Head and Neck Cancer

British Association of Head and Neck Oncologists

British Association of Oral and Maxillofacial Surgeons

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British Academic Conference in Otolaryngology (BACO) and
British Association of Otorhinolaryngology – Head & Neck Surgery (BAO-HNS)

Multidisciplinary Management Guidelines

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Head and Neck Cancer: Multidisciplinary Management Guidelines

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Contents

Forewords

There is no doubt that this concise and comprehensive document is a triumph of collaboration by experts from all disciplines working in Head and Neck Oncology. Its production is part of an ongoing process. It builds on the earlier consensus documents and will be the handbook for Multidisciplinary Teams until such time as it too needs revision. The editors and contributors are to be congratulated for producing such a valuable document. It will prove to be essential reading and a key reference document for all those working in this field and will provide a benchmark for high quality care.

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I am delighted to contribute a short preface to this document. Nick Roland and Vin Paleri deserve our thanks and congratulations for their perseverance in developing a consensus document.

Two of the most significant changes to have occurred during my career in head and neck cancer care have been the development of the MDT and, in parallel, the emergence of interface training in head and neck cancer surgery. These two key evolutions have done so much to strengthen the collaboration between all our specialties and this has, in my view, led to enormous gains for our patients in terms of the quality of their care.

This consensus document can only add to the accuracy of decision-making within the MDT environment and, on behalf of my colleagues in oral and maxillofacial surgery involved in the care of patients with a diagnosis of head and neck cancer, I look forward to this publication being available to all head and neck MDT members.

Robert Woodwards MBBcH BDS FDSRCS FRCS
President, British Association of Oral
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I am pleased to read these guidelines which are being published under the joint auspices of four surgical specialties. The increasing recognition of the added value that all disciplines can bring to the management of complex tumours is reflected in the multidisciplinary approach to such documents. Since I took up a Consultant position 20 years ago, the cross fertilisation of ideas between specialties has developed in many centres, with much improved patient outcomes as a consequence. The institution of Training Interface Groups running specialised Fellowships in the final years of training has encouraged such working practices, and I hope that we will see greater and more rapid take up of such opportunities in the next few years. Sharing of ideas in an environment of mutual respect can only be to the benefit of good patient care and future research, and is the way forward for mature health care systems. I wholeheartedly commend this document for widespread use.

Tim Goodacre MBBS BSc FRCS FRCSEd
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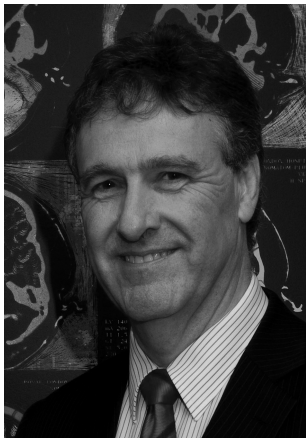

The editors of the UK Multi-disciplinary Consensus Guidelines for Head and Neck Oncology are indeed to be congratulated for producing this "Tour de Force". Consensus implies a harmonious agreement involving some compromise, in order to reach an accord. Achieving this from such a wide group of professionals is no small feat! This document conveys the current thoughts on management of head and neck cancer patients from all parts of the UK and from all of the many and varied specialties which are involved in providing care. Head and Neck Cancer is a relatively rare condition, and within that global term, there are an almost infinite number of sub-divisions, with every patient requiring personalised treatment planning. It therefore comes as no surprise that many of the recommendations within the guidelines are not supported by the highest levels of evidence. Nonetheless, these guidelines represent the combined experience of most of the units treating Head and Neck Cancer in the UK, and therefore are of enormous value. I am certain they will be widely used to inform and stimulate the debate in our MDTs. Perhaps of most importance they identify where there is significant variation in practice, and highlight the need for

better combined data collection and analysis. Only by close collaboration and pooling of our resources will we be able to answer some of the most pressing and difficult questions. The British Association of Head and Neck Oncologists represents the multi-disciplinary head and neck community within the UK, and as President I am delighted to offer the grateful thanks of our association to both the editors and the many contributing authors for their collective efforts in publishing this most valuable set of clinical guidelines.

Ian C Martin LLM FDSRCS FRCS FRCS(Ed)
President, British Association of Head and Neck Oncologists
President, Federation of Surgical Specialist Associations

On behalf of the British Association of Endocrine and Thyroid Surgeons, we welcome the publication of Head and Neck Cancer: Multidisciplinary Management Guidelines. We fully endorse the multidisciplinary approach to working with cancer and particularly support recording of prospective data and outcomes. We hope that this will be the first of many documents to come with support from all stakeholder professional organisations. With an impressive number of contributors from all relevant specialities, this publication comes highly recommended and will serve as a handy text for all practising clinicians involved in head and neck cancer care.

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Chapter 1
Introduction

It is with great pleasure that we introduce the fourth United Kingdom Multidisciplinary Management Guidelines for Head and Neck Cancer.

ENT UK, under its previous title as the British Association of Otolaryngologists – Head and Neck Surgeons, produced consensus documents for head and neck cancer in 1998, 2000 and 2002. There have been subsequent guidelines produced by NICE (Improving Outcomes Guidance 2004, updated 2010) and the Scottish Intercollegiate Guidelines Network (SIGN) in 2006. We feel that the production of a UK National Guideline based primarily on the clinical management of head and neck cancer patients to be timely.

Our aim was to produce a multidisciplinary consensus opinion on the management of head and neck cancer based on the experience of UK based international experts and current evidence in the medical literature. It was our desire to provide a clinical document which can be used as a ready reference source for MDT meetings. The document should also be an excellent educational foundation for all individuals involved in head and neck cancer care, particularly for trainees. Although the document aspires to be robust and evidence based, we have also attempted to keep it concise and pragmatic. The editorial team were keen to avoid a manuscript with lengthy reference lists and a document which resembled a textbook. The authors have therefore produced chapters with constraints on words and references, though it should be noted that many other sources may have been used in the development of their consensus view. Where appropriate, links have been provided from the guidelines directly to reference documents on the web for ease of access when read on electronic devices.

With over 120 authors from 10 specialities, the document truly represents a multidisciplinary effort and we are grateful to the Colleges and Societies and their representatives that have made this possible. We would particularly like to express our sincere thanks to the topic leads and the expert teams that have collated their views into what we believe to be an excellent product.

The levels of evidence used to make the recommendation grades are those espoused by the Scottish Intercollegiate Guidelines Network and reproduced below for reference.

Nick Roland and Vinidh Paleri
Editorial Leads

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Key to grades of recommendations in the guidelines

Levels of evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 *or* Extrapolated evidence from studies rated as 2+

Chapter 2
Risk Factors, Aetiology and Epidemiology in the United Kingdom

Authors: Richard Shaw, Nigel Beasley

1. INTRODUCTION

The major risk factors for head and neck squamous cell cancer (HNSCC) 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 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.

2. SMOKING

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

Quitting tobacco smoking for a short period of time (1–4 years) results in a head and neck cancer risk reduction of around 30% compared with current smoking and after 20 years can reduce the risk of developing oral cavity cancer to the level of a life long none smoker and the risk of laryngeal cancer by 60% after 10–15 years.

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 (Grade A)
- If they want to stop, refer them to an intensive support service such as NHS Stop Smoking Services (Grade A)
- If they are unwilling or unable to accept a referral, offer a stop smoking aid, e.g., pharmacotherapy (Grade A)

3. 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 and continued drinking has a negative impact on survival (HR1.28). 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 than of non drinkers.

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 the Fast Alcohol Screening Test (FAST).

Recommendations

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

4. HUMAN PAPILLOMA VIRUS

HPV-16 is an increasingly recognised causative agent in oropharyngeal and oral SCC, however doubt remains in other sites and for other HPV subtypes. Combined data from recently published (2006–2009) studies shows that 55% of 654 oropharyngeal SCC cases were HPV-16 positive. 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. Evidence seems currently insufficient to counsel avoidance 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 HNSCC.

5. 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% of biopsies of leukoplakia, but most erythroplakia. The significant clinical predictors of malignant transformation in oral dysplastic lesions are clinical appearance (HR 7.0 if non-homogeneous) and size (HR 5.4 if > 200mm^2). A recent systematic review of oral dysplasia (992 patients) showed malignant transformation in 12.1% after mean 4.3 years following biopsy. 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). Importantly, these data only reflect patients already referred for a specialist opinion and with biopsy proven dysplasia. In population based studies of oral leukoplakia 40–50% regress spontaneously and <1% transform. A systematic review of laryngeal dysplastic lesions (942 patients) showed transformation in 14% after a mean interval of 5.8 years, again severity of dysplasia correlated with risk of transformation. Many clinicians prefer to offer treatment and surveillance within a designated multidisciplinary dysplasia clinic.

Recommendations

- There is insufficient evidence to justify screening in the general population to prevent oral cancer (Grade A)
- Management of leukoplakia is not informed by high level evidence but consensus supports targeted use of biopsy and histopathological assessment (Grade D)
- The management of biopsy proven dysplastic lesions favours:
  i. advice to reduce known environmental carcinogens such as tobacco and alcohol (Grade A)
  ii. surgical excision when the size of the lesions and the patient's function allows (Grade D)
  iii. long term surveillance (Grade D)

6. PREMALIGNANT CONDITIONS

6.1. Inherited

Inherited conditions with increased risk of HNSCC include Fanconi Anaemia (FA), Ataxia Telangiectasia, Blooms Syndrome, & Li-Fraumeni Syndrome. FA has a very high risk of developing HNSCC (particularly oral SCC), most notably after hematopoietic stem cell transplantation. Recent evidence suggests a possibility that HPV may be implicated in FA related OSCC. FA 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. HNSCC can occur early in patients as young as 11-years old. Further guidance is available from www.fanconianaemia.nhs.uk

Recommendations

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

6.2. Acquired immunodeficiency

Patients who are immunosuppressed due to poor nutrition, advanced age, immunosuppressive therapy after transplant or 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 OSCC. 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.

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Chapter 3
Molecular Biology

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Contributors: Ken Parkinson, Margaret Stanley, Catharine West, Maxine Partridge

1. INTRODUCTION

The Tumour Node Metastasis (TNM) staging system is the best prognostic indicator for patients with head and neck squamous cell cancer (HNSCC), but the variation in treatment outcome within staging groups highlights the importance of differences in the underlying biology of individual tumours. Although assessment of molecular biology plays no role in the current management of the disease, the area of research is very active. With increasing understanding of molecular pathology of head and neck cancer and the development of new drugs targeting specific molecular processes, it is anticipated that molecular profiling will be introduced at some point into routine practice to further the individualisation of patient treatment. This section overviews recent developments and highlights areas with the best levels of evidence for their importance in influencing how patients respond to treatment.

2. THE MOLECULAR BASIS OF HNSCC

Many HNSCCs present without a noticeable pre-malignant stage although a microscopic dysplasia probably precedes the HNSCC based on genetic and microarray work. The genetic abnormalities associated with HNSCC reside at chromosomes 9p21 (p16), 3p, 17p and 8p, mutation of the p53 gene and amplification of cyclin D1. Making the distinction between a recurrent tumour and development of a true second primary is important and molecular analysis can differentiate between a recurrence and a second primary by identification of key genetic markers, e.g., identical p53 gene mutations in a recurrence.

Cases with p53 mutation-positive molecular fields have a 10% increase in local recurrence rate compared to p53 wild type. Likewise those patients with persisting HPV after treatment have a higher risk of recurrence.

3. DIAGNOSTIC AND PROGNOSTIC MARKERS

Molecular markers (p53, keratin, elf4E and E48) and genetic analysis can help distinguish between second primary tumours, second field tumours, recurrences

and metastases. Similar approaches have been used to detect residual disease and disseminated tumour cells in lymph nodes blood and bone marrow. Molecular markers in these areas and in non-invasive early diagnosis have tremendous potential, but are still experimental or only just approaching trials. A better understanding of the molecular pathogenesis of HNSCC will bring an opportunity to incorporate knowledge of the key pathways that are disrupted and generate robust classifiers that will augment clinico-pathological assessment.

Numerous markers (p53, keratin, elf4E and E48) and a range of exciting new techniques with huge potential in the diagnosis and management of HNSCC are currently still experimental rather than in routine clinical practice.

4. MOLECULAR TREATMENT

4.1. Human Papilloma Virus

Head and neck cancers are a biologically heterogeneous group of tumours with differing biology reflecting the variation in aetiology, e.g., whether tobacco or viral associated. It has been known for many years that Epstein Barr Virus (EBV) infection is important in the development of nasopharyngeal cancers and Human Papilloma Virus (HPV) plays a role in the aetiology of some head and neck cancers. HPV DNA is currently thought to be involved in ~26% of HNSCC and the frequency is rising with the oropharynx being a favoured site of infection.

Patients with HPV-associated tumours have a good prognosis, tend to be younger, have low or no tobacco exposure and have smaller tumours. These patients are possibly being over-treated and exposed to an unnecessary risk of toxicity, but further research is required to determine whether they should receive de-escalated therapy, e.g. radiotherapy alone rather than with concurrent chemotherapy.

HPV status is not determined routinely in head and neck cancer patients in most centres in the UK. Also, there is no accepted standard method for determining HPV positivity in head and neck cancers. The most widely used methods for assessing integration are in situ hybridisation using specific primers (mainly for HPV16) and immunostaining for the cell cycle brake p16ink4a. Staining of tumour cells with certain p16ink4a antibodies is a marker of high risk HPV infection as it is deregulated by HPV expression and is a surrogate marker of HPV function. A consensus is emerging in the UK that two methods should be used: a PCR approach combined with p16 immunohistochemistry.

There is a need to confirm the best approach for assessing HPV status as it has implications in the diagnosis and management of patients with oropharyngeal cancer and with the introduction of HPV vaccines. The incidence of HPV related tumours needs to be carefully monitored. Since there are many factors which may co-exist with HPV status eg p53, immunocompromised patients, this should be as part of a study so that patients treatment is not altered at the expense their survival. We need to know if HPV status alone is sufficient to de-escalate treatment or if there are other more or less important factors.

4.2. Epidermal Growth Factor Receptor (EGFR)

Cetuximab is an antibody that targets the epidermal growth factor receptor (EGFR). It stops growth factors from binding to the receptor and inhibits, amongst other cellular processes, tumour proliferation. Some tumours do not respond to cetuximab and there is interest in finding a marker that predicts likely benefit. Although approximately 90% of head and neck squamous cell cancers express EGFR, the level of expression does not predict benefit from cetuximab.

A recent randomised controlled trial has showed that adding cetuximab to radiotherapy improves the overall survival of patients with head and neck cancer (9% at 5 years). In 2008, the National Institute for Clinical Excellence (NICE) recommended the use of cetuximab in combination with radiotherapy as a treatment option only for patients with locally advanced squamous cell cancer of the head and neck with a Karnofsky performance-status score ≥ 90% and for whom all forms of platinum-based chemo-radiotherapy treatment are contraindicated. Data from multiple cancers, including head and neck, suggest that patients who develop an acneiform rash (a common side effect of anti-EGFR therapy) with a severity of ≥ grade 2 benefit from cetuximab. The rash may be a biomarker for immunological response.

As rash severity can only be determined following drug treatment, there is a need to find molecular biomarkers that predict response to anti-EGFR therapy prior to treatment. The use of KRAS mutation status as a selection biomarker for anti-EGFR monoclonal antibody treatment is emerging in other cancers, particularly metastatic colorectal cancer. Tumours with mutations in the KRAS gene do not benefit from anti-EGFR therapy and so KRAS wild type status is emerging as a biomarker for selecting patients for anti-EGFR treatment. In squamous cell carcinoma of the head and neck, almost 95% of patients have KRAS wild-type tumours.

Analysis of the Bonner trial data suggested cetuximab benefited certain subgroups of patients, e.g. oropharyngeal tumours, T1-3 tumours, advanced nodal stage and high Karnofsky performance status. An important question that needs confirming/addressing is: which head and neck cancer patients are most likely to benefit from EGFR targeting therapy and how can the patients be selected prior to treatment? Analysis is required of further data from trials involving cetuximab and other anti-EGFR therapy in head and neck cancer patients.

4.3. Hypoxia

There is a high level of evidence that head and neck tumours, which are hypoxic, respond less well to radiotherapy and that hypoxia modification strategies are effective in HNSCC . Despite this it is not used routinely in most countries including the UK. There is a need to investigate and develop a hypoxia modification strategy for use in patients with HNSCC receiving radiotherapy

5. FUTURE DEVELOPMENTS

The key issues for changing clinical practice in HNSCC are in the fields of early diagnosis and tumour classification. These tumours present late, progress rapidly

and need intensive and expensive treatment. Predictive biomarkers for radiation response, metastatic potential, side effects and EGFR targeting are likely to be exciting future developments having implications on future practice.

Key points

- HPV is involved in the development of some head and neck cancers.
- HPV positive head and neck cancers have a good prognosis.
- Determination of HPV positivity should be introduced into the routine assessment of patients with oropharyngeal cancer.
- HPV vaccination may reduce HPV positive HNSCC.
- Anti-EGFR treatment (cetuximab) is effective in patients with HNSCC.
- There is evidence that the severity of anti-EGFR induced rash and KRAS wild-type status predict benefit from treatment.
- Hypoxic head and neck tumours respond less well to radiotherapy than well-oxygenated tumours.

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Chapter 4
Organisation and Provision of Head and Neck Cancer Services in the UK

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Contributors: Jarrod Homer, Lisa Pitkin, Priyamal Silva

1. INTRODUCTION

The Calman-Hine Report "A Policy Framework for Commissioning Cancer Services" (1995), NHS Cancer Plan and the evidence based "Improving Outcomes Guidance" provide the basis for establishing the national standards for cancer care.

2. CALMAN-HINE REPORT

Calman–Hine was the first comprehensive cancer report to be produced in the UK, and set out seven principles (Table 1).

Table 1. The Calman–Hine report: seven principles to govern the provision of cancer care

• Access to uniform high-quality care in the community or hospital
• Early identification of cancer and availability of national screening programmes
• Patients to be given clear information at all stages
• Services to be patient centred
• Centrality of primary care and effective communications
• Psychosocial aspects of care are important
• Cancer registration and monitoring of treatment and outcome are essential

Since publication of the Calman-Hine Report, there have been a range of reports and policy documents that have had direct impact on planning for, and delivering cancer services.

Three levels of care were proposed:

– Primary care as the focus of care.
– Designated cancer units in many district general hospitals. These should be of a size to support clinical teams with sufficient expertise and facilities to manage the commoner cancers.
– Designated cancer centres should provide expertise in the management of all cancers, including common cancers within their immediate geographical locality and less common cancers by referral from Cancer Units. They will provide specialist diagnostic and therapeutic techniques including radiotherapy. Less common cancers (e.g., head and neck cancers) follow this model of care.

3. NICE IMPROVING OUTCOMES GUIDANCE IN HEAD AND NECK CANCERS

Stemming from the Calman–Hine Report, the Department of Health commissioned a series of evidence-based 'Improving Outcomes Guidance' (IOG's) reports. The National Institute of Health and Clinical Excellence improving outcome guidelines (NICE-IOG) manual for head and neck cancer was published in 2004. The aim was to facilitate the standardisation of head and neck cancer services which had previously been delivered in a widely heterogeneous way. The 'Hub and Spoke' model as described by Calman-Hine for many cancers was not applicable for head and neck cancer according to NICE-IOG.

The IOG recommended that:

1. Services for patients with head and neck cancers should be commissioned at the Cancer Network level. The Multi-disciplinary team (MDT) within each Cancer Centre should serve populations of *over a million patients.*
2. MDT's with a wide range of specialists will be central to the service, each managing *at least 100 new cases* of upper aerodigestive tract cancer per annum. They will be responsible for assessment, treatment planning and management of every patient.
3. Specialised teams within each network will deal with rare or particularly challenging conditions such as salivary gland and skull base tumours.
4. Thyroid cancer MDT's can be within or separate to the upper aerodigestive tract MDT.
5. Arrangements for referral at each stage of the patient's cancer journey should be streamlined. Diagnostic clinics should be established for patients with neck lumps.
6. A wide range of support services should be provided. Clinical nurse specialists, speech and language therapists, dietitians and restorative dentists play crucial roles but a variety of other therapists are also required, from the pre-treatment assessment period until rehabilitation is complete.
7. Co-ordinated local support teams should be established to provide long-term support and rehabilitation for patients in the community. These teams will work closely with every level of the service, from primary care teams to the specialist MDT.
8. MDTs should take responsibility for ensuring that accurate and complete data on disease stage, management and outcomes are recorded. Information collection and audit are crucial to improving services and must be adequately supported.
9. Research into the effectiveness of management – including assessment, treatment, delivery of services and rehabilitation – urgently requires development and expansion. Multi-centre clinical trials should be encouraged and supported.

4. THE CANCER REFORM STRATEGY (2007)

The key elements of the Cancer Reform Strategy are:

1. 14 day standard from urgent GP referral to assessment in clinic (by designated head and neck clinician at a local hospital which provides such services, or to a rapid-access neck lump assessment clinic). See tables 2 and 3 for criteria.
2. 31 day standard from diagnosis to treatment (including recurrent disease)
3. 62 day standard from GP referral to beginning of treatment

The Department of Health applies compliance targets to these standards, which vary and are subject to being updated (e.g., in 2011 96% for surgery 31 day target; 94% for radiotherapy; 90% for 62 day target).

Table 2. Head and neck cancer - Urgent referral guidelines (England)

- Hoarseness persisting for more than six weeks
- Ulceration of oral mucosa persisting for more than three weeks
- Oral swellings persisting for more than three weeks
- All red or red and white patches of the oral mucosa
- Dysphagia persisting for more than three weeks
- Unilateral nasal obstruction, particularly when associated with purulent discharge
- Unexplained tooth mobility not associated with periodontal disease
- Unresolving neck masses for more than three weeks
- Cranial neuropathies
- Orbital masses

(The level of suspicion is further increased if the patient is a heavy smoker or heavy alcohol drinker and is aged over 45 years and male. Other forms of tobacco use and/or chewing betel (areca nut) should also arouse suspicion.)

Table 3. Thyroid cancer - Urgent referral guidelines

Patients with thyroid lump AND:

- Age > 65
- Previous radiotherapy/family histpry
- Stridor
- Cervical lymphadenopathy
- Voice change

(Other thyroid lumps can be referred on a routine basis)

5. INITIAL INVESTIGATIONS AND DIAGNOSIS

Patients with suspected head and neck cancer should be seen at local hospitals by designated clinicians within a rapid assessment clinic.

Designated head and neck surgeons, haematologists, histopathologists / cytologists and radiologists should co-operate to ensure that an appropriate diagnostic work-up is provided for patients with neck lumps. Patients found or suspected to have cancer should be referred without delay to the appropriate MDT. There should be pre-booking systems for appointments at results clinics at which each patient with a diagnosis of cancer would be seen by a senior member of the MDT which deals with that type of cancer, and where support would be available from a clinical nurse specialist. The GP should be informed within 24 hours of the diagnosis.

6. THE PEER REVIEW PROCESS

In England, the National Cancer Peer Review programme involves both self-assessment by cancer service teams and external reviews of teams conducted by professional peers, against nationally agreed quality measures. The peer review process works at the level of the local support team, the MDT and the cancer network.

A national database has been developed with the intention of supporting the self assessment process. The online manual can be accessed at www.cquins.nhs.uk.

7. DATA FOR HEAD AND NECK ONCOLOGY (DaHNO)

DaHNO (see chapter 14) provides a continuous electronic comparative audit on management of head and neck cancer. The aim remains to achieve comprehensive and consistent data collection producing meaningful results that act as a vehicle to improve delivery of care to patients with head and neck cancer. Individual unit performance is fed back at a local level to assist in comparison with national averages.

The DaHNO sixth annual report, presented data collected on new registrations for a period of 12 months until October 2010. Approximately 97% of head and neck cancers are thought to be captured using DaHNO. However, questions remain regarding the accuracy and validity of the data. For example, only 45% of oral tongue cancers were treated by primary surgery, according to the 6th report. Further confusion arises from catagorising data under different Trusts involved in the patient's pathway.

8. COMPLIANCE WITH NICE-IOG

Amongst the key recommendations of the IOG were the management of *at least 100 cases per MDT* group in order to be compliant. It could be argued that a figure of 250 may be more appropriate as there is a belief that head and neck surgeons should be performing 30–40 cases per annum. This would provide the high volume and case mix experience to maintain quality and provide adequate training. A head and neck cancer centre according to NICE should have at least three surgeons providing resection and reconstruction. In general approximately half of all head and neck cancer patients undergo surgery, therefore the figure of 250 head and neck cancer cases in a year is reached.

Preliminary survey data has shown that there are:

- 33 cancer networks in the UK (some have merged)
- 69 MDT's in total- but some are "virtual" and/or have >1 surgical unit for head and neck cancer surgery, so the figure of actual surgical units is probably the better metric
- 79 head and neck cancer surgical units

Using this only 16/33 networks are compliant (48%). In order to comply with NICE-IOG, only networks with >2million should have 2 centres or surgical units. There are only 2 networks with >3million. Of the networks with >2million, 1 has 1 MDT/centre only. There are a few networks with <1million population. The minimum number of head and neck surgical units should be 48 to comply with current NICE-IOG given the cancer network geography and make up, as well as present situation. (i.e. there are 31 head and neck surgical units too many).

There are around 50 radiotherapy centres treating head and neck cancer in the UK. Many of these do not offer contemporary treatments, such as intensity modulated radiation therapy (IMRT) and Cetuximab. The precise figures are as yet unclear. Catchment areas for radiotherapy centres were not really covered in the NICE-IOG,

but the conclusion should arguably be that there should be only one per network, giving a target of 33. In the Cancer Reform Strategy, the vision for the head and neck cancer services by 2012 included the use of more targeted therapies, which would require more sophisticated molecular and immunohistochemical profiling of cancer specimens and the use of more complex advanced radiation techniques, such as IMRT.

9. FUTURE CHALLENGES IN THE UK

9.1. Changing epidemiology and treatment

The two drivers with regard to changing patterns of disease incidence are: (a) decreasing smoking; (b) rise of HPV-induced oropharyngeal squamous cell carcinoma. The observed and anticipated consequences appear to be:

1. Decrease in laryngeal and hypopharyngeal cancer
2. Increase in HPV-induced oropharyneal cancer
3. The incidence of oral cavity cancer appears to be steady

Added to this are the accepted and anticipated changes in treatment. A higher proportion of patients with advanced laryngeal and hypopharyngeal cancer are treated with chemoradiation. This is offset to a certain degree with more patients with early laryngeal cancer being treated with trans-oral laser microsurgery. However, the latter group is a small group of patients, and most are still treated by radiotherapy in the UK, according to DaHNO. With regard to oropharyngeal squamous cell carcinoma, especially that which is HPV-induced, the mainstay of treatment is chemoradiotherapy and this is unlikely to change. There is a role for neck dissection surgery in many of these patients however. Oral cavity cancers will continue to be treated with primary surgery.

9.2. Surgical manpower

If it is assumed that oral cavity cancer in the UK will remain mainly treated by oromaxillofacial surgeons, then the manpower needs in OMFS are unlikely to change. Within otolaryngology-head and neck surgery, there may be less overall major operations per annum but more complex cases (especially after chemo-radiation). There may therefore need to be a difference in manpower needs in the future between the two major head and neck cancer specialities.

9.3. Further rationalisation and centralisation

Many feel that the current NICE-IOG rationalisation should have been greater, with MDT's and cancer centres serving around 250 new cases per year of upper aerodigestive tract cancers (only a small proportion of whom will go on to have complex surgery), bringing the UK in line with many other European and countries and North America.

Furthermore, there is evidence that compliance with current NICE-IOG has been sub-optimal with still too many hospitals performing head and neck cancer surgery.

9.4. Data

There is a need for DaHNO to be validated. If accuracy is poor, then alternative solutions or adaptations are required, as accurate data collection and audit is essential in improving patient care.

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Chapter 5
Pre-Treatment Clinical Assessment

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1. INTRODUCTION

This section deals with the important area of pre-assessment and optimisation prior to treatment for head and neck cancer. The importance of grading and analysing comorbidity, pre-assessment within an agreed structure and prophylaxis against infection and venous thromboembolism is summarised in the section below. Much of the evidence is extrapolated from studies on patients undergoing general or orthopaedic surgery and may not be as relevant to head and neck surgery, for example in the field of venous thromboembolism prophylaxis.

2. COMORBIDITY

Comorbidity is the presence of illnesses unrelated to the tumour. It significantly affects prognosis in head and neck cancer (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 recommends that collection of an ACE 27 comorbidity score be mandated for all adult cancer patients. Information should be abstracted from notes rather than relying on self reporting. Functional status is not a reliable substitute for comorbidity evaluation as a prognostic measure. Severity as well as presence of a condition should be recorded.

The effects of increased pre-treatment comorbid burden include:

- Increased mortality in HNC patients, especially in the early years after treatment, and a greater impact on younger patients
- Adverse influence on disease specific survival, probably due to the advanced stage at presentation and the likelihood of such patients undergoing less aggressive treatment.
- Higher incidence of and more severe complications.
- Adverse impact on quality of life (QOL)
- Increased cost of treatment

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. There is good evidence that integrating comorbidity with staging systems produces better prognostic instruments.

Recommendations

- Comorbidity burden should be prospectively recorded (Grade D)
- Increased pre-treatment comorbidity has an adverse effect on prognosis in head and neck cancer (Grade B)

3. CLINICAL ASSESSMENT/PRE-ASSESSMENT

A good pre-assessment system will provide an appropriately informed, consented and prepared patient on the day of surgery, avoiding late cancellation and preventable risk.

Measures of the effectiveness of a pre-assessment service include:

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

These measures should be audited. The role of the anaesthetist in preassessment should be:

- Identification of the difficult airway.
- Risk stratification.
- Optimisation of comorbidities within the limited timeframe prior to surgery.
- Formulation of a plan for perioperative care.

Guidance for the use of preoperative testing is available from NICE (http://www.nice.org.uk/nicemedia/pdf/Preop_Fullguideline.pdf). A modification published by the Clinical Audit and Practice Advisory Group of ENT UK only deals with head and neck surgery briefly (http://www.entuk.org/publications/preoptestsbackground.pdf). Guidance is available for pre-assessment from the British Association of Day Surgery and Royal College of Anaesthetists.

There should be a clinical lead in each anaesthetic department for pre-assessment and for Head and Neck anaesthesia. Prompt referral or advice from a physician or a haematologist as necessary is an essential part of the pre-assessment service.

3.1. Identification of the difficult airway

This should be assessed by an experienced anaesthetist in conjunction with a surgeon; preoperative nasendoscopy helps identify problems with intubation. The

Mallampati test is unreliable as a single assessment tool. Anaesthetic records should be scanned for previous problems. Risk factors for a difficult intubation include:

- Previous problems with intubation.
- Laryngeal disease
- Previous radiotherapy or head and neck surgery

3.2. Risk stratification and optimisation of comorbidities

3.2.1. Cardiovascular and respiratory system

Comorbidities in these body systems predominate in this patient group in 40 to 50% and 20 to 30% respectively. Poor functional status is the most important predictor of perioperative mortality. This can be assessed by:

- The use of Metabolic EquivalenTS (METS) where 1 MET equates to the resting state and 4 METS equates to climbing 2 flights of stairs uninterrupted. Failure to achieve this increases mortality.
- Lack of independence.
- Living in sheltered accommodation.
- Assessment can be complicated by the presence of musculoskeletal disease, limiting mobility.

A combination of subjective and objective (eg Cardiopulmonary exercise testing, CPX) assessment tools are used but the relative low mortality in HNC surgery suggest that formal assessment tools may overestimate the risk of surgery.

Table 1 Risk factors predicting postoperative morbidity

Cardiovascular
Heart failure, associated with poor functional status
Unstable coronary disease, coronary event in last 6 months
Severe valvular disease
Pulmonary hypertension
Poorly controlled atrial fibrillation (AF)
Respiratory
Advanced COPD
Long operation

The cardiovascular risk factors in Table 1 merit cardiology referral. Treatments for heart failure such as ACE inhibitors and beta blockers should be continued perioperatively although hypotension may be a problem. If stenting is performed following angiography bare metal stents are preferred as these require only 6 weeks of clopidogrel therapy (which markedly increases perioperative bleeding) rather than drug eluting stents which require a year of antiplatelet therapy.

Recommendations

- Clopidogrel should be discontinued 5 days preoperatively, but aspirin should be continued without interruption (Grade B)
- Warfarin for uncomplicated atrial fibrillation can be discontinued 5 days before surgery (Grade B)
- When warfarin is stopped in patients with previous thromboembolic disease or artificial heart valves they require heparin therapy perioperatively (Grade B)

Neuroendocrine control of hypertension takes months to achieve and probably does not contribute to perioperative mortality *per se*. There is increasing evidence that statin therapy should be continued without interruption to prevent perioperative coronary syndromes. More comprehensive perioperative cardiac management in non-cardiac surgery guidelines can be found at http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/perioperative-cardiac-care.aspx?hit=dontmiss

COPD should be quantified with spirometry (http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/COPD/COPD%20Consortium/spirometry_in_practice051.pdf) and oximetry. The risk of respiratory mortality alone may outweigh any benefit from major surgery and FEV1 estimation helps prognosticate. The following actions will optimise a patient's condition for surgery:

1. Optimise bronchodilator therapy.
2. Trial of steroid responsiveness in moderate/severe disease.
3. Smoking cessation.
4. Perioperative nebuliser therapy.
5. Treatment of intercurrent chest infection, possibly delaying surgery.
6. Sputum sampling to enable 'best guess' treatment of chest infection.

