Similarly, because many of the patients are elderly and with limited support at home, the implications of post-operative result and how the patient will be able to cope should be part of the decision to offer surgical treatment.

General anaesthetic considerations

World Health Organization (WHO) checklist

All theatre staff are recommended to participate in this initiative to ensure that teams work effectively and that the right patients get the right surgical procedure they have consented to. In addition, reference should be made to anticipated airway problems and ensuring the necessary equipment is available.[2,3]

Monitoring requirements

The basic requirements for monitoring maintenance of anaesthesia and recovery are outlined in the Association of Anaesthetists of Great Britain and Ireland recommendations (4th edition, 2007) and advanced monitoring is usually only considered for long procedures or when excessive blood loss is a reasonable possibility.[4]

Prophylaxis for thromboembolism is discussed elsewhere in these guidelines[1]

Airway considerations

While patients presenting for head and neck surgery may have co-existent problems that could make airway management difficult (e.g. receding jaw, restricted neck movement, etc.), it is usually the size and site of tumour that causes concern. Any instrumentation needs to be judicious, including use of airway aids, in order that any problems with visualisation and/or airway soiling are not dramatically worsened. Patients with pharyngolaryngeal tumours frequently have residual food debris at laryngoscopy which may interfere with the view obtained especially for instruments with a limited field of vision. Contractures resulting from the previous treatment are common in patients with head and neck cancer. They may have obvious external deformities and restricted movements (e.g. limited neck extension). Rigidity and distortion of the oropharyngeal tissues can interfere with facemask ventilation and conventional laryngoscopy.

Oxygenation

Maintenance of oxygenation is fundamental to airway management and techniques that extend the apnoeic window allow more controlled, less hurried and more careful, gentle instrumentation. This may reduce the deterioration in the airway following instrumentation and the subsequent difficulty in facemask ventilation which can lead to a 'cannot intubate, cannot ventilate' scenario.[5] Traditional methods of increasing the apnoeic window involve spontaneous facemask ventilation with 100 per cent oxygen. Trans-nasal high-flow rapid insufflation ventilatory exchange or THRIVE delivered through a nasal high-flow oxygen delivery system has recently been shown to increase the apnoea time in head and neck patients including those with stridor to an average of 17 minutes. Trans-nasal high-flow rapid insufflation ventilatory exchange combines apnoeic oxygenation, continuous positive airway pressure and flow-dependent deadspace flushing and has the potential to change the nature of difficult intubations from a hurried stop–start process to a more controlled event, with an extended apnoeic window and reduced iatrogenic trauma.[6]

Induction of anaesthesia

If a patient is already at risk of airway obstruction due to tumour bulk, then it is probable that they will be at greater risk following induction of anaesthesia, whether intravenous or inhalational. Even local anaesthesia is not without risk because severe airway obstruction precipitated by laryngospasm has occurred. In some institutions, ventilation is established prior to induction of general anaesthesia via temporary cricothyroid or trans-tracheal access. (The latter is obviously preferable in patients with subglottic extension of a laryngeal tumour.) The use of muscle relaxant drugs to facilitate laryngoscopy in these cases is controversial because even if intubation conditions are improved this may be at the cost of greater risk of airway obstruction. Current practice has also been influenced by the introduction of many new intubation devices, very few of which have been reported in large series of head and neck cancer patients.

Fluid management and blood loss

Many resections and free tissue transfers will not be associated with significant bleeding, though this is not necessarily true for tongue and mandibular resections where brisk bleeding may occur. Hypotensive conditions may minimise blood loss and haemodilution is practiced in some institutions with a view to improved blood flow in free flaps. Intra-operative haemoglobin and central venous pressure measurements help in monitoring the need for blood transfusion. Cardiac monitoring was used regularly in only 9 per cent of UK units in an audit in 2012.[7]

Length of operative procedure

For lengthy operative procedures increased attention needs to be paid to the inevitable consequences of prolonged immobility, impaired homeostasis (associated with general anaesthesia) and the saturation of fatty tissue with anaesthetic agents. These equate to the need to protect from gravity-related pressure effects, thermal homeostasis, retention of urine and prolonged wake up time.

Post-operative airway management

Currently there is widely diverse practice in terms of post-operative airway management of head and neck cancer patients. For example, at one end of the spectrum almost all free-flap reconstructions are managed with temporary tracheostomy whereas elsewhere, overnight ventilation followed by extubation the following morning is the expected norm. There are differences as to which patients warrant this level of airway protection and even as to suitability for delivery of such care by immediate return to the ward *vs* high dependency or intensive care. The need for advanced airway protection is to avoid airway obstruction due to haemorrhage or other surgical complication affecting the airway. Tracheostomy is an intervention with its own risks including inadvertent decannulation and is also associated with increased hospital stay. Overnight intubation may carry increased risk for patients with significant comorbidity. The relative decrease in senior and junior intensive care unit staff with no airway training may also condition local perceptions of relative risk.

Recommendations

- **All theatre staff should participate in the WHO checklist process (R)**
- **Post-operative airway management should be guided by local protocols (R)**

Specific operative considerations

The compromised airway

In the patient who presents with acute airway compromise the obvious option is to consider a tracheostomy under local anaesthesia. Even this may not be an easy option in the patient who is already desaturated, uncooperative and unable to lie flat. Because of the need to attend to the problem, there will be limited time for radiological imaging. Heliox mixtures may provide symptomatic relief, while further information is obtained, e.g. nasendoscopy to assess the airway objectively. Many of these cases will prove to have a laryngeal tumour, in which case surgeons generally prefer that tracheostomy is avoided. It may be possible to de-bulk the tumour once intubation is achieved, but experienced practitioners need to be involved if this is to be attempted.

Tumour de-bulking to improve airway patency

Whether or not the patient presents as an emergency, there are two objectives. Firstly a biopsy will be taken for tissue diagnosis and secondly the tumour bulk will be reduced so as to minimise any likelihood of obstruction. Immediately after the procedure, the anaesthetist needs to confirm that the airway will be unobstructed (e.g. from a remaining tissue fragment acting as a ball-valve) and satisfactory from the point of view of bleeding.

Formal tumour assessment for treatment planning (examination under anesthesia and biopsy)

This is the more usual situation where the risk of airway obstruction is considered less likely. The anaesthetist will usually have information about the lesion (e.g. photograph or clinical diagram) under consideration and ideally, shared visualisation of the lesion prior to induction.

Tubeless anaesthesia

Ideally, any surgeon would wish to have an unrestricted view of the lesion to be operated on. In the case of laryngeal tumours, the most common compromise is to use a small diameter micro-laryngoscopy tube (6.0 mm ID or smaller). Other alternatives which allow a much less restricted field are: very narrow tubes used with gas exchanged by jet ventilation, a crico-thyroid airway (again usually with jet ventilation), *ad hoc* arrangements for repeated tube insertion and removal, and total intravenous anaesthesia with spontaneous respiration (usually also with local anaesthesia applied to the vocal cords). These alternatives tend to become more of a problem if the operative procedure is prolonged.

Laser surgery

The risk of airway fires due to laser is low provided careful precautions including laser safe tubes are used. Post-operative haemorrhage and oedema risks mean that tracheostomy remains an important consideration in extensive resections.

Free flaps

Attempts have been made to increase the success of free-flap anastomoses by medical means but there is no general consensus as to what if anything is efficacious. Doppler probes are available to monitor anastomotic vessel patency but are expensive and tend to be restricted in use to inaccessible sites, composite flaps (where skin colour may not reflect the deeper layer viability), continued arterial spasm risk and patients who have had previous radiation. Early return to theatre, however, in the event of compromise, may allow the flap to be salvaged if the blood flow can be restored.

Management of surgical complications

Neck haematoma, flap failures, fistulas and airway management issues (e.g. re-establishment of a closed tracheostomy) are common reasons for a return to theatre. When patients are admitted to a post-anaesthesia care unit with tracheal tubes in place, continuous capnography monitoring is appropriate and their removal remains the anaesthetist's responsibility.[8] It is important to be aware of the current state of the airway anatomy relative to the previous surgery and the time for healing. Severe bleeding is possible if major neck vessels are eroded. This sort of haemorrhage can arise suddenly and with little warning. Everyone involved needs to be acutely aware of what is needed by way of immediate measures (e.g. pressing on the neck in the event of a 'carotid blowout' or removing the skin clips in the event of a rapid expanding haematoma) *vs* the need to get to the theatre to attend to the problem directly. Proximity to the emergency theatres and kit available on the ward should be important considerations.

Recommendation

- **Patients admitted to post-operative care units with tracheal tubes in place should be monitored with continuous capnography. Removal for tracheal tubes is the responsibility of the anaesthetist (R)**

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Recovery from anaesthesia

Emergence from anaesthesia phenomena

Commonly seen problems include transient hypertension, disorientation and/or agitation and shivering. Analgesic requirements tend to be less than for body cavity surgery, but this will not necessarily be the case in patients on moderate doses of opiates for pre-operative pain problems. Flap donor sites may have their own analgesic requirements.

Immediate return to theatre from recovery

The most likely indications are bleeding and/or airway obstruction. The need for a covering tracheostomy may have been underestimated. Airway oedema can develop rapidly and is often precipitated by venous obstruction, posture change (e.g. allowing patients to lie down flat immediately prior to ward transfer) and Valsalva manoeuvres. Neck haematomas can be particularly deceptive because any associated airway oedema bears little resemblance to the apparent severity of neck swelling. If there is time it may be helpful to perform nasendoscopy prior to deciding how to anaesthetise for corrective surgical measures.

High dependency and intensive care

Many head and neck surgery patients will be looked after in enhanced care by virtue of their comorbidity, the length of surgical procedure or the need to closely monitor the free flap. It is unusual for any patient to be ventilated post-operatively. Standardised handover forms are commonly used to summarise surgery and anaesthesia intra-operative events with a description of the resulting airway anatomical configuration and advisory options in the event of potential airway problems.

Care of the tracheostomy

The Intensive Care Society has produced guidelines for the management of tracheostomy (and temporary tracheostomy in particular).[9] Percutaneous and surgical tracheostomy is commonly used to help manage lower airway and aspiration problems in the general intensive care setting. Anticipated complications include bleeding, tube obstruction and accidental decannulation. Dealing with any of these issues commonly requires senior and experienced staff and they will frequently resort to conventional oral intubation to secure the airway prior to re-establishing the compromised tracheostomy, but oral intubation may not be feasible either because this is physically impossible (e.g. the post-laryngectomy patient) or because oral intubation would seriously jeopardise the surgical result (e.g. immediately after partial laryngectomy or major tongue resection). These situations can be very serious both because of the technical challenges posed and the limited time available for re-establishing the compromised airway. It is essential that anyone dealing with these situations must know what surgery has been performed and whether oral intubation is a feasible alternative.

Enhanced recovery programmes (ERP) for head and neck cancer patients

An ERP can be formulated around the head and neck cancer patient's overall journey.[10,11] Stratified introduction of interventions with simple early objectives may yield a positive impact on outcomes. These programmes have been shown to improve outcomes in patients undergoing major colorectal and gynaecological procedures, by reducing length of stay and 30-day morbidity. Extrapolation of these concepts to patients with head and neck cancer undergoing major resections and free-flap surgery may help in improving outcomes. Relevant pre-operative measures might include carbohydrate loading with carbohydrate drinks 1–2 days before surgery. Intra-operative goals include: directed fluid therapy using cardiac output monitoring to optimise fluid management; maintenance of normothermia and tight glycaemic control. In the post-operative phase, early enteral feeding is advocated.

Recommendations

- **Anaesthetists should formally hand over care to an appropriately trained practitioner in the post-operative or intensive care unit (G)**
- **Intensive care unit staff looking after post-operative tracheostomies must be clear about which patients are not suitable for bag-mask ventilation and/or oral intubation in the event of emergencies (R)**

Key points

- The main difference between anaesthesia for major head and neck surgery and that for body cavity cancer is that because it is relatively superficial patients with greater comorbidity can be treated
- Overall care of the airway for these patients should be seen as an institutional responsibility where all the weakest points in care delivery are addressed
- Perioperative assessment should be comprehensive enough to make all airway issues predictable and suitably planned for
- Pre-oxygenation by trans-nasal high-flow rapid insufflation ventilator exchange ("Thrive") significantly extends the window for tracheal intubation, making it less stressful and less traumatic
- Operatively "shared airway" working (between the surgeon and anaesthetist) should be seamless with anticipation of one another's requirements
- Post-operative airway issues can occur even with minor surgical procedures, again these should be anticipated and planned for

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- Significant diversity exists in the expected post-operative care for major cases (mainly tracheostomy versus overnight intubation and extubation the following day)
- Staff caring for patients with tracheostomy and serious airway pathology must be aware of the special risks this implies, suitably trained and aware of the relevant guidelines
- Urgent airway issues need a planned response that takes into account local resource allocation and proximity between wards, theatre and HDU/ICU
- When urgent airway issues arise the institution must be able to match the response to the problem with appropriate seniority of expertise.

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GUIDELINE

Imaging in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This guideline is endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. This paper summarises the current imaging modalities in use for head and neck cancer evaluation. It highlights their role in the management with recommendations on modality choice for each cancer subsite.

Recommendations

- Offer appropriate radiological imaging, based on tumour extent, site and local expertise, to stage tumours and plan treatment for patients diagnosed with head and neck cancer. (G)
- Consider positron emission tomography combined with computed tomography (PET–CT) imaging if conventional cross-sectional imaging identifies no primary site. (R)
- Offer PET–CT imaging 12 weeks after non-surgical treatment to detect residual disease. (R)

Introduction

Imaging in head and neck cancer has developed enormously over the last few decades. Advanced cross-sectional imaging modalities allow accurate staging of disease and contribute significantly to management decisions and prognosis. As a core member of a multidisciplinary team, the radiologist has a key role in presenting relevant multi-modality findings that define disease extent, help with surveillance and highlight pertinent co-morbidities.[1] This approach also aids pre-treatment counselling and patient consent.

Prior to imaging, the primary site and the presence or absence of neck metastases of a head and neck cancer has often been established clinically and it is not unusual for a histological diagnosis to have been secured from a representative biopsy. Therefore, the primary role of radiology is in accurately staging the full extent and distant spread of disease with the current tumour–node–metastasis (TNM) system, with an emphasis on features that will influence surgical or non-surgical treatment options.

The areas that radiological assessment should focus on are:

- Local extent of the primary tumour
- Spread to locoregional cervical lymph nodes
- Detection of metastatic disease precluding cure and synchronous primary tumours of the lung and upper aero-digestive tract.

Imaging modalities

Computed tomography (CT)

Contrast-enhanced CT is the mainstay for imaging primary disease. It is widely available and established in practice. It incurs a significant radiation penalty and iodinated contrast medium is contraindicated in those with severe renal impairment. Conventionally, centres would image the neck and chest at presentation from the skull base to below the diaphragm.

Spatially good but at a radiation cost, CT provides limited soft tissue resolution. Bone detail such as with mandibular or skull base involvement is a major strength. Modern multislice, slip-ring CT detector technology rapidly acquires images without movement artefact as potential head and neck cancer patients may have difficulty with breathing, swallowing secretions and lying flat. Multiplanar and volume rendered images are easily reconstructed. Contrast-enhanced CT allows opacification of vascular structures whilst tumours generally tend to be slower to enhance with a reduced wash out.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging reflects biochemical tissue characteristics and is largely influenced by proton density and other in situ paramagnetic substances such as blood products and melanin content. Alongside the permanent bore magnet, additional

transient magnetic gradients allow the development of an ever increasing array of sequences that are able to reflect pathological processes from normal surrounding tissues. Multiple manufacturers may have differing terms for sometimes similar sequence parameters.

T1-weighted 'anatomical' images have excellent spatial resolution, whilst T2-weighted images preferentially highlight oedema and therefore pathology. A short tau inversion-recovery (STIR) sequence retains the positive attributes of a T2-weighted image and suppresses surrounding fat signal in normal or invaded tissues to best depict abnormal tissue as a bright, high signal. Magnetic resonance imaging has the ability to dramatically improve tissue contrast resolution when compared with CT and, in compliant patients without contraindications, it is the imaging modality of choice for defining the primary extent of oral and oropharyngeal cancers. Detrimentally, when compared with CT, scan times are much longer and can vary from about 2–10 minutes for each sequence, during which the patient must keep relatively still. Intravenous gadolinium contrast agents allow static and dynamic vascular assessments of a tumour and, when combined with fat suppression techniques, this can increase the conspicuity of occult pathology. Dental amalgam can reduce the image quality both for CT and MR imaging that makes interpretation more challenging.

Positron emission tomography combined with CT (PET–CT)

Positron emission tomography combined with CT whole-body imaging uses various labelled tracers to fuse conventional, anatomical CT images with a functional 'map' of the disease process. This is conducted on a single gantry at a single appointment. The commonest tracer is 18 fluoro-deoxyglucose, which is preferentially transported and trapped into hypermetabolic cancerous or inflamed tissues. It is detected with a gamma camera array. The patient's fasted baseline glucose level should be measured and the isotope is injected intravenously approximately 1 hour before imaging. The patient refrains from talking or chewing. Actual image acquisition takes about 30–45 minutes. Modern scanner design accurately co-registers metabolic tissue activity with its precise anatomical location.

In 2013, the Royal College of Radiologists published evidence-based guidelines for PET–CT use in head and neck cancer. Evaluating the patient with malignant cervical adenopathy from an unknown primary is one of the main, up-front indications. Positron emission tomography will detect an occult primary in approximately one third of cases. Positron emission tomography combined with CT is also valuable in the assessment of suspected recurrence of head and neck cancer when there are extensive, confounding post-treatment changes on conventional imaging modalities. Its added benefit in routine surveillance following treatment is still being assessed. Along with other modalities, it has a role in staging malignant thyroid disease including medullary thyroid carcinoma.

Ultrasound

Offered as part of a modern one-stop service, ultrasound, alongside fine needle aspiration cytology, allows rapid imaging assessments for those with an undiagnosed neck lump or suspected metastatic disease in the neck. This technique can be notoriously operator dependent, but has no detrimental patient effects. Following slide preparation, best cytological practice recommends prompt adequacy assessments and, ideally, the cytologist should be onsite for diagnostic advice. In reality, a shortage of radiology and histopathological input makes such universal service developments difficult.

Ultrasonography comfortably delineates thyroid pathology and can detect occult pathological nodes (necrosis, microcalcification, etc.) that may feel clinically normal in size. A normal node should remain ovoid in shape with a short axis diameter less than 10 mm with a preserved echogenic hilum. Retropharyngeal and superior mediastinal nodes cannot be assessed with this modality.

Current doctrine dictates that clinically and radiologically N0 disease from high-risk primary sites is presumed to have small volume nodal micrometastasis that routinely requires prophylactic first-line treatment as no available tests can guarantee a true pathological N0 status.

Fluoroscopy

There are a variety of scenarios when contrast swallows and fluoroscopy are used in head and neck cancer, although the availability of local expertise can be variable. Contrast swallows can be used to assess the length of a malignant proximal oesophageal stricture, while the risk of airway aspiration or penetration is dynamically assessed by videofluoroscopy. Alternative, non-oncological causes for dysphagia such as a pharyngeal pouch may be diagnosed. Water soluble contrast studies are advised when the risk of aspiration is high, for instance, following recurrent chest infections or diminished pharyngeal sensory/motor function after surgery or radiation. The integrity of a surgical anastomosis or the tract of an entero-cutaneous fistula can also be well evaluated. These studies are often jointly performed with a speech and language therapist to facilitate decision making and may improve functional outcomes.

Chest imaging

With common aetiological factors, patients with head and neck cancer have higher incidences of synchronous and metachronous primary lung tumours that may be

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disseminated at presentation. At staging, CT imaging of the thorax is routinely advised.

The most common protocol for patients with a head and neck cancer will therefore be to image the primary site by either contrast-enhanced CT or magnetic resonance imaging (MRI), perform CT imaging of the chest and PET–CT for the unknown primaries.

Specific tumour sites

This section deals with specific tumour sites and highlights areas where radiological evaluation is particularly important and often difficult.

Oral cavity

Preferred imaging modality: MRI

Tongue tumours are routinely evaluated with MRI to aid treatment choices and prognosis. Early or advanced cancers of the buccal mucosa, retromolar trigone, palatal and floor of mouth are more difficult to evaluate reliably by imaging alone and good clinical correlation is essential. Perineural and marrow involvement is best defined at MRI.

In an attempt to avoid osteoradionecrosis, orthopantomograms are still requested to proactively treat dental caries and peri-apical disease.

Oropharynx

Preferred imaging modality: MRI

Small or subclinical primaries in the tonsil and tongue base that often present with cervical lymphadenopathy can be difficult to identify with all forms of imaging including PET–CT. These tumours are often best evaluated at MRI with STIR sequences and often, may only be localised retrospectively after examination and biopsy under anaesthesia. Extension of mucosal tumours into the adjacent structures and neck spaces is well depicted with MR imaging.

Nasopharynx

Preferred imaging modality: MRI

Nasopharyngeal tumours commonly present at an advanced stage with palpable nodal neck disease. Magnetic resonance imaging allows accurate classification of the primary site and nodal disease as per the TNM classification, based on disease extent.

Hypopharynx

Preferred imaging modality: MRI

In those patients who have difficulty with swallowing, aspiration or breathing when supine, a CT scan will need to be strongly considered.

Larynx

Preferred imaging modality: MRI

Disease at the level of the vocal cords presents early with dysphonia and is well localised. Imaging is often unnecessary for T1 disease unless extralaryngeal disease, cartilage involvement, nodal metastasis or chest pathology is suspected. MRI with contrast is the gold standard for depiction of cartilage involvement.

Recommendations

- **Offer appropriate radiological imaging, based on tumour extent, site and local expertise, to stage tumours and plan treatment for patients diagnosed with head and neck cancer (G)**
- **Consider PET–CT imaging if conventional cross-sectional imaging identifies no primary site (R)**
- **Offer PET–CT imaging 12 weeks after non-surgical treatment to detect residual disease (R)**

Salivary glands

Malignant salivary glands neoplasms are a very heterogenous group of tumours, where tumour behaviour and prognosis is dictated by the histology. Ultrasound techniques have a significant role to play in assessing the parenchymal mass, local adenopathy and guiding biopsies. Perineural or skull base involvement often requires a combined multi-modality CT and MR approach. The best imaging modality may be guided by site-specific characteristics such as respiratory motion artefact.

Sinuses

MRI with contrast is the modality of choice to assess surgical resectability issues around intracranial and orbital disease spread. Skull base involvement usually requires a complementary CT study.

Post-operative imaging

The choice of imaging in the post-operative scenario is determined by the specific clinical question posed. Complications are frequent with difficult head and neck resections. When the specific question is over potential residual or recurrent disease, following either surgery or chemoradiotherapy, the choice for baseline imaging mainly falls between a contrast CT of the neck and chest and a timely PET–CT study. As an exception, MRI has a large role to play specifically for nasopharyngeal, sinonasal and skull base tumour follow up.[2] Early detection of residual disease is vital to planning further curative attempts. The timing of the scan is important. Dedicated CT gives better resolution and anatomical detail at the primary site as well as detecting subcentrimetre early metastatic disease in the lungs. Obliteration of fat planes and anatomical distortions makes interpretation difficult. A negative, normal PET–CT 12 weeks post-treatment likely offers the best prognostic reassurance currently.[3] PET–CT fails to reliably distinguish inflammatory

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elements from malignant foci. Ultrasound guided procedures still have a role to play in sampling indeterminate, persistent enlarged cervical nodes.

Key points

- Accurate image interpretation and staging heavily influences optimal treatment strategies
- Contrast-enhanced computed tomography of the skull base, neck and chest is ubiquitous in nature, readily available and the workhorse for routine tumour–node–metastasis staging of head and neck cancers
- Positron emission tomography combined with computed tomography is of proven diagnostic benefit when searching for the unknown primaries, when conventional imaging is non-informative
- In compatible patients, magnetic resonance imaging has superior soft tissue characterisation at several primary sites including oropharynx, nasopharynx/skull base and sinuses that greatly aid surgical planning and resections
- Ultrasound image guided diagnostic fine needle and core biopsies are well established and cost-effective in the context of good cytological/histological support
- In certain instances, multi-modality approaches are complementary to each other but should not adversely impact on the speed of the diagnostic pathway.

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GUIDELINE

Nutritional management in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

Nutritional support and intervention is an integral component of head and neck cancer management. Patients can be malnourished at presentation, and the majority of patients undergoing treatment for head and neck cancer will need nutritional support. This paper summarises aspects of nutritional considerations for this patient group and provides recommendations for the practising clinician.

Recommendations

- A specialist dietitian should be part of the multidisciplinary team for treating head and neck cancer patients throughout the continuum of care as frequent dietetic contact has been shown to have enhanced outcomes. (R)
- Patients with head and neck cancer should be nutritionally screened using a validated screening tool at diagnosis and then repeated at intervals through each stage of treatment. (R)
- Patients at high risk should be referred to the dietitian for early intervention. (R)
- Offer treatment for malnutrition and appropriate nutrition support without delay given the adverse impact on clinical, patient reported and financial outcomes. (R)
- Use a validated nutrition assessment tool (e.g. scored Patient Generated–Subjective Global Assessment or Subjective Global Assessment) to assess nutritional status. (R)
- Offer pre-treatment assessment prior to any treatment as intervention aims to improve, maintain or reduce decline in nutritional status of head and neck cancer patients who have malnutrition or are at risk of malnutrition. (G)
- Patients identified as well-nourished at baseline but whose treatment may impact on their future nutritional status should receive dietetic assessment and intervention at any stage of the pathway. (G)
- Aim for energy intakes of at least 30 kcal/kg/day. As energy requirements may be elevated post-operatively, monitor weight and adjust intake as required. (R)
- Aim for energy and protein intakes of at least 30 kcal/kg/day and 1.2 g protein/kg/day in patients receiving radiotherapy or chemoradiotherapy. Patients should have their weight and nutritional intake monitored regularly to determine whether their energy requirements are being met. (R)
- Perform nutritional assessment of cancer patients frequently. (G)
- Initiate nutritional intervention early when deficits are detected. (G)
- Integrate measures to modulate cancer cachexia changes into the nutritional management. (G)
- Start nutritional therapy if undernutrition already exists or if it is anticipated that the patient will be unable to eat for more than 7 days. Enteral nutrition should also be started if an inadequate food intake (60 per cent of estimated energy expenditure) is anticipated for more than 10 days. (R)
- Use standard polymeric feed. (G)
- Consider gastrostomy insertion if long-term tube feeding is necessary (greater than four weeks). (R)
- Monitor nutritional parameters regularly throughout the patient's cancer journey. (G)
- Pre-operative:
  - Patients with severe nutritional risk should receive nutrition support for 10–14 days prior to major surgery even if surgery has to be delayed. (R)
  - Consider carbohydrate loading in patients undergoing head and neck surgery. (R)
- Post-operative:
  - Initiate tube feeding within 24 hours of surgery. (R)
  - Consider early oral feeding after primary laryngectomy. (R)

- Chyle Leak:
  - Confirm chyle leak by analysis of drainage fluid for triglycerides and chylomicrons. (R)
  - Commence nutritional intervention with fat free or medium chain triglyceride nutritional supplements either orally or via a feeding tube. (R)
  - Consider parenteral nutrition in severe cases when drainage volume is consistently high. (G)
- Weekly dietetic intervention is offered for all patients undergoing radiotherapy treatment to prevent weight loss, increase intake and reduce treatments interruptions. (R)
- Offer prophylactic tube feeding as part of locally agreed guidelines, where oral nutrition is inadequate. (R)
- Offer nutritional intervention (dietary counselling and/or supplements) for up to three months after treatment. (R)
- Patients who have completed their rehabilitation and are disease free should be offered healthy eating advice as part of a health and wellbeing clinic. (G)
- Quality of life parameters including nutritional and swallowing, should be measured at diagnosis and at regular intervals post-treatment. (G)

Introduction

Nutrition and Dietetic services should be organised to provide a seamless service at any stage of the patient pathway. There should be access to dedicated, site-specific dietitians for high-quality service delivery and contribution as a core member of the head and neck multidisciplinary team.[1] Early identification of high-risk patients and intervention with nutrition support should be included as part of the planning for every patient when treatment options are being considered.[1,2] This should include quality of life (QoL) issues to address psychosocial, rehabilitation and survivorship needs of patients and carers.

Recommendation

- **A specialist dietitian should be part of the multidisciplinary team for treating head and neck cancer patients throughout the continuum of care as frequent dietetic contact has been shown to have enhanced outcomes (R)**

Nutritional screening

The purpose of nutritional screening is to identify patients who are malnourished or at risk of becoming malnourished as early as possible.[1,2] All inpatients on admission and all outpatients should be screened to identify those who require early nutritional intervention and prompt referral.[1,2] Table I shows the various screening tools available.

Monitoring

Screening should be repeated weekly for inpatients. For outpatients, weight should be recorded at each outpatient visit and weight loss of 2 kg or more within a two-week period reported to the dietitian.[1,2]

Recommendations

- **Patients with head and neck cancer should be nutritionally screened using a validated screening tool at diagnosis and then repeated at intervals through each stage of treatment (R)**
- **Patients at high risk should be referred to the dietitian for early intervention (R)**

Impact of malnutrition

Patients with head and neck cancer are at risk of malnutrition as a result of the site of their cancer, the disease process and the treatment. Patients may have long standing dietary habits and detrimental lifestyle factors such as alcohol misuse that may predispose them to malnutrition. Regardless of presenting body mass index (BMI), unintentional weight loss of 10 per cent or greater in the preceding six months may lead to a range of problems[3] as highlighted in Box I.[4]

BOX I
MALNUTRITION ASSOCIATED MORBIDITY

- Increased risk of infection
- Delayed wound healing
- Impaired function of cardiac and respiratory systems
- Muscle weakness
- Depression
- Poor QoL
- Increased risk of post-operative complications
- Reduced response to chemotherapy and radiotherapy
- Increased mortality rate

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TABLE I
NUTRITIONAL SCREENING AND ASSESSMENT TOOLS

Screening tool	Information	Validated in cancer patients
The Subjective Global Assessment (SGA) tool	Assesses nutritional status based on features of the history and physical examination	Yes
The patient generated – Subjective Global Assessment (PG-SGA)	An adaptation of the SGA tool for assessing the nutritional status and is patient generated	Yes
The Malnutrition Screening Tool	Compares favourably with the PG-SGA	Yes
The Malnutrition Universal Screening Tool	Currently used by many Trusts across the UK to screen patients	No

Early nutritional intervention is essential to correct pre-existing nutritional deficiencies with regular reviews throughout the patient's journey in order to optimise nutritional status and correct nutrition-related problems at each stage of treatment.[1,5]

Recommendation

- **Offer treatment for malnutrition and appropriate nutrition support without delay given the adverse impact on clinical, patient reported and financial outcomes (R)**

Nutritional assessment

Following nutritional screening a full nutritional assessment should be undertaken in a pre-treatment assessment clinic setting and at regular intervals during a patient's treatment trajectory[1,2] (Table II).

Recommendations

- **Use a validated nutrition assessment tool (e.g. scored Patient Generated–Subjective Global Assessment or Subjective Global Assessment) to assess nutritional status (R)**
- **Offer pre-treatment assessment prior to any treatment as intervention aims to improve, maintain or reduce decline in nutritional status of head and neck cancer patients who have malnutrition or are at risk of malnutrition (G)**
- **Patients identified as well-nourished at baseline but whose treatment may impact on their future nutritional status should receive dietetic assessment and intervention at any stage of the pathway (G)**

Cancer cachexia

Cachexia syndrome results in decreased appetite, weight loss, metabolic alterations and an inflammatory state that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Pro-inflammatory processes can lead to insulin resistance, increased loss of body fat, muscle mass and production of acute phase proteins. Cytokine-induced metabolic alterations can prevent cachectic patients from regaining body cell mass during nutritional support, and are not relieved by conventional nutritional intervention. Attempts to modulate these changes by other means should be integrated into the management of cancer patients. As a minimal goal body weight should be maintained and further loss prevented. The management approach should be multifactorial and includes assessment and ongoing monitoring with intensive nutritional support, anti-inflammatory treatment, symptom control as well as oncological treatment options to reduce the catabolic effect of the cancer.[6]

Estimating nutritional requirements

Cancer itself does not have a consistent effect on resting energy expenditure, but may be influenced by oncological treatment. Resting energy expenditure can be unchanged, increased, or decreased.[2] Cancer patients are mildly hypermetabolic with an excess energy expenditure of between 138 and 289 kcal/day. Total energy expenditure and protein requirements for non-obese ambulatory patients using their actual body weight can be estimated as follows:

Energy, 30–35 kcal/kg/day and protein, 1.2 g/kg/day.[1] These may be less accurate for severely malnourished, morbidly obese and surgical patients.

Recommendations

- **Aim for energy intakes of at least 30 kcal/kg/day. As energy requirements may be elevated post-operatively, monitor weight and adjust intake as required (R)**
- **Aim for energy and protein intakes of at least 30 kcal/kg/day and 1.2 g protein/kg/day in patients receiving radiotherapy or chemoradiotherapy**
- **Patients should have their weight and nutritional intake monitored regularly to determine whether their energy requirements are being met (R)**

Refeeding syndrome

Refeeding is a syndrome consisting of metabolic disturbances that occur as a result of reintroduction of nutrition to patients who are starved or severely

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TABLE II
NUTRITIONAL ASSESSMENT PARAMETERS

Clinical observation	• Ability to chew and swallow • Clinical signs of weight loss e.g. ill-fitting dentures/clothing • Medical history which may affect nutritional intake e.g. coeliac disease, diabetes
Dietary history	Review of recent intake (24 hours recall), with attention being paid to: • Fluid intake • Changes in texture • Reports of fullness • Length of time and effort taken to eat • Changes in appetite • Gastrointestinal function
Calculation of requirements	Energy: • 25–35 kcal/kg/day dependant on activity level. Can increase further if major complications. Protein: • 0.8–2.0 g/kg/day for depleted of treatment complications Fluid: • 30–35 ml/kg/day increases in infection and excessive fluid losses Vitamins and minerals: • As per recommended daily amounts unless considered deficient
Proposed treatment	• Disease status, tumour site • Nutritional implications of previous and current treatment plan
Anthropometry	• Height • Weight • Weight history • Percentage weight change • Body mass index; <18.5 kg/m^2 suggests undernutrition • Triceps skinfold thickness indicates fat stores • Mid arm muscle circumference indicates lean tissue mass • Hand grip strength assesses muscle function
Biochemistry	• Urea and electrolytes – indicate fluid status although can be disrupted by disease state and treatment • Albumin – not good indicator of nutritional status due to its long half-life (17–20 days) and it is affected by stress and sepsis • Pre-albumin – shorter half-life 2–3 days but also affected by infection and stress • C-reactive protein – indication of acute phase response • Transferrin – affected by inflammation and infection • Total lymphocyte count – affected by infection • Refeeding syndrome risk
Social information	• Alcohol intake • Smoking • Substance misuse • Social support • Dentition • Access to food and cooking skills • Social and financial circumstances • Time taken to eat and drink • Patient perception of nutritional status

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malnourished. It can occur irrespective of the feeding route. The main feature is hypophosphataemia but can feature abnormal sodium and fluid balance; changes in glucose, protein, and fat metabolism, thiamine deficiency, hypokalaemia and hypomagnesaemia.[7]

The nationwide incidence of refeeding syndrome in head and neck cancer is unknown. By defining refeeding syndrome as a reduction in serum phosphate to below 0.4 mmol/l,[1,7] retrospective data from a regional cancer centre found 37.5 per cent of patients to be at risk as defined by National Institute for Health and Care Excellence criteria (see Box II) with an incidence rate of 9.5 per cent. A suggested management plan for refeeding syndrome is shown in Figure 1.

Recommendations

- **Perform nutritional assessment of cancer patients frequently (G)**
- **Initiate nutritional intervention early when deficits are detected (G)**
- **Integrate measures to modulate cancer cachexia changes into nutritional management (G)**

BOX II
CRITERIA FOR DETERMINING PEOPLE AT MODERATE OR HIGH RISK OF DEVELOPING REFEEDING SYNDROME[2]

Patient has one or more of the following:

- Body mass index less than 16 kg/m^2
- Unintentional weight loss greater than 15 per cent within last three to six months
- Little or no nutritional intake for more than 10 days
- Low levels of potassium, phosphate, or magnesium prior to feeding

Or patient has two or more of the following:

- Body mass index less than 18.5 kg/m^2
- Unintentional weight loss greater than 10 per cent within last three to six months
- Little or no nutritional intake for more than 5 days
- A history of alcohol abuse or drugs, including insulin, chemotherapy, antacids or diuretics

Nutrition support

The aims of nutrition support are to:

- Improve the subjective QoL
- Enhance anti-tumour treatment effects
- Reduce the adverse effects of anti-tumour therapies,
- Prevent and treat undernutrition.

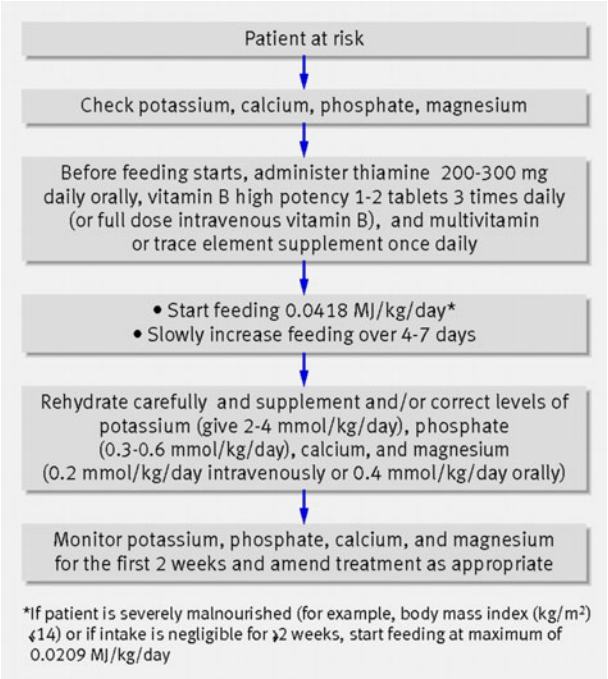

FIG. 1
Management of re-feeding syndrome (reproduced with permission from Mehanna *et al.*[7]).

Nutritional support should be considered in the following scenarios:

- Body mass index <18.5 kg/m^2
- Unintentional weight loss >10 per cent over three to six months
- A BMI <20 kg/m^2 and unintentional weight loss over three to six months
- Minimal intake >5 days
- Increased nutritional requirements due to catabolism.

Types of nutrition support

Nutritional intervention should be tailored to meet the needs of the patient and be realistic for the patient to achieve. There are three main methods of nutrition support: oral, enteral and parenteral. Parenteral nutrition support is rarely used in the head and neck setting. It should however be considered if required.

Oral nutrition support

Nutritional interventions include relaxation of previous therapeutic diets to minimise further nutritional compromise and to positively influence QoL outcomes.[8] Food fortification is first line advice; however, this may not necessarily be appropriate due to the side effects and intensity of treatment regimens. Patients may require more intensive nutritional support methods from the beginning of treatment over and above traditional food fortification methods with the

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early use of oral nutrition support, e.g. nutritionally complete liquid supplements. This can be initiated at any point from diagnosis. There are a variety of oral nutritional support products available. The choice will depend on patient preference, current macro and micro nutrient intake and local policy.

Enteral nutrition (EN) support

The choice of feeding route will depend upon local arrangements, however clinical considerations should include: site of tumour, treatment plan and intent, predicted duration of enteral feeding and patient choice.[9,10] The types of tubes available are nasogastric, nasojejunal, tracheo – oesophageal fistulae tubes, orogastric, gastrostomy, gastro-jejunostomy and jejunostomy. Nasogastric, nasojejunal, oro gastric, trachea – oesophageal fistulae tubes are all recommended for short-term use (less than four weeks). National Institute for Health and Care Excellence guidelines on enteral feeding suggest that if enteral feeding is expected to be required for longer than four weeks then gastrostomy insertion is recommended.[2]

Consideration should be made with regard to the timing and method of gastrostomy placement. Screening and assessment for suitability and method of gastrostomy insertion by endoscopic, radiological or surgical approach is essential. Assessment of co-morbidities and contraindications should be undertaken in order to prevent complications of tube insertion prior to oncological treatment. Variation exists for the preferred method of insertion and is dependent on local policy. There are no nationally agreed selection criteria for gastrostomy placement in head and neck patients. Comparison between studies is difficult and made more challenging by limitations in study design as well as the inability to stratify data meaningfully into groups with adequate patient numbers by similar treatment modality, type of gastrostomy and timing of tube placement.[9,10] Evidence-based practice guidelines, based on a systematic review of literature across the entire nutrition care pathway, following a National Health and Medical Research Council's process for assessing the level of evidence and evaluating the body of literature, have been published.[1] Although the optimal method of tube feeding remains unclear,[10,11] it is widely accepted that prophylactic tube feeding compared with reactive tube feeding or oral intake alone improves nutritional outcomes with reduced weight loss, and can therefore contribute towards clinical, financial and QoL aspects.[1,12] However, high-level evidence base is yet to be generated to confirm the benefits.[13,14] Appropriate decision making around prophylactic tube feeding must consider all factors that impact on nutrition including patient demographics, tumour site and staging, impact of treatment modalities on the patient's ability to meet and sustain nutritional requirements, nutritional status, dysphagia, type and placement technique of feeding tube and associated morbidity.[4,9,10] While there is no universally accepted definition of gastrostomy dependency, the principle is recognised and reported.[15] In clinical studies, gastrostomy tube is used as a proxy measure for poor swallowing in the absence of reviewing nutritional outcome data, intensity and frequency of dietary counselling and swallowing rehabilitation and co-ordination of these services before, during and after treatment.[9,10]

Enteral nutrition

The type and volume of EN will depend upon the patients' symptoms and current intake and is likely to change throughout and following treatment.[2] There are no data to suggest a role for cancer-specific enteral formulae and standard polymeric feeds should be used in this population group. There are a range of nutritionally complete feeds available. Local policies and feed contract arrangements determine the type and make.

Immune-enhanced nutrition

Immunonutrition are feeds containing amino acids, nucleotides and lipids. There are no additional benefits to immunonutrition pre-operatively over standard nutrition support. Preliminary data suggest that in the peri-operative period, *N*-3 enriched nutrition support may improve nutritional outcomes including weight, lean body mass and fat mass, reduce post-operative infections and reduce hospital stay.[16]

Monitoring nutritional support

Monitoring nutritional intervention is essential, as compliance with recommendations can be a problem. Monitoring should involve the multidisciplinary team, including dietitians, medical teams, speech and language therapist and clinical nurse specialists.

Recommendations

- **Start nutritional therapy if undernutrition already exists or if it is anticipated that the patient will be unable to eat for more than 7 days. Enteral nutrition should also be started if an inadequate food intake (60 per cent of estimated energy expenditure) is anticipated for more than 10 days (R)**
- **Use standard polymeric feed (G)**
- **Consider gastrostomy insertion if long-term tube feeding is necessary (greater than four weeks) (R)**
- **Monitor nutritional parameters regularly throughout the patient's cancer journey (G)**

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Nutrition considerations during surgical treatment

Enhanced recovery after surgery programmes are starting to be developed and implemented across Head and Neck Centres. Nutritional interventions are part of enhanced recovery and should be considered at all stages of the pathway from diagnosis to survivorship and wellbeing.

Pre-operative nutrition

Inadequate oral intake for more than 14 days is associated with a higher mortality. Patients with severe nutritional risk should receive nutrition support for 10–14 days prior to major surgery even if surgery has to be delayed.[5,16] Carbohydrate loading is becoming standard practice in some centres for all patients undergoing head and neck cancer surgery. It has been shown to be safe and well tolerated in patients undergoing head and neck surgery. The type of carbohydrate-loading products used will depend on local contractual arrangements. Enteral nutrition is indicated even in patients without obvious undernutrition, if it is anticipated that patients will be unable to eat for more than 7 days peri-operatively. Box III indicates criteria for initiating pre/peri-operative nutrition support and identifies patients with severe nutritional risk.

BOX III
CRITERIA FOR INITIATING PRE-OPERATIVE NUTRITIONAL SUPPORT[2,5]

Indications:

- Weight loss >10–15 per cent in 6 months
- Body mass index <18.5 kg/m^2
- Subjective Global Assessment Grade C
- Serum albumin <30 g/l
- Unable to maintain intake above 60 per cent of recommended intake for more than 10 days

Post-operative nutrition

Early post-operative tube feeding (within 24 hours) is indicated in patients in whom early oral nutrition cannot be initiated. Nutrition support, especially enteral nutrition, reduces morbidity. In some centres, as part of the enhanced recovery programme, very early nutritional intervention is being trialled. Standard polymeric enteral feeds are suggested post-operatively with currently very limited evidence to support the use of immunonutrition. Early oral feeding after primary total laryngectomy (from as early as 1 day post-operation to 7 days) is thought to reduce length of stay as there has been shown to be no difference in fistulae rates compared with delayed oral feeding of >7 days.

Nutritional management of chyle leaks

This is a rare complication with an incidence of 1–2 per cent following radical neck dissections, and less common with selective neck dissections often performed in current practice. The management may be conservative, including dietary manipulation or further surgery. A post-operative leak gives the fluid a milky appearance. A triglyceride level >110 mg/dl is diagnostic of a chyle leak. If the triglyceride level is <110 mg/dl, further analysis is required to demonstrate the presence of chylomicrons. A triglyceride level <50 mg/dl usually rules out a diagnosis of a chyle leak unless a patient is malnourished or has been fasted.

The principal aims of nutritional management are to reduce the flow of chyle whilst maintaining nutritional status, ensuring adequate fluid balance and replacing electrolyte losses.

The nutritional management is to use a fat free or high medium chain triglyceride (MCT) product. Medium chain triglyceride is recommended because it is directly absorbed into the portal system resulting in less chyle production. In clinical practice fat free products can be more accessible and practical than MCT feeds. If dietary manipulation is unsuccessful parenteral nutrition may be required. This should not be used as first line management except in extreme cases, e.g. very high-volume leaks (>1000 ml).

There is no consensus on how to nutritionally manage chyle leaks, how long nutrition management should be pursued, or what constitutes an acceptable amount of chyle output.[1,17,18] The nutritional intervention is usually dependant on clinician preference.

Recommendations

- **Pre-operative:**
  - **Patients with severe nutritional risk should receive nutrition support for 10–14 days prior to major surgery even if surgery has to be delayed (R)**
  - **Consider carbohydrate loading in patients undergoing head and neck surgery (R)**
- **Post-operative:**
  - **Initiate tube feeding within 24 hours of surgery (R)**
  - **Consider early oral feeding after primary laryngectomy (R)**
- **Chyle leak:**
  - **Confirm chyle leak by analysis of drainage fluid for triglycerides and chylomicrons (R)**
  - **Commence nutritional intervention with fat free or MCT nutritional supplements either orally or via a feeding tube (R)**
  - **Consider parenteral nutrition in severe cases when drainage volume is consistently high (G)**

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Nutritional considerations during curative radiotherapy ± chemotherapy

Concomitant mucositis during radiotherapy ± chemotherapy results in weight loss, which cannot be completely prevented by nutritional counselling alone.[19] Intensive dietary counselling and oral nutrition support to increase dietary intake and to prevent treatment associated weight loss is recommended for patients undergoing radiotherapy of the head and neck.[20] This is also advised to prevent interruptions to radiation treatment. Tube feeding is recommended if the cancer interferes with swallowing or if mucositis is anticipated which may interfere with oral and/or pharyngeal swallowing.[21] The optimal method of tube feeding remains unclear, therefore, the risks and benefits of both proactive and reactive approaches should be discussed by the dietitian with the patient to ensure individualised nutritional care.[1] Prophylactic tube feeding compared to oral intake alone or reactive tube demonstrates reduced weight loss in the short term, may reduce unplanned hospital admissions and may improve QoL during and after treatment.[1] The Clinical Oncological Society of Australia recommends that patients should be seen weekly during radiotherapy. However, in some centres twice weekly follow up is provided. Intensity Modulated radiotherapy is now used for the treatment of head and neck cancer. This treatment has not been found to reduce nutrition related toxicity and patients should be managed in the same way as conventional radiotherapy. Patients receiving biological agents such as cetuximab with radiotherapy should be nutritionally managed in the same way as those receiving chemoradiotherapy.[1]

Recommendations

- **Weekly dietetic intervention is offered for all patients undergoing radiotherapy treatment to prevent weight loss, increase intake and reduce treatments interruptions (R)**
- **Offer prophylactic tube feeding as part of locally agreed guidelines, where oral nutrition is inadequate (R)**

Nutritional considerations during palliative chemotherapy and radiotherapy

The use of chemotherapy and radiotherapy may be used to relieve symptoms caused by the cancer where the goal is to improve the QoL but not treat the disease. Palliative chemotherapy and radiotherapy is increasingly used in the treatment of head and neck cancer and the dietitian has a role in supporting the nutritional needs of patients receiving these treatments. Patients may experience side effects from these treatments which affect their ability to take adequate nutrition or require dietary intervention to support their QoL.[1,9]

Rehabilitation

Patients are at high risk of developing late and long-term effects of treatment resulting in eating difficulties requiring dietary modification, supplementation and alternative feeding. Patients should be seen fortnightly for at least six weeks post-treatment and patients should be reviewed by the dietitian for up to six months or for as long as they require management of chronic toxicities, weight loss or tube feeding.[1]

Guidance for clinical management and a strategic framework for structured head and neck 'local support' services as part of the multidisciplinary team are limited, but should be interpreted at a local level to deliver high-quality patient-centred nutritional care.[1,4]

Recommendation

- **Offer nutritional intervention (dietary counselling and/or supplements) for up to three months after treatment (R)**

Survivorship

The number of patients living with cancer or its long-term side effects is increasing. Many of our cancer survivor patients have unmet needs. It is recommended that patients are offered education and support events (Health and Wellbeing Clinics) after completion of treatment and rehabilitation.[22] Dietitians can play a key role in these events by offering tailored healthy eating advice that takes into consideration the long-term side effects that head and neck cancer patients may experience. Macmillan cancer support is currently developing a healthy eating toolkit that can be adapted for use with head and neck cancer patients.

Recommendation

- **Patients who have completed their rehabilitation and are disease free should be offered healthy eating advice as part of a health and wellbeing clinic (G)**

Quality of life

Head and neck-specific validated tools exist to evaluate QoL. These tools may include factors relating to eating and drinking, but there is no nutrition-specific module to assess the relationship between QoL, nutritional status, malnutrition and nutrition support in this patient group.[4] Reduction in QoL can be directly related to weight loss and malnutrition with an improvement seen when dietary counselling and

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aggressive nutritional support is maintained during treatment. The impact of having a feeding tube on patients' QoL requires further evaluation.

Recommendation

- **Quality of life parameters, including nutrition and swallowing, should be measured at diagnosis and at regular intervals post-treatment (G)**

Key points

- Nutrition has an important role in the management of head and neck cancer and its associated treatment modalities
- Specialist site specific dietitians should be part of the multidisciplinary team for treating head and neck cancer patients as frequent dietetic contact has been shown to enhance outcomes
- Comprehensive nutritional assessment is necessary to ensure early recognition of patients who have or are at risk of developing malnutrition to allow timely and appropriate intervention
- Nutritional interventions are varied and have an important role throughout the course of the disease, from diagnosis through to terminal care
- Effective nutritional interventions should ultimately aim to improve QoL and enhance the beneficial effects of treatment.

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GUIDELINE

Restorative dentistry and oral rehabilitation: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK and provides recommendations on the pre-treatment oral and dental assessment, during and after treatment and oral rehabilitation. Restorative dentists are core members of the multidisciplinary team treating head and neck cancer patients, involved from the treatment planning phase through to long-term rehabilitation.

Recommendations

- Preventative oral care must be delivered to patients whose cancer treatment will affect the oral cavity, jaws, salivary glands and oral accessibility. (G)
- Close working and communication between the surgeons, oncologists and restorative dental specialists is important in ensuring optimal oral health outcomes. (G)
- Intensity-modulated radiotherapy has been shown to reduce long-term xerostomia and should be offered to all appropriate patients. (R)
- If patients are deemed at risk of trismus they should be warned and its progressive and potentially irreversible nature explained. (G)
- Where it is known that adjuvant radiotherapy will be given, extractions should take place at primary surgery to maximise the time for healing and minimise the number of surgical events for patients. (G)
- Osseointegrated implants should be considered for all patients having resection for head and neck cancer. (G)

Introduction

The consultant in restorative dentistry and oral rehabilitation is a core member within the head and neck cancer team as many patients face complex oral rehabilitation and dental health issues during and after their treatment. This section addresses the issues relating to pre-treatment oral and dental assessment, preventative advice, during and after treatment and oral rehabilitation.

Oral and dental assessment prior to primary treatment

Patients whose oral cavity, teeth, salivary glands and jaws will be affected should have assessment and appropriate management as early as possible to allow time for any necessary dental treatment.[1] This should render patients dentally fit before treatment and ensure the oral cavity can be maintained and rehabilitated after treatment.[2]

The aims of pre-treatment assessment are:

- Avoidance of unscheduled interruptions to primary treatment as a result of dental problems
- Pre-prosthetic planning and treatment, e.g. planning for primary implants and/or impressions for obturator
- Planning for extraction of teeth which are of doubtful prognosis or are at risk of dental disease in the future and are in an area where there would be risk of osteoradionecrosis.[2] Extractions to be carried out as early as possible in the patient journey but, as a minimum, at least 10 days prior to radiotherapy
- Planning for restoration of remaining teeth as required
- Preventive advice and treatment
- Assess potential for post-treatment access difficulties, e.g. trismus, microstomia.

Treatment side effects

Treatment for head and neck cancer may involve surgery, chemotherapy and radiotherapy which can

cause adverse short- and long-term oral side effects as follows:

Short term:

- Mucositis: inflammation and ulceration of the mucosal lining of the oral cavity
- Infection: chemotherapy-induced neutropenia makes the patient susceptible to bacterial, viral and fungal infections. Oral candidal infections are extremely common following chemotherapy or radiotherapy
- Xerostomia: dry mouth resulting from a decrease in the production of saliva as a result of radiotherapy.

Long term:

- Altered anatomy: surgical ablation and reconstruction can cause permanent changes in oral anatomy making prosthetic rehabilitation difficult
- Rampant dental caries: radiogenic dental caries[3,4] is thought to be the result of reduced salivary flow as well as possible direct radiogenic damage to the amelo-dentinal junction by radiotherapy
- Trismus: may be caused by surgical scarring or by radiotherapy induced fibrosis of the masticatory muscles
- Mastication difficulties: if a significant number of opposing pairs of teeth are lost
- Osteoradionecrosis: hypovascularity and necrosis of bone followed by trauma-induced or spontaneous mucosal breakdown, leading to a non-healing wound
- Xerostomia: intensity-modulated radiotherapy (IMRT) reduces the risk of xerostomia after treatment and possibly osteoradionecrosis.[5]

Management

Preventive management

- Maintenance of good oral hygiene by effective tooth brushing; flossing daily
- Dietary advice with regard to caries prevention
- Daily topical fluoride application (5000 ppm fluoride toothpaste) in custom-made trays or brush-on.[6] Daily fluoride mouth rinse, remineralising agents
- Daily use of GC Tooth Mousse™ containing free calcium or other remineralising agent[7]
- Saliva replacement therapy and use of frequent saline rinses
- Jaw exercises to reduce trismus.

Peri-treatment and post-treatment management

Oral mucositis and ulceration. Treatments include Chinese medicines, hydrolytic enzymes, ice chips, benzydamine, calcium phosphate, etoposide bolus, manuka honey, iseganan and zinc sulphate.[8] All have been shown to demonstrate some level of benefit although the response seems to be patient specific. Benzydamine mouthwash has been recommended for those patients receiving moderate radiation without concomitant chemotherapy. The use of amifostine in this setting has now been refuted.

Oral candidal infections. There is strong evidence that some antifungal drugs prevent oral candidiasis caused by cancer treatment, but nystatin does not appear to work. Chlorhexidine gluconate has antifungal and antibacterial properties in addition to antiplaque effects; however, its value is still unconfirmed. Its tendency to stain teeth and its alcohol content, which can irritate inflamed tissues, are potential drawbacks.

Xerostomia. This can be managed by sipping sugarless fluids frequently, chewing sugarless gum or lozenges, and using a carboxymethyl cellulose saliva substitute as a mouthwash. Oral balance gel may be best accepted by patients because of its extended duration of effect. Acidic salivary stimulants such as Glandosane™ should not be used by dentate patients as their pH is below the critical pH of 5.5. Pilocarpine (5–10 mg/day) may improve radiation induced xerostomia in patients with evidence of some intact salivary function.

Altered anatomy. Prostheses may be required to replace missing oral and facial tissues. These may be implant supported.

Rampant dental caries. Management must be individualised, and patients must be assessed at regular intervals to determine the caries risk and caries activity to provide guidance for maintenance of the dentition.

Mastication difficulties. This can be minimised by maintenance of the dentition and use of well-made prostheses.

Trismus. Jaw exercises and the use of devices such as the Therabite™ prior to and during radiotherapy may limit the severity of trismus, but they will not mobilise fibrosis once it has occurred. They may help surgically induced trismus (as may coronoidectomy). Dental work that was deferred during radiotherapy should be completed. Frequent dental follow-up appointments (3–4 monthly), either with local general or community dental practitioner is warranted for these patients.

Oral rehabilitation using osseointegrated implants. Osseointegrated implants allow effective oral and facial rehabilitation following cancer treatment including radiotherapy.[9,10] They are used to support oral or facial prostheses.[11] Appropriate detailed planning and patient selection are important prior to proceeding with treatment. The use of hyperbaric oxygen may be considered prior to elective implant placement in the

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irradiated jaws (>60 Gy) in an attempt to improve implant survival rates but is a controversial area with currently no clear cut evidence.

Recommendations

- **Preventive oral care must be delivered to patients whose cancer treatment will affect the oral cavity, jaws, salivary glands and oral accessibility (G)**
- **Close working and communication between the surgeons, oncologists and restorative dental specialists is important in ensuring optimal oral health outcomes (G)**
- **IMRT has been shown to reduce long-term xerostomia and should be offered to all appropriate patients (R)**
- **If patients are deemed at risk of trismus they should be warned and its progressive and potentially irreversible nature explained (G)**
- **Where it is known that adjuvant radiotherapy will be given, extractions should take place at primary surgery to maximise the time for healing and minimise the number of surgical events for patients (G)**
- **Osseointegrated implants should be considered for all patients having resection for head and neck cancer (G)**

Primary dental implants. The placement of intra-oral implants at the same time as tumour resection may be beneficial for carefully selected patients and where there is continuity of the mandible or in patients who require the prosthetic obturation of significant maxillary defects where retention of the obturator is likely to be compromised or in patients undergoing rhinectomy or orbital exenteration.[9,12] In patients having segmental resection and reconstruction of the mandible, implant survival and usefulness is improved by delayed placement after suitable prosthodontic planning.[13]

Secondary dental implants. For many patients, the placement of osseointegrated implants will be considered following cancer treatment in response to ongoing problems with oral function. A secondary approach allows a detailed assessment of the patient's overall prognosis, their individual risk factors (alcohol, smoking, oral hygiene, radiotherapy, etc.) as well as their anatomical factors such as the presence of reconstructive hard and soft tissue grafts, metal hardware, tongue function and mouth opening. Comprehensive prosthodontic planning should be undertaken prior to surgery and the use of computerised planning and surgical guide stent technology is useful.

Key points

- Consultants in Restorative Dentistry are core members of the multidisciplinary team dealing with head and neck cancer patients
- Patients whose oral cavity, teeth, salivary glands and jaws will be affected by their treatment should have a dental assessment and appropriate management as early as possible to allow time for any necessary dental treatment
- Patients requiring maxillary obturation should be carefully prepared for treatment by a Restorative specialist who should ideally be present during surgery
- Consideration should be given to the placement of osseointegrated titanium implants at the time of primary resective surgery in selected patients in order to support dental and facial prostheses
- Liaison with the patient's general dental practitioner is important for ongoing dental care with support from the Restorative specialist where advice is required.

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GUIDELINE

Psychological management for head and neck cancer patients: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It provides recommendations on the assessment and interventions for the psychological management in this patient group.

Recommendations

- Audit of information supplied to patients and carers should be conducted on an annual basis to update and review content and media presentation. (G)
- Patients and carers should be invited to discuss treatment options and relate possible outcomes to functional retention or loss to provide a patient-centred approach. (G)
- Clinical staff should inspect their systems of assessment to make them sensitive enough to identify patients with psychological difficulties. (G)
- Flexibility, rather than rigid formulation is required to assess patients frequently, and to allow for change in circumstances to be noted. (G)
- Multidisciplinary teams should determine the supportive care services available and commission extra assistance to provide patients and carers with timely information, education or brief supportive advice. (G)
- Multidisciplinary teams need to inspect specialist services for mental health interventions at structured and complex levels for the small proportion of patients with more serious, but rarer, psychological difficulties. (G)
- Clinical staff at all levels should receive communication skills training to raise and maintain consultation expertise with difficult patient and/or carer interactions. (G)

Introduction

The head and neck cancer patient and their carers have considerable challenges to overcome.[1] The psychological experience of the patient with head and neck cancer has been closely described in a recent systematic review and meta-synthesis.[2] 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.[3] This section has benefited from recent research in the field and highlights the major psychological management concerns in the course of caring for the patient being treated for head and neck cancer.[4]

Communication of diagnosis and treatment

Evidence from other 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.[5,6] It is vital that the patient is told explicitly that they have a cancer, its nature and that all treatment available is presented to them in an unambiguous manner. This needs to be relayed consistently by all members of the team, so that the patient and carer are able to draw upon their coping abilities as well as possible. Recent evidence shows that delivering information without interruption, avoiding jargon and showing appropriate empathy are important features of the diagnostic interview to help prevent illness concerns developing.[6] Decision-making and designing tools to improve communication between clinician and patient is improving rapidly and highlights an important growth area for the future of head and neck cancer care

where complex choices are discussed and commitments made with patients.[7,8]

Delivering information about treatment and recovery

Considerable efforts have been expended to determine the information needs of head and neck cancer patients.[9,10] Poor satisfaction with information supplied by the team was predictive of patient lowered mood and quality of life (QoL) in the longer term.[11] More information was required on financial advice, support groups and ability to return to work. Virtually no studies have been reported on patient desire to be involved in treatment decision making. The nature of the disease and its complex profile of mixed treatment methods have favoured the multidisciplinary team's (MDT) sole authority to determine treatment regimens. However, recent reports have compiled large datasets of 'normative' QoL estimates linked to various treatment options, 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.[12]

Recommendations

- **Audit of information supplied to patients and carers should be conducted on an annual basis to update and review content and media presentation (G)**
- **Patients and carers should be invited to discuss treatment options and relate possible outcomes to functional retention or loss to provide a patient-centred approach (G)**

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 a means to identify those patients who may suffer during the process of treatment preparation, the treatment itself, initial stages of recovery and follow-up out-patient appointments.[13] These assessments have the ability to capture those patients who would not necessarily be identified by the MDT as needing psychological support.[14] Two issues follow however: an increased number of patients in need of assistance; and screening measures that may indicate substantial distress when there is none due to measurement error.

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 frequent 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.[15,16] 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.[17] Furthermore, it is now recognised that high recurrence fears promote more requests for medical services incurring higher treatment and surveillance costs. Acknowledgement of the patient experience of the severity and longevity of these fears is important and more in-depth approaches may be required to alleviate debilitating distress.[18]

The profile of staff expertise and skills needs close inspection to enable a flexible and tailored matching of need to professional training of support or specialist staff. Multidisciplinary teams need to plan their services to provide escalating level of care according to the specific need of psychological difficulty presented by the patient. The newly developing Map of Medicine describes in detail the levels of intervention (1–4). Timely support and educational approaches are conducted at levels 1 and 2. Structured interventions are provided at level 3 by staff with a mental health qualification. Level 4 interventions consisting of complex psychotherapeutic approaches are delivered by clinical psychologists, counselling psychotherapists and liaison psychiatrists.

Recommendations

- **Clinical staff should inspect their systems of assessment to make them sensitive enough to identify patients with psychological difficulties (G)**
- **Flexibility, rather than rigid formulation is required to assess patients frequently, and to allow for change in circumstances to be noted (G)**
- **Multidisciplinary teams should determine the supportive care services available and commission extra assistance to provide patients and carers with timely information, education or brief supportive advice (G)**
- **Multidisciplinary teams need to inspect specialist services for mental health interventions at structured and complex levels for the small proportion of patients with more serious, but rarer, psychological difficulties (G)**

Family and social support

It is important for the MDT to raise survivorship issues with patients.[19] 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. Firstly carers and spouses

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should be encouraged to use techniques to enhance 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.

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.[20] Areas such as assessing patient preferences concerning life expectancy, 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. The psychological burden to staff requires recognition, supervision and training.

Recommendation

- **Clinical staff at all levels should receive communication skills training to raise and maintain consultation expertise with difficult patient and/or carer interactions (G)**

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) for the aid of patients to enter into discussion with multidisciplinary team to agree on treatment plan
- Collect routine psychological assessments at key points during course of care. These indicators must be supported with dedicated and tailored interventions to prevent neglect of identified psychological distress or depression
- Focus on level of support and intervention that current team can realistically provide with current level of resource. 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 multidisciplinary team
- Introduce staff training to assist with management of potential burnout in multidisciplinary team 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, 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 to cancer network of a clinical or counselling psychologist or psychotherapist
- Identify liaison psychiatry service and negotiate referral pathway and response time.

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GUIDELINE

Quality of life considerations in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It identifies the current evidence base and role of health-related quality of life assessment for this group of patients.

Recommendations

- Health-related quality of life is integral to treatment planning, refining treatment protocols, and more personalised follow-up support. (G)
- Health-related quality of life and patient concerns should be regularly assessed during patient care. (G)
- Health-related quality of life assessment and patient concerns on an individual patient basis can be helpful to trigger multi-professional support and interventions. (G)

The evaluation of the quality of life (QoL) in patients with head and neck cancer is integral to optimal patient care.[1] Survival is usually the initial primary concern of patients and the focus is on treatments that offer the best chance of cure as a priority. However, after treatment there tends to be a shift towards QoL and living with the consequences of head and neck cancer treatment (survivorship).

What is quality of life?

Quality of life is a multifaceted construct comprising many different aspects leading to numerous definitions. The World Health Organization defines quality of life as an "*individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*".[2] Quality of life comprises a person's physical health and functioning, psychological state, level of independence, social relationships, occupation and finance, and personal beliefs. There is a complex relationship between factors such as the characteristics of the individual with respect to symptoms, personality, motivation, value preferences and the characteristics of the environment such as psychological, social and economic support.[2] The term 'health-related quality of life' (HRQoL) is more disease specific and allows the healthcare professions to focus upon the assessment of the impact of the disease and its treatment on the physical, psychological and social aspects.[3]

Why should we measure quality of life?

Health-related quality of life evaluation gives an indication of how the patient perceives the impact of their cancer and its treatment. This information can be used to give the patient and their family an indication of 'what will I be like'.[1] This patient reported outcome allows the health professional an opportunity to reflect on the patient's reaction. Individual patient-rated outcomes can often differ quite markedly from clinician-rated scores. Health-related quality of life measurement has a role in evaluating treatment outcomes, helping to define treatment protocols, as primary or secondary outcome(s) of clinical trials, providing additional information to assist in individual decision-making processes, to support the identification of poor outcomes, so that intervention and support can be considered.[4] Checklists such as the

Patients Concerns Inventory help patients express unmet concerns and can be used as part of holistic needs assessment.[5] A better understanding of patients' perception helps facilitate improvements in aftercare and serves to drive clinically relevant outcomes research.[6] Also patient-reported outcomes should be part of national outcome datasets.[7–9]

It is appreciated that there are many potential difficulties in assessing HRQoL in clinical practice.[10,11] Perhaps the biggest challenges are: (i) the burden of administration and processing of the questionnaires; (ii) the reality that patients tend to adapt over time, so that expected differences between treatments might not be as significant as anticipated; (iii) that HRQoL data are weighted to survivors; and (iv) that there is little evidence of agreed standards of analysis and reporting. Another barrier is the lack of evidence as to when HRQoL should have a major role on treatment decisions, or an important role simply as an additional factor, or perhaps where it has relatively little value. Hence, healthcare professionals can unrealistically rely too much on the value of HRQoL in certain clinical situations and this can lead to frustration and a perceived lack of benefit in the HRQoL process.

How should it be measured?

The commonest way to measure HRQoL is by patient self-completed questionnaire (quantitative) although other methods include open and semi-structured interview (qualitative).[11] There is no gold standard questionnaire and each has its own unique features and merits.[12–14] All questionnaires are inherently limited by the range of issues addressed, the wording used, and the scoring systems. The choice of questionnaire depends on the reason for using it, e.g. research, audit, integrated into routine clinical practice or to assist in the evaluation of a specific functional outcome.[15]

Questionnaires can be used either cross-sectionally or longitudinally. Longitudinal data from pre-treatment has the distinct advantage of allowing the measurement of change and also recording HRQoL during the different phases of treatment. It is a logistical challenge to ensure patients self-complete questionnaires before treatment and at regular intervals subsequently. Cross-sectional evaluation is simpler to conduct and easier to achieve larger patient numbers when stratifying for patient characteristics. Questionnaires can be divided into four main categories: (i) those asking on a range of broad issues not specific to cancer; (ii) those addressing issues common to all cancers; (iii) questionnaires with items specific to head and neck cancer; and (iv) those questionnaires that focus in detail on a particular aspect of head and neck function.[9]

With changes in treatments e.g. epidermal growth factor receptor inhibitors as part of chemotherapy, so existing HRQoL questionnaires might need to be modified to include additional side effects and functional deficits. As the relationship between unmet need and HRQoL becomes more clearly understood, further consideration needs to be given as to how, within the financial constraints of cancer care, questionnaires can be more easily integrated into routine practice. Advances in technology will assist in the collection and inclusion of patient-reported outcomes. The almost ubiquitous ownership of mobile phones allows developers in partnership with clinical researchers to construct 'Apps' that can send alerts to patients for HRQoL updates on certain features. This is an exciting area that is in its infancy but holds great promise to enable a more comprehensive, flexible and frequent opportunity to explore, study and intervene in patient HRQoL.

What are the key issues?

There are a considerable range of issues that impact on the HRQoL outcomes following head and neck cancer. This section makes only very brief comment on the type of issues involved (listed in alphabetical order). There are several review articles that give additional information.[12–14,16,17] At the present time there tends to be a lack of long-term outcomes reported in the literature. Also newer treatment strategies are under reported given the time necessary to get adequate HRQoL information.

- Carer: there is a need to promote positive carer support; carers can underestimate the HRQoL outcome
- Comorbidity: patient perception of disability, rather than the extent and severity of disease is of major influence in head and neck HRQoL
- Coping: social support seeking is beneficial whilst avoidance is bad
- Dental status: eating – social interaction and is linked to coping
- Disfigurement: appearance, body image, not only an issue in surgical patients
- Emotion: anxiety is high pre-treatment; mood disturbance and/or depression is treatable
- Family and children: the impact of cancer affects family and community
- Fatigue: common in the first year post-treatment; poor sleep; low energy
- Fear of recurrence: unpredictable by clinical characteristics; does not lessen over time; and high levels predict higher consumption of formal healthcare.
- Financial and work: employment; benefits; cost of treatment and follow-up; and retirement
- Function: pre-existing comorbidities; problems of combination treatment modalities – impact on recreation, hobbies, interests. In general, the less the consequence of the cancer and its treatment in terms of social function the better the HRQoL outcomes
- Fungating wounds: difficulties in palliation in head and neck; relatively few published papers

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- Information: varying amounts, in various ways, at different times the importance of communication skills and consistency of contact with named health professional for duration of clinical treatment; also access to patient and career support groups
- Intimacy: sexuality, worst in the younger patient as an unmet need
- Lifestyle choices: smoking; alcohol abuse
- Nutrition: low weight; diet; gastrostomy feeding
- Oral rehabilitation: chewing and/or eating – realistic expectations of rehabilitation
- Osteoradionecrosis: associated with pain; trismus; poor HRQoL; and nutrition problems
- Pain: need for opiates; poor sleep; linked with depression
- Personality: optimism and HRQoL and survival; high neuroticism poor HRQoL
- Self-esteem: social concerns; reactions of friends, wider community, work colleague; low self-esteem associated with poor HRQoL
- Sociodemographic: deprivation and social support; age; and finance
- Speech: complex function; various aspects; laryngeal speech outcomes; isolation
- Swallowing: nutrition; social; presence of feeding tube most significant to HRQOL
- Shoulder: shoulder discomfort and neck tightness; debate around avoiding a neck dissection or carrying out a selective dissection
- Trismus: difficulty in mouth opening associated with diet, social, and dental health
- Unknown: clinical art of the individual patient not a precise science
- Xerostomia: dry mouth has a profound impact on social function and HRQoL, intensity modulated radiation therapy should be used whenever feasible.

Examples of how HRQoL might change practice

Health-related quality of life is a factor that is weighed against treatment burden and toxicity, and also any survival benefit between treatments. In the three common head and neck cancer sites, HRQoL might be a driver for evolving strategies alongside other drivers such as survival, function and healthcare cost. Examples are described below.

Oropharynx

1. Early stage disease: There is an argument for transoral excision for early oropharynx lesions with selective neck dissection. This avoids the need for free tissue transfer and access procedures such as lip split mandibulotomy.
   Drivers for change: Health-related quality of life, survival, function, cost to National Health Service (reduced length of stay).
2. Advanced stage disease: Chemoradiotherapy is often advocated for larger oropharyngeal primaries if laser resection is not possible. The long-term outcomes remain unclear as does the success of salvage surgery and its impact on HRQoL. The benefit of salvage surgery and the impact on HRQoL is currently unclear. Transoral surgery is problematic due to the high-risk of local necrosis, non-healing and catastrophic bleeding. The use of free flap reconstruction in the post-chemoradiotherapy failures, is often associated with poor functional outcomes, poor HRQoL and limited cure rates.
   Drivers for change: Health-related quality of life; function; healthcare cost.
3. Human papilloma virus (HPV) testing: It is conceivable that it is possible to de-escalate treatment in some HPV positive patients. Similar survival outcomes may be achieved by the use of cetuximab and radiotherapy rather than platinum-based chemoradiotherapy.
   Drivers for change: Health-related quality of life.

Larynx

1. Early stage disease: Laser excision rather than primary radiotherapy for suitable lesions.
   Drivers for change: Patient choice based on equivalent HRQoL and survival.
2. Advanced stage disease: There is debate about chemoradiotherapy or laryngectomy. Following chemoradiotherapy the success and impact of laryngectomy for salvage remains to be fully determined.
   Drivers for change: Health-related quality of life, survival.

Oral cavity

1. Early stage disease: There is a rationale towards primary surgery without free tissue reconstruction accepting close margins with low risk of local recurrence
   Drivers for change: Health-related quality of life, survival, function, cost of overall treatment.
2. Advanced stage disease: Primary surgery with free tissue reconstruction as required. However, there is discussion around the benefit of adjuvant radiotherapy.
   Drivers for change: Health-related quality of life, survival.

Conclusion

The place of HRQoL assessment in head and neck cancer practice has become more defined in the last decade. It has had a major role in helping to shape treatment strategies and patient support. More evidence is yet to emerge to improve guidance as to how to use HRQoL at an individual patient level and also reflect the trade off between marginal survival improvements and increased treatment burden and poorer HRQoL. Advances in information technology will make it

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easier for HRQoL to assist in decision making, delivery of information, identification of problem areas, the identification of risk groups, and to drive support and interventions aimed at improving the HRQoL outcomes.

Recommendations

- **Health-related quality of life is integral to treatment planning, refining treatment protocols, and more personalised follow-up support (G)**
- **Health-related quality of life and patient concerns should be regularly assessed during patient care (G)**
- **Health-related quality of life assessment and patient concerns on an individual patient basis can be helpful to trigger multi-professional support and interventions (G)**

Directions for the future

1. Holistic assessment integrated into clinical practice and patient reported outcomes reported in national datasets.
2. Survivorship issues addressed through interventions and empowering patients to develop skills and confidence for self-management.
3. Evidence base related to interventions, e.g. AFTER intervention for fear of recurrence.
4. A better understanding of late effects of treatment.
5. Partnership and marital issues are no doubt of significant importance, as well as grandparents and children (family). Interventions need to include couple therapy and family therapy and practitioners need to be trained in these approaches as well as individual counselling etc.
6. Wider use of information technology to allow HRQoL and patient concerns to be more readily available in clinics and across the multi-professional team.

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GUIDELINE

Tumour assessment and staging: United Kingdom National Multidisciplinary Guidelines

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Abstract

In general, the first decision to be made in a patient with a confirmed head and neck cancer is whether or not to treat the patient before deciding what form of management strategy is appropriate. There is no more important an aspect of head and neck cancer care than the initial evaluation of the patient and the patient's tumour. The practice requires specific expertise and judgement. The current tumour–node–metastasis system relies on morphology of the tumour (anatomical site and extent of disease) but the final decision on treatment hinges on a full assessment of the patient including physiological age and general condition. The aim of this paper is primarily to describe why and how we appraise a patient and their tumour. It addresses the general principles applicable to the topic of evaluation, classification and staging. In addition, the limitations and pitfalls of this process are described.

Recommendations

- All patients with head and neck cancer (HNC) should undergo tumour classification and staging prior to treatment. (R)
- Pre-therapeutic clinical staging of HNCs should be based on at least a C2 factor (evidence obtained by special diagnostic means, e.g. radiographic imaging (e.g. computed tomography, magnetic resonance imaging or ultrasound scan), endoscopy, biopsy and cytology). (R)
- Imaging to evaluate the primary site should be performed *prior* to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma. (G)
- Panendoscopy is only recommended for symptomatic patients or patients with primary tumours known to have a significant risk of a second (synchronous) primary tumour. (G)

Introduction

There are many aspects affecting the outcome of patients with malignant head and neck tumours. These may relate to the tumour (e.g. the anatomical site and extent of the disease), the host (age, general condition and any concurrent disease) and management (treatment options, expertise available and patient preference).