Recommendations

- Severe hypertension (>180/110mmHg) or hypertension in the presence of other risk factors (AF, cardiac failure, left ventricular hypertrophy) needs aggressive management (Grade B)
- Cardiac drugs must be continued up to admission and administered as early as possible postoperatively (Grade C)
- An FEV1 of <25% when accompanied by hypoxia, hypercarbia or cor pulmonale are indicators of increased need for postoperative ventilatory support (Grade B)

3.2.2. Endocrine system

Poor glycaemic control is associated with increased intensive care and hospital mortality. Diabetics thus require tight control with insulin therapy. Oral hypoglycaemics should be omitted on the day of surgery and restarted when normal diet is resumed.

Patients taking in excess of 10mg Prednisone per day are at risk of relative post-operative adrenal failure. Intravenous supplementation at induction of 50-100mg hydrocortisone is normal with additional doses postoperatively (50-200mg daily in divided doses) until enteral function returns.

Recommendation

- Patients on oral steroids are at high risk of gastric ulceration and antacid therapy should be prescribed (Grade C)

3.2.3. Neurological system

Pre-existing cerebrovascular disease increases the risk of perioperative stroke if a hypotensive anaesthetic is used. Care should be taken with head positioning. Patients with rheumatoid arthritis should have cervical spine stability assessed radiologically.

3.2.4. Haematologic system

This may be associated with nutritional failure. A source of iron deficiency anaemia should be sought (occult malignancy, ulcer disease). Haematinic therapy should be initiated. In major surgery a target haemoglobin of >10g/dl is recommended and transfusion should be carried out at least 2 hours preoperatively to maximise the oxygen carrying capacity of the blood.

3.3. Alcohol and tobacco

3.3.1. Alcohol

Alcohol Withdrawal Syndrome (AWS) in the context of major surgery has a perioperative mortality of up to 10%; risk prediction systems (eg CAGE) can identify such patients and drug treatment commenced 48 hours preoperatively as an inpatient. 'As required' benzodiazepine or chlodiazepoxide regimes are probably as effective as fixed dosage regimes. Alcohol abuse is associated with cardiomyopathy, atrial fibrillation, hypophosphataemia and hypomagnesaemia.

3.3.2. Tobacco use

The use of tobacco before diagnosis in patients with HNC has a negative correlation with survival. A significant proportion of patients attending cancer diagnostic clinics are tobacco users. Continued tobacco use in the period leading up to surgery is associated with higher morbidity in general. Pulmonary complications are greater

in smokers with HNC undergoing surgery. Patients requiring pedicled and free flap reconstructions have higher flap failure rates. Continued smoking during radiotherapy treatment appears to increase complications in patients with laryngopharyngeal cancer and increase the risk of treatment failure. Ideally patients should be supported to stop smoking from the time of their initial clinic visit. The UK Government has set up a comprehensive NHS Stop Smoking Service and a range of products and interventions are available (www.smokefree.nhs.uk). Nicotine withdrawal should be treated with replacement therapy as appropriate.

Recommendation

- Smoking cessation, commenced preferably 4 weeks before surgery, decreases the incidence of postoperative complications (Grade A)

3.4. Nutritional failure

Nutritional failure impacts negatively on mortality, infection and wound healing. Detailed nutritional assessment and support should be instituted routinely. Dietician-led nutritional support intervention should be provided to any at-risk patients as part of their multidisciplinary management (see Chapter 8).

4. ANTIBIOTIC PROPHYLAXIS

HNC patients who smoke, have advanced disease or require free flap reconstruction have the greatest risk of surgical wound infection. This risk may be minimised by:

- Pre-assessment to enable same day admission where possible.
- MRSA screening.
- Aseptic surgical technique and careful tissue handling.
- Prompt discharge.

Evidence supports the use of prophylactic antibiotics in head and neck surgery for clean-contaminated wounds, but not for clean wounds. The first dose should be given at induction and continued for up to 24 hrs; longer courses may increase nosocomial infection. Broad spectrum prophylactic antibiotics should be chosen upon the advice of a local microbiologist.

Recommendations

- Antibiotics are necessary for clean-contaminated head and neck surgery, but unnecessary for clean surgery (Grade A)
- Antibiotic regimes longer than 24 hours have no additional benefit in clean-contaminated head and neck surgery (Grade B)

5. PROPHYLAXIS FOR VENOUS THROMBOEMBOLISM (VTE)

The most recent NICE guidance on VTE does not make specific mention of prophylaxis in Head and Neck Surgery (www.nice.org.uk/guidance/CG92). The incidence of VTE in patients undergoing head and neck cancer surgery is up to 0.6%. Malignancy is associated with a hypercoagulable state which increases the risk of VTE. There is no evidence specific to HNC surgery but SIGN guidelines recommend the same prophylaxis against VTE for otolaryngology patients as those undergoing general surgical operations. Both SIGN and NICE guidelines recommend that these patients should:

- wear thigh length graduated elastic compression stockings from admission
- receive intraoperative intermittent pneumatic compression
- be given subcutaneous low molecular weight heparin or low dose ultrafractionated heparin until discharge

VTE prophylaxis in patients undergoing operations outside the pelvis or lower limb lasting less than 90 minutes (e.g., endoscopy) is unnecessary unless there are specific risk factors. Adequate hydration and early mobilisation are essential. Starting heparin pre- or postoperatively does not affect VTE rates or intraoperative blood loss.

Recommendation

- Prophylaxis for venous thromboembolism is recommended for all patients undergoing head and neck surgical procedures expected to last over 90 minutes (Grade D)

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Chapter 6
Anaesthesia for Head and Neck Surgery

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1. 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.

2. PREOPERATIVE ASSESSMENT

Comorbidity and preoperative assessment are considered in Chapter 5. 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.

3. GENERAL ANAESTHETIC CONSIDERATIONS

3.1. World Health Organisation (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 surgical procedure they have consented to. In addition reference is made to whether any airway problems are anticipated and having the necessary equipment available. In these cases this may include emergency surgical tracheostomy trays etc.

3.2. 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 Ed, 2007) and advanced monitoring is usually only considered for long procedures or when excessive blood loss is a reasonable possibility.

3.3. Prophylaxis for thromboembolism (see chapter 5)

3.4. 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 pharyngo-laryngeal 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 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 oro-pharygeal tissues can interfere with facemask ventilation and conventional laryngoscopy.

3.5. Induction of anaesthesia

If a patient is already at risk of airway obstruction due to tumour bulk, 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 crico-thyroid or transtracheal 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 airway obstruction. Current practice has also been influenced by the introduction of many new intubation devices of these very few have been reported in large series of head and neck cancer patients.

3.6. Fluid management and blood loss

Many resections and free tissue flap repairs 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 minimize blood loss and haemodilution is practiced in some institutions with a view to improve blood

flow in surgical free flaps. Intra-operative haemoglobin and central venous pressure measurements help in monitoring the need for blood transfusion. Other than these considerations, background fluid replacement should generally be limited by comparison with body cavity surgery and 250-350mls/hr (crystalloid) is advised in the American Head and Neck Society guidelines.

3.7. 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 needs to protect from gravity related pressure effects, thermal homeostasis, retention of urine and prolonged wake up time.

4. SPECIFIC OPERATIVE CONSIDERATIONS

4.1. 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.

4.2. 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-value) and satisfactory from the point of view of bleeding.

4.3. Formal tumour assessment for treatment planning (EUA 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

(photograph, diagram) under consideration and ideally, shared visualisation of the lesion prior to induction.

4.4. Tubeless anaesthesia

Ideally, any surgeon would wish to have no restriction in the 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 (6.0mm 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/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.

4.5. 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.

4.6. Free flaps

Attempts have been made to increase the success of free flap anastamosis by medical means but there is no general consensus as to what if anything is efficacious. Doppler probes are available but 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 failure may allow the flap to be salvaged if the blood flow can be restored.

4.7. 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. 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 clips in the event of a rapid expanding haematoma) versus 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 an important consideration.

5. RECOVERY FROM ANAESTHESIA

5.5 Emergence from anaesthesia phenomena

Commonly seen problems include transient hypertension, disorientation and or agitation and shivering. Analgesic requirements tend to be much 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.

5.6. 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 under-estimated. 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.

5.7. 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 and the free flap. It is unusual for any patient to be ventilated post-operatively.

5.8. Care of the tracheostomy

The Intensive Care Society has produced guidelines for the management of tracheostomy (and temporary tracheostomy in particular). 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.

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Chapter 7
Imaging

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1. INTRODUCTION

The role of the radiologist and of imaging in head and neck cancer has developed enormously over the last two decades. Advanced cross sectional imaging modalities have allowed more accurate staging of disease and contributed significantly to accurate management decisions. The radiologist has a key role at multidisciplinary team meetings when high quality imaging allows the extent and stage of disease to be demonstrated to all team members and this has contributed significantly to confident mangement advice and appropriate consenting of the patient. The diagnosis of head and neck cancer has usually been established clinically and it is not unusual for a histological diagnosis to have also been made. The primary role of radiology is not usually one of diagnosis, but is one of accurate staging of the extent and spread of disease with emphasis on those features which will influence the choice of treatment and, where appropriate, in planning the best surgical approach. The areas which radiology should address are:

- the local spread of the primary tumour.
- the spread to locoregional lymph nodes
- metastatic spread of disease
- detection of synchronous primary tumours

This article considers two main sections: firstly the individual imaging modalities with a brief account of their specific value in the context of head and neck cancer and secondly a site by site radiological evaluation of difficulties in image interpretation.

2. IMAGING MODALITIES

2.1. Computerised tomography (CT)

CT images are essentially density maps of the human body utilising fairly high diagnostic radiation doses. Intravenous iodinated contrast allows some tumours through their abnormal vascularity to become easier to see, but in general the difference in density between neoplastic tissue and normal head and neck anatomical structures is small. The visualisation of tumours is therefore more reliant on changes in morphology and alteration of normal anatomy. CT is good at

demonstrating bone detail and this remains its major strength. Modern multislice CT technology provides scanners which are incredibly fast requiring just a few seconds of exposure to acquire a volume of data from which high spatial resolution images in all planes can be reconstructed. Many head and neck cancer patients have difficulty with breathing, swallowing, lying flat and keeping still and CT may well be the only imaging modality which can be tolerated. Where CT is being used in the main to stage the primary tumour the study should be contrast enhanced with around a 70 second delay before acquisition of images to allow even opacification of the arterial and venous structure of the head and neck. This improves the detection of abnormal nodes in the neck. Head and neck tumours tend to be slow to enhance after contrast injection.

2.2. Magnetic resonance (MR)

MR images reflect tissue biochemistry and are particularly influenced by the presence of protons within the tissues. The images of different weighting provide the means to not only visualise tissues but also to indicate what the tissue is made of. This is known as tissue characteristion. T1 weighted images carry a great deal of spatial resolution with excellent depiction of detailed anatomy. T2 weighted images are better at highlighting abnormal tissues. The STIR sequence retains this positive attribute of a T2 weighted image and suppresses all fat signal leaving all abnormal tissue and tissue with a high water content as high signal. The ability of MR therefore to show abnormal tumour tissue as high signal and normal tissue as low signal in an image creates improved contrast resolution when compared to CT. It is therefore the imaging modality of choice for soft tissue oropharyngeal cancers. Scan times compared to CT are much longer varying from around 2 to 5 minutes per sequence with scans sometimes taking 40 minutes in total during which the patient must keep still and for this reason MR will not always be suitable for all patients with head and neck cancer. Intravenous contrast agents allow the study to demonstrate the vascularity of a tumour, and when combined with fat suppression techniques, can increase the conspicuity of the pathology in the image.

2.3. Positron emission tomography-computerised tomography fusion scan (PET-CT)

PET images are maps reflecting levels of glucose metabolism within tissues. A short half life isotope 16 fluoro deoxy glucose (FDG) is injected intravenously. The PET scanner detects gamma rays caused by interaction of positrons emmitted by the isotope with electrons within the tissues. Modern scanners incorporate a CT scanner which co registers the activity with its exact anatomical location.

PET-CT has specific value in evaluating the patient with metastatic lymph nodes and an unknown primary. PET-CT will detect the clinically occult primary in approximately one third of cases. It is also valuable in the assessment of suspected recurrence of head and neck cancer. Its value in primary staging and surveillance following treatment is still being assessed.

2.4. Ultrasound (US)

US in experienced hands provides useful and rapid imaging assessment of patients with an undiagnosed neck lump. US is now usually offered as part of a 1 stop neck lump clinic. As well as providing imaging information on neck masses US can be used to guide a fine needle aspiration (FNA). A gold standard service for a neck mass clinic should therefore offer instant access to US, FNA and cytopathological assessment. Shortage of radiologists and histopathologists often makes organisation of such services difficult.

US is particularly useful in delineation of thyroid pathology and cervical lymphadenopathy. Imaging of the neck can suggest the presence of nodal metastases even when nodes are not obviously palpable (occult nodes). This occurs in approximately 20% of imaged cases. All imaging modalities rely on nodal size to indicate tumour involvement. Those nodes with a minimum axial diameter of more than 10mm have a high likelihood of neoplastic involvement with the exception of junctional nodes where a 15mm measurement is employed.

US is also useful in evaluating superficial salivary gland tumours.

2.5. Contrast swallow

There are a variety of clinical situations when contrast swallows are useful in head and neck cancer. Routine barium swallows can be of help in demonstrating the length of malignant strictures of the proximal oesophagus.

In general when there is a percieved risk of aspiration or when there has been recent surgery, water soluble contrast swallows are used. Barium once in the bronchial tree or in the soft tissues is difficult to move and can contribute to the exacerbation of chest infection.

Videofluoroscopy is a functional examination of the swallowing and or speech mechanism and can be valuable in assessing patients who have functional deficit after treatment for head and neck cancer. The examinations usually require the involvement of both a radiologist and a speech and language therapist if functional outcomes are to be improved. Other imaging techniques may have specific uses in specific clinical scenarios and these will be discussed in the relevant clinical sections.

2.6. Chest imaging

Many of the patients with head and neck cancer carry risk factors common to other tumours of the aerodigestive tract and studies have shown that the incidence of synchronous tumours in particular bronchial carcinoma is high. There is a wide variation in reported synchronous chest pathology but in general CT scanning of the thorax will identify occult pathology in 10% of cases with half due to metastatic disease and half due to a synchronous primary bronchial carcinoma. Routine chest imaging prior to treatment is therefore mandatory. Patients require at least a reported chest x-ray and many centres now perform CT of the thorax preoperatively.

This also allows metastatic disease to be detected. Some CT examinations will detect small non specific lung nodules and these should undergo follow up as per local guideleines.

3. SPECIFIC TUMOUR SITES

This section will deal with specific tumour sites and highlights the areas where radiological evalution is particularly important or difficult.

3.1. General comments regarding staging

The UICC TNM classification deserves some mention from a radiological perspective. Stages T1 to T3 deal with tumour size and the largest dimension of the tumour. The T4a and T4b status are more specifically aimed at potential surgical decision making. T4b stage indicates non operability of the tumour i.e. skull base involvement and/or internal carotid artery encasement and these can only be evaluated on cross sectional imaging. The encasement of the the carotid artery is a common factor for all head and neck cancers arising anywhere from skull base down to the subglottis and all staging scans must be able to evaluate this critical staging question. T4a stage indicates adverse features which require in the main a specific surgical solution if surgery is the treatment of choice e.g. bone involvement in oral cavity tumours or involvment of the medial pterygoid muscle in tonsillar carcinomas. This section deals therefore with those areas where the change in stage leads directly to a change in management options.

3.2. Lymph node disease

The lymph node status of the patient in head and neck cancer is important in deciding on a treatment plan and also in indicating an overall prognosis.

Most imaging modalities depend on evaluation of nodal size to decide on tumour involvement. In the axial plane on CT, MR and US, the minimum axial diameter is the accepted measurement with nodes more than 10mm regarded as being involved by tumour with the exception of junctional nodes such as the jugulodigastric node which has to be more than 15mm to indicate involvement. Using these criteria a sensitivity and specificity of only around 70% can be expected and this is due to the presence of micrometastases in non enlarged nodes. The demonstration of cystic change on any modality in the setting of head and neck cancer even in non enlarged lymph nodes is highly specific for nodal involvement by squamous cell carcinoma. Ultrasound guided FNA improves the overall specificity significantly and in those patients who present with a N0 neck, in whom a watch and wait policy is selected for neck disease, surveillance scanning at 3 monthly intervals for 18 months with ultrasound guided FNA of the 3 largest nodes has been advocated. There are obvious service issues associated with this policy.

PET-CT has a theoretical advantage in detecting FDG avid nodes but as yet there is little research evidence that this alters management or improves patient outcomes in the setting of a new presentation head and neck cancer.

The radiologist should report the site of all involved nodes using the numeric nodal classification system.

3.3. Oral cavity

Preferred imaging modality: MR

Tongue tumour evaluation by imaging is usually straightforward. Important features are restriction to the anterior tongue and to one side of the midline.

Floor of mouth and alveolar margin tumours are usually well defined. Important imaging features are extension into the tongue base, involvement of the neurovascular bundle and extension into bone. Correlation of MR findings with plain film orthopantomogram appearances is important as early bone invasion on MR can be mimicked by the presence of severe dental caries and periapical disease.

3.4. Oropharynx

Preferred imaging modality: MR

3.4.1. Tonsil tumours

Small tonsillar tumours can be difficult to identify as the normal lymphatic tissue of the tonsil is variable in size and is of high signal on T2 weighted images. Evaluation in both axial and coronal planes is important. The definition of the tumour is best evaluated on the STIR sequence. Particular attention to extension of tumour into the adjacent soft tissue planes around the pterygoid muscles in the infratemporal fossa must be given and it is worth specifically identifying whether there are enlarged retropharyngeal nodes. Involvement of the medial pterygoid muscle elevates staging to T4a and of the lateral pterygoid to T4b.

3.4.2. Tongue base tumours

These tumours often grow silently and deeply. Tumours can spread to the floor of mouth, the anterior tonsillar pillar and across the midline. Involvement of the valleculae and the pre epiglottic fat space is crucial as this would require a laryngoglossectomy for resection and this is no longer regarded as an appropriate surgical recommendation. Involvement of the deep intrinsic muscles of the tongue and or the extrinsic tongue muscles indicate a T4a stage of disease.

3.5. Nasopharynx

Preferred imaging modality: MR and CT

Nasopharyngeal tumours usually present late to the clinician and radiologist and are therefore of an advanced stage. The TNM classification of this group is much more anatomically dependant as opposed to other head and neck tumours where T staging is dependant on size until T4 features are encountered. T2 tumours require spread to the paraphayngeal space. T3 involves invasion of bone and or the sinuses while T4 stage indicates intracranial extension, masticator or infratemporal fossa space involvement or involvement of cranial nerves. As skull base involvement is so important, it is reasonable to stage using both MR and CT.

3.6. Hypopharynx

Preferred imaging modality: MR ideally but CT in those patients who have difficulty with swallowing or coughing while flat.

These tumours have a propensity to extend submucosally so there is often a disparity between initial clinical evaluation and the extent of disease radiologically. The radiologist needs to undertand the anatomical relationship of the hypopharynx and the larynx. Piriform fossa tumours aften spread to involve the larynx and the paralaryngeal space. T4 staging is indicated by invasion of adjacent structures such as thyroid/cricoid cartilage, the prevertebral fascia, thyroid or oesophagus. The use of coronal imaging sequences on MR or coronal reformats in CT can aid acurate staging in these crucial areas.

3.7. Larynx

Preferred imaging modality: MR.

Recent literature suggests that the accuracy of staging by MR is improved by around 10% when compared with CT. It is reasonable to recognise however that in many radiology departments CT access is often better than MR access and many departments using CT have a great deal of acquired expertise in laryngeal staging. CT images should be acquired during quiet respiration, as breath hold manoeuvres will oppose the cords, preventing accurate assessment of the primary tumour site.

Most early stage laryngeal cancers are not visible on CT or MR imaging. Staging is affected by clinical assessment of cord mobility so this information has to be provided with the request for imaging. A complex array of treatment options available with voice preservation surgery, are now available as a means of treating these often small but complex shaped tumours.

The radiologist needs to understand the following issues:

a. Supraglottic tumours

- involvement of the cricoid, thyroid and/or arytenoid cartilages.
- involvement of the apex of the piriform fossa
- involvment of the anterior commisure
- tongue base involvement
- transglottic tumour extension

b. Glottic tumours

- thyroid cartilage invasion, full thickness T4, inner cortex only T3.
- invasion patterns of the arytenoid and cricoid cartilages.
- degree of involvement of the contralateral cord
- degree of subglottic extension

MR has proven very sensitive for detecting cartilagenous invasion but can be non specific. The main difficulty is in reliably deifferentiating between perichondrial invasion, early cortex invasion (T3) and full thickness cartilage invasion (T4). Where there are specific such issues to answer it may be of help to consider supplementing MR with CT and correlating the imaging findings directly with the endoscopic appearances.

3.8. Salivary gland tumours

Preferred imaging modality: Varied.

Many benign superficial salivary gland tumours are well imaged by US. The major weakness of US is deep extension in relation to the adjacent mandible which may be difficult to demonstrate. The operator should have a low threshold to supplementing US with MR.

Imaging has a contributory role in the assessment of salivary gland tumours which is essentially triphasic: clinical evaluation, FNA and cytological evaluation and radiological evaluation.

The array of histological tumours in this group is large. The main aim of imaging is to accurately define the appearances of salivary gland tumours as benign or malignant with the acceptance of an intermediate group of mixed features.

Benign lesions are small, well defined and not associated with perilesional oedema or locoregional lymphanenopathy. Malignant lesions are large, poorly defined, associated with locoregional lymphadenopathy and perilesional oedema. Once histology demonstrates a malignant tumour then the role of imaging is to define the spread of tumour and to exclude any perineural spread which is particularlry common in adenoid cystic carcinomas. This is best achieved by gadolinium enhanced MR.

3.9. Sinus tumours

Preferred imaging modality: MR and CT.

The combination of the two imaging modalities improves radiological staging accuracy. Bone involvement is best assessed by CT while MR and the use of gadolinium enhancement allows the radiologist to differentiate sinus opacity due to fluid filled obstructed sinus air cells from soft tissue tumour causing opacity. The high staging of disease is dependant on spread into the infratemporal

fossa, the skull base and the orbit. These features are best assessed in the coronal and sagittal planes utilising MR with T1 weighted images before and after gadolinium enhancement accompanied by unenhanced high resolution CT for bone detail.

It is essential for the radiologist to be familiar with skull base anatomy on CT and MR if the subtle changes of skull base perineural spread are to be appreciated. The radiologist's main role is to identify those cases which are unsuitable for surgery and this rests on skull base perineural involvement.

The radiologist should also consider whether the disease could be explained by metastatic bone disease and isotope bone scanning can be helpful in differentiating true solitary primary sinus tumour pathology from disseminated bone metastases.

3.10. Skull base

Preferred imaging modality MR and CT.

A detailed account of skull base pathology is beyond the scope of this article but there are some basic principles that can be proposed:

- Both modalities are usually required to meet the challenge of the difficult area of skull base pathology.
- It is important to establish that the imaging changes firstly do represent true pathology and are not pseudolesions due to normal variants or asymmmetrical normal anatomy. Knowledge of the breadth of anatomical variance is essential.
- Is the abnormality a "leave me alone" lesion? Does it have features of a long standing abnormality e.g. well defined associated with bone remodelling or a sclerotic margin to the lesion? If this is the case and the clinical features are stable or this is a coincidental finding is it possible to perform interval scanning?
- Does the lesion show aggressive features such as a poorly defined bone border or soft tissue mass on either side of the bone?
- Does it conform to a known pattern of skull base pathology?
- Is the lesion accessible and safe to biopsy ie not a vascular structure or a vascular tumour of which there are many around the skull base.
- If in doubt do nothing and refer to a radiologist with a special interest in the skull base.

3.11. Thyroid cancer

Although there are many different histological types and grades of thyroid cancer this group of diseases can be broadly divided into two types: differentiated thyroid cancer and medullary cancer of thyroid.

An imaging strategy for thyroid cancers on this basis is proposed below in table 1.

Table 1. A suggested imaging strategy for thryoid cancers

Clinical presentation	Differentiated thyroid cancer	Medullary cancer of thyroid
Localised thyroid nodule (pre-intervention)	• Ultrasound neck + FNA • CXR (unenhanced CT in aggressive disease)	• Ultrasound neck + FNA • MR neck • CT chest and abdomen • In^{111} Octreotide scan
Neck node metastases (pre-intervention)	• Ultrasound neck + FNA • CXR • MR neck and chest (mediastinum)	• As above
Distant metastases at presentation	• Ultrasound neck + FNA • I^{131} scan (whole body) • CT chest *(no IV contrast if within 8 weeks of proposed I^{131} scan)* for lung metastases • Isotope bone scan for bone metastases	• As above
Early post-operative period	• I^{131} scan (neck)	• Nil routinely
Post I^{131} ablation	• I^{131} scan (whole body)	• N/A
Rising biochemical markers on follow up	• I^{131} scan (whole body) • CXR If CXR is negative, consider • Ultrasound neck +/- FNA • CT chest *(no IV contrast if within 8 weeks of proposed I^{131} scan)* • PET/CT	• Ultrasound neck +/- FNA • MR neck • CT chest and abdomen • In^{111} Octreotide scan (if –ve, consider I^{123} MIBG scan)
Clinical recurrence (neck)	• As for neck nodes pre-intervention	• As for localised thyroid nodule
Clinical recurrence (distant)	• As for metastases on presentation	• As for localised thyroid nodule
Other investigations	• TFT	• TFT, calcitonin, urinary catecholamines

Legend: CXR: chest X ray; MIBG: Meta-iodobenzylguanidine; TFT: thyroid function test

3.12. Post-treatment imaging

Imaging the post-treatment neck is a severe radiological challenge. The radiologist needs to understand the effect of chemoradiation on the appearances of the head and neck soft tissues as well as the complex appearances of microvascular composite free flaps. Treatment induced soft tissue oedema can last from 6 months to 2 years and can mask underlying tumour recurrence. Serial scanning by either CT or MR can allow enlarging recurrences to be identified. Increasingly PET-CT is being used as the imaging modality of choice in evaluating potential tumour recurrence. The major challenge of PET-CT is the differentiation of post treatment change and inflammation from tumour recurrence. Most head and neck cancer recurrences occur within the first 2 years, which coincides with the time period of post-treatment inflammation. Careful correlation with standard CT and MRI

imaging may be required. Functional MRI (diffusion and perfusion imaging) may assist in such cases, but these techniques are still undergoing assessment, and are not routine in most centres as yet.

4. CONCLUSION

The radiologist has a crucial role in evaluating head and neck cancer. An understanging of treatment options and the factors that influence management decisions is essential. The multi-disciplinary team meetings are the ideal forum to experience these discussions first hand and to appreciate the critical imaging changes of each of the cancer sites.

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Chapter 8
Nutrition

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1. 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 site specific dietitians for high quality service delivery to meet the patient's needs and contribute as a core member of the head and neck multidisciplinary team. Early identification of high risk patients and intervention with nutrition support should be included as part of the planning for every head and neck cancer patient when treatment options are being considered. This should be from diagnosis in preparation for treatment, and should include quality-of-life issues to address psychosocial and rehabilitation needs of patients and carers.

Recommendation

- A specialist dietitian should be part of the MDT for treating head and neck cancer patients throughout the continuum of care. Frequent dietetic contact has been shown to enhance outcomes (Grade A)

2. NUTRITIONAL SCREENING

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

3. MONITORING

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

Table 1. Nutritional screening 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 (MST)	Compares favourably with the PG-SGA.	Yes
The Malnutrition Universal Screening Tool (MUST)	Currently used by many Trusts across the UK to screen patients.	No

Recommendation

- Patients with head and neck cancer should be nutritionally screened using a validated screening tool (Grade D)

4. 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. At diagnosis, 50%–75% of patients already have malnutrition, and 80% will lose a significant amount of weight during multi-modal treatment. Malnutrition (10% or greater weight loss in previous 6 months) can lead to a range of problems as highlighted in Table 2.

Table 2. Malnutrition associated morbidity

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

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.

Recommendation

- At risk patients should receive early nutritional intervention by an experienced head and neck dietitian (Grade C)

5. NUTRITIONAL ASSESSMENT

Following nutritional screening a full nutritional assessment should be undertaken (Table 3).

Table 3. 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 effect nutritional intake e.g., coeliac disease, diabetes
Dietary history	Review of recent intake (24 hour recall) attention being paid to: • fluid intake • changes in texture • reports of fullness • length of time and effort taken to eat • changes in appetite • GI function
Calculation of requirements	Energy: • 25–35 kcal/kg/day dependant on activity level. Can increase further if major complications. Protein: • 0.8–2.0g/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
Anthropometry	• Height • Weight • Weight history • Percentage weight change • Body mass index (BMI) = wt(kg)/ht(m^2) Normal = 20–25kg/m^2 • <18.5kg/m^2 suggests undernutrition • Tricep skinfold thickness (TST) indicates fat stores • Mid arm muscle circumference (MAMC) indicates lean tissue mass (requires TST and mid arm circumference (MAC) for calculation) • 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 • Prealbumin—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

(continued)

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

6. CANCER CACHEXIA

Cachexia syndrome results in decreased appetite, weight loss, metabolic alterations and an inflammatory state. 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.

7. ESTIMATING NUTRITIONAL REQUIREMENTS

Cancer itself does not have a consistent effect on resting energy expenditure (REE), but may be influenced by oncological treatment. REE can be unchanged, increased, or decreased. Cancer patients are mildly hypermetabolic with an excess energy expenditure of between 138–289 kcals per day. The key challenge is to identify the right patients. Total energy expenditure and protein requirements for non obese ambulatory patients using their actual body weight can be estimated as follows:

Energy: 30–35 kcals/kg/day and Protein: 1.2 g/kg/day. These may be less accurate for severely malnourished, morbidly obese and surgical patients.

8. 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 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.

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 0.4mmol/l, retrospective data from a regional cancer centre found 37.5% of patients to be at risk as defined by NICE criteria (See Table 4) with an incidence rate of 9.5%. A suggested management plan for refeeding syndrome is shown in figure 1.

Table 4. Criteria for determining patients at moderate or high risk of developing refeeding syndrome

Patient has one or more of the following:
- BMI less than 16 kg/m^2.
- Unintentional weight loss greater than 15% within last 3–6 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:
- BMI less than 18.5 kg/m^2.
- Unintentional weight loss greater than 10% within last 3–6 months.
- Little or no nutritional intake for more than 5 days.
- A history of alcohol abuse or drugs including insulin, chemotherapy, antacids, or diuretics.

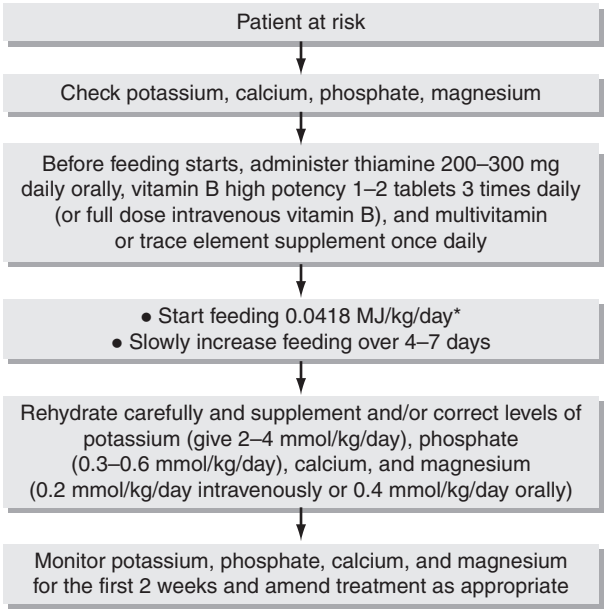

Figure 1: Management of re-feeding syndrome (reproduced with permission from Mehanna et al., BMJ 2008)

Recommendations

- Nutritional assessment of cancer patients should be performed frequently, and nutritional intervention initiated early when deficits are detected (Grade C)
- Attempts to modulate cancer cachexia changes by other means should be integrated into the management of cancer patients (Grade C)

9. NUTRITION SUPPORT

The aims of nutrition support are

- Improve the subjective quality of life (QoL)
- Enhance anti-tumour treatment effects
- Reduce the adverse effects of anti-tumour therapies
- Prevent & treat undernutrition

Nutritional support should be considered in the following scenarios:

- BMI < 18.5 kg/m^2
- Unintentional weight loss >10% over 3–6 months
- A BMI <20 kg/m^2 and unintentional weight loss over 3–6 months
- Minimal intake >5 days +/− minimal intake ≥ 5 days
- Increased nutritional requirements due to catabolism

9.1. 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 3 main methods of nutrition support. These include: oral, enteral and parenteral. Parenteral nutrition support is rarely used in the head and neck setting. It should however, be considered if required.

9.1.1. Oral nutrition support

Nutritional interventions include relaxation of previous therapeutic diets to minimise further nutritional compromise. 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 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 feed company contract.

9.1.2. Enteral nutrition 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. The types of tubes available are nasogastric, nasojejunal, tracheo–oesophageal fistulae tubes, orogastric, gastrostomy, gastro-jejunostomy, and jejunostomy. Nasogastric, nasojejunal, orogastric, trachea—oesophageal fistulae tubes are all recommended for short term use (<4weeks). There are no nationally agreed selection criteria for gastrostomy placement in head and neck patients. NICE guidelines on enteral feeding suggest that if enteral feeding is expected to be required for longer than 4 weeks then gastrostomy insertion is recommended.

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 dependant on local policy. There are no nationally agreed selection criteria for gastrostomy placement in head and neck patients. Prophylactic tube feeding compared to interventional tube feeding or oral intake alone improves nutritional outcomes with reduced weight loss, and can therefore contribute towards clinical, financial and quality of life aspects.

9.2. Enteral nutrition

The type and volume of enteral nutrition will depend upon the patients' symptoms and current intake and is likely to change throughout and following treatment. There is 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.

9.3. Immune enhanced nutrition

Immunonutrition are feeds containing amino acids, nucleotides and lipids. It has been suggested that immunonutrition may reduce post-operative infective complications. However, this premise is yet to be proven. There is evidence that patients given immunonutrition experience a reduction in hospital stay.

9.4. 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

Commencing Enteral Nutrition (Grade C):

- Nutritional therapy should be started if undernutrition already exists or if it is anticipated that the patient will be unable to eat for more than seven days. EN should also be started if an inadequate food intake (60% of estimated energy expenditure) is anticipated for more than 10 days.

Type of Formulae (Grade C):

- Use standard polymeric feeds
- Immunonutrition evidence is controversial and it is not possible to reach any firm conclusions with regard to improved nutritional status or physical function

Route of Feeding (Grade C):

- If long term tube feeding is necessary (greater than 4 weeks) consider gastrostomy insertion

Monitoring (Grade A):

- The regular monitoring of nutritional parameters should be continued throughout the patient's cancer journey.

10. NUTRITION CONSIDERATIONS DURING SURGICAL TREATMENT

10.1. Preoperative 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. 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. Table 5 indicates criteria for initiating pre/peri operative nutrition support and identifies patients with severe nutritional risk.

Table 5. Criteria for initiating pre-operative nutritional support

Indications:
• Weight loss>10–15% in 6 months
• BMI <18.5 kg/m2
• Subjective Global Assessment Grade C
• Serum Albumin <30 g/l
• Unable to maintain intake above 60% of recommended intake for more than 10 days

10.2. Postoperative 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.

10.3. Nutritional management of chyle leaks

This is a rare complication with an incidence of 1–4% in neck dissections. It occurs when the central lymphatic system has been damaged during surgery. The management may be conservative, including dietary manipulation or further surgery. A post operative leak gives the fluid a milky appearance. Confirmed diagnosis of a chyle leak requires the presence of chylomicrons although other biochemical analyses may help to confirm diagnosis. 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. MCT is recommended because it is directly absorbed into the portal system resulting in less chyle production. In clinical practice fat free products are 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 eg: very high volume leaks (>1000mls).

There is no consensus on how to nutritionally manage chyle leaks. The nutritional intervention is usually dependant on clinician preference.

Recommendations

Pre Operative (Grade A):

- Patients with severe nutritional risk should receive nutrition support for 10–14 days prior to major surgery even if surgery has to be delayed.

Post Operative (Grade A):

- Tube feeding should be initiated within 24 hours of surgery

Chyle Leak (Grade D):

- Confirmation of chylous leak should be sought by analysis of drainage fluid for triglyceride (higher) and chlolesterol (lower) with a cholesterol to triglyceride ratio < 1, as compared to plasma levels prior to commencing dietary restriction.
- Nutritional intervention should commence with fat free nutritional supplements either orally or via a feeding tube.
- An MCT formulation for enteral tube feeding is also acceptable
- TPN should be initiated in severe cases when drainage volume is consistently high.

11. NUTRITIONAL CONSIDERATIONS DURING RADIOTHERAPY +/− CHEMOTHERAPY

Concomitant mucositis during radiotherapy +/− chemotherapy results in weight loss which can not be completely prevented by nutritional counselling alone. 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. This also is 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 swallowing.

Recommendations

- Patients should be offered intensive dietary advice during treatment to prevent weight loss, increase intake and reduce interruption to radiotherapy (Grade A)
- Tube feeds should be considered if cancer interferes with swallowing and if mucositis is expected or thought to affect swallowing (Grade C)
- Tube feeding can be given by either nasogastric or gastrostomy routes (Grade C)

12. REHABILITATION/SURVIVORSHIP

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 can experience between 10–20% weight loss up to one year following treatment. Optimisation of nutritional status should continue to be a priority long term.

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.

13. QUALITY OF LIFE

Reduction in quality of life can be directly related to weight loss and malnutrition with an improvement seen when dietary counselling and aggressive nutritional support is maintained during treatment. Presence of long term feeding tubes have been shown to significantly impair quality of life.

Recommendation

- Quality of life parameters including nutritional and swallowing, should be measured at diagnosis and at regular intervals post treatment (Grade D)

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 MDT 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 quality of life and enhance the beneficial effects of treatment.

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Chapter 9
Restorative Dentistry/Oral Rehabilitation

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1. INTRODUCTION

It is important to include a Consultant in Restorative Dentistry/Oral Rehabilitation within the head and neck cancer team as many patients face complex oral rehabilitation and dental health issues during and after their oncology treatment. This section addresses the issues relating to pre-treatment oral and dental assessment, preventive advice, peri-post treatment management and oral rehabilitation.

2. 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. This should render patient dentally fit before treatment and ensure the oral cavity can be maintained and rehabilitated after treatment.

The aims of pre-treatment assessment are:

- Avoidance of unscheduled interruptions to primary treatment as a result of dental problems
- Pre-prosthetic planning/treatment e.g., planning for primary implants/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. Extractions 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.

Studies supporting oral care as stated above are cohort studies, case reports and expert opinion.

3. 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 chemo 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 is thought to be the result of reduced salivary flow as well as possible direct radiogenic damage to the amelodentinal 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

IMRT reduces the risk of xerostomia and may also do for osteoradionecrosis after treatment.

4. MANAGEMENT

4.1. Preventive management

- Maintenance of good oral hygiene by effective toothbrushing; flossing daily.
- Dietary Advice with regard to caries prevention.
- Daily topical fluoride application (2800ppm or 5000ppm fluoride toothpaste) in custom-made trays or brush-on. Daily fluoride mouthrinse.
- Daily use of GC Tooth Mousse ™ containing free calcium
- Saliva replacement therapy/ use of frequent saline rinses
- Jaw exercises to reduce trismus.

Recommendation

- Preventative oral care must be delivered to all patients undergoing treatment for head and neck cancer (Grade C)

4.2. Peri-treatment and post-treatment management

4.2.1. Oral mucositis and ulceration

Treatments include Chinese medicines, hydrolytic enzymes, ice chips, benzydamine, calcium phosphate, etoposide bolus, manuka honey, iseganan, and zinc sulphate. All have been shown to demonstrate some level of benefit although the response seems to be patient specific.

4.2.2. 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.

4.2.3. 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 the 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– 10mg per day) may improve radiation induced xerostomia in patients with evidence of some intact salivary function. There may be a protective effect by amifostine on the dental health after radiotherapy of the head and neck.

4.2.4. Altered anatomy

Prostheses may be required to replace missing tissue. These may be implant supported.

4.2.5. 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.

4.2.6. Mastication difficulties

These can be minimized by maintenance of the dentition and use of well-made prostheses.

4.2.7. 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 mobilize 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.

4.2.8. Oral rehabilitation using osseointegrated implants

Osseointegrated implants allow effective oral and facial rehabilitation following cancer treatment including radiotherapy. They are used to support oral or facial prostheses. Appropriate detailed planning and patient selection are important prior to proceeding with treatment. The use of hyperbaric oxygen (HBO) may be considered prior to elective implant placement in the irradiated jaws (>60Gy) in an attempt to improve implant survival rates, but is a controversial area with currently no clearcut evidence.

4.2.8.1 Primary dental implants

The placement of intra-oral implants at the same time as tumour resection may be beneficial for carefully selected patients; where there is continuity of the mandible, 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. In patients having segmental resection and reconstruction of the mandible, implant survival and usefulness is improved by delayed placement after suitable prosthodontic planning.

4.2.8.2. 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

- Oral and dental assessment by the restorative dental specialist prior to cancer treatment is essential in patients whose oral cavity, teeth, salivary glands and jaws will be affected in order to effectively plan oral rehabilitation and dental management.
- Dental extractions should be completed at least 10 days prior to the start of radiotherapy but ideally should be completed at time of cancer surgery where appropriate.

- Dentate patients should receive advice and instruction regarding the use of appropriate toothpastes, remineralising agents, mouthwashes and products to relieve mucositis and xerostomia.
- Dentate patients should not use acidic salivary stimulants (such as Glandosane™) due to their dental erosive potential.
- Patients with trismus or those at high risk of developing it should be given appropriate jaw exercises and treatment with devices such as the Therabite™ .
- The placement of dental implants into intact jaws at the time of primary surgery is beneficial for carefully selected patients.
- Dental implant placement into irradiated jaws and composite bone flaps is a successful treatment modality, but implant survival is worse than in non-irradiated patients.
- The use of HBO prior to dental extraction or implant treatment is a controversial area with currently no clear cut evidence.

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Chapter 10
Psychological Management

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1. INTRODUCTION

The head and neck cancer patient and their carers have considerable challenges to overcome. Although many patients appear to cope surprisingly well a sizeable minority suffer considerable psychological distress in a variety of forms. Treatment recovery may be hampered by mood changes for example, whereas longer term psychological states may feature some months and even years following initial treatment. This section highlights the major psychological management concerns in the course of caring for the patient being treated for head and neck cancer.

2. 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. It is vital that the patient is told clearly that they have a cancer and its nature and possible 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 best as possible.

3. DELIVERING INFORMATION ABOUT TREATMENT AND RECOVERY

Considerable efforts have been expended to determine the information needs of head and cancer patients. Poor satisfaction with information supplied by the team was predictive of patient lowered mood and quality of life in the longer term. 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 multi-disciplinary team (MDT) sole authority to determine treatment regimens. However recent reports have compiled large data sets of ‘normative’ quality of life 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.

Recommendations

- Audit of information supplied to patients and carers should be conducted on an annual basis to update and review content and media presentation (Grade C)
- 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 (Grade D)

4. 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 repeated out-patient check-ups. These assessments have the ability to capture those patients who would not necessarily be identified by the MDT. Two issues follow however. First, how does the MDT manage this increased need for assistance? Secondly, the risk of labelling a false positive, that is when there is no substantial distress, is raised by measures that are only able to screen and therefore include appreciable 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 a MDT assessment profile library for occasional use when required. Recurrence fears have been found to be linked closely to depression in patients and some evidence that patients can stimulate these fears in their carers. 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.

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. MDTs need to plan their services to provide escalating level of care according to specific need of psychological difficulty presented by the patient. The newly developing Map of Medicine describes in detail the levels of intervention (1 to 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 (Grade B)
- Flexibility, rather than rigid formulation is required to assess patients frequently, and to allow for change in circumstances to be noted (Grade C)
- MDTs should determine the supportive care services available and commission extra assistance to provide patients and carers with timely information, education or brief supportive advice (Grade C)
- MDTs 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 (Grade C)

5. END OF LIFE ISSUES

Communication with the patient assumes even greater importance when curative treatment options are not available and care switches to a palliative approach. Areas such as assessing level of knowledge that the patient prefers concerning life expectancy, how pain can be controlled, 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 and training.

Recommendation

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

Key Points

- Develop information services for patients and carers.
- Develop decision-making tools for the aid of patients to enter into discussion with the MDT to agree on their treatment plan.
- Collect routine psychological assessments at key points during course of care with considered steps for tailored care being triggered according to confirmed level of psychological distress or depression.
- Focus on level of support and intervention that current team can provide. Remain cautious when introducing change, but strengthen and build upon current supports already available.
- Develop more comprehensive support services with a focus on improving communication skills training for current staff.
- Introduce staff training to assist with management of potential burnout in MDT staff.

- Audit current psychological services applied in the head and neck cancer service. Identify current usage and gaps in service.
- Assess current capability of specialist clinical nurse (SCN) skills to support psychologically head and neck cancer patients.
- 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/psychotherapist.
- Identify liaison psychiatry service and negotiate referral pathway and response time.

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Chapter 11
Quality of Life

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The evaluation of the quality of life (QOL) in patients with head and neck cancer is integral to optimal patient care. 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).

1. WHAT IS QUALITY OF LIFE?

Quality of life is a multifaceted construct comprising of many different aspects leading to numerous definitions. The World Health Organisation (WHO) 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*". 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. 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.

2. WHY SHOULD WE MEASURE QUALITY OF LIFE?

HRQOL evaluation gives an indication of how the patient perceives the impact of their cancer and its treatment. 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. HRQOL 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. Patient Reported Outcomes may also be used to help patients' express unmet concerns. A better understanding of patients' perception helps facilitate improvements in aftercare and serves to drive clinically relevant outcomes research.

It is appreciated that there are many potential difficulties in assessing HRQOL in clinical practice. 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 is 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 as an important role simply as an additional factor, or perhaps where it has relatively little value. Hence healthcare professionals can unrealistically rely too much of the value of HRQOL in certain clinical situations and this can lead to frustration and a perceived lack of benefit in the HRQOL process.

3. 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). There is no gold standard questionnaire and each have their own unique features and merits. 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.

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 number of patients 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.

4. 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) and only one reference is used in order to direct the reader to further information on the topic. There are several review articles that give additional information. At this 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.
- 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 /depression is treatable.
- Family and children: The impact of cancer affects family.
- Fatigue: common in the first year post-treatment, poor sleep, low energy.
- Fear of recurrence: unpredictable by clinical characteristics, does not lessen over time.
- Financial / work: employment, benefits, cost of treatment and follow-up, 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 H&N, relatively few published papers.
- Information: varying amounts, in various ways, at different times. This includes the importance of communication skills and consistency of contact with named health professional for duration of clinical treatment, access to patient and carer support groups.
- Intimacy: sexuality, worst in the younger patient as an unmet need.
- Lifestyle choices: smoking, alcohol abuse.
- Nutrition: low weight, diet, PEG feeding.
- Oral Rehabilitation: chewing / eating – realistic expectations of rehabilation.
- Osteoradionecrosis: associated with pain, trismus, poor HRQOL, 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, finance.
- Speech: complex function, various aspects, laryngeal speech outcomes, isolation.
- Swallowing: nutrition, social, presence of feeding tube is most significant to HRQOL.
- Shoulder: shoulder discomfort and neck tightness, debate around avoiding a neck dissection or carrying a selective dissection.
- Trismus: difficulty in mouth opening associated with diet/social/dental health.
- Xerostomia: dry mouth has a profound impact on social function and HRQOL, IMRT should be used whenever feasible.
- Unknown: clinical art of the individual patient is not a precise science.

5. 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 along side other drivers such as survival, function, health care cost. Examples are described below.

5.1. Oropharynx

5.1.1. Early stage disease

There is an argument for laser excision for early oropharynx lesions with selective neck dissection. This avoids the need for free tissue transfer and access procedure such as lip split mandibulotomy.

Drivers for change: HRQOL, survival, function, cost to NHS (reduced length of stay).

5.1.2. Advanced stage disease

There seems to be a preference towards chemoradiotherapy for larger oropharynx lesions if laser is felt not possible. The long-term outcomes remain unclear as does the success of salvage surgery and its impact on HRQOL. Primary radical surgery with free flap reconstruction and post-operative radiotherapy should be considered and treatment options discussed.

Drivers for change: HRQOL, function, health-care cost.

5.1.3. HPV testing

It is conceivable that it is possible to de-escalating treatment in those patients HPV positive. Similar survival might be achieved by radiotherapy alone rather than chemoradiotherapy.

Drivers for change: HRQOL

5.2. Larynx

5.2.1. Early stage disease

Laser excision rather than primary radiotherapy for suitable lesions.

Drivers for change: Patient choice based on equivalent HRQOL and survival.

5.2.2. 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: HRQOL, survival

5.3. Oral Cavity

5.3.1. Early stage disease

There is a rationale towards primary surgery without free tissue reconstruction and also consideration for avoiding neck dissection.

Drivers for change: HRQOL, survival, function, cost of overall treatment.

5.3.2. Advanced stage disease

Primary surgery with free tissue reconstruction as required. However, there is discussion around the benefit of adjuvant radiotherapy.

Drivers for change: HRQOL, survival.

6. 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 and further work is required to identify its place in the MDT decision process and better guidance of how to use HRQOL at an individual patient level. Advances in computer technology should make it 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.

Directions for the future:

1. Holistic assessment integrated into clinical practice.
2. Survivorship issues addressed through interventions.
3. Patient reported outcomes measures combined with objective evaluation.
4. A better understanding of late effects of treatment.
5. Partnerships, marital issues are no doubt of significant importance, as well as grand parents 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.

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Chapter 12
Tumour Assessment and Staging

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1. INTRODUCTION

Many factors affect 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 intercurrent disease) and management (treatment options, expertise available, patient preference).

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

Table 1 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

The nature of staging has meant that the data to support the concept has been largely drawn from retrospective and observational studies (Level 3). Much of the systems development has been through the opinion of expert panels using this data (level 4).

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 seventh editions (2009) and have approval of all national TNM committees.

> ***Recommendation (Grade D)***
>
> All patients with Head and Neck cancer should undergo tumour classification and staging prior to treatment

2. GENERAL RULES

The TNM system for describing the anatomical extent of the disease is based on three components (Table 2)

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

Table 2 Basic Concepts in Staging using the TNM system

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		

All cases should be confirmed microscopically. Two classifications should be documented for each site, namely: Clinical (pre-treatment) classification (cTNM), and Pathological (post surgical histopathological) classification (pTNM). 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.

See site specific chapters for each detailed tumour classification.

3. 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 intraobserver error, it has been suggested such information in conjunction with other characteristics of the primary tumour is useful in the rational approach to therapy. The grade can be applied to all head and neck sites except thyroid (table 3)

Table 3 Histopathological Grading

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

4. ADDITIONAL DESCRIPTORS

Designation is now applicable when sentinel lymph node biopsy is attempted using the suffix (sn) after N stage. 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 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, pretherapeutic clinical staging of head and neck cancers is equivalent to C1, C2 and C3 whilst pathological classification is equivalent to C4.

Recommendation (Grade D)

Pre-therapeutic clinical staging of head and neck cancers should be based on at least a C2 factor. That would be evidence obtained by special diagnostic means e.g. radiographic imaging (e.g. CT, MRI or USS), endoscopy, biopsy and cytology.

5. RELATED CLASSIFICATIONS

The World Health Organisation (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, benign). This coded nomenclature is identical in the morphology field for neoplasms to the Systemised Nomenclature of Medicine (SNOMED). 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.

6. STAGE GROUPING

After TNM classification, tumours should be assigned a stage grouping between 0 and IV. The grouping adopted is designed to ensure, as far as possible, that each group is more or less homogenous in respect of survival and that the survival rates for each cancer site 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 and mucosal melanoma (see related topics).

Table 4 Stage Grouping

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

7. 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, 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 TNM clinical classification, the pTNM pathological 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/ AJCC TNM booklets.

8. 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 inter-current disease should all be documented.

CT and MRI are now established as the mainstay investigations in the preoperative work-up of patients with head and neck cancer, to delineate the extent and size of the primary tumour, to determine the presence (particularly when risk of occult nodes is > 20%), 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.

Recommendation (Grade D)

Scans to evaluate the primary site should be performed *prior* to biopsy to avoid the effect of upstaging from the oedema caused by biopsy trauma.

Endoscopy and biopsy should be performed by a senior surgeon and in *all cases* by the Head & 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. 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.

Recommendation (Grade D)

Panendoscopy is only recommended for symptomatic patients or patients with primary tumours known to have a significant risk of a second (synchronous) primary tumour.

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*.

9. REGIONAL LYMPH NODES

The status of the regional lymph nodes in head and neck cancer 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. Midline nodes are considered ipsilateral nodes except for thyroid cancer. Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.

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

Lymph nodes are subdivided into specific anatomic sites and grouped into seven levels for ease of description (see Chapter 29). 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. It is particularly poor for lymph nodes in the lower regions of the neck, i.e., Level IV and Level Vb (supraclavicular area).

UICC 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.

The definitions of the N categories (Table 5) for all head and neck sites except thyroid and nasopharynx are the same. The natural history and response to treatment of cervical nodal metastases from nasopharynx are different, in terms of their impact on prognosis, so they justify a different N classification. Regional lymph node metastases from well-differentiated thyroid cancer do not significantly affect the ultimate prognosis and therefore also justify a unique system.

Table 5 N-stage 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. 3cm or less in greatest dimension.
N2	N2a	Metastasis in a single ipsilateral lymph node, more than 3cm but not more than 6cm in greatest dimension.
	N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6cm in greatest dimension.
	N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6cm in greatest dimension.
N3		Metastasis in a lymph node more than 6cm in greatest dimension.

10. PATHOLOGICAL CLASSIFICATION (PTNM)

The pT, pN and pM categories correspond to the T, N and M categories. 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 6 or more lymph nodes; a radical or modified radical neck dissection specimen includes 10 or more lymph nodes.

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Chapter 13
Pathological Assessment

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1. INTRODUCTION

This chapter 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 with patients and with colleagues in a multidisciplinary setting. 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 prognostic factors, and in contributing evidence based criteria for the appropriate stratification of clinical outcomes.

2. USE OF CELLULAR PATHOLOGY SERVICES

2.1. Frozen section

Intraoperative frozen sections have a limited role in patient management which should be guided primarily by pre-operative biopsy and/or fine needle aspiration cytology. Frozen sections are appropriately used for the assessment of surgical excision margins when there is clinical doubt as to adequacy. Frozen sections are occasionally used to confirm the diagnosis of papillary, medullary or anaplastic thyroid carcinomas or to identify lymph node involvement in thyroid cancers; they should not be used to differentiate follicular 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.

2.2. Definitive operative specimen

Specimens should be submitted in an adequate amount of 10% neutral buffered formalin (at least three times the volume of the specimen) unless there is prior agreement with the laboratory. The site and nature of each specimen should be

clearly described on the request form and should be appropriately orientated and mounted. The form must include the clinical indication for the operation, the duration of signs and symptoms, pre-operative radiotherapy or chemotherapy, and details of previous biopsies or cytological investigations and relevant biochemistry (particularly for thyroid diseases).

2.3. 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. The optimal handling of biopsies for suspected lymphoma should be discussed with the laboratory; it is often useful to collect fresh tissue in transport medium for possible cytogenetic studies.

Clinical trials of the predictive value of sentinel node biopsy involve detailed pathological assessment of 3–4 lymph nodes with multiple sections and immunocytochemistry. This is highly demanding of laboratory time and expertise and should only be undertaken if appropriately resourced.

2.4. 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.

2.5. 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. 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 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 opinion 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.

3. 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 essential for thyroid cancers and is good practice for other situations.

4. MALIGNANCIES OF THE UPPER AERODIGESTIVE TRACT

4.1. 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, 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 radiotherapy 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.

4.1.1. Morphological variants of squamous cell carcinoma

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

Papillary squamous cell carcinoma 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 and the prognosis is relatively good due to the limited invasive component.

Verrucous squamous cell carcinoma 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 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 mucosal 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 is only helpful in identifying squamous epithelial differentiation in about 60–70% of cases.

4.1.2. Information to 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 (table 1); the basis in evidence for this information is provided in guidelines published by the Royal College of Pathologists.

Table 1. 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 perineural space of nerve trunks
Invasion of bone or cartilage
Distance of carcinoma from resection margins

4.2. 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 2 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 on which grading system should be recommended, although a majority of pathologists probably use the W.H.O. dysplasia system but regard severe dysplasia and in situ carcinoma as indistinguishable. Management decisions should take account of the microscopic severity of the lesion and its clinically-assessed extent.

Table 2. Grading systems for precursor lesions of squamous epithelial malignancies

W.H.O. Classification 2005	Squamous intraepithelial neoplasia (SIN)	Ljubliana classification; squamous intraepithelial lesions (SILs)
Squamous cell hyperplasia		Simple hyperplasia
Mild dysplasia	SIN 1	Basal/parabasal cell hyperplasia
Moderate dysplasia	SIN 2	Atypical hyperplasia
Severe dysplasia	SIN 3	Atypical hyperplasia
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.

4.3. Other mucosal malignancies

4.3.1. Adenocarcinomas

These tumours 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.

4.3.2. Sinonasal undifferentiated (anaplastic) carcinoma (SNUC)

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.

4.3.3. Olfactory neuroblastoma (esthesioneuroblastoma)

This tumour 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 distant sites, prognosis is good with a 78% five year survival after surgery and radiotherapy.

4.3.4. Malignant melanoma

Melanomas most often arise in the nasal 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% are amelanotic). Survival is poor with death due to widespread metastasis and/or extensive local recurrence.

4.3.5. Lymphomas

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

4.3.6. Nasopharyngeal carcinoma

This malignancy includes keratinising squamous cell carcinomas and non-keratinising differentiated and undifferentiated carcinomas. The synonym of 'lymphoepithelioma' should not be used. Keratinising carcinomas are more radioresistant than non-keratinising and undifferentiated carcinomas.

5. DIAGNOSIS AND MANAGEMENT OF NECK LUMPS

5.1. Fine needle aspiration (FNA)

When performed by a well-trained operator, the FNA is an essential part of the diagnostic assessment of patients with neck or thyroid lumps. The cytological diagnosis of metastatic squamous cell carcinoma 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. The main role of FNA cytology is 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.

5.2. Neck dissections

The presence or absence of nodal metastasis is a key component of TNM 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—collections of cells less than 0.2mm diameter
Micrometastasis—tumour deposits 0.2–2mm in diameter
Conventional metastasis—a tumour deposit more than 2mm 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 Table 3.

Table 3. 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.

6. SALIVARY NEOPLASMS

Most tumours arising in the major or minor salivary glands are benign (although the proportions vary greatly 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 differentiate benign neoplasms from malignant in 81–98% of cases, but which is less good at establishing a specific diagnosis. 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. Core pathological data from salivary resections for neoplasia are shown in Table 4.

Table 4. Prognostic information derived from salivary gland resections

Histological type of neoplasm (according to the WHO Classification).
Grade of malignancy (see text).
Distance to the resection margins.
Presence or absence of perineural or vascular invasion.
Presence or absence of lymph node involvement.

Grading of the degree of malignancy is prognostically useful for some salivary carcinomas. Grading of mucoepidermoid carcinomas (MEC) is related 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 accepted as a useful indicator of behaviour, except for rare tumours showing dedifferentiation. Assessment of Ki-67 (MIB1) labelling is of prognostic value, and acinic cell carcinomas with indices of >5% behaving more aggressively. The growth pattern of adenoid cystic carcinoma is related to metastatic potential, with 0–4% of cribriform, hyaline and tubular carcinomas, and 33% 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% express androgen receptors and 15% express HER-2; features which may influence therapy in the future. Carcinomas arising in pleomorphic adenomas may be of any or mixed histological type; the extent of invasion is prognostically useful as invasion more than 5–6mm from the capsule of the residual adenoma is associated with a high risk of local recurrence and distant metastasis. Noninvasive or minimally invasive carcinomas ex pleomorphic adenoma are true malignancies, but have a very low rate of disease progression.

7. THYROID CANCERS

Most lesions will have had FNA before surgery. The descriptive cytology report informs clinical decisions on management and will normally incorporate a categorical summary (Table 5).

Table 5. Revised categorisation of thyroid fine needle aspirates (RCPath and BSCC guidelines)

Thy 1 – Non-diagnostic for cytological diagnosis
Thy 1c – Non-diagnostic for cytological diagnosis - cystic lesion
Thy 2 – Non-neoplastic
Thy 2c – Non-neoplastic, cystic lesion
Thy 3a – Neoplasm possible—atypia/non-diagnostic
Thy 3f – Neoplasm possible, suggesting follicular neoplasm
Thy 4 – Suspicious of malignancy
Thy 5 – Malignant

For all malignant thyroid tumours, the national dataset for histopathology reports defines core data items of prognosis importance that will allow TNM staging (Table 6). 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.

Table 6. 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.
Extension into extrathyroidal tissues (macroscopic or microscopic)
Number of foci of lymphatic/vascular invasion.
Site and number of lymph nodes sampled and those involved.

7.1. 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. Incidentally recognised multifocal carcinomas are treated differently.

Tall cell and columnar variants of papillary carcinoma may show more aggressive behaviour, while the outcome 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 type of FVPC

has a metastatic potential similar to that of classical papillary carcinoma, while encapsulated FVPC is similar to follicular carcinoma with metastatic potential related to the number of foci of vascular invasion.

7.2. 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 metastases increases with the frequency of vascular involvement, particularly if four or more foci of vascular invasion are present. Widely invasive follicular carcinoma shows obvious gross invasion or extensive microscopic infiltration of thyroid parenchyma, vessels or extrathyroidal tissues. Prognosis worsens in proportion to the number of foci of vascular invasion.

7.3. Medullary carcinoma

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

7.4. Poorly differentiated carcinoma

This group is defined as follicular or papillary carcinoma with necrosis and/or a mitotic count of 5 or more in 10 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.

7.5. 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.

7.6. 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.

Key Points

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

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Chapter 14
Data Collection in Head and Neck Cancer

Lead authors: Richard Wight, Graham Putnam

1. INTRODUCTION

Historically, absence of accurate data on care pathways has been an obstacle to improving care standards. Cancer data collection by individual committed clinicians' and cancer registries datasets failed to deliver the necessary depth and consistency of information required for comparative audit. Thus, a need for National audit was identified.

The National Comparative Audit in Head and Neck Cancer (DaHNO-Data for head and neck oncology) supported by BAHNO (British Association of Head and Neck Oncologists) in conjunction with the NHS Information Authority commenced data collection in 2004. Initially collection was limited to England, but now includes Wales. Agreement has been reached with all trusts which treat head and neck cancer in England and Wales that this process will be fully supported.

2. THE IMPORTANCE OF COMPARATIVE AUDIT IN HEAD AND NECK CANCER

Worldwide, head and neck professionals have sought to establish a comprehensive picture of care delivered. This has been to assure and continuously improve standards of care delivered as well as providing high quality clinical data bases that serve a number of additional functions. Clinical data repositories enable clinical audit, evaluative research and facilitate service planning. Furthermore they are means to support informed patient choice of care.

National head and neck cancer audit allows outcome assessment and provides a tool to improve standards of care, identifying areas of good and weak practice.

A number of key areas in head and neck cancer impact on the incidence and outcomes of the disease and form areas for audit:-

- prevention
- early presentation
- timely referral from 'diagnostic' to 'therapy' team
- management by multi-professional specialist teams
- consistent standards and patterns of treatment
- timely access to care.

As identified elsewhere within this document multi-professional management is recognised as the gold standard, bringing substantial patient benefits and is an increasing focus for audit.

3. DAHNO

Core issues addressed in the first and second phases of the National Head and Neck Cancer Audit are:

- delivery of appropriate primary treatment (including adjuvant therapy) in the management of head and neck cancer affecting the larynx, oral cavity, pharynx and major salivary glands by a multi-professional team, and delivery of care to agreed standards.
- detailed assessment, for larynx and oral cavity cancer, of the care provided by specialist nurses, dieticians and speech and language therapists (in particular related to surgical voice restoration)

Current inclusion criteria can be found in table 1

Table 1. Inclusions in the head and neck cancer audit Phase II

The National Head and Neck Cancer Audit aims to identify and include the following details from contributory centres:
• new primary cases of head and neck carcinoma involving the larynx, oral cavity, pharynx, and major salivary glands
• presence of co-morbidity at diagnosis
• whether the cancer care pathway has been agreed by a MDT and delivered to agreed standards with equity of care and without undue delay
• the primary treatment modality(ies) received (including adjuvant therapy) for all sites
• in larynx and oral cavity, care provided by clinical nurse specialists
• multi-professional care provided by dieticians, and speech and language therapists (including for larynx surgical voice restoration)
• disease eradication

DAHNO aims to deliver casemix adjusted outcomes and a number of key contributory factors are outlined in table 2.

Table 2. Important factors to facilitate casemix adjustment outcome assessment

The key factors considered are:
• age and sex
• comorbidity
• performance status
• stage at presentation
• pathological staging following surgery

DAHNO has produced five annual reports with data submitted on just under 13,000 cases of head and neck cancer

4. NATIONAL CANCER INTELLIGENCE NETWORK (NCIN)

NCIN, launched in 2008, brings together cancer registries, clinicians, researchers and other parties (including the Office for National Statistics; National Clinical

Audit Support Programme; NHS Information Centre) under the auspices of the National Cancer Research Institute (NCRI). Collection, analysis and publication of high quality data on clinical outcomes are one of the key drivers for implementation of the Cancer Reform Strategy.

The National Head and Neck Cancer Audit is working closely with the evolving NCIN Head and Neck Clinical Reference Group, with common membership across groups. An initial piece of work has been to profile of head and neck cancers in England.

Key points

- Head and neck cancer clinicians should see contribution to comparative audit as an essential part of their role and the management of head and neck cancer.
- Head and Neck Cancer Audit should continue to be a priority for trusts and cancer networks, to promote clinical governance and provide assurance to patients and carers of the quality of services provided.
- Each MDT should facilitate all of its professionals to contribute to the audit process in head and neck cancer, and ensure adequate administrative support to achieve this is available.

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Chapter 15
Radiotherapy

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Radiotherapy 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 radiotherapy 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, radiotherapy allows preservation of natural speech and swallowing in carcinomas of the larynx and tongue base. 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 advanced squamous cell carcinoma of the head and neck single modality treatment (either surgery or radiotherapy alone) is associated with poor outcomes. For these tumours, the combined use of surgery and post-operative radiotherapy or use of combined chemotherapy and radiation schedules frequently offers the highest chance of achieving cure.

In recent years radiotherapy 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 state of the art imaging technology including CT, MRI, PET 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 submillimetre accuracy allowing radiation to be focussed on the tumour bearing tissues and minimising radiation to normal tissue structures.

Intensity-modulated radiotherapy (IMRT) is a new 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 standard radiotherapy) from 75% to 39% ($p=0.004$) at 12 months following treatment. A similar result has been demonstrated for patients with nasopharyngeal cancer.

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 2–3 low-dose fractions per day) radiotherapy. These treatments have not shown consistent improvements in overall survival, and for that reason have not been adopted widely outside of North America.