Staging of head and neck cancer (HNC) is a system designed to express the relative severity, or extent, of the disease. The objectives are illustrated in Table 1.

The nature of staging has meant that the data to support the concept have been largely drawn from retrospective and observational studies. Much of the systems development has been through the opinion of expert panels using these data.

Both the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) published rules on classification and staging which correspond in their 7th editions (2009) and have approval of all national tumour–node–metastasis (TNM) committees.[1,2]

Sites in the head and neck region

The TNM classification applies only to carcinomas and melanomas in the following sites: lip and oral cavity, pharynx (oropharynx, nasopharynx and hypopharynx), larynx, maxillary sinus, nasal cavity and ethmoid sinus, mucosal malignant melanoma, major salivary glands and thyroid gland. Each site is described having rules for classification, anatomical sites and subsites where appropriate, the clinical TNM (cTNM) classification, the pathological TNM (pTNM) classification, G histopathological grading, stage grouping and a summary. The main aspects are described here, but specific details can be found in the most recent UICC and AJCC TNM booklets.[1,2]

TABLE I
OBJECTIVES OF STAGING

1. To aid the clinician in the planning of treatment
2. To give some indication of prognosis
3. To assist in evaluation of the results of treatment
4. To facilitate the exchange of information between treatment centres
5. To contribute to the continuing investigation of human cancer

General rules

The TNM system for describing the anatomical extent of the disease is based on three components (Tables II–IV):

T – Extent of the primary tumour
N – Absence or presence and extent of regional lymph node metastases
M – Absence or presence of distant metastases

All cases should be confirmed microscopically. Two classifications should be documented for each site, namely: cTNM (clinical (pre-treatment) classification) and pTNM (post-surgical histopathological classification). The clinical stage is essential to select and evaluate therapy, while the pathological stage provides the most precise data to estimate prognosis and calculate end results. It should be remembered that if there is doubt concerning the correct T, N or M category to which a particular case should be allotted, then the *lower* (*i.e. less advanced*) category should be chosen. After assigning the cTNM and pTNM categories, the patient should then be classified in a Stage Group. Once established, this must remain unchanged in the medical records.[1,2]

See site-specific chapters for each detailed tumour classification.

TABLE II
AN OVERVIEW OF THE TNM STAGING TERMINOLOGY

T – Primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1, T2, T3, T4	Increasing size and/or local extent of the primary tumour
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No evidence of regional lymph node metastases
N1, N2, N3	Increasing involvement of regional lymph nodes
M – Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

The previously included MX category is now considered to be inappropriate.
The category M1 may be further specified according to the following notation:

Pulmonary	PUL	Bone marrow	MAR
Osseous	OSS	Pleura	PLE
Hepatic	HEP	Peritoneum	PER
Brain	BRA	Adrenals	ADR
Lymph nodes	LYM	Skin	SKI
Other	OTH		

TABLE III
HISTOPATHOLOGICAL GRADING SYSTEM FOR SQUAMOUS CELL CARCINOMA

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

G = Histopathological grading

Histopathological grading

The histological grading of squamous cell carcinoma represents estimation by the pathologist of the expected biologic behaviour of the neoplasm. Although it is subject to inter- and intra-observer errors, it has been suggested such information in conjunction with other characteristics of the primary tumour is useful in the rational approach to therapy.[3] The grade can be applied to all head and neck sites except thyroid.

Additional descriptors

Designation is now applicable when sentinel lymph node biopsy is attempted using the suffix (sn) after N stage. Optional descriptors for perineural invasion (Pn), lymphatic invasion (L) and venous invasion (V) may be used.

The absence or presence of residual tumour after treatment may be described by the symbol R. A recurrent tumour, when classified after a disease-free interval is identified by the prefix 'r'. The prefix 'a' indicates that classification is first determined at

TABLE IV
OPTIONAL DESCRIPTORS USED FOR HISTOPATHOLOGICAL REPORTING IN SQUAMOUS CELL CARCINOMA

Optional descriptors	
Pn – Perineural invasion	
PnX	Perineural invasion cannot be assessed
Pn0	No perineural invasion
Pn1	Perineural invasion
L – Lymphatic invasion	
LX	Lymphatic invasion cannot be assessed
L0	No lymphatic invasion
L1	Lymphatic invasion
V – Venous invasion	
VX	Venous invasion cannot be assessed
V0	No venous invasion
V1	Microscopic venous invasion
V2	Macroscopic venous invasion

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autopsy. The suffix 'm' is used to indicate the presence of multiple primary tumours at a single site. In cases where multimodality treatment is used, the cTNM or pTNM is identified by a 'y' prefix which categorises the extent of tumour actually present at the time of that examination.

The C-factor, or *certainty factor*, reflects the validity of classification according to the diagnostic methods employed (C1–C5). C1 would be evidence from standard diagnostic means whereas C5 is evidence from autopsy. Generally speaking, pre-therapeutic clinical staging of HNCs is equivalent to C1, C2 and C3, whilst pathological classification is equivalent to C4.[1,2]

Related classifications

The World Health Organization (WHO) has developed a series aimed at classification of tumours. The WHO International Classification of Diseases for Oncology (ICD-O) is a coding system for neoplasms by topography and morphology and for indicating behaviour (e.g. malignant and benign).[4] This coded nomenclature is identical in the morphology field for neoplasms to the Systemised Nomenclature of Medicine.[5] It is recommended that the WHO classification of tumours is used for classification and definition of tumour types and that the ICD-O code is used for storage and retrieval of data.

Stage grouping

After TNM, classification of tumours should be assigned a stage grouping between 0 or I and IV (Tables V). The grouping adopted is designed to ensure, as far as possible, that each group is more or less homogeneous in respect of survival and that the survival rates for each cancer stage are distinctive. Carcinoma in situ is categorised as stage 0; cases with distant metastasis as stage IV. The exceptions to this grouping are for carcinoma of the nasopharynx, carcinoma of the thyroid (Tables VI and VII) and mucosal melanoma.[1,2]

Methods of assessment

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

Computed tomography (CT) and magnetic resonance imaging are now established as the mainstay investigations in the pre-operative work-up of patients with HNC, to delineate the extent and size of the primary tumour, to determine the presence (particularly when risk of occult nodes is >20 per cent), number and position of cervical lymph nodes, to search for an occult primary and to locate a synchronous primary or distant metastases (particularly the chest). Appropriate screening for synchronous tumours and distant metastases is particularly important in advanced tumours. Several studies have suggested that a CT scan should be obtained in preference to a plain chest X-ray as this may miss significant lung pathology.[6] There is a

TABLE V
STAGE GROUPING FOR HEAD AND NECK CANCERS EXCLUDING NASOPHARYNX, THYROID AND MUCOSAL MELANOMA

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

TABLE VI
STAGE GROUPING FOR CARCINOMA OF THE NASOPHARYNX

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0,N1	M0
Stage III	T1,T2	N2	M0
	T3	N0, N1, N2	M0
Stage IVA	T4	N0, N1, N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

TABLE VII
STAGE GROUPING FOR THYROID CARCINOMA

Papillary or follicular *under 45 years*			
Stage I	Any T	Any N	M0
Stage II	Any T	Any N	M1
Papillary or follicular *45 years and older*			
Stage I	T1a, T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3	N1b	M0
Stage IVB	T4a	N0, N1	M0
Stage IVC	T4b	Any N	M0
	Any T	Any N	M1
Medullary			
Stage I	T1a, T1b	N0	M0
Stage II	T2, T3	N0	M0
Stage III	T1, T2, T3	N1a	M0
Stage IVA	T1, T2, T3	N1b	M0
Stage IVB	T4a	Any N	M0
Stage IVC	T4b	Any N	M0
	Any T	Any N	M1
Anaplastic (all cases are stage IV)			
Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Separate stage groupings are recommended for papillary and follicular, medullary and undifferentiated carcinomas

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growing body of evidence that points to the value of 18F fluoro-deoxyglucose-positron emission tomography/CT in the management of HNC patients and predicting patient-related outcomes. It is invaluable in the detection of the unknown primary and useful in the confirmation of residual or recurrent disease, but is not routinely used in initial staging assessment.[7]

Endoscopy and biopsy should be performed by a senior surgeon and in *all cases* by the head and neck surgeon responsible for any future procedure. This should include for each tumour a description, diagrammatic representation and preferably also photographic documentation. Routine panendoscopy (oesophagoscopy and bronchoscopy) is contentious. Proponents point out that these procedures require very little time, and may be performed easily during planned, direct laryngoscopy. A large meta-analysis found a small advantage to panendoscopy in detection of second primary tumours during analysis of multiple prospective studies.[8] Opponents point out that the appropriate use of symptom directed investigations in addition to routine chest radiography have a similar detection rate compared with screening endoscopy and avoid unnecessary risk and expense in asymptomatic patients.[9] McGarey *et al.*[10] concluded that while rigid oesophagoscopy is safe, the utility is low for cancer staging and for detection of non-malignant oesophageal disease. Review of the literature and analysis of a large national cancer dataset indicate that the incidence of synchronous oesophageal malignant neoplasms in patients with head and neck squamous cell carcinoma is low and has been decreasing during the past three decades.[10] Thus, screening oesophagoscopy should be limited to patients with head and neck squamous cell carcinoma who are at high risk for synchronous oesophageal malignant neoplasms.

There is a natural desire to confer a stage on the tumour at presentation in the clinic and certainly after endoscopy. This should be avoided. It is better to rely on descriptive text to avoid changing the stage as more information becomes available. The clinical (pre-treatment) classification (cTNM) based on examination, imaging, endoscopy and biopsy should be clearly documented in the case-file only when all of the above information is collated. The UICC book should be available in every theatre and clinic to assist in applying the *correct stage.*

Regional lymph nodes

The status of the regional lymph nodes in HNC is of such prognostic importance that they must be assessed for each patient and tumour. Lymph nodes are described as ipsilateral, bilateral, contralateral or midline; they may be single or multiple and are measured by size, number and anatomical location (Table VIII). Midline nodes are considered ipsilateral nodes except in the thyroid. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.[1,2]

TABLE VIII
N STAGING FOR REGIONAL LYMPH NODES

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

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

Lymph nodes are subdivided into specific anatomic sites and grouped into seven levels for ease of description. The pattern of lymphatic drainage varies for different anatomic sites. However, the location of the lymph node metastases has prognostic significance. Survival is significantly worse when metastases involve lymph nodes beyond the first echelon of lymphatic drainage.[11] It is particularly poor for lymph nodes in the lower regions of the neck, i.e. levels IV and V (supraclavicular area).

International Union Against Cancer and AJCC recommend that each N-staging category be recorded to show, in addition to the established parameters, whether the nodes involved are located in the upper (U) or lower (L) regions of the neck, depending on their location above or below the lower border of the thyroid cartilage.[1,2]

The definitions of the N categories for all head and neck sites are the same (Table VIII) except thyroid (Table IX) and nasopharynx (Table X). The natural history and response to treatment of cervical nodal metastases from nasopharynx are different, in terms of their impact on prognosis, so they justify a different N classification. Regional lymph node metastases from well-differentiated thyroid cancer do not significantly

TABLE IX
N STAGING FOR THYROID CARCINOMA

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
N1a	Metastasis in level VI (pre-tracheal, pre-laryngeal, paralaryngeal) nodes
N1b	Metastasis in other unilateral, bilateral or contralateral cervical or retropharyngeal or superior mediastinal lymph node(s)

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TABLE X
N STAGING FOR NASOPHARYNX

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral cervical, unilateral or bilateral retropharyngeal lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa
N2	Bilateral cervical lymph node(s), 6 cm or less in greatest dimension, above supraclavicular fossa
N3	Metastasis in lymph node >6 cm and/or (in the supraclavicular fossa:
(N3a)	Greater than 6 cm in dimension
(N3b)	In the supraclavicular fossa

Note: Midline nodes are considered ipsilateral nodes, and the supraclavicular triangle is defined by the lines joining the following three points – the superior margin of the clavicle at its sternal and acromial ends, and the point where the line of the neck meets the shoulder.

affect the ultimate prognosis and therefore also justify a unique system.

Pathological classification (pTNM)

The pT, pN and pM categories correspond to the T, N and M categories, respectively. The extent of the tumour in terms of the location and level of the lymph node should be documented. In addition, the number of nodes that contain tumour and the presence or absence of extracapsular spread of the tumour should be recorded. Histological examination of a selective neck dissection including central compartment specimen usually includes six or more lymph nodes; a radical or modified radical neck dissection specimen includes 10 or more lymph nodes.[1,2]

The current TNM system relies on morphology of the tumour (anatomical site and extent of disease) with little or no attention given to patient factors. However, the literature does suggest that symptom severity[12] and comorbidity[13] have a significant impact on outcomes. It is therefore recommended that these data be recorded. Definitions of TNM categories may be altered or expanded for clinical or research purposes as long as the basic definitions are recorded and not changed. Despite the obvious value of staging, both in the management of individual patients and for the grouping of patients in trials and reports of treatment, it does have its limitations. The most insidious of these is that attempts to increase the accuracy of staging leads to greater complexity, and hence paradoxically to more errors and an increased likelihood of non-compliance by the person responsible for staging. Advances in methods of collecting and recording data will hopefully reduce these errors. Changes in the TNM classification should and will only occur, based on the appropriate collection, presentation and analysis of data, in the forum of the UICC and AJCC.[3,4] The principles, practice and limitations of the current staging system are well documented in many major texts.[14–16] Changes between editions tend to be conservative and commentaries regarding HNC reflect this.[17] It is seven years since the 7th edition of the UICC and AJCC staging manuals and the updated version is eagerly awaited. The early indications are that changes will be only subtle and few.

Key points

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

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GUIDELINE

Pathological aspects of the assessment of head and neck cancers: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It introduces the current best practice in histopathology and cytopathology as it pertains to head and neck and thyroid cancers.

Recommendations

- Accurate diagnosis of the type of malignancy is a key component of effective management. (R)
- Surgeons and oncologists should understand the scope and limitations of cellular pathology in order to inform multidisciplinary discussions. (R)
- A clinically suspected diagnosis of malignancy should be confirmed by biopsy or cytology before operation. (R)
- Cytopathological diagnoses should be discussed with surgeons and radiologists to maximise the information gained from each modality of investigation. (R)
- Pathological investigations are the basis for accurate cancer staging and stratification of clinical outcomes. (R)

Introduction

This paper is an overview of the use of laboratory investigations and focuses on the important elements of cancer pathology reports that clinicians should use when discussing the implications of a diagnosis and management options with patients and with colleagues in a multidisciplinary setting. The recommendations for pathology practice are based on published evidence; key references are provided in the World Health Organisation (WHO) Classification of Tumours[1] and in the series of Histopathology Datasets published by the Royal College of Pathologists.[2,3] Pathologists have critically important roles in confirming or excluding specific diseases on the basis of cytology or diagnostic biopsy, in assessing the adequacy of treatment, recognising key predictive and prognostic factors, and in contributing evidence-based criteria for the appropriate stratification of clinical outcomes.

Use of cellular pathology services

Frozen section

Patient management should be guided primarily by pre-operative biopsy and/or fine needle aspiration (FNA) cytology. Intra-operative frozen sections have a limited role and are appropriately used for the assessment of surgical excision margins when there is clinical doubt as to adequacy.[4] Frozen sections are occasionally used to confirm the diagnosis of branchial cleft cysts in older people, of papillary, medullary or anaplastic thyroid carcinomas[5] or to identify lymph node involvement in thyroid cancers; they should not be used to differentiate follicular thyroid carcinoma from adenoma or follicular variant papillary carcinoma. It should be appreciated that the quality of frozen sections is not as good as paraffin sections and that important information may be missed or destroyed through inappropriate use of frozen sections, particularly if small pieces of tissue are submitted for examination.

Definitive operative specimen

Specimens should be submitted in an adequate amount of 10 per cent neutral buffered formalin (at least three times the volume of the specimen) unless there is prior agreement with the laboratory.[2] The site and nature of each specimen should be clearly described on the request form and should be appropriately orientated. The form must include the clinical indication for the operation, the duration of signs and symptoms, pre-operative radiotherapy (RT) or chemotherapy, and details of previous biopsies or

cytological investigations, and relevant biochemistry (particularly for thyroid diseases).

Lymph node specimens

The site of origin of lymph nodes should be recorded, and formal neck dissections should clearly state which nodal groups are included and should be clearly orientated, preferably with a diagram.[6] The optimal handling of biopsies for suspected lymphoma should be discussed with the laboratory; it is often useful to collect fresh tissue in a transport medium for possible cytogenetic and molecular studies.

The predictive value of sentinel node biopsy is now recognised and is becoming established practice, particularly for the early-stage oral carcinoma.[7] The pathological assessment of sentinel nodes is highly demanding of laboratory time and expertise, involving multiple sections and immunocytochemistry.[8] This should only be undertaken if appropriately resourced.

Resection specimens including bone

When cancer resection specimens contain bone, it is often possible to obtain a preliminary report on the soft tissue components of the specimen while the bone is decalcified before processing the tissues to assess the extent of bone invasion and bony margins. Decalcification may take several days or weeks depending on the density of the bone.

Immunocytochemistry and molecular pathology

Immunocytochemistry plays an important role in the correct diagnosis of primary head and neck cancers, particularly for the less common entities. The prognostic value of assessing oropharyngeal carcinomas for evidence of human papilloma virus infection (HPV) is established, with current guidance recommending a combination of immunocytochemistry for p16 protein overexpression and in situ hybridisation for high-risk HPV DNA. Morphologically similar poorly differentiated carcinomas arising in the oropharynx and nasopharynx, and their nodal metastases may be distinguished by the presence of HPV and Epstein–Barr virus DNA, 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 sites of squamous cell carcinomas (SCCs) but may be helpful in identifying adenocarcinomas arising in the gastrointestinal tract, lungs or prostate. Clinicians should note that immunocytochemical 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 and the balance of probabilities. Clinical features, such as the pattern of nodal disease, and imaging studies should be incorporated into the multidisciplinary assessment of these patients. Molecular genetic profiling of head and neck cancers is not currently recommended outside the research setting.[2,9,10]

Multidisciplinary team working

Cellular pathologists are core members of cancer MDTs and are essential to the provision of a successful service. The MDT should have a risk-based approach to developing its policy on pathology review, particularly for patients who have had diagnostic biopsies in other hospitals. Pathological review is essential for thyroid cancers and is good practice for other situations.

Malignancies of the upper aerodigestive tract

Squamous cell carcinoma

The initial diagnosis may be obvious clinically on the basis of an irregularly infiltrating mass with ulceration, but should always be confirmed by biopsy as some inflammatory diseases, e.g. tuberculosis and sarcoidosis, can mimic carcinomas clinically and other mucosal malignancies, e.g. lymphoma, may require consideration of other treatment options. Practical problems that may preclude definitive diagnosis on diagnostic biopsies include 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. Patients who have been treated with RT and/or chemotherapy may have biopsies or resections to assess any residual or recurrent disease at primary or nodal sites. Extensive scarring, radiation-associated nuclear atypia and loss of the normal anatomical landmarks may make assessment of these specimens difficult. A good chemotherapeutic response may leave a mass of necrotic tissue containing degenerate keratinocytes; viable carcinoma may not be identified even after extensive histological sampling.

Morphological variants of SCC. Some variants of SCC are associated with particular difficulties in diagnosis and clinical assessment but should be managed, stage for stage, in line with classical carcinomas.

Papillary SCC is typified by an exophytic growth pattern with fronds of fibrovascular tissue covered by squamous epithelium showing in situ carcinoma; areas of invasive carcinoma are often small and limited in extent. Diagnostic biopsies may show only in situ carcinoma despite a bulky tumour. The prognosis is relatively good due to the limited invasive component.

Verrucous SCC has an exophytic growth and is formed by extremely well-differentiated squamous epithelium with minimal atypia and abundant surface keratin. Diagnostic biopsies may not show invasion and the minimal cellular atypia makes pathologists

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reluctant to diagnose malignancy. Repeated biopsies and appreciation of the discrepancy between a clinically obvious carcinoma and minimal microscopic atypia are often needed to make a diagnosis of 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 in situ or more typical invasive carcinoma are identified. Immunohistochemistry only identifies squamous epithelial differentiation in about 60–70 per cent of cases.

Oropharyngeal SCCs are usually related to high-risk HPV infection. Typical HPV-associated carcinomas are non-keratinising (basaloid) carcinomas, but may be of any histological type.

Information that should be provided in histopathology reports. The information available from diagnostic biopsies is limited but should normally include whether any carcinoma is invasive or in situ and, for invasive carcinomas, should provide a provisional estimate of the degree of differentiation and the growth pattern. In the oral cavity, the depth of invasion or tissues involved (mucosa, muscle) may guide the extent of surgery.

Resection specimens provide sufficient tissue to describe the full range of prognostic information[2,11] (Box I); the basis in evidence for this information is provided in guidelines published by the Royal College of Pathologists and varies between anatomical sites.

BOX I
PROGNOSTIC INFORMATION DERIVED FROM PRIMARY CARCINOMAS

- Site and subsite
- Histological type of carcinoma
- Grade of differentiation
- Growth pattern
- Maximum diameter
- Maximum depth of invasion
- Invasion of lymphatic or blood vessels
- Invasion of the peri-neural space of nerve trunks
- Invasion of bone or cartilage
- Distance of carcinoma from resection margins

Dysplasia and intra-epithelial neoplasia

Squamous cell carcinomas are the result of a combination of genetic mutations, some of which are manifest in precursor lesions by atypia of the epithelial cells collectively referred to as dysplasia or intra-epithelial neoplasia. Severe cytological atypia is associated with a high risk of progression to carcinoma and, in resection specimens, its presence at resection margins may predict local recurrence. The various, commonly used, grading systems are summarised in Table I and, although different criteria are used, each seeks to place a particular abnormality in a continuous spectrum of appearances from mild to severe atypia. There is no UK consensus[12] on which grading system should be recommended, although a majority of pathologists probably use the WHO dysplasia system but regard severe dysplasia and in situ carcinoma as indistinguishable. A proposed consensus system for laryngeal lesions based on the Ljubljana classification[13] is gaining recognition, but its translation to UK practice is limited. Management decisions should take account of the microscopic severity of the lesion and its clinically assessed extent.

TABLE I
GRADING SYSTEMS FOR PRECURSOR LESIONS OF SQUAMOUS EPITHELIAL MALIGNANCIES

WHO Classification 2005	Squamous intraepithelial neoplasia (SIN)	Ljubljana classification; squamous intraepithelial lesions (SILs)
Squamous cell hyperplasia		Simple hyperplasia
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia
Moderate dysplasia	SIN 2	Low grade SIL
Severe dysplasia	SIN 3	High grade SIL
Carcinoma in situ	SIN3	Carcinoma in situ

Note: The categories in the different systems are not strictly comparable as different morphological and architectural criteria are used

Other mucosal malignancies

Adenocarcinomas. This may be of surface or salivary type. Those derived from surface epithelium of the nose and sinuses may resemble intestinal carcinomas and have a relatively poor prognosis compared with other low grade adenocarcinomas.

Sinonasal undifferentiated (anaplastic) carcinoma. This is a rare, clinically aggressive neoplasm composed of cells that are undifferentiated on routine stains but which show varying degrees of neuroendocrine differentiation on immunocytochemistry. These carcinomas often result in bone destruction and extension into the orbit or cranial cavity and have a poor prognosis despite aggressive surgery and chemoradiotherapy.

Olfactory neuroblastoma (esthesioneuroblastoma). This presents as a polypoid mass high in the nasal cavity. The histological features are characteristic and immunocytochemistry is positive for neuroendocrine markers. Morphological grading systems are of limited prognostic value. Despite spread to regional nodes and more

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distant sites, prognosis is good with a 78 per cent five-year survival after surgery and RT.

Malignant melanoma. This most often arises in the nasal cavities and less often in the sinuses, presenting in adults over 50 years as polypoid, friable haemorrhagic masses. Histologically there is a wide range of appearances with very variable melanin production (30 per cent are amelanotic). Survival is poor with death due to widespread metastasis and/or extensive local recurrence.

Lymphomas. This may present as primary mucosal malignancies in the sinonasal tract and tonsils. Almost all are non-Hodgkin's lymphomas with natural killer/T-cell lymphomas mainly affecting the sinonasal tract and B-cell lymphomas arising in the tonsils.

Nasopharyngeal carcinoma. This includes keratinising SCCs and non-keratinising differentiated and undifferentiated carcinomas and is usually related to Epstein–Barr virus infection. The synonym of 'lymphoepithelioma' should not be used. Keratinising carcinomas are more radioresistant than non-keratinising and undifferentiated carcinomas.

Diagnosis and management of neck lumps

Fine needle aspiration

Fine needle aspiration (FNA) of tissue by a well-trained operator is an essential part of the diagnostic assessment of patients with neck or thyroid lumps and as part of staging procedures for patients with the known head and neck cancer.[14,15] High-quality preparations are essential for an effective service. Either rapidly air-dried slides or needle washings into preservative solution may be required depending on the clinical circumstance. The cytological diagnosis of metastatic SCC in cervical nodes is usually straightforward, but cystic metastases can be difficult to distinguish from benign cystic lesions containing squamous cells such as branchial cleft cysts; a high degree of clinical suspicion for malignancy is required in older patients with cystic lesions containing squamous cells. Haemorrhage into cystic neck nodes may conceal underlying malignancy, particularly metastatic papillary carcinoma from the thyroid. Multidisciplinary correlation of findings is of fundamental importance.

FNA cytology is the method of choice for monitoring patients known to have lymphoma as cytology can document disease recurrence and can indicate transformation from low to high grade disease. The primary diagnosis of lymphoma can be made from FNA specimens if the laboratory repertoire includes molecular techniques and flow cytometry. FNA cytology is an effective method to triage patients into those in whom significant disease can be excluded, those in whom a definitive diagnosis of benign disease or metastatic malignancy can be made, and those with possible lymphoma who need lymph node biopsy. Where malignancy is identified, additional immunocytochemical and molecular testing for planning management is possible with appropriate specimen collection procedures.

Neck dissections

The presence or absence of nodal metastasis is a key component of tumour–node–metastasis (TNM)[16] staging and determines further management. The pathological assessment of nodes in resection specimens verifies pre-operative imaging studies and identifies small volume nodal disease that is beyond the resolution of current imaging techniques.

The terminology of possible nodal involvement by carcinoma includes:

- Isolated tumour cells (ITCs) – collections of cells <0.2 mm diameter
- Micrometastasis – tumour deposits 0.2–2 mm in diameter
- Conventional metastasis – a tumour deposit more than 2 mm diameter
- Extracapsular spread – carcinoma extending through a breach in the capsule from a lymph node into surrounding connective tissue.

For TNM staging, the presence of ITCs is classified as pN0 as their significance is unknown. Micrometastases are recorded as pN1(mi), pN2b(mi) or pN2C according to their extent in multiple nodes. Core pathological data for nodal metastases are shown in Box II.

BOX II
PROGNOSTIC INFORMATION DERIVED FROM LYMPH NODE EXCISIONS

Number of positive nodes
Sites of positive nodes
Size of largest metastasis
Presence or absence of extracapsular spread

Salivary neoplasms

Most tumours arising in the major or minor salivary glands are benign (although the proportions vary from site to site), but pre-operative suspicion of malignancy may be raised on clinical examination, from imaging studies or from pre-operative FNA cytology. All tumours of the major salivary glands should have pre-operative FNA cytology to guide treatment, which can usually accurately diagnose pleomorphic salivary adenoma and Warthin's tumour with confidence, differentiate benign neoplasms from malignant in 81–98 per cent of cases, but which is less good at establishing a specific type of carcinoma. The main categories of salivary carcinoma are well defined, but these tumours have many morphological variants and precise histological diagnosis often requires a specialist opinion.

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Many salivary neoplasms have characteristic genetic translocations[17] which aid diagnosis and may lead to targeted therapeutics. The core pathological data from salivary resections for neoplasia are shown in Box III.

BOX III
PROGNOSTIC INFORMATION DERIVED FROM SALIVARY GLAND RESECTIONS

The histological type of neoplasm (according to the WHO Classification)
The grade of malignancy (see text)
The distance to the resection margins
The presence or absence of peri-neural or vascular invasion
The presence or absence of lymph node involvement

Grading of the degree of malignancy is prognostically useful for some salivary carcinomas. Grading of mucoepidermoid carcinomas relates to metastatic potential and survival, whichever grading system is used. Acinic cell carcinomas are usually circumscribed but incompletely encapsulated; grading on the basis of cytological features is not generally useful, except for rare tumours showing dedifferentiation. Assessment of Ki-67 (MIB1) labelling is of prognostic value, and acinic cell carcinomas with indices of >5 per cent behaving more aggressively. The growth pattern of adenoid cystic carcinoma is related to metastatic potential, with 0–4 per cent of cribriform, hyaline and tubular carcinomas, and 33 per cent of solid (basaloid) carcinomas metastasising to local lymph nodes. Distant metastasis is more common in solid tumours. Salivary duct carcinoma is a high-grade malignancy morphologically resembling ductal carcinoma of the breast. About 70 per cent express androgen receptors and 15 per cent express HER-2 (human epithelial growth factor receptor 2); features which may influence therapy. Carcinomas arising in pleomorphic adenomas may be of any or mixed histological type; the extent of invasion is prognostically useful as invasion more than 5–6 mm from the capsule of the residual adenoma is associated with a high risk of local recurrence and distant metastasis. Non-invasive or minimally invasive carcinomas ex pleomorphic adenoma are true malignancies, but have a very low rate of disease progression.

Thyroid cancers

Most lesions will have had FNA before surgery. Immediate assessment of the adequacy of aspirates may be helpful. The descriptive cytology report informs clinical decisions on management and should incorporate a categorical summary[3,18] (Table II).

For all malignant thyroid tumours, the national dataset for histopathology reports[3] defines core data items of prognosis importance that will allow TNM staging[16] (Box IV). Some histological variants of thyroid carcinomas have prognostic importance. For diagnostic purposes, oncocytic (Hürthle cell) follicular tumours are regarded as a variant of follicular tumours and the criteria for malignancy are the same. The presence of any poorly differentiated or anaplastic component affects prognosis.[3]

TABLE II
CATEGORISATION OF THYROID FNAS WITH LIKELIHOOD OF MALIGNANCY (LOM) (RCPATH AND BSCC GUIDELINES)

Thy 1	Non-diagnostic for cytological diagnosis	LOM 0–10%
Thy 1c	Non-diagnostic for cytological diagnosis – cystic lesion	
Thy 2	Non-neoplastic	LOM 0–3%
Thy 2c	Non-neoplastic, cystic lesion	
Thy 3a	Neoplasm possible – atypia/non-diagnostic	LOM 5–15%
Thy 3f	Neoplasm possible, suggesting follicular neoplasm	LOM 15–30%
Thy 4	Suspicious of malignancy	LOM 60–75%
Thy 5	Malignant	LOM 97–100%

BOX IV
PROGNOSTIC DATA FROM THYROID RESECTION SPECIMENS

Histological type of malignancy
Whether carcinoma is unifocal or multifocal
Maximum dimension of carcinoma (largest if multifocal)
Closest distance to surgical resection margin (R status)
Extension into extrathyroidal tissues (macroscopic or microscopic)
Presence of lymphatic or vascular invasion
Site and number of lymph nodes sampled and those involved

Papillary carcinoma

A single papillary microcarcinoma (≤10 mm diameter) discovered incidentally in a resection performed for another disease is not thought to have a significant risk of recurrence or metastasis. Some microcarcinomas are potentially more aggressive including those with multifocal disease, extrathyroid extension and lymphatic invasion.

Tall cell and columnar variants of papillary carcinoma may be more aggressive, while the outcome of the diffuse sclerosing variant is a matter of debate.

Diagnosis of the follicular variant of papillary carcinoma (FVPC) may be difficult and require specialist opinion. The non-encapsulated invasive FVPC has a metastatic potential similar to that of classical papillary carcinoma, while encapsulated FVPC has metastatic potential related to the number of foci of vascular invasion.

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Follicular carcinoma

A follicular neoplasm is defined as carcinoma on the basis of capsular and/or vascular invasion. Minimally invasive follicular carcinomas show only focal microscopic vascular and/or capsular invasion. Tumours showing only capsular invasion have a minimal risk of metastasis. The risk of metastasis increases with vascular invasion, but no significance is attached to the number of foci of vascular invasion. Widely invasive follicular carcinoma shows obvious gross invasion or extensive microscopic infiltration of thyroid parenchyma, vessels or extrathyroidal tissues. The number of foci of vascular invasion should be described but is not prognostically significant.

Medullary carcinoma

The diagnosis should be confirmed by calcitonin immunoreactivity, although some poorly differentiated carcinomas only express carcinoembryonic antigen (CEA). Although there are variations in the cellular pattern and presence of amyloid these are unimportant prognostically compared with the tumour stage and completeness of excision. In the syndromes of multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma, medullary carcinoma is often multifocal and preceded and/or accompanied by C-cell hyperplasia. Genetic testing for RET mutations will detect familial syndromes.

Poorly differentiated carcinoma

This group is defined as follicular or papillary carcinoma with necrosis and/or a mitotic count of five or more in ten high-power microscopic fields. The growth pattern may be insular, trabecular or solid. Poorly differentiated carcinomas have a poorer prognosis than differentiated carcinomas with variable response to radio-iodine treatment.

Undifferentiated/anaplastic carcinoma

Anaplastic carcinoma is diagnosed where a follicular or papillary carcinoma shows even a minor undifferentiated (anaplastic) component. Most undifferentiated tumours will be diagnosed by FNA cytology, core or open biopsy and will not have a surgical resection. The report should describe how immunocytochemistry has been used to exclude other poorly differentiated malignancies, especially lymphoma.

Lymphoma

The diagnosis of thyroid lymphoma is usually made on core or open biopsy rather than resection specimens and may require extensive immunocytochemical and molecular testing. It is important to distinguish between primary thyroid lymphoma and involvement of the thyroid by lymphoma as part of a wider disease.

Recommendations

- **Accurate diagnosis of the type of malignancy is a key component of effective management (R).**
- **Surgeons and oncologists should understand the scope and limitations of cellular pathology in order to inform multidisciplinary discussions (R)**
- **A clinically suspected diagnosis of malignancy should be confirmed by biopsy or cytology before operation (R)**
- **Cytopathological diagnoses should be discussed with surgeons and radiologists to maximise the information gained from each modality of investigation (R)**
- **Pathological investigations are the basis for accurate cancer staging and stratification of clinical outcomes (R)**

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GUIDELINE

Radiotherapy in head and neck cancer management: United Kingdom National Multidisciplinary Guidelines

C NUTTING

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Radiotherapy is one of the key treatment modalities used in head and neck cancer management. This paper summarises the current role and some of the recent advances in radiotherapy in head and neck cancer management.

Radiotherapy (RT) and surgery are the two most frequently used therapeutic modalities in head and neck cancer. For early-stage tumours in many sites, surgical excision or RT have similar cure rates but have a different side-effect profile. Radiotherapy traditionally offered higher rates of organ preservation and for some cancers where function is important, it is the treatment of choice. For example, RT allows preservation of natural speech and swallowing in carcinomas of the larynx and tongue base.[1] At other sites (e.g. carcinoma of the oral cavity), surgical excision alone may be curative and be associated with a very satisfactory functional outcome. The choice of treatment modality therefore depends on individual factors including patient preference.

For an advanced squamous cell carcinoma of the head and neck, single modality treatment (either surgery or RT alone) is associated with poor outcomes. For these tumours, the combined use of surgery and post-operative RT or use of combined chemotherapy and radiation schedules frequently offer the highest chance of achieving cure.

In recent years, RT has benefited from advances in cancer imaging, treatment planning computer software and developments in radiation delivery technology. It is now one of the most technology-driven branches of medicine. Typically head and neck cancer patients will have radiation therapy which is based on the state-of-the-art imaging technology including computed tomography, magnetic resonance imaging, positron emission tomography or other imaging techniques. Optimisation of treatment planning is performed on high-speed computer software, which intelligently selects the most appropriate beam directions and shapes. Treatment is delivered by computer-driven linear accelerators with sub-millimetre accuracy allowing radiation to be focused on the tumour bearing tissues and minimising radiation to normal tissue structures.

Intensity-modulated radiotherapy (IMRT) is now an established form of radiation therapy which allows better control of radiation dose delivery in the head and neck. In a randomised trial performed in the UK, IMRT has been shown to reduce radiation-induced xerostomia (the main long-term side effect of the standard RT) from 75 to 39 per cent ($p = 0.004$) at 12 months following treatment.[2] A similar result has been demonstrated for patients with nasopharyngeal cancer.[3] Intensity-modulated radiotherapy in now used to treat 70–80 per cent of patients with advanced head and neck cancer, where sparing of salivary glands is required.

Improvements in local tumour control have been demonstrated with accelerated (delivery of radiation over a shorter time period) or hyperfractionated (delivery of a higher dose of radiation by two to three low-dose fractions per day) RT. These treatments have not shown consistent improvements in overall survival, and for that reason have not been adopted widely outside of North America.[4]

Particle therapy such as with protons or stereotactic RT may allow additional advantages to patients with tumours close to particularly radiosensitive organs such as the brain, spinal cord or in children's cancers. Presently, proton therapy is not available in the UK, but the NHS Proton Clinical Reference Panel can

approve treatment abroad for adult head and neck cancer patients with base of skull chordoma or chrodrosarcoma, as well as a variety of paediatric cancers. UK proton facilities at The Christie Hospital in Manchester and University College Hospital in London will be treating patients within the next few years and additional indications for head and neck cancer patients may become apparent based on future research.

In a large meta-analysis of 93 trials and over 17 000 patients, concomitant chemotherapy (given during RT) was shown to improve locoregional control rates and was associated with a 6.5 per cent increase in survival ($p < 0.0001$).[5,6] The benefits were largely confined to chemotherapy given during RT rather than the adjuvant or neo-adjuvant setting. In addition, combining chemotherapy with radiation improves the rates of organ conservation. Cisplatin chemotherapy schedules are the most effective.

Similarly the concurrent administration of cetuximab, an anti-epidermal growth factor receptor antibody, with RT, was shown to increase overall survival and locoregional control in this setting.[7,8] This was the first demonstration of activity of a biologically targeted therapy in cancer treatment.

In the post-operative setting, two randomised controlled trials have demonstrated the use of concomitant cisplatin during radiation to increase tumour control and overall survival in high-risk patients with positive resection margins or extracapsular lymph node spread.[9,10]

While concomitant chemotherapy has a proven role in improving outcomes for head and neck cancer, the role of neo-adjuvant chemotherapy remains controversial. Two large studies suggested that the use of docetaxel, cisplatin and 5-fluorouracil prior to definitive RT improved survival.[11,12] The use of non-standard RT and/or chemoradiation schedules in these trials has led to uncertainty as to the benefits of this approach when a standard chemoradiation is prescribed. Induction chemotherapy is now becoming less frequently used, and its benefit is probably limited to patients who are at high risk of systemic metastatic spread.

There is increasing evidence that human papilloma virus-related oropharyngeal cancer has an excellent outcome with chemoradiotherapy and that less intensive RT schedules may be more appropriate, which is currently being investigated.

Key points

- Radiotherapy is a key modality in the treatment of head and neck cancer
- Conformal radiotherapy planning and chemoradiation techniques should be available in all treatment centres
- Intensity-modulated radiotherapy has been shown to reduce long-term xerostomia and should be offered to all appropriate patients.

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GUIDELINE

Surgery in head and neck cancer: United Kingdom National Multidisciplinary Guidelines‡

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Surgery is one of the key modalities used in head and neck cancer treatment. Recent advances and a greater awareness of the short- and long-term toxicities associated with non-surgical modalities and newer technologies that permit minimal access resections have led to a resurgence in surgery. This paper provides an overview of the role of surgery in head and neck cancer practice.

The aim of surgery with curative intent in head and neck cancer (HNC) is complete microscopic surgical excision. Excision margins are a consistent prognostic factor[1–3] and a major consideration for more radical post-operative adjuvant therapy (and therefore more attendant morbidity),[4] with the possible exception of thyroid cancer.[5] Whilst there has been considerable progress with less invasive surgical access techniques, the underlying principle of profound importance in head and neck surgery is that surgical resection achieves complete, microscopic clearance of the tumour with the appropriate safely margin according to the type, site and stage of cancer. There is virtually no oncological role for debulking surgery in order to improve the chances of cure with subsequent chemoradiation. Debulking may be necessary for airway preservation and for symptom palliation, however.

One of the most prominent surgical advances of recent times has been the development and popularisation of transoral access techniques for oropharyngeal, supraglottic and glottic cancers, via transoral laser microsurgery (TLM) and transoral robotic surgery (TORS). Transoral robotic surgery should be seen as an evolutionary refinement of TLM, especially useful for tongue base and supraglottic resections, and the evidence for these procedures should be considered together. When minimal access surgery is compared to open techniques, the advantages relating to reduction in morbidity are obvious. This applies to endoscopic approaches for sinonasal tumour resection, either with or without craniotomy. Here, the relevant comparison is to open transfacial access techniques, and the advantages of less radical access are obvious, with no compromise in prognosis (at least in selected cases).[6] Any surgeon managing sinonasal tumours should be able to offer the full range of surgical techniques, open and endoscopic, and, as an oncology surgeon, be a core member of the multidisciplinary team.

However, with the transoral techniques of TLM and TORS, the relevant comparison is really to primary radiotherapy (RT) or chemoradiotherapy in the main. Even in glottic cancer, it has only been shown that there is equipoise between TLM and RT for T1a.[7]. There is less robust evidence for T1b cancers[8] and clearly insufficient data for T2 glottic cancers and for supraglottic cancers. For oropharyngeal cancers, there is much work to do in order to define the role of transoral surgery in place of, or in concert with, chemoradiation.[9] Much of this depends on whether and how post-operative RT and chemoradiotherapy can be modified in patients treated with primary surgery, and, especially for oropharyngeal cancer, the influence of human papilloma virus status and neck metastases. There appears to be consistent evidence that swallowing outcomes may be better in patients treated primarily with surgery, if post-operative treatment can be restricted to RT only and perhaps to a lower dose.[10–12]

A further issue with transoral techniques in particular is the proof of surgical margins. The practice of basing this on further biopsies or submission of additional tissue from the tumour bed has been shown to be less reliable in glossectomy and less prognostic than

‡The original version of this guideline was published with one of the authors' names omitted. A notice detailing this has been published and the error rectified in the online PDF and HTML copies.

defining surgical margins from the main tumour.[13] However, with small tumours, especially from the glottis, then: (a) smaller margins may be oncologically safe; and (b) the impact of thermal artefact is such that it is difficult to prove histological clearance without submitting separate material from the margins.[3] The same issues apply to complex resections in which it can be very difficult for the pathologist to determine where the true margins are, for example with anterior and lateral skull base resections. The key is to good interdisciplinary working between surgeon and pathologist. The bottom line is that the determination of accurate surgical margins is critical, whatever the surgical technique employed.

For advanced disease, in which more radical, open surgery is required, the issues to consider are:

- Can a complete resection be achieved? If this is not realistic, then the morbidity of such surgery can rarely be justified
- Even if complete resection can be achieved, is the mortality risk and morbidity justified by the chances of overall survival?
- If radical surgery is to be done, it should be done comprehensively. There should be no compromise in the extent of the resection, when the attendant morbidity is not materially affected by a more radical approach with appropriate reconstruction in expert hands. This may mean pharyngolaryngectomy instead of laryngectomy, mandibulectomy instead of soft tissue resection only in the oral cavity or extending a maxillectomy posteriorly or superiorly.

For defects that will require reconstruction with microvascular free flaps, in most cases having two consultant surgeons has obvious advantages, regardless of specialties involved. The use of free flaps is increasing.[14] There has been continued evolution of reconstruction options, with a greater variety of composite flaps suited to the defect involved. With regard to soft tissue reconstruction, the anterolateral thigh flap is ideal for most soft tissue defects,[15] except when a thin flap might be required for smaller oral cavity defects.

When applying these principles to salvage surgery, these principles are even more important. The focus is defining what the role of salvage surgery is (cure, palliation) and what the chance of achieving the aim actually is in the setting of greatly increased chances of serious post-operative morbidity, with, in many cases, low chance of cure.[16–19]

With regard to neck dissection, for many N+ cases, conservation techniques allow the preservation of key non-lymphatic structures and the restriction of levels dissected according to the primary tumour and the amount of disease. Shoulder and neck dysfunction has been correctly recognised as an important contributor to quality of life after treatment. For N0 cases, it is reasonably clear which cases require elective neck dissection, when surgery is the primary treatment modality. In practice, when this is the case, the nature of surgery is such that the addition of a selective neck dissection adds little to the overall surgery. When this is not the case, there is a role for sentinel node biopsy.[20] For neck disease treated with RT or chemoradiotherapy, neck dissection is only required for residual disease shown on conventional or positron emission tomography–computed tomography imaging.[21]

Training and manpower in head and neck surgery

The situation in the UK contrasts with many other countries, in that HNC surgery is divided between the two major specialties of otorhinolaryngology–head and neck surgery (ORL–HNS) and oral and maxillofacial surgery (OMFS), in a more equitable fashion than most other countries. Should there continue to be the distinction of, in general, OMFS managing and operating on oral cavity cancer and performing most microvascular reconstruction, with ORL–HNS managing the pharynx, larynx and thyroid? There are areas of overlap, but the division largely remains, irrespective of the influence of interface interdisciplinary fellowships.

There is no consensus about the volume of major surgery required in order to achieve and maintain competence. Whilst there is a clear relationship between both hospital and individual surgeon volume with better outcomes, it is difficult to define a minimal cut-off in terms of volumes required.[22] Even with something as easily defined as microvascular free flap surgery (with easily measurable outcomes), it many come as a surprise that there is no guidance on how may free flaps a surgeon or hospital should do per year in order to maintain and evidence competence.

In summary, the evolution of surgery for HNC continues to give rise to the ability to perform more complex tumour ablation together with more refined reconstruction and, at the same time, there has been significant progress in minimal access techniques without oncological compromise. The increasing use of chemoradiotherapy means there is an increase in salvage surgery (when appropriate) which always represents the most difficult challenge for a head and neck surgeon. These changes make the need for the clarification of training and minimal volumes for surgeons and hospitals even more important.

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GUIDELINE

Chemotherapy: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. This paper summarises the role of chemotherapy in head and neck cancer management, recent advances and what the future holds for this modality.

Introduction

Chemotherapy alone cannot cure head and neck cancer. It is used in conjunction with other treatments, surgery and radiotherapy (RT), to improve outcomes in terms of local control, organ preservation with continued organ function and to decrease the incidence of subclinical micro-metastatic spread.

Chemotherapy is not given routinely for early primary T1/T2 disease without nodal involvement. Chemotherapy is given for its direct tumouricidal effect, at both the local primary and distant metastatic sites. If given with RT it can have a radio sensitising effect, making cancer cells more susceptible to RT and increasing the cancer cell kill. It may be used as induction chemotherapy (ICT), almost always before RT rather than surgery. If ICT is used, further chemotherapy is usually given with subsequent RT, and this is known as sequential chemotherapy. More commonly, chemotherapy is given only concurrently with radiotherapy (combined chemoradiotherapy) with only a minority of patients having induction or sequential regimens. Combined chemoradiotherapy has been shown to improve local control and increase survival where primary surgery has been the definitive treatment in selected populations.

Induction (neoadjuvant) chemotherapy

The response to neoadjuvant chemotherapy could give important prognostic information, as it can act as a surrogate marker for response to later treatment.

This latter advantage was used in one of the earliest trials of neoadjuvant chemotherapy for organ preservation, the 'Veterans' trial,[1] where patients were given two cycles of cisplatin and 5-fluorouracil (5-FU), and if there was a response to chemotherapy patients went on to have chemotherapy and RT, but if there was no response, the patients went directly to laryngectomy.

Induction chemotherapy is considered beneficial for several reasons. If ICT could shrink primary tumour volumes before the principal treatment of RT or chemoradiotherapy, this might allow better blood flow into the tumour allowing a greater tumouricidal dose of drugs into the tumour and decrease the volume of hypoxic areas which would decrease the radio-resistance that hypoxic cancer cells show. Improved local control would lead to a greater chance of organ preservation and functionality. Since surgery and RT are both locoregional treatments, ICT could theoretically treat distant subclinical metastatic disease. The response to ICT could give important prognostic information, as it can act as a surrogate marker for response to later treatment.

One of the main evidence sources for the use of chemotherapy in head and neck cancer is the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) which was originally published in 2000 and updated in 2007 and 2009.[2] This overview reviewed 87 trials containing data on over 16 000 patients, with overall survival as the primary endpoint. There was no overall survival benefit with the use of ICT when compared with primary surgery or RT alone, although cisplatin and 5-FU delivered as combined chemoradiotherapy did show some benefit. It also suggested that ICT may reduce the incidence of distant metastases more effectively than combined chemoradiotherapy.

Debate continues as to whether ICT followed by combined chemoradiotherapy is more beneficial than combined chemoradiotherapy alone. Some large trials, such as the Spanish Head and Cancer Corporative Group trial have shown no benefit,[3] while others, such as a large Italian trial comparing ICT followed by combined chemoradiotherapy to combined chemoradiotherapy alone showed significantly improved overall survival for the former arm.[4] Interest was rekindled in ICT when two trials, one European, and one from North America, TAX 323[5] and TAX 324[6] showed a benefit by including a taxane, such as

docetaxel or paclitaxel in the chemotherapy regimen in addition to cisplatin and 5-FU. The evidence suggested that adding a taxane, such as docetaxel or paclitaxel to cisplatin and 5-FU, i.e. docetaxel/cisplatin/5-FU (TPF) *vs* cisplatin/5-FU (PF) did improve survival in the TPF arm, but at a cost of much higher toxicity. However, these trials have been criticised for not using optimal concurrent chemotherapy schedules. Based on further phase 3 studies (DeCIDE,[7] PARADIGM trial and[8] TREMPLIN study[9]) the evidence to date does not suggest ICT is in general beneficial in head and neck cancer.

Usually, induction and sequential regimens are offered to patients with good performance status, fewer comorbidities and those with bulky nodal disease, stage N2b and above, and where surgery is not appropriate.

Concurrent or concomitant chemotherapy

The main advantage of combined chemoradiotherapy, over sequential chemotherapy, is the reduced chance of patients having to stop treatment because of toxicity, and resulting in breaks in RT, which is radiobiologically suboptimal and can be detrimental to treatment outcome.

In the MACH-NC trial,[2] the use of combined chemoradiotherapy showed that it gave a survival benefit when added to RT alone, giving a 6.5 per cent decrease in mortality at five years, in absolute terms. This benefit was not seen in patients over 70 years of age. The most commonly used combined chemoradiotherapy regimens are cisplatin 100 mg/m^2 on days 1, 22 and 43 of RT, either alone or with 5-FU, 1 g/day on days 1–4, and then repeated 3 weekly with cisplatin. If 5-FU is added, the cisplatin dose is usually reduced. Although this regimen is commonly used, there are few direct comparisons with other combined chemoradiotherapy within randomised controlled trials.

Increased toxicity produced by adding platinum chemotherapy to RT can be considerable. A significant proportion of patients do not receive all three cycles of chemotherapy because of toxicity, but one study has shown no survival difference in patients receiving two cycles of cisplatin rather than three cycles, but the RT given was not identical within the arms of this study.[10] chemotherapy toxicity can also interfere detrimentally with RT delivery causing breaks during treatment which are associated with poorer outcomes.

If cisplatin is contraindicated because of renal function status, the presence of neuropathy, tinnitus or deafness, or where there is a danger of fluid overload with the necessary pre-hydration used in cisplatin administration, carboplatin can be considered as it causes less nephrotoxicity, ototoxicity and peripheral neuropathy but is more myelosuppressive. It is not thought to be as tumouricidal as cisplatin and for this reason it has now been largely overtaken by the epidermal growth factor receptor inhibitor, cetuximab in clinical practice when cisplatin is contraindicated.

Concurrent radio-sensitisers

It is known that tumour cell hypoxia induces radioresistance, and there has been renewed interest in giving hypoxic cell radiosensitising drugs during RT. The two most common in use are the antihelminthic drug nimorazol, which is extensively used in some parts of Europe, and tirapazamine, an anticoagulant which is activated in hypoxic environments. Although established in some parts of the world, trials are ongoing with these agents to establish efficacy and with nimorazol, patient tolerability.

Chemotherapy and human papilloma virus (HPV)-positive tumours

Human papilloma virus is known to have an aetiological role in inducing some head and neck cancers, especially in the oropharynx where HPV infection may be linked to 50–80 per cent of tumours. There is evidence from several studies that outcomes are better following treatment in patients with HPV-positive tumours. There is also growing evidence that continuing to smoke negates the outcome benefit associated with HPV positivity.

Given the good prognosis, the question arises if HPV-positive cancers are being overtreated with standard head and neck chemoradiotherapy regimens and being given unnecessary morbidity. At present there is not enough evidence to alter chemotherapy or indeed RT treatment regimens depending on the patient's HPV status, outside of the context of a clinical trial.

Several trials are now investigating these questions, most using cetuximab comparing with cisplatin (see below). These include the RTOG 1016 in the USA, the De-ESCALATE HPV study in the UK and the Trans-Tasman Radiotherapy Group 12.01 study in Australia.

Targeted biological agents

Targeted therapy in head and neck cancer developed with the recognition that epidermal growth factor receptor (EGFR) is overexpressed in the majority of head and neck cancers, up to 90 per cent in some studies, and is associated with a poorer prognosis. When a growth factor attaches to its receptor on the cell surface, cells are stimulated to divide and consequently tumours grow. If the receptor is abnormal because of a mutation the stimulation to divide may even occur without growth factors interacting with the receptor. Cetuximab is a mouse–human chimaeric monoclonal antibody which binds to the extracellular portion of EGFR and turns this signalling system off.

In the initial innovative cetuximab trial by Bonner *et al.*,[11] patients with advanced head and neck cancer were randomised to receive radical RT with or without cetuximab. At three years, survival (55 *vs* 45 per cent) and local control (50 *vs* 41 per cent) was better in the patient group who had received cetuximab.[12] Although these initial results were encouraging,

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a major drawback to the study was that, since the study had started, RT alone as used in this study had been overtaken as a standard of care by combined chemoradiotherapy. So, comparing radiation alone *vs* radiation plus cetuximab was much less relevant in the context of contemporary standard practice. Also in the initial trial patients were not stratified by HPV status.

Despite initial hopes that cetuximab would give less toxicity than the standard chemotherapy, and can therefore be given to older patients and those with a poorer performance status, it has been shown to have a different, although not necessarily less toxic, morbidity profile in the form of grade 3 and 4 radiation dermatitis. Patients may also develop an acne-like rash predominantly over the face, neck and trunk with a more eczema-like condition at the fingertips and elbows. In a minority of patients this reaction can be so severe that cetuximab may need to be stopped as these side effects can usually be managed by increasing the treatment interval and supportive care with topical medications. There is some suggestion that patients who develop this rash may also have a better tumour response with improved overall survival.

Other targeted EGFR monoclonal antibodies are under investigation such as panitumamab or zalutumumab, but to date with less encouraging results showing no improvement in overall survival.

Another potential target further down this biological pathway, offering a different mechanism of action is used by erlotinib, a small molecule inhibitor of EGFR tyrosine kinase. One phase II trial of erlotinib given alone or combined with cisplatin, unfortunately did not show any benefit in outcome for the combination. Despite this other targets in the epidermal growth factor receptor pathway are being investigated.

Chemotherapy for recurrent or metastatic head and neck cancer

Chemotherapy or targeted biological agents may be indicated for patients with recurrent and/or metastatic disease but prognosis for patients with metastatic disease has a median survival of approximately 6–12 months in most studies.

Appropriateness of chemotherapy depends on several factors such as extent and burden of disease; whether symptoms are present or not; whether failure of control has taken place at the primary site only; and whether there is metastatic disease only or both. The most important factor often is the fitness and performance status of the patient and whether they could tolerate the proposed chemotherapy, and how much it would reduce their pre-treatment quality of life, for whatever limited survival period they have.

Locoregional failure

In this group of patients where salvage surgery or retreatment with RT or combined chemoradiotherapy is being considered, it is important to be aware if distant metastatic disease is also present and also to establish that the locoregional recurrent disease is not a second primary head and neck cancer. Discovering that metastatic disease is also present is not an absolute contraindication to salvage treatments at the primary site, as locoregional failure and metastatic disease can be considered as two separate problems in the patient's management plan. If good palliation at the primary site or locoregionally can be achieved relatively easily, by a salvage procedure, the presence of metastatic disease, especially small volume metastatic disease, should not necessarily stop treatment to the primary or locoregional site. The patients who do better with salvage treatment are those with smaller volumes of recurrence, a longer disease-free interval and less comorbidity. Some particular head and neck subsites such as the larynx, also have better outcomes.[13]

Distant metastases

Chemotherapy is often indicated here, as part of a best supportive care package to improve symptoms, but has not been shown to significantly extend survival. The therapeutic window for giving chemotherapy in this situation would be when the patient still has an appropriate performance status to receive and benefit from chemotherapy, with the trade-off being, an improved symptom state for the inevitable morbidity caused by the chemotherapy. The choice of regimen depends on factors such as performance status, comorbidities, renal function, estimated physiological reserve of the patient and the interval since last chemotherapy.

If chemotherapy is to be given for distant metastatic disease then which regimen is most appropriate depends on several factors including performance status, comorbidities present, renal function and the estimated physiological reserve of the patient. Also which regimens the patients had before and the interval since last chemotherapy may be important.

The most common regimens used are cisplatin or carboplatin with 5-FU. These give an expected response rate of approximately 30 per cent. Carboplatin is used more in this palliative metastatic setting than with induction or concurrent regimens, because although deemed slightly less effective than cisplatin; its less toxic side-effect profile, can be seen to be more appropriate in the palliative setting. Elderly patients do appear to respond to platinum-based chemotherapy in the metastatic setting,[14] in contrast to a lack of benefit in the elderly when used in primary chemoradiotherapy regimens. Other more toxic chemotherapy regimens have also been investigated using platinum and a taxane (docetaxel or paclitaxel), in combination, but no survival benefit has been demonstrated.

Cetuximab added to cisplatin and 5-FU, can increase both response rate and improve short-term survival slightly as shown in the EXTREME trial,[15] but five-year follow-up published recently in abstract form shows very low survival for patients in both arms of the study. The EXTREME study did not allow

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crossover between regimens, so similar results might be achieved by the use of cisplatin and 5-FU followed by cetuximab used sequentially. In patients who have become refractive to cisplatin and 5-FU, cetuximab as a single agent does have a low response rate of approximately 10–15 per cent.[16,17]

Key points

- Concurrent chemoradiotherapy is at present the standard of care for treatment of locally advanced head and neck cancer with a confirmed survival benefit of 6.5 per cent at five years
- Single agent cisplatin, which in the past has been shown to be as effective as multiple drug regimes, is now being challenged by the introduction of the use of taxanes
- Targeted biological agents, such as cetuximab, have a role to play in both advanced head and neck cancer and recurrent or metastatic disease but those roles are still being established
- At present human papilloma virus status does not alter management regimens, although there are multiple studies underway examining if less intense treatment, both with radiotherapy and chemotherapy, could be given to achieve the same outcome but with less toxicity
- The potential benefit of neoadjuvant or induction chemotherapy is being re-examined now, but most recent work has not shown a substantial benefit
- Elderly patients benefit least in terms of survival advantage with the use of concurrent chemotherapy.

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GUIDELINE

Laryngeal cancer: United Kingdom National Multidisciplinary guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Significantly new data have been published on laryngeal cancer management since the last edition of the guidelines. This paper discusses the evidence base pertaining to the management of laryngeal cancer and provides updated recommendations on management for this group of patients receiving cancer care.

Recommendations

- Radiotherapy (RT) and transoral laser microsurgery (TLM) are accepted treatment options for T1a–T2a glottic carcinoma. (R)
- Open partial surgery may have a role in the management of selected tumours. (R)
- Radiotherapy, TLM and transoral robotic surgery are reasonable treatment options for T1–T2 supraglottic carcinoma. (R)
- Supraglottic laryngectomy may have a role in the management of selected tumours. (R)
- Most patients with T2b–T3 glottic cancers are suitable for non-surgical larynx preservation therapies. (R)
- Concurrent chemoradiotherapy should be regarded as the standard of care for non-surgical management. (R)
- Subject to the availability of appropriate surgical expertise and multi-disciplinary rehabilitation services, TLM or open partial surgical procedures ± post-operative RT, may be also be appropriate in selected cases. (R)
- In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to at least lymph node levels II, III and IV bilaterally. In node positive disease, it is recommended that lymph node levels II–V should be treated on the involved side. If level II nodes are involved, then elective irradiation of ipsilateral level Ib nodes may be considered. (R)
- Most patients with T3 supraglottic cancers are suitable for non-surgical larynx preservation therapies. (R)
- Concurrent chemoradiotherapy should be regarded as the standard of care for non-surgical management. (R)
- Subject to the availability of appropriate surgical expertise and multi-disciplinary rehabilitation services, TLM or open partial surgical procedures ± post-operative RT, may also be appropriate in selected cases. (R)
- In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to at least lymph node levels II, III and IV bilaterally. In node positive disease, lymph node levels II–V should be treated on the involved side. (R)
- As per the PET-Neck clinical trial, patients with N2 or N3 neck disease who undergo treatment with chemoradiotherapy to their laryngeal primary and experience a complete response with a subsequent negative post-treatment positron emission tomography combined with computed tomography (PET–CT) scan do not require an elective neck dissection. In contrast, patients who have a partial response to treatment or have increased uptake on a post-treatment PET–CT scan should have a neck dissection. (R)
- Larynx preservation with concurrent chemoradiotherapy should be considered for T4 tumours, unless there is tumour invasion through cartilage into the soft tissues of the neck, in which case total laryngectomy yields better outcomes. (R)
- In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to bilateral lymph node levels II, III, IV, V and VI. (R)

Introduction

The aim of any clinician involved in the treatment of laryngeal squamous cell carcinoma should be to cure the disease whilst maintaining maximal laryngeal function. Whilst this seems a simple concept, deciding how best to achieve this aim in any given patient is often difficult and results in well-rehearsed complex discussions within multi-disciplinary team (MDT) meetings throughout the UK on a regular basis. Underpinning this lack of clinical certainty is a lack of level I evidence, particularly with respect to the comparative merits of surgical and non-surgical treatment modalities. Thus, for most laryngeal tumours, perceived treatment equipoise exists. In light of this dearth of good quality comparative data, what treatment any given patient receives is typically related to local MDT dynamics and clinical resources.

Although we are unable to rectify this lack of evidence, in this document we highlight the treatment options available for any given tumour and attempt, based on published evidence, to highlight the relative merits or disadvantages of each approach.

During 2011, 2360 patients were diagnosed with laryngeal carcinoma in the UK. Of these, 1506, 108, 245 and 73 were diagnosed in England, Wales, Scotland and Northern Ireland, respectively. Accordingly, European Age Standardised Rates per 100 000 for England, Wales, Scotland and Northern Ireland are 2.7, 3.0, 4.2 and 4.3, respectively; highlighting the fact that larynx cancer is more common in Wales, Scotland and Northern Ireland. For the UK as a whole, 1932 (82 per cent) cases occurred in men and 428 (18 per cent) in women (M:F; 4.5:1). Larynx cancer accounts for 1 per cent of all cancers in men and 0.3 per cent of all cancers in women. However, this amounts to a 22 per cent reduction of cases diagnosed in men when comparing 1992–1994 with 2009–2011. A comparable reduction (19 per cent) has occurred in women over this timeframe. (http://info.cancerresearchuk.org/cancerstats/types/larynx) in keeping with the geographical variation in incidence, larynx cancer is more commonly diagnosed in patients of lower socio-economic groups.[1]

It is well documented that alcohol and tobacco, separately and synergistically are the main causes of larynx cancer. However, in contrast to oropharynx cancer, it appears that human papilloma virus infection is not a major cause.[2]

Larynx cancer is rare in patients younger than 40 years of age, with incidence increasing with age, rising to a peak in the eighth decade. Three-quarters of all diagnoses occur in patients older than 60 years. (http://info.cancerresearchuk.org/cancerstats/types/larynx)

In 2012, 618 men (79 per cent) and 166 women (21 per cent) died of larynx cancer (M:F; 3.7:1). This constitutes a marked decrease – 25 and 16 per cent, respectively – in age-standardised mortality for men and women over the last decade. (http://info.cancerresearchuk.org/cancerstats/types/larynx)

However, Rachet *et al.*[1] previously demonstrated a startling differential mortality rate between socio-economic groups, with patients from lower socio-economic groups suffering higher death rates from larynx cancer than those from higher socio-economic groups.

Clinical presentation

The clinical presentation of laryngeal cancer is highly variable and depends on the site and size of the primary tumour. Tumours of the glottis, for example, typically present at an early stage as they manifest as hoarseness. In comparison, tumours of the supraglottis are likely to present later with symptoms of pain, hoarseness or swallowing difficulty. However, it is not uncommon for patients presenting with laryngeal cancer to delay seeking medical advice on developing 'early' symptoms, only to present at a much later stage with symptoms of pain, swallowing difficulty, a palpable neck mass or even, in extreme cases, with airway compromise.

Assessment and staging

As with all head and neck cancers, diagnosis of laryngeal cancer relies initially on good history taking and clinical examination in the clinic. Laryngeal cancers are, in most cases, obvious following inspection of the larynx with a fibreoptic laryngoscope in the outpatient department. Initial assessment of the tumour stage relies on imaging. Whilst exact protocols vary according to local imaging preferences, it is typical for patients suspected of having laryngeal cancer to undergo either magnetic resonance imaging or computed tomography (CT) of the head and neck and CT scan of the thorax and upper abdomen. The exception to this is in patients presenting with the early stage, T1 lesions of the glottis without anterior commissure involvement, where imaging is unhelpful. Definitive diagnosis is achieved by histological examination of a tissue biopsy, obtained usually at the time of a general anaesthetic endoscopic examination of the larynx, pharynx and upper oesophagus. The examination under anaesthesia is extremely important for staging and should routinely involve inspection with rigid (plane 0° and angled 30° and/or 70°) fibreoptic endoscopes. The aggregate information provided by the imaging and the endoscopic examination facilitates the staging of the tumour according to the tumour–node–metastasis (TNM) system outlined below (Table I). It is by recourse to the TNM stage of the tumour, in addition to the general fitness of the patient, that treatment decisions are ultimately made.

Management

Early (T1–T2a) glottic carcinoma

Early laryngeal cancer (T1–T2a N0 M0) is characterised by low tumour volume and a low incidence of metastatic neck disease. Consequently, the chances of

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TABLE I
TNM STAGING SYSTEM FOR LARYNGEAL CANCER

Supraglottis	
T1	Tumour limited to one subsite of supraglottis with normal vocal fold mobility
T2	Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g. mucosa of base of tongue, vallecula, medial wall of piriform sinus) without fixation of the larynx
T3	Tumour limited to larynx with vocal fold fixation and/or invades any of the following: post-cricoid area, pre-epiglottic tissues, paraglottic space, and/or with minor thyroid cartilage erosion (e.g. inner cortex)
T4a	Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck, including deep/extrinsic muscle of tongue (e.g. genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades pre-vertebral space, mediastinal structures or encases carotid artery
Glottis	
T1	Tumour limited to vocal fold(s) (may involve anterior or posterior commissure) with normal mobility T1a. Tumour limited to one vocal fold T1b. Tumour involves both vocal folds
T2	T2a. Tumour extends to supraglottis and/or subglottis with normal vocal fold mobility T2b. Tumour extends to supraglottis and/or subglottis with impaired vocal fold mobility
T3	Tumour limited to larynx with vocal fold fixation and/or invades paraglottic space, and/or with minor thyroid cartilage erosion (e.g. inner cortex)
T4a	Tumour invades through the thyroid cartilage or invades tissues beyond the larynx, e.g. trachea, soft tissues of neck, including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures or encases carotid artery
Subglottis	
T1	Tumour limited to subglottis
T2	Tumour extends to vocal fold(s) with normal or impaired mobility
T3	Tumour limited to larynx with vocal fold fixation
T4a	Tumour invades through cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid and oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures or encases carotid artery

cure are extremely good whichever of the main treatment options – radiotherapy (RT), transoral laser microsurgery (TLM) or open partial laryngeal surgery – is employed. A systemic review[3] has confirmed there is insufficient evidence to determine which of these three treatment options is most effective for the treatment of early glottic carcinoma.

Radiotherapy with surgery in reserve or TLM are the two most commonly used treatment modalities in the UK. Whilst survival outcomes and local control rates are similar,[4] they have not been compared in randomised trials. Individual treatment selection depends on patient and tumour factors (e.g. indistinct tumours diffusely infiltrating the vocal fold mucosa and larger volume tumours involving the anterior commissure may be more suitable for RT than transoral laser surgery) and local expertise. Single-modality treatment is sufficient and combining surgery with RT should be avoided as functional outcomes (and perhaps survival in the context of incompletely resected tumour) may be compromised by combined-modality therapy. Radiotherapy is delivered using megavoltage photons from a linear accelerator (typical energies 4–6 MV); hypofractionated RT schedules, using a fraction size greater than 2 Gray (Gy), results in equivalent outcomes to longer schedules, without increased toxicity. Typical schedules include 50–52 Gy in 16 fractions and 53–55 Gy in 20 fractions over three to four weeks.[5] Elective treatment of the neck is not recommended because of the very low risk of occult nodal disease. Radiotherapy results in significant acute toxicity, including thick, sticky secretions, hoarse voice, odynophagia and skin reactions. Most of these effects resolve four to six weeks after the completion of treatment and significant late effects are rare. Should tumour recurrence occur, partial laryngeal surgery provides a salvage option in appropriate clinical settings, resulting in good oncological and functional outcomes. However, these techniques are rarely offered in the UK and, therefore, total laryngectomy is most commonly performed.

Transoral laser microsurgery is usually undertaken using a CO_2 laser as a day case procedure and has minimal acute morbidity. Whilst there is equipoise with respect to voice outcome between RT and TLM for smaller tumours, long-term quality of voice for T2 glottic cancers is generally accepted to be better after RT than after TLM. Voice outcome following TLM is dependent on the extent of the resection and/or whether the resection includes the anterior commissure.[4] Certain patient factors, may preclude TLM, such as restriction of neck movement and difficult access. In these patients, hypofractionated RT is the preferred option.

Contrary to the practice in other countries, in the UK, partial open surgical procedures are used less commonly for the treatment of early *de novo* glottic carcinoma. However, they provide an option for the treatment of *de novo* tumours which are not accessible to TLM and for recurrent tumours after TLM or RT. Meta-analysis data show similar rates of local control and survival after partial laryngectomy (comparable with TLM and

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RT) with larynx preservation rates of 98.3 per cent for *de novo* tumours and 84.6 per cent for radio-recurrent tumours.[6,7] Open surgical procedures include laryngofissure cordectomy, vertical partial laryngectomy (VPL) ± reconstruction, frontolateral vertical partial laryngectomy, supraglottic laryngectomy, supracricoid partial laryngectomy plus cricohyoidoepiglottopexy or cricohyoidopexy reconstruction (SCPL–CHEP or CHP) and extended supraglottic laryngectomy.

Overall, for T1a glottic tumours the local control is similar between RT and TLM (five-year local control rate 90–93 per cent). In the case of T1b disease, the local control rate is lower (85–89 per cent).

Similarly, the local control and overall survival rates for T2a glottic cancers are comparable when treated with TLM, partial laryngeal resection or RT.

Recommendations

- **Radiotherapy and transoral laser microsurgery are accepted treatment options for T1a–T2a glottic carcinoma (R)**
- **Open partial surgery may have a role in the management of selected tumours (R)**

T1–T2 supraglottic cancers

Radiotherapy, TLM and transoral robotic surgery (TORS) are valid treatment options for all patients with T1–T2 supraglottic cancers. As with glottic carcinomas, open partial surgical procedures (supraglottic laryngectomy) are used less commonly in the UK but open supraglottic laryngectomy may have a role in selected cases in units with appropriate surgical expertise and multi-disciplinary support services. Survival outcomes appear to be similar with RT and surgery although, once again, there are no randomised comparative data. Whilst long-term functional (voice and swallowing) outcomes appear similar, early swallowing function is usually poorer after surgery: swallowing rehabilitation may be prolonged and in a small proportion of patients, adequate swallowing function may never be achieved. Consequently, patient selection, based on tumour burden and performance status, is imperative. Again, every effort should be made to avoid combining surgery with RT because functional outcomes may be compromised by combined-modality therapy.

The supraglottis has a rich lymphatic supply and, as a consequence, the risk of nodal disease is significantly higher for T1–T2 supraglottic cancers than for T1–T2 glottic cancers. Thus, even in the absence of clinical or radiological evidence of nodal involvement, elective treatment of at least bilateral lymph node levels II and III – either with RT or selective neck dissection – is recommended.

Whilst RT or surgery alone, is sufficient for the treatment of node negative T1–T2 supraglottic cancers, concurrent platinum-based chemoradiotherapy or surgery followed by post-operative RT is recommended for node positive supraglottic carcinoma (T1–T2 N1+, stage III–IV) in patients whose performance status is sufficient to tolerate this treatment. The role of induction chemotherapy prior to chemoradiotherapy or surgery remains unclear but may be appropriate for patients presenting with advanced nodal disease (e.g. N2c/N3), particularly if this is rapidly progressive and/or symptomatic.

All treatment options appear to effect similar locoregional control and survival rates: For T1 disease, five-year local control rates following treatment with RT, TLM, TORS or open supraglottic laryngectomy range from 77 to 100 per cent. For T2 tumours, the five-year local control rates range from 80 to 97 per cent for TLM or open supraglottic laryngectomy and from 62 to 83 per cent for primary RT.[8]

Recommendations

- **Radiotherapy, transoral laser microsurgery and transoral robotic surgery are reasonable treatment options for T1–T2 supraglottic carcinoma (R)**
- **Supraglottic laryngectomy may have a role in the management of selected tumours (R)**

T2b–T3 glottic tumours

Most patients with T2b–T3 glottic cancers are suitable for radiation-based larynx preservation therapy. However, subject to the availability of appropriate surgical expertise and multi-disciplinary rehabilitation services, TLM or open partial surgical procedures ± post-operative RT, may also be appropriate in selected cases. Open partial surgical procedures which might be considered include VPL ± reconstruction, frontolateral VPL, supraglottic laryngectomy, SCPL–CHEP or CHP and extended supraglottic laryngectomy. In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to at least lymph node levels II, III and IV bilaterally, because of the risk of occult nodal metastasis. Intensity-modulated radiotherapy (IMRT) allows a convenient solution to elective nodal treatment, enabling differential doses of RT to be given to different nodal groups simultaneously, depending on the presence or absence of macroscopic disease and the risk of subclinical disease.

In node positive disease, it is recommended that lymph node levels II-V should be treated on the involved side. If level II nodes are involved, then elective irradiation of ipsilateral level Ib nodes may be considered.

The potential of RT and chemotherapy for larynx preservation was established by the landmark Veterans Affairs Laryngeal Cancer Study Group

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(VALCSG) study[9] in which induction chemotherapy and RT (IC + RT) yielded similar overall survival (68 per cent at two years) to laryngectomy followed by adjuvant RT for stage III–IV laryngeal cancer with high rates of larynx preservation (64 per cent at two years). Rates of salvage laryngectomy were significantly lower for T3 *vs* T4 disease (29 per cent *vs* 56 per cent, $p = 0.001$). Subsequently, the RTOG (Radiation Therapy Oncology Group) 91-11 trial[10] demonstrated that concurrent chemoradiotherapy was superior to IC + RT and RT alone in terms of laryngeal preservation (88 *vs* 75 *vs* 70 per cent, respectively, at three years), although overall survival in each treatment arm was similar. Of note, 10-year follow-up data have confirmed the superiority of concurrent chemoradiotherapy, but a significant increase in non-cancer deaths in the group treated with chemoradiotherapy was reported.[11] The use of concurrent chemoradiotherapy for locally advanced head and neck cancers, including laryngeal cancers, is also supported by meta-analysis data.[12] Standard concurrent chemotherapy regimens include cisplatin (100 mg/m^2) on days 1, 22 and 43 of RT and carboplatin/5-FU on weeks 1 and 5 of RT.

Concurrent chemoradiotherapy is, however, associated with a significant increase in acute and late toxicity compared with RT alone. The long-term side effects of chemoradiotherapy are well documented: 43 per cent of patients develop severe (grade III/IV) late toxicity, including a reduction in speech and swallowing function which can lead to life-long dependence on a feeding tube (13 per cent of patients two years after treatment) and have a profound effect on quality of life (QoL).[13] (Although these late severe toxicities are likely to affect fewer patients when contemporary RT delivery schedules are used.) Older age, advanced T stage, larynx/hypopharynx primary site and neck dissection after chemoradiotherapy all increase the risk of severe late toxicity after chemoradiotherapy and the additional benefit of chemotherapy must be balanced against the risks for individual patients. The benefit of chemotherapy decreases with age and is non-significant above 70 years of age. Thus, its use may be less appropriate in older patients. Other systemic therapies that may be given concurrently with RT include cetuximab, a monoclonal antibody which competitively inhibits the cell-surface epidermal growth factor receptor. Cetuximab has been shown to improve locoregional control (three-year LRC 47 *vs* 34 per cent, $p < 0.01$) and overall survival (by 10 per cent – three-year OS 55 *vs* 45 per cent) over RT alone in a study of patients with locally advanced (stage III/IV) head and neck cancer (27 per cent of whom had laryngeal cancer). The benefit was maintained on longer follow-up (five-year OS 46 *vs* 36 per cent).[14] Toxicities of cetuximab include an acneiform rash and hypersensitivity reactions but it does not increase the rate of severe radiation-related mucositis. It is an alternative to concurrent chemoradiotherapy for patients with laryngeal cancer who cannot receive concurrent chemoradiotherapy, as per the guidelines published in 2008 by the National Institute for Health and Care Excellence (http://www.nice.org.uk/guidance/ta145).

Induction chemotherapy with cisplatin and 5-FU (PF) prior to RT may also improve survival,[15] but the benefit of induction chemotherapy prior to standard concurrent chemoradiotherapy schedules is currently unproven. If induction chemotherapy is used, taxane (docetaxel or paclitaxel) in combination with cisplatin and 5-FU has been shown to be superior to PF doublet chemotherapy in a meta-analysis of five randomised trials.[16]

Radiotherapy may be used as a single modality where comorbidity precludes the use of concurrent chemotherapy, cetuximab or surgery. Conventional RT alone may be suboptimal for the treatment of advanced laryngeal cancer. Altered fractionation regimens (including acceleration and hyperfractionation) improve locoregional control and overall survival compared with standard fractionated RT for head and neck cancer patients who elect or are selected to receive RT alone (albeit at the cost of higher mucosal toxicity).[17] However, altered fractionation regimens do not appear to improve outcome compared with or when combined with concurrent chemoradiotherapy which should be regarded as the 'standard of care' for the non-surgical management of advanced laryngeal cancer. Accelerated fractionation with hypoxia modification using either nimorazole or carbogen/nicotinamide shows promising results and requires further study. To that end, the UK clinical trial NIMRAD (a randomised placebo-controlled trial of synchronous NIMorazole *vs* RADiotherapy alone in patients with locally advanced head and neck squamous cell carcinoma not suitable for synchronous chemotherapy or Cetuximab) (NCT01950689) is currently recruiting in several UK centres.

It is important to note that, despite the laryngeal preservation and survival rates conferred by non-surgical strategies, there is a dearth of robust data relating to laryngeal function after chemoradiotherapy. By comparison with non-surgical treatments, any larynx-preserving surgical procedure – TLM or partial open procedure – undertaken for T2b/T3 carcinoma of the larynx will result in dysphonia and prolonged swallowing rehabilitation. Although most patients appear to achieve satisfactory swallowing function eventually, a small percentage of patients will require a total laryngectomy for functional reasons.

Whilst TLM or partial open surgical procedures may be considered as an alternative to non-surgical treatment for selected cases in appropriate centres, laryngectomy may be preferred for patients with significant pre-existing laryngeal destruction by tumour and/or a pre-treatment tracheostomy; however, reports of whether a pre-treatment tracheostomy negatively affects outcome after RT are conflicting and concurrent chemoradiotherapy remains an option for these patients (25 per cent of patients in the VALCSG study[9] had a baseline tracheostomy and they were not excluded from RTOG 91-11).

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Vocal cord fixation is not a contraindication to larynx preservation (for either surgical or non-surgical modalities), although it is likely that these patients will have a poorer functional and oncological outcome than patients with mobile vocal folds.

In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to at least lymph node levels II, III and IV bilaterally.

Recommendations

- **Most patients with T2b–T3 glottic cancers are suitable for non-surgical larynx preservation therapies (R)**
- **Concurrent chemoradiotherapy should be regarded as the standard of care for non-surgical management (R)**
- **Subject to the availability of appropriate surgical expertise and multi-disciplinary rehabilitation services, TLM or open partial surgical procedures ± post-operative RT, may also be appropriate in selected cases (R)**
- **In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to at least lymph node levels II, III and IV bilaterally. In node positive disease, it is recommended that lymph node levels II–V should be treated on the involved side. If level II nodes are involved, then elective irradiation of ipsilateral level Ib nodes may be considered (R)**

T3 supraglottic carcinoma

The principles of organ preservation for T3 supraglottic cancers are the same as for glottic cancers. Tumour size, pre-treatment laryngeal function and performance status should direct the management of individual patients. Rates of salvage laryngectomy after surgical and non-surgical treatment of supraglottic cancers are lower than for glottic cancers. Vocal cord function is usually well preserved following TLM or supraglottic laryngectomy; however, rehabilitation of swallowing function following supraglottic surgery may be prolonged and, whilst most patients achieve satisfactory swallowing function, this cannot be guaranteed.

T3 supraglottic cancers have a significantly higher risk of nodal disease (occult and clinical) than glottic tumours and this must be taken into account when considering how to manage the neck. In the absence of clinical or radiological evidence of nodal disease, elective treatment – RT and/or selective neck dissection – is recommended to at least lymph node levels II, III, IV bilaterally.

There is general agreement that chemoradiotherapy is sufficient to treat early nodal disease (N1, single lymph node <3 cm) in patients with glottic cancers. Since publication of the last edition, management of N2 (multiple lymph nodes and/or >3–6 cm) or N3 (>6 cm) nodal disease has been informed by the PET-Neck clinical trial.[18] The data confirm that positron emission tomography combined with computed tomography (PET–CT) surveillance of the neck in chemoradiotherapy complete responders, obviates the need for an elective neck dissection in patients with a negative PET–CT scan result.

Recommendations

- **Most patients with T3 supraglottic cancers are suitable for non-surgical larynx preservation therapies (R)**
- **Concurrent chemoradiotherapy should be regarded as the standard of care for non-surgical management (R)**
- **Subject to the availability of appropriate surgical expertise and multi-disciplinary rehabilitation services, TLM or open partial surgical procedures ± post-operative RT, may also be appropriate in selected cases (R)**
- **In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to at least lymph node levels II, III and IV bilaterally. In node positive disease, lymph node levels II–V should be treated on the involved side (R)**
- **As per the PET-Neck clinical trial, patients with N2 or N3 neck disease who undergo treatment with chemoradiotherapy to their laryngeal primary and experience a complete response with a subsequent negative post-treatment PET–CT scan do not require planned neck dissection. In contrast, patients who have a partial response to treatment or have increased uptake on a post-treatment PET–CT scan should have a neck dissection (R)**

T4 laryngeal carcinoma

Larynx preservation with chemoradiotherapy should be considered for T4 tumours, unless there is tumour invasion through cartilage into the soft tissues of the neck, in which total laryngectomy followed by adjuvant treatment yields better outcomes. The VALCSG study[9] showed reduced tumour response to chemotherapy and higher rates of salvage laryngectomy for T4 tumours (56 per cent for T4 *vs* 29 per cent for T3 tumours, $p = 0.001$). Nevertheless, larynx preservation can be achieved in a significant proportion of patients with T4 disease, without detriment to survival when salvage laryngectomy is incorporated. However, once again, few data are available correlating laryngeal

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preservation with function and QoL. Good patient selection is of paramount importance. Patients with large-volume T4 tumours – defined as extension of tumour through thyroid cartilage or tumour extension greater than 1 cm into the base of tongue – were excluded from RTOG 91-11[10] as they are poor candidates for organ preservation. Patients with significant pre-existing laryngeal destruction by tumour and/or a pre-treatment tracheostomy may also be better suited to a total laryngectomy. Total laryngectomy may confer a better QoL than a preserved, but poorly functioning, larynx.

Patients with large-volume T4 tumours who are unsuitable for surgery because of inoperable (T4b) disease have been treated with combined-modality organ preservation therapy with significant rates of disease control (71 per cent at four years) and overall survival (56 per cent at four years) in retrospective studies. Induction chemotherapy may be used to treat large volume, symptomatic disease prior to commencement of concurrent chemoradiotherapy.

Lymph node levels II–V bilaterally should be treated, irrespective of the pre-treatment clinical nodal status. As per the findings of the PET-Neck trial[18] (see above), a planned neck dissection is not necessary in patients who experience a complete response to chemoradiotherapy and have a post-treatment negative PET–CT scan. Improved systemic therapies and RT dose intensification using IMRT may improve outcomes for this patient group in future.

Recommendations

- **Larynx preservation with concurrent chemoradiotherapy should be considered for T4 tumours, unless there is tumour invasion through cartilage into the soft tissues of the neck, in which case total laryngectomy yields better outcomes (R)**
- **In the absence of clinical or radiological evidence of nodal disease, elective treatment (RT or surgery ± post-operative RT) is recommended to bilateral lymph node levels II, III, IV, V and VI (R)**

Post-operative RT /chemoradiotherapy

Radiotherapy delivered post-operatively to the primary site and/or neck in patients at high risk of locoregional recurrence can improve locoregional control and survival. Post-operative RT is recommended for pT4 laryngeal cancers of any nodal stage, pT1/T2/T3 tumours with N2–N3 nodal stage and for all patients with close or positive resection margins and/or extracapsular spread; other unfavourable pathological factors, including peri-neurial and vascular invasion, are relative indications for post-operative RT. Administration of concurrent cisplatin chemotherapy with post-operative RT improves locoregional control and disease-free survival compared with post-operative RT alone for locally advanced tumours,[19,20] albeit at the expense of increased mucosal and haematological toxicity and possibly increased deaths. This approach improves overall survival in selected patients, particularly with extracapsular spread and/or positive margins, and should be used selectively for patients at highest risk of relapse.

Key points

- Approximately 2400 patients are diagnosed with laryngeal squamous cell carcinoma and ~800 patients die of the disease per annum in the UK
- Early stage tumours of the glottis present with hoarseness, whilst tumours of the supraglottis and more advanced glottic tumours may present with pain, odynophagia and/or dysphagia, a neck lump or even airway compromise
- Meticulous endoscopic inspection of the tumour under general anaesthetic and imaging of the head, neck and thorax is needed for staging
- Radiotherapy and transoral laser microsurgery are reasonable treatment options for T1a–T2a glottic and T1–T2 supraglottic carcinomas
- Most patients with T2b–T3 glottic and T3 supraglottic cancers are suitable for non-surgical larynx preservation therapies. Transoral laser microsurgery or open partial surgical procedures ± post-operative radiotherapy may be also be appropriate in selected cases
- Concurrent chemoradiotherapy should be regarded as standard of care for the non-surgical management of stage III/IV laryngeal cancer
- Patients with N2 or N3 neck disease who experience a complete response with a subsequent negative post-treatment PET–CT scan do not require planned neck dissection
- Post-operative (chemo)radiotherapy is recommended in the presence of advanced disease or adverse histological features.

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GUIDELINE

Oral cavity and lip cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It provides recommendations on the assessment and management of patients with cancer of the oral cavity and the lip.

Recommendations

- Surgery remains the mainstay of management for oral cavity tumours. (R)
- Tumour resection should be performed with a clinical clearance of 1 cm vital structures permitting. (R)
- Elective neck treatment should be offered for all oral cavity tumours. (R)
- Adjuvant radiochemotherapy in the presence of advanced neck disease or positive margins improves control rates. (R)
- Early stage lip cancer can be treated equally well by surgery or radiation therapy. (R)

Introduction

In order of decreasing frequency, malignant tumours of the oral cavity affect the anterior two-thirds of the tongue, floor of mouth, buccal mucosa, retromolar trigone, hard palate and gingivae. Tumours of the lip require separate consideration as their natural history differs from oral cavity disease. The overwhelming majority of oral cavity cancers are squamous cell carcinomas (SCCs). Non-squamous cell tumours are predominantly of salivary gland origin and are discussed elsewhere in these guidelines. The heterogeneous nature of oral cavity tumours, the functional and cosmetic sequelae of their management and the frequent medical co-morbidities that co-exist in this patient group demand that treatment options should be considered by a multidisciplinary team before reaching a final plan through consensus with the patient and carers. The overall treatment intention, whether curative or palliative, should be clearly communicated at the outset.

Pathology

Oral cavity

Carcinoma of the oral cavity 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 or alcohol is thought to be important. Carcinogenesis is a multistep process that involves over expression of oncogenes and inactivation of tumour suppressor genes. The p53 suppressor gene has been identified as being important in oral cavity carcinomas in smokers. The presence of human papilloma virus (HPV) that expresses the p16 oncoprotein in oral cavity carcinoma in non-smokers is of significant importance as the cancers tend to occur in younger patients. However, HPV-related disease does not appear as frequently in the oral cavity as it does in the oropharynx and appears not to proffer as much of an improvement in prognosis.[1] The importance of epidermal growth factor receptor (EGFR) status in oral cavity carcinoma remains unclear. Whilst over expression does appear to be related to poor prognosis, EGFR status does not yet appear to be correlated with response to targeted molecular therapies such as cetuximab.

Within the diagnosis of oral cavity SCC, several histological subtypes exist with different prognoses such as verrucous (better prognosis) and basaloid (worse prognosis) carcinomas. Oral SCCs are classified according to grade depending on several histopathological features such as degree of keratinisation, nuclear pleomorphism, cellular atypia and mitotic activity. They are divided into well, moderate and

poorly differentiated carcinomas. However, tumour grade is of limited prognostic value due to the heterogeneity within a tumour and sampling error. Several other histopathological factors have been shown to be of prognostic importance such as tumour thickness, extra-capsular spread (ECS) of nodal metastasis[2] and patterns of invasion. Oral tongue SCC of greater than 4 mm tumour thickness is considered to represent a >20 per cent risk of cervical lymph node metastatic involvement.[3] Extra-capsular spread in cervical lymph nodes is consistently associated with an increased risk of local regional recurrence, distant metastasis and decreased survival. The pattern of invasion in oral SCC appears to be important in determining prognosis in that those cancers that have a non-cohesive invasive front and/or peri-neurial invasion appear to be associated with an increased risk of loco-regional relapse.[4] These pathological factors therefore supplement the tumour–node–metastasis classification and are now incorporated in pathological datasets.

Lip

Cancer of the lip is the most common malignant tumour affecting the head and neck. Its clinical behaviour is similar to that of skin cancer. Incidence rates are around 13.5 per 100 000 in Oceania, 12 per 100 000 in Europe and 12.7 per 100 000 in North America.[5] The factors commonly cited as important in lip cancer are solar radiation, tobacco smoking and viruses. 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.

Squamous cell carcinoma is the commonest histological tumour type in lip cancers, followed by basal cell carcinoma. The most common non-mucosal form of lip cancer arises from tumours of the minor salivary glands, with in converse to mucosal lip cancer the upper lip being more commonly involved than the lower.

Clinical presentation

The majority of SCCs (>95 per cent) of the oral cavity are presented as ulcers or masses. Early lesions can be subtle and appear as flat, discoloured areas (leukoplakia or erythroplakia).[6] A non-healing ulcer is the most common presentation. Advanced tumours can present with invasion of neighbouring structures causing tooth mobility, trismus, sensory change, referred otalgia and neck 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.[7]

TABLE I
T STAGING FOR ORAL CAVITY TUMOURS

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or smaller in greatest dimension
T2	Tumour larger than 2 cm but 4 cm or smaller in greatest dimension
T3	Tumour larger than 4 cm in greatest dimension
T4a	Tumour invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate or mandible
T4b	Tumour invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx or skull base or encases carotid artery

Assessment and staging

Clinical examination

Clinical examination is useful in identifying new tumours and for surveillance after treatment. Given its importance in diagnosis and treatment planning, a systematic approach must be adopted to include the primary site and neck, with assessment of the index tumour size as well as any potential invasion of local structures. The examination should be preceded by a focused history to elucidate any potential co-morbidities and social circumstances that may influence the choice of treatment.

Imaging considerations

Imaging of early stage tumours of the lip is usually not indicated. However, advanced tumours of the lip (particularly if they are adherent to the adjacent mandible) require computed tomography (CT) or magnetic resonance imaging to allow complete staging and treatment planning with regard to resection margins which may of necessity include adjacent bone.

Oral cavity tumours are almost always staged with cross-sectional imaging to include the chest where the demonstration of simultaneous pulmonary parenchymal disease may influence curability.[8,9] Sentinel node lymph node biopsy has been shown to be an effective method of assessment of the neck in early stage oral cancers.[10]

Pre-treatment staging

Staging of primary cancer of the lip and oral cavity is similar and shown in Table I. T4 tumours of the lip usually only invade the anterior mandible or maxilla rather than other structures.

Management

Oral cavity

Although there is no randomised data exclusively comparing the different treatment modalities available in the management of oral cavity cancer, non-surgical clinical trials often present this subsite in combination with others in the head and neck. Two-year crude survival rates are around 85 per cent for stage I disease, 70 per cent for stage II disease[11], 50 per cent for stage III disease and 40 per cent for stage IV disease.[12]

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General principles

Surgery. Factors such as fitness for anaesthesia, previous cancer treatment and patient choice as well as the skill mix and resources available to the treating team must be considered.[13,14] There are a number of different options available under the broad banner of surgery: conventional surgery, laser surgery, thermal surgery and photodynamic therapy (PDT).[15] Curative surgery for cancer of the oral cavity involves resection of tumour with an appropriate safety margin and subsequent reconstruction of the tissues in order to maintain function. The size and location of the primary tumour determine the need or otherwise for adjuncts such as temporary tracheostomy and access procedures. Many tumours in the anterior aspect of the oral cavity can be accessed via the transoral route. This is ideal, since in so doing the circumferential muscular sphincter is maintained and scars avoided. However, as tumours increase in size and become more posteriorly placed, a controlled resection may only be possible by performing either a lingual release or resorting to lip-split and mandibulotomy. There are several options for the lip skin incision with some form of *Z*-plasty being desirable to both disguise and lengthen the scar, thus preventing post-operative wound contraction and distortion to the vermilion border.

Effective tumour ablation is achieved by ensuring good visibility which in turn is dependent on appropriate access. In order to maximise the chances of achieving complete tumour resection with a clear margin of normal tissue, both visual inspection and palpation must be employed. The method of ablation, be it scalpel, laser, diathermy or coblation, is a matter of personal preference. For small, superficial lesions laser vaporisation may be employed although this often does not permit accurate histological assessment of the adequacy of resection and so may compromise decisions surrounding the need or otherwise for adjuvant treatments. Lasers and thermal techniques, whilst reducing the amount of intra-operative bleeding, can cause histological artefact and morphological distortion of tissue margins. Coblation involves the generation of bipolar radio-frequency waves. Tissue temperatures of around 60 °C ensue, much lower than temperatures generated by conventional diathermy. Although this is claimed to reduce post-operative pain, the technique has been associated with increased levels of haemorrhage in certain head and neck sites.

The primary aim of surgery in oral cavity cancer is tumour resection with a clinical clearance of ideally 1 cm (vital structures permitting). 'Close' margins (defined as a histopathological margin of less than 5 mm) mean further surgery or adjuvant radiotherapy (RT) and should be discussed by the multidisciplinary team. The use of intra-operative frozen sections to assist marginal clearance is controversial.[16] Although the accuracy is good in histological terms, they can give a false sense of security and invariably prolong operative time. Adoption of a Mohs-type technique where the whole of the resection bed is mapped out is impractical given the size of the average intra-oral resection. Intra-operative tumour tissue marking has been attempted with agents such as toluidine-blue but this has limited value in marginal clearance because of high false positive rates.[17] Where bony resection is required, the assessment is largely based upon clinical and radiological findings.[18] Intra-operative techniques such as periosteal stripping however remain reliable. Frozen section of cancellous bone can be used to guide the extent of the resection.

Cervical lymphadenectomy in the form of elective neck dissection offers improved overall and disease-free survival compared with therapeutic neck dissection for the majority of oral cancers with recent evidence suggesting advantages even for tumours less than 4 mm in thickness.[19] Sentinel node lymph node biopsy may be indicated for small (T1 and T2) cancers since a negative sentinel node biopsy can avoid the morbidity of neck dissection and may be more cost-effective.[10]

Recommendations

- **Surgery remains the mainstay of management for oral cavity tumours (R)**
- **Tumour resection should be performed with a clinical clearance of 1 cm vital structures permitting (R)**
- **Elective neck treatment should be offered for all oral cavity tumours (R)**

Radiotherapy ± chemotherapy. In the oral cavity, primary radiochemotherapy is less commonly utilised than other head and neck sites. However, it should be considered in selected patients. Concurrent radiochemotherapy combines platinum-based chemotherapy with external beam radiotherapy (EBRT) to 70 Gy. While the most recognised concurrent chemotherapy regimen is cisplatin 100 mg/m^2 three weekly, varying doses and schedules are acceptable practice, as is substitution by carboplatin. Patients undergoing radiochemotherapy require speech, swallow and dietetic support, in both the acute and long-term setting. Patients who are excluded from platinum-based chemotherapy may be considered for EBRT with cetuximab under National Institute for Health and Care Excellence guidance. Neo-adjuvant chemotherapy with taxanes, cisplatin and 5-fluro-uracil (TPF) is a potent combination in advanced, inoperable disease in fit patients, if followed by concurrent radiochemotherapy.

External beam radiotherapy is not usually recommended as the primary curative treatment in oral cavity tumours because the significant morbidity of

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treatment limits radiation dose and therefore cure rates. Severe mucositis of the treated volume during and immediately after treatment is inevitable and will affect function and nutrition. Long-term pain is a common sequelae if high enough radiation doses to cure primary tumours are used while osteoradionecrosis of the mandible is a particular risk when irradiating the oral cavity. External beam radiotherapy alone can be used to treat the neck prophylactically after excision of a small primary without a neck dissection. Brachytherapy as sole treatment or as a boost after EBRT can produce cure rates equivalent to those in surgical series. As the radiation dose is concentrated in the tumour tissue more effectively than with EBRT, higher doses and fewer long-term side effects can be achieved. Brachytherapy requires specific expertise which is not widely available in the UK.

Adjuvant RT improves local control and overall survival when added to surgery in locally advanced cancers. It should be considered in all patients with larger T3 or T4 tumours, where there is ECS or N2–3 neck disease. Other poor prognostic factors such as grade or peri-neurial invasion may also inform the decision.[4] The morbidity of radiation to the primary site in the oral cavity means the benefits and side effects should be carefully considered with each individual patient.

Concomitant chemotherapy improves the effectiveness of adjuvant RT – more so in oral cavity tumours than in other primary sites of the upper aerodigestive tract – and should always be considered in patients over 71 years old with relevant histological features when RT is discussed.[20] However, it increases the acute and late morbidity of treatment. In patients with incurable disease, a short course of palliative RT may help to improve local symptoms. Palliative chemotherapy with platinum-based drugs and 5FU or capecitabine can also be considered to help symptoms and improve survival.

Early stage cancer. Early stage tumours (T1 and small T2) can be adequately treated with either surgery or brachytherapy. Treatment choice may be influenced by tumour size, location, depth of invasion, proximity to bone, growth patterns including differentiation, neck nodal disease and access to services.

Advanced stage cancer. For advanced disease, stages III and IV (T3, T4 N0 and T1–4 N1), traditional management includes surgical resection, neck dissection, reconstruction and post-operative RT. The latter should be offered to at least 60 Gy equivalent and optimally start within 6 weeks of surgery. In fit patients under the age of 71, adjuvant radiochemotherapy up to 66 Gy with concurrent platinum-based chemotherapy should be considered for those with positive surgical margins and/or ECS.[21]

Recommendation

- **Adjuvant radiochemotherapy in the presence of advanced neck disease or positive margins improves control rates (R)**

Recurrent cancer. Patients with locally recurrent disease should be fully restaged and assessed for consideration of curative treatment in the form of repeat surgery, possible EBRT or brachytherapy if available. Palliative RT may be used, either over short fractionation schedules or split course, for patients with advanced and inoperable disease, or those who are not fit for a more toxic, radical approach. Palliative chemotherapy should be considered for inoperable, recurrent and or metastatic disease, when possible patients should be offered entry to clinical trials.

Reconstruction following surgical ablation of oral cavity tumours. 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.[22,23] However, there are no randomised controlled trials. The literature suffers from a wide range of heterogeneous factors introducing bias including tumour sites, stages, patient variables, operators, surgical techniques, study designs, small numbers, lack of clarity for treatment intention and the reporting of different outcome measures.

Reconstructive options include local flaps, regional pedicled flaps and microvascular free tissue transfer discussed elsewhere in the guidelines.[24] Hard tissues may be reconstructed using free autologous bone grafts but more commonly involve the use of free tissue transfer from iliac crest, fibula, radius or scapula.

Lip

General principles. Early stage cancer can be treated equally well by surgery or radiation therapy. The five-year crude survival rates for surgical treatment are about 75–80 per cent for T1 to T2 tumours, dropping to 40–50 per cent for T3 and T4 tumours. The primary lymphatic drainage of the lower lip is to submental and submandibular level cervical lymph nodes. Neck dissection is generally not performed in the absence of clinically suspicious cervical lymph nodes as more than 5 per cent of patients are likely to develop recurrence in the neck following treatment of the primary lesion. The presence of cervical nodes at presentation is a poor prognostic indicator. Small lesions are managed by simple surgical excision and primary closure. Equally good results can be achieved with fractionated EBRT or brachytherapy. External beam radiotherapy using electrons or orthovoltage photons minimises dose to the oral cavity so that mucositis occurs only on the treated lip.

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Larger lesions of the lip require more consideration with regard to reconstruction techniques. The functional outcome of the repair with regard to lip sensitivity and muscle function also needs to be taken into consideration. Whenever possible full thickness skin flaps (skin, muscle and mucosa) should be used. The repair should provide sufficient mucosa contiguous to the commissure to avoid contracture. Superficial field change lesions affecting the external vermilion of the lip such as leukoplakia or actinic keratosis are best managed via a lip shave and mucosal advancement.

Various studies have shown that for small tumours radiation therapy can achieve a cure rate equivalent to that obtained surgically. However, the cosmetic results of EBRT to the lip are usually not as satisfactory as surgical excision and repair. Surgical excision of small lip tumours involves relatively minor surgery, often under local anaesthetic and may be therefore less burdensome for the patient than a course of RT. The lower lip is one of the few ideal sites for orthovoltage therapy. Using a single anterior field a fractionated course of 50 Gy in 15 fractions over 3 weeks is administered. Brachytherapy can produce good aesthetic results but is not widely available in the UK. Iridium[192] can be used in the treatment of lip cancer. Patients can be treated twice a day for 4–5 days with a total radiation dose between 40 and 45 Gy in 8–10 fractions.

Lower lip. Small lesions invading into the adjacent muscle are amenable to a wedge excision. The excision can also be completed using a 'W' plasty or half 'W' plasty to avoid the inferior aspect of the excision encroaching on the crease line of the chin. If the dimensions of the lip resection require the introduction of tissue to minimise functional problems and microstomia, then this may be by means of Abbe, Abbe-Estlander or Karapandzic flaps. The Estlander modification of the cross-lip flap is used to reconstruct the oral commissure. The Karapandzic flap is useful for defects involving more than two-thirds of the lower lip, where the defect is in the midline. The main advantage of the Karapandzic flap is that the nerve and blood supply is retained and the underlying orbicularis muscle rotated so that a sensate functional lip reconstruction results. The various reconstructive options are identified in Table II. With larger defects of the lower lip reconstruction requires either large cheek flaps to be advanced to repair the defect or the use of free tissue transfer. The common forms of cheek flap include the bilateral Gillies fan flaps or the Bernard–Webster cheek flap reconstruction. Free tissue transfer is required for lip reconstruction when the total remaining lip or adjacent rotated tissue is insufficient to create a reasonable circular stoma.

Recommendation

- **Early stage lip cancer can be treated equally well by surgery or radiation therapy (R)**

Upper lip. Similar to lower lip defects wedge excisions and advancement flaps can address upper lip defects which involve up to one half of the width of the upper lip. Care should be taken to respect the relevant aesthetic subunits. Defects of less than a third in the midline can be closed primarily. Defects involving greater than half of the lip can be reconstructed with cross-lip flaps from the lower lip. Peri-alar crescentic advancement flaps can be used to disguise the advancement of the upper lip when the advancement encroaches to the medial part of the nose. For defects involving more than two-thirds of the lip, a Burow-Diffenbach reconstruction can be performed. This flap replaces upper lip defects by utilisation of laterally based advancement flaps. Bilateral peri-alar crescentic excisions are required to provide adequate advancement. The various reconstructive options are identified in Table III.

Most large series in the literature show that the majority of patients have small lesions without palpable cervical metastases although the incidence of synchronous cervical metastases increases as the size of the primary tumour increases. The local recurrence rate is low due to the relative ease of surgical excision. Even re-excision because of local failure leads to salvage in 75–80 per cent of cases.

Developing therapeutic regimens

Neoadjuvant chemotherapy with TPF followed by surgery and then RT is accruing evidence in other primary sites. Radio chemotherapy with the addition

TABLE II
RECONSTRUCTIVE OPTIONS FOR LOWER LIP DEFECTS

Defect size	Procedure
<1/2	Wedge excision
1/2 to 2/3	Karapandzic flap Abbe-Estlander flap
>2/3	Bernard Burow Gillies fan flap Webster flap Free flap

TABLE III
RECONSTRUCTIVE OPTIONS FOR UPPER LIP DEFECTS

Defect size	Procedure
<1/2	Wedge excision
1/2–2/3	Peri-alar crescentic flap Reverse Karapandzic flap Abbe–Estlander flap
>2/3	Burow–Diffenbach flap Free flap

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of targeted agents requires further evaluation. Radiotherapy alone *vs* RT plus cetuximab in intermediate cancers and the use of positron emission tomography–computed tomography to define the gross tumour volume and to assess response to non-surgical treatments is the subject of ongoing research. Agents such as palifermin and amifostine are under investigation to reduce radiation toxicity but are not yet in routine use. Molecular mapping to determine the individualised, sub-clinical spread to inform the clinical target volume requires further evaluation. Likewise further work is required to establish the long-term quality of life, toxicity recognition, management and support in head and neck cancer patients receiving radiochemotherapy.

Xerostomia is one of the most unpleasant permanent complications from RT of the oral cavity. Sparing of the salivary glands by intensity-modulated radiation therapy may improve toxicity without reduction in local control.

The efficacy of hyperbaric oxygen in the prevention of osteoradionecrosis remains unproven, as does the use of medical therapies such as pentoxifylline and tocopherol in established cases.

Photodynamic therapy has been advocated as a technique which causes selective tumour destruction by cell apoptosis. Advocates suggest minimal scarring and preservation of uninvolved tissue thereby minimising any functional deficit caused by tumour ablation. Unfortunately the photograph-sensitising agents currently available are insufficiently selective to prevent normal tissue damage and patients must be protected from exposure to sunlight for several days. Since the wound sloughs and heals by secondary intention, there is little benefit in functional terms of PDT over the more traditional techniques. Foscan® mediated PDT can also be used to treat primary cancer of the lip, where treatment yields complete response rates comparable with those published for surgery or RT. The lack of tissue memory for PDT means that unlike RT this treatment can be repeated on a number of occasions.

Key points

- The majority of malignant tumours of the oral cavity are squamous cell carcinomas
- The clinical behaviour of lip cancer is akin to skin cancer
- While tobacco and alcohol are the main carcinogens implicated in oral cavity cancer, a small but significant role for human papilloma virus is recognised
- Surgical resection is the primary modality used to manage most oral cancers
- Elective neck management is indicated for any tumour when the risk of occult nodal involvement is >20 per cent
- Several reconstructive options exist to repair soft tissue and bony defects after tumour resection
- Tumour thickness, positive margins and extra-capsular spread of nodal metastasis and pattern of invasion have been shown to have significant prognostic value
- Post-operative adjuvant radiation or radiochemotherapy should be considered in the presence of unfavourable disease factors.

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GUIDELINE

Oropharyngeal cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. There has been significant debate in the management of oropharyngeal cancer in the last decade, especially in light of the increased incidence, clarity on the role of the human papilloma virus in this disease and the treatment responsiveness of the human papilloma virus positive cancers. This paper discusses the evidence base pertaining to the management of oropharyngeal cancer and provides recommendations on management for this group of patients receiving cancer care.

Recommendations

- Cross-sectional imaging is required in all cases to complete assessment and staging. (R)
- Magnetic resonance imaging is recommended for primary site and computed tomography scan for neck and chest. (R)
- Positron emission tomography combined with computed tomography scanning is recommended for the assessment of response after chemoradiotherapy, and has a role in assessing recurrence. (R)
- Examination under anaesthetic is strongly recommended, but not mandatory. (R)
- Histological diagnosis is mandatory in most cases, especially for patients receiving treatment with curative intent. (R)
- Oropharyngeal carcinoma histopathology reports should be prepared according to The Royal College of Pathologists Guidelines. (G)
- Human papilloma virus (HPV) testing should be carried out for all oropharyngeal squamous cell carcinomas as recommended in The Royal College of Pathologists Guidelines. (R)
- Human papilloma virus testing for oropharyngeal cancer should be performed within a diagnostic service where the laboratory procedures and reporting standards are quality assured. (G)
- Treatment options for T1–T2 N0 oropharyngeal squamous cell carcinoma include radical radiotherapy or transoral surgery and neck dissection (with post-operative (chemo)radiotherapy if there are adverse pathological features on histological examination). (R)
- Transoral surgery is preferable to open techniques and is associated with good functional outcomes in retrospective series. (R)
- If treated surgically, neck dissection should include levels II–IV and possibly level I. Level IIb can be omitted if there is no disease in level IIa. (R)
- If treated with radiotherapy, levels II–IV should be included, and possibly level Ib in selected cases. (R)
- Altering the modalities of treatment according to HPV status is currently controversial and should be undertaken only in clinical trials. (R)
- Where possible, patients should be offered the opportunity to enrol in clinical trials in the field. (G)

Introduction and epidemiology

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is increasing significantly in developed countries.[1] In the USA, the incidence increased by 22 per cent from 1.53 per 100 000 to 1.87 per 100 000 between 1999 and 2006, after showing no change between 1975 and 1999. The UK has seen a doubling of incidence between 1990 and 2006. There has been a further doubling in incidence between 2006 and 2010.

The increasing incidence of OPSCC is due to human papilloma virus (HPV) infection, with HPV-16 being the predominant subtype responsible. The proportion of cases with evidence of HPV infection has risen rapidly and HPV is now responsible for over 70 per cent of OPSCCs in Europe and the USA.[1,2] The rise in HPV-related OPSCC has been called an 'epidemic' and is expected to continue.

Clinical presentation

Patients often present with a painless neck lump, with few other symptoms. They may also complain of a sore throat or tongue, otalgia, pain and/or difficulty swallowing and/or a change in voice quality (hot potato voice).

Assessment and staging

Clinical examination

Flexible direct endoscopy of the upper aerodigestive tract is now available in virtually all ear, nose and throat clinics in the UK. It is vital for assessing the limits of spread, such as direct through and through invasion of the soft palate from anterior to posterior surfaces, the inferior extent of lateral pharyngeal wall tumours into the vallecula and pyriform fossa, and the superior extension of tonsillar cancers into the postnasal space and skull base.

Imaging considerations

Cross-sectional imaging is required in all cases to complete assessment and staging. Magnetic resonance imaging (MRI) scanning with contrast is optimal for staging the primary tumour, particularly when assessing soft tissue spread, such as in the tongue base and/or body of the tongue.[3,4] Computed tomography (CT) scanning may also be required, particularly to assess the extent of nodal disease and bony invasion, e.g. body of the mandible and skull base in tonsillar tumours and cervical spine in posterior pharyngeal wall tumours.

The presence of nodal metastases should be evaluated by CT or MRI in all patients. Ultrasound with or without needle biopsy should be carried out for all patients presenting with a neck lump and is an accurate method of staging nodal disease in experienced hands.

Distant metastases should be assessed by CT scanning of the chest and upper abdomen, to exclude metastatic disease to the lungs and liver.[3] Magnetic resonance imaging scanning is not suitable for this due to the relatively slow acquisition process leading to movement artefact caused by breathing.

Fluoro-deoxy-glucose positron emission tomography combined with computed tomography (F-FDG PET–CT) scanning may be used to give additional staging information when it is available, particularly where staging is difficult clinically (e.g. patient with trismus) or where there is uncertainty on other imaging and/or equivocal findings that would preclude radical treatment. Positron emission tomography (PET) also has a role in the assessment of recurrent tumours and can detect recurrence at primary sites, neck nodes and/or distant metastases.

Supported by the results of the UK PET-Neck randomised controlled trial (RCT) study,[5] F-FDG PET–CT scanning is now also recommended for the assessment of response approximately three months post-chemoradiotherapy, particularly in patients with advanced nodal disease. PET-CT guided active surveillance showed similar survival outcomes to the planned neck dissection arm, but resulted in considerably fewer neck dissections, and fewer complications, and was cost effective, supporting its use in routine practice.[5]

Examination under anaesthetic and panendoscopy

Examination under anaesthetic and panendoscopy is strongly recommended to assess the extent and resectability of the primary tumour and to exclude second primaries, especially in hypopharynx and oesophagus. Examination under anaesthetic is mandatory if thorough endoscopic examination is not possible in the clinic as above and/or if no biopsy can be obtained.

Recommendations

- **Cross-sectional imaging is required in all cases to complete assessment and staging (R)**
- **Magnetic resonance imaging is recommended for primary site and CT scan for neck and chest (R)**
- **Positron emission tomography combined with computed tomography scanning is recommended for the assessment of response after chemoradiotherapy, and has a role in assessing recurrence (R)**
- **Examination under anaesthetic is strongly recommended, but not mandatory (R)**

Pre-treatment staging

Pre-treatment staging for the primary tumour based on the tumour–node–metastasis classification (7th edition) for oropharyngeal tumours is shown in Box I.

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BOX I
TNM STAGING FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- Tis: Carcinoma in situ
- T1: Tumour 2 cm or less in greatest dimension
- T2: Tumour larger than 2 cm but 4 cm or less in greatest dimension
- T3: Tumour larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
- T4a: Tumour invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate or mandible
- T4b: Tumour invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Pathology

Formal tissue biopsy of the primary cancer is one of the cornerstones of the management pathway in oropharyngeal cancer. Tumours can be biopsied under local or no anaesthetic in the clinic. Otherwise, direct biopsy and staging under general anaesthetic is necessary.

In very few circumstances, a positive cancer diagnosis from fine needle aspiration (FNA) of involved nodes may suffice, provided the cytology result has been considered in conjunction with the clinical presentation and appropriate imaging at a head and neck cancer multidisciplinary team meeting. Such circumstances may arise in a person who is unfit to have an anaesthetic for an open biopsy and in whom local anaesthetic biopsies have not been successful. There is limited information on the reliability of p16 and HPV tests on FNA material and HPV testing is not currently routinely recommended on FNA samples.

The majority of oropharyngeal cancers are squamous cell carcinomas. It is recommended that they are reported according to The Royal College of Pathologists UK Guidelines for the histopathology reporting of mucosal malignancies of the pharynx (2013). Human papilloma virus testing is a core item for OPSCC to allow the stratification of treatment outcomes. Human papilloma virus status should be assessed using validated methods with appropriate controls. Human papilloma virus testing for oropharyngeal cancer should be performed within a diagnostic service where the laboratory procedures and reporting standards are quality assured. The immunohistochemical identification of over-expression of p16 protein is a useful screening method for HPV infection as HPV-associated carcinomas show strong nuclear and cytoplasmic expression of p16 in over 70 per cent malignant cells and p16-negative cases are almost certainly not HPV associated. Carcinomas showing p16 over-expression should have the presence of HPV confirmed by high-risk HPV DNA in situ hybridisation, if possible. Polymerase chain reaction analysis for HPV is not currently recommended in clinical practice as there is a risk of false positive results from formalin-fixed tissues.[6]

Recommendations

- **Histological diagnosis is mandatory in most cases, especially for patients receiving treatment with curative intent (R)**
- **Oropharyngeal carcinoma histopathology reports should be prepared according to The Royal College of Pathologists Guidelines (G)**
- **Human papilloma virus testing should be carried out for all oropharyngeal squamous cell carcinomas as recommended in The Royal College of Pathologists Guidelines (R)**
- **Human papilloma virus testing for oropharyngeal cancer should be performed within a diagnostic service where the laboratory procedures and reporting standards are quality assured (G)**

Prognosis

Prognosis is dependent on stage at presentation as well as HPV status.[7] The status of human papilloma virus is a strong and independent prognostic factor for survival, and HPV-positive OPSCC has a 58 per cent reduction in the risk of death compared with HPV-negative OPSCC (hazard ratio 0.42, 95 per cent; confidence interval 0.27–0.66), with 3 year overall survival rates of 82.4 per cent for HPV-positive disease compared with 57.1 per cent ($p < 0.001$) for HPV-negative disease.[8] Factors including smoking, particularly current smoking,[9,10] which may be a surrogate of genetic instability, and nodal stage, may influence prognosis in HPV-positive OPSCC. Several immunological markers have also been shown to correlate with prognosis and a UK study showed significant associations between the presence of tumour infiltrating lymphocytes and improved survival.[11] Although there are no head-to-head comparisons of primary surgical *vs* non-surgical management for OPSCC, similar survival outcomes have been reported in studies of primary chemoradiotherapy and of surgery followed by post-operative radiotherapy (RT) and/or chemoradiotherapy, albeit there is a lack of prospective randomised trials of surgical management.[8,12–14]

To date, there is no evidence that patients with HPV-positive and HPV-negative OPSCC should be treated differently, outside of the context of randomised,

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controlled clinical trials. In view of the excellent prognosis from lower-risk HPV-positive disease, current and future UK studies (De-Escalate HPV, ISRCTN33522080 and PATHOS, UKCRN ID 18645) will investigate whether reduced intensity treatment can maintain favourable outcomes but reduce acute and late toxicity for patients. On the other hand, because HPV-negative and higher risk HPV-positive patients have a poorer prognosis, future trials (CompARE, ISRCTN41478539) will investigate whether escalating treatment will result in better outcomes for these patients.

Management

Early (T1–T2 N0) oropharyngeal carcinoma

General principles of management. Early stage (T1–T2 N0 M0) oropharyngeal carcinoma should ideally be treated with single modality therapy, either primary surgery or RT. There are no high-quality comparative studies of the two treatment modalities within the same population. Retrospective case series demonstrate five-year disease-specific survival rates of 81–100 per cent for primary surgery[15](with adjuvant therapy where appropriate) and 77–89 per cent for primary RT, with surgical salvage.[16] Treatment decisions are made based on the size and position of the tumour overall functional deficit.

Surgical management of early (T1–T2 N0) oropharyngeal cancer. Surgery for T1–T2 N0 OPSCC should usually be carried out transorally, either by transoral laser microsurgery (TLM) or transoral robotic surgery (TORS). Oncologic results after transoral resection of the oropharynx appear to be comparable to open surgery and good functional outcomes have been reported after transoral surgery in retrospective series.[17] Open approaches are associated with increased severe morbidity and treatment complications and have now fallen out of favour for early stage disease.

During TLM, tumours are removed in several (at least two) planned pieces following trans-tumoural resection. This can cause difficulty in pathological scrutiny of the resected tissue to determine margins, which is compounded by laser artefact and difficulty in orientation. Representative marginal biopsies, taken from the peripheral mucosal resection margins and tumour bed can be carried out and examined pathologically to help rule out the presence of residual microscopic disease after TLM. In contrast to TLM, TORS involves *en bloc* removal of the tumour in the majority of cases. As a result, surgical margins can be more easily interpreted.

About 10–31 per cent of patients who are clinically T1–T2 N0 will have occult nodal disease. Therefore, patients having surgery to the primary should also undergo ipsilateral selective neck dissection. Surgery to the contralateral neck may also be considered in tumours arising at or very near the midline (in the soft palate, tongue base or posterior pharyngeal wall) in order to obtain pathological staging of the contralateral neck. Evidence suggests dissecting levels II, III and IV and possibly level I if there is anterior extension.[18] Retrospective studies suggest that level IIb does not need to be dissected, as long as there are no findings pre-operatively of level IIa disease. For transoral resections, the neck dissection may be performed at the same time, or as a staged procedure, around two weeks before transoral resection of the primary. A staged approach may help prevent the development of a fistula if there is lateral pharyngeal wall transoral resection. Concomitant transoral resection and neck dissection can also be carried out and good results have been reported. In the latter, local muscle transposition (digastric or sternomastoid) can be performed to augment any defect and decrease risk of fistula. For any transoral resection of the oropharynx, ligation of the individual feeding vessels from the external carotid artery should be performed (ascending pharyngeal, lingual and facial branches) to limit the risk of potentially life-threatening haemorrhage. This should be done in any neck dissection performed as a prior staged procedure.

Although the goal for T1–T2 N0 disease should be single modality treatment, adjuvant RT and/or chemoradiotherapy may be required due to adverse pathological features for recurrence following surgery. Post-operative RT should be planned using the same principles as radical RT; a dose of 60 Gy in 30 fractions is typically recommended. Adjuvant treatment may affect functional outcomes following surgery.

Radical RT for early oropharyngeal cancer. Prior to RT, patients should undergo dietetic, speech and language therapy and dental review. A total dose equivalent of 70 Gy in 35 fractions is used in radical treatment. Hypofractionated schedules (typically 65–66 Gy in 30 fractions) are frequently used. Patients are managed as category 1 patients and RT should be completed on time.

Target volume definition is performed using a contrast-enhanced planning CT scan. Co-registration of the planning CT scan with the diagnostic MRI scan can aid target volume delineation. An anatomical (inclusion of the whole oropharynx) or geometric (inclusion of gross tumour volume with a defined margin) approach may be used for primary target volume delineation. Prophylactic RT should be given to the ipsilateral cervical lymph nodes for lateralised (e.g. tonsillar) tumours and to both sides of the neck for non-lateralised tumours (defined as tumours which involve greater than 1 cm of a midline structure e.g. soft palate and/or tongue base). Radiotherapy to levels II, III and IVa is recommended; level Ib may also be included in cases with anterior extension of tumour and/or involvement of the anterior tonsillar pillar. Planning can be carried out using three-dimensional conformal planning (typically using a 'wedged pair' of RT fields) or intensity modulated radiotherapy (IMRT) and/or Arc therapy.

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Recommendations

- **Treatment options for T1–T2 N0 oropharyngeal squamous cell cancer include: radical radiotherapy or transoral surgery and neck dissection (with post-operative (chemo)radiotherapy if there are adverse pathological features on histological examination) (R)**
- **Transoral surgery is preferable to open techniques and is associated with good functional outcomes in retrospective series (R)**
- **If treated surgically, neck dissection should include levels II–IV and possibly level I. Level IIb can be omitted if there is no disease in level IIa (R)**
- **If treated with RT, levels II–IV should be included, and possibly level Ib in selected cases (R)**

Advanced (T3–T4 N0 and T1–T4 N1–N3) oropharyngeal cancer

General principles of management. A thorough review of the literature relating to the management of oropharyngeal cancer was published as a Cochrane report in 2009. The only evidence of statistically significant benefit was for the addition of concomitant chemotherapy to post-operative RT.[19] All other treatment comparisons did not show any statistical differences.

In recent years, there has been a tendency to offer primary RT and/or chemoradiotherapy for oropharyngeal carcinoma, as part of an 'organ preservation' strategy. Although there are no good head-to-head comparisons of primary surgery and chemoradiotherapy for stage III/IV OPSCC, outcomes from randomised trials of chemoradiotherapy (e.g. RTOG 0129) are at least comparable to the results of surgical series. One potential concern with an organ preservation approach is that although salvage surgery has been shown to have a high success rate for laryngeal cancer, the success rate of salvage surgery is not the same in other head and neck sites, such as the oropharynx.

The 2013 National Head and Neck Cancer Audit (9th DAHNO Report) concluded that variation in treatment strategies for OPSCC is evident across cancer networks in England and Wales. This is not surprising in view of the fact that current published evidence does not provide a consensus view to define the most appropriate treatment strategy. Treatment decisions for individual patients will depend on the size, position and overall functional deficit, as well as on patient preference and local expertise. Human papilloma virus status has a profound influence on prognosis, and in future, could potentially affect selection of treatment modality. Recruitment into randomised controlled clinical trials addressing these issues is highly recommended.

Surgical management of advanced oropharyngeal carcinoma. Where facilities and expertise exist, transoral resection (by TLM or TORS) of base of tongue, tonsil and pharyngeal wall primary tumours (usually with post-operative (chemo)radiotherapy) has been shown to offer rates of cure which appear to be as good as primary chemoradiotherapy in non-randomised comparisons, with promising functional results. Transoral resection is generally restricted to T1–T2 tumours, although resection of some T3 tumours may be considered if it is anticipated that negative margins can be achieved via a transoral approach. Transoral resection is rarely appropriate for T4 primary tumours. Also, where a larger resection of the soft palate is required, the general consensus is that surgery gives a poor functional outcome. It should be noted that approximately 80 per cent of patients who undergo primary surgery will also receive post-operative RT or chemoradiotherapy.

If transoral resection is not appropriate, e.g. for large primary tumours, then chemoradiotherapy should be considered. Alternatively, open surgical procedures may be considered, which usually require paramedian mandibulotomy for access and reconstruction with a flap. Trans-cervical pharyngotomy alone can be used for tongue base resections. Other approaches, such as glossotomy and lingual release can be used but are not often employed. Reconstruction is generally performed using radial artery free flaps or anterolateral thigh free flaps. Reconstruction using pedicled flaps, such as pectoralis major should be considered sub-optimal. Functional results following open surgery can be poor, particularly when followed by adjuvant therapy.

There are several published case series that report the likelihood of nodal metastasis for advanced oropharyngeal carcinoma to be over 50 per cent. When managing T3 and T4 oropharyngeal cancers, the N0 neck should be treated electively. When managing the N0 neck surgically, a selective level II, III and IV neck dissection is generally recommended, and in some cases level I may be included. All patients with node positive disease should have a modified neck dissection or at least level I–IV selective neck dissection.

Primary chemoradiotherapy for loco-regionally advanced (stage III–IVb) oropharyngeal carcinoma. Chemoradiotherapy (organ preservation) is an effective treatment choice for advanced head and neck tumours. A RT dose equivalent of 70 Gy in 2 Gy fractions with concurrent cisplatin chemotherapy is considered standard for stage III and/or IV OPSCC. Concurrent weekly cetuximab (a monoclocal antibody targeting the epidermal growth factor receptor) may be given with RT if there is a contraindication to platinum chemotherapy (e.g. renal dysfunction or hearing impairment). Alternatively, radical RT alone can be given for patients with advanced disease who are not fit for concurrent treatment, particularly if they are over 70 years of age when the benefits of concurrent chemotherapy are reduced. Induction chemotherapy may be considered

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for patients with advanced (T4, N3, N2c) disease to reduce the risk of distant metastases[20] and for selected other patients with bulky primary (T4) and/or nodal disease (N3), but there is currently no high-quality evidence of its efficacy in these indications.

The principles of RT outlining and planning are as described for earlier stage disease. Neck nodes should be included in the treatment fields depending on their probability of involvement and according to the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines and atlas which were updated in 2013.[21] Radiotherapy to levels Ib–IVa, V(a,b) and the retropharyngeal nodes (level VIIa) at the level of the oropharynx is generally recommended in a node positive neck. The retrostyloid space (level VIIb) is included when level II is involved and the supraclavicular fossa (levels IVb and Vc) is included when level IVa or V is involved. Radiotherapy should be given to at least the ipsilateral cervical lymph nodes for lateralised tumours and to both sides of the neck for non-lateralised tumours. The issue of whether the contralateral neck should be treated in patients with lateralised oropharyngeal tumours and advanced (N2+) nodal disease remains controversial and will depend on local practice.

Chemoradiotherapy is associated with greater toxicity than RT alone and late toxicity, particularly swallowing dysfunction, can have a significant impact on quality of life.[22] Gastrostomy tube dependence rates of up to 24 per cent at 1 year and 14 per cent at 2 years post-chemoradiotherapy have been reported, although others have reported much lower rates. Improvements in RT techniques (including IMRT) have been shown to reduce late complications following RT. The UK PARSPORT randomised study showed a significant reduction in xerostomia rates with parotid sparing IMRT compared with conventional RT (using parallel opposed fields) in patients with advanced OPSCC.[23] Ongoing studies are exploring the role of IMRT in improving swallowing function following RT, by reducing radiation dose delivery to the pharyngeal constrictor muscles and other swallowing structures.

Traditionally, patients with advanced nodal disease (N2 or N3) being treated by chemoradiotherapy required a planned neck dissection, with little evidence to support whether neck dissection before or after chemoradiotherapy is more effective. There is now level I evidence from the PET-Neck trial that a PET–CT guided active surveillance policy, with neck dissection only being carried out if residual abnormal or equivocal nodes are present on imaging 10–12 weeks after the end of chemoradiotherapy, results in similar survival rates to a planned neck dissection, with less morbidity, and with higher cost effectiveness.[5]

Post-operative radiotherapy and chemoradiotherapy for advanced oropharyngeal carcinoma. The indications for post-operative RT and chemoradiotherapy for OPSCC depend on pathological risk factors for recurrence common to most head and neck squamous carcinomas. Randomised controlled trials and a meta-analysis of results confirm that patients with extra-capsular invasion and/or microscopically involved (<1 mm) surgical resection margins around the primary tumour experience significant benefit in terms of overall and disease free survival from post-operative chemoradiotherapy compared with RT alone.[24] Post-operative chemoradiotherapy is associated with significant acute and late toxicity and is not generally recommended in patients over 70 years of age and/or patients with poor performance status. Indications for post-operative RT alone include multiple nodal metastasis, T3 or T4 tumours, and tumours with other adverse features, including perineural or lymphovascular invasion. Patients with close (1–5 mm) surgical margins around the primary tumour may be treated with post-operative chemoradiotherapy or RT alone according to the presence or absence of other risk factors for recurrence. Patients should start their adjuvant RT as soon as possible after surgery (ideally within five weeks (35 days) and no later than six weeks (42 days)) to avoid reduced local control and survival due to protracted treatment.

The relevance of traditional risk factors for recurrence (including extra-capsular spread) and the benefit of adjuvant chemotherapy with RT in the context of HPV-positive OPSCC has been questioned by some studies. However, no change in management of patients should occur outside clinical trials. Clinical trials which aim to modify adjuvant treatment based on HPV status are currently ongoing in the UK and USA.

Ongoing Research

Human papilloma virus status appears to have profound influence on prognosis and, in the future, potentially on selection of treatment modality. There are several ongoing or planned clinical trials for HPV-positive and HPV-negative OPSCC and recruitment into clinical trials addressing these issues is highly recommended. Development of biomarker classifiers for treatment selection is also high recommended.

Recommendations

- **Advanced oropharyngeal carcinoma can be treated with primary chemoradiotherapy or transoral surgery and adjuvant (chemo)radiotherapy (R)**
- **The N0 neck should be treated electively – either by radiotherapy or selective neck dissection (R)**
- **Patients with advanced nodal (N2 or N3) disease receiving radical chemoradiotherapy should have a PET-CT scan 10–12 weeks after treatment, with a subsequent neck dissection within 4 weeks if residual abnormal or equivocal nodal disease is detected (R)**

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- **Intensity modulated radiotherapy reduces toxicity in patients treated with radical radiotherapy, compared with conventional radiotherapy (R)**
- **Post-operative chemoradiotherapy is currently recommended in patients treated with surgery who have involved primary tumour resection margins and/or extracapsular spread of nodal disease. Otherwise, post-operative radiotherapy alone may be indicated (R)**

Key points

- Oropharyngeal cancer incidence is increasing rapidly in the UK due to the Human papillomavirus (HPV).
- HPV association confers better outcomes regardless of treatment modality
- Early stage disease should be receive single modality treatment
- Advanced disease should receive combined modality treatment
- PETCT scanning undertaken at 10-12 weeks post chemo-radiation results in similar survival to planned neck dissection, but with considerably fewer patients requiring neck dissection, less morbidity and is cost-effective
- There is insufficient evidence to alter treatment on the basis of HPV status
- Patients should be offered the opportunity to participate in the ongoing clinical trials.

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GUIDELINE

Nasopharyngeal carcinoma: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Although much commoner in the eastern hemisphere, with an age-standardised incidence rate of 0.39 per 100 000 population, cancers of the nasopharynx form one of the rarer subsites in the head and neck.[1] This paper provides recommendations on the work up and management of nasopharyngeal cancer based on the existing evidence base for this condition.

Recommendations

- Patients with nasopharyngeal carcinoma (NPC) should be assessed with rigid and fibre-optic nasendoscopy. (R)
- Nasopharyngeal biopsies should be preferably carried out endoscopically. (R)
- Multislice computed tomographic (CT) scan of head, neck and chest should be carried out in all patients and magnetic resonance imaging (MRI) where appropriate to optimise staging. (R)
- Radiotherapy (RT) is the mainstay for the radical treatment for NPC. (R)
- Concurrent chemoradiotherapy offers significant improvement in overall survival in stage III and IV diseases. (R)
- Surgery should only be used to obtain tissue for diagnosis and to deal with otitis media with effusion. (R)
- Radiation therapy is the treatment of choice for stage I and II disease. (R)
- Intensity modulated radiation therapy techniques should be employed. (R)
- Concurrent chemotherapy with radiation therapy is the treatment of choice for stage III and IV disease. (R)
- Patients with NPC should be followed-up and assessed with rigid and/or fibre-optic nasendoscopy. (G)
- Positron emission tomography–computed tomography (PET–CT), CT or MRI scan should be carried out at three months from completion of treatment to assess response. (R)
- Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan whenever possible and specially in advanced cases with suspected recurrence. (R)
- Surgery in form of nasopharyngectomy should be considered as a first line treatment of residual or recurrent disease at the primary site. (R)
- Neck dissection remains the treatment of choice for residual or metastatic neck disease whenever possible. (R)
- Re-irradiation should be considered as a second line of treatment in recurrent disease. (R)

Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma (SCC) arising from the mucosal surface of the nasopharynx. The most common site is the fossa of Rosenmüller which is a recess just medial to the medial crura of the eustachian tube. Nasopharyngeal carcinoma is frequent in patients of Southern Chinese, Northern African and Alaskan origin. The incidence in the Hong Kong population is between 20 and 30 per 100 000 inhabitants a year, but in Western countries the adjusted incidence is very low; around 1 per 100 000 per annum.[2]

Aetiology and risk factors

The Epstein–Barr virus (EBV) and consumption of salted fish containing *dimethylnitrosamine* have been implicated in its aetiology. Genetic alterations include

deletion of chromosomal regions at 1p, 14q, 16p and amplification of 4q and 12q.

Clinical presentation

Nasopharyngeal carcinoma is more common in men than in women (3:1), with a median age at presentation of 50 years. The most common symptoms are:

- Nasal obstruction
- Epistaxis
- Conductive hearing loss secondary to otitis media with effusion (OME) due to eustachian tube orifice obstruction
- Cranial nerve neuropathies secondary to skull base invasion (cranial nerves III, IV, V and VI)
- Neck lumps and swellings due to cervical lymph node metastasis, which is usually in the upper levels of the neck and often bilateral due to the midline lymphatic drainage of the tumour.

Assessment and staging

Clinical assessment

Full history and otorhinolaryngological examination with rigid or fibre-optic nasendoscopy in the outpatient setting should be performed. Examination under anaesthetic with endoscopic assessment and biopsy of the nasopharyngeal abnormality is mandatory with targeted biopsies of the fossa of Rosenmüller, when indicated. Biopsies should be preferably done after staging scans to avoid false artefacts.

Pathologic considerations

Histological examination is required for the definitive diagnosis. Fine needle aspiration cytology (FNAC) can be used as an adjunct for staging neck disease and distant metastases.

Nasopharyngeal carcinoma (NPC) comprises three histological types: non-keratinising carcinoma (incorporating differentiated and undifferentiated subtypes), keratinising carcinoma and basaloid SCC. All NPCs share morphological and immunohistochemical features of squamous differentiation to varying degrees.

Non-keratinising carcinoma is by far the most common type in both high and low incidence areas. The diagnosis of keratinising carcinoma and basaloid SCC is facilitated by the identification of malignant epithelium that shows overt keratinisation. By contrast, non-keratinising carcinoma has subtle morphological features that are often obscured by a dense lymphoid stroma, from which the synonym lymphoepithelial carcinoma is derived. Immunohistochemistry is required to identify the production of keratin intermediate filaments. Antibodies AE1/AE3 and MNF116 can be used to detect of a broad range of keratin molecules and when the malignant cells are positive they support a diagnosis of carcinoma. Cytoplasmic expression of cytokeratins 5/6 and nuclear expression of p63 can be used as evidence of squamous differentiation. Epstein–Barr virus (EBV) has been recognised as a primary aetiological agent in non-keratinising NPC. The presence of EBV is most reliably detected using in situ hybridisation for EBV encoded early RNA (EBER), whereas the expression of latent membrane protein-1 is less sensitive and is positive in about a third of cases.

Serological markers of EBV infection are detected in almost all cases of non-keratinising carcinoma, but have limited diagnostic utility. They can be used as an adjunct to monitor disease progression and response to treatment, although the practical clinical use remains unproven. Detection of immunoglobulins to viral capsid antigen and early antigens are the most commonly used tests. In addition, the detection of EBV nucleic acid (DNA and RNA) in serum and plasma, using quantitative polymerase chain reaction techniques, has been developed to aid disease surveillance.

Human papilloma virus (HPV) has been recognised as a primary aetiological agent in a subset of head and neck SCCs, primarily oropharyngeal in origin. A number of studies have reported HPV-positivity in NPCs, either with or without concurrent EBV association. The clinical significance of this relationship has not yet been established.

Imaging considerations

Staging investigations should include multislice computed tomography (CT) scan of the head, neck and chest. Magnetic resonance imaging (MRI) scans of the skull base are useful especially in locally advanced tumours. The use of positron emission tomography–computed tomography (PET–CT) should be reserved for patients with a suspected occult primary tumour in the nasopharynx and should be carried out before diagnostic procedure. Ultrasound guided FNAC of suspected cervical lymph node metastases is recommended, if they cannot be definitively labelled as malignant on cross-sectional imaging.

Staging

See Tables I–IV.

TABLE I
PRIMARY TUMOUR (T)

T1	Tumour confined to nasopharynx or extends to oropharynx and/or nasal cavity
T2	Tumour with parapharyngeal extension
T3	Tumour invades bony structures and/or paranasal sinuses
T4	Tumour with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space

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TABLE II
REGIONAL LYMPH NODE METASTASES (N)

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph nodes, 6 cm or less in the greatest dimension, above the supraclavicular fossa
N2	Bilateral metastasis in lymph nodes, 6 cm or less in the greatest dimension, above the supraclavicular fossa.
N3	Metastasis in a lymph node greater than 6 cm in dimension or extension to the supraclavicular fossa N3a Greater than 6 cm in dimension N3b Extension to the supraclavicular fossa

TABLE III
DISTANT METASTASIS (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

TABLE IV
STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T1	N1	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVa	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVb	Any T	N3	M0
Stage IVc	Any T	Any N	M1

Recommendations

- **Patients with NPC should be assessed with rigid and fibre-optic nasendoscopy (R)**
- **Nasopharyngeal biopsies should preferably be carried out endoscopically (R)**
- **Multislice CT scan of head, neck and chest should be carried out in all patients and MRI where appropriate to optimise staging (R)**

Management

Radiotherapy

Radiotherapy (RT) is the mainstay for the radical treatment for nasopharyngeal carcinoma (NPC).[3] The anatomical location, propensity for loco-regional spread, and proximity of critical structures makes wide field surgical treatment unacceptably morbid as a first line option. The therapeutic ratio of RT is improved by the addition of synchronous chemotherapy (CT) and advances in radiation delivery techniques, both of which may help to achieve improved disease control and survival along with lower rates of long-term toxicity. Intensity modulated radiotherapy (IMRT) delivery techniques allow concavities to be created in the RT dose distribution, which is particularly useful for the treatment of head and neck cancer. It facilitates improved dosimetric coverage of the primary tumour volume, particularly in the pharyngeal recesses, and sparing of normal organs, including the parotid gland, substantially reducing long-term xerostomia, thereby improving quality of life.

Proton beam therapy is a newly emerging technology which may further improve radiation dose conformality. Evidence to support a difference in outcomes compared to those achieved with conventional radiotherapy is lacking. Currently, nasopharyngeal tumours in paediatric, teenage and young adult patients, are included as permitted indications in the NHS England Proton Programme and these patients should be referred accordingly.

Radiotherapy is also useful in the palliative setting. It can be used to treat symptomatic metastases and local disease in the presence of widespread metastases when aggressive local therapy is clinically inappropriate.

Recommendation

- **Radiotherapy is the mainstay for the radical treatment for NPC (R)**

Chemotherapy

There is evidence confirming significant improvement in overall survival (OS) in the patients treated concurrently with chemoradiotherapy for NPC as compared to RT alone. The addition of chemotherapy has been shown to confer a small, but significant benefit in OS and event-free survival (EFS). A meta-analysis of eight randomised trials and 1753 patients reported an 18 per cent reduction in the hazard ratio for death with the use of any form of chemotherapy with RT, corresponding with an absolute survival benefit of 6 per cent at five years. The greatest benefit was observed with concomitant chemotherapy. The roles of neo-adjuvant and adjuvant chemotherapy are more controversial with no proven survival advantage but confirmed EFS benefit with neo-adjuvant chemotherapy. Adjuvant chemotherapy after RT is less well tolerated and benefits are still unproven. Cisplatin-based chemotherapy is used concurrently with radiation and combination of cisplatin and fluorouracil may be used in the neo-adjuvant setting, in selected cases. Platinum-based chemotherapy has been effective in palliation of recurrent and metastatic NPC. Single centre (level 2) studies have reported activity with the use of capecitabine, gemcitabine and taxanes as

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single agent or in combination with platinum for second- and third-line treatments for metastatic disease.

A randomised trial including 803 patients with stages III–IVB NPC compared induction and concurrent chemotherapy, replacement of fluorouracil with oral capecitabine and/or accelerated RT found no benefit by changing to an induction–concurrent sequence.[4–7]

Recommendation

- **Concurrent chemoradiotherapy offers significant improvement in OS in stage III and IV diseases (R)**

Primary surgery

Surgery is only used in the following scenarios:

- To obtain tissue for diagnosis. Contact endoscopic diagnosis of NPC remains experimental
- To obtain tissue from clinically involved neck nodes using FNAC or core biopsy. If these techniques are non-diagnostic, open biopsy can be used. In cases with obvious fungation open biopsy is the method of choice
- To deal with OME.

Recommendation

- **Surgery should only be used to obtain tissue for diagnosis and to deal with otitis media with effusion (R)**

Treatment recommendations

Stages I and II

Patients with early disease can be treated with RT alone, resulting in disease free survival rates of 90 and 84 per cent. The dose to the primary tumour should be equivalent to 70 Gy in 2 Gy fractions and at least 50 Gy in 2 Gy fractions to the bilateral neck and other sites of potential microscopic spread. Intensity modulated radiotherapy techniques should be used. Evidence of benefit from the addition of chemotherapy to RT in early disease is lacking.

Intermediate stage II disease can be treated with RT alone (T2N0M0), but most cases are treated with combination chemoradiotherapy. Intensity modulated radiotherapy should be considered mandatory. A dose of 70 Gy is recommended to the primary, 66–70 Gy to gross disease in lymph nodes and 50 Gy to the bilateral neck and other sites of potential microscopic spread. Radiobiological equivalents are given if a fraction size other than 2 Gy is employed, for example with intensity modulation. The most commonly used chemotherapy schedule is cisplatin 100 mg/m^2 on days 1, 22 and 43 of RT based on the United States Intergroup Study 0099. Weekly cisplatin at a dose of 40 mg/m^2 is effective, but has not been compared with the standard regimen in a randomised study. It can be considered for older patients and/or those with significant comorbidities.

Stages III and IV

Concurrent chemoradiotherapy is the standard of care for advanced nasopharyngeal cancers. This improves OS by up to 6 per cent at five years compared with radical RT. A dose of 70 Gy (2 Gy per fraction) with concurrent cisplatin chemotherapy is recommended. Several trials have explored the role of neo-adjuvant chemotherapy, with a recent meta-analysis confirming an improvement in disease-free survival, whilst having no effect on OS. Radiotherapy target volume definition must include gross tumour (clinical, endoscopic and radiological), the nasopharynx and the pterygopalatine fossa, the base of skull and clivus, the posterior part of sphenoid sinus, the posterior third of the nasal cavity and the maxillary sinus, retropharyngeal lymph nodes and parapharyngeal space. Prophylactic irradiation must include uninvolved level I–V nodal areas.

IMRT is used with either fixed gantry linear accelerator-based techniques (fixed field or volumetric arc) or with helical tomotherapy techniques with confirmed benefits in preserving parotid gland function. Studies are currently exploring the role of further dose escalation with IMRT to improve local control.[8–10]

Surgical treatment is reserved for salvage following chemoradiotherapy failure.

Recommendations

- **Radiation therapy is the treatment of choice for stage I and II diseases (R)**
- **Intensity modulated radiation therapy techniques should be employed (R)**
- **Concurrent chemotherapy with radiation therapy is the treatment of choice for stage III and IV diseases (R)**

Assessment of treatment response and follow-up

Assessment of treatment response and follow-up is imperative in nasopharyngeal carcinoma (NPC). Patients should be assessed clinically with endoscopic examination and neck palpation. Currently there is no consensus on the best mode of radiological assessment to determine completeness of response to treatment. PET–CT, CT or MRI follow-up scans have been adopted in some centres at three months and at a year from completion of treatment.

Following treatment, it can take up to three months for NPC to disappear histologically. Post-treatment disease can be monitored using biopsies. However, accurate interpretation of the material can be

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confounded by persistent areas of degenerate tumour, the biological significance of which needs to be assessed in the context of the temporal relationship to treatment. Furthermore, tissue changes in the radiation field can also mimic residual disease and need to be interpreted with caution. The presence of morphologically viable malignant cells with evidence of EBER by in situ hybridisation is strongly suggestive of residual disease. If a biopsy contains carcinoma, repeat sampling two weeks apart is recommended and remission is defined as two sequential negative biopsies. The recommended follow-up strategy is addressed elsewhere in the guidelines.

Recommendations

- **Patients with NPC should be followed-up and assessed with rigid and/or fibre-optic nasendoscopy (G)**
- **Positron emission tomography–computed tomography, CT or MRI scan should be carried out at three months from completion of treatment to assess response (R)**
- **Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan whenever possible and specially in advanced cases with suspected recurrence (R)**

Management of residual and recurrent disease

Surgery

Chemoradiotherapy or RT resistant tumours may be amenable to salvage surgery to the primary site or the neck. Surgery for recurrence is associated with less morbidity than re-irradiation of recurrent disease. Nasopharyngectomy and/or neck dissection should be the first option for locoregional residual and recurrent disease. When surgery is not possible either palliative chemotherapy or re-irradiation should be considered.

Surgery to the primary site. Endoscopically guided microwave coagulation of small volume (rT1) recurrent disease has been described as having low morbidity with OS and local progression-free survival of 93.6 and 90.7 per cent at five years.

The likelihood of successful surgical excision diminishes in proportion to the size and extent of the recurrent and/or persistent disease at the primary site. Transcranial approaches are associated with high morbidity. Transnasal and transantral approaches provide poor access to the paranasopharyngeal space. Experience with combined transoral and transnasal endoscopic resection is increasing and may become the favoured approach for small lesions, because of the low associated morbidity. Robotic surgical techniques, although used in only a few studies, have been shown to offer equivalent local control in highly selected cases.

The anterolateral approach with maxillary swing (facial translocation) allows access to the nasopharynx and paranasopharyngeal space and has a local control rate of up to 62 per cent. Palatal fistulae occur in 20–25 per cent of patients, whilst 60 per cent have some degree of trismus. A lateral approach with radical mastoidectomy and exposure of the infratemporal fossa after mobilisation of the internal carotid, trigeminal nerve and floor of the middle cranial fossa has been described. Its use is associated with considerable risk of morbidity.[11–13]

Surgery to the neck. Re-irradiation of the involved neck to treat persistent and/or recurrent disease carries a high risk of tissue necrosis and fibrosis. Persistent or recurrent nodal disease following chemoradiotherapy demonstrates a high incidence of extracapsular extension (54–65 per cent). For this reason salvage radical neck dissection (with the placement of brachytherapy tubes for after loading where there is extensive disease), remains the treatment of choice. It may be necessary to excise involved skin and repair with pedicled or microvascular flaps. Transferred tissue flaps should be placed so as to overlie brachytherapy tubes as they are often more tolerant of irradiation than previously irradiated skin. Salvage neck dissection gives up to 66 per cent five-year local control of disease.[14]

Non-surgical options

Re-irradiation. Local nasopharyngeal recurrences respond better to re-irradiation than other sites.[15] The scope for re-irradiation depends on the tumour volume, current T stage and the disease free interval or time since primary irradiation. The dose that can be delivered depends on the dose received by adjacent critical organs, time since initial irradiation and the technique of RT delivery. In general, a dose of greater than 50 Gy needs to be deliverable for re-irradiation to be worthwhile. This is more achievable using highly conformal techniques, including IMRT, intracavitary and interstitial brachytherapy, stereotactic radiosurgery, fractionated stereotactic RT or proton beam therapy. Overall survival rates of 60 per cent at five years have been reported. The toxicity rate for re-irradiation is significant. A prognostic scoring system for locally recurrent nasopharyngeal carcinoma (NPC) has been validated. When re-irradiation is not possible, then palliative chemotherapy should be considered.

Conventional chemotherapy. Palliative systemic chemotherapy is the central component of the treatment for metastatic disease.[16] Cisplatin-based chemotherapy produces response rates of up to 80 per cent in chemotherapy-naive patients resulting in median survival rates of up to 15 months. There are no randomised

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comparisons of different chemotherapy schedules. Whilst cisplatin and fluorouracil remain the most widely used combinations, the gemcitabine and cisplatin doublet has also been shown to produce high response rates and be well tolerated, and can be considered above other agents that have higher toxicity. Triplet combinations also produce higher response rates, but at the cost of higher toxicity. The decision to give palliative chemotherapy should take into account previous therapy and the performance status of the patient.

Molecular therapies and immunotherapy

There is no evidence for the routine use of molecular therapies for metastatic NPC outside clinical trial settings. Phase II trials have demonstrated limited activity in the second- and third-line settings. The utility of immunotherapy based either adoptive or active means against Epstein–Barr virus (EBV) antigens, remains investigational.

Recommendations

- **Surgery in form of nasopharyngectomy should be considered as a first-line treatment of residual or recurrent disease at the primary site (R)**
- **Neck dissection remains the treatment of choice for residual or metastatic neck disease whenever possible (R)**
- **Re-irradiation should be considered as a second line of treatment in recurrent disease (R)**

Treatment outcomes

Stages I and II

Five-year OS rates of 90 per cent for stage I and 84 per cent for stage II have been reported from a review of 2687 patients from Hong Kong, based on the AJCC 1997 staging. Data for non-endemic regions are sparse given the relative rarity of the condition in these areas. Serum Epstein–Barr virus (EBV) DNA copies before treatment have been shown to have prognostic significance; for stages I and II <4000 copies per ml have a 91 per cent survival at five years and >4000 copies per ml have a 64 per cent five-year survival.

Stages III and IV

Chemoradiotherapy regimes have improved the OS of nasopharyngeal carcinoma (NPC) patients from 77 to 81 and 56 to 62 per cent at two and five years, respectively. The benefit for chemotherapy was not lost for advanced stage disease.

Recent studies using simultaneous integrated boost delivered following neo-adjuvant chemotherapy with IMRT, in locally advanced NPC, have suggested local progression free and distant metastases free survival rates of 80–90 per cent. Accelerated RT schedules or post-RT brachytherapy boost have produced excellent local control rates, but more studies and longer follow-up data are awaited to confirm the benefits.

Patients with systemic metastases have been treated with cisplatin containing regimes with response rates ranging from 40 to 80 per cent, and median survival of about 14 months.

Controversies

The role of ventilation tubes in the management of the middle-ear effusion in nasopharyngeal cancer patients

The rate of complications (otalgia and otorrhoea) is higher if grommets are inserted after RT. Eustachian tube function may improve in an irradiated patient up to five years after RT. However, if an effusion is present or develops during RT tubal function remains poor. Grommets bypass tubal obstruction, but may exacerbate the inflammatory process. Up to 29 per cent of patients will develop non-healing perforation of the tympanic membrane, if grommets are inserted during or after RT and 49 per cent will go onto develop intermittent otorrhoea. Middle ear effusion arising during or after RT is best managed using repeated paracentesis, aspiration and a hearing aid. Grommets should be used as a last resort.[17,18]

Salvage surgery for local recurrence

The maxillary swing nasopharyngectomy approach has now been adopted as an adequate mode of salvaging patients with recurrent nasopharyngeal carcinoma (NPC) with survival rates of up to 73 per cent in selected cases. The use of a purely endoscopic approach has been attempted, without evidence of any benefit. The controversy arises mainly on the accurate assessment, patient selection and extent of the resection, weighing the benefits of the procedure against their morbidity.

Salvage treatments for recurrent disseminated disease

Isolated, potentially surgically treatable metastases in NPC are rare and only limited reported cases specific for NPC are available in the literature.

The role of neo-adjuvant and adjuvant chemotherapy

Recent meta-analyses have confirmed improvement in local control but no improvement in OS. Recent studies using neo-adjuvant chemotherapy followed by concurrent chemoradiotherapy have produced encouraging early results, but longer term data are awaited.[19,20]

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The use of routine tumour markers in the management of NPC

Testing for Epstein–Barr virus (EBV) infection has potential as a screening tool, but only in high risk regions or populations. Epstein–Barr virus DNA testing has also been used as diagnostic and prognostic tool, and in the detection of recurrence. However, no consensus exists on either the appropriate cut-off values or the additional value to clinical management.