Particle therapy such as with protons or stereotactic radiotherapy may allow additional advantages to patients with tumours close to particularly radiosensitive organs such as the brain, spinal cord or in children's cancers.

In a large meta-analysis of 93 trials and over 17,000 patients, concomitant chemotherapy (given during radiotherapy) was shown to improve loco-regional control rates and was associated with a 6.5% increase in survival ($p<0.0001$). The benefits were largely confined to chemotherapy given during radiotherapy 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.

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

In the postoperative 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.

While concomitant chemotherapy has a proven role in improving outcomes for head and neck cancer, the role of neo-adjuvant chemotherapy remains controversial. Two recent studies suggested that the use of docetaxel, cisplatin and 5-fluorouracil prior to definitive radiotherapy improved survival. The use of non-standard radiotherapy/chemoradiation schedules in these trials has led to uncertainty as to the benefits of this approach when standard chemoradiation is prescribed.

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 centers
- Intensity-modulated radiotherapy has been shown to reduce long term xerostomia and should be offered to all appropriate patients

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Chapter 16
Surgery

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The aim of surgery with curative intent in head and neck cancer is complete microscopic surgical excision. Emphasis has moved from being radical to the patient to cure the cancer, to being radical to the tumour but to consider the consequences for the patient and preserve functions that optimise patients' quality of life. However, 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. Whether this is through radical or endoscopic surgical technique, that principle remains of the utmost importance. There is virtually no oncological role for debulking surgery in order to the chances of cure with subsequent chemo-radiation. Debulking may be necessary for airway preservation and for symptom palliation however.

Primary tumour considerations

One of the most important surgical advances of recent times has been the development and popularisation of transoral laser microsurgical (TLM) excision of primary tumours. The emphasis has been on using this modality for early glottic laryngeal cancers. However, this is also applicable for early as well as more advanced tumours of the supraglottic larynx and oropharynx. It is important that patient selection is careful and that the surgery achieves the same sort of safety margin that open surgery would achieve.

There is little doubt as to the advantages of transoral techniques over open techniques, as long as the resection is not compromised. The controversy around transoral surgery relates to the use of such techniques in place of or in concert with chemo-radiation. There is a clear lack of clinical evidence. Even in early glottic cancer, there is no level 1 or 2 evidence comparing outcomes of treatment following surgery with radiotherapy. The absence of evidence applies even more to other applications of TLM techniques. For example, the use of such for advanced tumours of the oropharynx or supraglottis in the context of these patients generally going on to have post-operative radio- or chemo-radiotherapy, instead of primary treatment with chemoradiotherapy only. Further refinement of these techniques may be achieved through trans-oral robotic surgery.

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? Surgeons have debated the concept of "functional inoperability" in this context, with varying definitions.
- 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.

For defects that will require reconstruction with microvascular free flaps, in most cases having two consultant surgeons has obvious advantages, regardless of specialities involved. 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 major recent evolution has been the continued expansion and poularisation of the antero-lateral thigh flap, which appears to be ideal for most soft tissue defects, except when a thin flap might be required for smaller oral cavity defects.

Metastatic neck disease considerations

With regard to neck dissection, there has been and continues to be a similar progression to conservation techniques - both in terms of the preservation of non-lymphatic structures and restriction of levels dissected according to the primary tumour. Shoulder and neck dysfunction has been correctly recognised as an important contributor to quality of life after treatment, and the evolution in neck dissection has been an important area of advancement. The issues that need clarification presently are (a) how far can level selection go and is there material difference between a "super-selective" neck dissection and an excision biopsy? (b) when is a neck dissection required before or after definitive chemoradiation treatment that includes the neck? The present UK PET-NECK trial may shed light on the latter issue. The issue of when neck dissection is required after chemo-radiation will also be evidenced by that trial, although the general global trend and level 3 evidence supports clinical and radiological monitoring and intervention only if residual disease is suspected.

Finally, following the identification of the need for structured and more formal training of head and neck oncologic surgeons in the USA , this additional educational requirement has been followed in the UK and imminently to be followed by the UEMS for European surgeons . How far this should and can go is unknown. The situation in the UK contrasts with many other countries, in that head and neck cancer surgery is divided between the two major specialities of ORL-HNS and OMFS, in a more equitable fashion than most other countries. Should there continue to be the distinction of 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 should we evolve into training surgeons who are experts in resection of every site and reconstruction? Should there be an ablative/reconstruction divide? Where does plastic surgery fit in? These are questions that will need to be answered, as these influence not only training but future manpower planning in the UK.

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Chapter 17
Chemotherapy

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Chemotherapy alone, unlike either surgery or radiotherapy cannot cure head and neck cancer but concurrent chemotherapy given with radiotherapy has now become the standard of care in advanced disease and has been shown to improve local control and add a survival benefit compared to radiotherapy alone but with the price of greater toxicity.

Chemotherapy is added to radiotherapy for its direct cytotoxic effects, its role as a radio-sensitiser, when it may reduce the repair of DNA damage caused by radiotherapy, and its potential systemic effect in sterilising metastatic malignant cells which may have escaped the primary site. It can be given either before radiotherapy as neoadjuvant or induction chemotherapy; with radiotherapy as concurrent treatment, (the most common regimen at present) or after radiotherapy as adjuvant chemotherapy.

It was initially added to radiotherapy with the hope of giving as good survival rates as had been seen using surgery as a primary treatment but with the benefit of organ preservation, maintaining speech and swallowing function. One of the first studies investigating organ preservation was the Veterans Administration Larynx Preservation Study, where a positive response to induction chemotherapy was followed by radiotherapy with the hope of preserving laryngeal function. If there had been no response to induction chemotherapy, the patient proceeded to laryngectomy. This was using chemotherapy as a surrogate marker for radiotherapy response, but did show that by using chemoradiotherapy, patients had similar survival outcomes to those who had undergone surgery and could be left with a functioning larynx. Other studies confirmed these positive results and interest in organ preservation and the usage of primary chemoradiotherapy in advanced head and neck cancer grew. Since this pioneering work, several trials have shown the benefit of adding concurrent chemotherapy to radiotherapy for either improved local control or survival advantage, or both in laryngeal cancer, oropharyngeal cancer and advanced unresectable head and neck tumours.

The meta-analysis of chemotherapy on head and neck cancer (MACH-NC) published in 2000, summarised the results of treatment giving radiotherapy with and without chemotherapy in 63 randomised trials, including almost 11,000 patients. This showed a significant overall survival benefit at five years of 8% in those patients who had concomitant chemotherapy compared to radiotherapy alone; with no statistically significant benefit in those patients who had had induction (neoadjuvant) or adjuvant chemotherapy before or after radiotherapy, compared to those who had radiotherapy alone. Updates of this meta-analysis have confirmed these positive findings, but also failed to show a survival benefit in patients more than

70 years of age. These studies also suggested that single agent cisplatin had as beneficial an effect is multiagent chemotherapy, an assertion that is now being challenged again with the use of taxane/platinum combinations. The MACH-NC studies excluded nasopharynxgeal cancers, but other studies and meta-analysis have also shown a significant survival improvement at five years by adding chemotherapy to radiotherapy.

Radiotherapy regimens for head and neck cancer are also changing with interest in altered fractionation regimes. Hyper-fractionated radiotherapy breaks down the total dose delivered (which is often higher than that normally used) into smaller than usual individual fractions given 2 or 3 times per day; accelerated fractionation reduces the overall treatment time and these two techniques are often used together in "CHART" regimens – combined hyper fractionated, accelerated radiotherapy, which so far have been disappointing in improving survival in head and neck cancer. In North America, concomitant boost regimens are popular, where an additional smaller radiotherapy volume covering the most high-risk area is added and given usually towards the end of standard treatment as a second daily radiotherapy treatment. Advocates of these regimens have shown some improved local control in some trials, at a cost of greater acute morbidity. Whichever altered radiotherapy regimen is used, there does seem to be an accompanying benefit by adding chemotherapy, but as both adding chemotherapy and using a more intensive radiotherapy regime both increase acute side-effects, while it may be theoretically advantageous and possible to pursue combined chemotherapy, and a more intensive radiotherapy course in younger, more fit patients, it may not be possible to complete treatment without unwanted breaks in treatment, in an elderly patient population or those with significant co-morbidities.

Chemoradiotherapy has also been shown to increase local control rates and improve survival in patients who have had primary surgery as an initial treatment, although it is probably more effective in those patient subgroups who have poorer prognostic markers and a higher risk of recurrence, such as nodal involvement, especially multiple nodes involved, extracapsular spread and positive surgical margins.

It is known that many head and neck cancers overexpress the EGF receptor and that this is associated with a worse prognosis. From these advances in the understanding of the molecular biology of head and neck cancer, there have been developments in attempting to block EGFR by the use of either extracellular monoclonal antibody receptor blockers such as cetuximab, or by using intracellular small molecule inhibitors of EGFR downstream effects such as lapatinib.

The initial major publication using one of these biological agents was that published by in the New England Journal of Medicine in 2006 and this showed a survival benefit in adding the targeted monoclonal antibody cetuximab to radiotherapy in advanced head and neck cancer. Unfortunately, one of the major failings with the study was that it was a comparison of radiotherapy with or without cetuximab, instead of chemoradiotherapy (which had become the standard of care, since this study had started) with or without cetuximab, which was the question that needed to be answered in the real world. But there also, subsequently appeared to be an underreporting of one of cetuximab's main toxicities, an acneiform rash, which although

irritating for many patients, and markedly distressing for some, may correlate with a better response to this biological agent.

Further trials are underway investigating the efficiency of cetuximab with chemoradiotherapy but a very recently published abstract at the American Society for Clinical Oncology 2011, showed no significant benefit from adding cetuximab to chemoradiotherapy. But these are preliminary results and needs to be confirmed by further evidence. At present in the UK, cetuximab can be used in patients with advanced head and neck tumours where concurrent chemotherapy would be contraindicated, and in selected patients with recurrent or metastatic disease, based on the published "Extreme" study.

The benefit of chemotherapy is less well investigated and documented in recurrent and metastatic head and neck cancer, and there is little evidence for benefit using palliative chemotherapy when compared to best supportive care. Platinum based chemotherapy regimens have a response rate of about 30% in recurrent or metastatic disease, but with a wide range around this median. Cisplatin is most commonly used but in a palliative setting, carboplatin can also have a role because of its lower renal and neurological morbidity, although it is also considered slightly less effective and more toxic to the bone marrow. Methotrexate has been used in palliative setting in head and neck cancer for decades now but can cause mucositis which may be relatively more important in the palliative stage of a patient's head and neck cancer pathway. Taxanes, either alone or in combination with platinum have been under investigation, but can carry a relatively high price in toxicity; and cetuximab has been shown the "Extreme" trial to have some effect in recurrent head and neck cancer.

Although the MACH-NC studies did not report a benefit for neoadjuvant chemotherapy, two more recent trials using docetaxel, cisplatin and 5FU (TPF) have shown positive findings when used in a neoadjuvant setting in stage III and IV head and neck cancer. The TAX 323 trial randomised between cisplatin and fluorouracil plus or minus docetaxel as an induction regimen, followed by radiotherapy alone. TAX 324 randomised patients to platinum and fluorouracil plus or minus docetaxel followed by concurrent weekly carboplatin chemotherapy with radiotherapy. Both of these trials showed some survival benefit, but both trials did face criticism in that some viewed the radiotherapy and concurrent chemoradiotherapy regimens as suboptimal; the trials compare different induction regimens rather than induction versus concurrent chemoradiotherapy; using this approach extends overall treatment time considerably and using taxanes can increase acute morbidity. These trials did reawaken both an interest in the role of induction or neoadjuvant chemotherapy and whether such an approach may benefit patients in eradicating distant micrometastatic disease as well as having an effect on locoregional disease and in the role of taxanes in head and neck chemotherapy.

In the future there will be more investigation of the combination of chemotherapy and targeted biological agents; the role of combination chemotherapy with taxanes and other new drugs and the use of the above with altered radiation fractionation regimens. There may also be the revival of interest in hypoxic sensitisers such as nimorazol and tirapazamine, which is activated in hypoxic environments.

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.
- 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 have a role to play in both advanced head and neck cancer and recurrent or metastatic disease but that role is still being established.
- At present HPV status does not alter management regimens.
- The potential benefits of neoadjuvant or induction chemotherapy is being re-examined.
- Elderly patients benefit least in terms of survival advantage with the use of concurrent chemotherapy.

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Chapter 18
Laryngeal Cancer

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1. INTRODUCTION AND EPIDEMIOLOGY

The aim of any clinician involved in the treatment of laryngeal squamous cell carcinoma (LSCC) should be to cure the disease whilst maintaining maximum 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 meetings (MDTM) throughout the United Kingdom 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 MDTM dynamics and local 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 2008, 2,292 patients were diagnosed with laryngeal carcinoma in the UK thereby accounting for 0.7% of the non-melanomatous squamous carcinoma (NMSC) burden. Of these, 1,798, 142, 280 and 72 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 2.8, 3.6, 4.3 and 3.6 respectively; highlighting the fact that larynx cancer is more common in the Principalities, with Scotland recording the highest incidence. Larynx cancer is the 18th most common cancer presenting in men in the UK (1,492 cases; 1.2% of MNSC in 2008). In comparison only 306 cases occurred in women (0.3% NMSC). However, this amounts to a 12% reduction of cases diagnosed in men when comparing the three year cohorts 1997-1999 and 2006-2008. No similar reduction has been seen in cases diagnosed in women (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. It is well documented that alcohol and tobacco, separately and synergistically are the main causes of larynx cancer. However, recent data

have suggested that up to 20% of larynx cancer might be associated with human papilloma virus infection.

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 2008, 685 men and 164 women died of larynx cancer. This constitutes a marked decrease in age-standardised mortality for men since the early 1990`s whilst the death rate for women has remained static over this period (http://info.cancerresearchuk.org/cancerstats/types/larynx). However, recent studies have 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.

2. 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 un-common 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.

3. 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 (MRI) or computed tomography (CT) of the head and neck and CT scan of the thorax and upper abdomen. 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 0º and angled 30º and/or 70º) fibreoptic endoscopes. The aggregate information provided by the imaging and the endoscopic examination facilitates the staging of the tumour according to the TNM system (table 1). 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.

Table 1. T staging for laryngeal cancers

Supraglottis	
T1	Tumour limited to one subsite of supraglottis with normal vocal cord 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 cord fixation and/or invades any of the following: postcricoid 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 (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery
Glottis	
T1	Tumour limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
	T1a. Tumour limited to one vocal cord
	T1b. Tumour involves both vocal cords
T2	**T2a.** Tumour extends to supraglottis and/or subglottis with normal vocal cord mobility
	T2b. Tumour extends to supraglottis and/or subglottis with impaired vocal cord mobility
T3	Tumour limited to larynx with vocal cord 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, oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery
Subglottis	
T1	Tumour limited to subglottis
T2	Tumour extends to vocal cord(s) with normal or impaired mobility
T3	Tumour limited to larynx with vocal cord 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, oesophagus
T4b	Tumour invades prevertebral space, mediastinal structures, or encases carotid artery

4. MANAGEMENT

4.1. 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 cure are extremely good whichever of the main treatment options – radiotherapy, transoral

laser microsurgery (TLM) or open partial laryngeal surgery – are employed. A recent systemic review showed there is insufficient evidence to confirm 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 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 cord mucosa and larger volume tumours involving the anterior commissure may be more suitable for RT than TLM) and local expertise. Single-modality treatment is sufficient and combining surgery with radiotherapy must 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 radiotherapy schedules, using a fraction size greater than 2 Gy, results in equivalent outcomes to longer schedules, without increased toxicity. Typical schedules include 50–52 Gray (Gy) in 16 fractions and 53–55 Gy in 20 fractions over 3–4 weeks. Elective treatment of the neck is not recommended because of the 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 4–6 weeks after completion of treatment and late effects are rare. Should tumour recurrence occur, partial laryngeal surgery provides a suitable salvage option, resulting in good oncological and functional outcomes. However, these techniques are rarely offered in the UK and therefore total laryngectomy is most commonly performed.

TLM 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.

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 radiotherapy. Meta-analysis data shows similar rates of local control and survival after open partial laryngectomy (comparable to TLM and RT) with larynx preservation rates of 98.3% for de novo tumours and 84.6% for radio-recurrent tumours. Open surgical procedures include laryngofissure cordectomy, vertical partial laryngectomy (VPL) +/- reconstruction, frontolateral vertical partial laryngectomy, supraglottic laryngectomy, supracricoid 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 radiotherapy and TLM (5 year local control rate 90 to 93%). In the case of T1b the local control is less (85%-89%). Similarly, the local control and overall survival rates for T2a glottic cancers are comparable when treated with TLM, partial laryngeal resection or RT.

Recommendations

- Radiation therapy and transoral laser microsurgery are reasonable treatment options for T1a –T2a glottic carcinoma (Grade B)
- Open partial surgery may have a role in the management of selected tumours (Grade B)

4.2. T1–T2 supraglottic cancers

Radiotherapy and TLM should be considered 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 radiotherapy 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 bilateral lymph node levels II and III – either with radiotherapy or selective neck dissection - is recommended.

Whilst radiotherapy or surgery alone, is sufficient for the treatment of node negative T1/T2 supraglottic cancers, concurrent platinum-based chemoradiotherapy (CRT) or surgery followed by post-operative radiotherapy is recommended for node positive supraglottic carcinoma (T1–2 N2+, 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, particularly if this is rapidly progressive and/or symptomatic.

For T1 disease, 5 year local control rates following treatment with RT, TLM or open supraglottic laryngectomy range from 77%-100% whilst for T2 tumours the 5 year local control rates range from 80-97% for TLM or open supraglottic laryngectomy and from 62-83% for primary RT.

Recommendations

- RT and TLM are reasonable treatment options for T1 –T2 supraglottic carcinoma (Grade B)
- Supraglottic laryngectomy may have a role in the management of selected tumours (Grade B)

4.3. 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 radiotherapy, may be also be appropriate in selected cases. Open partial surgical procedures which might be considered include VPL +/- reconstruction, frontolateral vertical partial laryngectomy, supraglottic laryngectomy, SCPL – CHEP or CHP and extended supraglottic laryngectomy. In the absence of clinical or radiological evidence of nodal disease, elective treatment (radiotherapy or surgery +/- post-operative radiotherapy) is recommended to 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 radiotherapy to be given to different nodal groups simultaneously, depending on the presence or absence of macroscopic disease and the risk of subclincal disease. In node positive disease, it is recommended that lymph node levels II-V should be treated on the involved side.

The potential of RT and chemotherapy for larynx preservation was established by the landmark Veterans Affairs Laryngeal Cancer Study Group (VALCSG) study in which induction chemotherapy and RT (IC+RT) yielded similar overall survival (68% at 2 years) to laryngectomy followed by adjuvant RT for stage III/IV laryngeal cancer with high rates of larynx preservation (64% at 2 years). Rates of salvage laryngectomy were significantly lower for T3 vs T4 disease (29% vs 56%, p=0.001). Subsequently, RTOG 91–11 demonstrated that CRT was superior to IC+RT and RT alone in terms of laryngeal preservation (88% vs 75% vs 70% respectively at 3 years) although overall survival in each treatment arm was similar. The use of CRT for locally advanced head and neck cancers, including laryngeal cancers, is also supported by meta-analysis data. Standard concurrent chemotherapy regimens include cisplatin (100mg/m^2) on day 1, 22 and 43 of RT and carboplatin/5-FU on weeks 1 and 5 of RT.

CRT is however associated with a significant increase in acute and late toxicity compared with RT alone. The long-term side effects of CRT are well documented: 43% 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% of patients 2 years after treatment) and have a profound effect on quality of life. Older age, advanced T stage, larynx/hypopharynx primary site and neck dissection after CRT all increase the risk of severe late toxicity after CRT 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 (EGFR). Cetuximab has been shown to improve locoregional control (47% vs 34% at 3 years, p<0.01) and overall survival (55% vs 45% at 3 years) over RT alone in a study of patients with locally advanced (stage III/IV) head and neck cancer (27% of whom had

laryngeal cancer) and the benefit is maintained on longer follow-up (46% vs 36% at 5 years). 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 CRT for patients with laryngeal cancer who cannot receive CRT.

Induction chemotherapy with cisplatin and 5-FU (PF) prior to RT may also improve survival but the benefit of induction chemotherapy prior to standard CRT schedules is currently unproven. If induction chemotherapy is used, docetaxel in combination with cisplatin and 5-FU (TPF) has a higher overall response rate and larynx preservation rate compared to PF in patients with stage III/IV laryngeal cancer and may improve overall survival.

Radiotherapy may be used as a single modality where comorbidity precludes the use of concurrent chemotherapy, cetuximab or surgery. Conventional radiotherapy 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 to standard fractionated radiotherapy for head and neck cancer patients (albeit at the cost of higher mucosal toxicity) who elect or are selected to receive radiotherapy alone. However, altered fractionation regimens do not appear to improve outcome compared to or when combined with CRT 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. In future, IMRT may allow RT dose intensification for this group of tumours and its potential is being investigated in an ongoing UK trial (ART-DECO: http://public.ukcrn.org.uk).

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 CRT. 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 CRT remains an option for these patients (25% of patients in the VALCSG study had a baseline tracheostomy and they were not excluded from RTOG 91–11). 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 outcome than patients with mobile vocal cords.

In the absence of clinical or radiological evidence of nodal disease, elective treatment (radiotherapy or surgery +/- post-operative radiotherapy) is recommended to lymph node levels II, III and IV bilaterally,

Recommendations

- Most patients with T2b–T3 glottic cancers are suitable for non-surgical larynx preservation therapies (Grade A)
- Concurrent chemoradiotherapy (CRT) should be regarded as the standard of care for non-surgical management (Grade A)
- Subject to the availability of appropriate surgical expertise and multidisciplinary rehabilitation services, TLM or open partial surgical procedures +/- post-operative radiotherapy, may be also be appropriate in selected cases (Grade B)
- In the absence of clinical or radiological evidence of nodal disease, elective treatment (radiotherapy or surgery +/- post-operative radiotherapy) is recommended to 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 (Grade B)

4.4. T3 supraglottic carcinoma

The principles of organ preservation for T3 supraglottic cancers are the same as for glottic cancers and tumour size and pre-treatment laryngeal function as well as 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 lymph node levels II, III, IV bilaterally.

Recommendations

- Most patients with T3 supraglottic cancers are suitable for non-surgical larynx preservation therapies (Grade A)
- Concurrent chemoradiotherapy (CRT) should be regarded as the standard of care for non-surgical management (Grade A)
- Subject to the availability of appropriate surgical expertise and multidisciplinary rehabilitation services, TLM or open partial surgical procedures +/- post-operative radiotherapy, may be also be appropriate in selected cases (Grade B)
- In the absence of clinical or radiological evidence of nodal disease, elective treatment (radiotherapy or surgery +/- post-operative radiotherapy) is recommended to lymph node levels II, III and IV bilaterally. In node positive disease, lymph node levels II-V should be treated on the involved side (Grade B)

4.5. T4 laryngeal carcinoma

Larynx preservation with CRT should be considered for T4 tumours, unless there is tumour invasion through cartilage into the soft tissues of the neck when total laryngectomy yields better outcomes. The VALCSG study showed reduced tumour response to chemotherapy and higher rates of salvage laryngectomy for T4 tumours (56% for T4 vs 29% 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 preservation with function and quality of life. Good patient selection is of paramount importance. Patients with large-volume T4 tumours - defined as extension of tumour through thyroid cartilage or tumour extension >1cm into the base of tongue - were excluded from RTOG 91-11 as they are poor candidates for organ preservation. Patients with significant pre-existing laryngeal destruction by tumour and/or a pretreatment tracheostomy may also be better suited to a total laryngectomy. Total laryngectomy may confer a better quality of life than a preserved but poorly functioning larynx.

Patients with large-volume T4 tumours who are unsuitable for surgery either because of inoperable (T4b) disease or medical comorbidities have been treated with combined-modality organ preservation therapy with significant rates of disease control (71% at 4 years) and overall survival (56% at 4 years) in retrospective studies. Induction chemotherapy may be used to treat large volume, symptomatic disease prior to commencement of CRT.

Lymph node levels II–V bilaterally should be treated, irrespective of the pretreatment clinical nodal status. Until evidence to the contrary becomes available, patients presenting with N2/N3 disease should undergo a neck dissection if fit enough. Improved systemic therapies and RT dose intensification using IMRT may improve outcomes for this patient group in future.

Recommendations

- Larynx preservation with concurrent CRT should be considered for T4 tumours, unless there is tumour invasion through cartilage into the soft tissues of the neck when total laryngectomy yields better outcomes (Grade A)
- In the absence of clinical or radiological evidence of nodal disease, elective treatment (radiotherapy or surgery +/- post-operative radiotherapy) is recommended to lymph node levels II, III and IV and V and VI bilaterally (Grade B).

4.6. Post-operative radiotherapy/chemoradiotherapy

Radiotherapy delivered postoperatively 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 positive

resection margins and/or extracapsular spread; other unfavourable pathological factors, including perineural and vascular invasion, are relative indications for postoperative RT. Administration of concurrent cisplatin chemotherapy with postoperative RT improves locoregional control and disease free survival compared to postoperative RT alone for locally advanced tumours, albeit at the expense of increased mucosal and haematological toxicity and possibly increased deaths. It improves overall survival in selected patients, particularly with extracapsular spread and/or positive margins, and should be used selectively patients at highest risk of relapse.

Key Points

- 2,000-2,500 patients are diagnosed with LSCC and 800-900 patients die of the disease per annum in the UK.
- The male:female ratio is 5:1, there is wide geographical variation between the constituent countries of the UK, with Scotland recording the highest incidence.
- Whilst rates of LSCC in men have reduced by 12% since the late 1990`s, the rates in women remain unchanged.
- Larynx cancer is more commonly diagnosed in patients of lower socio-economic group and these patients have worse survival outcomes than those from higher groups.
- Alcohol and tobacco use remain the main causes of LSCC, however up to 20% of tumours may be associated with human papilloma virus infection.
- LSCC is rare in the under 40`s. The incidence increases with age, peaking in the eighth decade.
- Early stage tumours of the glottis present with hoarseness, whilst tumours of the supraglottis and more advanced glottis tumours may present with pain, odynophagia/dysphagia, a neck lump or even airway compromise.
- Meticulous endoscopic inspection of the tumour, under general anaesthetic is mandatory in the initial tumour assessment. Imaging of the head and neck (CT or MRI) and a CT scan of the thorax completes the staging assessment.
- Radiotherapy (RT) and Transoral laser microsurgery (TLM) are reasonable treatment options for T1a –T2a glottic and T1 –T2 supraglottic carcinomas. In both cases, open partial surgery may have a role in the management of selected tumours.
- Most patients with T2b-T3 glottic and T3 supraglottic cancers are suitable for non-surgical larynx preservation therapies. 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.
- Larynx preservation with chemoradiotherapy (CRT) should be considered for T4 tumours, unless there is tumour invasion through cartilage into the soft tissues of the neck when total laryngectomy yields better outcomes.
- CRT should be regarded as standard of care for the non-surgical management of stage III/IV laryngeal cancer because it yields higher laryngeal preservation rates (but similar overall survival) compared to induction chemotherapy followed by RT and RT alone. Treatment options for patients who are unsuitable for CRT, include altered fractionation RT or RT with concurrent cetuximab.

- 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 positive resection margins and/or extracapsular spread.
- Cisplatin chemotherapy with postoperative RT improves loco-regional control and disease free survival compared to post-operative RT alone for locally advanced tumours, albeit at the expense of increased mucosal and haematological toxicity and possibly increased deaths.

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Chapter 19
Oral Cavity and Lip

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1. INTRODUCTION

Malignant tumours of the oral cavity affect in order of frequency, 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 is different from the oral cavity tumours. The overwhelming majority of malignant tumours in the oral cavity are squamous cell carcinomas (SCC). Non-squamous cell tumours are predominantly of salivary gland origin, and are discussed in Chapter 27. The heterogeneous nature of oral cavity tumours and the frequent association with medical co-morbidities requires that treatment options for each patient should be considered by a multi-disciplinary team, taking all relevant factors into account, before reaching a final treatment plan through consensus with the patient and carers. Treatment intention, curative or palliative should be clearly recorded at the outset.

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 vary and examples are 13.5 per 100,000 in Oceania, 12 per 100,000 in Europe and 12.7 per 100,000 in North America. The factors commonly cited as important in lip cancer are: solar radiation, tobacco smoking and viruses. About 90% of tumours arise in the lower lip with 7% occurring in the upper lip and 3% at the oral commissure.

2. PATHOLOGY

2.1. Oral cavity

Carcinoma of the oral cavity may develop de-novo or from a pre-malignant dysplastic lesion that appears clinically as leukoplakia or erythroplakia. In both instances chronic exposure to carcinogens in tobacco, alcohol or local trauma are thought to be important. Carcinogenesis is a multi-step process that involves over expression of oncogenes and inactivation of tumour suppressor genes. The p53 tumour suppressor gene has been identified as being important in oral cavity carcinomas in patients who are 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 tends to occur in younger patients and have a better prognosis. 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 variable prognostic value 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. Tumour grade is however 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 of nodal metastasis and pattern of invasion. Oral tongue SCC of greater than 4mm tumour thickness is considered to represent a significant risk of cervical lymph node metastatic involvement. Extra–capsular spread (ECS) of cervical lymph node metastasis is significantly associated with a poor prognosis. The presence of ECS is consistently associated with 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 perineural invasion appear to be associated with an increased risk of loco-regional relapse. These pathological factors therefore supplement the TNM classification and are now incorporated in pathological datasets.

2.2. Lip

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

3. CLINICAL PRESENTATION

The majority of SCCs (>95%) of the oral cavity present as ulcers or mass lesions. Early lesions can be subtle and appear as flat, discoloured lesions (leukoplakia and erythroplakia) or lesions that cause poorly fitting dentures. A non-healing ulcer is the most common presentation. Advanced tumours can present with invasion of neighbouring structures causing loose teeth and trismus, 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 crusting, colour change, thinning of the lip and various associated areas of leukoplakia.

4. ASSESSMENT AND STAGING

4.1. Clinical examination

Clinical examination is very useful in identifying new tumours and for surveillance after treatment. A systematic approach must be adopted as this is important for diagnosis and for treatment planning.

4.2. 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 CT or MRI imaging to allow complete staging and treatment planning with regard to resection margins which may include adjacent jaw bone.

4.3. Pre-treatment staging

Staging of primary cancer of the lip and oral cavity is similar and shown in Table 1.

Table 1. T staging for oral cavity tumours

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

5. MANAGEMENT

5.1. Oral cavity

There are no randomised trials comparing the different treatment modalities available for treatment of malignant tumours of the oral cavity.

5.1.1. General principles

5.1.1.1. Surgery

Patient factors such as fitness for anaesthesia, convenience, previous cancer treatment and patient choice, as well as the skill mix and resources available to the

treating team must be considered. There are a number of different options available under the broad banner of surgery: conventional surgery, laser surgery, thermal surgery and photodynamic therapy (PDT).

Curative surgery for cancer of the oral cavity involves resection of tumour with an appropriate safe margin, and subsequent reconstruction of the tissues in order to facilitate maintenance of function. The size and location of the primary tumour determines 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 trans-oral 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 a 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 maximize 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 vaporization may be employed although this often does not permit accurate histological assessment of the adequacy of resection and so may compromise the 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 post-operative 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 1cm (vital structures permitting). “Close” margins (defined as a pathological margin of less than 5mm) often are a prelude to adjuvant treatment or further resection. The use of intra-operative frozen sections to assist marginal clearance is controversial. Although the accuracy is good in histological terms they can give a false sense of security and invariably prolong operative time. Adoption of a Moh’s-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.

Where bony resection is required the assessment is largely based upon clinical and radiological findings. 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.

Recommendation

- Surgery remains the mainstay of management for oral cavity tumours (Grade B)

5.1.1.2. Chemoradiation

In the oral cavity primary chemo-radiotherapy is less commonly utilised than other head and neck sites. However, it should be considered in selected patients. Concurrent chemo-radiotherapy combines platinum-based chemotherapy with external beam radiotherapy (EBRT) to 70Gy. While the most recognised concurrent chemotherapy regimen is Cisplatin 100mg/m^2 three weekly, varying doses and schedules are acceptable practice, as is substitution by Carboplatin. Patients undergoing chemoradiotherapy 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 NICE guidance. Neo-adjuvant chemotherapy, with taxanes, cisplatin and 5FU (TPF) is a potent combination in advanced, inoperable disease in fit patients, if followed by concurrent chemo-radiotherapy.

5.1.2. Early stage cancer

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

5.1.3. Advanced stage cancer

For advanced disease, Stage III and IV (T3, T4 N0 and T1-4 N+), traditional management includes surgical resection, neck dissection, reconstruction and post-operative radiotherapy. Post-operative radiotherapy should be offered to at least 60Gy equivalent and optimally start within 6 weeks of surgery. In fit patients under the age of 60, adjuvant chemo-radiotherapy up to 66Gy with concurrent platinum-based chemotherapy should be considered for those with positive surgical margins, and or, extra-capsular spread.

Recommendation

- Adjuvant chemoradiation in the presence of advanced neck disease or positive margins improves control rates (Grade A)

5.1.5. Recurrent cancer

Patients with locally recurrent disease should be fully assessed by the team for operability, re-irradiation including brachytherapy and chemotherapy (see chapter 32). Palliative radiotherapy 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. The main stay of first line chemotherapy remains cisplatin or carboplatin and 5FU.

5.1.6. 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. However there are no RCTs. The literature suffers from a wide range of heterogeneous factors introducing bias, including tumours sites, stages, patient variables, operators, surgical techniques, study designs, small numbers, lack of clarity for treatment intention, and reporting on different outcome measures.