Key points

- Nasopharyngeal carcinoma is frequent in patients of Southern China, Northern African and Alaskan origin, but in western countries the adjusted incidence is very low with only up to 1 per 100 000
- The most common signs and symptoms are nasal obstruction, epistaxis, conductive hearing loss secondary to otitis media with effusion, cranial nerve neuropathies and cervical lymphadenopathy
- Intensity modulated radiotherapy, with or without concurrent chemotherapy, is the mainstay of curative treatment, with concurrent chemotherapy for stage III and IV disease
- A positron emission tomography–computed tomography, computed tomography or magnetic resonance imaging scan should be carried out at three months from completion of treatment to assess response
- Salvage surgery should be considered for residual or recurrent disease at the primary site
- Controversy exists in the management of otitis media with effusion in patients with nasopharyngeal carcinoma, the best mode of salvage surgery, salvage treatments for disseminated disease, the use of neo-adjuvant and adjuvant chemoradiotherapy and the use of tumour markers.

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GUIDELINE

Hypopharyngeal cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. With an age standardised incidence rate of 0.63 per 100 000 population, hypopharynx cancers account for a small proportion of the head and neck cancer workload in the UK, and thus suffer from the lack of high level evidence. This paper discusses the evidence base pertaining to the management of hypopharyngeal cancer and provides recommendations on management for this group of patients receiving cancer care.

Recommendations

- Cross-sectional imaging with computed tomography of the head, neck and chest is necessary for all patients; magnetic resonance imaging of the primary site is useful particularly in advanced disease; and computed tomography and positron emission tomography to look for distant disease. (R)
- Careful evaluation of the upper and lower extents of the disease is necessary, which may require contrast swallow or computed tomography and positron emission tomography imaging. (R)
- Formal rigid endoscopic assessment under general anaesthetic should be performed. (R)
- Nutritional status should be proactively managed. (R)
- Full and unbiased discussion of treatment options should take place to allow informed patient choice. (G)
- Early stage disease can be treated equally effectively with surgery or radiotherapy. (R)
- Endoscopic resection can be considered for early well localised lesions. (R)
- Bulky advanced tumours require circumferential or non-circumferential resection with wide margins to account for submucosal spread. (R)
- Offer primary surgical treatment in the setting of a compromised larynx or significant dysphagia. (R)
- Midline lesions require bilateral neck dissections. (R)
- Consider management of silent nodal areas usually not addressed for other primary sites. (G)
- Reconstruction needs to be individualised to the patients' needs and based on the experience of the unit with different reconstructive techniques. (G)
- Consider tumour bulk reduction with induction chemotherapy prior to definitive radiotherapy. (R)
- Consider intensity modulated radiation therapy where possible to limit the consequences of wide field irradiation to a large volume. (R)
- Use concomitant chemotherapy in patients who are fit enough and consider epidermal growth factor receptor blockers for those who are less fit. (R)

Introduction

The hypopharynx is subdivided into the piriform sinuses, the posterior pharyngeal wall and the post-cricoid area. The majority of cancers arise in the piriform sinuses (65–85 per cent), 10–20 per cent arise from the posterior pharyngeal wall and 5–15 per cent from the post-cricoid area. As is the case at other sites in the head and neck, the overwhelming majority (95 per cent) of cancers are squamous cell carcinomas (SCCs). Five-year survival is poor with overall survival at 30 per cent, although for T1 and T2 tumours the survival is almost 60 per cent. This discrepancy is a reflection of late presentation, as hypopharynx tumours remain relatively asymptomatic until they are quite

advanced. Cases of T1N0 account for only 1–2 per cent of all cases seen and 80 per cent of patients are stage III or IV at presentation. Half of all patients present because of cervical nodes and the incidence of distant metastases at presentation are higher than that for any other head and neck cancer.

Clinical presentation

The cardinal symptoms of hypopharyngeal cancer are:

- Neck mass, with approximately half of patients presenting such, which reflects the fact that late presentation is common
- Sore throat, particularly if well localised and associated with referred ear pain on swallowing
- Dysphagia, which is progressive and frequently results in significant weight loss and malnutrition
- Hoarseness, voice change and/or upper airway obstruction, a late symptom indicating advanced disease.

Assessment and staging

Clinical examination

Assessment of hypopharyngeal cancer requires a full symptomatic history, evaluation of associated medical conditions or comorbidity, determination of weight loss as well as performance status (Karnofsky or World Health Organization). The medical history and performance status are critical in recommending the extent and intention of treatment. Mortality and morbidity rates are much higher in patients with significant weight loss, comorbidity or poor performance indicators.

A full head and neck examination, including nasendoscopy, is necessary in order to assess the size and position of the primary tumour, mobility of the vocal fold and cervical metastases. Clinical examination is also important in assessment of pre-vertebral fascia involvement and can be assessed by examining laryngopharyngeal mobility in the lateral direction. This is then complemented by radiological assessment and staging endoscopy under general anaesthetic.

Imaging considerations

It is widely agreed that imaging is better performed prior to biopsy, as this can potentially avoid post-operative oedema which may overstage the disease on subsequent imaging. In addition, it allows assessment of any additional abnormalities that have been uncovered by radiological evaluation such as second primary tumours.

Cross-sectional imaging is mandatory in the work up and can take the form of either computed tomography (CT) or magnetic resonance imaging (MRI). In addition to this, the chest should always be imaged due to the increased incidence of lung metastases in advanced hypopharyngeal cancer and to look for synchronous primaries. There is debate about which modality to use. The critical points in imaging are assessing extent of disease (particularly the lower limits of the primary cancer) and the presence of thyroid cartilage invasion. Magnetic resonance imaging gives better soft tissue definition and has greater sensitivity (80 per cent) for cartilage invasion, however, is less specific (74 per cent) than CT, and can therefore potentially overstage disease. The multiplanar capabilities of MR can also help in staging the disease. When compared with histological assessment, CT and MRI produce sensitivities of 66 and 89 per cent, respectively, and specificities of 94 and 84 per cent, respectively. The benefit of CT is that the chest can be imaged at the time of the neck imaging as well as the reduced potential for motion artefact due to the speed of the assessment, whereas, if MRI is used the patient needs additional imaging which may be less convenient for the patient. There is debate whether or not a simple chest X-ray is sufficient or whether CT is necessary. There is evidence to support both arguments, however, as hypopharyngeal cancer usually presents with stage III or IV diseases, it seems reasonable to recommend chest CT, as there is a higher incidence of distant metastatic disease in hypopharyngeal cancer.

Currently, the Royal College of Radiologists 2014 guidelines recommends CT or MRI scanning for imaging the hypopharynx.[1] Computed Tomography should use slice thickness acquired at 0.625–1.25 mm and reformatted at no greater than 2.5 mm for viewing. Scans should be performed during quiet respiration with arms at the side of the patient. Patients should be instructed not to swallow during the evaluation. Magnetic resonance imaging scanning will require a combination of axial, sagittal and coronal T1W and T2W sequences, often with contrast enhancement with spectral fat suppression to assess the extent of soft tissue involvement and cartilage invasion.

Positron emission tomography (PET)–CT is now recommended for assessment of advanced hypopharyngeal primaries, the lower limit of disease in cases not accessible via endoscopy as well as in imaging post-treatment patients to assess for residual and/or recurrent disease.

Examination under anaesthetic and endoscopy

Endoscopy in theatre serves three functions: first, it allows assessment of the extent of the primary tumour, second, it allows biopsy of the tumour to confirm pathology and finally it allows assessment of other potential primary sites. This last indication was the rationale of the old fashioned triple endoscopy philosophy which incorporated bronchoscopy as well as pharyngolaryngoscopy and oesophagoscopy. It is generally recognised that with the advent of good imaging of the chest the role of formal bronchoscopy has become virtually obsolete.

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TABLE I
T STAGING FOR HYPOPHARYNGEAL TUMOURS

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to one subsite of the hypopharynx and 2 cm or less in greatest dimension
T2	Tumour invades more than one subsite of the hypopharynx or an adjacent site, or measures more than 2 cm but 4 cm or less in greatest diameter without fixation of hemilarynx
T3	Tumour measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumour invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus or central compartment soft tissue, which includes pre-laryngeal strap muscles and subcutaneous fat
T4b	Tumour invades pre-vertebral fascia, encases carotid artery or involves mediastinal structures

At the end of all these assessments then a clinical stage can be reached using the tumour–node–metastasis (TNM) classification system (Table I).

Recommendations

- **Cross-sectional imaging with CT of the head, neck and chest is necessary for all patients; MRI of the primary site is useful particularly in advanced disease; and CT–PET to look for distant disease (R)**
- **Careful evaluation of the upper and lower extents of the disease is necessary, which may require contrast swallow or CT–PET imaging (R)**
- **Formal rigid endoscopic assessment under general anaesthetic should be performed (R)**

Management

High importance should be placed on exploring patient preferences and involving them in treatment decisions. A clear and unbiased discussion of all options will help the patients and the medical team make the most appropriate decisions. Many of these patients present with dysphagia and significant weight loss and can be profoundly malnourished. This needs to be managed proactively soon after diagnosis and may require insertion of nasogastric or gastrostomy feeding tubes prior to any treatment taking place. A full assessment of the patient's performance status should be carried out to determine their ability to undergo major surgery or their ability to lie flat for radiotherapy and attend daily for seven weeks.

Although some prospective randomised data exists, several aspects of the decision making for hypopharyngeal SCC remain controversial as no treatment has been shown to be superior in terms of disease control and survival.[2] This section summarises the principles of surgical and non-surgical treatment for these tumours.

Recommendations

- **Nutritional status should be proactively managed (R)**
- **Full and unbiased discussion of treatment options should take place to allow informed patient choice (G)**

Surgical treatment

Based on the extent of the tumour, transoral and open surgical options exist for hypopharyngeal cancer.[3] Transoral approaches have a greater ability to preserve function suitable for smaller tumours where resections can be achieved with clear margins. Radiation therapy is favoured over open partial pharyngeal resections nowadays.

Early stage disease. Early stage (I and II) disease can be treated with equal effectiveness with surgery or radiation.[4,5] Early lesions of the hypopharynx can be treated by transoral resection or open partial laryngopharyngectomy with or without reconstruction. Surgery offers the advantage of providing prognostic information, such as peri-neural or angioinvasion and lymph node status. This allows the use of post-operative irradiation for those patients likely to gain the most benefit, while sparing other patients side effects without a significant survival advantage. Occult nodal disease is present in 30–40 per cent of patients, so any treatment plan should include elective treatment of the cervical nodes.

Late stage disease. Unfortunately, more than 80 per cent are advanced stages III and IV at presentation (with locally advanced disease present in the majority). Submucosal extension is present in more than 60 per cent of surgical specimens and is occult in one-third.[6] Local recurrence rates have been reported to occur in equal proportion between patients with negative margins and those with positive margins, underscoring the difficulty in clearing disease. Histological studies have reported submucosal extension ranging from 1 to 2 cm, resulting in the recommendation that minimal resection margins of 1.5 cm superiorly, 3 cm inferiorly and 2 cm laterally are required in patients treated surgically. The incidence and extent of submucosal spread is higher in patients who have undergone previous radiotherapy, with macroscopically undetected submucosal spread present in 80 per cent. Bulky advanced tumours will usually require circumferential or non-circumferential resection with free flap cover.

Recurrent disease. Surgical salvage after failure of irradiation therapy has a lower success rate for

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hypopharyngeal cancer than at any other site in the head and neck, and larynx preservation is rarely possible.[7] Patients who have undergone previous irradiation require even greater resection margins.

Recommendations

- **Early stage disease can be treated equally effectively with surgery or radiotherapy (R)**
- **Endoscopic resection can be considered for early well localised lesions (R)**
- **Bulky advanced tumours require circumferential or non-circumferential resection with wide margins to account for submucosal spread (R)**
- **Offer primary surgical treatment in the setting of a compromised larynx or significant dysphagia (R)**

Management of the neck. Midline lesions, those involving the posterior pharyngeal wall or post-cricoid area, and lesions of the medial wall of the piriform sinus, require bilateral neck dissection or irradiation, because of a higher incidence of failure in the contralateral neck. In surgically treated patients with a clinically N0 neck, unilateral or bilateral neck dissection is warranted, depending on the site and size of the primary. In the clinically positive neck, a modified radical neck dissection or a selective neck dissection on one or both sides should be considered. Due attention must be given to nodal involvement of the 'silent nodal areas' – retropharynx, parapharynx, paratracheal and mediastinum.

Recommendations

- **Midline lesions require bilateral neck dissections (R)**
- **Consider management of silent nodal areas usually not addressed for other primary sites (G)**

Reconstruction. Reconstruction of pharyngeal defects and in particular circumferential defects present major challenges. Modern chemoradiotherapy protocols, medical comorbidity and poor nutritional status increase surgical morbidity. The aims of reconstruction are to restore swallowing and speech, keeping mortality and morbidity, in particular fistula and stricture rates, to a minimum.

Partial pharyngeal defects. Partial pharyngeal defects with more than 3.5 cm of unstretched remaining pharyngeal mucosal width may be closed primarily. Defects with less than 3.5 cm of pharyngeal mucosal width remaining may be reconstructed using a pedicled flap – usually a pectoralis major flap. Free flaps, such as the radial forearm flap and the anterolateral thigh flap may also be used. These reconstructions are also called 'patch' grafts. If the pharyngeal mucosal remnant is very narrow (<1 cm in width), some surgeons would recommend excision of the remnant and undertaking a total circumferential reconstruction. However, many surgeons preserve this remnant and reconstruct around it as it may reduce the stricture rate.

Total circumferential pharyngolaryngectomy defects. Lower anastomosis above the clavicles: Where the lower anastomosis of a total circumferential pharyngolaryngectomy reconstruction would lie above the clavicle, several options exist: jejunal free flap (JFF), gastro-omental free flap (GOFF), tubed radial forearm free flap (RFFF) and a tubed anterolateral thigh free flap (ALT).[8] All the above options carry the risk of free flap failure, anastomotic leaks, stricturing, donor site morbidity, failure of voice rehabilitation, swallowing problems and a small peri-operative mortality rate.

Previously untreated cases: jejunal free flaps have been associated with poorer swallowing thought to be due to uncoordinated peristalsis and wet sounding speech. The RFFF is easy to tube but has donor site issues related to the size of the flap required. Recent literature has suggested that in previously untreated cases, ALTs tubed over a salivary bypass tube appear to provide the lowest complication rates – with minimal donor site morbidity, lower leak rates and lower stenosis rates.[9] Good swallowing and voice rehabilitation have been reported. However, many authors have not been able to replicate results in the literature and continue to use the JFF. Use of a salivary bypass tube appears to reduce the fistula rates in fasciocutaneous flaps.

Post-chemoradiotherapy (salvage cases): In general, reconstructive surgery using free flap surgery post-chemoradiotherapy carries a higher risk of complications due to the deleterious effects of chemoradiotherapy on tissue vascularity and wound healing. In such cases, limited case series suggest that the use of the GOFF may have an advantage due to the availability and vascularity of the omentum.[10] The omentum can be wrapped around the anastomotic site to decrease the possibility of leakage and also improve the vascularity of the overlying skin quality. Any of the other options mentioned previously may also be used in the salvage cases. In the patients at high risk of breakdown, a pectoralis major flap may be used to reinforce the anastomotic suture lines in the pharynx.

Lower anastomosis below the clavicles: If the resection extends below the clavicles, a gastric pull through or colonic transposition flap may be used.[11] Both these techniques carry increased morbidity and mortality due to the need to enter multiple visceral cavities. Gastric pull through carries a mortality rate of 5–15 per cent,

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morbidity of 31–55 per cent and reported fistula rates of 3–23 per cent. Colonic transposition carries similar risks, and appears to be less commonly used. It can however provide a higher cranial reach than gastric pull through, and is therefore useful for tumours that extend up high into the oropharynx.

Swallowing after reconstruction with fasciocutaneous flaps (RFFF and ALT) and GOFF is reported to be superior to that after JFF reconstruction. There is little literature on the outcome of speech rehabilitation following free flap reconstruction of total pharyngeal defects. However, speech rehabilitation is thought to be best when fasciocutaneous flaps are used to reconstruct the pharynx. There is a question as to the advisability of primary tracheoesophageal puncture in these cases. It has been argued that the presence of a puncture site and valve or catheter can increase the chance of infection and flap failure, and for this reason, many surgeons would recommend secondary puncture once the patient has healed and received their post-operative radiotherapy as indicated. Some centres perform a puncture if there is a reasonable distance between the lower anastomosis and the site of the puncture. As there is no evidence to support either position, it is best to decide on an individual case basis and depending on the experience of the team.

Recommendation

- **Reconstruction needs to be individualised to the patients' needs and based on the experience of the unit with different reconstructive techniques (G)**

Non-surgical management

Definitive radiotherapy is a potentially organ-sparing alternative to surgery in the treatment of early SCC of the hypopharynx. In combination with systemic therapy, it also has a role in the curative management of locally advanced cancers, although typically not those in which the cartilage is extensively involved or the function of both vocal cords significantly impaired. Post-operative radiation or chemoradiation improves locoregional disease control and overall survival in the presence of well-established high-risk features such as a positive margin or extra-capsular nodal extension of disease.[12]

There has been no randomised side-by-side comparison of surgery and radiotherapy in T1 and 2 N0 hypopharyngeal cancer. In advanced cancers, prospective trials have shown equivalent rates of local control and survival when surgery and adjuvant treatment was compared with primary non-surgical therapy.[13] Given that the risk of local or locoregional failure is greater than that of distant metastases, cancers that prove radiation resistant are sometimes surgically salvageable. The choice of initial therapy is often driven by pragmatic clinical factors such as age, performance status, medical comorbidity and patient wishes as well as more subjective considerations such as tumour accessibility, local expertise or predicted functional outcome after radiotherapy. A multidisciplinary approach involving surgical and radiation oncologists, speech and language therapists and clinical nurse specialists is required.

The lymphatic drainage of the hypopharynx and the resulting significant risk of occult nodal disease at presentation typically mandate extensive irradiation of at-risk nodal groups as well as treatment of the primary tumour site and clinically apparent nodes. Intensity modulated radiation therapy (IMRT) is now well established in UK radiotherapy centres. This technique, in combination with adherence to consensus guidelines regarding target volume delineation and sophisticated imaging of patient position and anatomical changes during radiotherapy, allows much more precise and accurate targeting of tumouricidal radiation dose to the target. Intensity modulated radiation therapy also reduces radiation dose to organs at risk, such as the parotid, resulting in reduced medium term toxicity. There is also some evidence that patients treated with IMRT rather than three-dimensional conformal radiotherapy achieve higher rates of local control and better functional outcomes. Intensity modulated radiation therapy should therefore be considered the standard of care.

The predominantly loco-regional pattern of treatment failure in hypopharyngeal cancer has generated interest in treatment intensification, particularly in the setting of locally advanced disease. Intensity modulated radiation therapy has facilitated attempts at escalation of radiation dose. The addition of concomitant systemic therapy in the form of cisplatin (or cetuximab in patients with contraindications such as impaired renal function) confers a modest improvement overall survival at the expense of increased acute toxicity. All but the least fit patients under the age of 71 with stage III or selected stage IV disease should therefore be considered for combination treatment. Patients aged 71 or more were shown in the meta-analysis of chemotherapy in head and neck cancer to be unlikely to benefit from the addition of systemic therapy.[14,15]

The optimal use of induction chemotherapy in hypopharyngeal cancer, as in other anatomical subsites, remains a topic of discussion. Two large trials have demonstrated its utility in an organ preservation approach with comparable survival to surgery in laryngeal cancer. Induction therapy reduces the incidence of distant metastases but does not have a consistent effect on overall survival, although individual studies comparing induction schedules with and without a taxane have shown a significant benefit for triple-agent chemotherapy.[16] One pragmatic approach is to offer

induction chemotherapy prior to chemoradiation to fit patients with bulky T3 or early T4 disease,[13] with laryngectomy for those who do not respond to chemotherapy, and to patients at high risk of distant relapse such as those with N2b or c or N3 disease.

Recommendations

- **Consider tumour bulk reduction with induction chemotherapy prior to definitive radiotherapy (R)**
- **Consider IMRT where possible to limit the consequences of wide field irradiation to a large volume (R)**
- **Use concomitant chemotherapy in patients who are fit enough and consider EGFR blockers for those who are less fit (R)**

Palliative care

It has been estimated that up to 25 per cent of patients are not suitable for curative treatment at presentation because of age, the extent of locoregional disease, distant metastases, comorbidity or refusal of surgery. Following treatment, 50–60 per cent of patients develop a recurrence in less than 12 months, and most mortality in the first two years following diagnosis is due to locoregional recurrence. The overall five-year disease specific survival rate is approximately 30–35 per cent with five-year survival rates of 14–22 per cent for stage IV disease. Volume of disease and laryngeal involvement adversely impact survival. Combination chemotherapy has been shown to improve overall survival.[17]

Patients with hypopharyngeal cancer may suffer from severe symptoms; including pain, swallowing difficulties, aspiration, chest infections, anorexia and weight loss. In many cases, symptoms will have been aggravated by previous treatments; surgery, radiation and chemotherapy (mucositis, hypopharyngeal stenosis, infections, pharyngocutaneous fistula, psychological distress and cachexia). All of these require attention and some may be relieved by surgical interventions such as tracheostomy and the insertion of a gastrostomy to relieve breathing and restore hydration and nutrition.

Some patients, with minimal local symptoms are suitable for targeted agents in recurrent local and/or metastatic disease. These are highly selected patients and palliative treatments should be discussed and offered to patients through the multidisciplinary team (MDT). Patients with symptomatic lung metastases are often those who benefit most from palliative chemotherapy. Palliative radiotherapy may be used for patients, unsuitable for curative treatment, who present with bleeding or uncontrolled pain from the hypopharynx and can be excellent for cutaneous metastases, painful lymph nodes or bony disease.

Key points.

- The majority of cancers arise in the piriform sinuses (65–85 per cent), 10–20 per cent arise from the posterior pharyngeal wall and 5–15 per cent from the post-cricoid area
- Patient choice and involvement in treatment decisions is of high importance and a clear and unbiased discussion of their options will help them and their medical team make the most appropriate treatment decisions
- Primary non-surgical treatment is recommended for most locally advanced tumours unless the laryngeal function is compromised or significant dysphagia exists
- Early stage (I and II) disease can be treated with equal effectiveness with surgery or radiation
- Bulky advanced tumours will usually require circumferential or non-circumferential resection with free flap cover
- Five-year survival is poor with overall survival at 30 per cent, although for T1 and T2 tumours the survival is almost 60 per cent
- Up to 25 per cent of patients are not suitable for curative treatment at presentation because of age, the extent of locoregional disease, distant metastases, comorbidity or refusal of surgery.

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GUIDELINE

Nose and paranasal sinus tumours: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. With only limited high-level evidence for management of nasal and paranasal sinus cancers owing to low incidence and diverse histology, this paper provides recommendations on the work up and management based on the existing evidence base.

Recommendations

- Sinonasal tumours are best treated *de novo* and unusual polyps should be imaged and biopsied prior to definitive surgery. (G)
- Treatment of sinonasal malignancy should be carefully planned and discussed at a specialist skull base multidisciplinary team meeting with all relevant expertise. (G)
- Complete surgical resection is the mainstay of treatment for inverted papilloma and juvenile angiofibroma. (R)
- Essential equipment is necessary and must be available prior to commencing endonasal resection of skull base malignancy. (G)
- Endoscopic skull base surgery may be facilitated by two surgeons working simultaneously, utilising both sides of the nose. (G)
- To ensure the optimum oncological results, the primary tumour must be completely removed and margins checked by frozen section if necessary. (G)
- The most common management approach is surgery followed by post-operative radiotherapy, ideally within six weeks. (R)
- Radiation is given first if a response to radiation may lead to organ preservation. (G)
- Radiotherapy should be delivered within an accredited department using megavoltage photons from a linear accelerator (typical energies 4–6 MV) as an unbroken course. (R)

Introduction

Tumours in the sinonasal region are rare, affecting less than 1 in 100 000 people per year.[1] They are histologically a diverse group of tumours and potentially pose significant management problems due to their close proximity to the orbit and intracranial cavity. Squamous cell carcinoma (SCC) is the most common malignant tumour, but tumours of every histological type can occur. The commoner epithelial tumours include adenocarcinoma, olfactory neuroblastoma, malignant melanoma and adenoid cystic carcinoma. Sarcomas, e.g. chondrosarcoma and rhabdomyosarcoma and haemoproliferative tumours, e.g. lymphoma may also occur.

Benign tumours include inverted papilloma (IP), osteoma, juvenile angiofibroma (JA), haemangiopericytoma, haemangioma, schwannoma, pleomorphic adenoma and meningioma. All areas of the nasal cavity and paranasal sinuses can be affected, but the lateral wall, ethmoids and maxillary sinus are the most common primary sites. The frontal and sphenoid sinuses are rare primary sites for reasons that are unknown.

Clinical presentation

Initial symptoms such as nasal blockage, blood-stained discharge and loss of smell are often overlooked though their unilateral nature should raise suspicion. Delayed presentation is common. Subsequent extension into the orbit, nasolacrimal system, anterior cranial cavity, cavernous sinus, pterygomaxillary fissure, palate, skin and infratemporal fossa may produce symptoms such as proptosis, diplopia and epiphora, trismus, pain, oro-antral fistula, paraesthesia or other neurological deficits or a mass.

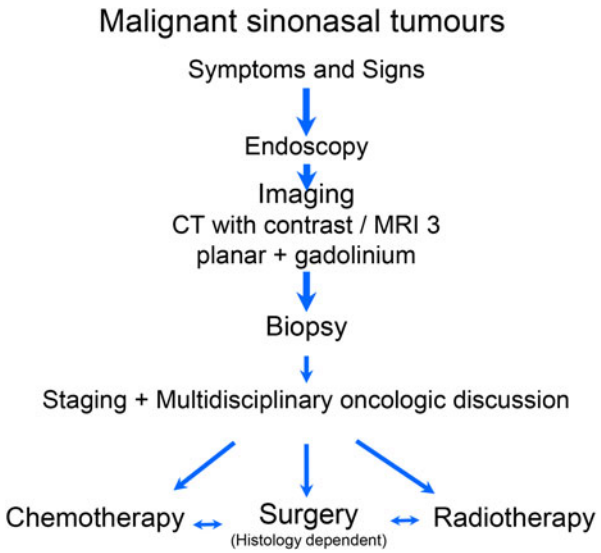

FIG. 1
Management algorithm for malignant sinonasal tumours.[7]

Assessment and staging

Investigation should include computed tomography (CT) and magnetic resonance imaging (MRI) which are complementary in the skull base, and biopsy (Figure 1). Computed tomography scans give excellent bony details and are helpful in determining whether a tumour remains confined within these natural boundaries or has eroded through the surrounding bone. They also provide details of the extent of local bony invasion and are useful in assessing the lamina papyracea, orbital floor, cribriform plate and pterygoid plates. Magnetic resonance imaging allows better distinction of tumour from adjacent soft tissues and retained mucus and is particularly useful for determining invasion of the orbital contents, dura, brain and cavernous sinus. An MRI may also be better for assessing carotid artery invasion. Positron emission tomography-computed tomography (PET-CT) imaging is utilised where the tumour could be an unusual metastatic site from a primary tumour elsewhere in the body, e.g. adenocarcinoma or occasionally where widespread metastatic disease is a clinical possibility, e.g. an aggressive sarcoma. Table I shows the staging system for nasal and paranasal sinus malignancies.[2]

Recommendations

- **Sinonasal tumours are best treated *de novo* and unusual polyps should be imaged and biopsied prior to definitive surgery (G)**
- **Treatment of sinonasal malignancy should be carefully planned and discussed at a specialist skull base multidisciplinary team (MDT) meeting with all relevant expertise (G)**

TABLE I
T STAGING FOR NASAL AND PARANASAL SINUS TUMOURS (EXCEPT SINONASAL MALIGNANT MELANOMA)

Maxillary sinus	
T1	Tumour limited to the mucosa with no erosion or destruction of bone
T2	Tumour causing bone erosion or destruction, including extension into hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve V2, nasopharynx, clivus
Nasal cavity and ethmoid sinus	
T1	Tumour restricted to one subsite of nasal cavity or ethmoid sinus, with or without bony invasion
T2	Tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion
T3	Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate or cribriform plate
T4a	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
T4b	Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, clivus

Management

Discussion about management of these rare tumours should ideally occur in a specialist skull base MDT.

Benign sinonasal tumours

Sinonasal inverted papilloma. Sinonasal IP is the most common pathology and much of the literature on management of benign nasal tumours concerns itself with IP.[3] It is a locally aggressive tumour, which usually arises in the nasal cavity. Inverted papilloma is associated with a risk of malignant transformation (about 2 per cent) and it is known to carry a high risk of post-treatment recurrence and/or residual disease if a subperiosteal resection is not undertaken. Expert histopathology review is essential as well differentiated SCC can easily be mistaken for IP.

Juvenile angiofibroma. Juvenile angiofibroma is a slow growing highly vascular tumour which arises predominantly from the sphenopalatine region in adolescent and young adult males. The tumour is locally invasive and can cause life-threatening epistaxis. As with inverted papilloma this lesion can extend to involve

the sinuses, orbits and intracranial space. The basisphenoid is the commonest site of residual disease usually due to invasion via the vidian canal.

Treatment. Despite differences in tumour behaviour across the range of pathologies, all share the same basic treatment aims of complete surgical removal without damage to adjacent organs and with prevention of recurrence.

The mid-facial degloving approach has been the mainstay for access if the frontal sinus or anterior ethmoids are not involved. Complex frontal tumours and those with intracranial extension have required use of osteoplastic flap and craniofacial approaches. In a large series of open surgery for inverted papilloma, an overall recurrence rate of 17 per cent is found. For juvenile angiofibroma, 'recurrence' rates fell from 21 to 2 per cent when drilling of the basisphenoid was employed during midfacial degloving. More recently, endoscopic surgery and endoscope assisted, minimal access surgery (see below) are more often employed, having been shown to be effective alternatives with equivalent results and reduced morbidity compared to open approaches.[4]

Recent studies of endoscopic surgery for inverted papilloma suggest recurrence rates of around 14 per cent are achievable by experienced endoscopic surgeons. A similar recurrence rate has been reported for juvenile angiofibroma resected endoscopically though the series are relatively small.

Recommendation

- **Complete surgical resection is the mainstay of treatment for inverted papilloma and juvenile angiofibroma (R)**

Malignant sinonasal tumours

Surgical approaches (Figure 2)

Endoscopic resection of sinonasal tumours. The accepted method of resecting tumours of the anterior skull base is craniofacial resection.[5] However, recent technological advances have facilitated endoscopic resection of malignant tumours of the lateral nasal wall and anterior skull base with safety and precision.[6–9]

In some cases, tumour resection may be entirely endoscopic, but the endoscope may also be combined to enhance surgical resection with craniotomy, midfacial degloving and lateral rhinotomy. Patients with sinonasal malignancy undergoing purely endonasal resection are reported to have outcomes as good as conventional external surgical techniques with the potential for lower morbidity and shorter hospital stays. Endoscopic resection of sinonasal tumours should be managed in units that have comprehensive skull base expertise that can manage all facets of the patient's care.

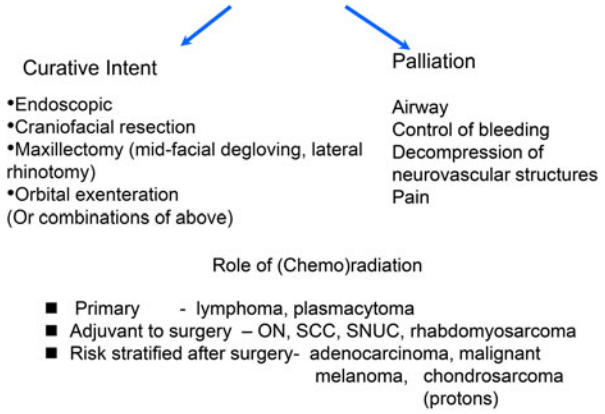

FIG. 2
Management algorithm for malignant sinonasal tumours continued.[7]

Indications for endoscopic endonasal resection. Prior to undertaking this means of treatment, a clear operative plan must be considered by an MDT with the full range of expertise in the management of sinonasal malignancy. Surgeons undertaking endoscopic resection must be experienced in both endoscopic techniques and the full range of other surgical options with which they may be combined and must also be familiar with the natural history of the wide range of malignant sinonasal tumours. Once a decision has been made to treat a tumour surgically, the clinician should define whether this is with curative intent or palliation.

Contraindications to endoscopic resection (Table II): Tumours invading facial soft tissues should not be attempted endoscopically.

Tumours that are very vascular would pose a considerable problem if resected endoscopically. Embolisation within days of definitive surgery should be considered in these cases. Relative contraindications to endoscopic resection include extension to the orbital apex or laterally to the pterygomaxillary space and infratemporal fossa. Malignant tumour invasion of the cavernous and sagittal sinuses and brain parenchyma is difficult to clear endoscopically, but a decision to operate under these circumstances would mainly be for palliation rather than cure.

Surgical considerations. Intra-operative computer assisted navigation should ideally be available. Some systems incorporate CT–MR fusion and three-dimensional CT angiography. Powered instruments should also include a microdebrider and high-speed drill systems with long diamond burrs and curved drills designed for intranasal use. Diathermy instruments designed for endoscopic intranasal use should be available, bipolar diathermy being preferable. Resecting tumours endoscopically is aided by having two surgeons using a 3–4 handed technique via both sides of the nose. This technique is facilitated by partial excision of the nasal septum. En bloc resection is usually not possible in the skull base. The most important principle is to obtain clearance of tumour usually by

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TABLE II
LIMITATIONS OF ENDOSCOPIC SURGERY WITH CURATIVE INTENT[7]

Absolute
When the following are required:
Orbital exenteration
Maxillectomy (except medial wall)
Skin excision
Anterior +/or lateral involvement of frontal sinus
Dura or brain involvement lateral to mid orbital roof or lateral to optic nerve
Brain parenchyma invasion
Vascular invasion (internal carotid artery, cavernous sinus)
Chiasm invasion

piecemeal resection, confirmed with frozen section when necessary. The extent of resection is determined by the histology: for olfactory neuroblastoma, the olfactory bulbs and tracts may be resected, but for high grade malignancy invading critical structures such as the cavernous sinus, complete resection is not possible. The incidence of positive tumour-margins is reported to be similar in patients with advanced anterior skull base disease undergoing either endoscopic resection or traditional craniofacial resection. Dura may be resected if invaded by tumour, but if extensive, an open approach may be more suitable. Reconstruction of the skull base defect is essential at the time of the primary surgery if the skull base or dura have been included in the resection. A multilayered technique is recommended and graft materials include autologous fascia, cartilage, fat, split calvarial bone and local mucosal flaps and grafts. Large pedicled septal mucosal flaps based on the sphenopalatine artery have been described, but are only suitable if the mucosa is not invaded by the tumour.

Recommendations

- **Essential equipment is necessary and must be available prior to commencing endonasal resection of skull base malignancy (G)**
- **Endoscopic skull base surgery may be facilitated by two surgeons working simultaneously, utilising both sides of the nose (G)**
- **To ensure the optimum oncological results, the primary tumour must be completely removed and margins checked by frozen section if necessary (G)**

Results. Five-year disease-specific survival rates of 85 per cent after endoscopic resection of sinonasal malignancy are reported though selection bias needs to be taken into account.[10,11] Encouraging results with good local control are reported following the endoscopic resection of olfactory neuroblastoma.[12,13] The overall survival of adenocarcinoma after endoscopic resection is reported at 92 per cent with a median follow-up of 30 months. The results following endoscopic resection of SCC are significantly worse.

The outcome is dependent on the histology of the primary tumour as well as the presence of intracranial spread and positive surgical margins. With more recent larger series, survival is worse with increasing T-stage with the exception of malignant melanoma.[14] However, endoscopic resection of melanoma is associated with improved five-year survival (though not 10-year survival) irrespective of extent. Survival is best for patients who have not undergone previous surgery with incomplete resection.

Maxillectomy. Maxillary tumours represent 3 per cent of all head and neck tumours. Of these tumours, 75 per cent are malignant. Of the malignant tumours, 80 per cent are of epithelial origin, with the remainder being most commonly salivary gland (adenoid cystic carcinoma > muco-epidermoid carcinoma > adenocarcinoma), malignant melanoma or sarcomas. There is a slight male preponderance, with most tumours occurring in the fifth and sixth decades. The five-year survival is between 30 and 50 per cent.

Pre-operative planning It is important that a clear reconstructive plan is derived for the maxillectomy defect prior to surgery with a decision to either obturate the cavity with a prosthesis or perform some form of biological reconstruction. The latter includes local or regional flaps in addition to free-tissue transfer of a soft tissue only or composite nature. Ultimately the decision will depend on competing factors such as the site and size of the defect, available dentition after resection, concurrent comorbidity and prognosis. The reconstructive and prosthetic aspects of maxillectomy rehabilitation are dealt with in greater detail elsewhere in these guidelines. In summary, obturators have the advantage in that they reduce the length of surgery, impart no additional donor site morbidity, restore the dentition more immediately and theoretically retain the ability to inspect the post-ablative cavity, although in the era of PET–CT the latter argument is declining. However, obturators have their disadvantages. In the short term, this includes the need for frequent changes initially under general anaesthesia along with the requirement for repeated adjustment and refashioning as the maxillectomy cavity settles down. In the longer term, obturators impart more discomfort and demand patient compliance to remove and clean them. Studies that compare obturators with biological reconstruction demonstrate improved quality of life metrics for the latter group and as such the standard of care is to favour appropriate vascularised flap reconstruction as discussed elsewhere in these guidelines unless patient preferences or other contraindications exist.

Surgical technique. Access to the maxilla may be transoral, transcutaneous or extended. The trans-

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oral route can be supplemented with a mid-facial degloving procedure. The transcutaneous incision (Weber–Ferguson) involves division of the upper lip and extension around the nasal vestibule and alar of the nose towards the medial canthus. Additional exposure of the ethmoid sinuses may be aided with a Lynch extension. Likewise access to the lateral and posterior-lateral maxilla may be improved with a trans-conjunctival, subciliary or infra-orbital extension. Skin flaps are raised in a submuscular plane to maintain blood supply and also minimise damage to the facial nerve. It is important to ensure adequate exposure by elevating skin flaps as far back as the posterior-lateral surface of the maxilla and under the surface of the zygoma in order to gain adequate access to the pterygo-palatine fissure. Bony osteotomies are performed through tooth sockets or edentulous areas with either drills or saws. After the osteotomies are completed the specimen is delivered with division of the posterior soft tissue attachments. Care should be taken here to avoid bleeding from the palatine vessels and branches of the maxillary artery. The infra-orbital nerve can only be preserved if a low maxillectomy is performed. Management of the orbit is discussed below. If immediate obturation is to be carried out, it is imperative that the ablative cavity is adapted. Sharp spicules of bone should be removed, but undercuts retained to aid retention of the prosthesis. If obturation is to be performed, a simultaneous coronoidectomy should be carried out.

Craniofacial resection. Approaches. Type 1 craniofacial or transorbital cranial facial uses the lateral rhinotomy incision extended up into a Lynch incision. There is no need to extend this incision around the nasal alar so avoiding any asymmetry of the alar base. Wide release of the orbital periosteum and lacrimal duct allows gentle lateral reflection of the orbital contents giving excellent exposure of the ethmoids and cribriform plate, lateral nasal wall, fronto-nasal recess, lamina papyracea and orbital periosteum all of which can be resected. Small areas of ethmoidal roof, cribriform plate and the olfactory bulb can be resected from below and dura resected and repaired as necessary. Type 2 craniofacial includes a shield shaped window craniotomy over the frontal sinus allowing excellent exposure of the superior surface of the cribriform plates allowing en bloc resection of dura, cribriform plate and early brain involvement. It allows robust repair of the dura under direct vision with fascia lata or pericranium. Type 3 craniofacial involves an approach to the ethmoids via a lateral rhinotomy-type incision and a large frontal craniotomy approached by a bicoronal incision. This is only required for significant intracranial disease requiring neurosurgical input.

Orbital management. An understanding of the anatomical barriers to the disease is very important. Both the dura and the orbital periosteum provide significant barriers. In particular the orbital periosteum may still be intact despite considerable intra-orbital tumour with proptosis. Although care must be taken to avoid attempting orbital preservation at the potential cost of decreased local disease control and survival, at present the most commonly performed approach with frozen section control is to resect involved orbital periosteum and preserve the orbital contents in cases where there is no invasion through the periosteum into orbital fat, orbital musculature or orbital apex. There does however remain some debate about the oncological basis for this. Although the loss of an eye psychologically is often very difficult for patients to consider, it must be remembered that preservation of a painful eye with diplopia and poor vision following RT is a significantly worse outcome than orbital clearance with an excellent prosthesis.

Contraindications to surgery. Anatomical areas which preclude surgical intervention differ with the aggressiveness of the pathology. An aggressive tumour invading the cavernous sinus, particularly if it reaches the internal carotid artery or with massive intra-cranial extension, would be deemed incurable and the morbidity of surgical intervention would outweigh any potential benefits. These, however, are probably the only anatomical contraindications to surgery. With slower growing tumours quite significant intracranial disease may well still be amenable to surgical intervention with a hope of long-term survival. Significant involvement of both eyes or the loss of an only seeing eye is a devastating consequence of surgery and this would be a relative contraindication to any surgical resection.

Regional nodes. Lymph node involvement at diagnosis is low. Rates are higher with increasing T stage, and squamous and undifferentiated histology. In T3–T4 SCC maxillary tumours elective nodal treatment of ipsilateral levels Ib and II has been advocated. In contrast, ethmoid sinus tumours have been associated with low rates of both lymph node involvement at diagnosis and nodal recurrence (approximately 2 and 7 per cent, respectively).

Olfactory neuroblastoma can be associated with lymphatic spread, both uni- and bi-lateral in up to 25 per cent of cases.[15]

Results. Results from combined surgery and RT are very dependent on pathology and the anatomical areas involved by tumour with results if orbit and brain are involved being extremely poor. Involvement of the periorbita or dura also reduces survival. The following figures indicate published five years overall survival for common histological variants: SCC 30–55 per cent, adenocarcinoma 45–60 per cent and olfactory neuroblastoma approximately equal to 75 per cent.

Radiation therapy

Role of RT. Sino-nasal tumours are often advanced at presentation, invading adjacent structures and lie in

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close proximity to many organs at risk of damage from radiation (lens, retina, optic nerve and chiasm, brain tissue, pituitary gland). This makes irradiation to a radical dose difficult.[16] The added numerous air-tissue interfaces within the treated volume also make for inhomogeneous dose absorption and efforts should be made to eliminate these using tissue bolus techniques where possible. If orbital or brain invasion occurs, survival rates are extremely poor despite aggressive treatment.

The most common management approach is surgery followed by post-operative RT, although some protocols have used chemotherapy alongside, where the tumour is recognised to be chemosensitive, e.g. SCC (Figure 2).

Following surgery that involves a dural repair a longer interval before RT may be preferred to allow healing. The sequence of surgery and RT remains open to debate, with no significant differences in outcome found.

Pre-operative (chemo) RT may allow for less extensive surgery in advanced tumours.

The implementation of new advanced radiation techniques such as intensity modulated radiotherapy (IMRT) is especially attractive in sinus tumours as the dose distributions achieved with conventional techniques are rather inhomogeneous, with areas of low dose that can potentially contribute to local recurrence.[17] IMRT has demonstrated improved coverage of the tumour bed and potential sites of spread, whilst ensuring levels of radiation exposure are kept within the tolerance of adjacent neurological structures. Prospective studies with mature outcome data are not yet available.

Dose escalation above conventional dose levels is achievable with IMRT and this will be an active area of future study to improve local control, since the majority of local failures occur within the radiation field. Patients with the most advanced tumours, previously thought to be suitable only for palliation, may then become treatable radically.

Proton therapy is currently under evaluation and may have a role in treating small volume disease, e.g. low grade tumours at the skull base or close to radiosensitive structures, due to rapid dose fall off. It has been used in chondrosarcoma and olfactory neuroblastoma is included in the recommendations for specialised services in paediatric oncology. Sub-volumes may also be potentially treated using protons as a boost to residual tumour masses within a larger photon field as mixed plans.

Radiation toxicity. Doses delivered with conventional RT are of the order of 60–70 Gy and are known to cause blindness in up to a third of patients, and too often sacrifice of the sight in one eye is unavoidable.[18] Care must be taken to avoid a dry eye, caused by radiation injury from quite modest doses to the lacrimal gland (30 Gy), as optic pain, perforation and even enucleation may ensue.

Brain radionecrosis is a potentially devastating complication of RT and the risk depends on the total dose, dose per fraction, overall treatment time and volume, with tolerance for partial volume irradiation set at 55–60 Gy/30 fraction equivalent dose. There is, however, very little information on the effect of irradiating large volumes of tissue to lower doses as occurs with IMRT, due to the multiple radiation portals.

Conventional dose prescriptions include 60–70 Gy in 30–35# over 6 to 7 weeks for SCC, adenocarcinoma, undifferentiated carcinoma and olfactory neuroblastoma. Doses for lymphoma are approximately 40–50 Gy in 20–25# over 4 to 5 weeks. Accelerated, hyper and hypo-fractionated regimens remain investigational.

Recommendations

- **The most common management approach is surgery followed by post-operative radiation therapy ideally within six weeks (R)**
- **Radiation is given first if a response to radiation may lead to organ preservation (G)**
- **Radiotherapy should be delivered within an accredited department using megavoltage photons from a linear accelerator (typical energies 4–6 MV) as an unbroken course (R)**
- **Intensity modulated radiotherapy is the standard of care as it can improve target coverage, allow for dose escalation and facilitate organ sparing to reduce toxicity (R)**

Chemotherapy. Consensus statements are difficult due to the lack of adequately powered, randomised evidence. This is given either as a short course induction and/or neoadjuvant regime pre-RT or surgery for rapid symptom control, and/or concurrently as a radiation sensitiser.

The neoadjuvant approach is not associated with improved overall outcomes, but is a practical solution to pre RT tumour shrinkage, as modern RT delivery relies on a static patient contour, to deliver dose accurately and safely.[19] This is usually cisplatin-based and in the phase II setting produces a response in about two-thirds of patients.

Concurrent use of chemotherapy with RT is associated with a small, but measurable improvement in survival for SCCs of the head and neck in general, with improved disease-free and overall survival at five years to approximately 70 and 67 per cent, respectively suggested. For the rarer tumour types of the sinus area, there is no strong randomised evidence currently to support its use routinely.

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Small-scale observational studies have reported on topical and intra-arterial chemotherapy, but are not recommended.

Chemotherapy has also been reported to be of use in undifferentiated carcinomas, neuroendocrine and small cell carcinomas. Excellent local and distant control rates for olfactory neuroblastoma have been demonstrated with local therapy alone and chemotherapy in this setting is experimental, but often given in the presence of locally advanced disease. For sinonasal SCC, there is no randomised evidence in favour of the use of concomitant chemoradiation. Evidence supporting its use both in the primary and adjuvant setting can be extrapolated from other head and neck malignancies.

Chemotherapy may improve quality of life and offer a modest survival benefit in the palliative setting, translating from benefit seen in other head and neck SCC sites.[20] Molecular targeted treatments are under investigation, but none have proven benefit to date.

The role of chemotherapy in paranasal sinus malignancy is limited to the following settings: as part of triple therapy, e.g. embryonal rhabdomyosarcoma, concurrently with radiation in locally advanced disease, e.g. SCC of maxilla, for disseminated lymphoproliferative malignancy and for palliation, e.g. poorly differentiated SCC with disseminated disease.

Palliation. Some patients present with advanced disease where radical treatment is not appropriate. Surgery, RT and chemotherapy all have a potential role in palliation.

Palliative RT treatment requires high doses to achieve any significant tumour control, and short fractionation regimes are associated with marked acute toxicity. Regimens that can be considered on an individual basis include 55 Gy in 20# over four weeks, 27 Gy in 6# over three weeks and 36 Gy in 12# over two-and-a-half weeks. If the patient has a localised disease recurrence, then retreatment with IMRT or stereotactic RT may be considered especially if there has been a long disease-free interval.

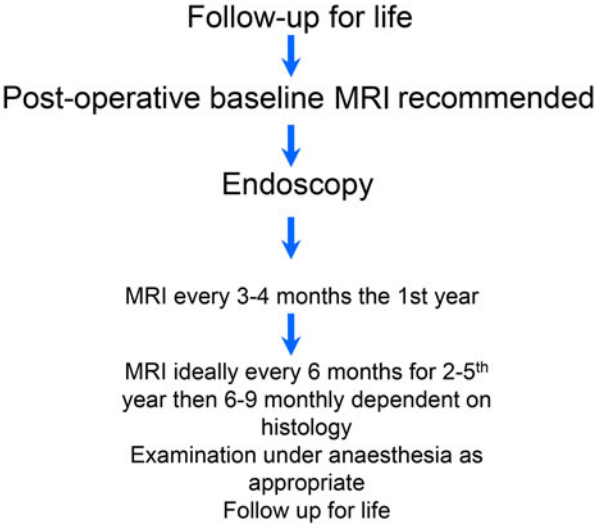

FIG. 3
Follow-up algorithm for malignant sinonasal tumours.[7]

Follow-up. Follow-up is needed for detection of recurrence and to manage surgical sequelae (nasal crusting, epiphora, etc.). Follow-up should be lifelong as some tumours can recur many years after treatment and should include careful examination of the cavity with the endoscope and MRI scans. Imaging should include the neck in olfactory neuroblastoma (see below). (Figure 3)

Key points

- Endoscopy and imaging (computed tomography and magnetic resonance imaging) are key to assessing tumour extent and planning surgical approach
- Endoscopic techniques enable low morbidity and low recurrence rates to be achieved in suitable tumours and may be performed for curative or palliative reasons
- A high level of expertise in endoscopic sinus surgery and skull base and/or dural reconstruction is a necessity before undertaking endoscopic resections
- Neurosurgical support and neuronavigation should be routinely available in centres undertaking this surgery
- Reconstruction and rehabilitation needs should be integrated into the treatment plan for patients undergoing open surgery
- The majority of patients will require adjuvant radiotherapy
- Diligent tumour surveillance with nasal endoscopy and interval magnetic resonance imaging scans is a necessity following treatment of sinonasal malignancy.

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GUIDELINE

Management of lateral skull base cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It provides recommendations on the work up and management of lateral skull base cancer based on the existing evidence base for this rare condition.

Recommendations

- All patients with more than one of: chronic otalgia, bloody otorrhoea, bleeding, mass, facial swelling or palsy should be biopsied. (R)
- Magnetic resonance and computed tomography imaging should be performed. (R)
- Patients should undergo audiological assessment. (R)
- Carotid angiography is recommended in select patients. (G)
- The modified Pittsburg T-staging system is recommended. (G)
- The minimum operation for cancer involving the temporal bone is a lateral temporal bone resection. (R)
- Facial nerve rehabilitation should be initiated at primary surgery. (G)
- Anterolateral thigh free flap is the workhorse flap for lateral skull base defect reconstruction. (G)
- For patients undergoing surgery for squamous cell carcinoma, at least a superficial parotidectomy and selective neck dissection should be carried out. (R)

Introduction

Primary cancers of the temporal bone (TB) and lateral skull base are comparatively rare, accounting for 0.2 per cent of all head and neck cancers. They consist of different sites of cancer with a range of pathologies. Consequently, there is little evidence as to best practice. Over ten times more frequent are cancers of the skin and parotid invading the TB. Despite this there is even less evidence of best practice. Lateral skull base cancer can be considered to comprise any of the entities described in Table I.

Clinical presentation

Late diagnosis of patients with cancers of the external auditory meatus (EAM) and middle ear (ME) is not uncommon and this should be considered in any patients with: chronic otalgia, bloody otorrhoea, bleeding, mass, facial swelling or palsy.[1] Clinical findings of excoriation, ulceration and granulation tissue should be considered as suspicious. Some patients may have a long history of chronic middle or external ear infection, which can be a pre-disposing factor.

Skin cancers present as visible or itchy skin and/or pinna lesions. Tumours of the infratemporal fossa may present with a subtle mass or fullness immediately above the zygoma or with pain (which can be easily misdiagnosed as temporal mandibular joint pain).

Assessment and staging

Clinical examination

Confirmation of diagnosis is mandatory before treatment and is gained by biopsy of the pinna, skin, EAM or ME. Advanced parotid cancers should be diagnosed through cytopathology or, occasionally if necessary, incision biopsy. Tumours of the infratemporal fossa often will require a surgical biopsy via access superior or inferior to the zygoma as necessary. Cytology is possible, but, as many tumours here are sarcomas, histopathology is required. The differential

TABLE I
ENTITIES THAT COME UNDER THE CATEGORY OF LATERAL SKULL BASE CANCER

Site	Main pathologies
Advanced skin cancer (conchal bowl/pinna/periauricular skin)	SCC BCC Melanoma
Advanced parotid cancers (involving ear/temporal bone)	Salivary gland malignant neoplasms (generally high grade), including metastatic skin SCC to intra-parotid lymph nodes
Infratemporal fossa temporomandibular joint	Sarcomas (e.g. chondrosarcomas, rhabdosarcoma, osteosarcoma)
EAM/ME	Most SCC (80%) BCC Skin adnexal cancers

diagnosis is myriad, but care must be taken to exclude pseudotumoral skull base osteomyelitis of the TB (also called necrotising otitis externa) and inflammatory diseases such as granulomatosis with polyangiitis.

Imaging considerations

In most cases, both computed tomography (CT) and magnetic resonance imaging (MRI) should be used. Computed tomography (fine cut, high resolution) is essential for external auditory canal (EAC) erosion, extent of middle ear and mastoid involvement, spread into jugular bulb, carotid canal, tegmen, temporomandibular joint (TMJ), parotid and beyond. It can also stage the neck. Magnetic resonance differentiates mucosal swelling or mastoid fluid from tumour; is superior at ascertaining dural or brain involvement; and gives more detail of parapharyngeal space and infratemporal fossa involvement.

Despite high-resolution scanning using both modalities, both over and under estimation of the extent of the tumour occurs. Patients should be prepared for more extensive surgery or abandoning surgery if the scans prove wrong.

Depending on the pathology of the tumour, imaging of the thorax (squamous cell carcinoma (SCC)) or whole body may be required (sarcomas, melanoma).

TABLE II
MODIFIED PITTSBURG STAGING SYSTEM[2]

T1	Tumour limited to the EAC without bony erosion or evidence of soft tissue extension
T2	Tumour with limited EAC erosion (not full thickness) or radiological findings consistent with limited (<0.5 cm) soft tissue involvement
T3	Tumour eroding the osseous EAC (full thickness) with limited (<0.5 cm) soft tissue involvement of middle ear and/or mastoid or causing facial paralysis at presentation
T4	Tumour eroding the cochlear, petrous apex, medial wall of middle ear, carotid canal, jugular foramen, or dura or with extensive (>0.5 cm) soft tissue involvement

Carotid angiography and balloon occlusion are occasionally required to assess ipsilateral carotid artery involvement. If a tumour is thought unresectable without internal carotid artery sacrifice, then a temporary balloon occlusion test can be performed. If successful, permanent pre-operative occlusion via coils can be performed (ideally two weeks pre-operatively).

Audiology

Pure tone audiogram of both ears should be performed pre-operatively.

Pre-treatment staging

There is no Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) staging system for cancers of the TB or lateral skull base. However, many use the revised Pittsburgh staging system (Table II). The standard UICC staging is used for neck and distant metastases.

Recommendations

- **All patients with more than one of: chronic otalgia, bloody otorrhoea, bleeding, mass, facial swelling or palsy should be biopsied (R)**
- **Magnetic resonance and CT imaging should be performed (R)**
- **Patients should undergo audiological assessment (R)**
- **Carotid angiography is recommended in select patients (G)**
- **The modified Pittsburg T-staging system is recommended (G)**

Treatment planning and prognosis

There should be a specific multidisciplinary team (MDT) dealing with skull base cancers. For sarcomas, there should be liaison with the sarcoma MDT, and, for paediatric sarcomas, with the paediatric oncology MDT.

Most patients with operable cancer of the lateral skull base are treated with primary surgery, with the exception of some sarcomas. Given the low incidence of lateral skull base cancer, the variety of precise sites of origin, heterogeneity of tumour pathology and individual circumstance, it is difficult to generalise treatment guidelines. The commonest scenarios are of SCC arising in the ear or TB (ME and/or EAM) and advanced parotid cancers. The situation of advanced cutaneous SCC invading the TB is not materially different.[3]

Cancers arising in the temporal bone

General principles

For cancer arising in the TB, the most favourable survival rates are achieved with an en bloc extended TB

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resection and post-operative radiotherapy (RT).[4–6] The influence of ME involvement on prognosis is critical. T1 and T2 lesions lateral to the tympanic membrane have cure rates near to 100 per cent with true enbloc resections without breach of the tumour. The majority of T3 tumours are also cured with disease specific survival rates over 70 per cent, whereas T4 five-year survival results vary between 30 and 50 per cent.[1,7,8] Nodal metastasis has a major influence on prognosis.[5,9] Equally critical for prognosis is a histologically-proven complete microscopic resection.[4,8]

Extension superiorly through the tegmen leads to dural and cerebral involvement. Dural involvement is an adverse prognostic indicator, but around one-third of such patients are curable with the appropriate surgery.[5] Cerebral involvement rarely confers any chance of cure.

On the other hand, T4 tumours that are T4 by virtue of anterior invasion to the TMJ and/or pre-auricular tissue have a much better prognosis than other T4 tumours.[9]

Resection of the intra-petrous carotid is possible. Some patients can benefit from pre-operative radiological permanent occlusion of the carotid artery, subject to successful balloon occlusion. However, the cancer-mortality in this group of patients with petrous apex involvement is high, due to difficulties achieving full microscopic resection around this area, and the post-operative morbidity is high due to, amongst other things, multiple cranial nerve deficits from a resection of this extent.

Thus, for patients with a combination of high morbidity with low chance of surgical cure, consideration should be given not to offer primary surgery.[5]

Temporal bone surgery

Lateral temporal bone resection (LTBR) should be regarded as the minimum oncological operation for T1 and T2 lesions[5,10]. Essential elements of LTBR are (1) excision lateral to facial nerve; (2) conchal bowl resection; and (3) bony cuts: mastoid to middle fossa dura (or leaving a thin layer of bone), anteriorly into zygomatic aircells and TMJ, inferiorly to stylomastoid foramen, hypotympanum to TMJ.

Additional options include (see below): resection of entire pinna and periauricular skin; condyle/mandible, parotid, extension of resection into parapharyngeal space and infratemporal fossa, neck dissection, facial nerve sacrifice and cable graft.

Extended temporal bone resection (ETBR) is required for more extensive tumours involving the middle ear[11]. The essential elements of EBTR are (1) facial nerve sacrifice; (2) posterior and middle craniotomy; (3) labyrinthectomy; (4) transection of internal auditory canal; (5) resection of petrous tip; (6) exposure of intra-petrous portion of the carotid; and (7) total parotidectomy.

Additional options include: craniectomy (squamous TB; sphenoid wing, posterior fossa); mandibulectomy; parapharyngeal and/or infratemporal fossa resection; extension to jugular foramen; lower cranial nerve sacrifice; internal carotid artery; dura; brain.

Recommendation

- **The minimum operation for cancer involving the temporal bone is a lateral temporal bone resection (R)**

Resection of other structures in TB surgery

Parotid gland. When performing TB resections for TB cancers and advanced skin cancers, the parotid gland may be either involved directly by tumour or be harbouring intra-parotid lymph node metastases (it may contain the primary echelon lymph node). The former may be suggested by pre-operative scans. Therefore, for all resections, at least a superficial parotidectomy should be carried out.[10] For advanced T3/T4 TB SCCs, total parotidectomy should be carried out, which also facilitates access to the parapharyngeal space, infratemporal fossa and masticator space. For basal cell carcinoma (BCC) without evidence of direct invasion into or near the parotid gland, parotidectomy can be omitted.

Temporo-mandibular joint/mandible. The standard anterior bony cut in a lateral TB resection goes into the TMJ. There is therefore some degree of disruption of TMJ function as a consequence. If there is involvement of or near the TMJ/condyle, it is recommended that a partial mandibulectomy is carried out, which may range from condylectomy to resection from mandibular notch to angle. If the latter is done, the inferior alveolar nerve should be preserved, if oncologically sound to do so. There is, however, no need for routine resection to include the TMJ in lateral temporal bone resection (LTBR).[5]

Temporal bone resection in parotid cancers

Almost all parotid cancers abutting the TB are easier to remove if an inferior TB resection is done to get medial and posterior to the tumour rather than finding the facial nerve outside the stylomastoid foramen and getting too close to the tumour. This improvement in surgical access both improves prognosis and ease of facial nerve grafting if required.[12,13] For parotid tumours with EAM or TB involvement, at least a lateral TB resection will be required.

Facial nerve

Facial nerve involvement by tumour is a significant adverse prognostic factor. Pre-operative facial nerve dysfunction due to facial nerve involvement by tumour requires sacrifice of the nerve as part of the resection required. For some patients with normal function pre-operatively, it may be technically impossible to resect a tumour without nerve sacrifice if the nerve is totally encased by tumour, bearing in mind the aim

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of surgery is complete, preferably monobloc, tumour resection with margins. When the facial nerve is sacrificed, the proximal stump at the limit of the sacrifice should be sent for frozen section pathology.

In cases in which nerve sacrifice is necessary, one or more of the following steps should be considered detailed below. 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.

A cable graft from ME facial nerve to intra-parotid branches can be performed if (a) there is enough proven tumour-free proximal facial nerve (otherwise a facial-hypoglossal anastamosis can be considered) and (b) if 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 greater auricular nerve, sural nerve or lateral cutaneous nerve of thigh (easily available if harvesting an anterolateral thigh free flap). If an alternative lengthening of telomeres (ALT) free flap is to be employed, this can be used as a chimaeric flap, with separate components for volume restoration and facial function and vascularised interposition nerve grafting.

Otherwise, either static procedures can be employed such as fascia lata sling for oral commissure/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. gold weight, canthoplasty) can be performed at the time of tumour resection or later on.

Recommendation

- **Facial nerve rehabilitation should be initiated at primary surgery (G)**

Reconstruction

The aims of reconstruction of lateral skull base defects can be considered hierarchically:

- Protection for the brain when the dura mater is breached.
- Skin defect.
- Auricular defect.
- Tissue volume defect and mandible defect.
- Functional defect-facial nerve.

Dural defects are normally repaired with non-vascularised tissue such as autologous fascia lata grafts, pericardial xenografts or synthetic materials.

Reconstruction of the skin defect should be considered with the volume defect, this being determined by extent of temporal bone resection, parotidectomy and mandibulectomy in particular.[14]

For smaller skin defects without much volume loss, options include radial forearm free flap, cervicofacial rotation flap, temporalis flap and supraclavicular artery island flap. These can be used to reconstruct small skin/auricle defects with modest volume loss.

For most defects after temporal bone resection, the anterolateral thigh free flap offers optimal reconstruction, offering bulk (variable by the inclusion of vastus lateralis), and enough skin for most defects (which can be reduced by de-epithelialisation if the auricle is not resected).[14] It is reliable, has the requisite tissue and minimal donor site morbidity. It allows vascularised fascia lata to be used for static facial resuspension 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 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, lower trapezius muscle island flap (if the transverse cervical vessels are intact) or superior trapezius flap (when a radical neck dissection has been performed) can be used. The use of pectoralis major or delto-pectoral flap is suboptimal as the lateral skull base is at or beyond the limits of rotation in many cases.

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 – scapular osteomusculocutaneous flap can restore a large mandibular and lateral skull defect.

Recommendation

- **Anterolateral thigh free flap is the workhorse flap for lateral skull base defect reconstruction (G)**

Neck dissection

Up to 20 per cent of patients with temporal bone SCC will have lymph node metastases. The need for neck dissection depends on the pathology. As for any head and neck cancer, clinically or radiologically staged N + necks require comprehensive neck dissection, but level 1a (submental) can be spared. In the setting of N0 neck, it is also recommended that neck dissection (levels 1b, 2–5) is performed for all temporal bone SCC.[15] The same applies to advanced parotid carcinomas with temporal bone involvement.

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Recommendation

- **For patients undergoing surgery for squamous cell carcinoma, at least a superficial parotidectomy and selective neck dissection should be carried out (R)**

Radiation therapy

Post-operative RT

Most T2–T4 SCCs will require post-operative RT,[5] as will advanced parotid cancers requiring temporal bone surgery. T1 and selected T2 SCCs without adverse histological features (particularly peri-neural infiltration) and with proven clear margins may not require adjuvant therapy. Dosimetry with electrons is unpredictable due to tissue heterogeneity and photon therapy is preferred using three-dimensional conformal or intensity modulated techniques (IMRT). The clinical target volume is determined from pre-operative imaging and further informed from MDT feedback on operative and histopathological findings.

Conformal RT is computer planned and the target volume often resembles a transaxial triangular shape with the base laterally. A simple pair of horizontal wedged lateral oblique fields may suffice, with beams exiting on either side of the contralateral parotid. An additional lateral field with vertical wedging may improve homogeneity longitudinally.

Intensity modulated techniques may well reduce dose to the ipsilateral cochlea (if this is separate from the tumour volume) and oral cavity. Chronic otomastoiditis and TB necrosis following RT can be reduced by restricting the volume of bone treated to high dose as far as possible. The contralateral parotid, bilateral submandibular glands, oral cavity, mandible, cochlea as well as central nervous system (CNS) structures should be routinely contoured and given constraint doses.

Post-operative doses used for head and neck cancer are 60 Gy in 30 fractions for moderate risk and 66 Gy in 33 fractions for high risk; these doses can potentially be applied for lateral skull base cancers, but the normal tissue (particularly CNS) complication rate is clinically significant at doses above 60 Gy. Synchronous post-operative treatment with cisplatin can be also considered.[16]

Primary RT

When primary surgery is not considered possible, or too morbid, definitive RT may be used, with overall cure rates of just under half of patients overall.[16] Clinical target volume is based on staging imaging, preferably with both CT and MR imaging (MRI). Higher biological doses are used compared with the post-operative setting so that optimal conformality is essential to reduce treatment complications. Standard IMRT doses can be used: 66 Gy in 30 fractions for macroscopic disease, 60 Gy for high risk microscopic areas and 54 Gy for moderate risk microscopic areas; these doses may be modified according to the volume of CNS tissue in the clinical target volume. In view of the emphasis on conformality, there may well be a role for proton beam therapy in some cases.

Synchronous treatment with cisplatin can be considered; an alternative strategy is to use cetuximab.

Other lateral skull base cancer operations

Tumours of the infratemporal fossa are more rare and heterogeneous and thus need an individualised operative approach. Examples include facial translocation, sub-temporal pre-auricular, orbito-zygomatic and trans-TB (Fisch) approaches.[17–20]

Post-operative care issues

In addition to VII nerve issues, all lower cranial nerves essential for swallowing and voice (IX, X, XII) are at risk of injury or sacrifice in surgery for advanced tumours. Care of the patient in this situation must include close involvement of speech and language therapy. Interventions include either pre- or post-operative percutaneous gastrostomy; naso-gastric tube; tracheostomy if aspirating on saliva. Later interventions include vocal cord medialisation and cricopharyngeal myotomy.

Ipsilateral total or total conductive hearing deficit is an inevitable outcome of TB 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 osseointegrated bone anchored hearing aid (BAHA). Total hearing loss can be rehabilitated through either a BAHA or a bilateral contralateral routing of signals (BI-CROS) aid.

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.

Palliative care

The local issues that affect patients when tumours are inoperable or recur are generally pain (particularly through dural involvement) and fungation. Therefore, the instigation of a comprehensive analgesic regimen is required. Fungation can be a particular problem, made worse by the prominent site of the cancer. Radiotherapy can be given for palliative intent, if not already given, and can be useful for both pain and fungation. Short fractionation schedules may well be appropriate in these situations using, for example, 30 Gy in 10 fractions and a single lateral megavoltage photon field. If RT has previously been given and there is a reasonable interval (more than 12 months), then re-irradiation is sometimes beneficial.

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Key points

- Cancer of the lateral skull base is rare and constitutes a heterogeneous group of cancers and sites of origin
- Most cancers are treated with primary surgery and post-operative radiotherapy
- For temporal bone cancers, the boundary of the tympanic membrane is paramount in prognosis. Most T1 and 2, and many T3 cancers are cured
- The minimum operation for a temporal bone cancer should be a lateral temporal bone resection
- Lateral temporal bone resection should be considered in advanced parotid cancers
- Achieving clear microscopic margins at surgery is critical
- Salvage surgery is often not successful: the best, and usually only, chance of cure is at initial surgery
- For patients with advanced cancers, particularly at the petrous apex or with dural or facial nerve involvement, cure rates drop considerably
- For patients with advanced cancers undergoing surgery, there are many rehabilitation issues
- The anterolateral thigh free flap is the workhorse for reconstruction.

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GUIDELINE

Non-melanoma skin cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. This paper provides consensus recommendations on the management of cutaneous basal cell carcinoma and squamous cell carcinoma in the head and neck region on the basis of current evidence.

Recommendations

- Royal College of Pathologists minimum datasets for NMSC should be adhered to in order to improve patient care and help work-force planning in pathology departments. (G)
- Tumour depth is of critical importance in identifying high-risk cutaneous squamous cell carcinoma (cSCC), and should be reported in all cases. (R)
- Appropriate imaging to determine the extent of primary NMSC is indicated when peri-neural involvement or bony invasion is suspected. (R)
- In the clinically N0 neck, radiological imaging is not beneficial, and a policy of watchful waiting and patient education can be adopted. (R)
- Patients with high-risk NMSC should be treated by members of a skin cancer multidisciplinary team (MDT) in secondary care. (G)
- Non-infiltrative basal cell carcinoma (BCC) <2 cm in size should be excised with a margin of 4–5 mm. Smaller margins (2–3 mm) may be taken in sites where reconstructive options are limited, when reconstruction should be delayed. (R)
- Where there is a high risk of recurrence, delayed reconstruction or Mohs micrographic surgery should be used. (R)
- Surgical excision of low-risk cSCC with a margin of 4 mm or greater is the treatment of choice. (R)
- High-risk cSCC should be excised with a margin of 6 mm or greater. (R).
- Mohs micrographic surgery has a role in some high-risk cSCC cases following MDT discussion. (R)
- Delayed reconstruction should be used in high-risk cSCC. (G)
- Intra-operative conventional frozen section in cSCC is not recommended. (G)
- Radiotherapy (RT) is an effective therapy for primary BCC and cSCC. (R)
- Re-excision should be carried out for incompletely excised high-risk BCC or where there is deep margin involvement. (R)
- Incompletely excised high-risk cSCC should be re-excised. (R)
- Further surgery should involve confirmed marginal clearance before reconstruction. (R)
- P+ N0 disease: Resection should include involved parotid tissue, combined with levels I–III neck dissection, to include the external jugular node. (R)
- P+ N+ disease: Resection should include level V if that level is clinically or radiologically involved. (R)
- Adjuvant RT should include level V if not dissected. (R)
- P0 N+ disease: Anterior neck disease should be managed with levels I–IV neck dissection to include the external jugular node. (R)
- P0 N+ posterior echelon nodal disease (i.e. occipital or post-auricular) should undergo dissection of levels II–V, with sparing of level I. (R)
- Consider treatment of the ipsilateral parotid if the primary site is the anterior scalp, temple or forehead. (R)
- All patients should receive education in self-examination and skin cancer prevention measures. (G)
- Patients who have had a single completely excised BCC or low-risk cSCC can be discharged after a single post-operative visit. (G)

- Patients with an excised high-risk cSCC should be reviewed three to six monthly for two years, with further annual review depending upon clinical risk. (G)
- Those with recurrent or multiple BCCs should be offered annual review. (G)

Introduction

The incidence of all types of skin cancer is increasing. The non-melanoma skin cancers (NMSCs) are mostly basal cell carcinoma (BCC), the commonest human cancer in Caucasians, and cutaneous squamous cell carcinoma (cSCC). Over 80 per cent of these tumours occur on the skin of the head and neck. Most NMSC is easily curable. Death is rare; when it occurs, it does so from metastatic cSCC, or from local invasion by neglected BCC or cSCC. The majority of research regarding the management of skin cancer relates to populations of Caucasians in Australia and North America, and different patterns of disease are likely to exist in Europe and the UK. There are no large prospective randomised, controlled trials in which different treatments of NMSC have been compared. Organisation of skin cancer services including the treatment of NMSC within the UK National Health Service is determined by National Institute for Health and Care Excellence (NICE) guidance.[1] This section discusses the management of NMSC, confined to BCC and cSCC of the head and neck. It briefly outlines the management of the primary lesion, and discusses the investigation and treatment of regional metastatic cSCC. Squamous cell carcinoma of the lip is dealt with elsewhere in the guidelines. The reader is advised to access current guidelines referenced in this document for further information on the management of NMSC.[2–6]

Epidemiology and aetiology

The incidence of NMCS is underreported in the UK due to inconsistent data collection. The incidence is known to be rising and is estimated to do so until 2040. Non-melanoma skin cancer is more common in men, and with increasing age. The age shift in the population has resulted in an overall increase in total number of skin cancers.

The major predisposing factor for the development of NMSC is chronic sunshine exposure, particularly in childhood. Other common factors include fair skin, other forms of ionising radiation, immunosuppression, previous skin malignancy and premalignant states, such as multiple actinic keratoses.

Immunosuppressed patients with skin cancers comprise mainly transplant patients and those with chronic haematological malignancies. These patients frequently develop multiple skin cancers, which are often aggressive in nature. Skin cancers comprise 40–50 per cent of post-transplant malignancies. There is an increased risk of skin cancer in patients who are taking anti-tumour necrosis factor drugs. Genetic conditions and exposure to sensitising chemicals are rare causes of NMSC as is the occurrence of cSCC in chronic wounds.

Presentation and diagnosis of NMSC

Basal cell carcinoma

Nodular lesions are the most common form of BCC. Morphoeic BCCs are found almost exclusively on the head and neck, the commonest single site being the nose. Superficial BCCs are predominantly found on the trunk. Nodular BCC may have clinical cystic or pigmented variants. Basal cell carcinoma has a number of well-described histological subtypes.[7]

The 2014 Royal College of Pathology[7] dataset adopts the term 'infiltrative BCC' for all high-risk histological variants and notes that many BCCs contain both high- and low-risk subtypes (Table 1).

Cutaneous squamous cell carcinoma

Cutaneous squamous cell carcinoma typically presents as an indurated nodular keratinising or crusted tumour that may ulcerate, or it may present as an ulcer without evidence of keratinisation. Cutaneous squamous cell carcinoma of the nasal vestibule or of the ear canal is often diagnosed late, with resulting poor prognosis, as it can be misdiagnosed as other common conditions.

Diagnosis

Diagnosis of NMSC is usually clinical, with subsequent histological confirmation following excision. The 'stretch test' has been shown to improve diagnostic accuracy in BCC. Dermoscopy improves initial diagnostic rate in all NMSC and may be of some assistance in determining a BCC sub-type. Pre-excisional tissue diagnosis can be indicated particularly if a graft or flap will be required for reconstruction, or in an anatomically complex area such as the nose. In most circumstances, this is best achieved by punch, incisional or shave biopsy under local anaesthetic. Shave biopsy is undesirable in possible cutaneous melanoma. Exfoliative cytology has a high diagnostic accuracy in NMSC, particularly where the tumour is ulcerated, and can be of use to guide management where surgical biopsy may be difficult, such as in the very elderly. A tissue diagnosis should also be obtained prior to radiotherapy (RT).

TABLE I
THE LOW RISK AND HIGH RISK

Low risk	High risk
1. Nodular 2. Superficial	1. Morphoeic/infiltrative 2. Micronodular 3. Basosquamous

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Recommendation

- **Diagnosis of NMSC is usually clinical. Biopsy (or exfoliative cytology) is recommended where the clinical diagnosis is in doubt, or where histological features may influence treatment, and prior to radiation therapy (G)**

High-risk features of NMSC

Some clinical and histological features are indicative of aggressive tumour behaviour.

High-risk features of BCC for recurrence:

- Tumour size >2 cm
- Tumour site (the central face)
- Poorly defined clinical margins
- High-risk histological sub-type
- Histological features of aggression; peri-neural or peri-vascular involvement
- Failure of previous treatment (the tumour is a recurrence)
- Immunosuppression.

High-risk features of cSCC for recurrence and metastasis:

- Size >2 cm
- Failure of previous treatment
- Immunosuppression
- Depth or invasion >2 mm thickness*
- Clark level >4*
- Peri-neural invasion*
- Primary site ear or hair-bearing lip*
- Poorly differentiated or undifferentiated*.

*Determined as high risk in Tumour–Node–Metastasis (TNM) Classification of Malignant Tumours, 7th Edition.

Of note, tumour depth is highly predictive for metastasis and local recurrence. Cutaneous squamous cell carcinoma less than 2 mm in depth has little or no metastatic potential. In cSCC 2.1–6.0 mm thick, the rate of metastasis is 4 per cent and for thickness greater than 6.0 mm the rate is 16 per cent. Tumours invading the sub-cutaneous fat have metastatic rates up to 46 per cent.

NICE[5] and the Royal College of Pathologists[7] use greater than 4 mm tumour depth or invasion into sub-cutaneous fat as indicators for referral to the MDT. The 7th edition of TNM Classification of Malignant Tumours[8] uses >2 mm tumour depth as a high-risk factor. There is a wide range of malignant behaviour of cSCC; head and neck surgeons are likely to deal with a higher proportion of high-risk tumours.

Recommendations

- **Royal College of Pathologists minimum datasets for NMSC should be adhered to in order to improve patient care and help work-force planning in pathology departments (G)**
- **Tumour depth is of critical importance in identifying high-risk cSCC, and should be reported in all cases (R)**

Staging

The most widely adopted staging system for staging cSCC and BCC is the TNM Classification of Malignant Tumours, 7th Edition (Table II).[8] Skin cancers of the eyelid, and Merkel cell carcinomas are included elsewhere.

Imaging to determine the extent of primary NMSC may be indicated when peri-neural involvement (magnetic resonance imaging) or bony invasion (computed tomography) is suspected. There is no evidence to support cross-sectional imaging in the clinically node negative patient.

In the clinically node positive patient, further assessment and management is as per the guidelines set out elsewhere in these guidelines, with the following additional points for consideration.

- Cross-sectional imaging should include the parotid.
- Clinically enlarged nodes should be examined initially by fine needle aspiration cytology (FNAC), ideally ultrasound guided. This can be repeated if negative, where clinical suspicion remains.
- Removal of a suspicious node for which FNAC has been non-diagnostic can be carried out via a considered incision which can be incorporated into a future neck dissection approach. This will enable accurate staging of a patient prior to therapeutic neck dissection.

TABLE II
T STAGING FOR CSCC AND OTHER CUTANEOUS CARCINOMAS

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T	Is carcinoma *in situ*?
T1	Tumour 20 mm or less in greatest dimension and (with the exception of BCC*) with less than two high-risk features*
T2	Tumour greater than 20 mm in greatest dimension or (with the exception of BCC*) any size and with two or more high-risk features*
T3	Tumour with invasion of maxilla, mandible, orbit or temporal bone
T4	Tumour with invasion of skeleton (axial or appendicular) or peri-neural invasion of skull base

*Rarely applies to BCC and not accordingly included in staging by The Royal College of Pathologists.

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- Sentinel node biopsy for the detection of metastatic disease in high-risk cSCC is only used within clinical trials.[9]

Recommendations

- **Appropriate imaging to determine the extent of primary NMSC is indicated when perineural involvement or bony invasion is suspected (R)**
- **In the clinically N0 neck, radiological imaging is not beneficial, and a policy of watchful waiting and patient education can be adopted (R)**

The role of the multidisciplinary team

The importance of multidisciplinary working relationships in the management of high-risk NMSC is paramount and patients should be treated by members of a skin cancer MDT. Low-risk BCC is treated in some regions by community practitioners as per updated NICE guidance.[5] Lesions above the clavicle are specifically excluded from this group, and these patients should receive treatment in secondary care. Cancer networks should establish two levels of MDTs to care for patients, with high-risk cSCC and BCC being discussed either at a local skin MDT or regional specialist skin cancer MDT. It is recognised that local and specialist MDT referral pathways will vary from region to region.

Patients in the following groups should be discussed at the skin cancer MDT as per NICE and Scottish Intercollegiate Guidelines Network Guidance; input from the head and neck cancer MDT will be appropriate in the following groups:

- All patients with high-risk cSCCs, cSCCs and BCCs that may involve the excision margins or are recurrent.
- Patients suitable for Mohs surgery.
- Skin cancers in patients who are immunocompromised or those with genetic predisposition.
- Patients with metastatic SCC or BCC diagnosed at presentation or on follow-up.
- Patients who may benefit from RT.
- Patients who may be eligible for entry into clinical trials.
- Specific challenging management issues, such as cognitive impairment or medical comorbidities.

Recommendation

- **Patients with high-risk NMSC should be treated by members of a skin cancer MDT in secondary care (G)**

Treatment of the primary lesion

Surgical excision

Basal cell carcinoma. Excision with a predetermined margin is the recommended treatment for the majority of BCCs.[10] Complete excision rates of 85 per cent with a 3 mm clinical margin have been reported and of 95 per cent with a 4–5 mm margin. The stretch test, dermoscopy, loupe magnification and prior curettage, may improve definition of the tumour margin and reduce incomplete excision rates. The deep margin should include fat, but will be determined by tumour extension – it can be clinically assessed at the time of surgery.

Infiltrative and large BCCs have a higher risk of subclinical tumour extension.

In the management of BCCs with a high risk of recurrence, reconstruction should be delayed until histological confirmation of clearance has been confirmed, either by Mohs micrographic surgery (MMS), or until the results of paraffin section are available.

Recommendations

- **Non-infiltrative BCCs <2 cm in size should be excised with a margin of 4–5 mm. Smaller margins (2–3 mm) may be taken in sites where reconstructive options are limited, when reconstruction should be delayed (R)**
- **Where there is a high risk of recurrence, delayed reconstruction[11] or MMS should be used (R)**

Cutaneous squamous cell carcinoma. Surgical excision with a predetermined clinical margin is the recommended treatment for the majority of cSCC. For clinically well-defined, low-risk tumours, a margin of 4 mm will achieve histological clearance in over 95 per cent of cases. In high-risk cSCC, the evidence on peripheral margins required is limited, but at least 6 mm should be included in the resection. The deep margin on the scalp should include the galea at least; the peri-osteum and outer table should be resected if there is clinical or radiological evidence of involvement. Conventional intra-operative frozen section is less accurate than paraffin section and is no longer recommended. The confirmation of histological clearance can be confirmed by awaiting the results of paraffin section, before reconstruction is undertaken. Both excised BCC and cSCC specimens should be marked for orientation in case further resection is required.

Mohs micrographic surgery. Mohs micrographic surgery is a precise technique which combines staged resection with comprehensive histological examination of the surgical margin. It is the treatment of choice in high-risk BCC and not only offers

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superior tumour control (97 per cent five-year cure rates), but better cosmetic outcomes as tissue removal is minimised. Mohs micrographic surgery is used less often for high-risk SCC due to concerns about the possible presence of in transit metastases and skip lesions, and the more challenging histological margin interpretation (permanent sections are more accurate than frozen sections). Disadvantages of MMS include the length of the procedure (which is carried out under local anaesthetic), the need for special equipment and training and the relatively high cost. The availability of the procedure in the UK is at present limited.

Recommendations

- **Surgical excision of low-risk cSCC with a margin of 4 mm or greater is the treatment of choice (R)**
- **High-risk cSCC should be excised with a margin of 6 mm or greater (R)**
- **Mohs micrographic surgery has a role in some high-risk cSCC cases following MDT discussion (R)**
- **Delayed reconstruction should be used in high-risk cSCC (G)**
- **Intra-operative conventional frozen section in cSCC is not recommended (G)**

Destructive techniques

Curettage and cautery. This can be used by experienced practitioners for small (<4 mm), well-defined BCC with non-aggressive histology in non-critical sites with a five-year cure rate of up to 97 per cent. Curettage and cautery is used in some centres to treat small (<1 cm) low-risk cSCCs with excellent cure rates, but histological clearance cannot be confirmed. Its use should be confined to experienced practitioners in the technique, employing careful case selection criteria. Curettage and cautery is not indicated in recurrent or high-risk NMSC.

Cryosurgery. Cryosurgery is used in low-risk BCC. Disadvantages include scarring, difficulty in assessing recurrence and lack of tissue diagnosis or proof of tumour clearance. Good short-term cure rates have been reported for small histologically confirmed cSCC treated by cryosurgery in experienced hands. Prior biopsy is necessary to establish the diagnosis histologically. For this reason, caution should be exercised in the use of cryotherapy for cSCC although it may be an appropriate technique for selected cases especially in very elderly patients and in specialised centres. Cryosurgery is not appropriate for locally recurrent disease or high-risk tumours.

Photodynamic therapy. This therapy is effective in low-risk superficial BCC, but with lower oncologic efficacy than surgery in nodular BCC. It is not recommended for other BCC sub-types or for cSCC.

Topical 5 per cent imiquimod. This is an immune response modifier which is licensed for and effective in the treatment of small primary superficial BCC.

Vismodegib. This drug is licensed for locally advanced or metastatic BCC not suitable for surgery or RT. This new drug is an antagonist for the smoothened G-protein-coupled receptor molecule, and thus inhibits the aberrant signalling pathway involving Hedgehog (Hh) genes. Early trials show efficacy in 50 per cent of BCCs with mean duration of response around nine months. It is a suitable treatment in recurrent, inoperable BCCs post-RT or in patients with Gorlin's syndrome, and in the very rare occurrence of metastatic BCC.

Radiotherapy in primary NMSC

Radiotherapy is an alternative to surgery for primary BCC and cSCC of the head and neck region in the following scenarios:

- Elderly or frail patients
- Anatomical sites where RT is likely to lead to a superior cosmetic or functional outcome
- Surgery is contraindicated
- Patient choice.

At most head and neck sites, cosmetic outcomes and cure rates with RT are inferior to excisional surgery.

Radiotherapy is normally not used in the following circumstances:

- Patient age over 50 years, due to the risk of second malignancies and inferior cosmetic outcome
- Sites of previous RT
- Cartilage or bone involvement due to risk of radionecrosis
- Over the lateral half of the upper eyelid due to risk of lacrimal gland damage.

Basal cell carcinoma and cSCC are usually treated with low-energy (KV) X-rays, but may be treated with electrons. Alternatively, high-energy (MV) X-rays may be used in the presence of deep extension or tumour fixation. Common fractionation schedules range from five fractions in one week for lesions greater than 2–3 cm; to 9–10 fractions in two to three weeks for intermediate size; and 20–30 fractions over four to six weeks for very large (>6 cm) lesions or where regional lymph node irradiation is also required. The dose is usually higher and a larger margin included in the treatment field when treating cSCC than BCC.[12,13]

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Recommendation

- **Radiotherapy is an effective treatment for primary BCC and cSCC (R)**

Incomplete margins of excision

Incomplete excision of BCC can occur in the setting of high-risk tumour factors, low operator expertise and when multiple tumours are removed at the same procedure. Incompletely excised NMSC should be discussed at the MDT, as should those with a margin of excision less than 1 mm. Options for management include observation (many low-risk tumours will not recur), re-excision (by standard surgery or with marginal control) and adjuvant treatment (radiation therapy or topical therapy)

British Association of Dermatology recommendations for consideration of re-excision of transected BCC include:

- Anatomically critical site
- Infiltrative histology
- Deep margin involvement
- Flap or graft reconstruction.

Incompletely excised high-risk cSCC should be re-excised to reduce the risk of recurrence and metastasis. In closely excised high-risk cSCC, re-excision or the use of adjuvant RT should be discussed at the MDT and may be influenced by local anatomy, and reconstructive factors. Where further treatment of NMSC is indicated and re-excision is not possible, adjuvant RT is indicated to decrease recurrence rates.[14,15]

If a margin is involved by superficial BCC only, topical imiquimod may be indicated.

Recommendations

- **Re-excision should be carried out for incompletely excised high-risk BCC or where there is deep margin involvement (R)**
- **Incompletely excised high-risk cSCC should be re-excised (R)**
- **Further surgery should involve confirmed marginal clearance before reconstruction (R)**

Management of regional metastatic CSCC

Patterns of metastasis

The overall regional metastatic rate of cSCC in a UK population has been reported at around 5 per cent.[16] These rates can be higher in the presence of adverse histological features; for instance, 33 and 47 per cent for poor differentiation or peri-neural infiltration, respectively. Tumour thickness is strongly correlated with risk of nodal metastasis. The presence of metastatic nodal disease is associated with a five-year survival of 35 per cent.

Lymph node metastases of NMSC of the head and neck are known to follow different pathways to the classically understood patterns of mucosal malignancies of the upper aerodigestive tract (Figure 1). The parotid nodes and the superficial lymphatic system need to be addressed, in contrast to mucosal head and neck mucosal malignancies. Sentinel node biopsy studies have shown a high lack of concordance between the primary skin site and the first echelon node. The external jugular node is of particular relevance as it is not included in standard neck dissections for head and neck squamous cell carcinoma.

Over 50 per cent of cSCC occurs on the anterior scalp and forehead and the ears, and the parotid is the site for up to 70 per cent of metastasing cSCC. Where the parotid is involved (P+), there is an increased chance of the neck containing occult and overt metastases (10–35 per cent). In the P+N+ scenario, the incidence of metastases in level V approaches 30 per cent.

N+ P0 disease is seen where the primary site was the face or upper neck or posterior scalp. The posterior scalp is the site for 5 per cent of cSCC, and tumours here will metastasise initially commonly to post-auricular, occipital or level V nodes.[17,18] Resection of

FIG. 1
Patterns of metastasis of cSCC to the external jugular node and the superficial lymphatics.

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structures such as the facial nerve, the internal jugular vein, the accessory nerve and the sternocleidomastoid muscle are required in a nodal dissection in the presence of invasion by the malignant process.

Management of nodal involvement

Surgery is the primary mode of treatment for established nodal involvement and adjuvant RT may improve survival in high-risk cases. The dissection employed should include established nodal involvement and extend to those levels where there is a high risk of occult disease. In most cases, parotid surgery will involve a superficial parotidectomy; deep lobe or facial nerve involvement will require more extensive resection.

Recommendations

- **P+ N0 disease:**
  Resection should include involved parotid tissue, combined with levels I–III neck dissection, to include the external jugular node (R)
- **P+ N+ disease:**
  Resection should include level V if that level is clinically or radiologically involved (R)
  Adjuvant RT should include level V if not dissected (R)
- **P0 N+ disease:**
  Anterior neck disease should be managed with a levels I–IV neck dissection to include the external jugular node (R)
  P0 N+ Posterior echelon nodal disease (i.e. occipital or post-auricular) should undergo dissection of levels II–V, with sparing of level I (R)
  Consider treatment of the ipsilateral parotid, if the primary site is the anterior scalp, temple or forehead (R)

Role of RT in P+ and/or N+ disease

Retrospective studies suggest that locoregional control and survival are improved by adjuvant RT in cases of cSCC where neck involvement is staged greater than N1, or where there is extracapsular spread. Of note, ECS is seen in up to 70 per cent of head and neck cSCC nodal dissection, and therefore consideration can be given to more selectivity in nodal dissection, as post-operative RT will be indicated for the majority of patients.[19]

Follow-up

Follow-up in secondary care may detect local recurrence, regional metastasis and new skin cancers at an earlier stage. Of note, the risk of a second BCC is 44 per cent, and up to 50 per cent of Australian cSCC patients develop a second cSCC within two years. Minimisation of immunosuppression in an organ transplant patient with multiple or recurrent high-risk cSCC should be considered by the MDT in conjunction with the patient's relevant physician. Oral retinoids can be used for secondary prevention skin cancers in the immunosuppressed.

Recommendations

- **All patients should receive education in self-examination and skin cancer prevention measures (G)**
- **Patients who have had a single completely excised BCC or low-risk cSCC can be discharged after a single post-operative visit (G)**
- **Patients with an excised high-risk cSCC should be reviewed three to six monthly for two years, with further annual review depending upon clinical risk (G)**
- **Those with recurrent or multiple BCCs should be offered annual review (G)**

Key points

- Diagnosis of NMSC is usually clinical.
- Excisional surgery with predetermined margins is the treatment of choice for the majority of cases.
- Imaging is recommended in large primary tumours, but does not have a role where the regional nodes are clinically N0.
- Reconstruction should be delayed in high risk NMSC.

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GUIDELINE

Head and neck melanoma (excluding ocular melanoma): United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the United Kingdom. This paper provides consensus recommendations on the management of melanomas arising in the skin and mucosa of the head and neck region on the basis of current evidence.

Recommendations

- At-risk individuals should be warned about the correlation between ultraviolet radiation (UVR) exposure and skin cancer, and should be given advice on UVR protection. (R)
- Dermatoscopy can aid in the diagnosis of cutaneous melanoma. (R)
- Histological examination after biopsy is essential to confirm the diagnosis and the tumour thickness. (G)
- Excisional biopsy is method of choice. (G)
- Staging investigations can be performed for both regional and distant disease. (R)
- Scanning (computed tomography (CT) and/or magnetic resonance imaging) is recommended for patients with high-risk melanoma. (G)
- Patients with signs or symptoms of disease relapse should be investigated by imaging. (R)
- Imaging of the brain should be performed in patients who have stage IV disease. (G)
- Patients with melanoma of unknown primary should be thoroughly examined and investigated for a potential primary source. (R)
- Primary cutaneous invasive melanoma should be excised with a surgical margin of at least 1 cm. (G)
- The maximum recommended excision margin is 3 cm. (R)
- The actual margin of excision depends upon the depth of the melanoma and its anatomical site. (G)
- Ultrasound-guided fine needle aspiration (FNA) or core biopsy of suspected lymphadenopathy is more accurate than 'blind' biopsy. (R)
- Open biopsy should only be performed if FNA or core biopsy is inadequate or equivocal. (R)
- Prior to lymph node dissection, staging by CT scan should be carried out. (R)
- If parotid disease is present without neck involvement, both parotidectomy and neck dissection should ideally be performed. (R)
- There is no role for elective lymph node dissection. (R)
- Sentinel lymph node biopsy (SLNB) can be considered in stage IB and above by specialist skin cancer multidisciplinary teams. (G)
- Patients should be made aware that SLNB is a staging procedure, and should understand that it has, as yet, no proven therapeutic value. (R)
- All patients with cutaneous melanoma should have their original tumour checked for BRAF gene status, and their subsequent targeted biological therapy based on this. (R)
- Patients who develop brain metastases should be considered for stereotactic radio-surgery. (R)

Cutaneous melanoma of the head and neck

Introduction

Cutaneous melanoma, also known as cutaneous malignant melanoma, is a malignant tumour of neural crest-derived cutaneous melanocytes. The incidence of melanoma has been increasing rapidly for the last few decades in most parts of the world. It is the fifth commonest cancer in the UK, with a male:female ratio of 10:11. The number of melanoma cases doubled in this country over the three decades following 1970. Over that same period the prognosis dramatically improved. This improvement is mostly attributable to a higher proportion of thinner tumours as a result of earlier diagnosis, and reflects the

considerable effort expended in raising public and professional awareness over that period. Although melanoma is the major cause of skin cancer mortality, it is usually curable if treated at an early stage. Melanoma in its advanced stages remains largely resistant to currently available treatments, although in the last five years, new targeted biological agents and immunotherapies have offered the potential for improved survival.

Aetiology and risk factors

Melanomas can arise in pre-existing naevi, or *de novo* in normal skin. Like most tumours, the aetiology of melanoma is complex and not fully understood. It is, however, thought to be caused by ultraviolet radiation (UVR) in susceptible individuals. It is estimated that around 86 per cent of melanomas in the UK in 2010 were linked to exposure to UVR from the sun and sun-beds.[1] Fair-skinned individuals who burn easily in the sun, have fair or red hair, and have a tendency to freckle are about three times more likely to develop melanoma. A number of case–control studies conclude that intense burning sun exposure of unacclimatised white skin is a major risk factor for cutaneous melanoma. Migration studies show that exposure to intense UVR at a young age may be particularly important. This is in contradistinction to squamous cell and basal cell carcinomas, which are associated with chronic, long-term sun exposure. Patients with xeroderma pigmentosum have a significantly higher risk of all types of skin cancer, including melanoma, as a result of inability to repair the DNA damage induced by UVR.

Recommendation

- **At-risk individuals should be warned about the correlation between UVR exposure and skin cancer, and should be given advice on UVR protection (R)**

While it is understood that melanoma is related to UVR exposure, it is not clear why the body site distribution of melanoma is different to other sun-related cancers such as cutaneous squamous cell carcinoma. This suggests that the pattern of UVR exposure is important, with sites that are intermittently exposed being more at risk than continually exposed sites. The gaps in our knowledge of the aetiology have recently been critically evaluated.

Other risk factors include a large number of banal naevi, a tendency to freckle, and more atypical or dysplastic naevi.[2] About 2 per cent of melanoma patients have a positive family history in one or more first degree relatives. The major melanoma susceptibility gene identified to date is CDKN2A gene. Mutations in this gene are found in 10–30 per cent of melanoma patients with a positive family history. Melanoma is more prevalent in those of high socio-economic status, but the converse applies to mortality.

Clinical presentation

Cutaneous melanoma is divided into subtypes on the basis of clinical features and pathology.

Superficial spreading melanoma (SSM). This is the most frequently encountered type of melanoma; characteristically an asymmetrical pigmented lesion with irregular borders, irregular pigmentation and sometimes an irregular outline. Patients may have noted growth, a change in sensation and/or colour, crusting, bleeding or inflammation of the lesion. The duration of the symptoms varies from a few months to several years.

Nodular melanoma (NM). The second most common type of melanoma is NM. This usually has a shorter presentation and a greater tendency to bleed and/or ulcerate.

Lentigo maligna melanoma (LMM). The next in frequency is the type that occurs most often in sun-damaged skin on the head and neck of older patients. This is the only variety that has a clearly recognised and often lengthy pre-invasive (*in situ*) lesion termed lentigo maligna (LM) before progressing in some instances to an invasive melanoma (LMM).

Acral lentiginous melanoma (ALM). The least common type of melanoma in the UK is the ALM. This occurs on sites, including the palms, soles and beneath the nails. It is the most common melanoma found in African and Asian populations.

Desmoplastic neurotropic melanoma. This type is associated with higher local recurrence than other forms of melanoma. This is thought to be a consequence of its propensity for peri-neural spread. Desmoplastic neurotropic melanoma is predominantly found in the head and neck.

Assessment and staging

Suspicious pigmented lesions are best examined in a good light with or without magnification and should be assessed using the seven-point checklist[3] (Table I) or ABCDE systems (Table II). The presence of any major feature in the seven-point checklist, or any of the features in the ABCDE system, is an indication for referral. The presence of minor features should

TABLE I
SEVEN POINT CHECKLIST FOR PIGMENTED SKIN LESIONS

Major features	Minor features
Change in size of lesion	Inflammation
Irregular pigmentation	Itch/altered sensation
Irregular border	Lesion larger than others
	Oozing/crusting of lesion

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TABLE II
THE ABCDE CHECKLIST FOR PIGMENTED SKIN LESIONS

A	Geometrical **A**symmetry in two axes
B	Irregular **B**order
C	At least two different **C**olours in lesion
D	Maximum **D**iameter >6 mm
E	**E**levation of lesion

increase suspicion. Some melanomas will have no major features.

Clinical diagnosis of melanoma can be difficult and the accuracy of diagnosis varies according to a clinician's level of experience, with reports of variation in sensitivity from 50 to 86 per cent. High magnification dermatoscopy is more sensitive than non-dermatoscopic diagnosis, when used by those trained and experienced in the technique.[4] Hand-held (lower magnification) dermatoscopy improves diagnostic accuracy in those trained to be 'expert', but it may decrease diagnostic sensitivity of 'non-expert' or untrained dermatologists.

Diagnostic biopsy. The thickness of cutaneous melanoma greatly influences both its treatment and its prognosis. It is essential, therefore, to obtain a full-thickness biopsy of suspected lesions. Excisional biopsy is the preferred technique, and is aimed at excising the lesion with a 2–5 mm peripheral margin, including a cut-off of subdermal fat. This allows accurate assessment of the tumour thickness and depth of penetration, without transgressing tumour boundaries. Excisional biopsy may not be practical when the lesion is large or located near structures such as an eyelid or lip. Punch biopsy is an alternative where excision biopsy could lead to significant disfigurement. A punch biopsy is usually performed with a 2–4 mm biopsy punch at the thickest or highest part of the lesion. Incisional biopsy is not usually recommended, but the indications are the same as those for punch biopsy. Again, it should be performed at the thickest or highest part of the lesion and must reach the full depth of the lesion

Recommendations

- **Dermatoscopy can aid in the diagnosis of cutaneous melanoma (R)**
- **Histological examination after biopsy is essential to confirm the diagnosis and the tumour thickness (G)**
- **Excisional biopsy is method of choice (G)**

Staging. The latest revisions to the staging of cutaneous melanoma were published in the 7th Edition of the American Joint Committee on Cancer (AJCC) in 2009 (Table III).[5] Of note, primary tumour mitotic rate (mitoses/mm^2) is now considered an important independent prognostic indicator, with an inverse correlation between mitotic rate and survival. The mitotic rate replaces Clark's level of invasion as a primary criterion for separating T1 tumours into T1a and T1b.

TABLE III
TNM STAGING SYSTEM FOR CUTANEOUS MELANOMA

T classification	Thickness	Ulceration status/ mitoses
Tis	N/A	N/A
T1	≤1.0 mm	a: w/o ulceration and mitoses <1/mm^2 b: with ulceration or mitoses ≥1/mm^2
T2	1.01–2.0 mm	a: w/o ulceration b: with ulceration
T3	2.01–4.0 mm	a: w/o ulceration b: with ulceration
T4	>4.0 mm	a: w/o ulceration b: with ulceration
N classification	No of metastatic nodes	Nodal metastatic mass
N0	0 nodes	N/A
N1	One node	a: micrometastasis* b: macrometastasis†
N2	Two to three nodes	a: micrometastasis* b: macrometastasis† c: in-transit met(s)/ satellite(s) without metastatic nodes
N3	Four or more metastatic nodes, or matted nodes, or in-transit met(s)/ satellite(s) with metastatic node(s)	
M classification	Site	Serum lactate dehydrogenase (LDH)
M0	0 sites	N/A
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastases	Elevated

* Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed)
† Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension

Anatomical staging

Imaging considerations. Staging investigations for regional lymph node metastases are often performed, and may comprise computed tomography (CT), magnetic resonance imaging (MRI), and/or ultrasound, depending upon local protocols. The use of scans to detect distant metastasis is indicated in patients with high-risk melanoma (stages IIC, IIIB, IIIC and stage IIIA with a macroscopic sentinel lymph node), and in patients with new

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TABLE IV
CLINICAL AND PATHOLOGICAL STAGING FOR CUTANEOUS MELANOMAS

Clinical staging*				Pathological staging†			
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T1–4a	N1a	M0
					T1–4a	N2a	M0
				IIIB	T1–4b	N1a	M0
					T1–4b	N2a	M0
					T1–4b	N1b	M0
					T1–4b	N2b	M0
					T1–4b	N2c	M0
				IIIC	T1–4b	N1b	M0
					T1–4b	N2b	M0
					T1–4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

* Clinical staging includes microstaging of the primary melanoma and clinical and/or radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases
† Pathological staging includes microstaging of the primary melanoma and pathological information about the regional lymph nodes after partial or complete lymphadenectomy. Pathological stage 0 or IA patients are the exception; they do not require pathological evaluation of their lymph nodes

symptoms, anaemia, elevated lactate dehydrogenase or a chest X-ray abnormality. Computed tomography scanning is used for the evaluation of potential metastatic sites in the lungs, bones, liver and lymph nodes. Imaging of the brain is recommended in patients with stage IV, but is optional in stage III disease. Positron emission tomography (PET)-CT is more accurate than CT or MRI alone in the diagnosis of metastases. It should complement conventional CT and MRI imaging in patients who have distant metastases and where surgical resection is being considered.

Recommendations

- **Staging investigations can be performed for both regional and distant disease (R)**
- **Scanning (CT and/or MRI) is recommended for patients with high-risk melanoma (G)**
- **Patients with signs or symptoms of disease relapse should be investigated by imaging (R)**
- **Imaging of the brain should be performed in patients who have stage IV disease (G)**

Unknown primary. The patient presenting with regional or visceral metastatic melanoma of unknown primary (MUP) origin should be seen by a dermatologist for a skin examination, an ophthalmologist for examination of the eye, and a head and neck surgeon for visualisation of the upper aerodigestive tract. Staging investigations should be carried out, including PET-CT to detect occult metastases. In 10–20 per cent of patients with regional or visceral melanoma metastases, the primary melanoma is never found. Such patients should be treated as if they have regional or visceral metastases from a known primary melanoma.[6] It has been suggested that the most likely explanation for MUP is immune-induced regression of the primary tumour, and this may be the reason for the slightly better outcomes in such patients.

Recommendation

- **Patients with a melanoma of unknown primary origin should be thoroughly examined and investigated for a potential primary source (R)**

Management

Surgery for primary disease

Wide local excision. This remains the most effective treatment for primary cutaneous melanoma.[2,7] The optimal width of excision margins has been contentious.[8,9] Current treatment guidelines are based on a relatively small number of prospective randomised trials.[10–12] The current recommended excision margins for cutaneous melanoma in the UK are as follows:

- In situ melanoma (LM): 5 mm peripheral margins
- Lesions <1 mm thick: 1 cm excision margins
- Lesions 1–2 mm thick: 1–2 cm excision margins
- Lesions 2.1–4 mm thick: 2–3 cm margins (2 cm preferred)
- Lesions thicker than 4 mm: 2–3 cm margins.

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It should be stressed that these recommendations are for cutaneous melanomas in all body sites; in the head and neck region, anatomical restrictions and cosmetic considerations may preclude even a 1 cm margin. In these circumstances, however, the width of excision should remain uniform. For example, if a clear margin of only 8 mm is possible near to an eyelid or an ear, the rest of the peripheral surgical margins should also be 8 mm.

Recommendations

- **Primary cutaneous invasive melanoma should be excised with a surgical margin of at least 1 cm (G)**
- **The maximum recommended excision margin is 3 cm (R)**
- **The actual margin of excision depends upon the depth of the melanoma and its anatomical site (G)**

Mohs micrographic surgery (MMS). Mohs micrographic surgery may have a role in the primary treatment of cutaneous melanoma of the head and neck, especially that of the face.[13] There is growing evidence of the efficacy of MMS in comparison to traditional surgery but the majority of reports compare MMS with historical controls. Further study, in the form of prospective comparative trials, is required before firm recommendations can be made regarding the use of MMS.

Reconstruction. When possible, the surgical defect after wide local excision should be closed primarily. If primary closure is not possible, reconstruction by local flaps or skin grafts will be required. Local flaps are the preferred option when the surgical defect is on the face, because of a superior aesthetic outcome. Rarely, distant flaps will be required for complex or very large surgical defects. If there is any doubt as to the adequacy of surgical clearance, definitive reconstruction should be delayed pending histological confirmation.

Surgery for regional disease

The regional lymph node basin in head and neck cutaneous melanoma comprises the nodes found in the parotid gland (superficial portion), neck levels I–V, the occipital nodes, mastoid nodes and pre-auricular nodes. There may be clinically apparent lymphadenopathy, representing metastatic melanoma, or occult metastases in the head and neck nodes.

Clinical lymphadenopathy. When patients present with a neck mass or a radiologically identified suspicious node(s) a tissue diagnosis should be obtained. The preferred stepwise diagnostic algorithm to follow is: (1) palpable lymph node in the neck or radiologically identified suspicious node; (2) ultrasound-guided or clinically-guided FNA; (3) ultrasound-guided core biopsy; (4) open biopsy.

Fine needle aspiration is more accurate when performed with ultrasound guidance, and this should be subsequently performed if a clinically guided FNA is non-diagnostic. If an open biopsy is performed, the incision should be placed in a manner which permits subsequent excision of the biopsy tract if a neck dissection is necessary. If metastatic melanoma is confirmed, lymphadenectomy of the involved nodal basin should be performed.

The extent of lymphadenectomy performed for melanoma is determined by the location of the primary, the location of the neck disease, and the general fitness of the patient. If parotid lymphadenopathy is present, a neck dissection should also be performed as a high proportion of patients with parotid lymph node involvement will have occult cervical metastases. If neck disease is present without parotid involvement then the location of the primary should be considered. If the draining basin of that primary site is likely to pass through the parotid gland, a concomitant superficial parotidectomy should be considered. It is reasonable to perform a selective neck dissection for some melanoma sites that have metastasised to the neck when there is low volume, mobile lymphadenopathy. For example, omitting excision of level IA and IB neck nodes for a well-lateralised occipital melanoma would be accepted management.

Recommendations

- **Ultrasound-guided FNA or core biopsy of suspected lymphadenopathy is more accurate than 'blind' biopsy (R)**
- **Open biopsy should only be performed if FNA or core biopsy is inadequate or equivocal (R)**
- **Prior to lymph node dissection, staging by CT scan should be carried out (R)**
- **If parotid disease is present without neck involvement, both parotidectomy and neck dissection should ideally be performed (R)**
- **If neck disease is present without parotid involvement, parotidectomy should be considered if the lymphatic drainage of the primary site is likely to have passed through the parotid gland (R)**

Occult lymph nodal disease. The most accurate means of staging the regional lymph nodes in head and neck melanoma is by sentinel lymph node biopsy (SLNB). This staging tool has a learning curve and involves the administration of a radiocolloid into the site of the excision biopsy. Pre-operative lymphoscintigraphy identifies the approximate location of the sentinel nodes and the intra-operative use of blue dye and a gamma probe

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aids in location of the sentinel node(s). The removed sentinel nodes are histologically examined with multiple sections and immunohistochemical stains for the presence of occult metastases. Sentinel lymph node biopsy identification of regional lymph node metastasis should be followed by lymphadenectomy of the at-risk nodal basin.

Whether or not SLNB is performed for staging the regional lymph nodes is a matter for local policy. Sentinel lymph node biopsy provides highly accurate staging information but there is controversy as to whether or not it improves disease-specific survival. The long-term results of the Multicentre Selective Lymphadenectomy Trial-I (MSLT-I) indicate that SLNB is associated with improved disease-free survival for patients with intermediate thickness (1.2–3.5 mm) and thick (≥3.5 mm) melanomas,[14] but this has been questioned in a recent editorial in the *British Medical Journal*.[15] Furthermore, there is the question of biological false-positivity.[16] Some clinical trials require information on disease stage and an SLNB can provide this information. Sentinel lymph node biopsy has replaced elective lymph node dissection in melanoma and there are few indications to perform the latter.

The Options Grid Collaborative, based at Dartmouth University, is an organisation which attempts to improve shared decision-making between healthcare professionals and patients, their carers and families. They produced, in collaboration with the National Institute for Health and Care Excellence, three tools to try and help patients with practical decision-making in managing melanoma. These can be found at http://optiongrid.org

Recommendations

- **There is no role for elective lymph node dissection (R)**
- **Sentinel lymph node biopsy can be considered in stage IB and above by specialist skin cancer multidisciplinary teams (G)**
- **Patients should be made aware that sentinel lymph node biopsy is a staging procedure, and should understand that it has, as yet, no proven therapeutic value (R)**

Metastatic disease. Distant melanoma metastases occur preferentially and earliest in intra-abdominal organs, liver, lung, brain and bone. Whilst these are the commonest sites, metastases to almost every organ and tissue have been reported.

Distant metastases can be divided into two groups: metastases already established at presentation of the primary (stage IV disease) and metastases that subsequently become apparent. Metastases at presentation carry the worst prognosis, while for delayed metastases the prognosis improves in direct proportion to the time taken for the metastasis to develop. In practice the questions to be addressed are what, if any, improvement in survival time may be gained from treatment of metastatic disease and what symptomatic improvement will occur?

Treating metastases in patients with distant metastases confirmed at presentation (stage 4 disease) has proved very disappointing. Survival rates in such individuals have not improved over the last two decades.

Resection of late-appearing metastases to non-liver intra-abdominal organs or gastro-intestinal mucosa yields the best improvement with a disease-free survival in the region of 23 months compared with a median survival of only 12 months if untreated.[17] Patients undergoing surgical resection of late-appearing metastatic melanoma to the liver also have improved disease-free survival compared with untreated patients.[18,19]

Surgical resection of pulmonary metastases and solitary brain metastases from melanoma may yield a survival advantage of a few months more than any other method of dealing with these lesions. Stereotactic radiosurgery (SRS) for brain metastases also offers some patients extended survival. Early treatment of spinal cord secondaries can preserve mobility. Bone metastases are associated with short survival irrespective of treatment.

Biological markers have been studied extensively in metastatic melanoma with regard to prognosis and as a guide to resectability of metastases. Of these, lactate dehydrogenase (LDH) and the c-kit mutation may be helpful. A high serum LDH level suggests a large disease burden and a poor result from treatment of metastases.

Aggressive surgical treatment of distant metastases from melanoma at any site must be carried out on highly selected patients and, even then, it is best regarded as a palliative procedure, usually improving survival by only a matter of months. Nevertheless, quite long remissions may be obtained in fit patients with apparently solitary, or oligometastatic, disease.

Non-surgical treatment

Primary tumour. There is no established role for primary radiotherapy (RT) (instead of surgery) in the management of early stage (stages Ia, b and IIa, b, c) malignant melanoma, other than in elderly patients with extensive facial LMM. It is unlikely that this situation will change in the foreseeable future. Similarly, chemotherapy, biological agents and immunotherapy have no proven place in the management of early stage melanoma.[20]

Regional disease. In patients with stage III (nodal) or IV (M1) disease, the prognosis is significantly worse. Surgery remains the key initial treatment with the goal of securing local control, even in the setting of metastatic disease. There is no established role for RT

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in the management of patients with micrometastatic nodal disease (N1a, N2a). These patients are treated with surgery alone (±entry into studies of adjuvant systemic therapies). Recent adjuvant trials in malignant melanoma have included those testing immunotherapies (interferon, interleukin-2, peptide gp100:209–217(210 M), Canvaxin™) and anti-angiogenic agents, such as bevacizumab (Avastin).[20] For patients with macrometastatic nodal disease (N1b, N2b), there is no consensus that RT is beneficial following surgery, but for patients with cervical lymph node disease it is frequently used. There is no currently defined role for chemoradiation in this setting. The findings of the Phase III TROG 02.01 trial suggest that entry to an adjuvant systemic therapy trial may be a preferable alternative to adjuvant RT.[21]

Distant metastases. Patients with established metastatic melanoma are treated with palliative intent and should be referred to specialist melanoma units.

The chemotherapy management options for metastatic melanoma have greatly expanded in the last five years with the introduction of biologically targeted agents.[22] About 50 per cent of melanomas show a mutation in the BRAF gene, with valine substituted for glutamate at codon 600, and this mutation is known as V600E or V600K. If this mutation is present then patients will have a 60–70 per cent chance of responding to a BRAF inhibitor drug such as vemurafenib[23] or dabrafenib. Those patients who develop the most slowly but continued response to these BRAF inhibitors appear to achieve a more sustained response when compared with those patients who develop a very rapid tumour clearance. One potential sideeffect of these drugs, which must be monitored, is the development of squamous cell carcinoma of the skin.

The second major advance in the management of metastatic melanoma was the introduction of immunotherapy. Ipilimumab is a monoclonal antibody which targets cytotoxic T lymphocyte-associated protein 4 (CTLA-4) which is a protein receptor which can be made to switch off cytotoxic T lymphocytes (CTLs) by melanoma cells. Ipilimumab removes this brake on the immune response and allows the CTLs to recognise and destroy melanoma cells. This agent's efficacy does not depend on the patient's BRAF status. Although the response rate is only 15–20 per cent, in those patients who do show a response this can be sustained for some considerable time. There are hopes that some patients may have even been cured but follow-up has generally not been long enough to establish this.

There is much interest in metastatic melanoma at present, with numerous trials underway, especially in combining targeted therapies where by blocking two different steps in the same pathway a much greater melanoma cell kill may result. Another drug which blocks a specific pathway target is trametinib which is a MEK inhibitor. When combined with dabrafenib, there is both a progression free survival benefit and an overall survival benefit. Another MEK inhibitor cobimetinib, shows benefit when given with vemurafenib, when compared with giving vemurafenib alone.

Nivolamab is also a novel agent. It is a programmed death 1 (PD-1) checkpoint inhibitor which also shows complimentary benefit in metastatic melanoma when given together with ipilimumab, compared with each drug alone and this is now proposed as a standard of care in those patients who have wild-type BRAF, i.e. not showing a BRAF mutation. If this regimen does become standard of care it may not remain so for very long as the field is advancing so quickly.

For patients who become refractory to ipilimumab, and to the BRAF and MEK inhibitors there is a further new agent pembrolizumab, which targets the PD-1 receptor, and can extend progression-free survival.

Palliative RT is often used in metastatic disease (stages IV, M1a–c). Radiotherapy dose fractionation is non-standard in most of these treatments. Commonly used regimens include 8 Gy single fraction, 20 Gy in five fractions, 30 Gy in six fractions (alternate days), the latter fractionation being used most commonly for all brain RT for brain metastasis, and a host of local variations in different RT departments. There is no accepted role for the use of concomitant chemotherapy (although temozolomide has been tested with RT in cerebral metastases). There is emerging evidence that SRS can be beneficial in those patients who have a small number of brain metastases, usually less than three, where very focused high-dose RT can be given to the metastases, with very little dose to the surrounding brain.

Recommendations

- **All patients with cutaneous melanoma should have their original tumour checked for BRAF status, and their subsequent targeted biological therapy based on this (R)**
- **Patients who develop brain metastases should be considered for stereotactic radiosurgery (R)**

Mucosal melanoma (upper aerodigestive tract)

Introduction

Mucosal melanoma of the upper aerodigestive tract is a rare malignancy with a poor prognosis. Management recommendations are based upon retrospective case series, few of which exceed 100 patients. Mucosal melanoma accounts for less than 1 per cent of all melanomas, and less than 10 per cent of all head and neck melanomas. The median age of patient presentation is the sixth decade, but case reports span the age range.

The function of melanocytes in mucosa is uncertain. The most common sites of head and neck mucosal melanoma are the nasal and oral cavities. Pharyngeal,

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laryngeal and oesophageal melanomas are exceedingly rare. Melanocytes in the nasal cavity can be found in the respiratory epithelium, nasal glands, nasal septum, and the middle and inferior turbinates. In oral mucosa, melanocytes are located along the tips and peripheries of the rete pegs. Unlike cutaneous melanoma, no risk factors for the development of this disease have been identified, though cigarette smoke and other air pollutants may play a role. It is thought that a preceding atypical melanocytic hyperplasia occurs in a significant proportion.

Clinical presentation

Sinonasal melanoma presents in the same way as other sinonasal malignancies and is primarily influenced by site of origin. Nasal obstruction, followed by discharge and bleeding, predominates. The commonest site is the anterior portion of the nasal septum. Oral mucosal melanoma most often presents as a painless mass, which may or may not be pigmented. Ulceration and bleeding are also common. The majority occur on the alveolar gingiva and palate.

Assessment and staging

Endoscopic assessment and imaging, as appropriate to the primary site, is necessary, following which staging is performed (Table V).

Management

The prevailing opinion is that localised disease is best managed with primary surgery which aims to achieve clear surgical margins.[9] Craniofacial resection for skull base extension from sinonasal melanoma is associated with poor survival and is seldom justified. Radical surgical excision involving severe functional deficits should not be performed in the context of established metastatic disease.

Reports indicate high rates of local recurrence (31–85 per cent), regional recurrence, and distant metastasis (25–50 per cent) as well as poor five-year survival rates (13–48 per cent), and a median survival of less than two years, for head and neck mucosal melanoma. The predominant mode of treatment failure is local recurrence, and this usually occurs within a year of initial treatment. It is frequently accompanied by the appearance of regional and distant metastases. Distant metastasis is associated with short survival time.

While the view of mucosal melanoma as a 'radioresistant' tumour has been challenged, the role of post-operative RT remains unclear. Its use has been reported to improve local control. Short-course, hypofractionated schedules (e.g. 30 Gy in six fractions over two weeks, 50 Gy in 20 fractions), to relatively small volumes, compared with other head and neck practice are frequently employed. Adjuvant chemotherapy and biological therapeutic strategies have been employed with encouraging response rates. For metastatic disease, unfortunately only a tiny percentage of mucosal melanomas show a BRAF mutation; therefore it is usually not appropriate to use BRAF inhibitors, so chemotherapy in the form of biological agents has to depend on immunotherapy with ipilimumab[24] or the newer agents such as pembrolizumab, although to date there has been no specific study of the latter agent's efficacy specifically in mucosal melanoma.

TABLE V
TNM STAGING SYSTEM FOR MUCOSAL MELANOMAS

I–Primary tumour			
TX	Primary tumour cannot be assessed		
T3	Epithelium and/or submucosa (mucosal disease)		
T4a	Deep soft tissue, cartilage, bone, overlying skin		
T4b	Brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, mediastinal structures		
N–Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M–Distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping:			
Stage III	T3	N0	M0
Stage IVA	T3	N1	M0
	T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Note: Mucosal melanomas are aggressive tumours, therefore T1 and T2 are omitted as are stages I and II

Key points

- Cutaneous melanoma is the fifth commonest cancer in the UK; the incidence of melanoma doubled in the three decades following 1970
- Despite widely used checklists, the clinical diagnosis of melanoma can be difficult and a biopsy is needed for diagnosis
- The thickness of cutaneous melanoma greatly influences both its treatment and its prognosis
- Staging includes microstaging of the primary melanoma and clinical/radiological evaluation for metastases
- Mucosal melanoma is a poor prognostic disease
- Wide local excision, with appropriate margins based on the thickness of the tumour, with or without lymph node dissection of the involved nodal basins, is the mainstay of treatment for primary cutaneous melanoma
- Excision of localised mucosal melanoma with clear margins is the mainstay of treatment, but radical excision with functional compromise has not shown oncological benefits. Advances in immunotherapy have revolutionised the management of distant metastases

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GUIDELINE

Management of Salivary Gland Tumours: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Salivary gland tumours are rare and have very wide histological heterogeneity, thus making it difficult to generate high level evidence. This paper provides recommendations on the assessment and management of patients with cancer originating from the salivary glands in the head and neck.

Recommendations

- Ultrasound guided fine needle aspiration cytology is recommended for all salivary tumours and cytology should be reported by an expert histopathologist. (R)
- Adjuvant radiotherapy (RT) following surgery is recommended for all malignant submandibular tumours except in cases of small, low-grade tumours that have been completely excised. (R)
- For benign parotid tumours complete excision of the tumour should be performed and offers good cure rates. (R)
- In the event of intra-operative tumour spillage, most cases need long-term follow-up for clinical observation only. These should be raised in the multidisciplinary team to discuss the merits of adjuvant RT. (G)
- As a general principle, if the facial nerve function is normal pre-operatively then every attempt to preserve facial nerve function should be made during parotidectomy and if the facial nerve is divided intra-operatively then immediate microsurgical repair (with an interposition nerve graft if required) should be considered. (G)
- Neck dissection is recommended in all cases of malignant parotid tumours except for low-grade small tumours. (R)
- Where malignant parotid tumours lie in close proximity to the facial nerve there should be a low threshold for adjuvant RT. (G)
- Adjuvant RT should be considered in high grade or large tumours or in cases where there is incomplete or close resection margin. (R)
- Adjuvant RT should be prescribed on the basis of clinical factors in addition to histology and grade, e.g. stage, pre-operative facial weakness, positive margins, peri-neural invasion and extracapsular spread. (R)

Introduction

Salivary gland malignancies are rare and the understanding of this disease is mostly based on clinical series rather than randomised evidence which is unlikely to emerge for these tumours. Approximately 300 cases are registered each year in England and Wales of which fewer than 10 occur in children (under 19 years of age).[1] Population-based studies report that in a population of one million, eight to nine malignant salivary gland tumours can be expected per annum. Interspersed with this, malignant salivary gland disease is a larger workload of benign tumours, often performed by the non-head and neck oncological surgeon that also presents challenges from a management perspective.

Although, overall, tumours are more common in the parotid, the incidence of malignancy is higher in the submandibular and minor salivary glands.[2] Salivary tumours are uncommon in children, but a greater proportion (20–30 per cent) of them are malignant (usually low-grade mucoepidermoid carcinomas).

Salivary gland tumours present a diverse range of histological and clinical behaviours. The rarity of these tumours combined with the diverse histology means that there is a lack of studies that can be used to provide strong recommendations for each individual

TABLE 1
WHO CLASSIFICATION OF SALIVARY GLAND TUMOURS 2005[3]

Malignant epithelial tumours
Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial myoepithelial carcinoma
Clear cell carcinoma, not otherwise specified
Basal cell adenocarcinoma
Sebaceous carcinoma
Sebaceous lymphadenocarcinoma
Cystadenocarcinoma
Low-grade cribriform cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Squamous cell carcinoma
Undifferentiated carcinoma
Small cell carcinoma
Large cell carcinoma
Lymphoepithelial carcinoma
Adenocarcinoma, not otherwise specified
Carcinoma ex pleomorphic adenoma malignant mixed tumour
Myoepithelial carcinoma
Soft tissue tumours
Haemangioma
Haematolymphoid tumours
Hodgkin lymphoma
Metastasising pleomorphic adenoma
Diffuse large B-cell lymphoma
Extranodal marginal zone B cell lymphoma
Secondary tumours
Soft tissue
Haematopoetic
Benign epithelial tumours
Pleomorphic adenoma
Myoepithelioma
Basal cell adenoma
Warthin's tumour (adenolymphoma)
Oncocytoma
Cystadenoma
Papillary cystadenoma
Mucinous cystadenoma
Keratocystoma
Canalicular adenoma
Sialadenoma papilliferum
Sebaceous adenoma
Sialoblastoma
Lymphadenoma
Benign papilloma (intraductal/inverted ductal/ductal)

WHO = World Health Organization

histologic subtype of salivary tumour. The World Health Organization (WHO) classification has been modified on a number of occasions, the last being in 2005.[3] A list of the more common adenomas and carcinomas is given in Table 1. Each histologic subtype is supposedly a unique entity in itself, but this notion has to be accepted with caution. Salivary gland neoplasms are generally slow growing lesions and patients have to be followed up for 10 years or more before one is confident of the natural history of the histological entity. In most instances, this information is not available. At present the unique clinical behaviour of many of the new subtypes is still to be identified.

Carcinomas are often further classified as high grade, low grade or mixed, the latter inferring a variable behaviour depending on the histological picture. Except in the case of mucoepidermoid tumours, the clinicopathological correlation has proved unreliable. It should be recognised that the clinical behaviour rather than the histology of a tumour provides a better treatment guide and it is important to consider clinical factors in addition to histology and grade when planning treatment.[4]

Clinical presentation

In general, salivary tumours are present in two forms: a simple palpable lump (well-defined, discrete and mobile) or a lump with significant accompanying symptoms (pain, rapid growth, fixity to surrounding structures, nerve involvement or neck metastasis). The latter features are all suggestive of malignancy. Both should be seen in a rapid access neck lump clinic ideally to have the appropriate assessments and management plans formulated.

Assessment and staging

A third of malignant tumours have an indolent nature and may be clinically indistinguishable from benign lesions. Open biopsy is not encouraged in apparently benign lesions as it carries a theoretical risk of seeding, but it sometimes has a role in the frankly malignant lesion (open or core biopsy) especially when radical surgery is being contemplated. As indolent lesions may masquerade as benign lumps the definitive histology sometimes may not be available until after surgical resection. Diagnosis and management of these tumours is therefore based on the clinical presentation, imaging and cytology and/or histology results.

Fine needle aspiration cytology (FNAC) and core biopsy

This is the primary diagnostic tool for salivary gland lesions (parotid, submandibular and minor salivary), and has additional value if examined by a cytopathologist or pathologist experienced in the diagnosis of salivary gland disease. This can distinguish malignant from benign disease in 90 per cent of cases.[5] However, it is essential to ensure that fine needle aspiration results are interpreted in the context of all clinical information.

Imaging considerations

Ultrasound by a skilled head and neck radiologist is an essential tool as part of initial assessment and provides excellent information about the primary tumour as well as cervical lymph node status.[6] It can be combined with FNAC and in experienced hands, helps distinguish benign from malignant lesions in about 80 per cent of cases.

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Recommendation

- **Ultrasound guided FNAC is recommended for all salivary tumours and cytology should be reported by an expert histopathologist (R)**

Non-homogeneous, muscle infiltration or suspicious regional lymph node appearances on cross-sectional imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) are suggestive of malignancy. However, its main role is to determine size, position and relationship to adjacent structures. Computed tomography imaging is useful in proven malignancy to exclude distant metastases which carry a poor prognosis.

Open biopsy

This should be avoided in major salivary gland lesions due to a risk of spillage unless the lesion appears frankly malignant and no cytological diagnosis has been made. In this instance, histological confirmation may inform planning of a more radical surgical approach. Histology may still be obtained by the use of ultrasound guided core biopsy specimens rather than an open biopsy. For minor salivary glands, open biopsy is permissible, but where possible should be undertaken by a dermatological punch.

Frozen section

Accurate diagnosis is often difficult and false negative rates are significant therefore it is essential that if frozen section is being considered it must be done by an expert pathologist.[7] On some occasions pre-operative cytology and/or histology may remain unclear and therefore the frozen section may have a role in parotid surgery. It is important not to breach the tumour capsule during parotid surgery and a partial parotidectomy specimen should be sent for the frozen section which may help determine the presence of malignancy and therefore help inform a decision regarding proceeding to radical surgery. This may be preferred rather than waiting for results of a partial parotidectomy as completion parotidectomy at a later stage carries a significant morbidity, especially with regards to facial nerve function.

Staging

The Tumour–Node–Metastases (7) system staging for salivary gland primary tumour is shown in Table II.

The staging of metastatic neck nodes for salivary gland cancer is similar to that for other metastatic disease.

TABLE II
T-STAGING FOR SALIVARY GLAND TUMOURS

Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤2 cm in greatest dimension without extraparenchymal extension*
T2	Tumour >2 cm but ≤4 cm in greatest dimension without extraparenchymal extension*
T3	Tumour >4 cm and/or tumour having extraparenchymal extension*
T4a	Tumour invades skin, mandible, ear canal and/or facial nerve
T4b	Tumour invades skull base and/or pterygoid plates and/or encases carotid artery

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

Management

Submandibular gland

Benign tumours. The submandibular gland should be excised in a supracapsular plane. A wide dissection of local tissues is not required.

Malignant tumours. Historical survival rates in submandibular gland cancer are lower than those achieved in parotid or minor salivary gland malignancy.[8,9] This has been attributed to the absence of a pre-treatment malignant diagnosis and therefore performance of conservative resection. It is important that if a neoplasm is suspected or a firm supposedly fibrotic submandibular gland encountered then every effort should be made to establish whether it is benign or malignant prior to surgery.

Surgical management of the primary tumour. Wide excision is appropriate for tumours confined to the gland combined with some form of neck dissection. Some argue in favour of a wider resection for adenoid cystic tumours but even with radical surgery, it is frequently difficult to obtain adequate surgical margins.[10] The advice for radical surgery in submandibular malignancy is at variance with recommendations for the preservation of the uninvolved facial nerve in parotid disease. Clinically high-grade tumours should be treated aggressively with excision of the gland plus a 2 cm margin of apparently healthy tissue. Resection of involved nerves with microscopic negative margins is desirable. Large infiltrative tumours with bony involvement are treated with composite resection of tumour, adjacent soft tissue cuff and bony resection as appropriate.

Surgical management of the neck metastases. In the N0 neck, patients should undergo clearance of nodes with a selective neck dissection (levels 1 and 2A). Clinically high-grade tumours or tumours with suspicious MRI appearances should have an elective selective dissection (levels 1–3).

The following histological types have higher risk of metastasis: high-grade mucoepidermoid carcinoma, squamous cell carcinoma (SCC), anaplastic tumours and carcinoma ex pleomorphic adenoma. Carcinoma ex pleomorphic adenoma has been redefined and some types act as benign tumours.[11] It is the frankly malignant variety that carries the risk of metastases. Patients with clinically confirmed neck metastasis

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(N+) should have a neck dissection, the extent of which will be based on disease stage and location.

Primary radiotherapy (RT). Primary RT may be applicable in inoperable tumours where palliation can be achieved.[12] The role of heavy ions such as proton and carbon ion therapy is being explored and is as yet unresolved.

Post-operative RT. 'The 4 cm rule': survival is significantly worse in tumours greater than 4 cm in diameter.[12] With increasing size the risk of occult metastasis is greater and tumour size is a major determinant of distant metastasis. Tumours greater than 4 cm in size fall into the class of high risk or complex tumours, and adjuvant RT is advised. Post-operative RT should be commenced within six weeks of surgery.

Indications for post-operative RT:

- High-grade or advanced stage tumours (>4 cm) with a high risk of local recurrence
- Residual neck disease or microscopic extracapsular spread from lymph nodes
- Following surgery for recurrent disease
- Adenoid cystic carcinomas (ACC).

Surveillance. Following surgery alone or surgery followed by RT careful surveillance is required. Ultrasound offers an accurate method of detecting recurrence but a baseline MRI three months following treatment is useful for comparison.

Recommendation

- **Adjuvant RT following surgery is recommended for all malignant submandibular tumours except in cases of small, low-grade tumours that have been completely excised (R)**

Parotid gland

Benign tumours. Traditional management of benign parotid tumours is by dissection of the facial nerve leading to a superficial or total parotidectomy. There is currently no agreement in the literature as to the extent of resection to obtain an adequate margin in benign tumours.[13] There is increasing recognition that operations less than the traditional procedures (extracapsular dissection, partial parotidectomy and even endoscopically assisted parotidectomy) are as effective in selected patients.[14] It is preferable that these procedures should be performed by expert surgeons in appropriately selected cases, such as small tumours confined to the superficial lobe. A 'lumpectomy' procedure should not be done due to high recurrence rates. As the facial nerve not infrequently is very close to the tumour (especially in larger tumours) careful dissection avoiding tumour rupture is important. Tumour spillage carries an increase in the rate of recurrence over a prolonged period and therefore long-term follow-up is recommended in such cases.[15] Adjuvant RT for such cases should be discussed in a multidisciplinary team (MDT) setting, but the use of RT in these cases is controversial and is generally not recommended especially in younger patients due to the risk of radiation-induced tumours.

Recurrent benign parotid tumours. These will usually be treated surgically. Careful pre-operative ultrasound marking may be helpful. A widefield removal of tissue in the parotid bed with preservation of the facial nerve is recommended. The patient should be discussed in the MDT for the suitability of post-operative RT to reduce re-recurrence.

Recommendations

- **For benign parotid tumours complete excision of the tumour should be performed and offers good cure rates (R)**
- **In the event of intra-operative tumour spillage, most cases need long-term follow-up for clinical observation only. These should be discussed in the MDT to discuss the merits of adjuvant RT (G)**

Malignant tumours

Surgical management of the primary tumour. In carcinoma, surgery is the treatment of choice with management tailored to the individual case.[16] A conservative parotidectomy should be performed with preservation of the functioning facial nerve providing there is no tumour invasion. For small, low-grade superficial tumours a partial parotidectomy (superficial parotidectomy or wide local resection with an adequate margin of at least 1.5 cm) may suffice but otherwise a total conservative parotidectomy is advocated with resection of adjacent structures if necessary to achieve an en-bloc resection. Any part of the facial nerve not infiltrated by tumour should be preserved and a frozen section may be needed to determine nerve involvement. If the facial nerve is functional pre-operatively, then primary nerve grafting should be performed following radical resection. Adenoid cystic carcinoma characteristically has a diffuse pattern of spread and incomplete surgical clearance is the norm. A total parotidectomy with sacrifice of any part of any of the nerves overtly involved in tumour is desirable.

Management of the facial nerve in the context of parotid tumours. The facial nerve can be damaged as a sequelae of parotid surgery, either as a planned event when removing a malignant tumour or inadvertently. The damage can be a division of the nerve or can occur with the nerve intact, i.e. a neuropraxia. If the

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nerve is divided, it should be repaired as soon as possible, ideally acutely. Direct microsurgical repair without tension, or repair utilising a nerve graft, offer the best chance of a good recovery. A delay of more than a year in nerve repair has been shown to be an adverse factor in patient recovery. If a proximal nerve stump is not available or significant amounts of facial muscle have been removed, facial re-animation will require importation of a new muscle and nerve supply. The facial nerve can routinely be found and exposed in the mastoid segment of the temporal bone if the nerve cannot be found in the neck. Re-animation techniques can be one stage using either microsurgical importation of a free muscle transfer, or regional involving a temporalis myoplasty. Such techniques require substantial expertise and patients with significant facial paralysis should be referred to a service which can offer a full spectrum of reconstructive options regarding facial re-animation, including care of the eye.

Recommendation

- **As a general principle, if the facial nerve function is normal pre-operatively then every attempt to preserve facial nerve function should be made during parotidectomy and if the facial nerve is divided intra-operatively then immediate microsurgical repair (with an interposition nerve graft if required) should be considered (G)**

Surgical management of the neck metastases. The literature reports rates between 13 and 39 per cent of pathological neck node metastases in parotid cancer. Neck dissection should be performed in patients with clinical or radiological evidence of nodal disease.[17]

A prophylactic selective neck dissection should be considered for patients with high-stage and/or clinically high-grade tumours (i.e. adenocarcinoma, squamous and undifferentiated carcinomas, high-grade mucoepidermoid carcinoma and carcinoma ex pleomorphic adenoma).[18,19] In addition, neck dissection provides a histological specimen which provides important prognostic information such as extracapsular spread which has been shown to be a poor prognostic indicator.

Recommendation

- **Neck dissection is recommended in all cases of malignant parotid tumours except for low-grade small tumours (R)**

Radiotherapy. Radiotherapy is effective in reducing the risk of recurrent benign tumours. It has application in high risk of recurrence pleomorphic adenoma cases, namely gross wound contamination and as an adjuvant therapy for treatment of multinodular recurrent disease.[15]

Adjuvant RT is appropriate for large tumours (>4 cm), recurrent disease, patients with incomplete or close margins, peri-neural invasion, extension beyond the gland, nodal disease, in metastatic disease and is increasingly the norm following treatment of ACC and high-grade tumours.[12]

Recommendations

- **Where malignant parotid tumours lie in close proximity to the facial nerve there should be a low threshold for adjuvant RT (G)**
- **Adjuvant radiation should be considered in high-grade or large tumours or in cases where there is incomplete or close resection margin (R)**
- **Adjuvant radiation should be prescribed on the basis of clinical factors in addition to histology and grade, e.g. stage, pre-operative facial weakness, positive margins, peri-neural invasion and extracapsular spread (R)**

Recurrent cancer. This requires careful evaluation of the patient with repeat imaging and a review of the histology from the initial excision. It will usually require more radical surgery with sacrifice of the facial nerve and overlying skin if there is suspicion of involvement by tumour. Super-radical resections of the skull base have not to date shown convincing evidence of improved survival. Consider chemotherapy and/or RT for palliation.

Minor salivary glands

The natural history of intra-oral minor salivary gland tumours is similar to the parotid and submandibular glands. Outcome is worse for 'hidden sites', i.e larynx, nasopharynx and nose. The prognosis for these patients as with parotid and submandibular glands is related to stage of disease rather than the histology.

Benign tumours. Tumours of the palate can be safely resected at the subperiosteal level without removing palatal bone. Proven benign tumours in soft tissue can be removed by careful local dissection.

Malignant tumours

Surgical management of the primary tumour. Most cases are treated in a similar way to SCC, with en-bloc resection with depth of excision compatible with treatment of SCC to ensure adequate resection margins.[20] Significant defects are repaired as appropriate.

Surgical management of the neck metastases. Therapeutic neck dissection is indicated for lymph node involvement. Elective neck dissection is indicated

for high-stage and clinically high-grade disease such as high-grade adenocarcinoma, invasive carcinoma ex pleomorphic adenoma, SCC, high-grade mucoepidermoid and undifferentiated carcinoma.[18]

Radiotherapy. The following factors are indications for post-operative RT[12]:

- Microscopic residual disease
- Adenoid cystic tumours
- Aggressive undifferentiated tumours
- A'4 cm rule'.

Natural history and management principles for common salivary malignancies

Acinic cell carcinomas

These tumours account for about 3 per cent of parotid tumours, where they occur most commonly. Peak incidence is in the fifth decade. Other features include:

- A variable histological pattern, multifocal origin and occasionally bilateral location
- Determinate survival rates of 90 per cent at five years and 55 per cent at 20 years[9]
- Lymph node metastatic rate of approximately 10 per cent.

Most acinic cell cancers are low grade (approximately 80 per cent). Small indolent peripheral lesions can be managed by less than a total parotidectomy. In low-grade acinic cell cancers, adjuvant RT following complete excision may not confer survival benefit and therefore the role of adjuvant RT should be considered carefully in such cases.[21] Total parotidectomy with preservation of uninvolved nerves is recommended. Elective neck dissection is usually not indicated.

Mucoepidermoid tumour

These tumours have variable malignant potential with low-grade lesions following an indolent course. Histologically high-grade lesions have a natural history similar to SCC. The histological grade correlates with several prognostic factors including presence of lymphatic spread and survival.[9,22] The key features are detailed below:

- Most common major salivary gland tumour (4–9 per cent) with over 90 per cent occurring in the parotid but overall more frequent in minor salivary glands
- Most common malignant salivary gland tumour in children and usually presents in its indolent form
- Highest incidence third to fifth decade with no difference in gender incidence
- In the parotid, it is almost always in the superficial lobe
- Histological division into low, intermediate and high-grade correlates with prognosis, although 'low-grade' tumours can on occasion be aggressive[22]
- Five-year survival varies between 86 per cent for low-grade and 22 per cent for high-grade tumours. Peri-neural and lymphovascular invasion is not uncommon in these tumours
- Incidence of lymph node metastases is 40 per cent in intermediate and high-grade tumours
- Small low-grade tumours can be removed by less than a total parotidectomy and bigger ones (>2 cm) will frequently be in close contact with the facial nerve and the aforementioned advice pertains regarding adjuvant RT
- Adjuvant RT indicated for high-grade tumours.

Recommendation

- **In cases of mucoepidermoid carcinoma, the histologic grade is an important factor correlating to outcome and should be considered when planning treatment (G)**

Adenoid cystic carcinoma

This is the most common salivary gland malignancy (20–25 per cent of all malignant salivary gland neoplasms), occurs at mucosal sites more frequently than in major salivary glands, and accounts for 2–6 per cent of parotid tumours and approximately 15 per cent of submandibular tumours. It is characterised by:

- Slow, pervasive growth and a high incidence of peri-neural infiltration. Relapsing neuralgic type pain can be a feature of early hidden disease. Patients can be 'labelled' as having atypical facial pain with consequent diagnostic delay
- Variable histologic appearance but difficult to correlate with clinical behaviour although some report cribriform pattern to have better prognosis than tubular or solid pattern tumours.

Treatment should involve wide local excision with preservation of uninvolved major nerves. Adjuvant post-operative RT is often indicated.[10] Stage I and II cancers can be cured although the survival curve never flattens even after 20 years. Patient with stage III and IV diseases have a poor prognosis with low survival rates at 10 years. Slow growth rate makes five-year survival rates unreliable marker of cure. Only 20 per cent of patients with pulmonary metastases survive more than five years.

Adenocarcinoma

This uncommon tumour is most frequently (90 per cent) found in the parotid gland. It is characterised by:

- Equivalent gender incidence, affecting any age and is one of the commonest tumours seen in children

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- Histologic appearances varying between low-grade well-differentiated papillary or mucinous patterns to high-grade, undifferentiated lesions
- Distant metastatic incidence rates of 40 per cent for high-grade tumours, directly related to survival rates
- A 75 and 19 per cent five-year survival for low-grade and high-grade tumours, respectively.

Treatment is by wide local resection with elective neck dissection and adjuvant RT for clinically high-grade tumours.

Malignant mixed tumour (carcinoma ex pleomorphic adenoma)

Carcinoma ex pleomorphic adenoma is a broad category of carcinomas of the salivary glands.[11] The name is probably a misnomer for only a minority of malignant mixed tumours arise from pleomorphic adenomata. These are typically tumours with a history of multiple recurrences with surgery and RT. The remainder are probably not a homogeneous group of tumours and may occur *de novo* rather than following a malignant generation of pleomorphic adenoma. The frequency varies between 2 and 5 per cent.

Different patterns of malignant change can occur in pleomorphic adenoma of which the most commonly encountered is carcinoma ex pleomorphic adenoma, the other types being a true malignant mixed tumour and metastasising pleomorphic adenoma.

The tumours are classed as in situ carcinoma, non-invasive (intra-capsular including in situ carcinoma) minimally invasive (<1.5 mm) and invasive.[11] The clinical behaviour of early or minimally invasive tumours is similar to that of pleomorphic salivary adenoma. Clinical malignant behaviour is associated with only the malignant foci that extend beyond the capsule of the tumour and these tumours tend to be high grade with a high incidence of haematogenous metastasis. Cure rates at 5, 10 and 15 years are 40, 24 and 19 per cent, respectively.

Squamous cell carcinoma

This rare primary tumour is often mistaken for either a high-grade mucoepidermoid lesion or metastasis from another primary site; however, it is commonly metastases from a skin cancer. Features of this cancer include:

- Male to female incidence ratio 2:1
- Tendency to occur in the elderly (seventh decade)
- Metastatic disease presents initially as a discrete lump in the parotid however unlike salivary neoplasms SCC has a propensity for early extracapsular extension. In the parotid, this threatens local structures and prompt surgical intervention should be the rule. A few weeks' delay can make a significant difference to the complexity of surgery
- A poor prognosis and should be treated as high-grade mucoepidermoid lesions.

Radical resection with adjuvant RT offers the best form of management.

Key points

- There is a limited amount of clinical evidence for the management of salivary gland tumours
- Salivary gland tumours exhibit a diverse range of histological type and clinical behaviour
- Salivary gland malignancies are rare
- Investigations are essential to help tailor appropriate treatment and should include an FNA reported by an expert pathologist
- The majority of tumours will be treated by surgery, the extent of which should be tailored to the size, clinical and histological type of tumour
- As a general principle in cases where there is normal facial nerve function then the facial nerve should be preserved during surgical treatment
- Adjuvant radiotherapy should be considered in malignant cases with adverse clinical or histological features
- Elective treatment of the neck will be required in the majority of malignant tumours.

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GUIDELINE

Management of thyroid cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. This paper provides recommendations on the management of thyroid cancer in adults and is based on the 2014 British Thyroid Association guidelines.

Recommendations

- Ultrasound scanning (USS) of the nodule or goitre is a crucial investigation in guiding the need for fine needle aspiration cytology (FNAC). (R)
- FNAC should be considered for all nodules with suspicious ultrasound features (U3–U5). If a nodule is smaller than 10 mm in diameter, USS guided FNAC is not recommended unless clinically suspicious lymph nodes on USS are also present. (R)
- Cytological analysis and categorisation should be reported according to the current British Thyroid Association Guidance. (R)
- Ultrasound scanning assessment of cervical nodes should be done in FNAC-proven cancer. (R)
- Magnetic resonance imaging (MRI) or computed tomography (CT) should be done in suspected cases of retrosternal extension, fixed tumours (local invasion with or without vocal cord paralysis) or when haemoptysis is reported. When CT with contrast is used pre-operatively, there should be a two-month delay between the use of iodinated contrast media and subsequent radioactive iodine (I^{131}) therapy. (R)
- Fluoro-deoxy-glucose positron emission tomography imaging is not recommended for routine evaluation. (G)
- In patients with thyroid cancer, assessment of extrathyroidal extension and lymph node disease in the central and lateral neck compartments should be undertaken pre-operatively by USS and cross-sectional imaging (CT or MRI) if indicated. (R)
- For patients with Thy 3f or Thy 4 FNAC a diagnostic hemithyroidectomy is recommended. (R)
- Total thyroidectomy is recommended for patients with tumours greater than 4 cm in diameter or tumours of any size in association with any of the following characteristics: multifocal disease, bilateral disease, extrathyroidal spread (pT3 and pT4a), familial disease and those with clinically or radiologically involved nodes and/or distant metastases. (R)
- Subtotal thyroidectomy should not be used in the management of thyroid cancer. (G)
- Central compartment neck dissection is not routinely recommended for patients with papillary thyroid cancer without clinical or radiological evidence of lymph node involvement, provided they meet all of the following criteria: classical type papillary thyroid cancer, patient less than 45 years old, unifocal tumour, less than 4 cm, no extrathyroidal extension on ultrasound. (R)
- Patients with metastases in the lateral compartment should undergo therapeutic lateral and central compartment neck dissection. (R)
- Patients with follicular cancer with greater than 4 cm tumours should be treated with total thyroidectomy. (R)
- I^{131} ablation should be carried out only in centres with appropriate facilities. (R)
- Serum thyroglobulin (Tg) should be checked in all post-operative patients with differentiated thyroid cancer (DTC), but not sooner than six weeks after surgery. (R)
- Patients who have undergone total or near total thyroidectomy should be started on levothyroxine 2 μg per kg or liothyronine 20 mcg tds after surgery. (R)
- The majority of patients with a tumour more than 1 cm in diameter, who have undergone total or near-total thyroidectomy, should have I^{131} ablation. (R)
- A post-ablation scan should be performed 3–10 days after I^{131} ablation. (R)
- Post-therapy dynamic risk stratification at 9–12 months is used to guide further management. (G)
- Potentially resectable recurrent or persistent disease should be managed with surgery whenever possible. (R)
- Distant metastases and sites not amenable to surgery which are iodine avid should be treated with I^{131} therapy. (R)

- Long-term follow-up for patients with differentiated thyroid cancer (DTC) is recommended. (G)
- Follow-up should be based on clinical examination, serum Tg and thyroid-stimulating hormone assessments. (R)
- Patients with suspected medullary thyroid cancer (MTC) should be investigated with calcitonin and carcino-embryonic antigen levels (CEA), 24 hour catecholamine and nor metanephrine urine estimation (or plasma free nor metanephrine estimation), serum calcium and parathyroid hormone. (R)
- Relevant imaging studies are advisable to guide the extent of surgery. (R)
- RET (Proto-oncogene tyrosine-protein kinase receptor) proto-oncogene analysis should be performed after surgery. (R)
- All patients with known or suspected MTC should have serum calcitonin and biochemical screening for phaeochromocytoma pre-operatively. (R)
- All patients with proven MTC greater than 5 mm should undergo total thyroidectomy and central compartment neck dissection. (R)
- Patients with MTC with lateral nodal involvement should undergo selective neck dissection (IIa–Vb). (R)
- Patients with MTC with central node metastases should undergo ipsilateral prophylactic lateral node dissection. (R)
- Prophylactic thyroidectomy should be offered to RET-positive family members. (R)
- All patients with proven MTC should have genetic screening. (R)
- Radiotherapy may be useful in controlling local symptoms in patients with inoperable disease. (R)
- Chemotherapy with tyrosine kinase inhibitors may help in controlling local symptoms. (R)
- For individuals with anaplastic thyroid carcinoma, initial assessment should focus on identifying the small proportion of patients with localised disease and good performance status, which may benefit from surgical resection and other adjuvant therapies. (G)
- The surgical intent should be gross tumour resection and not merely an attempt at debulking. (G)

Differentiated thyroid cancer

Introduction

Thyroid nodules are common, the incidence of palpable nodules in women and men being approximately 5 and 1 per cent, respectively. Use of ultrasound scanning (USS) substantially increases their detection in the general population to approximately 50–70 per cent. Thyroid cancer remains rare, with an incidence in the UK of approximately 5 per 100 000 women and 2 per 100 000 men. Thyroid cancer is the most common endocrine malignancy, but accounts for only 1 per cent of all malignancies. Evidence suggests an increasing incidence; however, the survival rates remain static.

Long-term prognosis for differentiated thyroid cancer (DTC) is excellent, with survival rates for adults being 92–98 per cent at 10-year follow-up. However, 5–20 per cent of patients develop local or regional recurrence requiring further treatment and 10–15 per cent go on to develop distant metastases. Factors influencing prognosis include gender, age at presentation, histology and tumour stage. Accurate diagnosis, treatment and long-term follow-up are essential to achieve and maintain excellent survival rates.

There have been several sets of detailed guidelines published on the diagnosis and management of thyroid cancer. Two key ones are the Guidelines for the Management of Thyroid Cancer (2014) by the British Thyroid Association and Royal College of Physicians,[1] and the Revised American Thyroid Association Guidelines (2016).[2] These documents are extensive and cover every aspect of care in great detail. Given differences in presentation, pathophysiology and outcomes, separate guidelines exist for children with DTC,[3] and consensus statements on the various surgical interventions.[4] Patients may initially be seen by a surgeon, endocrinologist, clinical oncologist or nuclear medicine physician, who must be a core member of the thyroid cancer multidisciplinary team (MDT). The goals of treatment for DTC are set out in Box I.

BOX I
GOALS OF TREATMENT FOR DTC

- Remove the primary tumour and involved lymph nodes
- Minimise treatment related morbidity
- Allow accurate staging of the disease
- Facilitate post-operative treatment with radioactive iodine in appropriate patients
- Enable long-term surveillance for disease recurrence
- Minimise the risk of disease recurrence and distant metastases

Clinical presentation

In all cases, a detailed history is required. Clinical features associated with an increased risk of malignancy in individuals with a thyroid nodule include:

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- age younger than 20 or older than 60 years
- firmness of the nodule on palpation
- rapid growth
- fixation to adjacent structures
- vocal cord paralysis
- associated lymphadenopathy
- history of neck irradiation
- family history of thyroid cancer
- history of Hashimoto's thyroiditis (risk factor for thyroid lymphoma).

Symptoms warranting immediate referral. Patients presenting with airway compromise, including stridor, associated with a thyroid nodule or goitre should be referred for an immediate opinion.

Symptoms warranting urgent general practitioner (GP) referral (two-week wait rule). Patients presenting with hoarseness of voice or a change in their voice associated with a thyroid nodule or goitre, children with a thyroid nodule, individuals with cervical lymphadenopathy associated with a thyroid nodule or a painless thyroid mass, which is rapidly enlarging over a period of weeks should be referred for an urgent opinion.

Investigation

Recommended clinical investigations. These include:

- Clinical evaluation of thyroid, cervical and supraclavicular nodes
- Thyroid-stimulating hormone (TSH)
- Ultrasound of the nodule (Table I)
- Fine needle aspiration cytology (FNAC) if ultrasound features are suspicious of malignancy
- Documented cytological score (Table II). A core biopsy (with or without USS guidance) is warranted if a diagnosis of lymphoma is suspected
- Calcitonin only in suspected cases of medullary thyroid cancer (MTC) (routine use not recommended)
- Pre-operative vocal cord check
- Note that a serum thyroglobulin (Tg) is not recommended.

Ultrasound of thyroid nodules. Ultrasound is very useful in the investigation of thyroid nodules and should be used to guide the need for further investigation including FNAC. Ultrasound-guided FNAC increases the yield of diagnostic cytology significantly. Current guidelines recommend that ultrasonographers use the U grade (Table I) to classify nodules according to ultrasound appearances.[5]

Ultrasound evaluation of cervical lymphadenopathy. Pathological studies suggest that microscopic lymph node metastases are very common in papillary thyroid cancer (PTC). However, macroscopic disease is less common (20–50 per cent). Pre-operative ultrasonography is effective in identifying suspicious nodes in approximately 20–30 per cent of patients with PTC and may alter the surgical approach. FNAC of suspicious nodes is recommended. Tg estimation of cystic fluid may be of use in the absence of sufficient diagnostic material.