Reconstructive options include (see chapter 33): local flaps, regional pedicled flaps, microvascular free tissue transfer. 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.

5.2. Lip

5.2.1. 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 around 75–80% for T1 to T2 tumours, dropping to 40–50% for T3 and T4 tumours. The presence of cervical nodes at presentation is a poor prognostic indicator. About 15% of patients fail initial therapy and this usually presents as local or regional failure.

Small lesions are managed by simple surgical excision and primary closure. Equally good results are achieved with external beam radiotherapy (which may be more acceptable in elderly patients). Larger lesions of the lip require more consideration with regard to reconstruction techniques. The 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.

Recommendation

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

5.2.2. 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 bottom of the excision encroaching on the crease line of the chin. The dimensions of the lip resection require the introduction of tissue from the other lip by means of an Abbe or an Abbe-Estlander flap or rotation of tissue from the adjacent lip via a Karapandzic flap. 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 to the underlying orbicularis oris muscle is retained and the underlying orbicularis muscle is rotated so that a sensate functional lip reconstruction results. The various reconstructive options are identified in table 2.

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.

Table 2. Reconstructive options for lower lip defects

Defect size	Procedure
< ½	Wedge excision
½ to ⅔	Karapandicz flap Abbe/Estlander flap
>⅔	Bernard Burrow Gillies fan flap Webster flap Free flap

5.2.3. Upper Lip

Similar to lower lip defects, wedge excisions and advancement flaps can address upper lip defects which involve up to one half of the width of the upper lip. Care is taken to respect the relevant aesthetic subunits. Defects of less than a third in the midline can be closed primarily.

Defects greater 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 ⅔rds of the lip, a Burrow-Diffenbach reconstruction can be performed. The Burrow-Diffenbach flap replaces upper lip defects by utilization of laterally based advancement flaps. Bilateral peri-alar crescentic excisions are required to provide adequate advancement. The various reconstructive options are identified in table 3.

Table 3. Reconstructive options for upper lip defects

Defect size	Procedure
< ½	Wedge excision
½ to ⅔	Peri-alar Crescentic flap Reverse Karapandicz flap Abbe/Estlander flap
>⅔	Burrow – Diffenbach flap Free flap

Most large series in the literature show that the majority of patients have small lesions without palpable cervical metastases. The local recurrence rate is low due to the relative ease of surgical excision and even re-excision because of local failure leads to salvage 75–80% of cases. The incidence of synchronous cervical metastases increases as the size of the primary tumour increases. The primary lymphatic drainage of the lower lip is to the submental and submandibular level Ia and Ib cervical lymph nodes. Neck dissection is generally not performed in the absence of clinically suspicious cervical lymph nodes as less than 5% of patients are likely to develop recurrence in the neck following treatment of the primary lesion.

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 radiotherapy. The lower lip is one of the few ideal sites for orthovoltage x-ray therapy. Using a single anterior field a fractionated course of 50 Gray in 15 fractions over three weeks is given. 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 four to five days with a total radiation dose between 40–45 Grays in 8–10 fractions.

6. DEVELOPING THERAPEUTIC REGIMES

Neoadjuvant chemotherapy with TPF followed by surgery and then radiotherapy is accruing evidence in other primary sites. Chemo-radiotherapy with the addition of targeted agents requires further evaluation. Radiotherapy alone versus radiotherapy plus cetuximab in intermediate cancers and the use of PET-CT 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.

Xerostomia is one of the most unpleasant permanent complications from radiotherapy of the oral cavity. Sparing of the salivary glands by IMRT may improve toxicity without reduction in local control. The efficacy of hyperbaric oxygen in the prevention and treatment of osteo-radionecrosis remains unproven. Within the oral cavity, experience is still relatively limited. Further work is required to establish the long term quality of life, toxicity recognition, management and support in head and neck cancer patients receiving chemo-radiotherapy.

PDT has been advocated as a technique which causes selective tumour destruction by cell apoptosis. Advocates suggest minimal scarring and preservation of uninvolved tissue thereby minimizing any functional deficit caused by tumour ablation. Unfortunately the photo-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 photodynamic therapy can also be used to treat primary cancer of the lip. This form of treatment yields complete response rates comparable to those published for surgery or radiotherapy. The lack of tissue memory for photodynamic therapy means that unlike radiotherapy this treatment can be given 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
- Several reconstructive options exist to repair soft tissue and bony defects after tumour resection
- Tumour thickness, positive margins, extra-capsular spread of nodal metastasis and pattern of invasion have been shown to have significant prognostic value
- Post-operative adjuvant radiation or chemo-radiation should be considered in the presence of unfavourable disease factors

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Chapter 20
Oropharyngeal Cancer

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1. INTRODUCTION AND EPIDEMIOLOGY

The incidence of oropharyngeal carcinoma is increasingly significantly in developed countries. In the United States, the incidence of oropharyngeal squamous cell carcinoma increased by 22% 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 United Kingdom has seen a doubling of incidence of oropharyngeal squamous cell carcinoma between 1990 and 2006. In Scotland it has shown an estimated 2.9 fold increase of oropharyngeal cancer in males, and a 2.4 fold increase in females between 1987 and 2006.

Human papillomavirus (HPV) has been increasingly recognised as a causative agent in oropharyngeal cancer, with HPV-16 being the predominant subtype responsible. The proportion with evidence of HPV infection is rising rapidly. Combined data from recently published studies (2006–2009) shows that 55% of 654 reported oropharyngeal SCC cases were HPV positive.

2. CLINICAL PRESENTATION

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

3. ASSESSMENT AND STAGING

3.1. Clinical examination

Flexible direct endoscopy of the upper aerodigestive tract is now available in virtually all ENT 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 valleculae and pyriform fossa, and the superior extension of tonsil cancers into the postnasal space and skull base.

3.2. Imaging considerations

Cross-sectional imaging is required in all cases to complete assessment and staging. MRI scanning is optimal for staging the primary tumour, particularly when assessing extensive soft tissue spread, such as into the body of the tongue. CT scanning may also be required to assess the primary site to identify the extent of possible bony invasion, such as the 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 is also an accurate method of staging nodal disease in experienced hands. Distant metastases should be assessed by CT scanning of the chest and upper abdomen, which excludes metastatic disease to the lungs, liver and adrenal glands. MRI scanning is not suitable for this due to the relatively slow acquisition process leading to movement artefact caused by breathing.

PET-CT scanning has a role in the assessment of recurrent tumours to detect recurrence at primary sites, neck nodes and /or distant metastases. It may also have a role in assessment of response to chemo+/-radiotherapy in advanced nodal disease – which is currently being assessed in a phase 3 trial.

Recommendations

- Cross-sectional imaging is required in all cases to complete assessment and staging (Grade C)
- MRI is recommended for primary site and CT scan for neck and chest (Grade D)
- PET-CT scanning has a role in assessing response after therapy and assessing recurrence (Grade C)
- Examination under anesthetic is recommended, but not mandatory in most cases (Grade D)

3.3. Examination under anesthetic and panendoscopy

Is recommended to assess the extent and resectability of the primary site and to exclude second primaries, especially in hypopharynx and oesophagus. Examination under anesthetic is mandatory if thorough examination is not possible clinically or if no biopsy can be obtained.

3.4. Pre-treatment staging

Primary tumour stage based on the TNM classification for oropharyngeal tumours is shown in Table 1.

Table 1. T staging for oropharyngeal tumours

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

4. 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 FNA of involved nodes may suffice provided it has been reviewed by experienced head neck pathologists. 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.

The majority of oropharyngeal cancers are squamous cell carcinomas. The Royal College of Pathologists have published UK guidelines for the histopathological reporting of head and neck carcinomas and salivary neoplasms. It is recommended that these guidelines are applied to oropharyngeal carcinomas.

The increasing importance of high risk HPV in oropharyngeal SCC has prompted two professional associations in the USA to recommend HPV testing for oropharyngeal SCC. The National Comprehensive Cancer Network recommend HPV testing with polymerase chain reaction (PCR) or in situ hybridisation (ISH) and the College of American Pathologists advocate the use of HPV16 in-situ hybridisation and/or detection of p16 using immunohistochemistry (IHC). HPV testing for oropharyngeal cancer should be performed within a diagnostic service where the laboratory procedures and reporting standards are quality assured.

HPV positive cases have better prognosis with reported hazard ratio between 0.2 and 0.6 for 5 year overall survival when compared with HPV negative cases. Even in HPV positive cases, alcohol and smoking act as a confounding factors, worsening survival.

Recommendations

- Histological diagnosis is mandatory in most cases (Grade D)
- Oropharyngeal carcinoma histopathology reports should be prepared according to The Royal College of Pathologists guidelines (Grade D)
- HPV testing for oropharyngeal cancer should be performed within a diagnostic service where the laboratory procedures and reporting standards are quality assured (Grade D)
- Currently, in routine clinical practice, HPV testing for oropharyngeal SCC is desirable, but not mandatory (Grade D)

5. MANAGEMENT

5.1. Early (T1/2 N0) oropharyngeal carcinoma

5.1.1. General principles of management

Early stage (T1-2 N0 M0) oropharyngeal carcinoma can be treated be either primary surgery or radiotherapy. There are no high quality comparative studies of the two treatment modalities within the same population. Retrospective case series demonstrate 5-year disease specific survival rates of 81–100% for primary surgery, with adjuvant therapy where appropriate and 77–89% for primary radiotherapy, including surgical salvage.

5.1.2. Surgical management of early oropharyngeal cancer

Surgery for T1-2 N0 OPSCC can be done either transorally or through open approaches with reconstruction. Open approaches may require paramedian mandibultomy for access, and usually require reconstruction with a flap.Transcervical 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 (particularly for T1-2 tumours) and leads to inferior function.

There is increasing interest in transoral resections for OPSCC, particularly T1-2 tumours. This is usually performed by laser and very recently, transoral robotic surgery (TORS). The advantages of transoral resections are improved functional outcomes through the avoidance of the morbidity associated with access approaches, tracheostomy in many cases, reconstruction with an insensate flap as well as reduced overall morbidity and operation time. However, at present, these advantages are not substantiated by comparative outcomes evidence. The main disadvantage is the difficulty in pathological scrutiny of the resected tissue to determine margins. This is due to laser artefact and difficult orientation. Most patients after transoral resections of the oropharynx have post-operative RT or CRT with oncologic results that appear to be comparable to open surgery and post-operative radiotherapy or chemoradiotherapy.

About 10–31% of patients who are clinically T1-2 N0 will have occult nodal disease Therefore, patients having surgery to the primary should also have an ipsilateral selective neck dissection. The contralateral neck should also be treated in tumours arising at or very near the midline, in the soft palate, posterior pharyngeal wall. Evidence suggests dissecting levels II, III and IV and possibly level I. Recent retrospective studies suggest that level IIb does not need to be dissected, as long as there are no findings per-operatively of level IIa disease. When operating on the primary tumour by open resection/reconstruction, the neck dissection is performed at the same time. For transoral resections, the neck dissection is usually performed around two weeks later. This allows further primary tumour bed resection if there are concerns about histopathological margins; and may help prevent the development of a

fistula if there is lateral pharyngeal wall transoral resection. However concomitant transoral resection and neck dissection have also been reported with good results.

5.1.3. Radical radiotherapy for early oropharyngeal cancer

A total dose of 70 Gy in 35 fractions (or equivalent) is used in radical treatment. However, often a 4 week hypofractionated schedule of 55Gy in 20 fractions is preferred for early stage disease. Target volume definition is performed using contrast enhanced CT scans. For well lateralized, small oropharyngeal carcinoma, the gross tumour with a margin is treated using a "wedged pair" of radiotherapy fields. Such conformal techniques can reduce exit dose to the contralateral parotid gland thereby reducing the probability of long term xerostomia. For tumours involving the midline, a "parallel opposed pair" field arrangement is often used. Level II lymph nodes (ipsilateral if lateralised and bilateral if midline disease) are routinely included within the treatment fields.

Improvements in radiotherapy techniques (including intensity modulated radiation therapy; IMRT) have reported reduced complications following radiotherapy. A recent UK based randomised study showed clear benefit in reducing xerostomia rates with parotid sparing IMRT in oropharyngeal carcinoma. Multiple studies have explored the role of IMRT in improving swallowing function and trismus, but none so far have shown good evidence of benefit. Studies using IMRT in oropharyngeal carcinoma have reported very low rates of osteoradionecrosis. Submandibular gland sparing IMRT techniques are emerging and may be applicable in lateralised early oropharyngeal carcinoma, but larger, preferably phase 3 studies are needed to establish its role.

The indications for post-operative radiotherapy and chemoradiotherapy (CRT) are no different from other primary tumours.

Recommendations

- Treatment options include: radical radiotherapy, transoral surgery + neck dissection (usually with post-operative radiotherapy) or open surgery + free flap reconstruction + neck dissection (post-operative radiotherapy dependent on histology) (Grade C)
- Transoral surgery preferable to open techniques in theory but there is no strong evidence to support this yet (Grade D)
- 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 (Grade C)

5.2. Advanced (T3/T4 N0-N3) oropharyngeal cancer

5.2.1. 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 radiotherapy. All other treatment comparisons did not show any statistical differences.

In recent years there has been a tendency to offer primary radiotherapy or chemoradiotherapy for oropharyngeal carcinoma. This is sometimes referred to as an "organ preservation" strategy. Much of the evidence in favour of organ preservation relates to laryngeal surgery where salvage surgery has been shown to have a high success rate. This success rate of salvage surgery is not the same in other head and neck sites such as the oropharynx.

HPV status appears to have profound influence on prognosis, and in future, potentially on selection of treatment modality. Recruitment into clinical trials addressing these issues is highly recommended.

5.2.2. Surgical management of advanced oropharyngeal carcinoma

Overall survival in advanced tumours has been shown to be best in patients receiving radical surgery and post operative radiotherapy. However, functional results can be poor. Where facilities and expertise exist, trans-oral laser resection of base of tongue, tonsil and pharyngeal wall primary tumours (usually with post-operative radiotherapy if there are close margins or extracapsular spread) has been shown to offer rates of cure as good as primary chemoradiotherapy whilst preserving speech and swallowing function. Transoral laser resection is not appropriate where resection margins are likely to be positive as patients would then be recommended post-operative chemoradiotherapy. If transoral laser resection is not appropriate, for example with larger primary tumours, then transcervical or approaches with lip splitting and mandibulotomy for access would be required, usually with reconstruction.

Where a larger resection of the soft palate is required then the general consensus is that surgery gives a poor functional outcome. However provided free flap surgery can be offered and the tumour is T3 or smaller then good, functional outcomes have been reported.

There are several case series published that report the likelihood of nodal metastasis for oropharyngeal carcinoma at over 50%. When managing T3 and T4 oropharyngeal cancers, the N0 neck should be treated electively. When managing the N0 neck surgically, a selective level II to IV neck dissection should be performed as a minimum. All N+ disease should have a modified neck dissection or at least levels I to IV selective neck dissection.

5.2.3. Primary chemoradiotherapy in advanced oropharyngeal carcinoma

Chemoradiotherapy (organ preservation) is an effective treatment choice for advanced head and neck tumours. Radiotherapy dose of 70Gy in 2 Gy fractions (or equivalent) with concurrent cisplatin chemotherapy is considered as standard. Neck nodes should be included in the treatment fields depending on their probability of involvement. Improvements in radiotherapy techniques (including IMRT techniques) have reported reduced complication rates following radiotherapy (as described above).

Advanced cases (stage IV) cases may warrant treatment with induction chemotherapy followed by concomitant chemotherapy as discussed in chapter 17. Advanced

nodal disease (N2 or N3) in patients being treated by chemoradiotherapy requires a neck dissection. There is little evidence to support whether neck dissection before or after CRT is more effective. There is emerging evidence that there may be a role for PET CT guided surveillance policy instead of planned neck dissection.

5.2.4. Post-operative radiotherapy and chemoradiotherapy for advanced oropharyngeal carcinoma

The indications for post-operative radiotherapy and chemoradiotherpy are no different from other primary tumours. Randomised controlled trials and a metanalysis of results confirm that patients with extra capsular invasion or microscopically involved surgical resection margins experience significant benefit in terms of overall and disease free survival when receiving postoperative chemoradiotherapy compared to radiotherapy alone. Indications for post-operative radiotherapy alone include multiple nodal metastasis, T3 and T4 tumours, and tumours with other adverse features, such as perineural or lymphovascular invasion.

Recommendations

- Advanced oropharyngeal carcinoma can be treated with primary chemoradiotherapy or surgery and radio/chemoradiotherapy (Grade A)
- N0 neck should be treated electively, either by CRT or selective neck dissection (Grade C)
- Advanced nodal disease requires a neck dissection (Grade C)
- IMRT may improve the functional outcomes of patients being treated by chemoradiotherapy (Grade A)
- Postoperative chemoradiotherapy is required in patients treated with surgery who have involved resection margins or extracapsular spread. Otherwise post-operative radiotherapy alone may be indicated (Grade A)

6. RESEARCH

HPV status appears to have profound influence on prognosis, and in the future, potentially on selection of treatment modality. There are several clinical trials in planning or set up examining different treatment regimens for HPV related oropharyngeal carcinoma. Recruitment into clinical trials addressing these issues is highly recommended.

Recommendation

- Altering the modalities of treatment according to HPV status is currently controversial and should be addressed only in clinical trials (Grade D

Key Points

- HPV plays a significant role in the etiology of oropharyngeal SCC and is responsible for the increased incidence being witnessed in the last few decades
- HPV testing for oropharyngeal SCC is desirable and will help prognosticate
- Treatment options for early cancer include: radical radiotherapy, transoral surgery + neck dissection or open surgery + free flap reconstruction + neck dissection
- Transoral surgery, where possible, leads to rapid recovery with equivalent control rates
- Advanced oropharyngeal carcinoma can be treated with primary chemoradiotherapy or surgery and radio/chemoradiotherapy
- The N0 neck should be treated electively – either by CRT or selective neck dissection.
- If treated surgically, neck dissection should include at least levels II to IV; level IIb dissection can be omitted if there is no disease in level IIa.
- IMRT may improve the functional outcomes of patients being treated by chemoradiotherapy
- Postoperative chemoradiotherapy is required in patients treated with surgery who have involved resection margins or extracapsular spread. Otherwise postoperative radiotherapy alone may be indicated

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Chapter 21
Nasopharyngeal Cancer

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1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma arising from the mucosal surface of the nasopharynx. The most common site is the fossa of Rosenmuller which is a recess just medial to the medial crura of the eusthachian tube.

NPC is frequent in patients of Southern Chinese, Northern African and Alaskan origin. The incidence in the Hong Kong population is between 20 to 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 (EPV) and consumption of salted fish containing dementhylnitrosamine have been implicated in its aetiology. Genetic alterations include deletion of chromosomal regions at 1p, 14q, 16p, and amplification of 4q and 12q.

3. CLINICAL PRESENTATION

NPC 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 opening 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 location of the tumour.

4. ASSESSMENT AND STAGING

4.1. 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 blind biopsies of the fossa of Rosenmuller, when indicated.

4.2. Pathologic considerations

Histological examination is required for definitive diagnosis. Fine needle aspiration cytology (FNAC) can be used as an adjunct for staging neck disease and distant metastases. Rendering a diagnosis of NPC can represent a challenge due to the practical difficulties of acquiring sufficient tissue with adequate preservation from the nasopharynx.

NPC comprises three histological types: non-keratinising carcinoma (incorporating differentiated and undifferentiated subtypes), keratinising carcinoma and basaloid squamous cell carcinoma. 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 squamous cell carcinoma 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. AE1/AE3 and MNF116 antibodies 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. Recognition of the role of Epstein Barr virus (EBV) in NPC has greatly facilitated diagnosis because all non-keratinising carcinomas harbour EBV. 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 (LMP-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 to as an adjunct to monitor disease progression and response to treatment. Detection of immunoglobulins to viral capsid antigen (VCA) and early antigens (EA) 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 (Q-PCR) techniques, has been developed to aid disease surveillance.

4.3. Imaging considerations

Staging investigations should include multi-slice CT scan of the head, neck and chest. MRI scans of the skull base is useful especially in locally advanced tumours. The use of 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.

4.4. Staging

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 invovement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space.

Regional Lymph Nodes 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 greatest dimension, above the supraclavicular fossa
N2	Bilateral metastasis in lymph nodes, 6 cm or less in 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

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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 nasopharyngeal carcinoma should be assessed with rigid and fibreoptic nasendoscopy (Grade B)
- Nasopharyngeal biopsies should be preferably carried out endoscopically (Grade B)
- Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan in locally advanced cases (Grade B)

5. MANAGEMENT

5.1. Radiotherapy

Radiotherapy (RT) is the mainstay for the radical treatment for NPC. 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 greatly by the synchronous use of chemotherapy (CT) and advances in radiation delivery techniques, both of which result in better disease control and survival along with lower rates of long term toxicity. Intensity modulated radiotherapy (IMRT) allows concavities to be created in the RT dose distribution, which is particularly useful for the treatment of head and neck cancer. It facilitates improved coverage of the primary tumour volume, particularly in the pharyngeal recesses, and reduction of parotid gland dose, substantially reducing long term xerostomia, thereby improving quality of life.

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 (Grade A)

5.2. Chemotherapy

There is evidence confirming significant improvement in overall survival (OS) in the patients treated concurrently with chemo-radiotherapy for NPC as compared to RT alone. The roles of neo-adjuvant and adjuvant chemotherapy are more controversial with no proven survival advantage but confirmed event free survival (EFS) benefit with neo-adjuvant chemotherapy. Adjuvant chemotherapy after RT is less well tolerated and benefits are still unproven. Cisplatin based chemotherapy is commonly 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 single agent or in combination with platinum for second and third line treatment for metastatic disease.

Recommendation

- Concurrent chemo-radiotherapy offers as significant improvement in overall survival in stage III and IV disease (Grade A)

5.3. 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 otitis media with effusion.

Recommendation

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

6. TREATMENT RECOMMENDATIONS

6.1. Stages I and II

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

Intermediate stage II disease is treated with combination chemo-radiotherapy (CRT). IMRT should be used where possible. A dose of 70 Gy is recommended to the primary, 66 to 70Gy to gross disease in lymph nodes and 50Gy to the bilateral neck and other sites of potential microscopic spread. Radiobiological equivalents are given if a fraction size other than 2Gy is employed, for example with intensity modulation. The most commonly used chemotherapy schedule is Cisplatin 100mg/m^2 on days 1,22 and 43 of radiotherapy based on the United States Intergroup Study

0099. Weekly cisplatin at a dose of 40mg/m^2 is effective but has not been compared to the standard regimen in a randomised study. It can be considered for older patients and/or those with significant comorbidities.

6.2. Stages III and IV

Concurrent CRT is the standard of care for advanced nasopharyngeal cancers. This improves overall survival by up to 6% at 5 yrs compared to radical RT. A dose of 70 Gy (2Gy 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 (DFS) whilst having no effect on overall survival (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, posterior part of sphenoid sinus, posterior third of the nasal cavity and the maxillary sinus, retropharyngeal lymph nodes, and parapharyngeal space. Prophylactic irradiation must include uninvolved level I to V nodal areas.

IMRT is increasingly being used with either fixed gantry linear accelerator based techniques 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.

Surgical treatment is reserved for salvage following CRT failure.

Recommendations

- RT is the treatment of choice for stage I and II disease (Grade A)
- IMRT techniques should be employed whenever possible (Grade A)
- CRT is the treatment of choice for stage III and IV disease (Grade A)

7. ASSESSMENT OF TREATMENT RESPONSE AND FOLLOW UP

Assessment of treatment and follow-up is imperative in NPC. Patients should be assessed clinically with endoscopic examination and neck palpation. The recommended follow-up strategy is addressed in Chapter 39.

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 3 months and at a year from completion of treatment.

Following treatment, it can take up to 3 months for NPC to disappear histologically. Post-treatment disease can be monitored using biopsies. However, accurate interpretation of the material can be 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.

Recommendations

- Patients with nasopharyngeal carcinoma should be followed-up and assessed with rigid and/or fibreoptic nasendoscopy (Grade B)
- PET-CT, CT or MRI scan should be carried out at 3 months from completion of treatment to assess response (Grade B)
- Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan in advanced cases with suspected recurrence (Grade B)

8. MANAGEMENT OF RESIDUAL AND RECURRENT DISEASE

8.1. Surgery

CRT or RT resistant tumours may be amenable to salvage surgery (SS) 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.

8.1.1. Surgery to the primary site

Endoscopically guided microwave coagulation of small volume (rT1) recurrent disease has been described as having low morbidity and overall survival and local progression-free survival of 93.6% and 90.7% at five years.

The likelihood of successful surgical excision diminishes in proportion to the size and extent of the recurrent/persistent disease at the primary site. Transcranial approaches are associated with high morbidity. Transnasal and transantral approaches provide poor access to the para-nasopharyngeal 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 are as yet experimental.

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%. Palatal fistulae occur in 20–25% of patients, whilst 60% 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.

8.1.2. Surgery to the neck

Re-irradiation of the involved neck to treat persistent/recurrent disease carries a high risk of tissue necrosis and fibrosis. Persistent or recurrent nodal disease following CRT demonstrates a high incidence of extracapsular extension (53.8%–64.7%). For this reason salvage radical neck dissection (with the placement of brachytherapy tubes for afterloading 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% 5 year local control of disease.

8.2. Non-surgical options

8.2.1. Re-irradiation

Local nasopharyngeal recurrences respond better to re-irradiation than other sites. The scope for re-irradiation depends on the tumour volume, current T stage and the disease free interval/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 radiotherapy 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 IMRT, intracavitary and interstitial brachytherapy, stereotactic radiosurgery, fractionated stereotactic radiotherapy or proton beam therapy. 5-year overall survival rates of 60% have been reported. The toxicity rate for re-irradiation is significant. A prognostic scoring system for locally recurrent nasopharyngeal carcinoma has been validated When re-irradiation is not possible, then palliative chemotherapy should be considered.

8.2.2. Conventional chemotherapy

Palliative systemic chemotherapy is the central component of the treatment for metastatic disease. Cisplatin based chemotherapy produces response rates of up to 80% in chemotherapy-naive patients resulting in median survival rates of up to 15 months. There are no randomised comparisons of different chemotherapy schedules. Whilst cisplatin and 5-flurouracil remains 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.

8.3. Molecular therapies and immunotherapy

There is no evidence for the routine use of molecular therapies for metastatic nasopharyngeal carcinoma outside clinical trial settings. Phase II trials have demonstrated limited activity in the second and third line setting. The utility of immunotherapy, based either adoptive or active means against 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 (Grade B).
- Neck dissection remains the treatment of choice for residual or metastatic neck disease whenever possible (Grade B).
- Reirradiation should be considered as a second line of treatment in recurrent disease (Grade B).
- Conventional chemotherapy has only a palliative role in the management of recurrent NPC (Grade B)

9. TREATMENT OUTCOMES

9.1. Stages I and II

Five-year OS rates of 90% for stage I and 84% for stage II have been reported from a Hong Kong review of 2687 patients based on AJCC 1997 staging. Data for non-endemic regions is sparse given the relative rarity of the condition in these areas.

Serum Epstein Barr virus DNA copies before treatment have been shown to have prognostic significance; for stage I and II <4000 copies per ml have a 91% survival at 5 years and >4000 copies per ml have at 64% 5 year survival.

9.2. Stages III and IV

CRT regimes have improved the OS of NPC patients from 77% to 81% and 56% to 62% at 2yrs and 5 yrs 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%. Accelerated RT schedules or post-radiotherapy 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%, and median survival of about 14 months.

10. CONTROVERSIES

10.1. 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 radiotherapy. Eustachian tube function may improve in an irradiated patient up to 5 years after RT. However, if an effusion is present or develops during radiotherapy tubal function remains poor. Grommets bypass tubal obstruction, but may exacerbate the inflammatory process. Up to 29% of patients will develop non-healing perforation of the tympanic membrane, if grommets are inserted during or after radiotherapy and 49% will go onto develop intermittent otorrhoea. Middle ear effusion arising during or after radiotherapy is best managed using repeated paracentesis, aspiration and a hearing aid. Grommets should be used as a last resort.

10.2. Salvage surgery for local recurrence

The maxillary swing nasopharyngectomy approach has now been adopted as an adequate mode of salvaging patients with recurrent NPC with survival rates as up to 73% 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.

10.3. 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.

10.4. 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 neoadjuvant chemotherapy followed by concurrent CRT have produced encouraging early results, but longer term data is awaited.

10.5. The use of routine tumour markers in the management of NPC

Testing for EBV infection has potential as a screening tool, but only in high risk regions or populations. EBV 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

- NPC is frequent in patients of Southern China, Northern Africa and Alaska 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.
- Patients with NPC should be assessed with rigid and fibreoptic nasendoscopy.
- Nasopharyngeal biopsies should be carried out endoscopically.
- Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan in locally advanced cases.
- Radiotherapy is the mainstay of the radical treatment for NPC.
- Concurrent CRT offers a significant improvement in overall survival in stage III and IV disease.
- Surgery should only be used to obtain tissue for diagnosis and to deal with OME.
- Patients with NPC should be followed-up and assessed with rigid and/or fibreoptic nasendoscopy.
- A PET-CT, CT or MRI scan should be carried out at 3 months from completion of treatment to assess response.
- Multislice CT scan of head, neck and chest should be carried out in all patients and MRI scan in advanced cases with suspected recurrence.
- Salvage surgery in the form of nasopharyngectomy should be considered as a treatment of residual or recurrent disease in the primary site.
- Neck dissection is the treatment of choice for residual or metastatic neck disease.
- Re-irradiation should be considered as a second line of treatment in recurrent disease.
- Conventional chemotherapy has only a palliative role in the management of recurrent NPC.
- Controversy exists in the management of the OME in patients with NPC, the best mode of salvage surgery, salvage treatments for disseminated disease, the use of neo-adjuvant and adjuvant CRT and the use of tumour markers.

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Chapter 22
Hypopharyngeal cancer

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1. 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%), 10–20% arise from the posterior pharyngeal wall and 5–15% from the post cricoid area. As is the case at other sites in the head and neck, the overwhelming majority (95%) of cancers are squamous cell carcinomas (SCC).

Five-year survival is poor with overall survival at 30%, although for T1 and T2 tumours the survival is almost 60%. This discrepancy is a reflection of late presentation, as hypopharyngeal tumours remain relatively asymptomatic until they are quite advanced. T1N0 cases account for only 1–2% of all cases seen and 80% of patients are stage III/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.

2. CLINICAL PRESENTATION

The cardinal symptoms of hypopharyngeal cancer are:

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

3. ASSESSMENT AND STAGING

3.1. 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, World Health Organisation). The medical history and performance status are critical in recommending the extent and intention of treatment. Mortality and complication rates are much higher in patients with significant weight loss, comorbidity or poor performance indicators.

A full head and neck examination is essential, including nasendoscopy, in order to assess the size and position of the primary tumour, mobility of the vocal fold, as well as the presence of neck metastases. Clinical examination is also important in assessment of prevertebral fascia involvement and can be assessed by looking at laryngopharyngeal mobility in the lateral direction. This is then complemented by radiological assessment and staging endoscopy under general anaesthetic.

3.2. Imaging considerations

It is generally thought that radiology is better performed prior to biopsy, which can produce post-operative oedema leading to over-staging of the disease on subsequent imaging. In addition, it allows assessment of any incidental abnormalities uncovered by radiological evaluation.

Cross sectional imaging is mandatory and can take the form of either high resolution computerised tomography (CT) or magnetic resonance (MR) imaging. In addition to this the chest should always be imaged due to the increased incidence of lung metastases or second primaries. The critical points in imaging are assessing extent of disease (particularly the lower limits of disease) and the presence of thyroid cartilage invasion. MR gives better soft tissue definition and has greater sensitivity (80%) for cartilage invasion, but is less specific (74%) than CT, and can therefore potentially over-stage disease. The multi-planar capabilities of MR can also help in staging the disease. In general comparisons with histological assessment, CT and MRI produced sensitivities of 66% and 89%, respectively, and specificities of 94% and 84%, respectively (2). The benefit of CT is that the chest can be imaged at the time of the neck imaging, whereas, if MR is used the patient needs additional imaging. As hypopharyngeal cancer usually presents with stage III or IV disease, chest CT is recommended.

Currently, the Royal College of Radiologists recommend MR scanning for the hypopharynx. However, the recent Dutch consensus document on hypopharyngeal cancer recommended high resolution CT imaging. At the present time, there is no indication for the routine use of positron emission tomography (PET) scanning in this group of patients.

3.3. Examination under anaesthetic and panendoscopy

Endoscopy in theatre serves three functions: firstly it allows assessment of the extent of the primary tumour, secondly 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 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.

At the end of all these assessments, a clinical stage can be reached using the UICC TNM classification system.

3.4. Pre-treatment staging

Table 1. T staging for hypopharyngeal tumours

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of the hypopharynx and 2 cm or less in greatest dimension
T2	Tumor 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	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue, which includes prelaryngeal strap muscles and subcutaneous fat
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

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 (Grade B)
- Careful evaluation of the upper and lower extent of disease is necessary, which may require contrast swallow (Grade C)
- Formal rigid endoscopic assessment under general anaesthesia should be performed (Grade C)

4. MANAGEMENT

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. Many of these patients present with dysphagia and significant weight loss and can be profoundly malnourished. This needs to be managed proactively early after diagnosis and may require insertion of naso-gastric or gastrostomy feeding tubes prior to any treatment taking place. Treatment factors involve a full assessment of the patient's performance status and their ability to undergo major surgery or their ability to lie flat for radiotherapy and attend daily for 7 weeks.