Recommendations

- **Ultrasound scanning of the nodule or goitre is a crucial investigation in guiding the need for FNAC (R)**
- **FNAC should be considered for all nodules with suspicious ultrasound features (U3–U5). If a nodule is smaller than 10 mm in diameter, USS-guided FNAC is not recommended unless clinically suspicious lymph nodes on USS are also present (R)**
- **Cytological analysis and categorisation should be reported according to the current British Thyroid Association Guidance (R)**
- **Ultrasound scanning assessment of cervical nodes should be done in FNAC-proven cancer (R)**
- **Magnetic resonance imaging (MRI) or computed tomography (CT) should be done in suspected cases of retrosternal extension, fixed tumours (local invasion with or without vocal cord paralysis) or when haemoptysis is reported. When CT with contrast is used pre-operatively, there should be a two-month delay between the use of iodinated contrast media and subsequent radioactive iodine therapy (R)**
- **Fluoro-deoxy-glucose-positron emission tomography imaging is not recommended for routine evaluation (G)**

Staging

The tumour, nodes and metastases (TNM) staging system (Table III) is used to stage thyroid cancers and this should be used in all cases. Post-operatively, an 'R' classification can be given which indicates the amount of residual disease present. The TNM classification can then be used in combination with patient characteristics to define likely prognosis (Table IV).

Surgery

Surgeons performing operations for confirmed or suspected thyroid cancer should be core members of the thyroid cancer MDT and should perform a minimum of 20 thyroidectomies per year. Complex surgery and lymph node surgery should be undertaken by nominated surgeons in the cancer centre with specific training in, and experience of, thyroid oncology. All

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TABLE I
U GRADING OF THYROID NODULES

U1 normal	U2 benign	U3 indeterminate/ equivocal	U4 suspicious	U5 malignant
Normal thyroid tissue	Halo Iso-echoic or mildly hyper-echoic Cystic change ± ring down sign Micro-cystic/spongiform Peripheral egg shell calcification Peripheral vascularity	Homogeneous Hyper-echoic Solid, halo (follicular lesion) Equivocal echogenic foci Cystic change mixed/central vascularity	Solid Hypo-echoic or very hypo-echoic Disrupted peripheral calcification Lobulated outline	Solid Hypo-echoic Lobulated or irregular outline Micro-calcification Globular calcification Intra-nodular vascularity Shape (taller >wide) Characteristic associated lymphadenopathy
No follow-up required	No follow-up required – routine FNAC not recommended, unless high level of clinical suspicion of thyroid cancer	FNAC	FNAC	FNAC

FNAC = fine needle aspiration cytology

patients with suspected or confirmed thyroid cancer should have pre-operative imaging with ultrasound. Cross-sectional imaging with CT or MRI may also be indicated.

In the context of thyroid cancer, surgery may be diagnostic (e.g. hemithyroidectomy following Thy 3 or Thy 4 cytology) or therapeutic.

Thyroid surgery for papillary thyroid cancer (PTC). A strategy for the surgical treatment of PTC is detailed in Table V. All cases should be discussed pre-operatively at the thyroid cancer MDT.

Initial surgery for follicular thyroid cancer. The majority of patients undergoing surgery for follicular thyroid cancer will be undiagnosed at the time of the initial surgery (Thy 3). Frozen section histology cannot currently reliably differentiate benign follicular lesions from follicular thyroid cancer, and therefore this strategy is not recommended. An operative strategy for surgical treatment of follicular cancer is outlined in Table VI.

Low-risk patients with a diagnosis of minimally invasive tumour less than 4 cm following hemithyroidectomy do not require further treatment. Hurthle cell cancers (follicular oncocytic) tend to be more aggressive and should be treated by total (completion) thyroidectomy (see Table VI).

Management of lymph nodes in differentiated thyroid cancer (DTC). Prophylactic level VI lymph node dissection is associated with a higher incidence of recurrent laryngeal nerve damage and long-term permanent hypoparathyroidism.[6] It is therefore not routinely recommended, but in individuals with high-risk tumours, this should be discussed in the spirit of personalised decision making. Prophylactic level VI nodal dissection is not recommended in low risk, small papillary and most follicular cancers.

Prophylactic level VI nodal dissection is recommended in patients with known involved lateral

TABLE II
THYROID FNAC DIAGNOSTIC CATEGORIES

Thy 1	Thy 2	Thy 3		Thy 4	Thy 5
		Thy 3F	Thy 3A		
Non-diagnostic	Non-neoplastic, e.g. colloid nodule or thyroiditis	Follicular lesion	Atypia present	Suspicious of thyroid cancer	Diagnostic of thyroid cancer
Repeat FNAC	No follow-up if no suspicious US features and no clinical suspicion of thyroid cancer	Diagnostic hemithyroidectomy* Consider total thyroidectomy in lesions >4 cm where incidence of malignancy is higher	Repeat ultrasound and FNAC If second Thy 3A cytology obtained, discuss at MDT and consider diagnostic hemithyroidectomy*	Discuss at MDT Diagnostic hemithyroidectomy*	Discuss at MDT Appropriate further investigations for staging where indicated Total thyroidectomy ± central node clearance in appropriate high risk patients

*Hemithyroidectomy consists of removal of a thyroid lobe and the isthmus

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TABLE III
TUMOUR, NODES AND METASTASES 7TH EDITION STAGING SYSTEM FOR DIFFERENTIATED THYROID CANCER

T stage – primary tumour	TX primary tumour cannot be assessed T0 no evidence of primary tumour T1 tumour ≤2 cm in greatest dimension limited to the thyroid T1a tumour ≤1 cm, limited to the thyroid T1b tumour >1 cm but ≤2 cm in greatest dimension, limited to the thyroid T2 tumour >2 cm but ≤4 cm in greatest dimension, limited to the thyroid T3 tumour >4 cm in greatest dimension limited to the thyroid or any tumour with minimal extrathyroidal extension (e.g. extension to sternothyroid muscle or peri-thyroid soft tissues) T4 tumour of any size extending beyond the thyroid capsule T4a tumour invades subcutaneous soft tissues, larynx, trachea, oesophagus or recurrent laryngeal nerve T4b tumour invades pre-vertebral fascia or encases carotid artery or mediastinal vessel
N stage – regional lymph nodes (cervical or upper mediastinal)	NX regional lymph nodes cannot be assessed N0 no regional lymph node metastasis N1 regional lymph node metastasis N1a metastases to level VI (pretracheal, paratracheal and prelaryngeal/Delphian lymph nodes) N1b metastases to unilateral, bilateral, or contralateral cervical (levels I–IV or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)
M stage – distant metastases	MX distant metastases cannot be assessed M0 no distant metastasis M1 distant metastasis
R stage – residual disease	RX cannot assess presence of residual primary tumour R0 no residual primary tumour R1 microscopic residual primary tumour R2 macroscopic residual primary tumour

MDT = multidisciplinary team

nodes. Therapeutic level VI nodal dissection is recommended when the presence of lymph node metastasis is confirmed.

Clinically involved lateral cervical lymph nodes should be managed by selective neck dissection (levels II–V). Involvement of level I or VII node is rare in DTC and should only be dissected if involved. Prophylactic lateral neck compartment dissection for node negative patients is not recommended.

Completion thyroidectomy. Completion thyroidectomy is not needed in low-risk, unifocal, intrathyroidal tumours less than 4 cm in diameter, with clinically negative lymph nodes.

Locally advanced disease. Where possible, locally advanced disease should be resected. Preservation of recurrent laryngeal nerves should be attempted in almost all cases. Extensive resection of trachea, larynx and oesophagus should be considered if potentially curative. Where disease is unresectable, radiotherapy and radioiodine should be considered.

Microcarcinomas. Microcarcinomas are differentiated thyroid carcinomas less than 10 mm in maximum dimension and are predominantly papillary carcinomas. The management of papillary microcarcinomas is outlined in Figure 1.

TABLE IV
GROUP STAGING AND SURVIVAL FOR DIFFERENTIATED THYROID CANCER

Stage	Age <45 years	Age >45 years	10-year survival (%)
I	Any T, any N, M0	T1, N0, M0	98.5
II	Any T, any N, M1	T2, N0, M0	98.8
III		T3, N0, M0 or T1–3, N1a, M0	99.0
*IVA		T4a, any N, M0 or T1–3, N1b, M0	75.9
IVB		T4b, any N, M0	62.5
IVC		Any T, any N, M1	63.0

*Undifferentiated or anaplastic carcinomas are all stage IV

Recommendations

- **In patients with thyroid cancer, assessment of extrathyroidal extension and lymph node disease in the central and lateral neck compartments should be undertaken pre-operatively by USS and cross-sectional imaging (CT or MRI) if indicated (R)**
- **For patients with Thy 3f or Thy 4 FNAC a diagnostic hemithyroidectomy is recommended (R)**
- **Total thyroidectomy is recommended for patients with tumours greater than 4 cm in diameter, or tumours of any size in association with any of the following characteristics: multifocal disease, bilateral disease, extrathyroidal spread (pT3 and pT4a), familial disease, and those with clinically or radiologically involved nodes and/or distant metastases (R)**

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- **Subtotal thyroidectomy should not be used in the management of thyroid cancer (G)**
- **Central compartment neck dissection is not recommended for patients without clinical or radiological evidence of lymph node involvement, provided they meet all of the following criteria: classical type PTC, below 45 years, unifocal tumour, less than 4 cm, no extrathyroidal extension on US (R)**
- **Patients with metastases in the lateral compartment should undergo therapeutic lateral and central compartment neck dissection (R)**
- **Patients with follicular tumours greater than 4 cm should be treated with total thyroidectomy (R)**

Post-operative management

After total or near total thyroidectomy patients should be commenced on suppressive doses of levothyroxine (2 μg/kg) or liothyronine 20 mcg tds in accordance with local protocols.

Calcium levels should be routinely checked within 24 hours and hypocalcaemia treated appropriately.

Thyroglobulin levels should be checked no earlier than six weeks after surgery.

All patients with thyroid cancer should be clinically staged using the TNM classification and also scored using one of the clinicopathological scoring systems to enable planned follow-up, identification of high risk patients and those who would benefit from radio-iodine therapy. In addition, all patients should have access to a thyroid cancer clinical nurse specialist and be given written information.

Persistent voice dysfunction should be investigated and referral to a specialised practitioner for assessment and speech therapy sought.

Patients with long-term hypocalcaemia (hypoparathyroidism) should have their calcium levels regularly monitored either in association with an endocrinologist or with their GP.

Following surgery, initial post-operative risk stratification for risk of recurrence can occur.

Low-risk patients have the following characteristics:

- No local or distant metastases
- All macroscopic tumours have been resected, i.e. R0 or R1 resection
- No tumour invasion of locoregional tissues or structures
- The tumour does not have aggressive histology (tall cell or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements) or angioinvasion.

TABLE V
INITIAL SURGERY FOR PAPILLARY THYROID CARCINOMA

	Tumour <4 cm	Tumours >/=4 cm	T3 and T4 tumours +N1 level VI nodes, M1
Recommendation	With no other clinical features such as age >45 years, extrathyroidal spread, nodal involvement, angioinvasion, multifocality, distant metastases	Papillary cancer diagnosed following hemithyroidectomy, multifocal disease, thyroid radiation in childhood, familial disease (first degree relative)	Treat all above tumours as high risk
Hemithyroidectomy	Yes	No	No
Total thyroidectomy	Discuss at MDT	Completion total thyroidectomy	Yes
Prophylactic level VI nodal dissection	No	Personalised decision making	Yes
Therapeutic level VI nodal dissection (clinically involved)	Yes	Yes	Yes

TABLE VI
INITIAL SURGERY FOR FOLLICULAR THYROID CANCER

	Clinical details	
Recommendation	Low-risk patient (with all of following) <45 years >1–≤4 cm Minimally invasive No angioinvasion No extracapsular invasion No extrathyroidal spread	High-risk patient (one or more of the following) >45 years Tumour >4 cm Extra-capsular invasion Extrathyroidal disease Widely invasive Angioinvasion Hurthle cell tumours
Hemithyroidectomy	Yes	No
Total thyroidectomy	No	Yes
Level VI nodal dissection	No	Only where clinically involved nodes present

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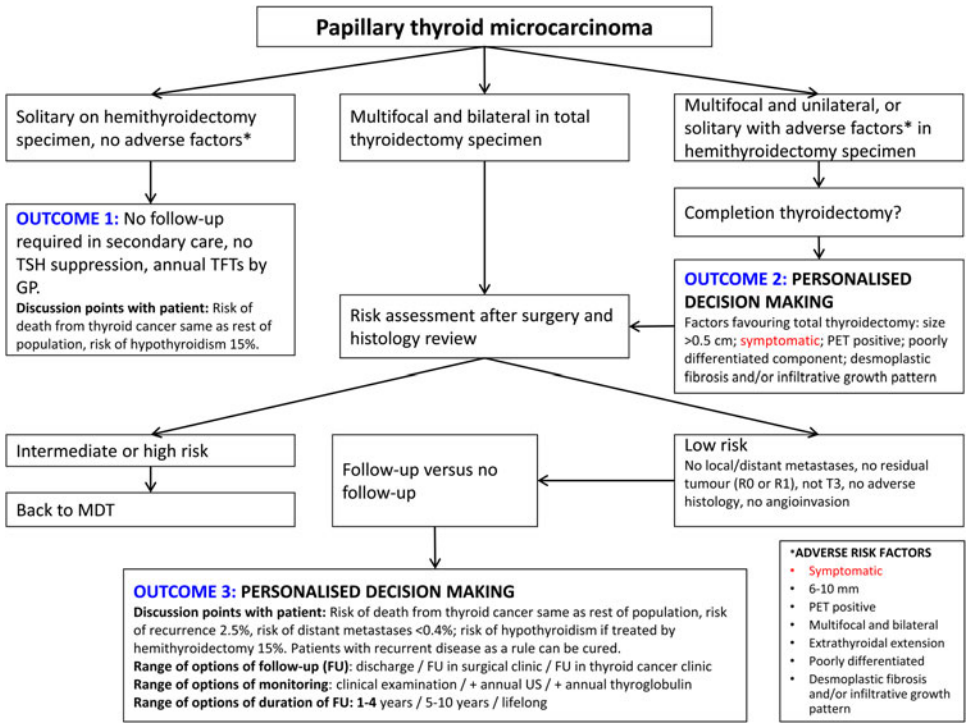

FIG. 1

Flow diagram outlining management of papillary microcarcinomas. Multiple risk factors may tip the balance in favour of total thyroidectomy.

Intermediate-risk patients have any of the following characteristics:

- Microscopic invasion of tumour into the peri-thyroidal soft tissues (T3) at initial surgery
- Cervical lymph node metastases (N1a or N1b)
- Tumour with aggressive histology (tall cell or columnar cell PTC, diffuse sclerosing PTC, poorly differentiated elements) or angioinvasion.

High-risk patients have any of the following characteristics:

- Extrathyroidal invasion
- Incomplete macroscopic tumour resection (R2)
- Distant metastases. (M1)

Radioiodine (I^{131}) ablation and external beam radiotherapy (EBR) in DTC

The current recommendations with regards to I^{131} ablation following total thyroidectomy are outlined in Table VII.

Patients should be prepared for I^{131} by having a low-iodine diet for one to two weeks prior to treatment. Recombinant TSH (rhTSH) therapy prior to I^{131} is preferable to thyroid hormone withdrawal, and is preferred by patients, providing they meet the following criteria: pT1 to T3, pN0 or NX or N1, and M0 and R0 (no microscopic residual disease). Pregnancy should be excluded prior to giving I^{131}. A post-ablation

TABLE VII

INDICATIONS FOR I^{131} ABLATION FOLLOWING TOTAL THYROIDECTOMY FOR DIFFERENTIATED THYROID CANCER

Recommendation	Clinical details
Definite I^{131} ablation	Tumour >4 cm Any tumour size with gross extrathyroidal extension Distant metastases present Risk factors indicating higher risk of recurrence where I^{131} should be considered include: Large tumour size Extrathyroidal extension Unfavourable cell type (tall cell, columnar or diffuse sclerosing papillary cancer, poorly differentiated elements) Widely invasive histology Multiple lymph node involvement, large size of involved lymph nodes, high ratio of positive-to-negative nodes, extracapsular nodal involvement
Probable I^{131} ablation Consider on individual case merit (MDT)	
No I^{131} ablation (all criteria must be met)	Tumour <1 cm unifocal or multifocal Histology classical papillary or follicular variant of papillary carcinoma, or follicular carcinoma Minimally invasive without angioinvasion No invasion of thyroid capsule (extrathyroidal extension)

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scan should be performed after I^{131} when residual activity levels permit satisfactory imaging. Practically, this is generally 2–10 days following treatment.

Following I^{131}, TSH should be suppressed to <0.1 mIU/l pending dynamic risk stratification at 9–12 months.

Adjuvant EBR should be considered in unresectable tumours in addition to I^{131} and where there is residual disease following surgical resection even if the residual tumour concentrates I^{131}.

In the 9 to 12 months following surgery and I^{131} for DTC with an R0 resection, patients should undergo dynamic risk stratification (Table VIII). Patients are then categorised as having either an excellent response, an indeterminate response or an incomplete response.

Monitoring Tg levels. Thyroglobulin monitoring is most effective following total or near total thyroidectomy and I^{131} and is an important modality in detecting residual or recurrent disease. Physicians should be aware that Tg estimations vary according to the assay method, the individual laboratory and the presence of anti-Tg antibodies and take these considerations into account when evaluating Tg levels in individual patients.

The patient should have their Tg levels checked at 6–12 monthly intervals. Rising Tg levels are highly suspicious of recurrent disease. Thyroglobulin evaluation is most effective following TSH stimulation, either by direct rhTSH stimulation or by withdrawal of thyroid hormone replacement.

Following total or near total thyroidectomy and I^{131} ablation, low-risk patients with undetectable Tg levels on TSH suppression should have a TSH-stimulated Tg assessment along with ultrasound of cervical nodes at 9–12 months following I^{131} ablation. If Tg levels remain undetectable following TSH stimulation, then future recurrent disease is highly unlikely and patients may revert to yearly Tg estimation whilst remaining on TSH suppression.

A rise in Tg may be suggestive of recurrent or residual disease, but is usually from a thyroid remnant. In low-risk patients, an expectant policy can be maintained and repeated TSH stimulated assessment performed, with the expectation that Tg levels will fall. Rising or persistently elevated Tg needs further evaluation.

The use of rhTSH-stimulated Tg estimation or rhTSH I^{131} therapy is necessary in the following cases: hypopituitarism, functional metastases (suppressing TSH), severe angina, advanced disease (frail patient) and history of psychiatric disturbance from hypothyroidism.

TABLE VIII

DYNAMIC RISK STRATIFICATION FOLLOWING TREATMENT FOR DTC AND TSH SUPPRESSION TARGETS FOR PATIENTS TREATED WITH TOTAL THYROIDECTOMY AND I^{131} ABLATION WITH R0 RESECTION

Excellent response	Indeterminate response	Incomplete response
All the following: Suppressed and stimulated Tg < 1 lg/l* Neck US without evidence of disease Cross-sectional and/or nuclear medicine imaging negative (if performed)	Any of the following: Suppressed Tg < 1 lg/l* and stimulated Tg ≥ 1 and <10 lg/l* Neck US with non-specific changes or stable sub centimetre lymph nodes Cross-sectional and/or nuclear medicine imaging with non-specific changes, although not completely normal	Any of the following: Suppressed Tg ≥ 1 lg/l* or stimulated Tg ≥ 10 lg/l* Rising Tg values Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging
Low risk Maintain TSH 0.3–2.0 mIU/l	Intermediate risk Suppress TSH 0.1–0.5 mIU/l for 5–10 years then reassess	High risk Suppress TSH < 0.1 mIU/l indefinitely

*Assumes the absence of interference in the Tg assay. Tg = thyroglobulin; TSH = thyroid stimulating hormone; US = ultrasound

Recommendations

- **I^{131} ablation or therapy should be carried out only in centres with appropriate facilities (R)**
- **Serum Tg should be checked in all post-operative patients with DTC, but not earlier than six weeks after surgery (R)**
- **Patients who have undergone total or near total thyroidectomy should be started on levothyroxine 2 µg/kg or liothyronine 20 mcg tds after surgery (R)**
- **The majority of patients with a tumour more than 1 cm in diameter, who have undergone total or near-total thyroidectomy, should have I^{131} ablation or therapy (R)**
- **A post-ablation scan should be performed 3–10 days after I^{131} ablation (R)**
- **Post-therapy dynamic risk stratification at 9–12 months is used to guide further management (G)**

Persistent and recurrent disease, locoregional recurrence and distant metastases

Potentially resectable disease is best managed by surgery (including local cervical nodes and soft tissue disease in the neck), followed by I^{131}. Residual disease not amenable to resection or resistant to I^{131} therapy is best treated with high dose palliative EBR.

Therapeutic central compartment, with or without lateral compartment, nodal clearance should therefore

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be performed for all persistent or recurrent disease confined to the neck. Impalpable nodes greater than 5–8 mm seen on USS or cross-sectional imaging following I^{131} therapy should be considered for removal. Removing nodes less than 5–8 mm has not be shown to be of benefit.

Where technically feasible, tumours invading the aero-digestive tract should be resected in combination with radiotherapy. Outcome is very dependent on completeness of resection and preservation of function. Great care should therefore be taken in the selection and discussion of such patients at the MDT.

Distant metastases develop in 5–23 per cent of patients with DTC. Sites not amenable to surgical resection should be treated with I^{131} therapy. Long-term survival may be expected in patients whose tumours take up I^{131}. Distant metastases are usually seen in the lungs and bones. There is no maximum limit to the cumulative dose of I^{131} that patients with persistent disease may receive and pulmonary fibrosis appears to be a rare side effect. Surgical resection of bony metastases should be considered (especially in patients below 45 years of age). Metastases not cured by I^{131} should be treated with EBR. Other modalities such as intra-arterial embolisation, pamidronate infusion, radiofrequency ablation or vertebroplasty may be considered in cases of painful lesions.

Recommendations

- **Potentially resectable recurrent or persistent disease should be managed with surgery whenever possible (R)**
- **Distant metastases and sites not amenable to surgery, which are iodine avid should be treated with I^{131} therapy (R)**

Long-term follow-up

Lifelong follow-up of DTC is recommended to monitor for late recurrence (often treatable and curable), effects of long-term TSH suppression (atrial fibrillation and osteoporosis) and late side effects of I^{131}. Clinical examination and history, Tg determination, TSH suppression and where necessary calcium monitoring should all be performed. Ultrasound scanning as per established protocols may also be undertaken.

Recommendations

- **Long-term follow-up for patients with DTC is recommended (G)**
- **Follow-up should be based on clinical examination, serum Tg and TSH assessments (R)**

Medullary thyroid cancer

Introduction

Medullary thyroid cancer (MTC) is a rare cancer (approximately 1–3 per cent of all thyroid cancer cases). All cases should be referred for surgical treatment to the designated cancer centre of the Thyroid Cancer Network. Twenty-five per cent of MTC cases are familial (MEN2A, MEN2B and familial non-MEN MTC). Genetic screening (*RET* mutation testing) of all patients is mandatory and the assessment, investigation and treatment of family members at potential risk requires a multidisciplinary approach within the cancer centre.[7]

Clinical presentation

Patients usually present clinically with a thyroid nodule or neck mass with or without cervical lymphadenopathy (in the same fashion as with DTC). History however, may reveal other symptoms such as flushing, loose stools or diarrhoea (which suggest MTC) and is vitally important in determining a potential familial element. FNAC may be diagnostic (when combined with calcitonin staining in suspicious cases), but often is reported as Thy 3.

Investigation

When MTC is suspected (or proven) patients must undergo the following investigations prior to surgery[8]:

- Calcitonin and CEA levels
- Twenty-four-hours urine estimation of catecholamines and nor metanephrines (or plasma nor metanephrines) to identify or exclude phaeochromocytoma
- Serum calcium and parathyroid hormone (PTH) to identify or exclude hyperparathyroidism
- CT, MRI or USS of the neck are indicated as they may help guide the extent of surgical resection at initial surgery
- RET proto-oncogene mutational analysis should be performed after surgery once diagnosis is established, even in the absence of a familial history.

Staging

TNM staging for MTC follows the same criteria as for DTC (Table IX).

TABLE IX
GROUP STAGING FOR MEDULLARY THYROID CANCER

Stage I	T1, N0, M0
Stage II	T2, T3, T4, N0, M0
Stage III	Any T, N1, M0
Stage IV	Any T, any N, M1

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Recommendations

- **Patients with suspected MTC should be investigated with calcitonin and CEA levels, 24 hours catecholamine and nor metanephrine urine estimation (or plasma free nor metanephrine estimation), serum calcium and PTH (R)**
- **Relevant imaging studies are advisable to guide the extent of surgery (R)**
- **RET proto-oncogene analysis should be performed after surgery (R)**

Management-surgery for MTC

All patients with MTC should undergo[8]:

- Total thyroidectomy and central compartment node clearance (level VI). This should be performed even in the presence of disseminated metastases to control local disease.
- In the presence of central compartment lymph node metastases, ipsilateral prophylactic neck dissection is recommended as up to 70 per cent of patients will have lateral nodal metastases.
- Patients with clinically involved lateral compartment nodes should have a therapeutic lateral neck dissection to eradicate local disease.
- All T2–T4 tumours should also undergo prophylactic bilateral selective neck dissection IIa–Vb.
- Intra-thoracic disease below the level of the brachiocephalic vein should be resected via sternotomy where feasible.
- Prophylactic thyroidectomy should be offered to RET-positive family members. Timing and extent of surgery are dependent on genotype (codon mutation), the calcitonin level and age at detection of RET positivity.

Persistent or recurrent MTC

Calcitonin levels are most informative six months after initial surgery. It is important to distinguish persistent locoregional disease (following either inadequate initial surgery or local lymph node metastases) from distant disease.

Early local recurrence following adequate local surgery (total thyroidectomy and level VI nodes) is unusual. The likely source of raised calcitonin in this circumstance is the lateral compartment cervical nodes, i.e. persistent disease. When indicated, re-operation including further central compartment surgery and lateral neck node dissection should be performed. The primary aim should always be to control local disease.

CT, MRI, USS, selective arteriography, I^{131}-metaiodobenzylguanidine, ^{18}Fluoro-deoxy-glucose positron emission tomography, In^{111}-octreotide and direct laparoscopic visualisation of the liver may all be useful in identifying the source of a raised calcitonin, but their use in patients with calcitonin levels <400–500 pg/ml is unlikely to identify metastases. When indicated, isolated metastases should be considered for surgical resection.

Recommendations

- **All patients with known or suspected MTC should have serum calcitonin and biochemical screening for phaeochromocytoma pre-operatively (R)**
- **All patients with proven MTC >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)**
- **Patients with central node metastases should undergo ipsilateral prophylactic lateral node dissection (R)**
- **Prophylactic thyroidectomy should be offered to RET-positive family members (R)**
- **All patients with proven MTC should have genetic screening (R)**

Radiotherapy and chemotherapy

Radiotherapy is of use in controlling local symptoms in patients with inoperable disease and improving the relapse-free rate following central or lateral compartment surgery where residual disease is present macroscopically or microscopically.

Tyrosine kinase inhibitors can be effective in controlling symptoms in patients with metastatic disease.

Somatostatin analogues may be effective in alleviating the unpleasant gastrointestinal symptoms that patients with advanced cases of MTC experience.

Recommendations

- **Radiotherapy may be useful in controlling local symptoms in patients with inoperable disease (R)**
- **Chemotherapy with tyrosine kinase inhibitors may help in controlling local symptoms (R)**

Follow-up

Lifelong follow-up is recommended for all patients with MTC. Screening should include calcitonin and CEA. Thyroid-stimulating hormone suppression is not necessary. Rising calcitonin levels should trigger

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investigations to identify potentially treatable metastatic disease.

Anaplastic thyroid cancer

The prognosis of patients with anaplastic thyroid cancer (ATC) is poor. Many patients present with a history of a rapidly enlarging thyroid mass in a long-standing goitre. Diagnosis can be established by fine needle aspiration or core biopsy. Core biopsy will help differentiate ATC from thyroid lymphoma which can present in a similar manner.

Total thyroidectomy may be curative for very small cancers. In more advanced disease surgery may be of benefit if R0/R1 resection is achievable.[9] External beam radiotherapy and chemotherapy may be used as adjuvant treatments in patients with R0/R1 resection and no evidence of distant disease. 'Debulking' surgery should be avoided when complete resection cannot be achieved. Palliative chemoradiation may be of some value in selected cases. Palliative care has a principal role in management of these patients.

Recommendations

- **Initial assessment should focus on identifying the small proportion of patients with localised disease and good performance status, who may benefit from surgical resection and other adjuvant therapies (G)**
- **The surgical intent should be gross tumour resection and not merely an attempt at debulking (G)**

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GUIDELINE

Management of neck metastases in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. A rational plan to manage the neck is necessary for all head and neck primaries. With the emergence of new level 1 evidence across several domains of neck metastases, this guideline will identify the evidence-based recommendations for management.

Recommendations

- Computed tomographic or magnetic resonance imaging is mandatory for staging neck disease, with choice of modality dependant on imaging modality used for the primary site, local availability and expertise. (R)
- Patients with a clinically N0 neck, with more than 15–20 per cent risk of occult nodal metastases, should be offered prophylactic treatment of the neck. (R)
- The treatment choice of for the N0 and N+ neck should be guided by the treatment to the primary site. (G)
- If observation is planned for the N0 neck, this should be supplemented by regular ultrasonograms to ensure early detection. (R)
- All patients with T1 and T2 oral cavity cancer and N0 neck should receive prophylactic neck treatment. (R)
- Selective neck dissection (SND) is as effective as modified radical neck dissection for controlling regional disease in N0 necks for all primary sites. (R)
- SND alone is adequate treatment for pN1 neck disease without adverse histological features. (R)
- Post-operative radiation for adverse histologic features following SND confers control rates comparable with more extensive procedures. (R)
- Adjuvant radiation following surgery for patients with adverse histological features improves regional control rates. (R)
- Post-operative chemoradiation improves regional control in patients with extracapsular spread and/or microscopically involved surgical margins. (R)
- Following chemoradiation therapy, complete responders who do not show evidence of active disease on co-registered positron emission tomography–computed tomography (PET–CT) scans performed at 10–12 weeks, do not need salvage neck dissection. (R)
- Salvage surgery should be considered for those with incomplete or equivocal response of nodal disease on PET–CT. (R)

Introduction

The presence, site and size of metastatic neck disease are important prognostic factors in head and neck squamous cell cancer. Head and neck tumours have a propensity to metastasise to neck nodes and several factors control the natural history and spread of disease. Controversy surrounds the management of the neck in head and neck squamous cell cancer. This is primarily due to the paucity of high-level evidence for many treatment paradigms, but this trend may be reversing with randomised controlled trials and systematic reviews published recently and a few

more in progress. This section discusses the management of neck metastases at initial presentation and for residual or recurrent neck disease. It outlines major clinical controversies regarding the management of occult and overt metastatic squamous cell carcinoma (SCC) to the neck nodes.

Assessment and staging

For the purpose of assessment and documentation, the neck is described in six anatomical levels, (Table I). Level VII is relevant for some head and neck tumours and is included in the table for completeness.

Clinical palpation

Clinical palpation is regarded as inaccurate (sensitivity and specificity 70–80 per cent) due to factors including inter-operator variability, shape of neck, absence or presence of significant subcutaneous fat and varying size of involved cervical nodes.

Computed tomographic (CT) and magnetic resonance imaging (MRI) scanning

These techniques have similar sensitivity (81 per cent) in detecting metastatic disease, with CT demonstrating better specificity.[1] Co-registered positron emission tomography–computed tomography scanning (PET–CT) has been shown to alter initial staging in up to one-third of patients, but the value of this is unclear. This technique has higher sensitivity in picking up clinically occult primaries, synchronous second primaries and distant metastases. PET-CT has demonstrated high negative predictive values in the assessment of neck disease after organ preservation regimes.

Ultrasound (US) scanning and US-guided fine needle aspiration cytology (FNAC)

Ultrasound has been demonstrated to have consistently high sensitivity (87 per cent) in diagnosing metastatic neck disease. Ultrasound-guided FNAC requires both expertise and experience, and has very high specificity rates (98 per cent) in diagnosis. It should be noted that there are no absolute ultrasound characteristics for differentiating benign from malignant disease.

Sentinel node biopsy

The aim of this technique is to identify and excise the echelon nodes using radioscintigraphy, which are then tested for occult disease. Patients with no occult disease in the sentinel nodes receive no further treatment for the neck. Meta-analyses suggest that sentinel node biopsy has sensitivity rates exceeding 90 per cent.[2,3] A recent prospective multicentre study that recruited 415 patients with 0.5–4 cm transorally resectable SCC and an N0 neck, showed that sentinel node biopsy had a sensitivity, negative predictive value and false negative rate of 86, 95 and 14 per cent, respectively.[4] Oncological outcomes were not compromised despite only 94 of 415 patients undergoing neck dissection in this cohort.

Recommendation

- **Computed tomographic or MR imaging is mandatory for staging neck disease, with choice of modality dependent on imaging modality used for the primary site, local availability and expertise (R)**

Neck nodal stage

This should be confirmed and documented in the case record after imaging (certainty factor 2) and prior to treatment planning, using the N category in the 7th edition of the TNM Classification of Malignant Tumours, Union for International Cancer Control (UICC) cancer staging manual. Table II shows the N category to stage neck metastases arising from all head and neck sites excluding those of the nasopharynx, thyroid gland and mucosal melanomas.

Treatment options

Surgery

Historically the mainstay of surgical management of metastatic neck has been neck dissection in its various forms. The standardised neck dissection terminology produced by the American Academy of Otolaryngology and Head and Neck Surgery in 1991 has been updated by the Committee for Neck Dissection Classification of the American Head and Neck Society in 2002[5] (Table III). There is an increasing trend to divide neck dissections into two broad types with subdivisions: comprehensive (removal of levels I–V) and selective (less than five levels). The need for less extensive surgery in the chemoradiation era, with neck dissection procedures that cannot be classified under the existing systems has led to calls for revision of this system.[6]

It is recommended that the levels or sublevels removed during selective neck dissection (SND) be precisely stated in the operation notes. In order to minimise confusion within labelling the levels during processing, the neck dissection specimen should be divided according to the levels in the operating room and sent to the laboratory in different containers. An alternative is to orientate the neck dissection specimen on a suitable base and label the levels with a marking pen, with or without a photograph, and send it to the laboratory. There is good evidence for reduced long-term morbidity with SND compared with the comprehensive types, namely modified radical neck dissection (MRND) and radical neck dissection (RND). Surgical

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TABLE I
LYMPH NODE LEVELS, SUBLEVELS AND BOUNDARIES

Level	Clinical location	Surgical boundaries	Radiological boundaries
Ia	Submental triangle	S: Symphysis of mandible I: Hyoid bone A (M): Left anterior belly of digastric P (L): Right anterior belly of digastric	Nodes above the level of lower body of hyoid bone, below mylohyoid muscles and anterior to a transverse line drawn through the posterior edge of submandibular gland on an axial image
Ib	Submandibular triangle	S: Body of mandible I: Posterior belly of digastric A (M): Anterior belly of digastric P (L): Stylohyoid muscle	
IIa	Upper jugular	S: Lower level of bony margin of jugular fossa I: Level of lower body of hyoid bone A (M): Stylohyoid muscle P (L): Vertical plane defined by accessory nerve	Superior and inferior limits as described under surgical boundaries Nodes posterior to a transverse plane defined by the posterior surface of submandibular gland and anterior to a transverse line drawn along the posterior border of the sternomastoid. NOTE: Nodes lying medial to the carotids are retropharyngeal and not level II
IIb	Upper jugular	S: Lower level of bony margin of jugular fossa I: Level of lower body of hyoid bone A (M): Vertical plane defined by accessory nerve P (L): Posterior border of sternomastoid muscle	
III	Mid Jugular	S: Level of lower body of hyoid bone I: Horizontal plane along inferior border of anterior cricoid arch A (M): Lateral border of sternohyoid muscle P (L): Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus	Superior and inferior limits as described under surgical boundaries Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries
IV	Lower jugular	S: Horizontal plane along inferior border of anterior cricoid arch I: Clavicle A (M): Lateral border of sternohyoid muscle P (L): Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus	Superior and inferior limits as described under surgical boundaries Nodes anterior to a transverse line drawn on each axial scan through the posterior edge of the SCM and lateral to the medial margin of the common carotid arteries
Va	Posterior triangle	S: Convergence of SCM and trapezius muscles I: Horizontal plane along inferior border of anterior cricoid arch A (M): Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus P (L): Anterior border of trapezius muscle	Nodes posterior to a transverse line drawn on each axial scan through the posterior edge of the SCM
Vb	Posterior triangle (supraclavicular)	S: Horizontal plane along inferior border of anterior cricoid arch I: Clavicle A (M): Posterior border of sternocleidomastoid muscle or sensory branches of the cervical plexus. P (L): Anterior border of trapezius muscle	
VI	Anterior compartment	S: Hyoid bone I: Sternal notch A (M): Common carotid artery P (L): Common carotid artery	
VII	Superior mediastinum	S: Sternal notch I: Innominate artery A (M): Common carotid artery P (L): Common carotid artery	

S = superior; I = inferior, A = anterior; P = posterior, L = lateral; M = medial; SCM = sternocleidomastoid

therapy must be delivered within accredited multidisciplinary teams, by members regularly involved in caring for head and neck cancer patients.

Radiotherapy

Radiotherapy (RT) should be delivered within an accredited department using megavoltage photons typically from a linear accelerator (typical energy 6 MV). Similar principles should be used for selecting the nodes for RT as are described above for surgery. The probability of microscopic involvement of other nodal groups rises with increasing T-stage and this leads to larger volumes of tissue-requiring irradiation.

Radiotherapy to the neck requires adequate immobilisation and a five-point fixation shell is recommended. Computed tomography scanning in the treatment position provides the anatomical and electron density information required for RT planning. Conventional and three-dimensional conformal RT often require the use of multiple phases of treatment using photons and electrons of appropriate energy. These techniques have now been superseded by intensity modulated radiotherapy (IMRT), particularly where bilateral nodal irradiation

TABLE II
TUMOUR–NODE–METASTASIS CLASSIFICATION OF REGIONAL NODES

N_x	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastases
N_1	Metastasis in a single ipsilateral lymph node 3 cm or less in greatest dimension
N_2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N_{2a}	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N_{2b}	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N_{2c}	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N_3	Metastasis in a lymph node more than 6 cm in greatest dimension

Note: Midline nodes are considered to be ipsilateral nodes

is indicated, where it has been shown to be associated with a reduced risk of late xerostomia and has become the standard of care.

There is now increasing use of concomitant chemoradiotherapy following publication of level 1 studies, suggesting that use of chemoradiotherapy improves overall and progression free survival in advanced head and neck cancer both in the primary and post-operative settings. Altered fractionation regimes have also been shown to offer some advantage over standard fractionation.

Management strategies for the various neck nodal stages

Treatment of cervical lymph nodes is either elective (in the clinically negative neck) or therapeutic (in the clinically positive neck).

Management of the clinically node negative neck (N0)

New primary. Clinical and radiological examinations are unable to detect microscopic disease in lymph nodes. Several large retrospective series have reported the incidence of metastases found on histological examination after RNDs in patients with clinically node negative (N0) necks. These figures are useful in identifying the risk of occult metastases in N0 necks and are used to guide clinicians when deciding whether prophylactic treatment of the neck is appropriate (Figure 1).

A study of risk–benefit analysis made in the 1990s using data from retrospective series, when RND was the only procedure widely used for elective neck treatment, suggested that prophylactic treatment of the neck was required if the risk of occult nodal metastases rose above 20 per cent. Given the low morbidity of either available treatment modality, there is support for elective treatment for lesser risk (5–15 per cent). Primary sites with greater than 15 per cent risk of occult metastatic disease in the neck would include almost all squamous cancers of the upper aerodigestive tract except T1 and T2 cancers of the glottis and selected T1 cancers of the oral cavity.

A recent randomised controlled trial (RCT) reported on 500 patients with lateralised stage T1 or T2 oral SCCs randomised to elective neck dissection (n = 245) or observation and intervention (n = 255), with a median follow up period of 39 months.[7] At three years, elective node dissection resulted in an improved rate of overall survival (80.0 per cent; 95 per cent confidence interval (CI), 74.1 to 85.8), as compared with therapeutic dissection (67.5 per cent; 95 per cent CI, 61.0 to 73.9), with a hazard ratio for death of 0.64 in the elective-surgery group (95 per cent CI, 0.45 to 0.92; p = 0.01 by the log-rank test). Patients in the elective-surgery group also had a higher rate of disease-free survival than those in the therapeutic-surgery group (69.5 per cent *vs* 45.9 per

TABLE III
CLASSIFICATION OF NECK DISSECTION TECHNIQUES

Radical neck dissection (RND)	Removal of levels I–V, accessory nerve, internal jugular vein and sternomastoid muscle
Modified radical neck dissection	Removal of levels I–V dissected; preservation of one or more of the accessory nerve, internal jugular vein or sternomastoid muscle (types I, II, III, respectively)
Selective neck dissection	Preservation of one or more levels of lymph nodes
Extended radical neck dissection	Removal of one or more additional lymphatic and/or non-lymphatic structures(s) relative to a RND, e.g. level VII, retropharyngeal lymph nodes, hypoglossal nerve

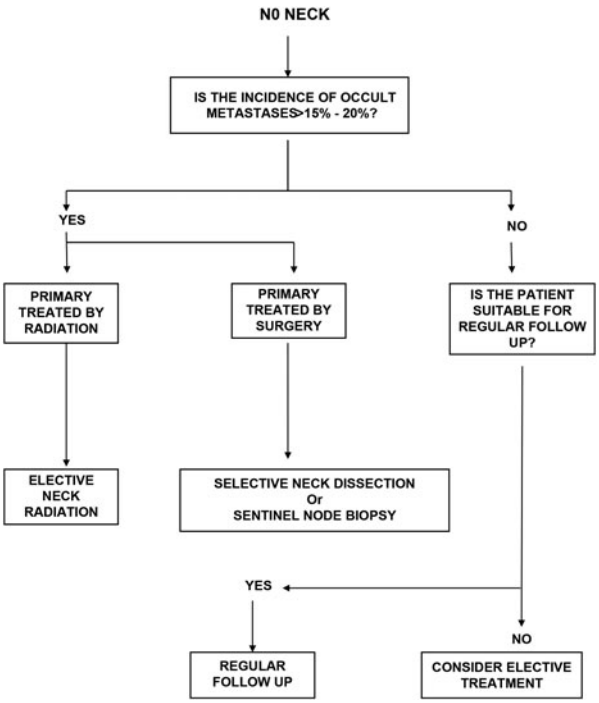

FIG. 1
Algorithm for management of the N0 neck.

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cent, $p < 0.001$). A meta-analysis of all previously published RCTs including data on 283 patients showed that elective neck dissection reduced the risk of disease-specific death (fixed-effects model relative risk = 0.57, 95 per cent CI 0.36–0.89, $p = 0.014$; random-effects model relative risk = 0.59, 95 per cent CI 0.37–0.96, $p = 0.034$) compared with observation.[8]

The classical RND has no role to play in elective treatment of the N0 neck.[9] The choice lies between an MRND and an SND. Prospective studies suggest SND is as effective as MRND for most primary sites with minimal morbidity. Table IV shows the suggested neck levels that should be addressed for various primary sites, with the recommendations based on a recent analysis of the evidence base.[9] For oral cavity tumours, SND of levels I to III should be performed. Due to the possibility of skip lesions in level IV, especially in tongue tumours, some studies recommend including level IV. In oropharyngeal, laryngeal and hypopharyngeal tumours, SND of levels II–IV should be performed. Level IIb dissection may not be necessary for the majority of patients, as the incidence of isolated metastasis at this site is less than 2 per cent.[10]

Elective neck irradiation is as effective as elective neck dissection in controlling subclinical regional disease, with control rates reported to be around 90 per cent. When the primary tumour is treated with RT, first echelon lymph nodes, which are at the greatest risk of harbouring occult disease, are usually included in the high dose or radical RT treatment volume. A large retrospective series comparing elective neck dissection and elective neck irradiation in patients with oral cavity, oropharyngeal and laryngeal cancer reported no statistically significant difference in local control at five years. In patients with hypopharyngeal cancers, local control was significantly better with RT compared with surgery. The consensus guidelines drawn up by experts from clinical research organizations within Europe, Asia, Australia/New Zealand and North America, published in 2014, should be followed for delineation of lymph nodal levels in the node negative neck.[11]

Large retrospective series have reported on the risk of contralateral nodal involvement by each anatomic tumour subsite. As in ipsilateral N0 necks, the contralateral neck should be treated if the estimated risk of occult spread exceeds 15–20 per cent, as occurs with tumours encroaching or crossing the midline. Elective nodal irradiation may be preferred to surgery when both sides of the neck are to be treated.

In long-term follow-up of the untreated N0 neck, consideration should be given where available to ultrasound surveillance and ultrasound-guided aspiration cytology as a method of detecting and treating early disease before it becomes clinically palpable.[12]

Recurrent primary cancer. Occult metastatic rates are low (5–10 per cent) in the setting of radiorecurrent cancer if the neck has been included in the radiation field. As neck dissection (ND) in the salvage setting is associated with more complications with no reported benefit, if access to the neck vessels is not needed for primary resection or reconstruction, routine elective neck dissection may not be needed during salvage surgery for locally recurrent primary cancers.

TABLE IV
RECOMMENDED NECK LEVELS TO BE DISSECTED FOR OCCULT NECK DISEASE BASED ON PRIMARY SITE

Oral cavity	I–III including IIb
Oropharynx	I–III including IIb; recognise significant chance of contralateral disease
Supraglottis	IIa–III; IIb and IV can be spared. Contralateral SND not indicated for lateralised tumours
Glottis	IIa–III; IIb can be spared. Include IV for T3 and T4 primaries
Subgottis	II–IV, VI
Hypopharynx	II–IV

Recommendations

- **Patients with a clinically N0 neck, with more than 15–20 per cent risk of occult nodal metastases, should be offered prophylactic treatment of the neck (R)**
- **The treatment choice of the N0 neck should be guided by the treatment to the primary site (G)**
- **If observation is planned for the N0 neck, this should be supplemented by regular ultrasonograms to ensure early detection (R)**
- **All patients with T1 and T2 oral cavity cancer and N0 neck should receive prophylactic neck treatment (R)**
- **Selective neck dissection is effective as MRND for controlling regional disease in N0 necks for all primary sites (R)**
- **Elective neck dissection and elective neck irradiation have equal efficacy in controlling occult neck disease (R)**

Management of the clinically node positive neck

When there is clinical or radiological evidence of disease in neck lymph nodes, active treatment is required. Level 1 studies exist to guide the treatment of metastatic neck disease in specific scenarios (Figures 2 and 3). The risk of occult metastases in other apparently uninvolved levels of the neck is high, and depending on the primary site, treatment of these nodes is also required. Level V is least likely to be involved, with between 3 and 7 per cent of patients undergoing RND having positive nodes at level V. The treatment choice of the N+ neck should be guided by the treatment to the primary site, and there is long-term data to support this premise.[13]

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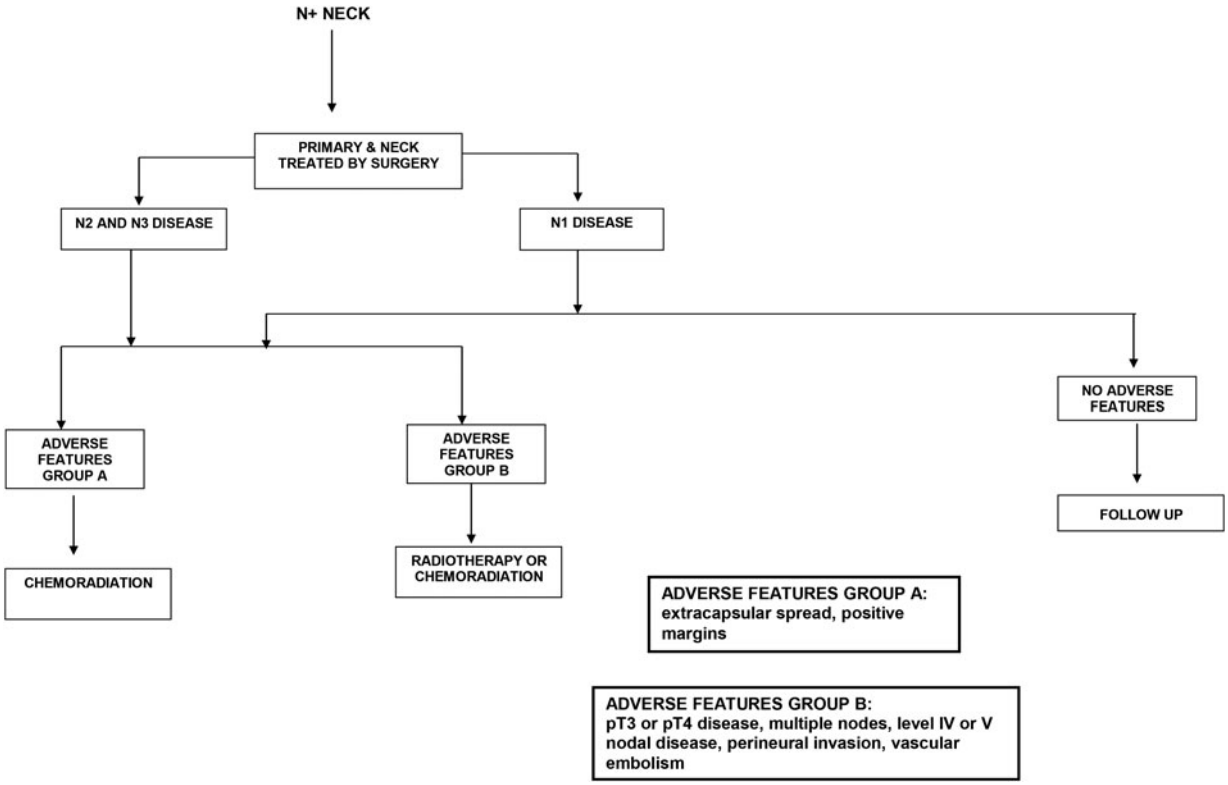

FIG. 2
Algorithm for management of the N+ neck when surgery is the primary modality.

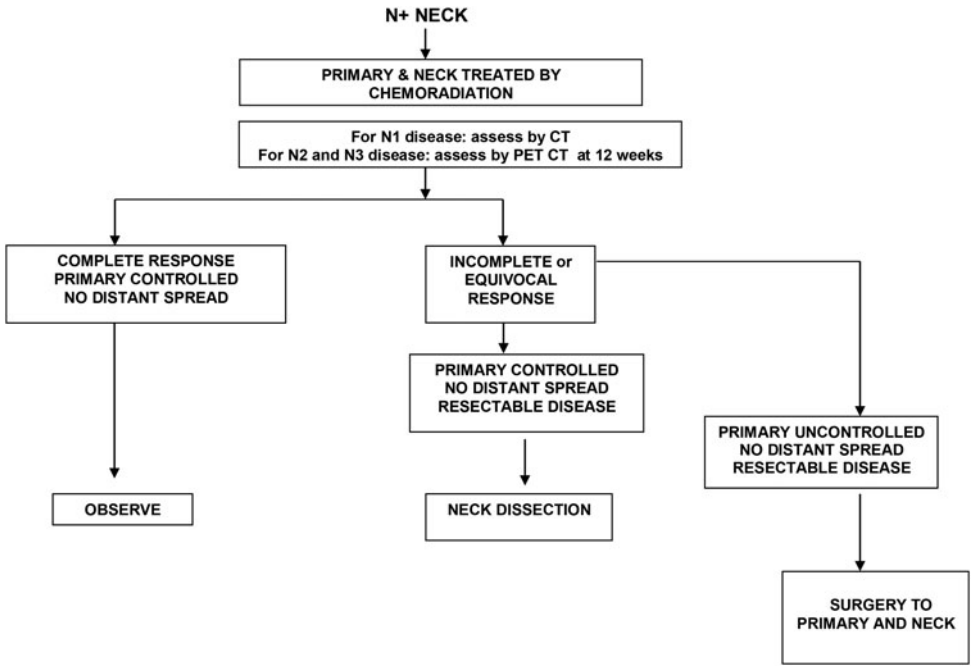

FIG. 3
Algorithm for management of the N+ neck when chemoradiation is the primary modality.

N1 neck disease. Prospective data from large cancer databases suggest that single modality therapy is sufficient to deal with ipsilateral, single nodes of less than 3 cm in size. If surgery is the chosen modality, SND may be appropriate. As approximately 50 per cent of clinically N1 necks are upstaged after pathological assessment, many patients subsequently require post-operative radiation. Prospective studies have shown that in the absence of bulky disease (N1, N2b), appropriate SND in combination with

postoperative RT result in neck control rates equivalent to those achieved by comprehensive neck dissection.[9] Complete response rates are much higher in patients with nodes of less than 3 cm in size and regional control rates following RT alone are best in patients with nodes less than 2 cm in size.

N2 and N3 neck disease. If the primary modality is surgery for this stage of neck disease, MRND and RND result in equivalent rates of disease control in the neck when performed in appropriately selected patients.[9] Retrospective and prospective studies suggest that adding irradiation post-operatively increases regional control,[14] especially in the presence of adverse features such as extracapsular nodal spread, positive margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, nodal disease in levels IV or V, perineural invasion and vascular invasion. Randomised controlled trials from the EORTC and RTOG have shown improved control with chemoradiotherapy in the post-operative setting, especially in the presence of extracapsular spread and/or microscopically involved surgical margins.[15] Patients with two or more histopathologically involved lymph nodes without extracapsular spread as their only risk factor did not benefit from the addition of chemotherapy. Morbidity of neck irradiation is higher in patients who have undergone an RND.

If the primary site is suitable for non-surgical treatment, the neck should be treated at the same time. For neck disease staged N2 and above, this will usually involve chemoradiotherapy. The PET-Neck phase III randomised trial compared PET–CT-guided active surveillance with planned neck dissection for neck disease staged N2 or N3 treated by chemoradiotherapy. The study recruited 282 patients into each arm and showed that the survival outcomes were similar with a minimum follow up of two years. A post treatment PET–CT surveillance strategy led to fewer neck dissections, fewer complications, was cost effective (per person cost saving of £1415) and provided 0.07 additional quality adjusted life years compared with planned neck dissection. Based on the results of the PET-Neck trial, there is no role for planned neck dissection after primary chemoradiotherapy.[16] The current standard of care should be a CT–PET scan between 10 and 12 weeks following chemoradiotherapy, with ND being offered to those who show incomplete or equivocal response of nodal disease. Complete responders may need no further intervention.[17] The extent of the salvage neck dissection can be based on local protocols, with the recognition that there is an increasing trend to perform a limited neck clearance in these individuals, with removal of the involved level alone or an adjacent level. In patients with fixed and unresectable nodal disease, RT or chemoradiotherapy will be the only options available, but a low likelihood of curative outcome should be recognised.

If the primary tumour is small but sited where resection is not feasible, and associated with advanced neck disease, resection of the nodal disease followed by treatment of the primary tumour by RT (± chemotherapy) plus post-operative RT to the involved neck could potentially be considered but this will be associated with a significant delay in the management of the primary disease which may result in interval primary disease progression.

Recommendations

- **The treatment choice to the N+ neck should be guided by the treatment to the primary site (G)**
- **Selective neck dissection alone is adequate treatment for pN1 neck disease without adverse histological features (R)**
- **Post-operative radiation for adverse histologic features following SND confers control rates comparable to more extensive procedures (R)**
- **Adjuvant radiation following surgery for patients with adverse histological features improves regional control rates (R)**
- **Post-operative chemoradiation improves regional control in patients with extracapsular spread and/or microscopically involved surgical margins (R)**

Assessing treatment response

Neck node size and fixity predict response rate and local control with RT alone. In patients with clinical N2 or N3 disease, there is poor correlation between clinical and pathological response following chemoradiotherapy. As discussed above, the PET-Neck trial demonstrated equivalent survival rates to planned neck dissection, with a lower morbidity and a higher overall cost-effectiveness. Co-registered PET–CT scans, performed at least 10 weeks after treatment is now considered the standard of care. A negative PET–CT scan following treatment portends a high disease free survival.[18] High standard uptake values are associated with residual disease and this can be used to decide the need for neck dissection following primary chemoradiotherapy.[17,19,20]

Recommendations

- **Following chemoradiation therapy, complete responders who do not show evidence of active disease on co-registered PET–CT scans performed at 10–12 weeks, do not need salvage neck dissection (R)**
- **Salvage surgery should be considered for those with incomplete or equivocal response of nodal disease on PET–CT (R)**

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Management of recurrent neck disease

Prior to planning salvage treatment, the patient should be meticulously evaluated for distant metastases. This group is likely to benefit from PET–CT scans to look for distant metastases. If the recurrence has occurred following RT or chemoradiotherapy and is surgically resectable, surgery should be offered but acknowledge the higher risk of complications. In patients who present with unresectable disease, re-irradiation with or without chemotherapy should be considered, particularly in those who present more than two years since their previous treatment. Evidence of partial repair of RT-induced spinal cord subclinical damage and newer RT delivery techniques (IMRT, Tomotherapy®, protons) that allow better sparing of neurological, vascular and soft tissue at risk make this a realistic option in a larger number of patients. In patients who recur after previous surgical treatment, options include re-resection followed by adjuvant radiation, or primary RT or chemoradiotherapy.

Palliative care

Patients who have incurable nodal recurrence present a significant challenge, particularly when distant metastases are not present as people can then live with recurrent disease for many months or longer. Fungating neck nodes have a significant effect on psychosocial function. The impact on speech and swallowing needs careful discussion with dieticians and speech and language therapists so that the potential benefits of tube feeding can be weighed against the risk of over-medicalising terminal care. Specialist palliative care teams should ideally be involved in these discussions before such complications develop.

There may be occasions where palliative RT, chemotherapy or surgery have the potential to improve quality of life (QoL) in this situation. The overall expected prognosis, patient perspective and goals, morbidity of treatment and likely benefits need to be openly discussed to ensure that there is a reasonable expectation that any intervention will improve QoL for a given individual.

Ongoing research

Current portfolio studies open to recruitment and relevant to neck metastases include: the role of SND in patients with early oral SCC (1–3 cm primary size) and no clinical evidence of lymph node metastases in the neck (SEND trial).

Key points

- The neck stage is the single most important tumour prognostic factor
- Prognosis is affected by number of involved nodes, the anatomic level in the neck, tumour load, the presence of extracapsular spread, perineural and vascular invasion, previous treatment by surgery or radiotherapy and resectability
- A large number of malignant nodes will measure less than 10 mm in diameter and extracapsular spread will occur in a substantial percentage of smaller nodes, as small as 2 mm. These may not be identified on conventional (CT and magnetic resonance) imaging
- Incidence of nodal metastases depends on site and size of the primary tumour. This figure may be as low as 1 per cent for early glottic tumours or as high as 80 per cent for nasopharyngeal carcinomas
- The majority of tumours will metastasise in a predictable manner to certain nodal groups but it should be remembered that tumours can metastasise to more remote sites (i.e. nasopharyngeal cancers to level V, tongue cancers to level IV) and that the pattern of spread will be disrupted by previous surgery or radiotherapy
- The possibility of bilateral nodal disease should be considered especially when the primary site involves the tongue base, nasopharynx or supraglottic larynx or when the primary site crosses midline
- Neck dissections should be documented as per the accepted classification system
- Radiotherapy target delineation should follow the internationally recognised consensus guidelines
- Standardised reporting of neck dissection specimens according to the Royal College of Pathologists data set is essential
- Issues of function and quality of life have to be considered in the management of metastatic neck disease.

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GUIDELINE

Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It discusses the evidence base pertaining to the management of metastatic neck disease in the setting of an unknown primary and provides recommendations on the work up and management for this group of patients receiving cancer care.

Recommendations

- All patients presenting with confirmed cervical lymph node metastatic squamous cell carcinoma and no apparent primary site should undergo:
  - Positron emission tomography-computed tomography whole-body scan. (R)
  - Panendoscopy and directed biopsies. (R)
  - Bilateral tonsillectomy. (R)
- Tongue base mucosectomy can be offered if facilities and expertise exists. (G)
- Concomitant chemotherapy with radiation should be considered in patients with an unknown primary. (R)
- Concomitant chemotherapy with radiation should be offered to suitable patients in the post-operative setting, where indicated. (R)
- Neo-adjuvant chemotherapy can be used in gross 'unresectable' disease. (R)
- Patients should be followed up at least two months in the first two years and three to six months in the subsequent years. (G)
- Patients should be followed up to a minimum of five years with a prolonged follow up for selected patients. (G)
- Positron emission tomography–computed tomography scan at three to four months after treatment is a useful follow-up strategy for patients treated by chemoradiation therapy. (R)

Introduction

An unknown primary is defined as a squamous cell carcinoma (SCC) presenting in a lymph node or nodes in the neck with no primary index site in the head and neck having been identified. These patients are best assessed comprehensively through a dedicated neck lump clinic. As part of this assessment the lymph node should be sampled and in general it is recognised that this is best achieved by ultrasound-guided fine needle aspiration (FNA) cytology and/or core biopsy under ultrasound guidance. The receipt of a cytological or histological report confirming SCC initiates the need for further investigation.

Clinical presentation

Neck lumps presenting with no discernible primaries can be solid or cystic lesions, which can be solitary or multiple lumps. The lumps are usually located in level 2, followed by level 3, with bilateral involvement and other symptoms (i.e. pain and dysphagia) reported in less than 10 per cent. The clinical N stage at presentation is usually N2a, N2b and N2c.[1] The presence of cystic malignant metastases in level 2 is often considered to be a hallmark of human papilloma virus (HPV)-related squamous carcinoma, usually with subclinical primaries in the oropharynx.[1] The first echelon lymph node or nodes, which are involved in SCC can act as an indicator for the potential origin of the index primary are shown in Table I.

It should be also noted that patients presenting with supraclavicular lymphadenopathy may represent a different clinical entity,[2] due to the potential for association with infraclavicular neoplasms, such as lung cancer.

TABLE I
FIRST ECHELON LYMPH NODES FOR VARIOUS PRIMARY SITES

Level 1	Oral cavity, oropharynx
Level 2	Oral cavity, oropharynx, larynx, nose, hypopharynx, parotid, nasopharynx
Level 3	Oral cavity, oropharynx, larynx, hypopharynx, thyroid, nasopharynx
Level 4	Larynx, thyroid, hypopharynx, oesophagus
Level 5	Nasopharynx, hypopharynx, thyroid, oropharynx
Level 6	Thyroid, larynx, hypopharynx, cervical oesophagus

Assessment and staging

Clinical examination of the nose, post-nasal space, oral cavity, oropharynx, larynx and hypopharynx, including palpation of the oral cavity and tongue base should be carried out under direct vision and using rigid and flexible endoscopes as appropriate. The skin and scalp of the head and neck region should be examined to ensure that there are no significant cutaneous lesions. If there is an obvious lesion, or high suspicion of a lesion, then further management in the form of imaging and panendoscopy of that sub-site should be carried out. If there is no obvious or highly suspicious lesion on out-patient assessment, then the patient should be regarded as having an unknown primary and should be evaluated further, this clinical entity being known as a 'clinical' unknown primary. To try to determine the site of the primary the following investigations and findings should be collated.

Pathology of lymph nodes

The advantage of a core biopsy over FNA cytology is that a clearer histological picture can be determined.[3] Although this is generally used to differentiate between squamous, thyroid, salivary, breast or bronchial origins, it may be possible from the cell architecture to suggest the potential origin of the index primary. Even though immuno-histochemical techniques may not be able to suggest the tumour origin they may, however, potentially exclude sites, e.g. by the use of lung or thyroid markers. More specific investigations such as identification of Epstein-Barr virus (EBV) may correlate highly with a nasopharyngeal site.

Human papilloma virus is a significant aetiological factor in oropharyngeal cancer and so the identification of HPV 16 and 18 in a lymph node sample would be strongly suggestive of an oropharyngeal origin.[1,4] P16 positivity is highly predictive of HPV overexpression and may be used as a surrogate marker to indicate the HPV status.

Cross-sectional imaging

All patients should have computed tomography (CT) imaging from skull base to diaphragm as part of the assessment of a newly diagnosed SCC of the head and neck.[1] In the clinical scenario of an unknown primary, it would be appropriate to undertake this as it would assess and confirm the extent of the lymphadenopathy and whether there is a second primary or metastasis in the lung. Computed tomography imaging may show evidence of a potential index primary site, although in general, it is infrequently of significant value in diagnosing low-volume tumours in the head and neck. If the disease presents in a level 2/3 lymph node magnetic resonance imaging (MRI) of the oropharynx, and in particular the tongue base, tonsil and tonsil lingual angle, should be carried out. It could be argued that all unknown primary patients should have an MRI of the neck up to skull base. It should be borne in mind, however, that positron emission tomography–computed tomography (PET-CT) may be carried out as the first-line investigation of these patients in which case 'plain' CT should not be carried out.

Positron emission tomography–computed tomography fusion scan

Positron emission tomography-computed tomography scanning is the recognised investigation of choice in the assessment of the unknown primary and has been shown to be superior to CT scanning alone. Recent meta-analysis reported an identification rate of 44 per cent, a sensitivity of 97 per cent and a specificity of 68 per cent.[5,6] The evidence in support of this modality is level 3 and is based on observational series. Within this assessment it should be noted that there is a significant false-positive identification rate associated with PET–CT scan. Despite these limitations, PET–CT has now been confirmed as not only the imaging modality of choice in the investigation of an unknown primary, but is now also regarded as the current standard of care.[1]

Panendoscopy

Following each of the clinical and radiological assessments it is necessary to carry out panendoscopy of the upper aerodigestive tract under general anaesthesia.

The timing of this should be following the completion of all of the imaging as any instrumentation and biopsy of these areas prior to scanning would compromise the accuracy of the subsequent radiological assessments. In addition, imaging may identify a potential primary site for a targeted biopsy.

Under general anaesthesia, each of the subsites of the head and neck should be examined under direct vision and by use of all types of straight and angled telescopes appropriate to that area. The subsites which should be examined are the nose, paranasal sinuses, nasopharynx, oral cavity, hard and soft palates, tongue base, tonsil, posterior pharyngeal wall, vallecula, supraglottis, glottis, subglottis, pyriform fossa, post-cricoid region and proximal oesophagus. Palpation of oral cavity and tongue base should also be carried out.

In any of these areas if there is any suspicion of ulceration, change in colour, asymmetry or fullness, then the area should be photographed and appropriate deep biopsies taken. If there is no obvious lesion,

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then the question of random biopsies arises. Although there is little evidence in support of this long-standing practice, biopsy of the post-nasal space, tongue base and/or pyriform fossa would still appear to be common practice especially if the positive lymph node is one of the first echelon lymph nodes draining the index site being biopsied.

There is an evolving evidence base in support of ever increasing oropharyngeal lymphoid tissue resection. It is now accepted that bilateral tonsillectomy should be carried out. An extension of this principle is an increasing body of evidence in support of excision or sampling the lingual tonsil (tongue base mucosectomy),[7–9] which is best accomplished by transoral robotic surgery.[10,11] Although this increases the yield of squamous carcinoma primaries the effect that this might have on structure and function within the oropharynx and ultimately how it relates to survival needs clarification.

Most current groups would suggest that PET–CT imaging, in conjunction with panendoscopy, directed biopsy as appropriate and bilateral tonsillectomy offer the greatest chance of identifying the occult primary tumour in the routine clinical setting. The role of tongue base mucosectomy by transoral laser or robotic approach, with or without PET–CT or HPV positivity needs prospective evaluation.

Following detailed clinical, radiological and operative assessment, if an index primary site is identified then treatment should be according to the guidelines for that site with nodal metastasis. If each of these investigations is negative, then this should be regarded as a 'true' unknown primary and the treatment considered as such.

Staging

The neck is staged as set out elsewhere in this supplement. It should be noted that the correct T stage for an unknown primary is T0 and not TX.

Treatment

The aim of the treatment of the majority of patients with a 'true' unknown primary tumour in the head and neck should be curative with the least morbidity to the upper aerodigestive tract possible. The treatment of an occult mucosal primary is often assumed and based on the well-studied natural history of mucosal squamous cell cancers of the upper aerodigestive tract. Most treatment regimens will therefore involve combined modality treatment, but on occasions, radiotherapy (RT), and even more rarely surgery, will be used as single modality treatment.[12] The rate of emergence of the primary tumour is approximately 3 per cent per year, which is equivalent to the development of second carcinomas in the head and neck, lung and oesophagus. Therefore the primary aim of treatment is locoregional control. However, the rarity of unknown primaries (approximately 1–2 per cent of all squamous head and neck cancers) means there is a dearth of literature to guide best practice. Many of the management decisions are therefore controversial, and based on individual centre case series.

Recommendations

- **All patients presenting with confirmed cervical lymph node metastatic SCC and no apparent primary site should undergo:**
- **Positron emission tomography–computed tomography whole-body scan (R)**
- **Panendoscopy and directed biopsies (R)**
- **Bilateral tonsillectomy (R)**
- **Tongue base mucosectomy can be offered if facilities and expertise exist (G)**

Surgery on its own may be sufficient treatment for N1 necks demonstrating no extracapsular spread, but in all other scenarios, needs to be supplemented by adjuvant (chemo) radiation (Table II).

For more advanced neck disease intensive combined treatment is required. This could be either a combination of neck dissection and RT or initial (chemo)-radiotherapy followed by planned neck dissection if a complete response is not evident on imaging. Both of these approaches appear to be equally effective. Of emerging significance is the question of HPV 16 and 18 positivity and the effect it has on treatment recommendations. Given the apparent good clinical response to HPV-positive lymph nodes then the question arises as to the advisability of surgical clearance of the neck with or without adjuvant (chemo) radiotherapy or whether primary RT should be considered as the only treatment modality in this specific group.

Surgery

T0N1

T0N1 – no extracapsular spread. Patients presenting with N1 disease and who are subsequently confirmed following surgery as having pN1 disease without extracapsular spread may be treated with surgery alone provided the surgery has been comprehensive. This should be in the form of a modified radical neck dissection (MRND), including levels 1–5, and in the vast majority preserving the ipsilateral sternomastoid muscle, internal jugular vein and accessory nerve. This has been shown to be as effective as RT and clearly avoids the potential side effects of RT. There are no randomised data to support MRND over selective neck dissection (SND).[13] However, in the absence of other adjunctive therapies for the N1 neck, a MRND may be preferred as its extent and subsequent radiological assessment may avoid the need for radiation.

T0N1 – with extracapsular spread. When extracapsular spread is found, however, then RT to at least the involved nodal levels is necessary, although it is more usual to irradiate the entire ipsilateral post-operative

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TABLE II
TREATMENT RECOMMENDATIONS

Stage	Surgery	Radiotherapy	Chemotherapy
T0N1 (no ECS)	SND or MRND	No unless for mucosal sites	No
T0N1 (ECS)	SND or MRND	Yes – either involved lymph nodes or ipsilateral neck and boost to involved lymph nodes	Should be considered
T0N2a, N2b, N2c	SND or MRND±contralateral SND or MRND	Yes – ipsilateral but bilateral should be considered	Should be considered
T0N3	Radical or type I MRND	Yes – ipsilateral but bilateral should be considered	Should be considered

SND = selective neck dissection; MRND = modified radical neck dissection

neck, and boost the involved levels. The addition of chemotherapy to RT for occult primary head and neck cancer has not yet been established. However, as post-operative chemoradiation has been demonstrated to be superior to post-operative radiation alone in the context of pathologically confirmed extracapsular spread, in patients with detectable upper aerodigestive tract cancers, the addition of concomitant platinum-based chemotherapy to radiation should be considered.[14] There are no robust data to support the additional use of total mucosal irradiation (TMI) with ipsilateral neck radiation following neck dissection for T0pN1 disease.

There are also some reports that locoregional tumour control is up to 40 per cent higher with surgery and radiation therapy compared with radiation alone, meaning radiation alone, even for N1 disease, must remain an option only for those who are inoperable on medical grounds or where it is considered appropriate for those who are HPV positive.

T0N2a, T0N2b and T0N2c

For each of these stages comprehensive clearance of the involved lymph node levels is usually required in the form of MRND or SND with possible contralateral SND or MRND. The rate of regional recurrence for SND is similar to reported rates for MRND, when combined with adjuvant radiation, such that SND may be an appropriate surgical option for more advanced neck disease in selected patients. Equally in less advanced disease it has been reported that SND can be used with similar efficacy to MRND. Radical RT to one or both sides of the neck should be considered, even for pN2a disease, as in one of the largest series of occult primary head and neck cancer in 136 patients from the MD Anderson Centre, combined surgery and post-operative radiation was associated with lower rates of locoregional relapse and higher disease-free survival. This radiation may be given with or without concomitant chemotherapy as described above. While there remains no randomised data to support the use of chemotherapy for pN2 disease from an occult head and neck primary, there are two case series both demonstrating excellent progression-free survival (PFS) and overall survival (OS) rates. The chemotherapy protocols used were heterogeneous, and included concomitant cisplatin, concomitant 5-fluorouracil (5-FU) and hydroxyurea, as well as paclitaxel.

In the absence of supportive data, radiation of potential index sites, depending on the lymph nodes levels involved, remains controversial. It should remain an area of active investigation, with the conventional management of patients with pN2 disease being as described above.

T0N3

It may not be possible to have a curative aim in patients with this staging. There is, however, a potential role for surgery as palliation, in the form of a radical neck dissection with the aim of preventing or delaying, the onset of fungation of the nodal metastasis. For curative intent a radical neck dissection or Type I MRND with post-operative chemoradiotherapy will usually be necessary.

Radiotherapy

Primary treatment. For N1 disease with extracapsular spread, N2 and N3 disease, initial chemoradiation with planned neck dissection only for those patients not achieving a clinical or metabolic complete response on post-treatment imaging is a valid management strategy.[12,15] The extent of the RT fields to be treated is controversial. In the absence of high-level evidence, the practice of radiation therapy in this setting includes involved field only or bilateral neck and TMI. The latter is practiced commonly in the UK.

Adjuvant treatment. There is a lack of consensus on the RT target volumes that should be treated after neck dissection.[16] Treatment of the ipsilateral hemi-neck alone is of considerably lower toxicity and has been shown to achieve local control rates in the cervical nodes of 90 per cent with contralateral relapse rates as low as 4.7 per cent, provided treatment strategies are determined using PET–CT. However, total mucosal and bilateral neck irradiation of the head and neck region is a common practice with the aim of eradicating the primary and the microscopic neck disease.

With the addition of cisplatin to primary RT for the treatment of head and neck cancer, an absolute survival benefit of 6.5 per cent is seen at five years. Investigating concomitant chemoradiation in the post-operative setting, the Radiation Therapy Oncology Group (RTOG) demonstrated a 10 per cent improvement in locoregional control rate, and a 22 per cent risk reduction of disease recurrence and death at two years, while the European Organisation for Research and Treatment

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of Cancer (EORTC) group showed a 13 per cent improvement in locoregional control, 25 per cent risk reduction of disease progression, and 30 per cent risk reduction of death at five years.[14,17] These findings were based on the concomitant use of cisplatin 100 mg/m^2 on days 1, 22 and 43, which must therefore remain the gold standard.

Total mucosal irradiation. This remains a controversial issue. In the largest series to date, no patient developed a metachronous primary in the follow-up period, and so would have experienced only toxicity rather than benefit from TMI. Some groups have recommended bilateral neck and TMI for occult primary head and neck cancer patients, claiming improved local control, but no OS benefit. There is no conclusive evidence to support the routine use of TMI.

What is clear, however, is that with conventional RT techniques, TMI is given at the price of significant acute toxicity and chronic morbidity, mainly xerostomia with its associated complications and effects on quality of life. Intensity modulated radiation therapy (IMRT) enables delivery of different doses during TMI, thus potentially reducing treatment related toxicity. Four centres have reported their experience of using IMRT to deliver TMI for unknown primaries, with excellent two-year locoregional control (85–88 per cent) and OS (74–85 per cent). The MD Anderson group, however, has most recently reported the most mature data, with five-year actuarial locoregional control of 94 per cent and OS of 89 per cent.[18] The TMI in all reports was well tolerated, and with significantly reduced xerostomia and mucositis. Due to the lack of randomised evidence, the post-operative RT volume treated should therefore be at the discretion of the treating clinician. If TMI is advocated the use of IMRT is recommended.[19,20]

Radiation dosage schedules:

- Post-operative neck: 60 Gy in 30 fractions or equivalent
- Post-operative neck with extracapsular spread: 64–66 Gy in 32–33 fractions or equivalent
- Gross macroscopic disease still present: 70 Gy in 30 fractions or equivalent
- Putative mucosal sites and the uninvolved neck: 50 Gy in 25 fractions or equivalent.

Chemotherapy

In the absence of randomised data to support chemotherapy, either before, during or after radiation for occult primary head and neck cancer, the indications for chemotherapy with post-operative or radical RT should be as for treatment of patients with detectable head and neck SCCs. The chemotherapy regimen used is at the discretion of the treating clinician, but will usually be platinum-based, single-agent cisplatin or carboplatin or cetuximab in patients with suboptimal renal function.

Recommendations

- **Concomitant chemotherapy with radiation should be considered in patients with an unknown primary (R)**
- **Concomitant chemotherapy with radiation should be offered to suitable patients in the post-operative setting, where indicated (R)**
- **Neo-adjuvant chemotherapy can be used in gross 'unresectable' disease (R)**

Neo-adjuvant chemotherapy. While the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) failed to demonstrate a significant benefit for the use of induction chemotherapy,[21] many of the historical trials included pre-dated the use of taxanes. Both the EORTC 24971 and TAX 323 studies and the TAX 324 trial found that the addition of docetaxel (T) to cisplatin (P) and 5-FU resulted in improved PFS, OS and response rate and yet lower associated toxicity. In the context of gross unresectable neck disease, it therefore seems reasonable to consider the use of such induction chemotherapy, particularly for patients with excellent performance status, as a cytoreductive measure prior to definitive concomitant chemoradiation, even for occult primary disease. The caveat remains that the outcome of such case series should be reported in the literature where possible, for this rare group.