The treatment of hypopharyngeal SCC remains controversial and the lack of prospective randomised data contributes to the ongoing debate regarding surgery or radiotherapy as the primary treatment modality. A large retrospective study of 595

patients showed no survival advantage for either radiotherapy +/− salvage surgery or surgery +/− postoperative radiotherapy. Second primary tumours are present in 10% of cases, with treatment options influenced by prior therapy, which may influence survival.

Recommendations

- Nutritional status should be proactively managed (Grade C)
- Full and unbiased discussion of treatment options should be done to allow informed patient choice (Grade B)

4.1. Surgical treatment

Based on the extent of the tumour, several surgical options exists for hypopharyngeal cancer (table 2)

Table 2. Surgical options for hypopharyngeal tumours

Internal Excision
"Cold steel" or CO_2 laser surgery +/− Robotic aided
External Excision: (with or without flap repair)
Partial pharyngectomy
Partial pharyngectomy / partial laryngectomy
Partial pharyngectomy / total laryngectomy
Total pharyngo-laryngectomy
Extended pharyngo-laryngectomy

4.1.1. Early stage disease

Early stage (I and II) disease can be treated with equal effectiveness with surgery or radiation. Early lesions of the hypopharynx can be treated by endoscopic laser excision or open partial laryngopharyngectomy with or without reconstruction. Surgery offers the advantage of providing prognostic information, such as perineural 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 those patients side effects without a significant survival advantage. Occult nodal disease is present in 30%–40% of patients and so any treatment plan should include elective treatment of cervical nodes.

4.1.2. Late stage disease

Unfortunately, as more than 80% are advanced stage III and IV at presentation, (with locally advanced disease present in the majority) it has been estimated that up to 25% are inoperable at the time of presentation. Submucosal extension is present in more than 60% of surgical specimens and is occult in one third. 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– 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%. Bulky advanced tumours will usually require circumferential or non-circumferential resection with free flap cover.

4.1.3. Recurrent disease

Surgical salvage after failure of irradiation therapy has a lower success rate for hypopharyngeal cancer than at any other site in the head and neck, and larynx preservation is rarely possible. Patients who have undergone previous irradiation require even greater resection margins, estimated 2 cm superiorly, 4 cm inferiorly, and 3 cm laterally.

Recommendations

- Early stage disease can be treated equally effectively with surgery or radiotherapy (Grade B)
- Endoscopic resection can be considered for early well localised lesions (Grade C)
- Bulky advanced tumours require circumferential or non circumferential resection with wide margins to account for submucosal spread (Grade B)

4.1.4. Management of the neck

Midline lesions, those involving the posterior pharyngeal wall or postcricoid 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 the surgically treated patient with a clinically N0 neck, unilateral or bilateral selective 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 mediastinal nodal areas.

Recommendations

- Midline lesions require bilateral neck dissections (Grade B)
- Thought must be given to the treatment of ‘silent nodal areas’ (Grade B)

4.1.5. Reconstruction

Reconstruction of pharyngeal defects and in particular circumferential defects present major challenges. Modern chemoradiotherapy protocols, medical co-morbidity 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.

The pectoralis major myocutaneous flap offers improved results in terms of reliability but fistula rates remain unacceptably high and the flap is difficult to tube. The pectoralis major flap is usually reserved for partial pharyngeal defects and can be used as a muscle only or a muscle and skin flap. It still has a role in reconstructing necrotic areas around tracheal stomas and to treat salivary fistulae.

Gastric pull up allows single stage reconstruction using well vascularised tissue and requiring only a single mucosal anastomosis. However, the mortality and morbidity can be high. Gastric pull up is now reserved for post cricoid tumours and following free flap failure.

The advent of microvascular surgery and free tissue transfer has resulted in a massive increase in reconstructive options. Free jejunal flaps have gained popularity due to the relatively low morbidity and the jejunum being a tubed structure with similar characteristics to the native oesophagus. However, abdominal complications can occur and long term speech and swallowing rehabilitation has been disappointing.

The gastro-omental flap gives the advantage that in addition to the tubed gastric mucosa, the omentum provides an extremely well vascularised apron not only to reinforce the mucosal anastomosis, but also to improve healing of the poorly vascularised skin in the neck. The radial forearm flap is a very reliable flap and easy to tube. However, the donor site can still be a problem due to the need for a skin graft and fistula rates can still be high. The anterolateral thigh flap, when raised as a perforator flap can be tubed easily (unless the patient is obese). It is reliable and has very low donor site morbidity as direct closure is possible. The fascia overlying the vastus lateralis, if included in the flap, can be used to reinforce the anastomotic line.

Stenting fasciocutanous tubed flaps with salivary bypass tubes may protect the anastomosis and reduced fistula rates. Swallowing after reconstruction with fasciocutaneous flaps and the gastoromental flaps is superior to that after jejunal 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 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. There are some surgeons who would carry out a primary 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 decided on a case by case basis and depends 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 (Grade C)

4.2. Non-surgical management

For each individual case, a series of tumour factors, patient factors and treatment factors need to be considered. Tumour factors predominantly involve the local extent of the tumour and the invasion of cartilage. Tumours showing cartilage invasion are less likely to be cured by radiotherapy and so surgery is a better option. In the past a large tumour bulk has also been considered a reason to opt for surgery over radiotherapy owing to the higher proportion of hypoxic, 'radioresistant', cells within the tumour. However, with the advent of modern induction chemotherapy schedules such as TPF (taxotere, cisplatin and 5-fluorouracil) and the very high response rates achieved, allowing significant reduction in tumour bulk prior to definitive chemoradiation, this may change and Phase 3 trial results are awaited. The presence of unilateral bulky nodal metastases is also a strong indication for primary surgical treatment of the neck.

That said, with technological advances in the delivery of high dose radiotherapy and the addition of chemotherapy to radiotherapy, there is progressively a move towards primary non-surgical treatment for all but the most locally advanced tumours. Due to the rich lymphatic drainage of the hypopharynx, there is a high incidence of nodal metastases-stage III and IV diseases are reported to have 67% incidence of retropharyngeal metastases. This necessitates large radiotherapy fields from skull base to below the cricoid cartilage and includes lymph nodes in levels II–V in addition to retropharyngeal lymph nodes. Commonly large lateral radiotherapy portals are used, usually angled inferiorly to optimise dose to the primary tumour. The aim is to deliver a dose of 70Gy in 35 daily fractions to primary disease and involved lymph nodes and a dose of 50Gy in 25 daily fractions to the nodal groups considered at risk of harbouring sub-clinical disease. Such long treatment portals make this a treatment with considerable toxicity with potential long-term side-effects of xerostomia and dysphagia. The advent of intensity modulated radiotherapy (IMRT) has greatly improved the achievable dose distributions compared to 3D-conformal radiotherapy, particularly to lymph nodes overlying the spinal cord.

It is known from the up-dated MACH-NC collaborative meta-analysis, that the addition of concomitant chemotherapy to radiotherapy adds 6.5% absolute survival benefit at 5 years. The most commonly used cytotoxic agent is cisplatin, given either as 100mg/m^2 every 3 weeks or weekly at doses of 30–40 mg/m^2 during the radiotherapy. There is no doubt that the addition of concomitant chemotherapy causes an increase in early radiation toxicity such as mucositis or skin desquamation although there is no evidence that this translates to an increase in late effects such as fibrosis. Other novel agents such as the monoclonal antibody cetuximab, an epidermal

growth factor receptor (EGFR) blocker, have been found to improve survival when given concomitantly with radiotherapy in the primary treatment setting, compared to treating with radiotherapy alone. It is currently indicated for patients who are unable to tolerate platinum based chemotherapy due to pre-existing medical conditions. Trials are currently in progress comparing the standard cytotoxic drugs such as cisplatin, with some of the novel agents to further optimise chemotherapy schedules. Many of these trials however are focussed upon improving outcomes often at the cost of increased toxicity to the patient. Unfortunately patients with hypopharyngeal cancer frequently present at an elderly age or with a poor performance status and may not be suitable for these treatments.

Recommendations

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

4.3. Palliative care

Hypopharyngeal cancer patients present with advanced disease in more than 80% cases. It has been estimated that up to 25% of patients are not suitable for curative treatment at presentation because of age, the extent of loco-regional disease, distant metastases, co-morbidity or refusal of surgery.

Following treatment, 50–60 % of patients develop a recurrence in less than 12 months, and most mortality in the first 2 years following diagnosis is due to loco-regional recurrence. The overall 5-year disease specific survival rate is approximately 30–35% with 5-year survival rates of 14–22% for stage IV disease. Volume of disease and laryngeal involvement adversely impact survival.

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 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%), 10–20% arise from the posterior pharyngeal wall and 5–15% from the post cricoid area.
- Five-year survival is poor with overall survival at 30%, although for T1 and T2 tumours the survival is almost 60%.
- Common symptoms include, hoarseness, dysphagia, odynophagia, referred otalgia and in the case of advanced cancers, laryngeal obstruction.
- The medical history and performance status are critical in recommending the extent and intention of treatment.
- Cross sectional imaging is mandatory and can take the form of either high resolution computerised tomography or magnetic resonance imaging.
- 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.
- The treatment of hypopharyngeal SCC remains controversial and the lack of prospective randomised data contributes to the ongoing debate regarding surgery or radiotherapy as the primary treatment modality.
- 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.
- For each individual case, a series of tumour factors, patient factors and treatment factors need to be considered.
- There is progressively a move towards primary non-surgical treatment for all but the most locally advanced tumours.
- Up to 25% of patients are not suitable for curative treatment at presentation because of age, the extent of loco-regional disease, distant metastases, co-morbidity or refusal of surgery.

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Chapter 23
Nose and Paranasal Sinus Tumours

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1. INTRODUCTION

Tumours in the sinonasal region are rare, affecting less than 1/100,000 people per year. They are histologically a diverse group and potentially pose significant management problems due to their close proximity to the orbit and intracranial cavity. Squamous cell carcinoma 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 include chondrosarcoma and rhabdomyosarcoma. Benign tumours include inverted papilloma,osteoma, juvenile angiofibroma, haemangiopericytoma, haemangioma, schwannoma, pleomorohicadenoma 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.

2. 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.

3. ASSESSMENT AND STAGING

Investigation should include CT and MRI which are complimentary in the skull base, and biopsy. CT 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. MRI 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. Table 1 shows the staging system for nasal and paranasal sinus malignancies.

Recommendations

- Sinonasal tumours are best treated de novo and unusual polyps should be imaged and biopsied prior to definitive surgery (Grade D)
- Treatment of sinonasal malignancy should be carefully planned and discussed at a skull base MDT meeting with available histology and all of the necessary imaging (Grade D)

Table 1. T staging for nasal and paranasal sinus tumours

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

4. MANAGEMENT

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

4.1. Benign sinonasal tumours

4.1.1. Sinonasal inverted papilloma (IP)

Is the most common pathology and much of the literature on management of benign nasal tumours concerns itself with IP. It is a locally aggressive tumour which usually arises in the nasal cavity. IP is associated with a risk of malignant transformation (~2%) and it is known to carry a high risk of post treatment recurrence/residual disease if a subperiosteal resection is not undertaken. Expert histopathology review is essential as well differentiated squamous cell carcinoma (SCC) can easily be mistaken for IP.

4.1.2. Juvenile angiofibroma (JA)

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 IP this lesion can extend to involve the sinuses, orbits and intracranial space. The basisphenoid is the commonest site of residual disease.

4.1.3. 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 is 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 large series of open surgery for IP, an overall recurrence rate of 17% is found. For JA, 'recurrence' rates fell from 21% to 2% when drilling of the basisphenoid was employed during midfacial degloving.

Endoscopic surgery and endoscope assisted, minimal access surgery (see below) promise lower morbidity, but it is essential that this is not achieved at the expense of high recurrence rates. Recent studies of endoscopic surgery for IP suggest recurrence rates of around 14% are achievable by experienced endoscopic surgeons. A similar recurrence rate has been reported for JA resected endoscopically though the series are relatively small.

Recommendation

- Complete surgical resection is the mainstay of treatment. This includes drilling the basisphenoid in JA (Grade C)

4.2. Malignant sinonasal tumours

4.2.1. Surgical approaches

4.2.1.1. Endoscopic resection of sinonasal tumours

The accepted method of resecting tumours of the anterior skull base is craniofacial resection. However, recent technological advances have facilitated endoscopic resection of malignant tumours of the lateral nasal wall and anterior skull base with safety and precision.

In some cases, tumour resection may be entirely endoscopic, but the endoscope may also be combined to enhance surgical resection with craniotomy, mid-facial 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.

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 aim should define whether this is with curative intent or palliation.

Contraindications to endoscopic resection

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 3-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.

Recommendation

- Essential equipment is necessary and must be available prior to commencing endonasal resection of skull base malignancy (Grade D)

En bloc resection is usually not possible in the skull base. The most important principle is to obtain clearance of tumour margins, confirmed with frozen section when necessary. 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.

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.

Recommendations

- Endoscopic skull base surgery may be facilitated by 2 surgeons working simultaneously, utilising both sides of the nose (Grade D)
- To ensure the optimum oncological results, the primary tumour must be completely removed and margins checked by frozen section if necessary (Grade D)

Reconstruction of the skull base defect is essential if the skull base or dura has 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.

Recommendation

- It is essential to perform a careful, substantial repair of any skull base or dural defect at the time of the primary surgery (Grade D)

Results

Five year disease specific survival rates of 85% after endoscopic resection of sinonasal malignancy are reported though selection bias needs to be taken into account. Encouraging results with good local control are reported following the endoscopic resection of olfactory neuroblastoma. The overall survival of

adenocarcinoma after endoscopic resection is reported at 92% 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, it appears that survival is worse with increasing T-stage. Survival is best for patients who have not undergone previous surgery with incomplete resection.

4.2.1.2. Maxillectomy

Maxillary tumours represent 3% of all head and neck tumours. 75% are malignant. 80% of the malignant tumours 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 5th and 6th decades. The 5-year survival is between 30 and 50%.

Pre-operative planning

One of the most important aspects of maxillectomy is pre-operative determination of the mode of reconstruction, which generally lies between prosthetic obturation and biological tissue (local, distant or free). Obturators have the advantage in that they reduce surgical time, impart no additional donor site morbidity, and theoretically retain the ability to inspect the post-ablative cavity. However they have disadvantages in that they demand increased patient compliance and commonly commit to interim obturator changes under general anaesthesia in the immediate post-operative phase. If extensive resections are necessary, facial moulage and photographs may assist the prosthetic technician.

Surgical technique

Access to the maxilla may be trans-oral, trans-cutaneous or extended. The trans-oral route can be supplemented with a mid-facial degloving procedure. The trans-cutaneous 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, subcilary 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 pterygopalatine 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.

4.2.1.3. Craniofacial Resection

Approaches

Type 1 craniofacial or trans orbital 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 duct, 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. The 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. The 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 intra cranial 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 radiotherapy 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 contra indications to surgery. With slower growing tumours quite significant intra

cranial 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 contra indication to any surgical resection.

Results

Results from combined surgery and radiotherapy 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.

SCC:	Overall five year survival is in the region of 30–50%.
Adenocarcinoma:	A five year survival is of the order of 45–60%.
Olfactory neuroblastoma:	A five year survival rate of 75% is attainable.

4.2.2. Radiation therapy

4.2.2.1. Role of Radiotherapy

Sino-nasal tumours are often advanced at presentation, invading adjacent structures and lie in close proximity to many organs at risk of damage from radiation (lens, retina, optic nerve and chiasm, pituitary gland). This makes irradiation to a radical dose difficult. 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 radiotherapy (RT), although some protocols have used chemotherapy.

Following surgery that involves a dural repair a longer interval before radiotherapy may be preferred to allow healing. The sequence of surgery and radiotherapy remains open to debate, with no significant differences in outcome found. Pre-operative chemoradiotherapy 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. 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 however not yet available.

Dose escalation above conventional dose levels are 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. Sub-volumes may also be potentially

treated using protons as a boost to residual tumour masses within a larger photon field as mixed plans.

4.2.2.2. Radiation toxicity

Doses delivered with conventional radiotherapy are of the order of 60-70Gy 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. Care must be taken to avoid a dry eye, caused by radiation injury from quite modest doses to the lacrimal gland (30Gy), as optic pain, perforation and even enucleation may ensue.

Brain radio-necrosis is a potentially devastating complication of radiotherapy and the risk depends on total dose, dose per fraction, overall treatment time and volume, with tolerance for partial volume irradiation set at 60Gy. 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 60-70Gy/30-35# over 6 to 7 weeks for squamous cell carcinoma, adenocarcinoma, undifferentiated carcinoma and olfactory neuroblastoma. Doses for lymphoma are ~40-50Gy/20-25# over 4-5 weeks. Accelerated, hyper and hypo-fractionated regimens remain investigational.

Recommendations

- The most common management approach is surgery followed by post-operative radiotherapy ideally within 6 weeks (Grade C)
- Radiation is given first if a response to radiation may lead to organ preservation (Grade C)
- Radiotherapy should be delivered within an accredited department using megavoltage photons from a linear accelerator (typical energies 4-6MV) as an unbroken course (Grade B)
- 3D conformal radiotherapy is the standard technique but Intensity Modulated Radiotherapy can improve target coverage, allow for dose escalation and facilitate organ sparing to reduce toxicity (Grade D)

4.2.3. Chemotherapy

Consensus statements are difficult due to the lack of adequately powered, randomised evidence. Small scale observational studies have reported on topical and intra-arterial chemotherapy but are not recommended. Neoadjuvant systemic chemotherapy, usually cisplatin based, in the phase II setting produces a response in about 2/3rd of patients and has been used prior to surgery or chemoradiation. Concomitant chemotherapy using various regimes have suggested improved disease free and overall survival at 5 years to ~70% and ~67% respectively. In this setting the chemotherapy agent, usually cisplatin, is acting as a radiation sensitiser.

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 squamous cell carcinoma there is no randomised evidence in favour of the use of concomitant chemo-radiation. 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 squamous cell carcinoma sites. Molecular targeted treatments are under investigation but none have proven benefit to date.

Recommendations

Chemotherapy may be given in the following settings:-

- as part of triple therapy e.g. embryonal rhabdomyosarcoma (Grade B)
- in concurrent combination with radiation in locally advanced disease e.g. squamous cell carcinoma of maxilla (Grade D)
- for palliation e.g. poorly differentiated squamous cell carcinoma with disseminated disease (Grade B)

4.2.4. Palliation

Some patients present with advanced disease where radical treatment is not appropriate. Surgery, radiotherapy and chemotherapy all have a potential role in palliation.

Palliative radiotherapy 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 50Gy in 20# over 4 weeks, 27Gy in 6# over 3 weeks and 36-39Gy in 12-13# over 2 ½ weeks

If patient has a localised disease recurrence then retreatment with IMRT or the cyberknife may be considered especially if there has been a long disease free interval.

4.2.5. Follow up

Follow up is needed for detection of recurrence and to manage surgical sequelae (nasal crusting, epiphora etc). Follow up should be extended as some tumours can recur many years after treatment and should include careful examination of the cavity with the endoscope and MR scans.

4.3. 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 (~2% and 7%, respectively).

Key Points

- Endoscopy and imaging (CT and MRI) 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/dural reconstruction is a necessity before undertaking endoscopic resections.
- Patients should be discussed at a skull base MDT meeting supported by all the necessary expertise. A multidisciplinary approach is paramount. The majority of patients will require adjuvant radiotherapy. Likewise many patients require either an immediate prosthesis or staged dental or orbital rehabilitation with osseo-integrated implants.
- Neurosurgical support, and neuronavigation should be routinely available in centres undertaking this surgery.
- Diligent tumour surveillance with nasal endoscopy and interval MRI scans is a necessity following treatment of sinonasal malignancy.

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Chapter 24
Lateral Skull Base Cancer

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1. INTRODUCTION

Primary cancers of the temporal bone and lateral skull base are comparatively rare, accounting for 0.2% 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 temporal bone. 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 1.

Table 1. Entities that come under the category of lateral skull base cancer

Site	Main Pathologies
Advanced skin cancer (conchal bowl/ pinna/peri-auricular skin)	Squamous cell carcinoma Basal cell carcinoma Melanoma
Advanced parotid cancers (involving ear/temporal bone)	Salivary gland malignant neoplasms (generally high grade), including metastatic squamous cell carcinoma from skin to intra-parotid lymph nodes
Infratemporal fossa Temporo-mandibular joint	Sarcomas (e.g. chondrosarcomas, rhabdosarcoma, osteosarcoma)
External auditory meatus/ Middle ear	Squamous cell carcinoma (80%) Basal cell carcinoma Skin adnexal cancers

2. 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 more than one of: chronic otalgia, bloody otorrhoea, bleeding, mass, facial swelling or palsy. Some patients may have a long history of chronic middle or external ear infection, which can be a predisposing factor.

Skin cancers present as visible or itchy skin/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 temporo-mandibular joint pain).

3. ASSESSMENT AND STAGING

3.1. Clinical examination

Confirmation of diagnosis is mandatory before treatment and is gained by biopsy of the pinna, skin, external auditory meatus or middle ear. 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 diagnosis is myriad but care must be taken to exclude pseudotumoral skull base osteomyelitis of the temporal bone (also called necrotising otitis externa) TB and inflammatory diseases such as Wegener's granulomatosis.

3.2. Imaging considerations

In most cases, both CT and MR should be used. CT (fine cut, high resolution) is essential for EAC erosion, extent of middle ear and mastoid involvement, spread into jugular bulb, carotid canal, tegmen, temporo-mandibular joint (TMJ), parotid and beyond. It can also stage the neck. MR 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 (for squamous cell carcinomas, SCC) or whole body may be required (sarcomas, melanoma). 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, a temporary balloon occlusion test can be performed. If successful, permanent pre-operative occlusion via coils can be performed (ideally 2 weeks pre-operatively).

3.3. Audiology

Pure tone audiogram of both ears should be performed pre-operatively.

3.4. Pre-treatment staging

There is no UICC or AJCC staging system for cancers of the temporal bone or lateral skull base. However, many use the revised Pittsburgh staging system (table 2). Standard UICC staging is used for neck and distant metastases.

Table 2. Modified Pittsburgh Staging System

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 (<0.5cm) 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.

Recommendations

- All patients with more than one of: chronic otalgia, bloody otorrhoea, bleeding, mass, facial swelling or palsy should be biopsied (Grade D)
- MR and CT imaging should be performed (Grade D)
- Patients should undergo audiological assessment (Grade D)
- Carotid angiography is recommended in select patients (Grade D)
- The modified Pittsburgh T-staging system is recommended (Grade D)

3.5. Treatment planning/prognosis

There should be a specific multidisciplinary team 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 temporal bone (ME/EAM) and advanced parotid cancers.

4. CANCERS ARISING IN THE TEMPORAL BONE

4.1. General principles

For cancer arising in the temporal bone, the most favourable survival rates are achieved with an en bloc extended temporal bone resection and post-operative radiotherapy. The influence of middle ear involvement on prognosis is critical. T1 and T2 lesions lateral to the tympanic membrane have cure rates between 80–100% with true enbloc resections without breach of the tumour. T3 and T4 five-year survival results vary between 35–50%. Equally critical for prognosis is a histologically-proven complete microscopic resection.

Extension superiorly through the tegmen leads to dural and cerebral involvement. Dural involvement is an adverse prognostic indicator, but around 1/3 of such patients are curable with the appropriate surgery. Cerebral involvement rarely confers any chance of cure.

Resection of the intrapetrous 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 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.

4.2. Temporal bone surgery

4.2.1. Lateral temporal bone resection (LTBR)

This procedure should be regarded as the minimum oncological operation for T1 and T2 lesions.

Essential elements of LTBR are: (1) excision lateral to facial nerve; (2) conchal bowl resection; (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.

4.2.2. Extended temporal bone resection (ETBR)

This procedure is required for more extensive tumours involving the middle ear.

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; (7) total parotidectomy.

Additional options include: Craniectomy (squamous temporal bone; sphenoid wing, posterior fossa); mandibulectomy; parapharyngeal/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 (Grade D)

4.3. Resection of other structures in temporal bone surgery

4.3.1. Parotid gland

When performing temporal bone resections for temporal bone 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. For advanced T3/4 temporal bone SCC's, total parotidectomy should be carried out, which also facilitates access to the parapharyngeal space, infratemporal fossa and masticator space. For BCC's without evidence of direct invasion into or near the parotid gland, parotidectomy can be omitted.

4.3.2. Temporo-mandibular joint and mandible

The standard anterior bony cut in a lateral temporal bone 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.

5. TEMPORAL BONE RESECTION IN PAROTID CANCERS

Almost all parotid cancers abutting the temporal bone are easier to remove if an inferior temporal bone 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. For parotid tumours with EAM or temporal bone involvement, at least a lateral temporal bone resection will be required.

6. 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 has totally encased by tumour, bearing in mind the aim 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, with the

exception of oculoplastic interventions, the best time to perform these interventions is at the time of tumour resection, as virtually every patient in this group will go on to have post-operative radiotherapy.

A cable graft from middle ear 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 antero-lateral thigh free flap).

Otherwise, static procedures can be employed, using temporalis myoplasty (Labbé) or sling or fascia lata for oral commissure/cheek suspension.

Recommendation

- Facial nerve rehabilitation should be initiated at primary surgery (Grade D)

7. RECONSTRUCTION

The aims of reconstruction of lateral skull base defects can be considered hierarchically:

1. Protection for the brain when the dura mater is breached
2. Skin defect
3. Auricular defect
4. Tissue volume defect and mandible defect
5. Functional defect i.e. 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.

For smaller skin defects without much volume loss, options include radial forearm freeflap, cervicofacial rotation flap and temporalis flap. These can be used to reconstruct small skin/auricle defects with modest volume loss.

For most defects after temporal bone resection, the antero-lateral 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-epithelisation if the auricle is not resected). 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 nerve of the thigh 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 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 flap is sub-optimal 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 flap can restore a large mandibular and lateral skull defect.

Recommendation

- Antero-lateral thigh free flap is the workhorse flap for lateral skull base defect reconstruction (Grade D)

8. NECK DISSECTION

Up to 20% 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. The same applies to advanced parotid carcinomas with temporal bone involvement.

Recommendation

- For patients undergoing surgery for SCC, at least a superficial parotidectomy and selective neck dissection should be carried out (Grade D)

9. RADIATION THERAPY

9.1. Post-operative radiotherapy

Most T3 and T4 SCC's will require post-operative radiotherapy, as will advanced parotid cancers requiring temporal bone surgery. T1 and T2 SCC's 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 radiotherapy 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.

IMRT may well reduce dose to the ipsilateral cochlea (if this is separate from the tumour volume) and oral cavity. Chronic otomastoiditis and temporal bone necrosis following radiotherapy 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 60Gy in 30 fractions for moderate risk and 66Gy 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 60Gy.

9.2. Primary radiotherapy

When primary surgery is not considered possible, or too morbid, definitive radiotherapy may be used, with overall cure rates of just under half of patients overall. Clinical target volume is based on staging imaging, preferably with both CT and 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:66Gy 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; however ototoxicity is enhanced compared with radiotherapy alone and brain toxicity is also likely to be increased. A more attractive strategy is to use an EFGR targeting agent such as Cetuximab which would not be expected to enhance CNS toxicity.

10. 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, subtemporal pre-auricular, orbito-zygomatic and trans-temporal bone (Fisch) approaches.

11. 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 crico-pharyngeal myotomy.

Ipsilateral total or total conductive hearing deficit is an inevitable outcome of temporal bone resection. Pre-operative audiological assessment of the contralateral ear will identify patients with a pre-existing deficit. This may be corrected or improved with appropriate aiding in either the pre or post-operative period. Total conductive hearing loss can be rehabilitated through an osseo-integrated bone anchored hearing aid (BAHA). Total hearing loss can be rehabilitated through either BAHA or a 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 serves should be considered.

12. 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 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 radiotherapy has previously been given and there is a reasonable interval (more than 12 months), then re-irradiation is sometimes beneficial.

Key Points

- Cancer of the lateral skull base is rare and constitutes a heterogeneous group of cancers and sites of origin.
- Late diagnosis is not uncommon.
- 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 T1/2 cancers are cured.
- The minimum operation for a temporal bone cancer should be a lateral temporal bone resection.
- 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 antero-lateral thigh free flap is the workhouse for reconstruction.

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Chapter 25
Non-Melanoma Skin Cancer

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1. INTRODUCTION

The incidence of all types of skin cancer is increasing. The non-melanoma skin cancers (NMSC) are mostly basal cell carcinoma (BCC), the commonest human cancer in Caucasians, and cutaneous squamous cell carcinoma (cSCC). Over 80% 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 RCTs 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 (NHS) is determined by NICE guidance. 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 locally metastatic cSCC. SCC of the lip is dealt with in Chapter 19. The reader is advised to access current Guidelines referenced in this document for further information on the management of NMSC.

2. 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 continue to do so until 2040. NMSC is more common in men, and with increasing age.The major predisposing factor for the development of NMSC is chronic sunshine exposure, particularly in childhood. Other common factors include fair skin, other foms 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% of post transplant malignancies. Genetic conditions and exposure to sensitising chemicals are rare causes of NMSC as is the occurrence of cSCC in chronic wounds.

3. PRESENTATION AND DIAGNOSIS OF NMSC

3.1. 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. BCC has a number of well described sub-types.

1. Nodular
2. Superficial
3. Cystic
4. Pigmented
5. Morphoeic
6. Micronodular
7. Infiltrative
8. Basosquamous

Subtypes 5-8 are associated with the most tissue invasion and destruction

3.2. Cutaneous squamous cell carcinoma

This entity typically presents as an indurated nodular keratinising or crusted tumour that may ulcerate, or it may present as an ulcer without evidence of keratinisation. cSCC of the nasal vestibule or of the ear canal is often diagnosed late as it can be misdiagnosed for other common conditions.

3.3. Diagnosis

Diagnosis of NMSC is usually clinical, with subsequent histological confirmation following excision. A punch or incisional biopsy may be indicated where the diagnosis is in doubt, particularly if a graft or flap may be required for reconstruction, or in an anatomically complex area such as the nose. A histological diagnosis should also be obtained prior to radiotherapy.

Recommendation

- Diagnosis of NMSC is usually clinical. Biopsy is recommended where the clinical diagnosis is in doubt, or where histological features may influence treatment (Grade B).

4. HIGH RISK FEATURES NMSC

Some clinical and histological features can indicate aggressive disease behaviour.

4.1. High risk features of BCC for recurrence

- Tumour size >2cm
- Tumour site: the central face, around eyes nose lips, and ears

- Poor definition of clinical margins
- Histological subtype: micronodular, morphoeic, infiltrative, basosquamous
- Histological features of aggression: perineural and/or perivascular involvement
- Failure of previous treatment.
- Immunosuppression

Metastatic basal cell carcinoma is exceptionally rare with just over 300 cases in the literature. It occurs in cases of giant neglected BCC.

4.2. High risk features of cSCC for recurrence and metastasis

- Size: > 2cm
- Depth: > 4 mm thickness, Clark level V or beyond
- Site of primary: ear or non-hair-bearing lip, scalp
- Histological features: perineural, lymphatic or vascular invasion: poorly differentiated or undifferentiated tumours
- Failure of previous treatment
- Immunosuppression

There is widely varying malignant behavior of tumours which fall within the diagnosis of primary cSCC. Head and Neck surgeons are more likely to deal with a higher proportion of high risk tumours.

5. STAGING

The AJCC in 2009 updated the previously problematic 2003 staging system for cSCC. BCC and cSCC, are included within the "Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas" chapter. Skin cancers of the eyelid, and Merkel Cell Carcinomas are included elsewhere.

The N staging has been modified to match that of mucosal head and neck cancers (see chapter 29), but does not include the status of the parotid; parotid status has been shown to be of independent prognostic significance.

Table 1. T staging for cutaneous squamous cell carcinoma and other cutaneous carcinomas

Primary tumour (T) cSCC or BCC	
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 with 2 or more high risk features
T2	Tumour more than 2 cm, but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour invades deep extradermal structures (i.e. cartilage, skeletal muscle or bone)

In the clinically N+ neck, further assessment and management is as per the guidelines set out in Chapter 29, with the following additional points for consideration.

- Cross-sectional imaging should include the parotid.
- Clinically enlarged nodes should be examined cytologically/histologically.
- Removal of a node for which FNAC has been non-diagnostic can be carried out via an incision which can be incorporated into a future neck dissection approach. This will enable accurate staging of a patient prior to therapeutic neck dissection.
- Sentinel node biopsy for the detection of metastatic disease in high-risk cSCC is only used within clinical trials.

Recommendation

- In the clinically N0 neck, radiological imaging is not beneficial, and a policy of watchful waiting and patient education can be adopted (Grade B).

6. THE ROLE OF THE MDT

The importance of interdisciplinary working relationships in the management of high risk NMSC is paramount and patients should be treated by members of a Skin Cancer MDT. Patients in the following groups should be discussed in a Skin Cancer MDT as per NICE guidance; input from the Head and Neck Cancer MDT will be appropriate in certain cases.

- All patients with cSCCs or high-risk BCCs that involve the excision margins or are recurrent.
- Patients suitable for Mohs' surgery.
- Immunocompromised patients with skin cancers and patients who have genetic conditions in which predisposition occurs.
- Any patient with metastatic SCC or BCC diagnosed at presentation or on follow-up.
- Patients who may benefit from radiotherapy.
- Patients who may be eligible for entry into clinical trials

7. TREATMENT OF THE PRIMARY LESION

7.1. Surgical excision

7.1.1. BCC

Excision with a predetermined margin is the recommended treatment for the majority of BCCs. Complete excision rates of 85% with a 3mm clinical margin have been reported and of 95 % with a "4-5mm" margin. Prior curettage may improve definition of the tumour margin. The deep margin should include fat.

Morphoeic and large BCCs have a higher risk of sub-clinical tumour extension. In the management of BCCs with a high risk of recurrence, reconstruction must be delayed until histological confirmation of clearance has been confirmed, either by Mohs' micrographic surgery (MMS), or where this is not available, by intraoperative frozen section analysis, or awaiting the results of paraffin section.

Recommendations

- Non-morphoeic BCCs less than 2cm in size should be excised with a margin of 4-5 mm (Grade A).
- Where there is a high risk of recurrence, delayed reconstruction or Mohs' micrographic surgery should be used (Grade A).

7.1.2. cSCC

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 4mm will achieve histological clearance in > 95% of cases. In high risk cSCC, histological clearance should be confirmed, either by MMS, or by intraoperative frozen section analysis, or 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.

Recommendations

- Surgical excision of low risk cSCC with a margin of 4mm is the treatment of choice. (Grade A)
- Delayed reconstruction or Mohs' micrographic technique should be used in high risk cSCC and is best practice (Grade A).

7.1.3. Mohs' micrographic surgery

MMS is a precise technique which combines staged resection with comprehensive histological examination of the surgical margin. It is recommended in recurrent NMSC and those with adverse histological features, especially in anatomically critical sites. It should be noted that some high risk cSCC will show the presence of microscopic in- transit metastases around and discontinuous from the primary tumour, and these will not be dealt with by MMS. Not only does MMS offer superior cure rates (97% 5 year cure rates), but because tissue removal is minimised, there are better cosmetic outcomes. The main problems with this technique include the length of the procedure, the need for special equipment and training, and the relatively high cost. The availability of the procedure in the UK is, at present, limited.

7.2. Destructive techniques

7.2.1. Curettage and cautery

can be used by experienced practitioners for small (< 4mm), well-defined BCC lesions with non-aggressive histology in non-critical sites with a 5-year cure rate of

up to 97%. Curettage and cautery is used in some centres to treat small (less than 1 cm) low risk cSCCs with excellent cure rates, but histological clearance cannot be confirmed. It 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.

7.2.2. Cryosurgery

is used in low risk BCC, but causes scarring, and difficulty in assessing recurrence, and does not result in a tissue diagnosis, or proof of tumour clearance. It is not indicated in cSCC.

7.2.3. Photodynamic therapy

is effective in low risk superficial BCC. It is not recommended for invasive cSCC.

7.2.4. Topical 5% imiquimod

is an immune response modifier which is licensed for, and effective in the treatment of small primary superficial BCC.

7.3. Radiotherapy in primary NMSC

Radiotherapy is an alternative to surgery for primary BCC and cSCC of the head and neck region in cases including

- Elderly or frail patients.
- Where radiotherapy may produce a cosmetic or functional outcome better than surgery.
- Where surgery is not possible, or through patient choice.

Radiotherapy is normally not used in the following circumstances:

- Patient age <50 years due to the risk of second malignancies and poorer cosmetic outcome.
- Sites of previous radiotherapy.
- Cartilage or bone involvement owing to risk of radionecrosis.
- Over the lateral half of the upper eyelid owing to risk of lacrimal gland damage.

BCC 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, for example where there is deep extension or tumour fixation. Fractionation schedules range from a single fraction to more than 30 daily fractions. The dose is usually higher and a larger margin included in the treatment field when treating cSCC than BCC.

Recommendation

- Radiotherapy is an effective therapy for primary BCC and cSCC (Grade A).

7.4. Incomplete margins of excision

Incompletely excised NMSC should be discussed at the MDT. Rates of recurrence of BCC are higher in high risk lesions, and where there is deep margin involvement. Incompletely excised cSCC should be re-excised to reduce the risk of recurrence and metastasis. Where re-excision of NMSC is indicated but not desirable, adjuvant RT will decrease recurrence rates. In closely excised high risk cSCC, such as poorly differentiated tumours or where there is perineural infiltration, the use of adjuvant RT should be discussed at the MDT.

Recommendations

- Re-excision should be carried out of incompletely excised high risk BCC or where there is deep margin involvement (Grade A)
- Incompletely excised cSCC should be re-excised (Grade A)
- Further surgery should be by Mohs micrographic surgery or intra-operative frozen section analysis or paraffin section results awaited to confirm clearance before reconstruction is done (Grade B).

8. THE MANAGEMENT OF REGIONAL METASTATIC CSCC

8.1. Patterns of metastases

The overall metastatic rate of cSCC in a UK population has been reported at around 5%. High risk tumours have much higher rates; up to 33% and 47% where there are adverse histological features such as poor differentiation or perineural infiltration respectively. Tumours thicker than 4mm have a metastatic rate of up to 45%.The presence of metastatic nodal disease is associated with a 35% 5 year survival.

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 considered, in contrast to deep nodal involvement in mucosal head and neck malignancies. SNB studies have shown a high lack of

Figure 1. Patterns of metastasis of cSCC to the external jugular node and the superficial lymphatics.

concordance between the primary skin site and the 1st echelon node. The external jugular node is of particular relevance as it is not included in standard neck dissections for HNSCC.

Over 50% of cSCC occurs on the anterior scalp/forehead and the ears, and the parotid is the site for up to 70% of metastasising cSCC. Where the parotid is involved (P+), there is an increased chance of the neck containing disease, both detectable and occult (10-35%).

In the P+N+ case the incidence of metastases in Level V approaches 30%. 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% of cSCC, and tumours here will metastasise initially commonly to post auricular, occipital or Level V nodes.

8.2. Management of nodal involvement

Surgery is the primary mode of treatment for established nodal involvement and adjuvant radiotherapy improves survival in some high risk cases. The neck 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 be a superficial parotidectomy- deep lobe or facial nerve involvement will require more extensive resection.

Recommendations

- P+ /N0 - resection of involved parotid tissue, combined with a Level I-IV neck dissection, to include the external jugular node (Grade B)
- P+ N+ - resection should include Level V if that level is clinically or radiologically involved (Grade B)
- P0 N+ - with anterior neck disease should be managed with a Level I-IV neck dissection to include the external jugular node (Grade B)
- P0 N+ - where the primary echelon node is posterior- occipital and/or post auricular nodes, dissection of Level V and Levels II to IV should be carried out, with sparing of the Level I nodes and the submandibular salivary gland i.e a posterolateral neck dissection (Grade B)
- Radical surgery - i.e, the sacrifice of structures such as the facial nerve, the internal jugular vein, the accessory nerve, and the sternocleidomastoid muscle are only included in a dissection in the presence of invasion by the malignant process (Grade B)

8.3. Role of radiation in P+/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 extra capsular spread.

9. FOLLOW-UP

Follow up in secondary care may detect both local recurrence and metastasis, and new skin cancers at an earlier stage. Of note, the risk of a second BCC is 44%, and up to 50% of Australian cSCC patients develop a second cSCC within 2 years.

Recommendations

- All patients should receive education in self- examination including written information (Grade D)
- Patients who have had a single completely excised BCC or low risk cSCC can be discharged after a single post-operative visit (Grade B)
- Patients with an excised high risk cSCC should be reviewed annually for 2-5 years. Those with recurrent or multiple BCCs can be offered annual review (Grade B)

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Chapter 26
Head and Neck Melanoma (excluding ocular melanoma)

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A. CUTANEOUS MELANOMA OF THE HEAD AND NECK

1. Introduction

Cutaneous melanoma, previously 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. In the United Kingdom, the number of melanoma cases has doubled over the three decades following 1970. Over that same period the prognosis has 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 resistant to currently available treatments.

2. Aetiology and risk factors

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. The fair skinned individuals who burn easily in the sun, have fair or red hair and have tendency to freckles 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. A number of studies have indicated increased risk of melanoma in pilots and other airline crew members. 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.

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 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 of melanoma have recently been critically evaluated.

Other risk factors include giant pigmented hairy naevi, a large number of banal naevi, a tendency to freckle and more atypical or dysplastic naevi. Around 2% 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% 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.

Recommendations

- Patients who are at moderately increased risk of melanoma should be advised of this and taught how to self-examine. This includes patients with atypical naevi and those with a previous melanoma (Grade B)
- Patients with giant congenital melanocytic naevi are at increased risk of melanoma and require long-term follow-up (Grade B)
- Individuals with a family history of three or more cases of melanoma should be referred to a clinical geneticist or specialised dermatology services for counselling (Grade B)

3. Clinical presentation

Cutaneous melanoma is divided into subtypes on the basis of clinical features and pathology.

3.1. Superficial spreading melanoma

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.

3.2. Nodular melanoma

The second most common type is nodular melanoma. This usually has a shorter presentation and a greater tendency to bleed and/or ulcerate.

3.3. Lentigo maligna melanoma

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 before progressing in some instances to an invasive melanoma.

3.4. Acral lentiginous melanoma

The least common type of melanoma in the UK is the acral lentiginous melanoma. This occurs on sites including the palms, soles and beneath the nails.

3.5. Desmoplastic neurotropic melanoma

Is associated with higher local recurrence than other forms of melanoma. This is thought to be a consequence of its propensity for perineural spread. This variant is predominantly found in the head and neck.

4. Assessment and staging

4.1. Clinical assessment

Suspicious pigmented lesions are best examined in a good light, with or without magnification, and should be assessed using the 7 point checklist (table 1) or the ABCDE system (table 2). The presence of any major feature in the 7 point checklist, or any of the features in the ABCDE system, is an indication for referral. The presence of minor features should increase suspicion. Some melanomas will have no major features.

Table 1. The 7 point checklist lesion system

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

Table 2. The ABCDE lesion system

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

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%. High magnification dermatoscopy is more sensitive than non-dermatoscopic diagnosis when used by those trained and experienced in

the technique. 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.

4.2. 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 2–5mm peripheral margin, including a cuff 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 2–4mm 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

- Diagnostic sensitivity is increased by the use of high magnification dermatoscopy (Grade B)
- Excisional biopsy is recommended for histological diagnosis (Grade B)

4.3 Imaging considerations

Staging investigations for regional lymph node metastases are usually performed and may comprise CT, MRI, and/or ultrasound depending upon local protocols. The use of scans to detect distant metastasis is indicated in patients with high risk melanoma (stage IIIB and IIIC, and stage IIIA with a macroscopic sentinel lymph node). Imaging was previously recommended for stage IIB and IIC disease, but has been shown to have a low incidence of true-positive, and a high incidence of false-positive, findings and should not be routinely performed. Chest and abdominal computed tomography (CT) scanning is used for the evaluation of potential metastatic sites in the lungs, lymph nodes and liver, and in patients with new symptoms, anaemia, elevated lactate dehydrogenase or a chest X-ray abnormality. 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/MRI imaging in patients who have distant metastasis and where surgical resection is being considered.

Recommendations

- Patients with stage I and II melanoma should not routinely be staged by imaging or other methods as the true positive pick-up rate is low and the false-positive rate is high (Grade E)
- Patients with stage IIIB or IIIC melanoma should be imaged by CT of head, chest, abdomen and pelvis prior to surgery (Grade A)
- Patients with stage IV melanoma should be imaged according to clinical need and review by the specialist multidisciplinary team. Lactate dehydrogenase should also be measured (Grade A)

4.4 Staging

The staging of cutaneous melanomas as recommended in the 7th edition of the UICC/AJCC TNM Classification of Malignant Tumours is shown in Table 3

Table 3. TNM staging for cutaneous melanomas

T – Primary tumour	
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour
pTis	in-situ melanoma
pT1a	<1mm, Clark level II 0r III, no ulceration
pT1b	<1mm, Clark Level IV or V, or ulceration
pT2a	>1–2mm, no ulceration
pT2b	>2–4mm, ulceration
pT3a	>2–4mm, no ulceration
pT3b	>2–4mm, ulceration
pT4a	>4mm, no ulceration
pT4b	>4mm, ulceration
N- Regional lymph nodes	
N1	1 node
N1a	microscopic
N1b	macroscopic
N2	2–3 nodes or satellites/in-transit without nodes
N2a	2–3 nodes microscopic
N2b	2–3 nodes macroscopic
N2c	satellites or in-transit without nodes
N3	> or = 4 nodes; matted; satellites/in-transit with nodes

(continued)

M – Distant metastasis			
M1	Distant metastases		
Stage grouping:			
Stage 0	pTis	N0	M0
Stage 1	pT1	N0	M0
Stage 1A	pT1a	N0	M0
Stage 1B	pT1b	N0	M0
	pT2a	N0	M0
Stage IIA	pT2b	N0	M0
	pT3a	N0	M0
Stage IIB	pT3b	N0	M0
	pT4a	N0	M0
Stage IIC	pT4b	N0	M0
Stage III	Any pT	N1, N2, N3	M0
Stage IIIA	pT1a–4a	N1a, 2a	M0
Stage IIIB	pT1a–4a	N1b, 2b, 2c	M0
	pT1b–4b	N1a, 2a,2c	M0
Stage IIIC	pT1b–4b	N1b, 2b	M0
	Any pT	N3	M0
Stage IV	Any pT	Any	M1

5. Management

5.1. Surgery

5.1.1. Primary disease

5.1.1.1.

Wide local excision remains the most effective treatment for primary cutaneous melanoma. The optimal width of excision margins has been contentious. Current treatment guidelines are based on a relatively small number of prospective randomised trials. The current recommended excision margins for cutaneous melanoma in the United Kingdom are as follows:

In situ melanoma (lentigo maligna) : 5 mm peripheral margins
Lesions <1 mm thick: 1 cm excision margins
Lesions 1 mm–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

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.

Recommended excision margins

Breslow thickness	Excision margins	Evidence grade
In situ	5mm	B
<1mm	1cm	A
1–2mm	1–2cm	B
2.1–4mm	2–3cm	A
>4mm	3cm	B

5.1.1.2. Mohs micrographic surgery

Mohs micrographic surgery (MMS) may have a role in the primary treatment of cutaneous melanoma of the head and neck, especially that of the face. 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.

5.1.1.3. 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.

5.1.2. Regional disease

The regional lymph node basin in the 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 preauricular nodes. There may be clinically apparent lymphadenopathy representing metastatic melanoma, or occult metastases in the head and neck nodes.

5.1.2.1 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 fine needle aspiration
3. Ultrasound guided core biopsy
4. Open biopsy

Fine needle aspiration (FNA) is more accurate when performed with ultrasound guidance and this should be subsequently performed if a clinically guided FNA is non-diagnostic. If clinical suspicion remains despite a negative FNA result, a core or open biopsy should be performed. 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 then lymphadenectomy of the involved nodal basin should be performed. A staging CT scan should be performed prior to lymph node dissection, unless this will cause undue delay.

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 then 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 then a concomitant superficial parotidectomy should be considered. Although a comprehensive neck dissection is usually recommended, it is reasonable to perform a selective neck dissection for some melanoma sites that have metastasised to the neck. For example, omitting excision of level Ia and Ib neck nodes for a well lateralised occipital melanoma would be accepted management.

Recommendations

- Nodes clinically suspicious for melanoma should be sampled using fine needle aspiration cytology (FNAC) prior to carrying out formal neck dissection. If FNAC is negative although lymphocytes were seen, a core or open biopsy should be performed if suspicion remains (Grade B)
- Prior to lymph node dissection, staging by CT scan should be carried out other than where this would mean undue delay (Grade B)
- In the presence of cervical nodal disease, a comprehensive neck dissection should be performed (Grade A)

5.1.2.2. Occult lymph nodal disease

The most accurate means of staging the regional lymph nodes in head and neck melanoma is with sentinel node biopsy (SNB). This staging tool has a learning curve and involves the administration of a radiocolloid into the site of the excision biopsy. Preoperative lymphoscintigraphy identifies the approximate location of the sentinel nodes and the intraoperative use of blue dye and a gamma probe aids 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. SNB identification of regional lymph node metastasis should be followed by lymphadenectomy of the at-risk nodal basin.

Whether or not a sentinel node biopsy is performed for staging the regional lymph nodes is a matter for local policy. Sentinel node biopsy provides highly accurate staging information but there is controversy as to whether it improves disease specific survival. Some clinical trials require information on disease stage and a sentinel node biopsy can provide this information. Sentinel node biopsy has replaced elective lymph node dissection in melanoma and there are few indications to perform the latter.

Recommendations

In clinically node-negative patients:
- There is no role for elective lymph node dissection (Grade E)
- Sentinel node biopsy can be considered in stage IB melanoma and upwards in specialist centres (Grade A)

5.1.3. Unknown primary

The patient presenting with regional metastatic melanoma of unknown primary 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. All patients should be staged with CT scans of head, chest, abdomen and pelvis.

A number of reports from single institution series suggest that patients presenting with nodal disease from an unknown primary have a better prognosis than those with a known primary. One published series suggested a survival advantage in patients with stage IV disease from an unknown primary compared with those with a declared primary. Patients presenting with isolated cervical lymph node disease from an occult primary should be presumed to have regional rather than distant metastasis, and treated as for stage III disease with a comprehensive neck dissection.

5.1.4. 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 question to be addressed is what, if any, improvement in survival time may be gained from treatment of metastatic disease?

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 gastrointestinal mucosa yields the best improvement, with a disease free survival in the region of 23 months compared to a median survival of only 12 months if untreated. Patients undergoing surgical resection of late appearing metastatic melanoma to the liver also have improved disease free survival compared to untreated patients.

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 for brain metastases also offers some patients extended survival. Early treatment of spinal cord secondaries can preserve mobility for a limited period. 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 and the c-kit mutation may be helpful. The latter has become a standard predictor of response to imatinib. A high serum lactate dehydrogenase level suggests a large disease burden and a poor result from treatment of metastases.

Aggressive 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 a matter of months. Nevertheless, quite long remittances may be obtained in fit patients with apparently solitary or oligometastatic disease.

5.2. Non-surgical treatment

5.2.1 Primary tumour

There is no established role for primary radiotherapy (instead of surgery) in the management of early stage (Stages Ia, Ib, IIa, IIb, and IIc) malignant melanoma other than in elderly patients with extensive facial lentigo maligna melanoma. 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.

5.2.2 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 radiotherapy in the management of patients with micrometastatic nodal disease (N1a, N2a). These patients are treated with surgery alone (+/- entry in to studies of adjuvant systemic therapies). Recent adjuvant trials in malignant melanoma have included those testing immunotherapies (interferon, IL–2, peptide gp100:209–217(210M), CanvaxinTM) and anti-angiogenic agents, such as bevacizumab (AVAST-M). For patients with macrometastatic nodal disease (N1b, N2b), there is no consensus that radiotherapy is beneficial following surgery but for patients with cervical lymph node disease it is frequently used. There is no currently defined role for chemo-radiation

in this setting. The ongoing Phase III TROG 02-01 study is likely to report in the next 1-2 years and will provide guidance on adjuvant radiotherapy. Future studies involving the addition of targeted agents to adjuvant radiotherapy may follow.

5.2.3 Distant metastases

Patients with established metastatic melanoma are treated with palliative intent and should be referred to specialist melanoma units. For palliative chemotherapy, single agent dacarbazine (DTIC) remains the treatment of choice. Many patients will be recruited into clinical trials of first- and second-line therapies. Palliative radiotherapy is often used in metastatic disease (stage IV). Radiotherapy dose fractionation is non-standard in most of these treatments. Commonly used regimens include 8 Gy single fraction, 20 Gy in 5 fractions, 33 Gy in 6 fractions (alternate days) and a host of local variations in different radiotherapy departments. There is no accepted role for the use of concomitant chemotherapy (although temozolomide has been tested with radiotherapy in cerebral metastases).

B. MUCOSAL MELANOMA (UPPER AERODIGESTIVE TRACT)

1. 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 approximately 1% of all head and neck melanoma in Caucasian patients. The median age of patient presentation is the sixth decade but case reports span the age range.

The most common sites of head and neck mucosal melanoma are the oral cavity and nasal passages. Pharyngeal, laryngeal and oesophageal melanoma are exceedingly rare. No risk factors for the development of this disease have been identified. It is thought that a preceding atypical melanocytic hyperplasia occurs in a significant proportion.

2. 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 predominate. Oral melanoma presents as a pigmented lesion of the oral mucosa in most cases but amelanotic tumours are reported. The majority occur on the hard palate or gum.

3. Assessment and staging

Endoscopic assessment and imaging is necessary as appropriate for the primary site. Reflecting the aggressive nature of this disease, the 7th edition of the UICC/AJCC

TNM Classification of Malignant Tumours recognises no stage I and II mucosal melanomas (table 4)

Table 4. TNM staging for mucosal melanomas

T – Primary tumour			
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	T4a	N1	M0
	T3,T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

5. Management

The prevailing opinion is that localised disease is best managed with primary surgery which aims to achieve clear surgical margins. 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%), regional recurrence, and distant metastasis (25–50%), as well as poor 5-year survival rates (13–48%) 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 postoperative radiotherapy remains unclear. Its use has been reported to improve local control. Short-course, hypofractionated schedules (eg 33 Gy in 6 fractions over 2 weeks, 50 Gy in 20 fractions) are frequently employed. Adjuvant chemotherapy and biological therapeutic strategies have been employed with encouraging response rates.

Key Points

Cutaneous melanoma

- The incidence of cutaneous melanoma has been increasing rapidly in most parts of the world.
- Incidence rates in the United Kingdom have increased from around 1.7 in 1971 to 8.0 per 100 000 population in 1997 for males, and from 3.1 to 9.7 per 100 000 population for females, a fourfold and a threefold rise, respectively.
- Despite the increased incidence, the prognosis for patients with cutaneous melanoma has improved dramatically.
- A major risk factor is exposure to ultraviolet radiation in susceptible individuals.
- The 7-point lesion checklist system or ABCDE lesion system should be used to clinically assess a suspicious pigmented lesion. It must be remembered, however, that a minority of melanomas are non-pigmented.
- The Breslow thickness of a melanoma is the single most important prognostic factor and, therefore, diagnosis should be made by excisional biopsy with a cuff of subdermal fat.
- Patients with stage IIIB or IIIC melanoma should be imaged by CT of head, chest, abdomen and pelvis prior to surgery. Patients with stage I and II disease should not be routinely staged.
- Surgery is the mainstay of treatment for both local and regional disease.
- Wide local excision is recommended for the primary lesion; the excision margin depends on the Breslow thickness.
- In the presence of cervical nodal disease, a comprehensive neck dissection should be performed.
- In clinically node-negative disease, sentinel node biopsy can be considered in stage IB melanoma and upwards in specialist centres. There is no role for elective neck dissection.
- There is no established role for radiotherapy in the management of either local or regional cutaneous melanoma, though it is often used after cervical lymphadenectomy. Palliative radiotherapy is frequently used in stage IV disease.
- Dacarbazine (DTIC) remains the chemotherapeutic agent of choice for palliation in stage IV disease, but this may change in the near future, with newer agents currently showing some promise.

Mucosal melanoma

- Mucosal melanoma is a rare malignancy of the upper aerodigestive tract, accounting for approximately 1% of cases of head and neck melanoma in Caucasian patients.
- The most common sites are the oral cavity and nasal passages.
- No risk factors have been identified.
- Sinonasal mucosal melanoma usually presents as nasal obstruction, discharge, and bleeding.
- Oral cavity mucosal melanoma usually presents as a pigmented lesion, often bleeding.

- Endoscopic assessment and imaging (CT/MRI) is necessary, as appropriate for the primary site.
- Mucosal melanoma is an aggressive disease, and the earliest lesions are classified as stage III.
- Localised disease should be managed by primary surgery which aims to achieve clear surgical margins.
- Rates of local and regional recurrence and metastatic disease are so high, and 5–year survival rates so low, that major surgical resection is seldom justified.
- The role of post-operative radiotherapy remains unclear, though its use has been reported to improve local control.
- There may be a role for adjuvant chemotherapy and biological therapy

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Chapter 27
Salivary Gland Tumours

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1. INTRODUCTION

Salivary gland malignancies are rare and the understanding of this disease is mostly based on clinical series rather than randomised evidence which remains unlikely to emerge for these tumours. Approximately 300 cases are registered each year in England and Wales of which less than 10 occur in children (under 19 years of age). Population-based studies report that annually in a population of one million, 8 to 9 malignant salivary gland tumours can be expected.

Although overall tumours are more common in the parotid, the incidence of malignancy is higher in the submandibular and minor salivary glands. A population based study found the ratio of salivary tumours (all types) between the parotid, submandibular and minor salivary glands was 10:1:1. Salivary tumours are uncommon in children, but a greater proportion (20–30%) is 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 histologic subtype of salivary tumour. The WHO classification has been modified on a number of occasions, the last being in 2005. A list of the more common adenomas and carcinomas is given in Table 1. Each histologic subtype is a unique entity in itself with varying clinical behaviour.

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 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.

2. CLINICAL PRESENTATION

In general salivary tumours 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.

Table 1. WHO classification of salivary gland tumours 2005

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 cribiform cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Squamous cell carcinoma
Undifferentaited 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
Metastasizing 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)

3. 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 tru-cut biopsy). However definitive histology is not usually available until after surgical resection. Diagnosis is therefore based on the clinical presentation and investigations.

3.1. Fine needle aspiration cytology

This is useful for all salivary gland lesions (parotid, submandibular and minor salivary), and has additional value if examined by a cytopathologist experienced in the diagnosis of salivary gland disease. This can distinguish malignant from benign disease in 90% of cases.

3.2. Imaging considerations

Ultrasound is a useful tool as part of initial assessment and provides excellent assessment of the primary tumour as well as cervical lymph node status. It can be combined with FNAC and in experienced operators helps distinguish benign from malignant lesions in about 80% of cases.

Recommendation

- Ultrasound guided FNAC is recommended for all salivary tumours and cytology should be reported by an experienced expert histopathologist (Grade D)

Non-homogenous, muscle infiltration or suspicious regional lymph node appearances on cross-sectional imaging (CT or MRI) are suggestive of malignancy. However its main role is to determine size, position and relationship to adjacent structures. CT imaging is useful in proven malignancy to exclude distant metastases which carry a poor prognosis.

3.3. 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. For minor salivary glands, open biopsy is permissible, but where possible should be undertaken by a dermatological punch.

3.4. Frozen section

Accurate diagnosis is often difficult and false negative rates are significant; hence frozen section should not be relied on except for establishing excision margins.

3.5. Staging

The TNM 7 system staging for salivary gland primary tumour is shown in table 2.

Table 2. T staging for major salivary gland tumours

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤2 cm in greatest dimension without extraparenchymal extension*
T2	Tumor >2 cm but ≤4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor >4 cm and/or tumor having extraparenchymal extension*
T4a	Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Tumor 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.

The staging of metastatic neck nodes for salivary gland cancer is similar to that for other metastatic disease as discussed in chapter 29.

4. MANAGEMENT

4.1. Submandibular gland

4.1.1. Benign tumours

The submandibular gland should be excised in a supracapsular plane. A wide dissection of local tissues is not required.

4.1.2. Malignant tumours

Historical survival rates in submandibular gland cancer are lower than those achieved in parotid or minor salivary gland malignancy. This has been attributed to the absence of a pre-treatment malignant diagnosis and therefore performance of conservative surgery. It is important that if a neoplasm is suspected in the submandibular gland every effort should be made to establish whether it is benign or malignant basis prior to surgery (FNAC, trucut biopsy).

4.1.2.1. 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. 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 2cm margin of apparently healthy tissue. Nerve 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 segmental mandibulectomy.

4.1.2.2. 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 with suspicious MRI appearances should have an elective selective dissection (levels 1 to 3).

The following histological types have higher risk of metastasis: high-grade mucoepidermoid carcinoma, squamous cell carcinoma, carcinoma ex pleomorphic adenoma, and anaplastic cancers. Patients with clinically confirmed neck metastasis (N+) should have a radical or modified radical neck dissection.

4.1.2.3. Primary radiotherapy

Primary radiotherapy may be applicable in inoperable tumours where palliation can be achieved.

4.1.2.4. Post-operative radiotherapy

"The 4cm rule": survival is significantly worse in tumours >4cm in diameter. With increasing size the risk of occult metastasis is greater and tumour size is a major determinant of distant metastasis. Tumours >4cm in size fall into the class of high risk or complex tumours, and adjuvant radiotherapy is advised.

Post-operative radiotherapy should be commenced within six weeks of surgery. Indications for post-operative radiotherapy are:

- high grade or advanced stage tumours (>4cm) with a high risk of local recurrence
- residual neck disease or microscopic extra-capsular spread from lymph nodes
- following surgery for recurrent disease
- adenoid cystic carcinomas

Recommendation

- Adjuvant radiotherapy following surgery is recommended for all malignant submandibular tumours except in cases of small, low grade tumours that have been completely excised (Grade C)

4.2. Parotid gland

4.2.1. Benign tumours

Traditional management of benign parotid tumours is by dissection of the facial nerve leading to a superficial or total parotidectomy. There is increasing recognition that operations less than the traditional procedures (extracapsular dissection, partial parotidectomy) are as effective in selected patients and have a reduced morbidity although a 'lumpectomy' procedure should not be done due to high recurrence rates. Tumour spillage carries a small increase in the rate of recurrence over a prolonged period and therefore long term follow-up is recommended in such cases. Adjuvant radiotherapy for such cases should be discussed in an MDT setting.

Recommendations

- For benign parotid tumours complete excision of the tumour should be performed and offers good cure rates (Grade B)
- If intra-operative tumour spillage occurs then the case should be discussed in an MDT setting for consideration of post-operative radiotherapy, although most cases would require close observation only (Grade C)

4.2.2. Malignant tumours

4.2.2.1. Surgical management of the primary tumour

In carcinoma, surgery is the treatment of choice with management tailored to the individual case. A conservative parotidectomy should be performed with preservation of the functioning facial nerve providing there is no tumour invasion. For low grade superficial tumours a superficial parotidectomy 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 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. Resection of an intact nerve has been shown to improve local disease control but will not improve survival. It is unlikely that nerve grafting will compromise outcome and therefore could be considered.

4.2.2.2. 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 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. These 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 (Grade D)

4.2.2.3. Surgical management of the neck metastases

The literature reports rates between 13–39% of pathological neck node metastases in parotid cancer. Neck dissection should be performed in patients with clinical or radiological evidence of nodal disease.

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). In addition, neck dissection provides a histological specimen which provides important prognostic information such as extra capsular 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 (Grade D)

4.2.2.4. 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.

Similar considerations should be applied when considering radiation as in malignant tumours of the submandibular gland and in any patient in whom the facial nerve is being preserved despite close proximity of tumour. It is appropriate for large tumours (>4cm), recurrent disease, patients with incomplete or close margins, perineural invasion, extension beyond the gland, nodal disease, in metastatic disease and is increasingly the norm following treatment of adenoid cystic carcinoma and high grade tumours.

Recommendation

- Adjuvant radiotherapy should be considered in high grade or large tumours or in cases where there is incomplete /close resection margin (Grade C)

4.2.3. Recurrent parotid gland tumours

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 any 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 radiotherapy for palliation.

4.3. Minor salivary glands

The natural history of intra-oral minor salivary gland tumours is similar to the parotid and submandibular glands. Minor salivary gland malignancies are staged according to their anatomical location (e.g., oral cavity, larynx), similar to the system for mucosal squamous cell carcinomas. 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.

4.3.1. 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.

4.3.2. Malignant tumours

4.3.2.1. Surgical management of the primary tumour

Most cases are treated in a similar way to squamous cell carcinoma, with en-bloc resection with depth of excision compatible to treatment of squamous cell carcinoma to ensure adequate resection margins. Significant defects are repaired as appropriate.

4.3.2.2. 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, carcinoma in pleomorphic adenoma, squamous cell carcinoma, high-grade mucoepidermoid and undifferentiated carcinoma.

4.3.2.3. Radiotherapy

The following factors are indications for post operative radiotherapy:

- microscopic residual disease
- adenoid cystic tumours
- aggressive undifferentiated tumours
- "4cm rule"

> ***Recommendation***
>
> - It is important to base treatment on clinical factors in addition to histology and grade e.g., stage, pre-operative facial weakness, positive margins, perineural invasion and extra-capsular spread (Grade D)

5. NATURAL HISTORY OF COMMON TUMOURS

5.1. Acinic cell carcinomas

These tumours account for about 3% of parotid tumours, where they occur most commonly. Peak incidence is in the 5th decade. Other features include:

- Demonstrate a variable histological pattern and can be multifocal in origin and occasionally bilateral. Usually considered a low grade malignancy.
- Determinate survival rates of 90% at five years and 55% at 20 years
- Lymph node metastases occur in approximately 10% of cases
- Total parotidectomy with preservation of uninvolved nerves recommended. Elective neck dissection usually not indicated. Not particularly radiosensitive.

5.2. 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 squamous cell carcinoma. The histological grade correlates with several prognostic factors including presence of lymphatic spread and survival.

- Most common major salivary gland tumour (4%–9%) with over 90% occurring in the parotid but overall more frequent in minor salivary glands
- Commonest 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 shows correlates with prognosis; although so called 'low-grade' tumours can on occasion be aggressive. Five year survival varies between 86% for low-grade to 22% for high-grade tumours. Perineural and lymphovascular invasion not uncommon in these tumours.
- 40% incidence of lymph node metastases in intermediate and high-grade tumours
- Low-grade tumours require local resection with adjuvant radiotherapy 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 (Grade C)

5.3. Adenoid cystic carcinoma

This is the most common salivary gland malignancy (20–25% of all malignant salivary gland neoplasms) and occurs at mucosal sites more frequently than in major salivary glands.

- 2% to 6% of parotid and approximately 15% of submandibular tumours
- Slow, pervasive growth and a high incidence of perineural infiltration
- 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.
- High rate of morbidity due to recurrence both locally and at distant sites particularly lung. Note 20% with pulmonary metastases survive more than 5 years
- Slow growth rate make five year survival unreliable. Spiro reports 5-year survival of 60% and 20year survival of 20%
- Treat by widest local excision with preservation of uninvolved major nerves. Adjuvant postoperative radiotherapy indicated.

5.4. Adenocarcinoma

This uncommon tumour is most frequently (90%) found in the parotid gland.