Concomitant chemotherapy. The addition of post-operative adjuvant chemotherapy concurrently with radiation has transformed with the publication of two trials from EORTC and RTOG. See section 'Adjuvant treatment' for detailed discussion.

Adjuvant chemotherapy. There are no convincing data that chemotherapy given after radiation or surgery is of benefit in terms of either disease-free or OS for patients with detectable primaries. This approach cannot therefore be recommended for patients with occult primary head and neck cancer.

Recommendations

- **Patients should be followed up at least two months in the first two years and three to six months in the subsequent years (G)**
- **Patients should be followed up to a minimum of five years with a prolonged follow-up for selected patients (G)**
- **Positron emission tomography–computed tomography scan at three to four months after treatment is a useful follow-up strategy for patients treated by chemoradiation therapy (R)**

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Follow-up

Follow-up schedules should be in keeping with the monitoring of all patients who have received treatment for low-volume head and neck SCC with cervical metastasis, as discussed elsewhere in these guidelines. The highest risk period for relapse of squamous carcinoma following treatment occurs in the first two years. A frequent follow-up programme of monitoring every 4 weeks up to 18 months is indicated for patients who have received radical treatment. This should identify the appearance of a primary, or any recurrence, in turn allowing their prompt and optimal management.

As previously discussed, PET–CT is frequently a standard part of the work up for patients presenting with cervical metastasis from an occult primary. There are data to suggest that it also plays a useful role in follow-up. A negative PET–CT scan after treatment with chemoradiotherapy is associated with a high negative predictive value (>95 per cent), and a negative scan undertaken three to four months after completion of therapy can therefore provide some reassurance for the patient and clinician that there is no residual disease. However, there are no data on the value of subsequent imaging to monitor either subclinical locoregional recurrence or the development of a primary cancer, at a later stage. The decision regarding subsequent imaging, whether annually or otherwise, remains therefore at the discretion of the treating clinician.

Key points

- All patients with a clinical unknown primary should have comprehensive imaging, including positron emission tomography–computed tomography imaging, followed by panendoscopy and bilateral tonsillectomy
- In the majority of cases, radical treatment should include surgical clearance of the neck followed by chemoradiotherapy
- Primary concurrent chemoradiation with planned neck dissection or neck salvage based on response is a valid alternative treatment strategy
- If total mucosal irradiation is to be considered, then intensity modulated radiation therapy should be used
- Follow-up should be similar to that employed in patients who have received the treatment for an identified tumour of the head and neck.

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GUIDELINE

Speech and swallow rehabilitation in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. The disease itself and the treatment can have far reaching effects on speech and swallow function, which are consistently prioritised by survivors as an area of concern. This paper provides recommendations on the assessments and interventions for speech and swallow rehabilitation in this patient group.

Recommendations

- All multidisciplinary teams should have rehabilitation patient pathways covering all stages of the patient's journey including multidisciplinary and pre-treatment clinics. (G)
- Clinicians treating head and neck cancer patients should consult the National Cancer Rehabilitation Pathway for head and neck cancers. (G)
- All head and neck cancer patients should have a pre-treatment assessment of speech and swallowing. (G)
- A programme of prophylactic exercises and the teaching of swallowing manoeuvres can reduce impairments, maintain function and enable a speedier recovery. (R)
- Continued speech and language therapist input is important in maintaining voice and safe and effective swallow function following head and neck cancer treatment. (R)
- Disease recurrence must be ruled out in the management of stricture and/or stenosis. (R)
- Continuous radial expansion balloons offer a safe, effective dilation method with advantages over gum elastic bougies. (R)
- Site, length and completeness of strictures as well as whether they are in the presence of the larynx or not, need to be assessed when establishing the likelihood of surgically improved outcome. (G)
- Primary surgical voice restoration should be offered to all patients undergoing laryngectomy. (R)
- Attention to surgical detail and long-term speech and language therapist input is required to optimise speech and swallowing after laryngectomy. (G)
- Patients should commence wearing heat and moisture exchange devices as soon as possible after laryngectomy. (R)

Introduction

Most head and neck cancers and their treatments affect speech and swallowing and this section therefore concentrates on the rehabilitation of these functions.[1–6] Allied health professional (AHP) head and neck cancer rehabilitation pathways are required as part of the implementation of the Improving Outlines Guidance rehabilitation measures and are required for peer review. These pathways should cover all stages of the patient's journey from diagnosis, through treatment, to survivorship and end of life care and should include relevant intervention from dietetics, physiotherapy, occupational therapy and speech and language therapy. Pathways for oral rehabilitation with input from hygienists, restorative dentists, dental implantologists, prosthetic technicians should also be considered.

The stages of the pathways and the allied health professional interventions appropriate to each stage are detailed along with an extensive evidence review in the National Cancer Rehabilitation Pathway for Head and Neck Cancers.[2]

Responsibility for the rehabilitation of voice, speech and swallowing rests with the whole multidisciplinary team (MDT), but is the specific role of the speech and language therapist within this team. Speech and language therapists should discuss their role and outline the need for the patient's active participation in therapy to maximise outcomes. The patient's family and carers are also involved in this rehabilitation. Within the MDT, the decision on an appropriate course of treatment should take into account the effects on functions such as voice, speech and swallowing as well as survival so as to suit each individual's preferences and lifestyle.

Recommendations

- **All MDTs should have rehabilitation patient pathways covering all stages of the patient's journey including multidisciplinary and pre-treatment clinics (G)**
- **Clinicians treating head and neck cancer patients should consult the National Cancer Rehabilitation Pathway for Head and Neck Cancers (G)**

Rehabilitation of voice, speech and swallow

Goals of rehabilitation

- Achieve the best possible functional outcome and quality of life (QoL)
- Identify and carry out interventions which are most effective for both the specific treatment and the individual patient at the optimal time
- Provide support and rehabilitation to patients and their carers.

Assessment

All head and neck cancer patients should have a pre-treatment assessment of speech and swallowing.[1–6] Baseline assessments should be undertaken by the speech and language therapist and appropriate interventions to maintain functions before treatment should be undertaken. Assessments of voice, speech and swallowing should be carried out at all stages of the pathway.

Clinical assessments include: oral-motor examination (lip closure, range of motion), articulation, tongue control and strength; evaluation of the oropharyngeal swallow (timing, efficiency, aspiration, tongue and laryngeal motion) and perceptual evaluation of voice quality.

Instrumental assessments of swallowing include flexible endoscopic examination of swallowing, videofluoroscopy and/or modified barium swallow.[5] Instrumental assessments of voice include: endoscopy, stroboscopy and speech studio/laryngograph. These assessments can provide useful biofeedback to patients and demonstrate the effectiveness of interventions.

Therapy/interventions

Pre-treatment. Pre-treatment counselling by AHP teams should be provided to advise on the anticipated effects of the cancer as well as subsequent treatments (chemoradiation, radiotherapy (RT), surgery and palliation).[7]

A strict programme of prophylactic exercises and the teaching of swallowing manoeuvres can reduce specific impairments, maintain functions and enable a speedier recovery ensuring post-treatment rehabilitation is more successful.[8] For those undergoing surgery the teaching of swallow strategies beforehand can reduce risk and maximise function. This may also reduce the need for tube feeding during treatment and the length of post-treatment tube feeding.

Post-treatment

Voice. Specific therapy techniques can be targeted at projection, pitch, reduction of fatigue, increased adduction, coordination of respiration, vocal hygiene and amplification. These are particularly relevant to those having laser surgery or RT to the larynx.

Speech. For those undergoing oral resections a programme of compensations, articulation and intelligibility can be started once suture lines have healed.

Swallowing. Following instrumental assessment, interventions should be targeted at specific physiological deficits and volitional control to compensate for the changes to the anatomy and physiology. This can reduce the risk of aspiration, malnutrition and improve QoL. These interventions include:[9]

- Postures to reduce aspiration, e.g. head turn, chin tuck
- Manoeuvres, e.g. supraglottic swallow, Mendelsohn.
- Therapeutic exercises, e.g. thermal tactile stimulation, range of motion, shaker
- Diet modifications regarding textures and recommendations on oral or non-oral intake.

Oral rehabilitation. Intra-oral prostheses providing palatal lift, obturation and augmentation can improve speech and swallow function after oral resections and the speech and language therapist and restorative dental surgeon and/or prosthetic technician need to work closely together. Radiation-induced fibrosis can present with trismus. This can cause pain, difficulty with oral intake, poor oral hygiene and lack of dental care. Exercises with tongue depressors or a specific device can increase mouth opening.

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Recommendations

- **All head and neck cancer patients should have a pre-treatment assessment of speech and swallowing (G)**
- **A programme of prophylactic exercises and the teaching of swallowing manoeuvres can reduce impairments, maintain function and enable a speedier recovery (R)**
- **Continued speech and language therapist input is important in maintaining voice and safe and effective swallow function following head and neck cancer treatment (R)**

Management of stenosis and stricture

Prevention, assessment and diagnosis

Dysphonia following RT and chemoradiotherapy to the oro/hypopharynx is multifactorial and difficult to treat. Xerostomia, loss of tongue base bulk and fibrosis/reduced function of constrictors all play a part. Speech and language therapy and AHPs' input as above remains of utmost importance, but stenosis and stricture can also develop.

Stenosis of the (hypo)pharynx and neopharynx is common following treatment for laryngeal and pharyngeal cancer.[10,11] After treatment of cervical oesophageal cancer some degree of stenosis is almost inevitable in this region especially following CRT.[6] Reported rates vary from 8 per cent following primary chemoradiotherapy to 40 per cent or more following salvage surgery after (chemo)radiotherapy, particularly if preceded by a pharyngocutaneous fistula.[10] Additional dysphagia occurs in extended surgery, particularly with posterior tongue resection and with extended neck surgery with sacrifice of glossopharyngeal and hypoglossal nerves (lesser), and vagus nerve (major).[12,13]

No standardised definition exists to help to measure stenosis rates. Anatomical stenosis might be of greatest interest to the surgeon, but functional stenosis is of no less impact and interest to the patient. Videofluoroscopy, supplemented by axial imaging, is the tool best able to identify the nature of a stenosis of the (neo)pharynx and assess the degree of impact on swallowing. Importantly, barium swallows also have the capacity to identify a proportion of occult recurrences masquerading as benign stenosis.

Predictors of stenosis are helpful to surgeons. Studies have shown that following laryngectomy and partial pharyngectomy a 3 cm (unstretched) to 8 cm (stretched) posterior pharyngeal strip is sufficient to allow normal post-treatment swallow and voice rehabilitation. Circular/circumferential rather than linear scars remain more stenosis prone, but no data exist on the minimum luminal diameter with a circular scar to allow normal swallowing. Repair of the suprahyoid muscles (which include the middle constrictor) to the thyropharyngeus muscles after laryngectomy has been advocated and may improve swallow by reducing the size and effect of a pseudoepiglottis as well as allowing better function of the middle constrictor. Cricopharyngeal myotomy and horizontal closure of the pharynx with laryngectomy is generally held to improve speech and swallow outcomes especially when performed with primary tracheo-oesophageal puncture and valve reconstruction for speech rehabilitation. In addition, the relationship between luminal diameter and the use of peristaltic *vs* non-peristaltic flaps have yet to be quantified in maintaining a functional post-operative voice and swallow.

The role of salivary bypass tubes may reduce fistula rates and hence possible stricture rates, but this needs further study.

Treatment

This depends on the type (functional *vs* anatomical, scar *vs* recurrence), site and comorbid factors such as fitness for further reconstructive surgery. Median feeding tube placement times following all forms of treatment for head and neck cancer are in the region of 20–26 weeks, and up to 50 per cent of patients reconstructed with free or pedicle flaps are tube-feed dependent at one year post-surgery. Reported rates of complication with percutaneous endoscopic gastrostomy and radiologically inserted gastrostomy tubes vary considerably with up to 3 per cent mortality rates reported in some series and 10 per cent significant complication in others. Clearly the use of different supplemental feeding techniques will depend on local experience in this respect.

Dilation of isolated short segment strictures remains a valuable means of controlling symptoms for patients with poor life expectancy or multiple comorbidities.[10] Continuous radial expansion balloons allow dilation up to 20 mm diameter and may be safer and more effective than traditional bougies. They can also be utilised without general anaesthesia. It is clear that many patients require multiple dilations, often without long-lasting relief of dysphagia.

Sternomastoid flaps can be useful in the non-irradiated patient, but are less reliable than pectoralis major, radial forearm flap (RFF), anterolateral thigh (ALT) and jejunal flaps. Choice of and reasons for a particular free flap vary depending on familiarity with the flap and perceptions of function *vs* cosmesis. Reported case series for RFF, jejunum or ALT describe similar complication rates (<5 per cent flap failure, up to 50 per cent pharyngocutaneous fistula) and success rates (speech intelligibility and swallow performance).[14]

The length and completeness of stenosis are important factors in advising patients whether significant improvement can be obtained. Complete stricture of the hypopharynx post-chemoradiotherapy can be

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improved with total laryngopharyngectomy, but patients need to be warned that swallowing outcomes are often poorer in this group than primary pharyngectomy patients.

Cricopharyngeal myotomy

Cricopharyngeal myotomy appears to have little value *per se* for improvement of dysphagia following surgical treatment of cancers of the oropharynx.[15] In combination with vocal fold medialisation, where needed, and laryngeal elevation, better success rates may be obtained.

Recommendations

- **Disease recurrence must be ruled out in the management of stricture and stenosis (R)**
- **Continuous radial expansion balloons offer a safe, effective dilation method with advantages over gum elastic bougies (R)**
- **Site, length and completeness of strictures as well as whether they are in the presence of the larynx or not, need to be assessed when establishing the likelihood of surgically improved outcome (G)**

Rehabilitation after laryngectomy

Speech

Laryngectomy results in significant alteration of anatomy and often complex rehabilitation. A range of voice prostheses are now available, with Blom Singer and Provox being the commonly used ones. If visual, cognitive and fine motor skills are intact, independence should be fostered by teaching patients to self change their voice prostheses. Where appropriate, 'hands-free' outer valves should be available for patients to try. Although surgical voice restoration techniques dominate, it is important to consider the use of oesophageal speech and electrolarynges. Electrolarynges use an external vibratory source and are either placed in the mouth or against the neck or cheek to produce sound. Both these methods can have their place in the rehabilitation process.[16]

Speech and language therapists with appropriate training and expertise in the management of the stoma and tracheo-oesophageal puncture should be part of all MDTs. The MDT should ensure that there are procedures to manage out of hours problems such as loss or aspiration of prosthesis. Patients and local teams should be aware that if a prosthesis cannot be replaced the puncture should be kept patent with a catheter or stent for instance. Speech and language therapists should be aware of the need for and rationale behind, amongst others, videoflouroscopy for trouble-shooting, botulinum toxin, antifungals, management of leakage through as well as peripheral leakage around a prosthesis. The Royal College of Speech and Language Therapists has recently published an excellent and comprehensive document covering these topics: 'Prosthetic Surgical Voice Restoration (SVR): The role of the speech and language therapist'.[1]

Swallow

There has been a growing appreciation in recent years that swallowing also requires rehabilitation in laryngectomy patients.[16–18] Although laryngectomy patients should not aspirate unless their voice prosthesis is leaking, they may have difficulty swallowing solid foods or take significantly longer than others to finish meals. It has been suggested that as many as 42 per cent of laryngectomy patients have a degree of dysphagia three years post-surgery with a 72 per cent incidence of self-reported dysphagia. Higher levels of depression and anxiety have also been documented in laryngectomees who have dysphagia.[19] Videofluoroscopy is one of a number of swallow evaluation tools used with laryngectomy patients and can contribute to surgical consideration of interventions such as botulinum toxin and dilatation to treat dysphagia. Further rehabilitation tools include the use of exercises to strengthen specific muscles such as tongue base. Appetite can also be affected by a significant loss of ability to taste and smell after laryngectomy. Olfactory rehabilitation utilising the 'polite yawn' has been proposed to help correct this.

Respiration

Respiration is altered significantly post-laryngectomy with the patient now breathing through an open neck stoma bypassing the nasal passages and throat. As a consequence of this anatomical change, the ability to filtrate irritants such as dust from the air and to humidify inhaled air is lost. This can result in increased mucus production and crusting of dried secretions. In recent years, humidification exchange devices have been developed to restore humidification and filtration. Rehabilitation of pulmonary function should be offered to all laryngectomy patients and should involve education about the use of stoma covers and bibs. The presence of an open neck stoma causes some patients anxiety and rehabilitation may include such diverse subjects as advice about maintaining appearance and showering safely.

The adjustment to life as a laryngectomee can be significant. Tools such as the EORTC Core Quality of Life Questionnaire and the University of Washington Quality of Life Tool, version 4 can be useful in identifying not only those at risk of psychosocial problems but also to help plan and focus rehabilitation.[19]

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Recommendations

- **Primary surgical voice restoration should be offered to all patients undergoing laryngectomy (R)**
- **Attention to surgical detail and long-term speech and language therapist input is required to optimise speech and swallowing after laryngectomy (G)**
- **Patients should commence wearing heat and moisture exchange devices as soon as possible after laryngectomy (R)**

Key points

- Speech and swallow rehabilitation needs should be assessed before treatment
- Assessment and appropriate interventions should take place throughout the patient journey, including ongoing after treatment
- Multidisciplinary assessment and management of swallowing problems is important
- Videoflouroscopy is an important tool in assessing swallow problems
- Dysphagia caused by pharyngeal stenosis after chemoradiotherapy can be difficult to correct and complex cases should be managed by expert teams.

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GUIDELINE

Recurrent head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. Recurrent cancers present some of the most challenging management issues in head and neck surgical and oncological practice. This is rendered even more complex by the poor evidence base to support management options, the substantial implications that treatments can have on the function and quality of life, and the difficult decision-making considerations for supportive care alone. This paper provides consensus recommendations on the management of recurrent head and neck cancer.

Recommendations

- Consider baseline and serial scanning with computed tomography and/or magnetic resonance (CT and/or MR) to detect recurrence in high-risk patients. (R)
- Patients with head and neck cancer recurrence being considered for active curative treatment should undergo assessment by positron emission tomography combined with computed tomography (PET–CT) scan. (R)
- Patients with recurrence should be assessed systematically by a team experienced in the range of management options available for recurrence including surgical salvage, re-irradiation, chemotherapy and palliative care. (R)
- Management of patients with laryngeal recurrence should include input from surgeons with experience in transoral surgery and partial laryngectomy for recurrence. (G)
- Expertise in transoral surgery and partial laryngectomy for recurrence should be concentrated to a few surgeons within each multidisciplinary teams. (G)
- Transoral or open partial laryngectomy should be offered as definitive treatment modality for highly-selected patients with recurrent laryngeal cancer. (R)
- Patients with OPC recurrence should have p16 human papilloma virus status assessed. (R)
- Patients with OPC recurrence should be considered for salvage surgical treatment by an experienced team, with reconstructive expertise input. (G)
- Transoral surgery appears to be an effective alternative to open surgery for the management of OPC recurrence in carefully selected patients. (R)
- Consider elective selective neck dissections in patients with recurrent primaries with N0 necks, especially in advanced cases. (R)
- Selective neck dissection (with preservation of nodal levels, especially level V, that are not involved by disease) in patients with nodal (N+) recurrence appears to be as effective as modified or radical neck dissections. (R)
- Use salivary bypass tubes following salvage laryngectomy. (R)
- Use interposition muscle-only pectoralis major or free flap for suture line reinforcement if performing primary closure following salvage laryngectomy. (R)
- Use inlaid pedicled or free flap to close wound if there is tension at the anastomosis following laryngectomy. (R)
- Perform secondary puncture in post chemoradiotherapy laryngectomy patients. (R)
- Triple therapy with platinum, cetuximab and 5-fluorouracil (5-FU) appears to provide the best outcomes for the management of patients with recurrence who have a good performance status and are fit to receive it. If not fit, then combinations of platinum and cetuximab or platinum and 5-FU may be considered. (R)
- Patients with non-resectable recurrent disease should be offered the opportunity to participate in phases I–III clinical trials of new therapeutic agents. (R)
- Chemo re-irradiation appears to improve locoregional control, and may have some benefit for overall survival, at the risk of considerable acute and late toxicity. Benefit must be weighed carefully against risks, and patients must be counselled appropriately. (R)
- Target volumes should be kept tight and elective nodal irradiation should be avoided. (R)
- Best supportive care should be offered routinely as part of the management package of all patients with recurrent cancer even in the case of those who are being treated curatively. (R)

Introduction

Traditionally patients with recurrence of head and neck cancer (HNC) are considered to have poor prognosis. As a result the majority of these patients are usually treated with palliative intent or receive best supportive care.

Recent systematic review of the literature would suggest, however, that outcomes of the management of recurrence are not as dire as is widely considered. For example, the management of laryngeal recurrence is reported to have good outcomes with rates of up to 71 per cent two-year overall survival.[1] A recent meta-analysis shows that the outcomes of management of oropharyngeal cancer recurrence appear to have improved significantly over the last two decades, reaching five-year survival of 50 per cent in patients treated surgically.[2] The latter may be the result of a combination of better patient selection, improved surgical care and the role of the human papilloma virus (HPV) as an aetiological factor.

These improvements in outcomes suggest the need for re-appraisal of the treatment paradigms of HNC recurrence, and the development of specific expertise in the management of recurrence including probably the concentration of expertise in centralised regional or super-regional services.

Evaluation of the patient with recurrence

Evaluation and careful selection of patients with recurrence is the crux of successful management.[3] There are several steps in the evaluation process of these patients.

History

It is important to elucidate the details of the previous treatments that the patient has had, including the chronology and duration since previous treatment. It is also important to identify any toxicity that the patient has experienced from previous treatments as this may have a bearing on any new treatments being offered. The patient's past medical history, and current morbidities and general health state are important, as these will help determine whether the patient is fit enough to receive further curative or palliative active treatments. A smoking and alcohol intake history should be taken. This should especially ascertain whether the patient is currently still smoking or drinking heavily. Finally, a social history of the patient's activities of daily living and their requirements in terms of speech and mobility, as well as their social support structures are important in determining their ability to cope with the demanding treatments that may be required for the management of the recurrence.

Assessment and staging

Clinical examination. Even under anaesthetic, examination can be deceiving if relied upon solely. One study showed a false negative rate of 31 per cent for examination under anaesthetic (EUA) biopsies in 131 patients who showed recurrence within six months of EUA. However, following identification of potential recurrence by scanning, EUA can help provide more information regarding the feasibility of surgical resection and aid planning. Furthermore, a biopsy can be used to assess HPV status, which recently has been found to be of prognostic value in patients with recurrence.[4] In the longer term, as personalised medicine develops, molecular profiling of the recurrent tumour may provide insights into the most appropriate systemic treatments for that particular tumour.

Performance status and co-morbidities Assessment of the patient's overall fitness for anaesthetic and/or systemic therapy is necessary, as that is likely to be an important determinant of whether the patient is able to receive additional treatment in both a curative and a palliative setting.

Imaging Positron emission tomography combined with computed tomography (PET–CT) scanning can be extremely helpful in the assessment of recurrence as it can identify the areas of local and nodal recurrence, and importantly distant metastasis. The negative predictive value of PET–CT scan is especially high for recurrence at both the primary site and the neck, approaching values between 93 and 95 per cent and 94 and 100 per cent respectively.[5] A meta-analysis also showed high sensitivity and specificity for detection of distant metastasis in patients with recurrent HNC (0.92 and 0.95 respectively),[6] and PET–CT scanning can change the management in 20 per cent of patients with HNC recurrence. In one study, 24 of 123 patients were identified to have silent recurrence or metastasis by PET–CT, of which 50 per cent had thoracic metastasis and 32 per cent had distant metastasis in other sites[7].

A single CT scan or magnetic resonance imaging (MRI) scan has low accuracy for differentiating between cancer, oedema, and interstitial radiation fibrosis and necrosis. Additional imaging such as an MRI or contrast CT scanning may however be important for planning surgical procedures and outlining radiotherapy (RT).

Recommendations

- **Consider baseline and serial scanning with CT or MRI to detect recurrence in high risk patients (R)**
- **Patients with HNC recurrence being considered for active curative treatment should undergo assessment by PET CT scan (R)**

Decision making for treatment

By combining the findings of the patient assessment process, the following factors need to be considered to help select cases that are appropriate for curative treatment.[3]

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- What was the previous disease and what were the treatments given? A review of the extent and features of the previous disease including any poor prognostic features and involved margins is necessary. Furthermore, it is important to elucidate the details of the previous treatment including the levels of neck dissection, the radiotherapy (RT) fields and doses as well as ascertaining any geographic misses and the time since treatment.
- Is there any evidence of distant metastasis? This severely limits the possibility of cure and therefore affects the choice and aggressiveness of treatments to be offered.
- Is it a recurrence at the primary site or a second primary tumour? It is important to ascertain the extent and the size of the recurrence of the primary tumour. Recurrence of a previous tumour has a poorer outcome than a second primary. Furthermore, recurrences in the oropharynx have significantly poorer outcomes than those in the larynx.
- Is there recurrence in the neck? What are the extent and the size of the neck recurrence and is there any evidence of soft tissue extension or extracapsular nodal extension by physical examination and on imaging? The presence of extracapsular extension without the ability to give additional adjuvant treatment significantly reduces the chance of cure and survival.[8]
- Is there evidence of involvement of the carotid arteries, brachial plexus and prevertebral muscles? Involvement of these makes surgical resection unlikely and curative resection almost impossible.
- Can the recurrence be excised surgically with no gross tumour left behind?
- Are there complications and toxicity of previous treatment evident, including osteoradionecrosis or dysphagia? If there are, then the addition of further treatment may result in considerable toxicity and quality of life detriment.
- Is it possible to give RT and/or chemotherapy, taking into account previous treatment, resultant toxicities and time of last treatment?
- What are the potential functional deficits of the proposed treatment for the recurrence?
- What is the state of the patient's reserve, psychological state, general health and family and social support? These factors will be important to consider if the patient is fit and able to undergo further treatment.

Patient selection criteria

Studies on the outcomes and prognostic factors for the treatment of head and neck recurrence are generally retrospective and of poor quality. They have described, however, several predictors of good outcome which can be classified under three main themes: patient factors, treatment factors and tumour factors.

Patient factors

The patient factor predictors of good outcome include patients who are non-smokers or who have stopped smoking, have good general heath (ECOG (Eastern Cooperative Oncology Group) status 0–1) and minimal comorbidities,[9] a good psychological state, good family support, those who are married, and those who are religious or spiritual.

Tumour factors

Patients with laryngeal recurrence or second primary tumours have better outcomes. Patients with small localised tumours (low T stage (rT1–T2) and a low overall stage[8] and those with no neck disease on recurrence demonstrate better outcomes. Patients with no nodal extracapsular spread also have better outcomes. Patients who have a recurrence more than 12 months after the end of their treatment appear to do better. Those with recurrence less than six months from treatment completion have persistent disease and a much worse prognosis.[8] Finally, patients who have HPV positive recurrent disease have longer survival following treatment for recurrence.[4]

Treatment factors

Patients having surgical resection,[2,4] who have received no previous RT or chemotherapy[8,9] or have not experienced severe ongoing toxicity from previous treatment appear to have the best outcomes, especially if they have HPV-positive disease.[4] Patients with resectable disease with no gross tumour remaining after resection and no involved surgical margins[8] also demonstrate better outcomes, as do patients with no involved vital structures.

Surgery

General principles

From the data available, surgery appears to be the modality that is likely to result in the best chance of cure,[2] especially if there is the possibility of receiving adjuvant treatment post-operatively,[8] or if the patient has HPV-positive disease.[4] The aim of surgical treatment is to remove the whole tumour with wide clear margins, leaving no gross residual tumour behind. However, this will usually result in large defects requiring reconstruction. The resulting large functional deficits have to be balanced against the benefit of longer survival and/or or improved palliation.

Surgical salvage is associated with high complication rates and morbidities. The Radiation Therapy Oncology Group (RTOG) 91–11 study reported an overall complication rate of 59 per cent, of which 19 per cent were classified as major complications.[1] A fistula rate of 30 per cent was reported following salvage laryngectomy after chemoradiotherapy, and 15 per cent if they had been treated with RT. The MD Anderson series of oropharyngeal salvage reported an overall complication rate of 48 per cent.[8] As a result

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of that and slower wound healing, patients experience long stays in hospital, which they need to be forewarned about. Such treatment also carries significant costs, which need to be accounted for in reimbursement. Specific interventions that have been shown to reduce complication rates are discussed below.

Recommendation

- **Patients with recurrence should be assessed systematically by a team experienced in the range of management options available for recurrence including surgical salvage, re-irradiation, chemotherapy and palliative care (R)**

It is important to note that patients should undergo appropriate and extensive counselling regarding expected survival and functional outcomes, including the long post-operative hospital stays and high complication rates. Early involvement of palliative care physicians in the counselling and treatment of patients, even in situations where curative treatments are being offered, is of benefit to control symptoms and provide psychological support.

Site-specific factors

Larynx. Total laryngectomy is a highly feasible and effective treatment for laryngeal recurrence. In the RTOG 91–11 study, 122 patients recurred after RT or chemoradiotherapy, all of whom had salvage total laryngectomy. The study reported two-year locoregional control rates of 74 per cent and two-year overall survival of 71 per cent.[1] However, it should be noted that there are several other feasible and highly effective modalities for the treatment of laryngeal recurrence that may also allow preservation of organ function. Transoral laser surgery has been found to be very effective in well-selected patients. In a study of 34 recurrent T1–T4 post-RT failures, 71 per cent were reported to be cured with one or more transoral laser procedure, 29 per cent of patients had tumours that could not be controlled, of which 18 per cent required total laryngectomy and 9 per cent required palliative treatment.[10] In another study of 53 T1–T4 tumours that recurred after RT,[11] 42 per cent were cured with one transoral procedure and 16 per cent required more than one procedure, 26 per cent could not be controlled and required total laryngectomy and 11 per cent could not undergo total laryngectomy for recurrence and required palliative treatment. Transoral surgery should however be performed in selected cases by experienced surgeons, as a meta-analysis of transoral laser surgery for radiorecurrent cancers showed around 30 per cent inferior local control compared with open partial laryngectomy.[12]

A systematic review and meta-analysis of 554 patients who underwent salvage open partial laryngectomy concluded that the pooled locoregional control rate was 87.2 per cent (83.3–90 per cent). Pooled overall survival was 83.5 per cent (79.4–87.3 per cent), with a pooled disease-free survival of 91.4 per cent (88.0–94.2 per cent). While 97 per cent of patients underwent successful decannulation, and of the 197 patients where swallowing outcomes were reported, 194 achieved full oral intake.[13] Supracricoid laryngectomy alone was assessed in a meta-analysis of 103 recurrent T1 and T2 glottic cancer[14] and local control could be achieved in 85 per cent. In the 15 per cent who had further recurrence, two thirds could be treated further with salvage laryngectomy.

Therefore, total laryngectomy is not the only option for treatment of laryngeal recurrence, and transoral and partial laryngectomy operations are feasible and highly effective. It is recommended that the management of patients with laryngeal recurrence includes input from surgeons who have expertise in transoral and open partial laryngectomy in the recurrence setting, and that this expertise is limited to a small number of surgeons providing regional services.

Recommendations

- **Management of patients with laryngeal recurrence should include input from surgeons with experience in transoral surgery and partial laryngectomy for recurrence (G)**
- **Expertise in transoral surgery and partial laryngectomy for recurrence should be concentrated to a few surgeons within the MDT (G)**
- **Transoral or open partial laryngectomy should be offered as definitive treatment modality for appropriate highly-selected patients with recurrent laryngeal cancer (R)**

Oropharynx. Recent data suggest that the outcomes of treatment of oropharyngeal recurrence have steadily and markedly improved over the last two decades. In a meta-analysis of five-year outcomes, survival outcomes are reported to have increased from 18 per cent for patients treated before the year 2000 to 51 per cent for patients treated after the year 2000.[2] It would also appear that the reported complication rates have also decreased considerably over that period of time. This improvement in outcomes may be due to a combination of several factors: better intra- and post-operative care, better use of reconstructive techniques, better patient selection and also the possible role of HPV. Recent data suggest that patients with HPV-positive recurrence of the oropharynx have longer survival rates than patients with HPV-negative recurrence.[4] Importantly, those patients who are HPV positive and who received surgical resection had significantly better outcomes than the other groups. This would suggest that there is a need for a change in the traditional view that patients with oropharyngeal

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cancer have very poor outcomes, and therefore are often offered palliative treatments instead of curative resections. It should, however, also be noted that surgical treatment of recurrence carries significant complication rates as well as considerable functional deficits, with reports on return to oral intake varying from 44 to 68 per cent.[8] Successful resection of oropharyngeal recurrence can be difficult due to the complex three-dimensional anatomy and proximity and adherence to the internal carotid artery. Access procedures through mandibulotomy or lingual release are usually required. Discussion with oncology colleagues regarding areas of highest RT delivery can help plan the siting of the mandibulotomy, as a median mandibulotomy may avoid the areas of the mandible that received the highest RT dose, and therefore avoid the areas at highest risk of osteoradionecrosis. Lingual release is also a good option, but provides limited access to the superior aspects of lateral tonsillar extensions, and may result in higher functional morbidity.

Recommendations

- **Patients with oropharyngeal recurrence should have p16 HPV status assessed (R)**
- **Patients with oropharyngeal recurrence should be considered for salvage surgical treatment by an experienced team, with reconstructive expertise input (G)**
- **Transoral surgery appears to be an effective alternative to open surgery for the management of oropharyngeal recurrence in carefully selected patients (R)**

Recently the advent of transoral surgery, and especially transoral robotic surgery (TORS), has facilitated better transoral access to the oropharynx.[15] This approach is now being utilised for surgical resection of smaller OPC recurrences with good outcomes. A recent multicentre case–control study showed that salvage patients treated with transoral robotic surgery had significantly lower incidence of tracheostomy, feeding tube use, and shorter hospital stay, with significantly decreased incidence of positive margins and significantly higher survival than matched patients treated with open surgery.

Nasopharynx. This is the one area traditionally where re-irradiation has been employed for salvage treatment, particularly where the recurrent disease is limited to the confines of the nasopharynx without extensive invasion of the bone of the skull base or intracranial structures. In areas of the world where major centres treat large numbers of these patients, notably Southern China, Hong Kong and Singapore, surgery for localised recurrent disease has been undertaken by means of maxillary swing or other forms of anterior mid-facial approaches. With varying degrees of nasopharyngectomy, cure rates in selected patients have been reported in the region of 40 per cent at five years.

Sinus and nasal cavity. Despite the rarity of these tumours and the diversity of pathology in these areas, salvage treatment can achieve good long-term cure rates in carefully selected patients. Endoscopic endonasal surgery is showing comparable outcomes and is the treatment of choice in certain situations for both primary and recurrent disease when compared with conventional open approaches.

Many recurrent tumours such as adenoid cystic carcinoma, chondrosarcoma, intestinal type adenocarcinoma and olfactory neuroblastoma will need a multimodality, multidisciplinary approach, which can only be effectively provided in large centres that have the expertise both in endonasal and in open anterior and anterolateral craniofacial resection. The tumour biology as well as its location determines the best approach. Oncological goals do not change in the endoscopic endonasal route with the goal being negative resection margins. En-bloc resection is often not possible. Despite this, outcomes in both overall survival and disease-free survival are comparable with open approaches and should be considered as a viable treatment option for recurrences.

Neck and nodal disease. Neck dissection in the salvage context may carry higher complication rates than in the primary setting. The type of neck dissection also has a bearing on complication rates, with modified radical neck dissections or radical neck dissections carrying higher major complication rates than selective neck dissections in the salvage setting. Furthermore, neck dissection was found to be a significant risk factor for pharyngocutaneous fistula after laryngectomy in a meta-analysis.[16] Studies looking at avoiding neck dissection in patients with recurrence at the primary site with no clinical evidence of nodal metastasis have shown that whilst the neck dissection is associated with higher complication rates, there was also a lower regional failure rate. On the other hand, other studies have found the pre-operative clinical staging of nodal status in patients undergoing salvage laryngectomy to be highly accurate.[17] Therefore it would appear that undertaking elective neck dissections in patients with N0 necks following recurrence should be considered, especially in patients with advanced recurrences.

As for patients with proven nodal recurrent disease, selective neck dissection is also as effective as modified radical neck dissections, but potentially carries less morbidity.[18] The evidence would suggest that using selective neck dissection reduces complication rates and results in similar control rates to more radical neck dissection in recurrence patients who have N0. Indeed, some have suggested that superselective neck dissection is also effective, although the evidence level for this is weak.[19]

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Recommendations

- **Consider elective selective neck dissections in patients with recurrent primaries with N0 necks, especially in advanced cases (R)**
- **Selective neck dissection (with preservation of nodal levels, especially level V, that are not involved by disease) in patients with nodal (N+) recurrence appears to be as effective as modified or radical neck dissections (R)**

Reducing complications in salvage surgery

There are interventions that are proven to reduce complications in salvage surgery. These include the following:

- Use of Montgomery salivary bypass tubes has been shown to decrease fistula rates and has also been shown to be cost-effective in laryngectomy[20]
- The use of flap closure for pharyngeal defects if there is any tension on wound closure has been shown to decrease fistula rates. A meta-analysis showed that use of a vascularised flap to augment the circumference or support the repair reduces the risk of fistula formation by one-third.[13] Flap reconstruction also reduces stricture rates and tube dependence compared with primary closure. The use of a pectoralis major pedicled-flap or a free flap is therefore recommended
- In patients where there is no tension at the anastomotic site, interposition flap reinforcement of the suture line has been shown to decrease fistula rates. This may be undertaken using a pectoralis major myofascial pedicled flap or an interposition free flap, both of which have been shown to reduce fistula rates[13]
- Secondary puncture has also been shown to reduce fistula rates in post-chemoradiotherapy salvage laryngectomies. Although no literature evidence exists, avoidance of three-point junctions in skin incision through the use of horizontal incisions (e.g. Attee or MacFee) may help reduce wound breakdown.

Palliative chemotherapy

Patients receiving only palliative care have an average overall survival of four months after diagnosis. Outcomes from studies of palliative chemotherapy generally show longer survival rates, depending on the regimen. However, no large well-designed randomised trial has been undertaken to definitively show an overall survival benefit of palliative chemotherapy over the best supportive care in these patients. Several chemotherapy regimens, either single agent or combination treatments have been tried in recurrent head and neck squamous cell carcinoma patients with different results. The active single agents in head and neck squamous cell carcinoma patients with response rates greater than 15 per cent include methotrexate, bleomyin, cisplatin, carboplatin, paclitaxel, docetaxel, cyclophosphamide, doxorubicin, hydroxyurea, vinblastine and fluorouracil (5-FU). Various randomised trials have been undertaken to compare different chemotherapy regimens in recurrence patients. Combination treatment has shown higher response rates than the single-agent therapy.

In comparison with PF (cisplatin 100 mg/m^2 and 5-FU 750 mg/m^2 days 1–5 every three weeks) in a randomised controlled trial, TPF induction chemotherapy (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2 days 1–5 every three weeks) was shown to yield a higher objective response rate as well as increased median progression-free and overall survivals in unresectable head and neck cancer patients without distant metastasis. However, this regimen is mainly used as induction chemotherapy before radical treatment for curative patients and it is not normally used as first line treatment in recurrent or metastatic head and neck squamous cell carcinoma patients with unresectable disease due to significant toxicities associated with this regimen.[21] Some of the selected chemotherapy regimens commonly used in palliative head and neck squamous cell carcinoma patients are listed in Table I.

Recommendations

- **Use salivary bypass tubes following salvage laryngectomy (R)**
- **Use interposition muscle-only pectoralis major or free flap for suture line reinforcement if performing primary closure following salvage laryngectomy (R)**
- **Use inlaid pedicled or free flap to close wound if there is tension at the anastomosis following laryngectomy (R)**
- **Perform secondary puncture in post CRT laryngectomy patients (R)**

Since a majority of head and neck squamous cell carcinoma tumours express or overexpress epidermal growth factor receptor, the epidermal growth factor receptor inhibitors including cetuximab has been tried in these patients. A phase III randomised trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic and/or recurrent head and neck cancer was done and it was shown that addition of cetuximab to cisplatin significantly improved response rate but did not significantly improve progression-free and overall survival.[22] The addition of cetuximab to platinum-based chemotherapy (either cisplatin 100 mg/m^2 or carboplatin are under the curve 5 with 5-FU 750 mg/m^2 days 1–4 every three weeks) improved objective response rate, median progression-free and overall survivals compared to platinum-base chemotherapy alone (EXTREME

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TABLE I
SELECTED PALLIATIVE CHEMOTHERAPY REGIMENS COMMONLY USED IN RECURRENT OR METASTATIC HEAD AND NECK SQUAMOUS CELL CARCINOMA PATIENTS (MODIFIED FROM REFERENCES 1–2)

Regimens	Usual doses	Response rate (%)	Reference
Cetuximab/5-FU/cisplatin	Cisplatin IV 100 mg/m^2 q3w 5FU IV 1000 mg/m^2 d1–4 q3w cetuximab IV 400 mg/m^2 loading dose and 250 mg/m^2 maintenance dose q1w	36	Gao *et al.*[6]
Cisplatin/5-FU	Cisplatin IV 100 mg/m^2 q3w 5FU IV 1000 mg/m^2 d1–4 q3w	27–50	Jayaram *et al.*[2], Zafereo *et al.*[8], Paleri and Kelly[9]
Cisplatin/paclitaxel	Cisplatin IV 75 mg/m^2 q3w paclitaxel IV 175 mg/m^2 q3w	26–41	Zafereo *et al.*[8], Steiner *et al.*[10]
Cisplatin/docetaxel	Cisplatin IV 75 mg/m^2 q3w docetaxel IV 75 mg/m^2 q3w	53	Roedel *et al.*[11], Ramakrishnan *et al.*[12]
Carboplatin/paclitaxel	Carboplatin IV AUC 6 q3w with paclitaxel IV 200 mg/ m^2 q3w or carboplatin IV AUC 2 q1w with paclitaxel 80 mg/m^2 q1w	27 52	Paleri *et al.*[13], Marioni *et al.*[14]
Docetaxel	Docetaxel 75–100 mg/m^2 q3w	21–42	White *et al.*[15], Paydarfar *et al.*[16]
Paclitaxel	Paclitaxel 80–100 mg/m^2 q1w paclitaxel 175 mg/m^2 q3w	13–40	Pezier *et al.*[17], van der Putten *et al.*[18]
Methotrexate	Methotrexate 40–60 mg/m^2, q1w	10–77	Dunsky *et al.*[7], Robbins *et al.*[19], Murray *et al.*[20]

IV = intravenous; q3w = every three weeks; q1w = every week; d1–4 = days 1–4
Note: some of the trials used different doses and regimens than those listed as 'usual' doses.

trial).[23] This regimen is recommended as the first-line systemic treatment for recurrent and metastatic head and neck squamous cell carcinoma patients with good performance status in many centres. However, the choice of EXTREME regimen as first-line treatment will depend on individual patient circumstances and performance status. In England, cetuximab in addition to 5-FU and platinum chemotherapy could be prescribed in the NHS through the cancer drug fund although this fund is not available in other parts of the UK and may only be available in the a short term. As the regimen is associated with high frequencies of toxicities, not all patients can tolerate or complete the treatment.

For patients who are deemed to be unfit to have EXTREME regimen, a modified version of cetuximab and a platin or reduced doses have been used for some patients. In addition, if cetuximab is not used or not available, many centres will use the combination platinum-based regimens (without cetuximab) as first-line treatment for these recurrent head and neck squamous cell carcinoma patients, including those regimens listed in Table I.

Once patients have progressed on platinum based chemotherapy, the prognosis is extremely poor and there is no standard second-line or third-line therapy for these patients. In some cases, another platinum-based combination chemotherapy can be given as second line, e.g. carboplatin and paclitaxel. However, some of these patients may have deteriorating or poor performance status and further combination chemotherapy treatment may be poorly tolerated. In addition, some patients may be platinum-resistant and are unlikely to benefit from further platinum-based chemotherapy. For second- or third-line chemotherapy, single agent taxane (paclitaxel or docetaxel) or methotrexate has also been used in patients who still have relatively good performance status.

For patients who are unfit to have palliative chemotherapy, best supportive care may be the best option, since palliative chemotherapy may worsen their quality of life without a survival benefit. This decision needs to be made by the doctors and patients together, with the involvement of a palliative care physician, focusing on the benefits of palliative chemotherapy *vs* the risks of treatment toxicity.

Patients with non-resectable recurrences being considered for palliative treatment should be offered the opportunity to participate in clinical trials of new therapeutic agents, including immunotherapy. If such trials are not available locally, patients should be referred to centres that offer these trials.

Recommendations

- **Triple therapy with platinum, cetuximab and 5-fluorouracil appears to provide the best outcomes for the management of patients with recurrence who have a good performance status and are fit to receive it. If not fit, then combinations of platinum and cetuximab or platinum and 5-FU may be considered (R)**
- **Patients with non-resectable recurrent disease should be offered the opportunity to participate in Phase I-III clinical trials of new therapeutic agents (R)**

Re-irradiation

Most patients with recurrence will have had previous radical RT, which would have reached the maximal

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acceptable tolerance dose for critical organs such as spinal cords and/or brainstem. Therefore, re-irradiation of these patients carries significant potential risks and complications.

Patient selection

Data on patient selection for chemo re-irradiation is sparse, with comorbidity and pre-existing organ dysfunction being the most important prognostic factors for patients undergoing re-irradiation. Other prognostic factors include interval from previous radiation, recurrent tumour stage, tumour bulk at re-irradiation, and re-irradiation dose.[24]

Re-irradiation using conventional and older RT techniques for unresectable recurrent cancers

Some single centre and phase 2 studies have shown very good control rates for re-irradiation of recurrent tumours with prolonged survival rates. However, replication of these results in phase 3 studies has not materialised, probably reflecting in part the importance of specialist expertise and careful patient selection. At the Gustave-Roussy Institute, full-dose re-irradiation was given to 169 patients with unresectable head and neck cancer, in the form of either RT alone or with concurrent chemotherapy (5-FU and hydroxyurea or mitomycin, 5-FU and cisplatin). The overall survival (OS) rate was 21 per cent at 2 years and 9 per cent at 5 years, with a median survival time of 10 months for the whole population. In the RTOG 96–10 study, 86 patients received re-irradiation with 5-FU and hydroxyurea. The two- and five-year survival rates were 15.2 and 3.8 per cent respectively with overall grade 3–4 acute toxicities of 56 per cent, grade 3–4 late toxicities of 22 per cent and deaths in 8 per cent of patients.[25] In the RTOG 99–11 study, recurrent head and neck cancer patients received twice-daily radiation (1.5 Gy per fraction bid 5 days every 2 weeks with low-dose paclitaxel and cisplatin). The estimated one- and two-year OS rates were 50.2 and 25.9 per cent, respectively. The study also showed 28 per cent grade 4–5 acute toxicities and 11 per cent treatment-related deaths.

A randomised phase III trial (Groupe d'Oncologie Radiotherapie Tete Et Cou (GORTEC) 98–03) compared re-irradiation with 5-FU and hydroxyurea chemotherapy with palliative methotrexate monotherapy in patients with recurrent or a second primary head and neck squamous cell carcinoma.[26] Despite the promising phase II studies, this phase III study showed that re-irradiation with concurrent chemotherapy did not improve OS compared with methotrexate alone (23 per cent *vs* 22 per cent at one year, NS). There were however four complete responses in the re-irradiation arm, and none in the chemotherapy alone arm. Twenty-eight per cent had grade 3 late toxicity in the re-irradiation arm compared with 9 per cent in the chemotherapy arm. The trial was closed prematurely and thus no definite conclusion could be drawn.

The Groupe d'Étude des Tumeurs de la Tête et du Cou (GETTEC) and Groupe d'Oncologie Radiotherapie Tête Et Cou (GORTEC) undertook a randomised study examining the efficacy of adjuvant chemo re-irradiation after salvage surgery. The study included patients who had salvage surgery with no gross residual disease and a good performance status. Patients were randomised to either observation or post-operative chemo re-irradiation (FHX (5-fluoro-uracil, hydroxyurea and radiation) regimen, daily radiation to 60 Gy). Patients in the post-operative chemo re-irradiation arm had significantly improved locoregional control (49 per cent *vs* 25 per cent) and disease-free survival. However, there was no significant difference in overall survival due to an increase in treatment-related deaths and second primary tumours following chemo re-irradiation, with 40 per cent of patients experiencing grade 3 or 4 late toxicity in the chemo re-irradiation arm, compared to 10 per cent in the observation arm.

Re-irradiation with intensity-modulated radiotherapy (IMRT)

Intensity-modulated radiotherapy (IMRT) can potentially limit the dose to critical areas. At the same time, however, it may increase the dose to surrounding non-critical areas. Therefore, it is not yet completely clear what the balance of benefit and harm will be. In one study, 105 patients with recurrent head and neck cancer underwent re-irradiation using IMRT (75 of whom also received concurrent chemotherapy) and the two-year locoregional progression-free survival and overall survival rates were 42 and 37 per cent, respectively. The acute and late grade 3 toxicities were reported in 23 and 15 per cent of patients respectively. In another study, 84 patients underwent re-irradiation using IMRT (20 per cent received concurrent chemotherapy), five-year locoregional control and overall survival were 40 and 20 per cent respectively, with grade 3 acute and late toxicities of 31 and 13 per cent. Although there was no grade 5 acute toxicity, there were two fatal vascular ruptures during follow-up.

Re-irradiation with biological therapies

The combination of an epidermal growth factor receptor inhibitor, cetuximab, with RT has been shown to significantly improve overall survival at five years compared with RT alone for locoregionally advanced head and neck cancer. Therefore, there is also rationale for combining cetuximab with re-irradiation in recurrent head and neck cancer patients. One recent study showed a median overall survival of 10 months in recurrent head and neck cancer patients retreated with stereotactic body radiation therapy plus cetuximab. Acute and late grade 3 toxicity was observed in 6 per cent of patients, which seems to be much lower than that of re-irradiation and chemotherapy.

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Toxicity of chemo re-irradiation

Chemo re-irradiation carries risk of very severe life-threatening toxicity, which has to be weighed against the relative survival benefit, and quality of life detriment. The resultant acute major toxicities are similar to those of primary chemoradiotherapy, including mucositis, dermatitis and hematologic suppression. These toxicities generally resolve after the completion of therapy, and most patients recover with supportive measures, although treatment interruptions may be necessary. Compared with re-irradiation alone, the addition of concurrent chemotherapy significantly increases acute toxicities.

Late toxicities are generally less predictable and irreversible, and therefore carry a higher potential for problems. In RTOG 9610, the cumulative incidence of grade 3+ late toxicity in patients surviving more than 1 year was 12.3 per cent. The most worrisome late complications are neurological toxicities as well as carotid rupture. Fortunately, these devastating complications occur rarely, even in patients who receive large lifetime radiation doses.

Recommendations

- **Chemo re-irradiation appears to improve loco regional control, and may have some benefit for overall survival, at the risk of considerable acute and late toxicity. Benefit must be weighed carefully against risks, and patients must be counselled appropriately (R)**
- **Target volumes should be kept tight and elective nodal irradiation should be avoided (R)**

Treatment volume definition

In re-irradiation, the potential benefit and toxicity of elective nodal irradiation need to be carefully considered, since the risk of toxicity is generally related to the volume of tissue irradiated. The literature suggests that the major risk of recurrence is within the region of gross recurrent disease. The probability of isolated failure in the electively treated areas is low. Treatment volume of the gross tumour should be expanded by a safety margin of 1–1.5 cm. Prophylactic treatment of draining lymphatic regions is generally avoided. In areas closely abutting critical structures, the margin may be smaller to reduce the risk of complications. After surgical resection, only the tumour bed of the high-risk areas (e.g. positive margin and extracapsular extension) is usually targeted.

Best supportive care

Palliative and best supportive care should be offered routinely as part of the management package of all recurrence patients, even in the case of those who are being treated curatively. The early involvement of the palliative care physician can help control symptoms in the lead up to curative or palliative treatment. Furthermore, it provides a more seamless transition into palliative care if required. Involvement of a palliative care physician gives the patients confidence that their symptoms will be managed regardless of the outcomes of the treatment, and also can speed up the provision of support for patient and family at home.

Key points

- Recent evidence suggests that outcomes of the management of recurrence are not as dire as is widely considered
- Evaluation and careful selection of patients with recurrence is the crux of successful management
- PET CT scanning is the most effective imaging method for the evaluation of recurrence
- Surgery appears to give the best outcomes for the management of recurrence, especially if HPV positive, but also has a high complication rate
- Patients who have the best outcomes from treatment are those with small recurrences and second primaries who do not smoke or who have stopped smoking, and have good performance status, and in whom the tumour can be completely removed with no involved margins, especially if chemoradiotherapy can be given afterwards if indicated
- The standard regimen for first-line palliative chemotherapy is cisplatin, 5-FU and cetuximab. However some patients may not be able to tolerate it
- Re-irradiation using tight target volumes may improve locoregional control, but does carry significant risk of toxicity
- Patients with recurrence often have significant symptoms, and should be offered best supportive care interventions regardless of the intent of therapy, as they can benefit from assessment and management by pain control teams and other clinicians.

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GUIDELINE

Reconstructive considerations in head and neck surgical oncology: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. The reconstructive needs following ablative surgery for head and neck cancer are unique and require close attention to both form and function. The vast experience accrued with microvascular reconstructive surgery has meant a significant expansion in the options available. This paper discusses the options for reconstruction available following ablative surgery for head and neck cancer and offers recommendations for reconstruction in the various settings.

Recommendations

- Microsurgical free flap reconstruction should be the primary reconstructive option for most defects of the head and neck that need tissue transfer. (R)
- Free flaps should be offered as 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)
- Composite free tissue transfer should be offered as first choice to all patients needing mandibular reconstruction. (R)
- Patients undergoing salvage total laryngectomy should be offered vascularised flap reconstruction to reduce pharyngocutaneous fistula rates. (R)

Introduction

The problems of reconstructive surgery for the head and neck are variable and can be very complex.[1,2] These guidelines have been divided into the management of the loss of skin, the maxilla, the mandible, including the associated soft tissues, the oropharynx and the laryngopharynx. There is very little level 1 evidence relating to the reconstruction of head and neck defects. Mandibular reconstruction techniques are fairly standard but 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.

Most reconstructions are performed primarily following tumour extirpation, but secondary reconstructions are also undertaken to treat problems such as fistulae or osteoradionecrosis. Modern techniques aim for one stage reconstruction utilising vascularised tissues with a high success rate and good overall results.

Priorities of reconstruction include restoring oral cavity lining, maintaining oral competence, maintaining function of speech and swallowing and providing an acceptable aesthetic result. Choice of reconstructive options depends on patient comorbidities, factors relating to the surgical defect, any future possible treatments including radiotherapy and donor site morbidity. No appropriately powered randomised controlled trials exist to determine flap selection in most instances and this is usually determined by the expertise of the individual surgeon. Patient factors include prior treatments, especially surgery and radiotherapy and the patient's overall health including medical and social history. Multiple tissue types often require to be reconstructed.

Oral cavity soft tissues

Oral soft tissues include tongue, floor of mouth, buccal mucosa and the retro-molar trigone extending to the tonsillar area. It is rare that only one of these areas is involved. Reconstructive access is usually determined by the extent of surgical resection and may involve a lip-split and mandibular osteotomy, although a per-oral approach is usually possible.

Microsurgical techniques provide the mainstay of oral soft tissue reconstructions as they allow importation of large volumes of healthy tissue from sites distant to prior surgical or radiotherapy fields. Flaps commonly used include the radial forearm flap (RFF) and the anterolateral thigh (ALT) flap. Less commonly the latissimus dorsi, rectus abdominus and flaps based on the scapular and/or para-scapular axis are utilised. More recently, the medial sural artery perforator flap (MSAP) and the superficial circumflex iliac artery perforator flap are being used. The first two represent the workhorse flaps in this field and will be discussed separately.

The RFF allows for importation of a large, thin, pliable flap with excellent reliability and simplicity of harvest.[3] Multiple skin paddles can be designed and the flap can be raised as a cutaneous, fasciocutaneous, fascial, adipofascial, osseo-fascial or osseo-cutaneous flap (see below). The principal disadvantage of this flap is the poor donor site aesthetics when skin grafting is required.

The ALT flap allows for importation of very large tissue volumes and is versatile.[4] Fascio-cutaneous and fascial flaps can be raised, along with muscle and fascia lata if required. The flap has a long pedicle, but can be technically challenging to raise. It is a relatively thick flap which can be thinned. If multiple perforating vessels are available, then the flap can be raised with two skin paddles. Donor site morbidity is minimal and use of the ALT is increasing in most reconstructive centres.

If microsurgery is considered, inadvisable local or regional flaps are still used. Within the oral cavity local mucosal flaps can be useful to help close small defects. Regional flaps such as pectoralis major and deltopectoral can be effective in importing tissue, but are not generally considered as a first choice.

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 importation of bone which can be tailored to fit the desired shape, is well vascularised and is amenable to osseo-integration. Several flaps are commonly used with high success rates, including the fibula flap, deep circumflex iliac artery (DCIA) flap, scapular flap and RFF.[5]

The fibular flap allows harvest of a long piece of bone which is of adequate height for osseo-integration and can be osteotomised several times for contouring.[6,7] This is now made easier with the availability of software to plan the osteotomies at the mandible and on the fibula prior to transfer. It is relatively easy to harvest as an osseus 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 DCIA 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 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. The bone is a good height, but two-team flap harvesting is generally not possible.

Radial forearm flap is rarely used for bone reconstruction as only a small volume of bone of low height can be harvested. There is a risk of subsequent fracture of the radius.

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):[8]

- Class I (70 mm)/Ic (84 mm): Subcondylar region to the ipsilateral canine and class Ic includes the condyle. Most of the flaps described above will work well as the length of this defect is around 7–8 cms and so all bone donor sites are adequate. In the lateral defect the height of the reconstruction is less problematic.
- Class II (85 mm)/IIc (126 mm): Hemimandibulectomy from subcondylar region including ipsilateral canine and class IIc includes condyle. 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. The choice of flap depends more on the plan of rehabilitation 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)/IVc (168 mm): This is an extensive mandibulectomy including at least one angle and both canines. The fibula flap is usually the best option for faithful reconstruction, but the mandible is often best made smaller for such major resections especially if there is loss of maxillary teeth.

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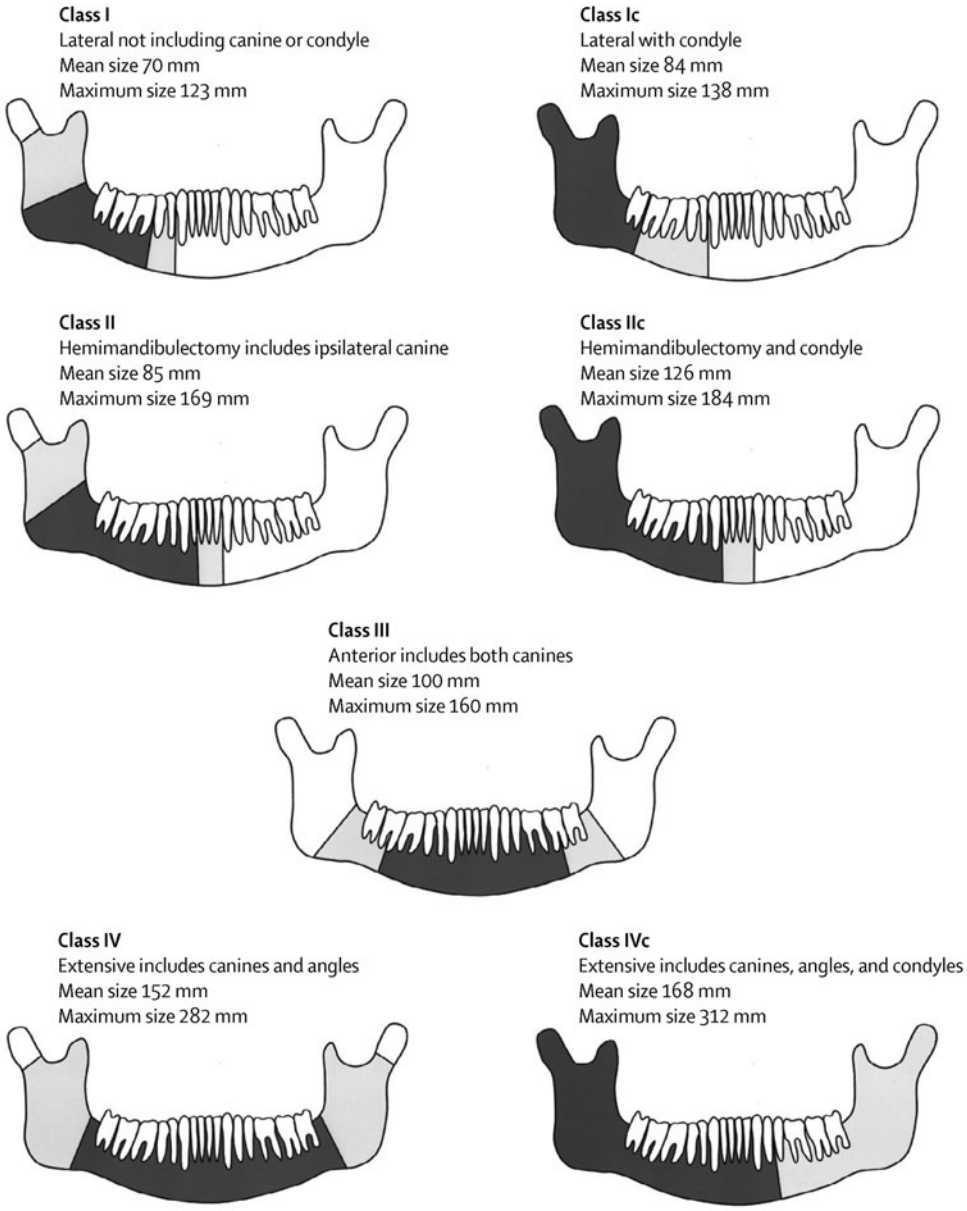

FIG. 1
Classification of mandibular defects.

Dental rehabilitation is a key part of mandibular reconstruction and pre-operative liaison with an appropriate team including consideration of osseo-integrated implants is mandatory.

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.

Throughout this section, it is necessary to refer to the classification suggested in Fig. 2.[9] The choice of a prosthetic option or reconstruction depends on the nature of the defect. In class I and II defects an obturator is a reasonable option, but this becomes less favourable as the orbital adnexae are involved (class III), orbital exenteration (class IV) and the midface defects of an orbitomaxillary (class V) or nasomaxillary (class VI) nature. This refers not only to the vertical component but also to the extent of the dental or alveolar part of the resection relevant to the prosthodontist in deciding on appropriate obturation. Other classifications suggested include those by Okay *et al*., but there is no distinction between classes III and IV.

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, the prosthodontist, maxillofacial technician, the patient and the family. There are clear advantages in simplifying the surgery and using prosthetic options, but this choice becomes more difficult to deliver and for the patient to cope as the defect becomes larger and more complex.

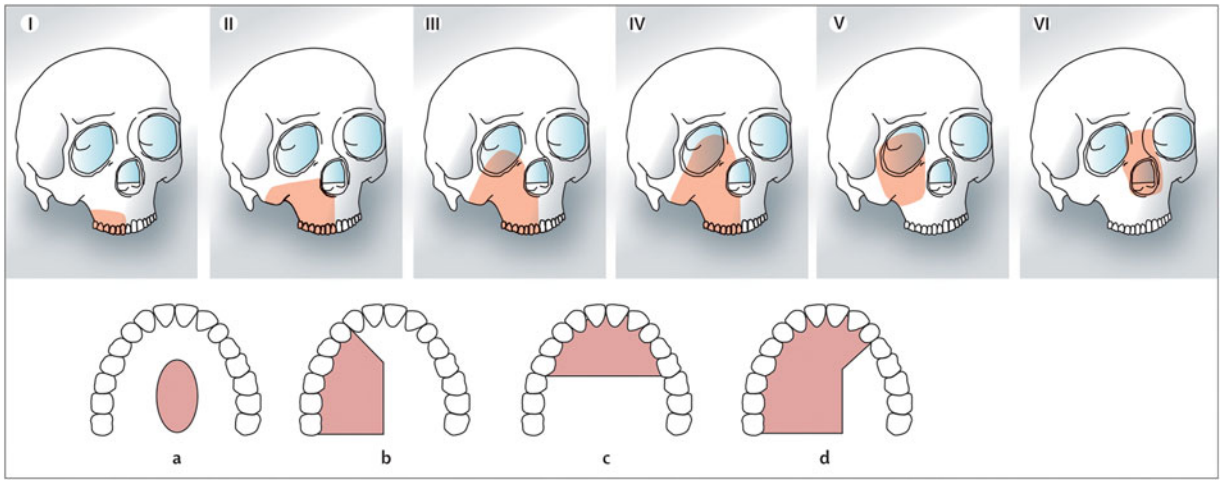

FIG. 2
Classification of the maxillary and midface defects. Classes I–VI relate to the vertical component of the defect including orbitomaxillary (class V) and nasomaxillary (class VI) when often the palate and dental alveolus are intact. Classes a–d relate to the increasing size of the palatal and dento-alveolar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

Class I: This includes resections of the alveolar bone not resulting in an oroantral fistula and these can either be left to granulate or treated with a local flap. Also included are defects involving the junction of the hard and soft palate usually obturated or reconstructed with a soft tissue flap, and minor maxillectomies which may occur following the removal of small inverted papillomas which generally do not require rehabilitation.

Class II: This is the standard hemimaxillectomy 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 not too large there is less of a problem for the patient in terms of retention and stability of the prosthesis. In more extensive cases (classes IIc–d), it is possible to gain very good retention with an implant-retained prosthesis, although reconstruction with the fibula flap has also shown good outcomes. A vascularised bone with greater height, such as the DCIA flap 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 which supplies the lateral scapula (scapula flap) through peri-osteal 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 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 reduce the soft tissue problems such as epiphora and ectropion. The iliac crest 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. The rectus abdominus with non-vascularised bone is also an option but is associated with a high ectropion rate and there is a risk of bone loss if radiotherapy is required. The vastus lateralis based on the descending branch of the lateral circumflex femoral artery is another option.

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 flap is also a good option.

Class V: In the orbitomaxillary defect, the main aim is not to obturate the orbital space with too much soft tissue so as 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 ALT in a thinner patient.

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 RFF can be ideal if harvested with fascia to line the nasal side of the radial strut and the skin to restore the face. The composite radial 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 nasal bones with vascularised tissue to prevent complications during and following radiotherapy.

Oropharyngeal reconstruction

The oropharynx can be divided into the walls of the oropharynx (lateral and posterior), the base of the tongue and the soft palate. The oropharynx is a muscular tube connecting the larynx and hypopharynx to the oral cavity. The role of reconstruction is to try and maintain the function of the residual tissue. From a functional point of view the most difficult area is the posterior tongue which allows normal movement of the epiglottis and maintains swallowing and speech. The use of transoral robotic and laser resections without reconstruction may give better functional results than reconstructing this muscular tube with non-sensate skin such as the radial forearm flap.

Reconstruction of the soft palate

The most commonly described method of soft palate reconstruction involves the use of the RFF often in combination with a local flap such as the superiorly based pharyngeal flap or the superior constrictor advancement flap. Some suggest the use of a folded RFF which is de-epithelialised in order to be sutured to the de-epithelialised posterior pharyngeal wall, but a superiorly based pharyngeal flap can be utllised to provide the nasal lining with good results.[10,11] The free flap is used in the horizontal part of the defect only if it is possible to close the posterior tongue to narrow the pharynx and maintain its function.

Reconstruction of the pharyngeal walls and tonsillar regions

Placing free tissue transfers will disrupt the muscular tube and probably decrease function. For this reason, transoral robotic and laser resections are preferred to address these tumours where possible.

Reconstruction of the posterior tongue

Most surgeons do not claim to be able to restore function in this region if more than half of the posterior tongue requires resection (Table I).

TABLE I
METHODS OF SOFT PALATE RECONSTRUCTION

No reconstruction	Obturation
Local flaps	Superiorly based pharyngeal
	Palatoplasty and lateral pharyngeal
	Palatal island mucoperiosteal
	Palatal island and pharyngeal
	Masseter and buccal mucosa transposition
	Masseter, buccal mucosa and pharyngeal
	Temporalis
	Superior constrictor advancement
	Velopharyngoplasty or masseter and buccal advancement
Pedicled flaps	Temporal osteocutaneous island
	Galeo-peri-cranial
Free flaps	Radial forearm
	Radial forearm and additional local
	Folded radial forearm
	Lateral arm
	Jejunum
	Anterolateral thigh

Pharyngo-laryngectomy reconstruction

Partial pharyngeal defects

Partial pharyngeal defects with more than 3.5 cm of remaining pharyngeal mucosal width may be closed primarily. Defects with less than 3.5 cm of pharyngeal mucosal width remaining may be reconstructed using a pedicled flap – usually a pectoralis major myocutaneous flap. Free flaps, such as radial forearm free flaps, may also be used. If the pharyngeal mucosal remnant is very narrow (<1 cm in width), then it is often better to excise the remnant and undertake a total circumferential reconstruction.

Total circumferential pharyngolaryngectomy defects

Lower anastamosis above clavicles. Where the lower anastamosis of a total circumferential pharyngolaryngectomy reconstruction would lie above the clavicle, several options exist:[12] jejunal free flap (JFF), gastro-omental free flap (GFF), tubed radial forearm free flap (RFFF) and tubed anterolateral thigh free flap (ALTF). All of the above options carry the risk of free flap failure, anastamotic leaks, anastamotic strictures, donor site morbidity, failure of voice rehabilitation, swallowing problems and a small peri-operative mortality rate.

Previously untreated cases. In previously untreated cases, ALTs, tubed over a salivary bypass tube, appear to provide the lowest complication rates – with minimal donor site morbidity, lower leak rates and lower stenosis rates. Good swallowing and voice rehabilitation have also been reported. Alternatives include the JFF[13] and the RFF. Swallowing problems due to hyper-peristalsis and a 'wet' sounding voice are common with JFF, which also carries a morbidity rate due to abdominal complications (≈5 per cent). Radial forearm flap carries lower donor morbidity rates, but higher stenosis and leak rates than JFF. Tubing of the RFF over a salivary bypass tube appears to decrease fistula rates.[14]

Post-chemoradiotherapy (salvage) cases. In general, reconstructive free flap surgery in the salvage setting carries higher risks of complications due to the deleterious effects of chemoradiotherapy on tissue vascularity and wound healing. In such cases, limited case series suggest that use of GFFs may have an advantage due to the availability of the omentum. This can be

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wrapped around the anastamotic site to decrease the possibility of leakage and also improve the overlying skin quality. Additional vascularised tissue can be included with the ALT as a chimaeric flap to resurface the neck in cases where there is poor quality skin or contracted skin that would not safely close post-operatively.

Any of the other options mentioned previously, for example JFF, RFF, may also be used in salvage surgery.

Lower anastamosis below clavicles. If the resection extends to below the level of the clavicles, then a gastric pull through or colonic transposition flap may be used. Both these techniques carry significant morbidity and mortality due to the need to enter three visceral cavities. Gastric pull through carries a mortality rate of 5–15 per cent, morbidity of 30–55 per cent and reported fistula rates of 3–23 per cent. Colonic transposition carries similar risks, and appears to be less commonly used. It can however provide a higher reach than gastric pull through, and is therefore useful for tumours that extend up high into the oropharynx.

Vascularised tissue after salvage laryngectomy

Pharyngocutaneous fistulae (PCF) are known to occur in nearly one-third of patients who undergo salvage total laryngectomy after chemoradiation. Pharyngocutaneous fistulae have severe impact on duration of admission and costs, quality of life and can even cause severe complications such as bleeding, infection and death. Recent meta-analyses suggest that there is a clear 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.[15,16] This intervention reduces the risk of PCF by one-third to a half.

Recommendations

- **Microsurgical free flap reconstruction should be the primary reconstructive option for most defects of the head and neck that need tissue transfer (R)**
- **Free flaps should be offered as 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)**
- **Composite free tissue transfer should be offered as first choice to all patients needing mandibular reconstruction (R)**
- **Patients undergoing salvage total laryngectomy should be offered vascularised flap reconstruction to reduce pharyngocutaneous fistula rates (R)**

Key points

Mandible and oral cavity

- The radial forearm and the anterolateral thigh free flaps are the preferred options for oral soft tissue reconstruction. Newer flaps such as the medial sural artery perforator flaps are increasing in popularity
- The fibula free flap is now considered the workhorse for mandibular reconstruction following ablative surgery. Planning software makes osteotomies easier
- The deep circumflex iliac artery with internal oblique provides a superior form for the mandible and facilitates deeper implant placement and should be considered if implant-retained oral rehabilitation is planned
- The scapula provides a good option for extensive soft tissue resections including the mandible and an alternative if atheroma precludes use of the fibula. The donor site is also the best tolerated

Midface and maxilla

- Multidisciplinary decision-making should include the patient, surgeon and dental prosthodontist
- Prosthetic options reduce the morbidity of treatment and can give excellent results but reconstructive options should be considered as the defect becomes larger and more complex

Oropharynx

- Using local tissue only to restore the constrictor tube is essential. Free tissue transfer is best reserved for the reconstruction of the soft palate
- Functional results for posterior tongue reconstruction are disappointing
- The greater role played by transoral surgery will reduce the need for reconstruction in this area

Pharyngolarynx

- Partial pharyngeal defects may be closed primarily or using a pedicled myocutaneous, usually a pectoralis major flap or with a free flap
- Total circumferential defects where the lower anastamosis is above the clavicle can be reconstructed with several free flaps. In previously untreated patients, anterolateral thigh free flaps, tubed over a salivary bypass tube, appear to carry lowest complication rates. In post-radiotherapy patients, limited evidence suggests that gastromental free flaps may have some advantages
- Tubing over and use of a salivary bypass tube appears to decrease complication rates with anterolateral thigh and radial forearm free flaps
- Total circumferential defects where the lower anastamosis is below the clavicle may be reconstructed by gastric pull through or colonic transposition

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Salvage laryngectomy

- Use of vascularised tissue to buttress or augment the pharynx in patients undergoing salvage total laryngectomy reduces pharyngocutaneous fistula rates

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GUIDELINE

Palliative and supportive care in head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It provides recommendations on the assessments and interventions for this group of patients receiving palliative and supportive care.

Recommendations

- Palliative and supportive care must be multidisciplinary. (G)
- All core team members should have training in advanced communication skills. (G)
- Palliative surgery should be considered in selected cases. (R)
- Hypofractionated or short course radiotherapy should be considered for local pain control and for painful bony metastases. (R)
- All palliative patients should have a functional endoscopic evaluation of swallowing (FEES) assessment of swallow to assess for risk of aspiration. (G)
- Pain relief should be based on the World Health Organization pain ladder. (R)
- Specialist pain management service involvement should be considered early for those with refractory pain. (G)
- Constipation should be avoided by the judicious use of prophylactic laxatives and the correction of systemic causes such as dehydration, hypercalcaemia and hypothyroidism. (G)
- Organic causes of confusion should be identified and corrected where appropriate, failing this, treatment with benzodiazepines or antipsychotics should be considered. (G)
- Patients with symptoms suggestive of spinal metastases or metastatic cord compression must be managed in accordance with the National Institute for Health and Care Excellence guidance. (R)
- Cardiopulmonary resuscitation is inappropriate in the palliative dying patient. (R)
- 'Do not attempt cardiopulmonary resuscitation' orders should be completed and discussed with the patient and/or the family unless good reasons exist not to do so where appropriate. This is absolutely necessary when a patient's care is to be managed at home. (G)

Introduction

Palliative care aims to improve the quality of life (QoL) of patients and their carers facing the problems associated with life threatening illness. This can be achieved by the prevention and relief of suffering, ensuring comfort and dignity, by means of early identification, assessment and management of pain and other, physical, psychosocial and spiritual issues.

Patients with head and neck cancer are a group in whom both specialist palliative and supportive care is especially appropriate whether the treatment intent is curative or not, since the disease and its treatments result in a huge burden of morbidity: short and long term – even lifelong for survivors. In addition to the physical symptoms, these patients often have very significant comorbidities, including tobacco and alcohol dependence, and complex psychosocial issues.

All professionals caring for head and neck cancer patients should assess palliative and supportive care needs in initial treatment planning, and throughout the illness, and be aware when specialist palliative care expertise is needed. This may involve core multidisciplinary team (MDT) members, social workers, psychologists etc. Levels of intervention may involve in-patient, out-patient, day care, home care and telephone advice, from a single, arm's length intervention

to a taking over of care. Support provided will need to accommodate any communication impediment. In turn, specialist palliative care practitioners need to be aware of when and how to use palliative interventions such as surgery, radiotherapy (RT) and chemotherapy. All this is best achieved by a high level of integration of services – team working, including the primary care team – and excellent communication, with the 'key worker' (usually a specialist nurse) at the centre.

BOX I
MAIN TARGETS FOR PALLIATIVE CARE INTERVENTIONS IN HEAD AND NECK CANCERS

Medical and surgical treatments
- Pain
- Hydration and nutrition
- Gastrointestinal symptom relief
- Anxiety
- Agitation
- Dysphagia
- Dyspnoea
- Bleeding
- Airway management
- Hypercalcaemia

Holistic, psychosocial and complementary
- Breaking bad news
- Patient aspirations and expectations
- Anxiety
- Counselling
- Psychological support
- Emotional support
- Support groups
- Massage therapy
- Aromatherapy

Recommendation

- **Palliative and supportive care must be multidisciplinary (G)**

Approaches

Palliative care takes a holistic approach, addressing physical, psychological, social and spiritual needs of the patient, their carers and family (Box I). Interventions which may be appropriate to palliative care include oncological and surgical approaches, drug management, psychological support, Allied Health Professional (AHP) input and complementary therapies. This paper focuses on medical and surgical interventions for physical symptoms, but these should be addressed as part of a wider holistic and multidisciplinary approach, which includes concern with psychosocial and spiritual issues.[1–3]

Whilst the distinctions between physical and psychosocial symptoms should not be overstated, different interventions will dominate in each category. Drugs, anticancer treatments such as RT, surgery and procedures will dominate in the first category, whilst counselling, honest communication, support groups and complementary therapies will be preferred in the second. This distinction is not clear-cut, however; counselling and honest communication are important parts of pain relief, whilst drugs have a role in the management of symptoms such as anxiety and depression. A well-developed multidisciplinary approach, coupled with an open-minded approach to intervention, is therefore essential.

It is the role of the MDT team to discuss treatment options in all patients. This includes decisions on who should be treated and what is untreatable disease. This is a complex issue and although broad guidelines can be applied each case should be assessed individually. Radical treatment in advanced or recurrent head and neck cancer may be futile and result in poorer QoL, therefore important decisions need to be made at presentation about which treatment pathway to take. The alternative where there is a low chance of cure is a palliative pathway. Palliative treatments include surgical and non-surgical interventions with the intention of slowing disease growth and symptom control, and extending life with focus purely on symptom control.

Effective decision making in the palliative setting is important. The patient and family should adequately understand the diagnosis and prognosis, especially if the trajectory changes due to intervention or disease progression. It should be made clear that symptoms will be identified and treated and patients should be asked if there are any new goals for their treatment since cure is not possible. In other words, the team should not convey a sense of hopelessness simply because the goal is not indefinite survival. Hope can be maintained within the context of the patient's own goals whether they are:

- physical – relief of symptoms
- psychological – fear of distress, suffocation, bleeding or uncontrollable pain at the end of life
- Social – desire to witness a family event, celebrate a birthday or make a trip.

Symptoms should be actively sought and treated in a proactive manner, and it should not be assumed or conveyed that any new symptom is as uncontrollable as the tumour itself. Treatment options should be discussed for the new symptom including those that may not extend life. Although patient choice is central to the treatment options taken, the treating clinician should make recommendations to guide treatment and share the burden of difficult decisions.

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Recommendation

- **All core team members should have training in advanced communication skills (G)**

Symptom control

Surgical palliation

Incurable end-stage head and neck cancer leads to distressing symptoms. Patients may remain active and self-caring while trying to cope with problems of pain, swallowing, breathing and bleeding. Palliative surgery may be indicated in such cases. Little high-level evidence is available to confirm the surgical benefit; however, descriptive studies support its use in selected cases. Surgery can reduce primary tumour bulk, reduce pain and bleeding, improve swallowing, nutrition and improve and airway (see below). Debulking surgery for advanced neck disease can achieve symptom control, but major resections only rarely offer levels of benefit, which justify the extent of surgical morbidity.

Newer endovascular techniques, including embolisation and vessel stenting, may offer symptom control for bleeding related to major vascular erosion, and these interventions can be considered in patients at high risk of erosion of major vessels.

Acute haemorrhage from carotid 'blow-out' (erosion of the carotid vessels) is a distressing end of life event. Whilst occasional success can be achieved with swift surgical intervention, many patients succumb rapidly. In these cases, attempts to reduce the flow of blood with direct pressure while administering appropriate rapid acting sedatives (e.g. benzodiazepines) should be made. Constant verbal support to the patient is a key to help handle anxiety. Do not leave the patient's side.

If surgical intervention is considered inappropriate careful discussion and measured information giving to the patient (if they wish to participate) or family members and carers is essential. This should include the anticipated clinical scenario and an acceptable plan of care should be devised to manage these circumstances. This may include the use of dark towels, anticipatory prescribing, and may influence preferred place of care.

Recommendations

- **Palliative surgery should be considered in selected cases (R)**
- **For control of bleeding endovascular stenting or embolisation should be considered (R)**

Non-surgical palliation

Radiotherapy. Debate continues around the optimal dosage regimen for palliative RT. Low-level evidence exists for the use of hypofractionation schedules and short course RT. Other protocols such as those described by the Radiation Therapy Oncology Group have also demonstrated benefit. Symptom control can be achieved in up to 80 per cent of selected patients with particular response in terms of pain control. No high-level evidence exists to support one protocol over another, but case series report benefit. Re-irradiation may be offered but may be associated with severe radiation toxicity.

A systematic review of RT for painful bone metastases reports benefit in up to 50 per cent of patients.[4] There is evidence to support the use of bisphosphonates to aid pain control of bone pain as an additional step once RT and conventional pharmacology has been used. The role of the new monoclonal drugs including RANK – ligand inhibitors (e.g. denosumab) has yet to be elucidated.

Chemotherapy. This includes the use of platinum-based agents, 5-fluorouracil and methotrexate, either as monotherapy or in combination with RT and demonstrates benefit in symptom control and QoL measures, but may increase toxicity and hence side effects from the treatment. Careful consideration of the balance between benefit and harm must be made on an individual patient basis. Non-platinum-based agents are reported as conferring symptom control in the selected cases.

Future modalities. Future research will include the role of taxanes, e.g. paclitaxel, monoclonal antibodies e.g. cetuximab, newer chemotherapeutic agents, photodynamic therapy and interstitial laser therapy. Descriptive series report some symptom controls using these modalities but without any evidence of improved survival.

Recommendations

- **Hypofractionated or short-course RT should be considered for local pain control and for painful bony metastases (R)**
- **Bisphosphonates can be considered for bone pain following RT (R)**

Palliation of dysphagia

Forty per cent of patients with head and neck cancer suffer from dysphagia. This is due to:

- mechanical obstruction
- functional obstruction
- drug induced side effects
- fistula
- pain.

Assessment of the swallow is essential in palliative head and neck patients. It is important to establish whether oral intake is possible and whether it is safe. Aspiration is not

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uncommon and may be silent in up to 40 per cent of patients, thus the bedside assessment is of limited value. Functional endoscopic evaluation of swallowing (FEES) is straightforward, easily repeatable, portable and can give good information on the aetiology of aspiration as well as feedback to the patient on trials of preventative manoeuvres. It can also be useful in the assessment of ability to deal with different textures and complements information obtained from videofluoroscopy.

Aspiration does not inevitably mean no oral intake. A degree of aspiration may be well tolerated and methods taught to clear the airway after swallowing can be implemented. Similarly certain textures may be better tolerated and the use of thickened fluids can help maintain oral intake. It is important to take into account the patient's wishes and the patient may make an informed choice to continue to swallow despite the potential and real risk of aspiration pneumonia. Quality of life is absolute.

In patients who are unable to swallow, the use of an enteral route via nasogastric tube (NGT) or gastrostomy allows for hydration, nutrition and medication. The type of tube used depends largely on ability to pass an NGT or fashion a gastrostomy, perceived duration of use and patient choice. If enteral nutrition via NGT is likely to extend beyond two to three weeks then gastrostomy should be considered and discussed with the patient.

There exists no clear guidance on when or if it is acceptable to withdraw nutritional support. Patient and family wishes are crucial in this decision process and full consultation is imperative.

Conventional treatments can be helpful in the palliation of swallowing. Surgical debulking either with or without the laser or debrider and RT may help reduce bulk in a hypopharyngeal tumour, dilatation can help in stricture formation and this can be surgical or radiologically guided. Stenting may play a role but often head and neck tumours are too high to accommodate a stent comfortably and without impacting on other functions.

Recommendations

- **All palliative patients should have a FEES assessment of swallow to assess for risk of aspiration (G)**
- **Establishment of enteral feeding must be considered early in patients who are unable to maintain their intake orally (G)**

Palliation of the airway

Where there is airway compromise it is common practice to consider a tracheostomy. However, it may be possible to avoid tracheostomy in some cases if the consideration is given to surgical debulking techniques. This is dependent on local expertise and equipment.[5]

Sometimes avoiding surgical intervention is the most appropriate course of action, for example, a patient with a tracheal tumour that has been repeatedly debulked, and has received palliative RT, is not a candidate for stenting. There will come a time when the airway compromise will be life threatening. A tracheostomy may not be an option in this instance. In such instances opioids for dyspnoea in addition to palliative sedation and reduction of secretions can support a patient in a terminal event.

These situations are difficult and information should be imparted to the patient sensitively. In the situation where the patient wants to fully discuss the anticipated scenario a sense of control can be restored to them by discussing what interventions can be undertaken pharmacologically to avoid any distress. If the patient does not want to participate in the discussion this should be documented and discussed with family and/or carers. This situation may influence the preferred place of care. To have the patient and the family prepared for the event is paramount. They must know what will be in place to prevent the dyspnoea and anxiety associated with such a situation and the patient must be comfortable to the end.

If a tracheostomy is indicated local protocols should exist or be developed to help the patient, the family and community staff manage tracheostomy wound care along with maintenance of a clean secure tube. Heat moisture exchange and voicing attachments may be used to aid patient communication.

Pain

Pain is very common, affecting most patients at any stage. It may be disease or treatment related, either acute and/or immediate or persistent and/or lifelong. Pain occurring after a long, pain free interval is likely to be recurrent disease. Assessment must take account of the presence of 'total pain' i.e. physical, spiritual, psychological and social elements. The three major pain types are all encountered – somatic, visceral and, particularly difficult, neuropathic.

Analgesic use is best based on the World Health Organization (WHO) 'pain ladder' (Box II) with three steps of increasing potency, and used depending on pain severity and response. The severity of the pain dictates the strength of the analgesic and the pathophysiology dictates the adjuvant used.

BOX II
WHO PAIN LADDER

Paracetamol ± non-steroidal anti-inflammatory drug ± adjuvant
Weak opioid (codeine or tramadol) + step 1 drugs
Strong opioid replacing the weak + step 1 drugs

The choice of formulation depends on whether the patient can swallow, is vomiting, or has a nasogastric (NG) or gastrostomy tube in situ.

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Somatic pain. Morphine remains the first choice strong opioid, other than perhaps in renal impairment when an alternative is preferred. It is initiated by titrating immediate release morphine oral solution or tablet (e.g. Oramorph™ solution or Sevredol™ tablet). Once responsiveness and dosage are known, then sustained release preparations are used, with immediate release doses for breakthrough at a sixth of the 24 hour sustained release dosage. If the patient can swallow, then sustained release tablets (e.g. MST Continus™) or capsules (e.g. Zomorph™) can be used. If a tube is in place then a morphine suspension (e.g. MST suspension™) or opened capsules (e.g. Zomorph™) can be used. If this is not feasible, usually because of vomiting, then a subcutaneous (SC) infusion of morphine or diamorphine can be used, with SC doses for breakthrough. Diamorphine is preferred since it is more soluble and can be used in much smaller volumes.

Transdermal preparations of fentanyl have theoretical and practical attractions for stable background pain as an alternative, particularly if there is morphine intolerance (e.g. sedation and dysphoria) or there is renal failure. For breakthrough pain, oral opioids can still be used. Alternatively, new preparations of buccal, sublingual or intranasal fentanyl may have a role in specific situations, with supervision of a specialist service.

Oxycodone can be an alternative to morphine where there is intolerance, particularly dysphoria; there is an immediate release solution and injection, but there is only a tablet form of sustained release oral preparation, limiting its use where swallowing is compromised. Hydromorphone is not useful orally where swallowing is impossible, both immediate and sustained release being capsules, but it may be injected. Methadone in liquid form can be very useful, being rapid in onset and long acting because of its half-life; it is best used by specialists as it can accumulate.

Neuropathic pain. This is very common both as a presenting feature of the disease and a result of treatment, particularly radiation. The drugs used can be referred to as adjuvants.

- A tricyclic antidepressant, most usually amitriptyline is available as tablet and liquid.
- Anticonvulsants such as gabapentin and pregabalin are the most used, available only as tablets or capsules unless through special arrangements with a pharmacy. Gabapentin can be opened and administered via the gastrostomy tube.
- Carbamazepine is an alternative and is available both as tablet, liquid and even suppositories. Sodium valproate is also available as a liquid preparation.

First line would be either antidepressant or anticonvulsant titrated to maximum dose tolerated (usually added to a conventional analgesic): second line would be to use both.

Some advocate corticosteroids (e.g. dexamethasone 8–16 mg daily) as first line for acute neuropathic pain where there is felt to be a significant inflammatory component. Appetite stimulation limits use if dysphagia is a concomitant feature. It is not for chronic or predictably long-term pain. Clonazepam is occasionally useful. Methadone and ketamine are useful, but only in specialist settings.

Visceral pain. Treatment depends on the cause, titrating analgesics and using the pain ladder. If the pain is poorly sensitive to opioids, adjuvants should be considered early, for example pain due to metastatic disease in the liver or nerve compression may be eased with Dexamethasone (4–8 mg daily).

Judicious use of all these drugs is best achieved by seeking advice from the specialist palliative care service whenever there is concern. Interventional pain techniques can be very effective where systemic treatments fail or if the patient is intolerant of the significant doses of combination analgesics.

Mucosal pain. This can be due to treatment, infection or tumour. Treatment of infection such as candida or herpes is essential. Useful additional topical agents include sulcralfate, benzydamine, chlorhexidine, steroids and topical local anaesthetics such as lignocaine preparations. Coating measures including bioadherent oral gel may be preferred by the individual patient.

Recommendations

- **Pain relief should be based on the WHO pain ladder (R)**
- **Specialist pain management service involvement should be considered early for those with refractory pain (G)**

Nausea and vomiting

The approach must take an account of the large number of patients who are enterally fed. Even with this there is often a need for injectable anti-emetics – subcutaneous (SC) boluses or continuous infusions, at least until initial control is established.

Enteral feeding poses its own challenge, and prokinetic drugs such as metoclopramide (tablet, oral solution or injection) or domperidone (tablet, suspension or suppository) may be needed to ensure best function.

Otherwise the approach is similar to that in general use. Remember the practical issue of providing a large bowl, tissues and water for the patient and be prepared to rehydrate using IV or SC fluids if appropriate.

Constipation

Constipation develops in half of patients who are terminally ill with cancer admitted to a hospice. In

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addition, it is common during treatment in many patients. This is due to dehydration, reduced physical activity and the use of constipating drugs, particularly opioids and anticholinergic medication. Laxatives should be initiated once opioid medication is prescribed. Hypercalcaemia and hypothyroidism are other causes, which may be overlooked.

The principle of treatment is avoidance and early recognition. Enquiry should be made on patient contact. Laxative agents include stimulants such as bisacodyl and senna and softeners such as lactulose, magnesium hydroxide and docusate. Polyethylene glycol preparations including movicol and laxido are commonly used. These should be used prophylactically. If constipation develops it can lead to nausea and vomiting and in the severe situation pseudobstruction. If rectal examination reveals hard stool then the use of suppositories and enemas can be helpful. Ultimately, a manual evacuation may be necessary.

Recommendation

- **Constipation should be avoided by the judicious use of prophylactic laxatives and the correction of systemic causes such as dehydration, hypercalcaemia and hypothyroidism (G)**

Confusion and agitation

It is important to distinguish anxiety (unsettled, frightened, panic) from confusion, particularly delirium. Confusion is common, affecting up to 75 per cent of cancer patients at some stage. Many head and neck patients have a history of heavy alcohol (and tobacco) consumption, predisposing them to the effects of withdrawal, and given that cancer is more commonly seen in old age; then cognitive impairment is not uncommon.

Benzodiazepines are the mainstay of pharmacological treatment of anxiety. Diazepam can be given orally, via a tube in liquid form, or by injection intravenously. Lorazepam can be swallowed or a tablet dissolved sublingually. If injections and/or infusions are needed, midazolam is preferred, as it can be given subcutaneously (most common route) or intravenously when almost immediate effect is needed. The key limiting factor, however, is rapidly developing tolerance; benzodiazepines are useful for short-term management of episodes of anxiety, but are limited where anxiety is pre-existing and established.

Delirium as a cause of confusion can be related to a number of organic causes – infection, dehydration, metabolic disturbance, respiratory failure, urinary retention, constipation, brain metastases, etc. Administered drugs are common causes, particularly opioids and drug withdrawal (see above). While treatment has to be aimed at the cause, symptom management is required in the short term. While benzodiazepines have a role, indeed a specific indication in drug withdrawal, most often delirium is better managed using haloperidol (as tablet, liquid or injection, including SC) or levomepromazine (as tablet or injection) where sedation is needed in managing paranoia etc.

In some cases, particularly for irreversible agitation or delirium in a dying patient, benzodiazepines and antipsychotics need to be combined and are often administered using a syringe driver.

Recommendation

- **Organic causes of confusion should be identified and corrected where appropriate, failing this, treatment with benzodiazepines or antipsychotics should be considered (G)**

Secretions

Although xerostomia is common in these patients, excess secretions and/or the inability to swallow or otherwise clear secretions is often troublesome. Physically the use of suction either by carer or the patient is often helpful.

There are three widely used antimuscarinic drugs.

- Hyoscine hydrobomide (scopolamine) is available as a transdermal patch, oral or sublingual tablet and is commonly used; however, it has central as well as peripheral actions and (unpredictable) sedation and/or confusion can result.
- Hyoscine butylbromide, which is not central nervous system active, but equally effective peripherally, and is arguably the drug of choice. It is available as a tablet, though often ineffective by that route; hence SC use may be preferred.
- Glycopyrronium, which is similarly peripherally active, and is most often given subcutaneously. A liquid form can be prepared but efficacy is unpredictable.
- Excess secretions at the end of life are treated similarly, but the evidence in a Cochrane review suggests they are of very limited benefit. Established practice accepts SC preparations of anticholinergic medication are available for use to support this end of life phase. Timely management is a key here; if secretions develop, then regular or continuous antisecretory drugs should be started as soon as practical, rather than relying on PRN drugs.

Steroids

As with other cancers, corticosteroids are widely used. Dexamethasone (Table I) is the most used, because of its potency, relative lack of mineralocorticoid properties, and wide range of formulations (water soluble tablets, solution, and injection, SC or intravenous).[6]

Dexamethasone 1 mg = Prednisolone 7.5 mg

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TABLE I
INDICATIONS AND DOSAGE FOR STEROID (DEXAMETHASONE) USE

Appetite, energy and wellbeing	4 mg initially
Adjuvant analgesic	8–16 mg initially
Anti-emetic	See above
Spinal cord compression	See NICE guidelines[7]
Tumour oedema (e.g. tracheal compression, superior vena cava obstruction)	8–16 mg initially

Long-term use also requires that attention be paid to bone mineral density, and bisphosphonates, and calcium and/or vitamin D supplements are indicated.

BOX III
SPINAL METASTASES

- Type of associated pain
  - Pain in spine (new or progressive)
  - Spinal pain aggravated by straining
  - Localised spinal tenderness
  - Pain in spine at night preventing sleep
- Neurological symptoms and signs
  - Radicular pain
  - Limb weakness
  - Difficulty walking
  - Sensory loss
  - Bladder or bowel dysfunction
  - Signs of caudal equina/spinal cord compression

If used for any length of time patients must carry a 'steroid card', keep it up to date, and be aware of the advice on it, i.e. to increase the dose when there is intercurrent illness or other stressor; and the need to reduce very gradually if used for more than three to four weeks – including at the end of life. Some advise that steroids given for poor appetite or fatigue can be discontinued then. This puts the patient at risk of steroid insufficiency, an unnecessary symptom burden even at that stage, and dexamethasone can be given in small volumes subcutaneously once daily, as part of end of life care if appropriate.

Spinal metastases

The incidence of spinal metastases in head and neck squamous cell carcinoma is reported to be less than 2 per cent; however, it is more common in thyroid cancer (2–13 per cent). The most important factor in determining outcome is neurological status prior to treatment. Due to the devastating neurological sequelae of spinal cord or cauda equina compression early recognition (Box III) and action is essential and consideration that symptoms may be suggestive of spinal metastatic disease is the first step.[7]

Neurological symptoms and signs should be assessed and a magnetic resonance imaging of the whole spine obtained. This is an oncological emergency and steroids should be commenced while investigations or admission are arranged. Treatment depends on findings and includes steroids, surgical stabilisation and RT. Clear guidelines on diagnosis and management have been published by National Institute for Health and Care Excellence (NICE) and the readers should familiarise themselves with these.[7]

Recommendation

- **Patients with symptoms suggestive of spinal metastases or metastatic cord compression must be managed in accordance with the NICE guidance (R)**

Care of the dying

Care of the dying is an important part of good palliative care. Dying patients may have significant and rapidly changing symptoms, together with a recognition that no further active intervention is appropriate. For these reasons, timely assessment, regular review and confident symptom control are essential. In addition, this is an important time for loved ones; as noted by Dame Cicely Saunders, 'How people die remains in the memories of those who live on'. Ongoing sensitive and honest communication, coupled with sensible and proactive decision-making are therefore essential.[8]

Reversible causes for a patient's deterioration should be considered and may be acted upon depending upon earlier discussions, clinical acumen and based on the best interests of the patient. The physical changes preceding death generally include decreasing mobility, decreasing level of consciousness and interaction, minimal intake, progressing to no oral intake, decreasing urine output, haemodynamic deterioration and changes in respiratory pattern. Recognising death is imminent, the doctor may lead multiprofessional decision making and communication ensuring the patient (if appropriate) and families or carers understand the expected trajectory.

The patient's values and preferences should be upheld where possible, these may include rapid discharge to enable the patient to die in the place of their choice, or enable their family to stay with them if in in-patient settings. Any religious, spiritual or cultural preferences should be identified.

The Liverpool Care Pathway (LCP) was a protocol developed at the Marie Curie Institute Liverpool, and in use in the UK between 1997 and 2014. Concerns about the use of the pathway were raised in the press, and a subsequent government review was undertaken. Whilst recognising both good and bad outcomes arising from the use of the pathway, the ultimate recommendation of the review body was that the LCP be withdrawn. Current approach is based on this framework but using a more individualised and tailored care plan. Such plans are currently subject to local variation but can be

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used in all care settings including patient homes. National guidance is being developed following consultation.

A key role of the doctor is to recognise that death is imminent, and, as recommended in the government review, the patient's senior clinician has a vital role in this decision in the MDT. Recognition of dying should prompt a thorough review of all care and interventions, with unnecessary medication being stopped, and essential medication continued, usually by SC infusions and boluses. In the head and neck patient, the frequent presence of NG and gastrostomy tubes allows continued use of some medications which would otherwise be impossible to administer.

It is important to highlight that recognising dying does not automatically lead to discontinuing any such interventions; only that their role in improving symptoms should be assessed.

Whilst nutrition is usually inappropriate in dying patients neither SC nor intravenous fluid is necessarily ruled out – although the benefits can be, indeed often are very limited. Enteral tubes provide a further option for those patients.

Sensitive discussion with the patient (if appropriate) and family or carers should be initiated to dispel any concerns held and agree a plan appropriate to the individual which may require modification depending upon the timescale and symptoms observed. A further vital aspect of end of life care, recognised both in the LCP and the review, is the need for regular multiprofessional assessment, and the possibility that patients may improve, for whatever reason, and hence the management plan be changed.

Whilst an individualised approach is vital for dying patients, certain symptoms are common enough to warrant 'anticipatory prescribing'. The four major symptoms for which this is appropriate are:

- pain
- nausea and vomiting
- agitation
- excess secretions.

The choice of drugs used is left to individual units and must be individualised further for some patients. For most purposes:

- analgesia – diamorphine or morphine
- anti-emetic – haloperidol or levomepromazine
- agitation – midazolam and/or levomepromazine or haloperidol
- antisecretory – hyoscine, either butyl or hydrobromide.

Common reasons for modifying the drugs of choice include poor tolerance of previous drugs, cases where other drugs have an already-established role, clinical contra-indications or renal failure. Fortunately, all the commonly needed drugs can be given subcutaneously, and feeding tubes increase the available options. Areas which require ongoing monitoring and vigilance include mouth care, tracheostomy and wound care, pressure areas, and continence.

Recommendation

- **All patients at the end of life should have anticipatory medication available to palliate common symptoms and should have an individualised care plan (G)**

Do not attempt resuscitation (DNAR) (cardiopulmonary resuscitation (CPR))

This is a subject of such wide clinical and ethical complexity (Box IV and V) that it is not possible to offer more than a few thoughts on the main points. Such a decision applies ONLY to the state of cardiopulmonary arrest – it does not imply withholding other treatments, including other 'resuscitation' measures (e.g. reinserting a dislodged tracheostomy tube).

BOX IV
FUNDAMENTAL ETHICAL PRINCIPLES

Respect for autonomy
Beneficence
Non-maleficence
Justice

BOX V
RELEVANT ARTICLES OF HUMAN RIGHTS ACT

The right to life
Freedom from inhuman or degrading treatment
The right to privacy
Freedom of expression and to be informed
Freedom from discrimination

When considering palliative and end of life care, one specific area for consideration is that of CPR. Ultimately, any decisions made around CPR should be undertaken in advance. In the event of a cardiac arrest, and where no such decisions have been made in advance, the default position is to perform CPR. In some cases, even in patients with incurable disease, this is appropriate. In the dying patient, however, or in cases where the chances of CPR succeeding are remote, then CPR adds no benefit to patient care. In such cases, a 'Do not attempt cardiopulmonary resuscitation' (DNACPR) order should be completed.

There exists a number of issues regarding DNACPR decisions, outlined in national guidance issued by the British Medical Association (BMA), Royal College of Nursing (RCN) and Resuscitation Council (RC),

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and recently examined in a Court of Appeal Judgement. Two key points stand out – the decision-making around CPR, and the discussion around such decisions. The current BMA, RCN and RC guidance is summarised here, but may be subject to review in the coming months.

Decisions around CPR

Where a cardiac arrest is a significant possibility, where CPR has a reasonable chance of success, and where no advance decisions have been made with respect to resuscitation, then CPR should be attempted. Examples of such cases include acute reversible illnesses or treatable arrhythmias. Similarly, if a cardiac arrest is unlikely, then CPR should be attempted if it occurs. Examples here include the otherwise healthy person admitted with a relatively minor illness or an out-of-hospital arrest in public. A presumption of patient consent exists here, and it is not relevant to discuss in advance unless requested (and in such a case, patient wish should be respected). Whilst this is applicable to many hospital patients, it is less relevant to palliative care patients, in whom life-threatening events are more likely, and CPR is less likely to succeed.

At the other extreme, where a patient is dying and no reversible causes for their condition exist, then CPR is inappropriate. In this context, cardiac arrest may be viewed as the final event in the process of natural death. Nevertheless, whilst the clinical decision may be clear, serious consideration needs to be given to discussion with the patient and family; this is covered in the section 'Discussing CPR decisions', below.

In many cases, including in palliative care, the benefits and burdens of CPR are less clear-cut. For example, in a patient with an ultimately palliative diagnosis but who is otherwise active and well, there is a small chance that CPR in the event of a cardiac arrest may succeed. It is beyond the remit of this work to outline factors that count for and against this. In such cases, the preferences of patients (or those delegated to make decisions on their behalf) are pivotal.

Discussing CPR decisions

As outlined above, discussing CPR decisions is not relevant in a large proportion of hospital patients, as presumption of consent exists. This section is concerned with those cases where cardiac arrest is a realistic possibility.

Where CPR would not succeed. In cases where it has been determined clinically that CPR has no realistic chance of success, the decision rests with the medical team. Any discussion revolves around sensitively informing the patient (and/or any person delegated to be involved in such discussions) of the decision that has been made. Difficulties here arise where the patient or delegated person objects to the decision. In such cases, seeking a second opinion is good practice. It is usually possible to work through such disagreements with time and sensitive communication.

In some such cases, the cited guidance allows for DNACPR decisions not to be discussed with the patient or their delegated decision-maker. This applies to situations where the treating team have strong reason to believe that such discussions will cause significant distress or where the patient has asked not to be involved in such discussions. Citing risk of distress should not be undertaken lightly; any such judgement should be carefully documented and backed up with evidence – such decisions have been challenged in court.

It is important to reinforce that the clarity of the decision is not a factor in considering whether to discuss a DNACPR order. Even where CPR has no chance of success, serious consideration should still be given to discussion.

Unclear benefits/burdens: a person with capacity. A competent patient can decline CPR and a DNACPR document can be completed based solely on this decision, provided the clinician completing the document is satisfied that the patient has capacity for the decision and understands it.

Whilst a competent patient may decline CPR, they may not insist on receiving CPR in the event that they suffer a cardiac arrest, if it is deemed that CPR would not succeed. Where there is a possibility of success, eliciting and respecting the patient's wish is crucial. Such discussions should be handled sensitively, and the patient given the opportunity to consider the discussion and invite family members/carers to support them.

There are further subtleties to these decisions, but such discussion is outside the remit of this work. Examples include a patient refusing discussion, or a patient delegating a decision to healthcare professionals. Current professional guidance is helpful in working through these situations.[9,10]

Unclear benefits/burdens: a person with recent loss of capacity. If the patient has recently lost capacity for such decisions, some questions need to be asked:

- Have they previously discussed and agreed to a DNACPR?
- Have they made some other form of advanced decision to refuse treatment/living will?
- Have they been party to 'Advance Care Planning'?
- If so, are the circumstances those previously envisaged?

It could then be seen as reasonable to let this inform the current decision. It is also important to know whether the patient, when competent, appointed someone with lasting power of attorney under the terms of the Mental Capacity Act, 2005 – in which

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case this person should be approached, bearing in mind that they, no more than the patient, can insist on treatment, only decline it – *see above*.

Unclear benefits/burdens: a person with longstanding loss of capacity. If the patient has a longstanding loss of capacity, then the decision is left to the doctor(s) and other members of the team to act in the patient's best interest, in accordance with the provisions of the Mental Capacity Act. Where available, family, next of kin and carers can be asked if they are aware of any opinions expressed previously by the patient, etc. – again noting that they cannot actually make the decision, only inform the process. In situations where the patient is alone then under the Mental Capacity Act one must involve Independent Mental Capacity Advocate to contribute to the decision- making process.

Further considerations

It is not possible to cover all eventualities for these decisions, and professional guidance exists and should be followed. Two further issues warrant discussion, however; managing unresolved disagreements and transfer to the home environment.

Despite the emotive nature of the subject and complexity of decisions, it is usually possible to work through DNACPR decisions to the agreement of the patient, their loved ones and the clinical team. As described above, a second opinion can be helpful in resolving a disagreement. Occasionally no agreement can be reached between doctor, the team, the patient and those close to the patient. In extreme cases, particularly where the patient lacks capacity, legal advice may be required and consideration given to more formal measures such as the involvement of the Court of Protection.

A further point to highlight is the transfer of DNACPR decisions to the home environment. In such context, the patient and their family/carers are responsible for the documentation and, as such, are able to ignore or withhold it if they wish. For this reason, clear communication and agreement in advance are vital.

Recommendations

- **Cardiopulmonary resuscitation is inappropriate in the palliative dying patient (R)**
- **'Do not attempt cardiopulmonary resuscitation' orders should be completed and discussed with the patient and/or the family unless good reasons exist not to do so where appropriate. This is absolutely necessary when a patient's care is to be managed at home (G)**

Key points

- Palliative care takes an holistic approach addressing physical,psychological, social and spiritual needs of the patient,their carers and family
- Symptoms should be actively sought and treated in a pro active manner by the multidisciplinary team
- Pain is very common, affecting most patients at some point and maybe disease or treatment related.
- Constipation develops in half of patients who are terminally ill with cancer admitted to hospice
- Confusion can affect up to 75% of cancer patients at some stage.
- Spinal metastases should be considered where there is new or progressive back pain and investigated pro actively
- A key role of the doctor is to recognise when death is imminent and should prompt a through review of all care and interventions with unnecessary medication being stopped.

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GUIDELINE

Follow-up after treatment for head and neck cancer: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. In the absence of high-level evidence base for follow-up practices, the duration and frequency are often at the discretion of local centres. By reviewing the existing literature and collating experience from varying practices across the UK, this paper provides recommendations on the work up and management of lateral skull base cancer based on the existing evidence base for this rare condition.

Recommendations

- Patients should be followed up to a minimum of five years with a prolonged follow-up for selected patients. (G)
- Patients should be followed up at least two monthly in the first two years and three to six monthly in the subsequent years. (G)
- Patients should be seen in dedicated multidisciplinary head and neck oncology clinics. (G)
- Patients should be followed up by dedicated multidisciplinary clinical teams. (G)
- The multidisciplinary follow-up team should include clinical nurse specialists, speech and language therapists, dietitians and other allied health professionals in the role of key workers. (G)
- Clinical assessment should include adequate clinical examination including fibre-optic rigid or flexible nasopharyngolaryngoscopy. (R)
- Magnetic resonance imaging and positron emission tomography combined with computed tomography imaging should be used when recurrence is suspected. (R)
- Narrow band imaging can be used in the follow-up in selected sites. (R)
- Second primary tumours should be part of rationale of follow-up and therefore adequate screening strategies should be used to detect them. (G)
- Patients should be educated with regard to the appearance and detection of recurrences. (G)
- Patients with persistent pain should be investigated to exclude recurrent disease. (R)
- Patients should be offered support with tobacco and alcohol cessation services. (R)

Introduction

It is accepted that the follow-up of patients who had treatment for head and neck cancers is a fundamental part of their care.[1–4] The reasons of post-treatment follow-up include:

- Evaluation of treatment response
- Early identification of recurrence
- Early detection of new primary tumours
- Monitoring and management of complications
- Optimisation of rehabilitation
- Provision of support to patients and their families.

Controversy exists in how these aims are achieved.[5,6] Increasing efforts are being made to rationalise the structure and timing of head and neck follow-up clinics.

The general structure of follow-up clinics is to have initial high-frequency visits especially in the first two years when the risk of loco-regional recurrence is known to be high and then reduce frequency, with follow-up often finishing at five years. In the UK, the structure of these clinics is often arbitrary and reflects institutional and clinician-led practices with very little evidence to support any one system.

Evidence to support follow-up for early detection of tumour recurrence is lacking. However, there is a belief that follow-up clinics have inherent value and to date all published studies recognise this fact.[7]

In order to rationalise follow-up, patients could be divided into low and high risk. This is well recognised in thyroid cancer, but it is not the case in all other types of head and neck cancer especially squamous cell carcinoma (SCC). It is a belief that, this categorisation could help to determine which patients should be followed for more than five years. It would also help to establish which screening test may be needed in order to detect recurrence or second primaries.

General considerations

Length

The length of follow-up is generally five years although there are many clinicians who follow-up patients for longer periods or even for life.[8] Follow-up of patients over five years would be justified for the following groups: high-risk patients, specific tumours (e.g. adenoid cystic carcinomas), patients who have undergone complex treatments who require on-going rehabilitation and support, detection of new primary tumours and patient preference. Fear of recurrence is prevalent in cancer patients and continued attendance at clinic helps to mitigate this.

Recommendation

- **Patients should be followed up to a minimum of five years with a prolonged follow-up for selected patients (G)**

Frequency

At present, there is no evidence that high frequency of follow-up visits confers any benefit in terms of morbidity and mortality. However, there is evidence that the majority of clinicians in the UK support the follow-up of patients, in regular high-frequency intervals in the first two years when the risk of locoregional recurrence is high followed by a decrease in frequency after the second year. The follow-up in the first two years should be between four to eight weeks and from three to six months thereafter.[7]

Recommendation

- **Patients should be followed up at least two monthly in the first two years and three to six monthly in the subsequent years (G)**

Setting

At present, 90 per cent of the clinicians treating head and neck cancer in the UK see the patients in dedicated head and neck clinics for the duration of the follow-up.

Recommendation

- **Patients should be seen in dedicated multidisciplinary head and neck oncology clinics (G)**

Type of health professional

At present patients are followed up by their treating clinicians and their teams. Allied health professionals including speech and language therapists, dieticians and clinical nurse specialists may offer specific follow-up in their areas of expertise, but this is usually in addition to the medical follow-up. The introduction of the clinical nurse specialist and the key worker role in the management of patients with head and neck cancer has opened lines of communication between the patient and family and the clinical team[9] should any problems arise.

Recommendations

- **Patients should be followed up by the dedicated multidisciplinary clinical teams (G)**
- **The multidisciplinary follow-up team should include clinical nurse specialists, speech and language therapists, dietitians and other allied health professionals in the role of key workers (G)**

Clinical assessment

Traditionally, clinical assessment has been the most important aspect of the follow-up in patients treated for head and neck cancer. The clinical evaluation is done by inspection, palpation and at present with fibre-optic rigid or flexible nasopharyngolaryngoscopy. Rigid stroboscopy can also be used in patients who have been treated for laryngeal cancer.

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Recommendation

- **Clinical assessment should include adequate clinical examination, including fibre-optic rigid or flexible nasopharyngolaryngoscopy (R)**

Screening investigations

Currently there is evidence that magnetic resonance imaging (MRI) and positron emission tomography combined with computed tomography (PET–CT) scanning are superior at detecting recurrence and second primaries.[10,11] This is especially true in some tumour sites such as the nasopharynx and following treatment with chemo-radiation. Positron emission tomography combined with computed tomography has also the advantage of being a systemic evaluation. Diffusion-weighted MR has been recently applied with promising results; however, its accurate interpretation requires specific training and experience. Narrow band imaging[12] (NBI), possibly associated with high definition television technology, has been shown to be an adjunctive imaging tool due to its specific capability to selectively address superficial persistences and/or recurrences or second primary tumours by enhancing their pathognomonic neoangiogenetic pattern. It has been reported that its use can detect 18 per cent more true positive laryngeal cancerous lesions than conventional white light endoscopy. This is true even after radiotherapy (RT) or chemoradiotherapy, due to the high accuracy (98 per cent) of NBI in differentiating between neoplastic disease and post-RT inflammatory and/or cicatricial changes.

Recommendations

- **Magnetic resonance imaging and PET–CT imaging should be used when recurrence is suspected (R)**
- **Narrow band imaging can be used in the follow-up in selected sites (R)**

Second primary tumours

The incidence of second primary tumours varies between 5 and 12 per cent at five years. There is good evidence to indicate that patients with head and neck SCC have an increased risk of developing second primary malignant tumours.[13,14] This risk appears to be constant throughout the follow-up period, with an incidence ranging from 2 to 4 per cent per year. Traditionally, patients undergoing follow-up for head and neck cancer underwent a chest radiograph every year. However, there is evidence that these have not been able to identify metastasis with any confidence.

Recommendation

- **Second primary tumours should be part of rationale of follow-up and therefore adequate screening strategies should be used to detect them (G)**

Specific considerations

Second-look microlaryngoscopy

In laryngeal cancer, especially in those patients treated with transoral laser microsurgical excision, it is advisable to perform second-look microlaryngoscopy,[15] especially in scenarios where there is lack of agreement between the intraoperative and histological findings regarding the completeness of resection. The rationale of this is to provide evidence of complete resection, detect residual tumour and to perform further treatment should this be necessary.

Patients with persistent or recurrent pain without clinical evidence of disease

Pain complaints must be regarded as a serious warning sign of recurrent disease during follow-up of HNC patients,[16,17] even in the absence of an endoscopically visible persistence and/or recurrence. Persistent neck pain can be the first symptom of recurrent disease in 70 per cent of patients and can be an independent predictor of both recurrence and five-year survival rate. Pain should always prompt the clinician to initiate a thorough set of investigations, both by imaging and/or endoscopy under general anaesthesia, in order to reduce possible diagnostic delays. Pain without endoscopic evidence of disease is more frequently encountered after RT or chemoradiotherapy, but it is possible even after surgery. This symptom is usually caused by submucosal disease recurrence possibly hidden by oedematous mucosa, or associated with chondritis, chondronecrosis or osteonecrosis as a result of previous treatments.

Tumour markers

There is no evidence that the use of tumour markers is any value in the follow-up of patients with head and neck SCCs. The use of tumour markers in the follow-up of patients with thyroid cancer is addressed elsewhere in these guidelines.

Patient education

It has been recognised that the education of patients plays an essential role in the detection of recurrences. The vast majority of recurrences are diagnosed following the occurrence of new symptoms and thus patients should be educated about the need to seek help when

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appropriate. It has also been recognised that continuing smoking and alcohol drinking increases the risk of recurrence and second primary tumours. It is therefore imperative that patients are advised and offered support with regards to the detrimental effects of tobacco smoking and alcohol addiction.

Recommendations

- **Patients should be educated with regards to the appearance and detection of recurrences (G)**
- **Patients with persistent pain should investigate to exclude recurrent disease (R)**
- **Patients should be offered support with tobacco and alcohol cessation services (R)**

Key points

- The aims of follow up of patients after treatment for head and neck cancers are manifold
- The frequency of follow-up is higher in the first two years, with reduced frequency subsequently, finishing at five years
- Medical, nursing and allied health professionals all play important roles in providing follow up care
- Change in patient symptoms during follow up is the most frequent indication of recurrent disease and must be regarded seriously, even if clinical examination reveals no abnormalities.

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GUIDELINE

The clinical nurse specialist's role in head and neck cancer care: United Kingdom National Multidisciplinary Guidelines

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Abstract

This is the official guideline endorsed by the specialty associations involved in the care of head and neck cancer patients in the UK. It discusses the role of the clinical nurse specialist in the head and neck cancer patient journey and provides recommendations on the clinical nurse specialist led assessments and interventions for this group of patients receiving cancer care.

Recommendations

- All cancer patients should meet a clinical nurse specialist at the point of diagnosis. (R)
- Clinical nurse specialists must act as gate keeper to the patients' cancer pathway to provide a seamless journey. (R)
- Holistic needs assessment should be completed at different stages of the patient's pathway to reflect the changes of the patients' needs. (R)
- Clinical nurse specialists to be part of local and national initiatives for health promotion and raising awareness in the public domain. (G)
- Clinical nurse specialists should lead in redesigning of services and policies to ensure they are responsive to patient's needs for the future. (G)
- Treatment summaries should become part of practice to provide good communication between primary and secondary care to enable continuity of care for the patient. (G)

Introduction

Distress is common among cancer patients; it is multifactorial, comprising of psychological, social and spiritual elements which can impact on an individual's ability to cope effectively with cancer. A diagnosis of cancer leaves patients frightened and vulnerable, often unable to understand the full implication of the treatment they are being offered.[1] It can, in extreme cases, impact on the ability to adhere to treatment and self-management. It is widely recognised that head and neck cancer patients are particularly vulnerable to psychological distress as many suffer life-changing, long-term consequences resulting from the cancer and the treatment.[2,3]

Carers of patients with head and neck cancer are under considerable stress during and after treatment as a result of disruption to daily life, the financial and emotional strain of long-term treatment and in many cases, role reversal within the family unit. Patients and carers look to healthcare professionals to provide information to help manage the psychological and social elements of head and neck cancer.[4] Supportive care, appropriate information and individualised care planning is a key to improve the experience of the patient and the carer.

It is the function of the clinical nurse specialist (CNS) to give the patient and carer the wherewithal to cope with the diagnosis, treatment and long-term consequences through the use of empathy and experience.[5–8] The Cancer Reform Strategy[9] recognises that the CNS is critical in the delivery of information, communication and co-ordination of care. It has been recognised that care co-ordination individualised to the patient during and after treatment is vital to deliver appropriate person-centred care.[10] The CNS' role within the multidisciplinary team

(MDT) also allows for easy and timely referral on to other resources, i.e. palliative care and psychological support.

The role of the clinical nurse specialist (figure 1)

The National Institute for Health and Care Excellence Improving Outcomes Guidance[11] identified the key worker as 'A person who with the patient's consent and agreement takes a key role in co-ordinating the patient's care and promoting continuity, ensuring the patient knows who to access for information and advice'. The CNS will act as the patient's key worker during their cancer pathway by providing specialist cancer knowledge and expertise to both the patient and carer, which can be both complex and disjointed, involving interventions from multiple professionals or agencies.[6] The CNS reinforces and imparts their specialist knowledge to the other professionals and agencies to improve the cancer process and in turn will improve the cancer journey for the patient and carer. The CNS may pass the key worker role on to another relevant professional when the patient is on a particular part of the pathway, as this may be in their best interests and provide the best support at that particular point of their journey.

The CNS workload can be complex and varied dependent on the patient's needs, it can be categorised into themes:

- Specialist technical knowledge of the cancer process and treatment options
- Acting as the patient's key worker for a specific part of the process and linking in with the MDT
- Utilising advanced communication skills to support the patient and carer psychologically through the disease process
- Lead on redesigning services to make them responsive to the patient's needs
- Health education and promotion to reduce the risk of recurrence and promote a healthy lifestyle
- Assisting in local and national initiatives to promote awareness and prevention.

The role of the CNS within the MDT

The CNS acts as the key accessible professional to the patient within this multiprofessional setting, and allows the CNS to influence the patient's pathway. They are well placed to support the patient at each stage of their pathway and promote integration within the team. The CNS should be recognised as the patient's advocate within the MDT meetings where they deliver patient-centred care tailored to the individual patient's needs. In acting as the patients' advocate, the CNS also plays a key role in ensuring that the multidisciplinary care is responsive to the patients' needs and preferences.[12]

The CNS and the patient's pathway

Clinical nurse specialists increasingly take the lead role in shaping patient care pathways and refining systems to make a difference to the patient experience and their safety. By acting as the key worker,[13] they provide information, support and liaison to improve

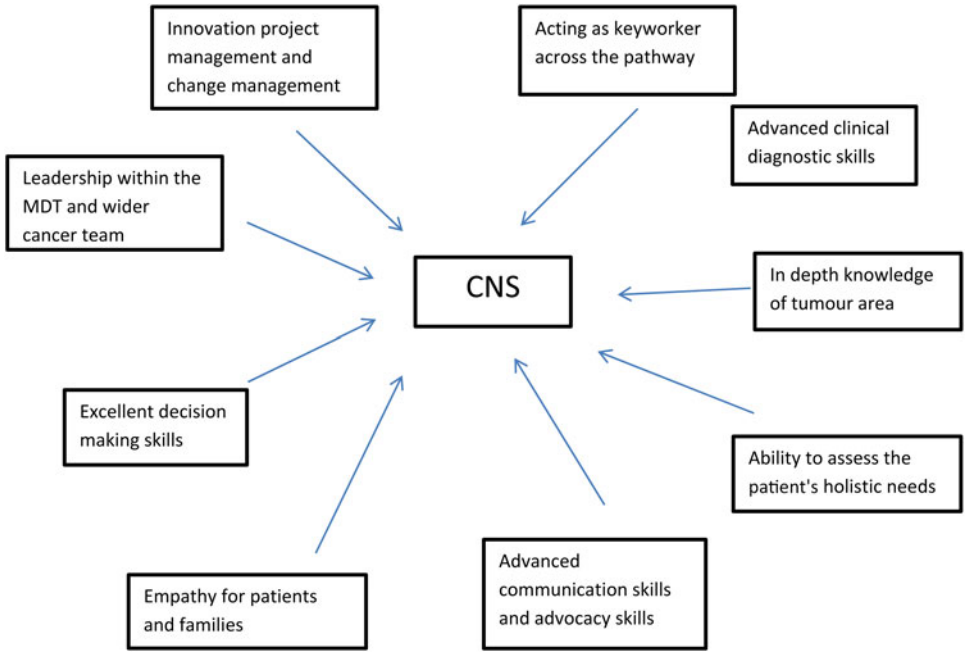

FIG. 1
Key contributions of the clinical nurse specialist to cancer care.

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the cancer care process for the patient. They can track the stage of their pathway and ensure it is seamless and prevent any problems from occurring. They are well placed with in the organisation to assist in system changes to ensure the pathway represents a quality service that fulfils the standards of cancer care and patients' expectations.

The patient's role as advocate

Patients and carers have always been at the centre of cancer services, but have not always been encouraged or empowered to help influence and shape them.[14] Patient support groups have traditionally played a large part in providing information, companionship and peer support for patients and carers throughout their cancer journey. They can also influence policy and services at local, national and at international level.

The Cancer Plan[15] saw the patient involvement being embedded in cancer services. This involvement has continued with organisations like National Cancer Research Institute (NCRI) having representation on all its clinical study groups and funding committees. This is also happening on cancer strategy committees and clinical network groups.

Patients and carers now have a realisation that they have considerable influence in gaining access to treatments and medicines, can participate in the designing of clinical trials and influence the amount of money spent by central government on research.[14] It is important to understand that patients provide a very different perspective on benefits *vs* risks of treatment.[16] They will very often opt for extensive and often life threatening treatment even if the benefits and outcomes are unclear.

Managing patients' and carers' expectations

A diagnosis of cancer has far reaching effects beyond the patient to their loved ones. This life-changing experience means that relationships and roles and responsibilities can often be changed. Treatments for head and neck cancer can have devastating effects on the lives of patients, including disfiguration, speech and swallowing impairment.[17]

'The Recovery Package'[18] has been designed by Macmillan Cancer Support to help 'provide a series of key interventions, which when delivered together can greatly improve outcomes for people living with and beyond cancer'. It is made up of:

- Holistic needs assessment
- Treatment summary
- Cancer care review
- Education and support events.

It also compliments stratified care plans, which enable individualised follow-up care and self-support. It facilitates urgent access back to the specialist team if needed or on-going support from healthcare professionals.

Recommendations

- **All cancer patients should meet a cinical nurse specialist at the point of diagnosis (R)**
- **Clinical nurse specialists must act as gate keeper to the patient's cancer pathway to provide a seamless journey (R)**
- **Holistic needs assessment (HNA) should be completed at different stages of the patient's pathway to reflect the changes of the patients' needs (R)**
- **Clinical nurse specialists to be part of local and national initiatives for health promotion and raising awareness in the public domain (G)**
- **Clinical nurse specialists should lead in redesigning of services and policies to ensure they are responsive to patient's needs for the future (G)**
- **Treatment summaries should become part of practice to provide good communication between primary and secondary care to enable continuity of care for the patient (G)**

Holistic needs assessment

An HNA ensures that the patients' and carers' physical, emotional and social needs are met in a timely and appropriate way, and that advice and support is available from the right source at the right time.[19] The HNA is the process of assessing the patient and/or carers by developing an understanding of what the person with cancer understands and needs at diagnosis and various time points thereafter which can be agreed by the MDT or when clinically appropriate (i.e. disease progression). This discussion may cover all or some of the following areas – physical, spiritual, emotional, social and environmental needs. Undertaking holistic needs assessment with a patient enables them to more fully engage in their own care and make informed choices. The information gathered at the HNA can also be shared with other members of the MDT and also have influence on service needs and data collection. The National Cancer Survivorship Initiative (NCSI) in 2010 highlights HNA as one of its 'Key Shifts' as well as it being a Peer Review Measure.

Different assessment tools are used, i.e. distress thermometer, concerns checklist and more recently the patient concerns inventory. The tools can be used at different stages along the patient trajectory, but with an emphasis being on assessing and eliciting patients' and carers' concerns and expectations. This leads to a discussion and care planning of the patients' needs and helps to manage expectations.

Pre-treatment clinics provide an opportunity for patients and carers to meet the CNS and other allied

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health professionals prior to surgical or oncological treatment. It allows HNA assessment to take place, but also facilitates discussion of acute treatment and rehabilitation with the key professionals involved prior to commencement of such.

Care plans

A care plan is based on the diagnosis and holistic assessment of the patient.[19] It will highlight the patient's issues, outlining any actions, approaches and timings to address them. Care plans change during the patient pathway according to the patient's needs at any one time; however, any change should be discussed and actions agreed with the patient. By working with the patient to develop care plans following an HNA, the patient is able to take more control of what happens to them and support themselves to self-manage their condition.[20]

Treatment summary

A key component to effective patient care is good communication between the primary and secondary care sectors. Making sure that general practitioners are fully informed about their patients' cancer journeys can ease the transition between acute and long-term care. For this to be effective, treatment summaries are provided at the end of any acute treatment by the MDT for the general practitioner and patient. The treatment summary describes the treatment that that person has received, including any adverse reactions, the side effects and signs and symptoms of recurrence. This treatment summary provides confidence to the patient that their care is continuing albeit in the community setting. Patients report feelings of abandonment and vulnerability once initial treatment is complete but with a treatment summary and care plan these feelings can be minimised. Patients' on-going self-management can be well supported through peer support groups and health and wellbeing events. The CNS is obliged to inform patients of what is available in the local area that may be accessed by the patient and carer.

Key points

Clinical nurse specialists should:

- meet every patient at the point of diagnosis to assist in a smooth transition along the cancer pathway
- ensure effective communication within the MDT, with patient and carer and within the community setting
- be at the centre of the patient's pathway and make effective use of resources
- act as the patient advocate, utilising support groups to act as patient voices in the changing healthcare environment to make them patient-centred
- perform holistic needs assessment for all patients at diagnosis and specific points along their journey to ensure patient-focused care is being provided
- offer treatment summaries to all people involved in the patient's recovery to ensure effective communication
- offer individualised care plans to help patients take control of the recovery phase.

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GUIDELINE

Clinical research, national studies and grant applications: United Kingdom National Multidisciplinary Guidelines

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Abstract

Head and neck cancer clinical research is thriving. Infrastructure for clinical research is supported through the National Institute for Health Research Clinical Research Network with operates through 15 local clinical research networks for studies within the UK Clinical Research Network Portfolio. The National Clinical Research Institute is a partnership of UK cancer research funders that support high-quality cancer research, although the National Institute for Health Research also has funding streams that will fund cancer-related research. Their websites provide up-to-date information regarding ongoing research projects. Other specialty organisations such as the British Association of Head and Neck Oncologists play important subsidiary roles in supporting research.

Clinical research into head and neck cancer is an active and increasing area of activity in the UK. Several active research centres where clinical trials are underway are distributed evenly through the UK. The framework for the organisation and infrastructure support of clinical cancer research is supported through the National Institute for Health Research (NIHR) Clinical Research Network (CRN). The NIHR CRN is the clinical research delivery arm of the National Health Service (NHS) in England, tasked with supporting the rapid set up and effective conduct of studies in the UK Clinical Research Network Portfolio, so that researchers can gather the robust evidence needed to improve treatments for NHS patients. The CRN operates across the NHS through a national coordinating centre and comprises 15 local clinical research networks (LCRNs) that cover the length and breadth of England. Each LCRN delivers research across 30 clinical specialties. At a local level the LCRN is responsible for the provision and allocation of research infrastructure including research nurses in collaboration with each partner organisation – each NHS Trust. The clinical specialties within each LCRN are managed across six divisions. Clinical research in head and neck cancer falls under 'division 1' – Oncology.

The National Cancer Research Institute (NCRI) is a partnership of UK cancer research funders, government, charity and industry. In addition to the NCRI, the NIHR has several funding streams that support cancer trials. The NCRI comprises both clinical and managerial leadership. For each tumour type there are clinical studies groups (CSGs) and there are also modality CSGs, which cross cut the tumour site specific groups (e.g. radiotherapy CSG). The head and neck CSG is a group of approximately 20 individuals. All the specialties related to clinical cancer research are represented – e.g. surgical specialties of head and neck surgery (otolaryngology and maxillofacial surgery), clinical and medical oncology, oral medicine, head and neck pathology, radiology, clinical trials and statistics, consumer representatives and administrative support. The head and neck CSG is also attended by representatives of the NCRI infrastructure as well as the main funders – Cancer Research UK. Over the last two years, the CGG has invited trainee representatives from the relevant specialties to attend meetings for a year, with the clear aim of growing tomorrow's research leaders. The membership of the CSG rotates regularly and advertisements for positions on the group are advertised both on the NCRI website as well as in the national press. The current chairman is Professor Hisham Mehanna at the University of Birmingham.

A broad range of national studies is currently open, including trials of surgery, radiation, chemotherapy and other topics. For an up-to-date list of the current

research protocols please consult the head and neck section of the NCRI website (http://www.ncri.org.uk) or search cancer 'head and neck' on the UK Clinical Trials Gateway: https://www.ukctg.nihr.ac.uk/

For individuals interested in developing clinical research several sources of help are currently available. The CSG members function as 'ambassadors' who can be approached for advice regarding the research idea. Research design services, funded by the NIHR, are distributed across CRNs to develop the idea and write a robust grant application, and also provide advice on the available and appropriate funding streams. For large randomised phase III trials, the two main funders at the present time are Cancer Research UK through the Clinical Trials Advisory and Awards Committee and also the health technology assessment (HTA) stream of the NIHR.

For feasibility studies Cancer Research UK remains the main funder and they also support translational research in relation to clinical trials. It is important to engage with a pathologist during the development of studies that might involve collecting and storing human tissue and to be aware of the requirements of the Human Tissue Authority. The role of pathology in research is addressed on the NCRI website and the MRC Data and Tissues Tool kit is being developed as a signpost to good guidance (http://www.mrc.ac.uk).

A number of other funding streams are available including those coming direct from the department of Health who put out regular calls for research proposals via the NIHR. For smaller research projects in single centres or pump priming grants the Royal College of Radiologists and the British Association of Head and Neck Oncologists are sources of potential funding. Both of the above and also the Royal College of Surgeons are sources of short-term research grants for individuals. Useful web addresses for individuals looking for research funding are given below.

http://www.cancerresearchuk.org/
http://csg.ncri.org.uk/
http://www.rcr.ac.uk
http://www.rcseng.ac.uk
http://www.bahno.org.uk
http://www.hta.ac.uk
http://www.nihr.ac.uk/funding-opportunities/
http://www.nihr.ac.uk/funding/funding-for-research.htm

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GUIDELINE

Education of trainees, training and fellowships for head and neck oncologic and surgical training in the UK: United Kingdom National Multidisciplinary Guidelines

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Abstract

Since the previous edition of these guidelines, significant changes have taken place in the training and assessment of surgeons and oncologists who treat patients with head and neck cancer. For those intending to become head and neck surgeons, a fellowship in head and neck surgery is virtually mandatory. This paper summarises the current career structure to specialise in head and neck oncology and surgery in the UK.

Recommendation

- Trainees applying for head and neck surgical oncology consultant posts should have completed additional training in the subspecialty.

Introduction

Education in the practice of head and neck oncology (HNO) has been identified as one of the key challenges in the management of head and neck cancer in the 21st century. The re-structuring and shortening of the training programmes over the last two decades has promoted the creation of interface and post-specialty training dedicated fellowship posts, with the ultimate aim of improving patient care. These changes however, require a much more substantial input from trainers which ultimately impacts on patient care, but there is no doubt that better structured and dedicated time in subspecialty training is required.

Educational principles

Training in head and neck surgical oncology (HNSO) in the UK, both in the parent specialty and for interface trainees are governed by a curriculum approved by the General Medical Council. From 2007, all surgical trainees have been required to follow the curriculum for training as set out in the Intercollegiate Surgical Curriculum project.[1] Clinical oncology and medical oncology training programmes are supervised by the Royal College of Radiologists (RCR)[2] and the Royal College of Physicians (RCP)[3], respectively.

A curriculum consists of an aim, a syllabus, an assessment matrix and a process for evaluation. As far as possible, trainees should be responsible for their own learning and achieve the objectives set out in the curriculum; trainers and overseeing bodies such as deaneries and the specialist advisory committees (SAC) should facilitate the process by ensuring that standards are met and that opportunities are available.

At the beginning of a rotation, trainees should self-assess their learning needs by comparing their current level of knowledge or technical competence against what is expected of them for their stage of training as per the curriculum. Objectives are available within the syllabus on the Intercollegiate Surgical Curriculum Programme (ISCP). This will identify the gap between what they know or can do compared with what they need to know or achieve for technical competence (a learning need). From this, a learning plan or agreement can be agreed. This plan needs to be constructed using SMART objectives (Specific, Measurable, Achievable, Relevant and Timely) so that, at the end of an attachment or programme, the trainee can be assessed to ensure that objectives have been achieved. The learning plan should be recorded in the trainee's portfolio.

Assessment

Assessment is formative or summative. Summative assessment usually takes the form of an examination (FRCS, FRCR), is high stakes (pass or fail) and usually occurs at the end of a programme or at crucial waypoints along a programme (e.g. Member of the Royal College of Surgeons (MRCS)). Formative assessment should be viewed as an assessment for learning, to identify strengths and weaknesses in a trainee's work and to highlight areas for development. Formative assessment tools usually take the form of workplace based assessments (WPBAs). These are designed to assess the essential domains of learning of knowledge, skills, professionalism and attitudes and should be viewed as developmental rather than punitive assessments.

An integral part of adult learning is the timely and regular provision of constructive feedback. This has to be used correctly to ensure it is viewed in a positive manner. Feedback should be timely, relevant and constructive, usually given to best effect in private immediately after a learning event. Provision of written and verbal feedback is an integral part of WPBAs and aids in the agreement of areas for development.

Each trainee will be awarded an Annual Record of Competency Progression certificate (ARCP). This is to ensure that there is documentary evidence to confirm that the trainee has met his or her targets for the year and is progressing satisfactorily. Annual Record of Competency Progression certificate panels are required to examine evidence of competence and increasingly this is being carried out with more structure and objectivity than was the case with the Record of In Training Assessment system. It is thus imperative that evidence to support acquisition of competency is recorded. An ARCP panel may recommend specific targets that need to be attained (ARCP 2) or an extension to training time if a trainee requires more time to progress safely (ARCP 3).

Trainees with specific needs (Trainees with Differing Needs) require skill, sensitivity and dedicated time to ensure specific personal targets for training can be agreed and met. Trainers and trainees should seek and receive support from their deanery, employing trust and SAC to ensure satisfactory progression.

Career structure in otorhinolaryngology, head and neck surgery

Training in otorhinolaryngology, head and neck surgery (ORL-NHS) starts as part of core surgical training (CST) for two years. Entry to ST3 is by competitive interview against personal specification including successful acquisition of the Member of the Royal Colleges of Surgeons (MRCS) (ENT).

Higher surgical training lasts six years and during this time all trainees are expected to develop competence in all aspects of the specialty. Trainees should take their Intercollegiate Exam from ST6 onwards. In the final two years trainees should spend more time in their area of special interest including advanced fellowship training. The SAC must prospectively approve these posts for training.

Career structure in oral and maxillofacial surgery

Oral and maxillofacial surgery (OMFS) is based on the practitioner having both medical and dental degrees. They must be on the specialist list in OMFS and be on the General Medical Council (GMC) register. Registration with the General Dental Council (GDC) is optional, but in order to train the dental graduates one must also be fully registered with the GDC.

Trainees traditionally have mostly followed the route of dentistry first then medicine though, increasingly medical graduates are following a path through a second degree in dentistry to train in OMFS.

Once the dual degree is obtained, those who studied medicine second, proceed through foundation training (often only one year) into CST and Member of the Royal College of Surgeons (MRCS). Once the MRCS is obtained they are eligible to apply for a post in specialty training in OMFS. Trainees with dentistry as a second degree need to decide if they are likely to practise dentistry outside of OMFS, in which case they will do dental foundation training for one to two years; once the MRCS is acquired, they can apply to a specialty training post in OMFS.

Specialty training in OMFS lasts five years. Trainees may opt to take additional training in one of the Interface Specialty Fellowships including HNSO, cleft lip and palate, and cosmetic and reconstructive surgery.

Career structure in plastic surgery

The training programme, designed to last an indicative eight years, includes training in areas of special interest. It comprises three stages: initial (CT1 and 2), intermediate (ST3–6) and final (ST7 and 8). Entry to ST3 is through a national recruitment process including a competitive interview against personal specification including successful acquisition of the intercollegiate MRCS (there is no specific plastic surgical Member of the Royal Colleges of Surgeons (MRCS) as there is for ENT). The training is six years and during this time all trainees will be expected to develop competence in all aspects of the specialty. Having completed the syllabus, attained the required levels of competence and passed the Intercollegiate Examination (usually taken from ST6 onwards), the candidate will be eligible to be awarded a Certificate of Completion of Training (CCT).

Increasingly, at the end of training (ST7 and 8) senior trainees are undertaking special interest fellowships (see below), which take between 12 and 24 months to complete and are appointed through advertisement and selection. These will usually result in the deferment of the CCT until this is completed.

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Subspecialty fellowship options include: head and neck surgery, aesthetic surgery, burns, ear reconstruction, genitourinary reconstruction, hand surgery, cleft lip and palate, craniofacial, lower limb, oncoplastic breast surgery (in combination with breast surgeons) and skin oncology.

Career structure in oncology

Currently, in the UK, there are two main types of oncologists concerned with the management of patients with cancer: medical oncologists (MOs) and clinical oncologists (COs). Both see and assess patients with cancer and both specialities are part of the core membership of cancer multidisciplinary teams (MDTs).

Medical oncologists are physicians trained in the use of systemic drug therapies for cancer, either alone or in combination with other treatments. The RCP supervises training for MOs. Completion of both foundation and core training programmes, culminating in full MRCP, is required prior to entry into MO training. Entry is at the ST3 level with a four-year specialist training programme leading, after passing the Specialty Certificate Examination (SCE), to a Certificate of Completion of Training in Medical Oncology.

Clinical Oncologists are trained in both systemic drug therapy and in the use of radiotherapy. Specialist training in CO also demands full MRCP for entry and begins at the ST3 level. Training takes five years and is supervised by the Royal College of Radiologists (RCR). There is a two-part examination leading to Fellowship of the RCR (FRCR): Part 1, usually passed by the end of ST4, covers the basic sciences of oncology and radiotherapy, whereas Part 2, usually passed during the fourth year of specialist training (ST6), is a clinically based exam and covers the practical aspects of assessing patients and delivering radiotherapy and systemic drug therapy. The award of CCT is, for UK trainees, dependent upon passing both parts of the FRCR examination and completing a further minimum period of one year to achieve advanced oncology training and competencies.

Integrated and advanced fellowships

The Joint Committee on Surgical Training is an advisory body to the four surgical Royal Colleges of the UK and Ireland for all matters related to surgical training and works closely with the surgical specialty associations in Great Britain and Ireland.

Although HNSO is yet to become a recognised specialty, the Joint Committee on Surgical Training and the Specialty Advisory Committees in OMFS, ORL-HNS and PS, through the Training Interface Group (TIG),[4] jointly have accredited and recognise several national advanced head and neck surgery posts for training. These fellowships are open to trainees in the three specialties who are in a recognised training post and have completed successfully their Intercollegiate Examination. The recognised fellowships are shown in BOX I.

BOX I
TRAINING INTERFACE GROUP ACCREDITED HEAD AND NECK SURGICAL ONCOLOGY FELLOWSHIP PLACEMENTS

- Northern – Newcastle Hospitals NHS Foundation Trust
- Northwest 1 – Central Manchester University Hospitals NHS Foundation Trust
- Northwest 2 – Pennine Acute Hospitals NHS Trust
- Oxford – Oxford University Hospitals NHS Trust
- West Midlands – University Hospital Birmingham NHS Foundation Trust
- West of Scotland – Glasgow Royal Infirmary and Southern General Hospital
- Yorkshire – Hull and East Yorkshire Hospitals NHS Trust
- South East Thames – Guy's and St Thomas' Hospital NHS Foundation Trust
- Kent-Sussex and Surrey – Queen Victoria Hospital NHS Foundation Trust
- North Trent – Sheffield Teaching Hospitals NHS Foundation Trust

Recently, the Royal College of Surgeons of England (RCSE) has accredited a number of advanced post-CCT head and neck fellowships. These posts are funded by the individual hospitals but are accredited by the RCSE. These include the advanced head and neck surgery fellowship at Guy's and St Thomas' Hospital and another one at Charing Cross Hospital.[5]

In addition, there are several hospitals that offer further advanced independent post-CCT HNSO fellowships although these are yet to be recognised by accredited bodies. These programmes are currently available in University Hospital Birmingham, Addenbrooke's Hospital Cambridge, Aintree University Hospitals, Liverpool, Nottingham University Hospital, and St George's Hospital in London.

In the European Union, subspecialty training in HNSO remains diverse.[6] However, the Union of European Medical Specialists has initiated steps to standardise subspecialty training in the EU and this is likely to have an impact on the current training structure in the near future. Currently, it is recommended that trainees applying for head and neck surgical oncology posts have the required additional and adequate training in this subspecialty. This is often an essential or a desired requirement in the job descriptions.

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Recommendation

- **Trainees applying for Head and Neck Surgical Oncology consultant posts should have completed additional training in the subspecialty**

Key points

- Current Educational Programmes consist of an aim, a syllabus, an assessment matrix and a process for evaluation
- Trainees applying for Head and Neck Surgical Oncology posts should have completed additional training in the subspecialty
- Interface Surgical Fellowships and advanced Post CCT Fellowships are currently available in the UK as part of additional training in Head and Neck Surgical Oncology
- In Clinical and Medical Oncology there are no dedicated Fellowships for additional training.

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GUIDELINE

Future perspectives: United Kingdom National Multidisciplinary Guidelines

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Abstract

The multidisciplinary management of head and cancer has changed radically in the last decade. This paper provides a glimpse of the emerging surgical and oncological interventions that may play major roles in the treatment paradigms of tomorrow.

Surgery

Advances in surgical techniques appear slow and cumbersome compared with the rapid unravelling of molecular mechanisms responsible for head and neck squamous cell carcinoma (SCC). It is now clear that head and neck SCC can be sub-divided into two main cohorts, those that are driven by human papilloma virus (HPV), and those that are not. This is only the first level of patient stratification on our way to personalised medicine. However, it provides a sensible basis for trial recruitment, which is a good starting point.

It is clear that the majority of HPV-driven head and neck SCC patients do well, irrespective of treatment. This is in stark contrast to those patients who have developed a tumour secondary to tobacco and alcohol use, who may only have a 5 per cent survival advantage compared to those patients treated over 20 years ago with the same disease. Clearly, this heterogeneous group deserves better outcomes, not just in terms of survival, but also functional outcome improvement.

Trials now capture data relating to swallow (i.e. PATHOS in HPV-positive disease), revealing the change in concern regarding treatment-associated morbidity. Ideally, this would also be reflected in ongoing national data collection, formerly Data for Head and Neck Oncology (DAHNO), to be replaced by Head and Neck Cancer Audit (HANA).

Despite the incidence of some head and neck SCCs decreasing over time (i.e. larynx), these numbers are outweighed by the continued increase in other subtypes, specifically oropharynx (Cancer Research UK). This undoubtedly has economic implications as combined head and neck clinics see more patients year on year, often without additional clinical support. It is predicted that by 2020 there will be more cases of HPV-driven head and neck SCC than cervical cancer.[1] Will the prophylactic HPV vaccine slow the trend? Despite not being introduced to address head and neck SCC, it undoubtedly should have an effect. There are ongoing discussions regarding vaccinating boys, to fall in line with Australia, the USA, Austria and parts of Canada, in view of the strong male predisposition to HPV-driven head and neck SCC. The arguments not to vaccinate boys relate to the short-term cost implications, which in many countries has been shown to be unsubstantiated,[2–4] and the absence of evidence of efficacy of the vaccine against oropharyngeal disease.

Surgical instruments have continued to evolve and many teams use lasers and harmonic scalpels routinely. Some units use robotic surgery as part of their surgical approach, with an evolving body of non-randomised data to support its use.[5,6] Long-term functional outcome data are still lacking with this new technology, but should be collected as a matter of course to ensure both survival outcomes and functional morbidity continue to improve.

Novel tools to improve the certainty of surgical resection margins intra-operatively are available in theatre, ranging from the use of Lugol's Iodine (LIHNCS – Lugol's Iodine in Head and Neck Cancer Surgery) to commercially available systems (PENTAX i-SCAN™, OLYMPUS narrow band imaging and STORZ spies™). Cutting edge molecular diagnostic tools (iKnife) require prospective data collection to support their use, but if confirmed may revolutionise the need for intra-operative frozen sections, with significant cost-saving associations.[7]

Advances in microvascular techniques push the limit of surgical resections, maximising the chances of

surgical clearance and the associated links with improved survival. In addition, microsurgical techniques are being employed to reduce tumour- and/or treatment-associated morbidity, examples including complex nasal, midface and mandibular reconstruction, most of which benefit from computer-aided planning to fit individual defects and laryngeal re-innervation.

Imaging modalities continue to evolve and help facilitate patient selection and operative limits. Recent results from the positron emission tomography-Neck trial will undoubtedly influence neck management and future surveillance imaging, but this will require backing from the Royal College of Radiologists to support the change in clinical practice. Other avenues that may provide enhanced imaging techniques include dual-energy computed tomography (CT).[8]

Finally, surgeons are well placed to talk to patients about research trials, even if it is just a matter of taking consent to send tumour to the tissue bank. Research is fundamental to improve our understanding and treatment of this disease.

Oncology

There have been significant recent advances in non-surgical oncological management of head and neck SCC. These developments are likely to continue to shape our thinking over the next decade as we develop more effective, less toxic treatments for head and neck SCC. The key themes are discussed below.

Improved radiotherapy (RT) techniques

In comparison with treatment techniques that would have been standards of care one or two decades ago, the current routine daily practice of RT is completely unrecognisable. Three-dimensional conformal RT and intensity-modulated radiotherapy are now considered to be gold-standard treatments and are available in almost every centre in the UK. Even these approaches are being refined further with increasing application of image-guided RT. This involves using imaging investigations performed during a course of treatment to allow oncologists to adapt the RT plan to ensure adequate coverage of target volumes that contain (or may contain) cancer cells while, at the same time, sparing normal tissues. Increasing availability of linear accelerators with on-board cone-beam CT and technologies that allow fusion of planning CT scans with diagnostic magnetic resonance imaging scans will continue to drive this process. In addition, the development of newer technologies, such as the MR-Linac and proton beam therapy, means that the next decade is likely to see significant advances in the therapeutic index of RT.[9,10]

Development of molecularly targeted radiosensitisers

As a result of meta-analyses of a large number of small- to medium-sized randomised trials, we now recognise RT delivered with concomitant platinum monotherapy as a standard of care for unresected, locally advanced head and neck SCC. A molecularly targeted antibody against epidermal growth factor receptor (EGFR), cetuximab, has also been shown to enhance the effect of RT in a single-phase III trial, but it did not yield additional benefit when combined with platin-based chemoradiotherapy.[11] In the next decade, we are likely to see a number of new targeted radiosensitisers developed for use in patients with head and neck SCC. Improved understanding of key molecular events in the response of cancer cells to radiation has highlighted potential targets for developing tumour-selective radiosensitisers. In particular, dysregulated cell cycle control and/or loss of key components of the DNA damage response represent a molecular 'Achilles' heel' that is vulnerable to therapeutic exploitation with new agents that include poly ADP ribose polymerase, Chk1, poly ADP ribose polymerase and Wee1 kinase inhibitors.[12]

Development of immuno-oncology (I-O) agents

In recent years, I-O has emerged as a major new modality in the treatment of many solid cancers, including head and neck SCC. This advance has been underpinned by huge strides in our understanding of the fundamental biological principles that guide the activity of the immune system. In particular, specific immune checkpoints have been discovered that are central components of normal immune responses. In health, such checkpoints function to inhibit T cells and prevent their chronic activation or misdirection against normal tissues. Effectively, they function as negative regulators or 'brakes' on the normal immune response. Many cancers subvert these inhibitory pathways in order to escape from immunosurveillance by activating brakes on the immune system. Immune checkpoint inhibitors are able to release these brakes on the immune system and trigger dramatic antitumour responses. Antiprogrammed death (PD)-1 and anti-PD ligand-1-targeted monoclonal antibodies have already shown activity in head and neck SCC[13] and it is highly likely that other, newer checkpoint-inhibiting drugs will enter clinical practice in the next 5–10 years. It is very probable that head and neck SCC will continue to represent a promising target for such drugs.

Development of effective adjuvant therapies

Previous attempts to use adjuvant chemotherapy in patients who had completed definitive treatment for locally advanced head and neck cancer were focused on cytotoxic chemotherapy and failed to demonstrate any benefit. Subsequent research moved towards assessment of small molecule inhibitors of growth factor receptors. Recent data have shown that the dual EGFR/human epidermal growth factor2 inhibitor, lapatinib, does not improve outcomes of post-operative chemoradiotherapy in patients judged to be at high risk of disease recurrence.[14] In ongoing studies, the irreversible inhibitor of EGFR, HER2 and HER4, afatinib, is being tested as an adjuvant therapy in high-risk patients after definitive chemoradiation (phase III LUX2 study NCT 01345669) or after post-operative

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chemoradiotherapy (GORTEC 2010-02, EudraCT 2010-023265-22). The increased prominence of I-O agents (vide supra) signifies that adjuvant trials of such agents will be conducted in the coming years. Hopefully, such studies will deliver a successful outcome against locoregional and metastatic recurrence of head and neck SCC.

Personalised treatment through molecular classification

We have made major advances in our understanding of cancer by examining the genetic nature of the disease [The Cancer Genome Atlas Network, 2015[15]]. Recent reports have provided detailed analysis of the mutational landscapes in different types of tumours and this work is beginning to provide insights that are likely to guide future therapeutic innovation. For example, the basis of the biological differences between HPV-positive and -negative cancers is clear when examining their different genetic profiles. The preponderance of inactivating events (mutations, epigenetic silencing) in the p53 pathway in HPV-negative disease contrasts strongly with the frequency of wild-type (i.e. normal) p53 in HPV-positive disease. In addition, specific abnormalities (e.g. PIK3CA mutations) are more common in HPV-positive disease and may be suitable targets for the specific drug therapies. It is likely that we will see further subcategorisation of head and neck SCC in the next decade and that will be accompanied by personalisation of treatment for individual patients based on the genetic content of their disease.

Key points

- Increased patient participation in clinical trials
- Patient stratification for personalisation of treatment
- Improved imaging techniques
- Advances in surgical tools including robotic surgery
- Improved outcomes through new radiotherapy technologies
- Incorporation of immuno-oncology agents in radical and palliative treatment approaches
- Development of effective post-radiotherapy/chemoradiotherapy adjuvant treatments

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