- Equivalent gender incidence and affects any age and is one of the commoner tumours seen in children
- Histologic appearance varies between low-grade well-differentiated papillary or mucinous patterns to high-grade, undifferentiated lesions

- The incidence of distant metastases is 40% for high-grade tumours and is directly related to survival rates -75% 5-year survival for low-grade tumours and 19% 5-year survival for high-grade tumours.
- Treatment is by wide local resection with elective neck dissection and adjuvant radiotherapy for clinically high-grade tumours.

5.5. Malignant mixed tumour (Carcinoma-ex pleomorphic adenoma)

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 radiotherapy. The remainder are probably not a homogenous group of tumours and may occur de novo rather than following a malignant generation of pleomorphic adenoma. The frequency varies between 2 and 5%.

- As a family these tumours tend to be high-grade with a high incidence of haematogenous metastasis in 5, 10 and 15 years with cure rates of 40%, 24% and 19% respectively.
- Metastatic disease presents initially as a discrete lump in the parotid. However, unlike salivary neoplasms squamous cell carcinoma has a propensity for early extra-capsular extension. In the parotid this threatens local structures and prompt surgical intervention should be the rule.
- Radical resection with adjuvant radiotherapy offer the best form of management

5.6. 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 metastasises from a skin cancer.

- Male to female incidence ratio 2 to 1
- Tends to occur in the elderly (7th decade)
- Has very bad prognosis and should be treated as high-grade mucoepidermoid lesions.

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Chapter 28
Thyroid cancer

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A. DIFFERENTIATED THYROID CANCER

1. Introduction

Thyroid nodules are common, the incidence of palpable nodules in women being approximately 5% and 1% in men. Use of ultrasound scanning (USS) substantially increases their detection in the general population to approximately 50–70%. Thyroid cancer remains rare, but evidence suggests an increasing incidence, although survival rates remain static.

Long term prognosis for differentiated thyroid cancer (DTC) is excellent, with survival rates for adults being 80–90% at 10 year follow up. 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.

In recent years, 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 (2007) by the British Thyroid Association and Royal College of Physicians, and the Revised American Thyroid Association Guidelines (2009). These documents are extensive and cover every aspect of care in great detail. 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 of DTC are set out in Table 1.

Table 1. Goals of treatment for differentiated thyroid cancer

• 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

2. Clinical presentation

In all cases, a detailed history, documenting in notes family history and previous exposure to ionising radiation is warranted.

2.1. Symptom needing immediate referral

Stridor associated with thyroid nodule/goitre.

2.2. Symptoms needing urgent GP referral (2 week wait rule)

These include hoarseness/voice changes associated with a nodule/goitre, thyroid nodule in a child, cervical lymphadenopathy associated with a thyroid nodule and/or rapidly enlarging painless thyroid mass over a period of weeks.

3. Assessment and staging

3.1. Recommended clinical investigations

These include:

- Clinical evaluation of thyroid, cervical and supraclavicular nodes
- Thyroid stimulating hormone (TSH)
- Fine needle aspiration cytology (FNAC) with or without USS guidance.
- Documented cytological score (Table 2)
- Core biopsy with or without USS guidance in suspected cases of lymphoma

Table 2. Thyroid FNAC diagnostic categories

Score	THY1	THY2	THY3 (Subdivided)	THY4	THY5
Diagnosis	A and C Non-diagnostic	A and C Non-neoplastic Consistent with colloid nodule/ thyroiditis	THY3F Follicular lesion Suspected follicular neoplasm THY3A Atypia present	Suspicious but not diagnostic of thyroid cancer (papillary, medullary, anaplastic, lymphoma)	Diagnostic of thyroid cancer (papillary, medullary, anaplastic, lymphoma)
Action	Repeat FNA Consider USS guidance Describe as cyst if no epithelial cells present	Repeat FNA if no surgery planned.	Discuss at multi-disciplinary team meeting (MDT) Diagnostic lobectomy usually recommended Consider total thyroidectomy in large lesions >4cm where incidence of malignancy is higher.	Discuss at MDT Diagnostic Lobectomy +/- on table frozen section to proceed to total thyroidectomy +/- central node clearance in high risk patients	Discuss at MDT Radiotherapy/ chemotherapy or surgery where indicated Appropriate further investigations for staging where indicated Total thyroidectomy +/- central node clearance in appropriate high risk patients

- Calcitonin only in suspected cases of MTC (routine use not recommended)
- Serum thyroglobulin (Tg) is not recommended
- Pre-operative vocal cord check

3.2. Radiological investigations

Pathological studies suggest that microscopic lymph node metastases are very common in papillary thyroid cancer, macroscopic disease less so (20–50%). Pre-operative USS is effective in identifying suspicious nodes in approximately 20–30% of patients with papillary thyroid cancer and may alter the surgical approach. FNA of suspicious nodes is recommended. Thyroglobulin estimation of lymph node cystic fluid may be of use in the absence of sufficient diagnostic material.

Recommendations

- USS guided FNAC for all patients with nodules over 10 mm should be done whenever possible (Grade B)
- If nodule below 10 mm USS guided FNA not recommended unless clinically suspicious nodes on USS are also present (Grade B)
- USS assessment is potentially of value in assessing co-existing dominant nodules (Grade B)
- Cytological analysis and categorization should be reported according to the current British Thyroid Association guidance (Grade B)
- USS assessment of cervical nodes should be done in FNA proven cancer (Grade B)
- MRI or CT (*without the use of iodinated contrast*) should be done in suspected cases of retrosternal extension, fixed tumours (local invasion +/- vocal cord paralysis) or when haemoptysis reported (Grade B)
- FDG-PET imaging is not recommended for routine evaluation

3.3. Staging

The TNM staging system (7th edition) for differentiated thyroid cancer is as follows:

T stage

T1	≤2 cm in greatest dimension limited to the thyroid.
	T1a ≤1 cm, limited to the thyroid.
	T1b >1 cm but ≤2 cm in greatest dimension, limited to the thyroid.
T2	>2 cm but ≤4 cm in greatest dimension, limited to the thyroid.
T3	>4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues).
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
T4b	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels.
T4a	Intrathyroidal anaplastic carcinoma
T4b	Anaplastic carcinoma with gross extrathyroid extension.

N stage

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, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII).

M stage

M0	No distant metastasis..
M1	Distant metastasis

Group staging

	Under 45 years	**45 years and older**
Stage I	Any T, any N, M0	pT1, N0, M0
Stage II	Any T, any N, M1	pT2, N0, M0
		pT3, N0, M0
Stage III		pT4, N0, M0
		Any pT, N1, M0
Stage IV		Any pT, any N, M1

Undifferentiated or anaplastic carcinomas are all Stage IV

Recommendation

- All patients should be staged by clinical and pathological TNM staging (Grade B)

4. Management

Surgeons performing operations for confirmed or suspected thyroid cancer should be core members of the thyroid cancer MDT. Complex surgery and lymph node surgery should be undertaken by identified/nominated surgeons in the cancer centre with specific training in and experience of thyroid oncology. Table 3 lists patients deemed to be '*High Risk*' and these patients should be considered for level VI lymph node dissection (pre-tracheal and para-tracheal nodes from the hyoid bone superiorly to the level of the sternal notch inferiorly). Lobectomy should include the isthmus in all patients. Sub-total thyroidectomy is not an appropriate operation for thyroid cancer.

Frozen section histology may be of use in confirming suspected papillary thyroid cancer (THY4) but is not recommended for use in cases of suspected follicular thyroid cancer (THY3).

Table 3. High Risk DTC Patients

- Male
- Age >45 yrs
- Tumour >4cm
- Extra-capsular disease
- Extra-thyroidal disease

Recommendations

- The management of DTC and MTC should be the responsibility of a specialist multidisciplinary team, the membership of which should be appointed by the regional cancer network (Grade C)
- The multidisciplinary team should comprise of surgeon, endocrinologist, oncologist or nuclear physician with support from pathologist, medical physicist, radiologist and clinical nurse specialist all with expertise and interest in the management of thyroid cancers (Grade C)

4.1. Surgical treatment

4.1.1. Initial surgery for known papillary thyroid cancer

A strategy for the surgical treatment of papillary thyroid cancer is detailed in Table 4. All cases should be discussed pre-operatively at the thyroid cancer MDT

Table 4. Initial surgery for known papillary thyroid cancer

Recommendation	**Tumour <1cm**	**Tumours >1cm**	**T3 and T4 Tumours +N1 level VI Nodes**
	With no other clinical features such as extra-thyroidal spread, nodal involvement, etc	Papillary cancer diagnosed following thyroid lobectomy Multifocal disease Thyroid radiation in childhood Familial disease (1st degree)	Treat all above tumours as high risk
Thyroid lobectomy	Yes	No	No
Total thyroidectomy	Discuss at MDT	Completion total	Yes
Prophylactic level VI nodal dissection	No	In high risk patients	Yes
Therapeutic level VI nodal dissection (clinically involved)	Yes	Yes	Yes

4.1.2. 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 (THY3). Frozen section histology is not recommended. An operative strategy for surgical treatment of follicular cancer is outlined in Table 5.

Low risk patients with a diagnosis of minimally invasive tumour, without vascular invasion, <2 cm following lobectomy may be managed by lobectomy and TSH suppression alone in most cases. No clear recommendations currently exist for low risk minimally invasive tumours of 2–4 cm and these cases should be discussed individually at MDT. In some cases lobectomy and TSH suppression alone may be sufficient.

Hurthle cell cancers (follicular oncocytic) tend to be more aggressive tumours and should be treated by total (completion) thyroidectomy (see Table 5).

Table 5. Initial surgery for follicular thyroid cancer

	Clinical Details	
Recommendation	**High Risk Patient** > 45 years Tumour > 4 cm Extracapsular invasion Extrathyroidal disease Hurthle cell tumours	**Low Risk Patient** Female < 45 years
Thyroid lobectomy	No	Yes
Total thyroidectomy	Yes	No
Level VI nodal dissection	Only where clinically involved nodes present	No

4.1.3. Management of lymph nodes in DTC

Therapeutic level VI nodal dissection is recommended when the presence of lymph node metastasis is confirmed by FNA / core or open biopsy/frozen section. Prophylactic level VI lymph node dissection is advised in high risk patients but is associated with a higher incidence of recurrent laryngeal nerve damage and long term permanent hypoparathyroidism, informed consent should reflect this. Prophylactic level VI nodal dissection is not recommended in low risk, small papillary and most follicular cancers.

Clinically involved lateral cervical lymph nodes should be managed by selective neck dissection (levels II-V). Isolated lymph node excision “berry picking” is not advocated. Involvement of level I or level VII nodes is rare in DTC and should only be dissected if involved. Prophylactic lateral neck compartment dissection for node negative (clinically/radiologically N0) patients is not recommended in DTC.

4.1.4 Completion thyroidectomy

Completion thyroidectomy is not needed in low risk, small (<1cm), unifocal, intrathyroidal, clinically node negative tumours.

4.1.5. Locally advanced disease

Where possible, locally advanced disease should be resected. In an attempt to perform curative resection unilateral RLN sacrifice may be necessary. Where both nerves are involved then residual tumour may be left to protect the nerve(s) and residual disease treated with external beam radiation and or radioiodine. Extensive resection of trachea, larynx and oesophagus should only be considered if potentially curative. Where disease is unresectable, radiotherapy and radioiodine should be considered.

Recommendations

- Surgeons performing surgery for thyroid cancer should have training and expertise in the management of thyroid cancer and be a member of the MDT (Grade C)
- The aims of the surgical procedure should be the removal of all tumour, elimination of clinical, radiological or biochemical evidence of recurrence and the minimisation of unwanted effects of the treatment (Grade B)
- Patients with a PTC more that 1 cm in diameter and high risk FTC should undergo total or near-total thyroidectomy (Grade B)
- Patients with low risk FTC or PTC less than 1 cm in diameter may be treated with thyroid lobectomy alone. (Grade B)
- Prophylactic central compartment neck dissection should be done for all tumours over 1cm in diameter in high risk patients or T2 to T4 tumours (Grade B)

4.2. Post-operative management

After total/near total thyroidectomy patients should be commenced on T3 (usually 20micrograms thrice daily). Calcium levels should be routinely checked within 24 hours and hypocalcaemia treated appropriately. Thyroglobulin (Tg) levels should be checked no earlier than 6 weeks after the operation.

All patients with DTC should be clinically staged using the TNM Classification (7th edition) and also scored using one of the clinico-pathological 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 clinical nurse specialist and be given written information.

4.3. Radioiodine ablation and external beam radiotherapy in DTC

The 2002 BTA UK Guidelines were in favour of virtually all patients with DTC <10 mm receiving I^{131} ablation. The 2007 BTA Guidelines along with their American counterpart the ATA 2009 Guidelines are less prescriptive. Table 6 outlines the current recommendations with regards to I^{131} ablation.

Table 6. Indications for I^{131} ablation post total/near thyroidectomy for DTC

Recommendation	Clinical Details
Definite I^{131} ablation	Tumour >4 cm, distant metastases, extra-thyroidal invasion, >10 involved nodes or >3 nodes with extra-capsular invasion
Probable I^{131} ablation **Consider on individual case merit (MDT)**	Tumour size <1cm where histology is associated with poorer prognosis Tumour size >1cm but <4 cm Multifocal tumours <1cm Lymph nodes not assessed at surgery Less than total thyroidectomy (consider further surgery to remove large remnant)
No I^{131} ablation	Multifocal tumours <1cm Unifocal cancer <1cm (favourable histology, N0 M0) Minimally invasive follicular cancer <2 cm without vascular invasion

Patients should be prepared by performing a pregnancy check where indicated, withdrawing T4 (2–4 weeks) or T3 (2 weeks), taking a thyroglobulin sample and ensuring that TSH is >30 mI U/L prior to I^{131} administration. Where T4 or T3 withdrawal is contraindicated or ineffective then rhTSH may be used.

Post-therapy diagnostic scanning assessing effectiveness of I^{131} therapy may be omitted in low risk patients if TSH stimulated Tg levels are checked along with USS of neck nodes. Otherwise diagnostic whole body scanning (WBS) scanning should always be performed 6 months after I^{131} ablation.

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}.

4.4. Post-treatment follow up

Persistent voice dysfunction should be investigated and referral to a specialised practitioner for assessment and speech therapy sought. The British Association of Endocrine and Thyroid Surgeons (BAETS) currently recommend that all patients undergoing thyroid surgery should have a post-operative vocal cord check.

Patients with long-term hypocalcaemia (hypoparathyroidism) should have their calcium levels regularly monitored either in association with an endocrinologist or their general practitioner.

Long-term suppression of TSH to levels below 0.1mI U/L has been demonstrated to improve outcome in patients with high risk cancers. There is no evidence to support this in low risk patients. TSH suppression may lead to exacerbation of angina and increase the risk of atrial fibrillation and osteoporosis in post-menopausal women.

TSH suppression to below 0.1mI U/L is therefore recommended for all high risk patients whilst maintaining a TSH level at or just below the lower level of normal is appropriate for low risk patients.

4.4.1 Monitoring thyroglobulin (Tg) levels

Thyroglobulin monitoring is most effective following total/near total thyroidectomy and radio-iodine ablation and is an important modality in detecting residual or recurrent disease. Physicians should be aware that thyroglobulin estimations vary according to the assay method, the individual laboratory and the presence of anti-thyroglobulin antibodies (TgAb) and take these considerations into account when evaluating Tg levels in individual patients. The presence of TgAb may result in false negative serum Tg results and such data should be interpreted with caution. Increasing serum concentrations of anti-TgAb may be indicative of recurrent disease. During follow-up stimulated serum Tg levels after rhTSH administration are not comparable to those after thyroid hormone withdrawal, the latter generally tends to elicit a more robust Tg response than rhTSH.

Patient should have their Tg levels checked at 6–12 monthly intervals. Rising Tg levels are highly suspicious of recurrent disease. Tg evaluation is most effective following TSH stimulation, either by withdrawal of T4 or T3 or by direct rhTSH stimulation.

Following total/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 USS of cervical nodes at 1 year 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.

Elevated Tg may be suggestive of recurrent/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, Tg levels should fall. Rising or persistently elevated Tg needs further evaluation.

The use of rhTSH stimulated Tg estimation after I^{131} therapy is an established alternative to thyroid hormone withdrawal and should be considered in most cases. rhTSH is strongly indicated in the following cases: hypopituitarism, functional metastases (suppressing TSH), severe angina, advanced disease (frail patient) and history of psychiatric disturbance from hypothyroidism.

Second generation assays for serum Tg with functional sensitivity 0.05-0.1 mcg/l have recently been introduced. Using highly sensitive Tg assays, a serum Tg <0.1 while on suppressive thyroxine therapy has been shown to a negative predictive value greater than 98% for recurrent or persistent thyroid cancer and in such cases there may be no need for TSH stimulation.

4.4.2. Whole body I^{131} scanning (WBS) and USS

The majority of patients following I^{131} ablation will undergo WBS at 6-9 months after treatment. Low risk patients do not need further WBS and may be assessed as above. Further WBS is only deemed necessary in the presence of persistently raised or rising Tg levels whilst on TSH suppression or in high risk patients where TSH (or rhTSH) stimulated Tg levels rise, strongly suggesting recurrent disease.

Cervical USS to evaluate central and lateral nodes at regular intervals may be of value in high risk patients, and especially in patients where TgAb's interfere with the accuracy of Tg estimation.

Recommendations

- I^{131} ablation or therapy should be carried out only in centres with appropriate facilities (Grade C)
- Serum thyroglobulin and serum TgAb should be checked in all post-operative patients with DTC, but not sooner than 6 weeks after surgery (Grade C)
- Patients should be started on triidothyronine 20 μg tds after surgery and this should be stopped 2 weeks before I^{131} ablation or therapy (Grade C)
- The majority of patients with a tumour more than 1cm in diameter, who have undergone total or near-total thyroidectomy, should have I^{131} ablation or therapy (Grade B)
- A post-ablation scan should be performed 3 to 10 days after I^{131} ablation (Grade B)

4.5. Persistent, recurrent, loco-regional 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}. Early detection and appropriate surgical intervention results in 30–50% of such patients becoming disease free. Residual disease not amenable to resection or resistant to I^{131} therapy is best treated with high dose palliative external beam radiotherapy.

Therapeutic central compartment +/- lateral and /or central nodal clearance should therefore be performed for all persistent/recurrent disease confined to the neck. Impalpable nodes >5–8 mm seen on USS or cross-sectional imaging following I^{131} therapy should be considered for removal. Removing nodes <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 therefore in the selection and discussion of such patients at the MDT.

Distant metastases develop in 5–23% of patients with DTC. Sites not amenable to surgical resection should be treated with I^{131} therapy if iodine avid. 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 <45 years of age), metastases not cured by I^{131} should be treated by radiotherapy. 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 (Grade C)
- Distant metastases and sites not amenable to surgery should be treated with I^{131} therapy (Grade C)

4.6 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}. After 5 years of MDT follow up, low risk patients may be followed up in a nurse led clinic or via a primary care setting with defined parameters for further referral back to the MDT.

Clinical examination and history, thyroglobulin determination, TSH suppression and where necessary calcium monitoring should all be performed. USS as per established protocols may also be undertaken.

Recommendations

- Long term follow up for patients with DTC is recommended (Grade B)
- Follow up should be done with clinical examination, serum TG and TSH suppression (Grade B)

B. MEDULLARY THYROID CANCER (MTC)

1. Introduction

MTC is a rare cancer (approximately 5% 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 percent of MTC cases are familial (MEN 2A, MEN 2B and familial non-MEN FMTC). Genetic screening (*RET* testing) of all patients is mandatory and the assessment and investigation treatment of family members at potential risk requires a multidisciplinary approach within the cancer centre.

2. 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 THY3.

3. Assessment and staging

When MTC is suspected (or proven) patients must undergo the following investigations prior to surgery:

i) Calcitonin and carcino-embryonic antigen (CEA) levels
ii) 24 hour urine estimation of catecholamines and metanephrines to identify or exclude phaeochromocytoma
iii) Serum calcium and parathormone to identify or exclude hyperparathyroidism
iv) CT, MRI or USS of the neck are desirable as they may help guide the extent of surgical resection at initial surgery.
v) *RET* proto-oncogene mutational analysis should be performed after surgery once diagnosis is established

Staging

TNM staging for MTC follows the same criteria than for DTC. The group staging is as follows:

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

Recommendations

- Patients with suspected MTC should be investigated with calcitonin and CEA levels, 24 hour urine estimation, serum calcium and PTH (Grade B)
- Relevant imaging studies are advisable to guide the extend of surgery (Grade C)
- RET proto-oncogene analysis should be performed after surgery (Grade B)

4. Management

4.1. Surgery for MTC

All patients with MTC should undergo:-

i) Total thyroidectomy and central compartment node clearance (level VI). This should be performed even in the presence of disseminated metastases to control local disease
ii) Patients with clinically involved lateral compartment nodes should have a therapeutic lateral neck dissection to eradicate local disease.

iii) All T2–T4 tumours should also undergo bilateral selective neck dissection IIa-Vb (even in absence of clinically palpable disease).
iv) Intra-thoracic disease below the level of the brachiocephalic vein should be resected via sternotomy where feasible.
v) Prophylactic thyroidectomy should be offered to RET positive family members. Timing and extent of surgery is dependant on genotype (codon mutation), the calcitonin level and age at detection of RET positivity.

4.2. Persistent or recurrent MTC

Calcitonin levels are most informative 6 months after initial surgery. It is important to distinguish persistent loco-regional 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} -MIBG, ^{18}FDG-PET, 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 proven MTC should undergo total thyroidectomy and central compartment neck dissection even in the presence of distant metastases (Grade B)
- Patients with N+ neck disease or those with T2–T4 with N0 neck disease should undergo bilateral selective neck dissections (IIa-Vb) (Grade C)
- Prophylactic thyroidectomy should be offered to RET positive family members (Grade B)

4.3. 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.

Chemotherapy has been generally ineffective, but the new tyrosine kinase inhibitors may offer an alternative treatment in alleviating symptoms 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 advisable in controlling local symptoms in patients with inoperable disease (Grade C)
- Chemotherapy with tyrosine kinase inhibitors may help in controlling local symptoms (Grade B)

5. Follow up

Lifelong follow up is recommended for all patients with MTC. Screening should include calcitonin and CEA. TSH suppression is not necessary. Rising calcitonin levels should trigger investigations to identify potentially treatable metastatic disease.

6. New treatments for advanced thyroid cancer

Several new agents including tyrosine kinase inhibitors appear to have efficacy in patients with advanced differentiated and medullary thyroid cancer. Patients who have progressive metastatic disease should be considered for enrolment in clinical trials.

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Chapter 29
Neck Metastases

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1. INTRODUCTION

The presence or absence, level and size of metastatic neck disease is one of the most 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 malignant neck disease. This is primarily due to the paucity of high level evidence to many treatment paradigms, but this trend may be reversing with some randomised controlled trials and systematic reviews published in the last decade and a few more in progress. However, many organisations have generated guidelines following rigorous evidence gathering exercises, suggesting best management practices based on available evidence in many countries. This section discusses the management of neck metastases at initial presentation, both for known and occult primaries, and when there is residual or recurrent neck disease. It outlines major clinical controversies regarding the management of metastatic squamous cell carcinoma.

2. ASSESSMENT AND STAGING

For the purpose of assessment and documentation, the neck is described in six anatomical levels (Table 1). Level VII is relevant for some head and neck tumours and is included in the table for completeness.

2.1. Clinical palpation

On its own, palpation is regarded as inaccurate (sensitivity and specificity 70%–80%) due to factors including inter-operator variability, shape of neck, absence or presence of significant subcutaneous fat and varying size of involved cervical nodes.

2.2. Computed tomographic (CT) and magnetic resonance (MR) scanning

Both of these modalities have similar sensitivity (81%) in detecting metastatic disease, with CT demonstrating better specificity. Co-registered positron emission

Table 1. 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

(*continued*)

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

Legend: S = superior; I = inferior; A = anterior; P = posterior; L = lateral; M = medial; SCM = sternocleidomastoid

tomography-CT scanning (PET-CT) has not shown any distinct advantage in staging the primary site and neck metastases, although 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.

2.3. Ultrasound (US) scanning and US-guided fine needle aspiration cytology (FNAC)

US has been demonstrated to have consistently high sensitivity (87%) in diagnosing metastatic neck disease. US-guided FNAC requires both expertise and experience, and has very high specificity rates (98%) in diagnosis. It should be noted that there are no absolute ultrasound characteristics for differentiating benign from malignant disease.

2.4. Sentinel node biopsy

Although this technique has been demonstrated to have sensitivity rates exceeding 90%, most centres currently use it within clinical trial settings. There is a small but significant false negative rate of 5% due to the skipping of levels in the neck by metastatic disease.

Recommendation

- Computed tomographic or magnetic resonance imaging is mandatory for staging neck disease, with choice of modality dependant on local availability and expertise (Grade B).

2.5. 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 current (7th) edition of the UICC/AJCC cancer staging manual. Table 2 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.

Table 2. TNM 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

3. TREATMENT OPTIONS

3.1. Surgery

Historically the mainstay of surgical management of metastatic neck is 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 (Table 3). 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.

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. There is good evidence for reduced long term morbidity with SND compared to the comprehensive types, namely modified radical neck dissection (MRND) and radical neck dissection (RND). Surgical therapy must be delivered within accredited multidisciplinary teams, by members regularly involved in caring for head and neck cancer patients.

Table 3. 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 (MRND)	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 (SND)	Preservation of one or more levels of lymph nodes.
Extended radical neck dissection (ERND)	Removal of one or more additional lymphatic and/or non-lymphatic structures(s) relative to a radical neck dissection, e.g., level VII, retropharyngeal lymph nodes, hypoglossal nerve

3.2. 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.

RT to the neck requires adequate immobilisation and a 5-point fixation shell is recommended. For 3dimensional conformal RT (3D-CRT), CT scanning in the treatment position provides the anatomical and electron density information required for RT planning. Conventional and 3D-CRT 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 is indicated, where it has been shown to be associated with a reduced risk of late xerostomia.

There is now increasing use of concomitant chemo-radiotherapy (CRT) following publication of level 1 studies, suggesting that use of CRT improves overall and progression free survival in advanced head neck cancer both in the primary and post-operative settings. Altered fractionations regimes have also been shown to offer some advantage over standard fractionation.

Treatment of cervical lymph nodes is either *elective* (in the clinically negative neck) or *therapeutic* (in the clinically positive neck).

4. MANAGEMENT STRATEGIES FOR VARIOUS NECK NODAL STAGES

4.1. Management of the clinically node negative neck (N0)

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

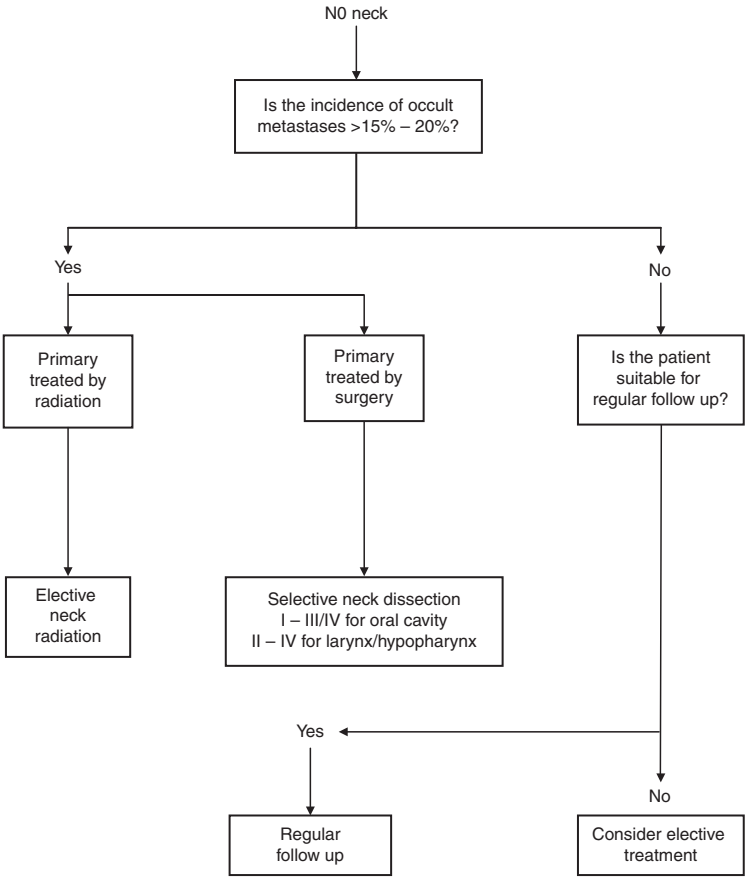

Figure 1: Algorithm for management of the N0 neck

metastases in clinically node negative necks and are used to guide clinicians when deciding whether prophylactic treatment of the neck is appropriate (figure 1).

There is no widely accepted threshold of occult metastatic risk over which prophylactic treatment of the neck is required. A study of risk-benefit analysis made in the 1970s 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%. Given the low morbidity of either available treatment modality, there is support for elective treatment for lesser risk (5% to 15%). Thus, primary sites with greater than 15% to 20% risk of occult metastatic disease in the neck would include all T3 and T4 cancers, some T2 tumours of the supraglottis and hypopharynx, many T2 oral cavity carcinomas and carcinomas of the tongue thicker than 3 mm.

No adequately powered RCTs have compared outcomes following management of the N0 neck with observation versus elective neck dissection. Of the two methodologically sound randomised trials in the literature, one showed an advantage for the group receiving neck dissection. The other with 71 patients showed no difference in disease free survival between the groups, although the observed group

had significantly higher incidence of regional recurrences which were picked up on close surveillance and successfully salvaged. Many retrospective studies and recently, other prospective non-randomized studies, including an evidence-based review, that have looked at the treatment of the N0 neck in oral cavity carcinomas suggested improved outcome when the neck was electively treated. Retrospective studies suggest that salvage rates for patients who recur following an observational policy of the clinically N0 neck is disappointing (30% to 50%). It must be noted that most studies have used clinical palpation, which has poor sensitivity, for detection of disease occurrence during follow up of these patients.

The classical RND has no role to play in elective treatment of the N0 neck. 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. In 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%.

Elective neck irradiation is as effective as elective neck dissection in controlling subclinical regional disease, with control rates reported to be around 90%. 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 radiotherapy compared to surgery. The DAHANCA, EORTC, GORTEC, NCIC and RTOG consensus guidelines, published in 2003, should be followed for delineation of lymph nodal levels in the node negative neck.

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%, 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 become clinically palpable.

Recommendations

- Patients with a clinically N0 neck, with more than 15%–20% risk of occult nodal metastases, should be offered prophylactic treatment of the neck (Grade D)
- The treatment choice of the N0 neck should be guided by the treatment to the primary site (Grade D)
- If observation is planned for the N0 neck, this should be supplemented by regular ultrasonograms to ensure early detection (Grade A)

- Selective neck dissection is as effective as modified radical neck dissection for controlling regional disease in N0 necks for oral cavity and laryngeal cancer (Grade B)
- Selective neck dissection is effective as modified radical neck dissection for controlling regional disease in N0 necks for all other primary sites (Grade C)
- Elective neck dissection and elective neck irradiation have equal efficacy in controlling occult neck disease (Grade C)
- Similar considerations as above apply to the contralateral N0 neck (Grade C)

4.2. 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 treatment of these nodes is also required. Level V is least likely to be involved, with between 3% and 7% of patients undergoing RND having positive nodes at level V.

4.2.1. N1 neck disease

Prospective data from large cancer databases suggest that single modality therapy is sufficient to deal with ipsilateral, single nodes less than 3 cm in size. If surgery is the chosen modality, SND may be appropriate. As approximately 50% of clinically N1 necks are upstaged after pathological assessment, many patients subsequently

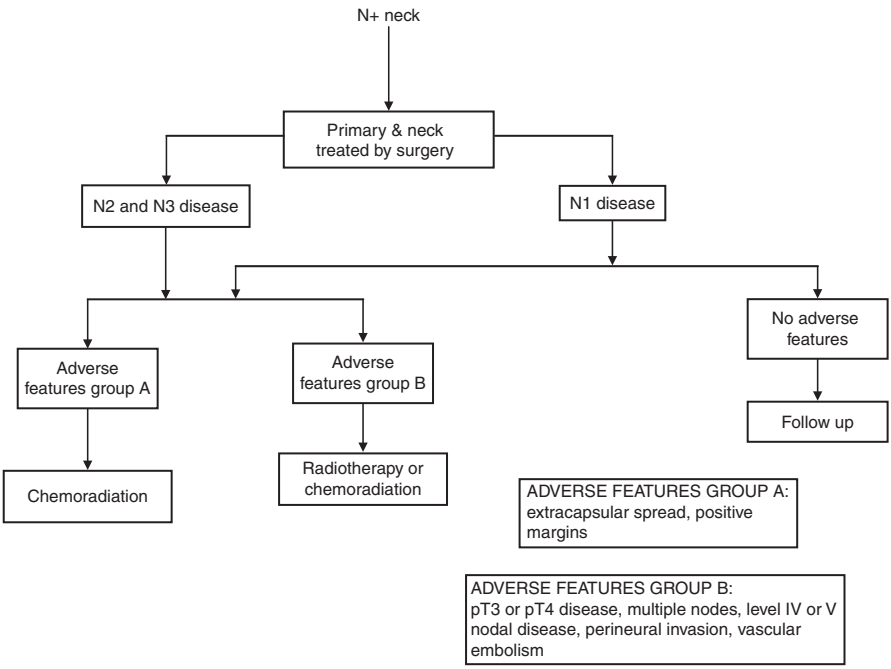

Figure 2: Algorithm for management of the N+ neck where the initial treatment is surgery

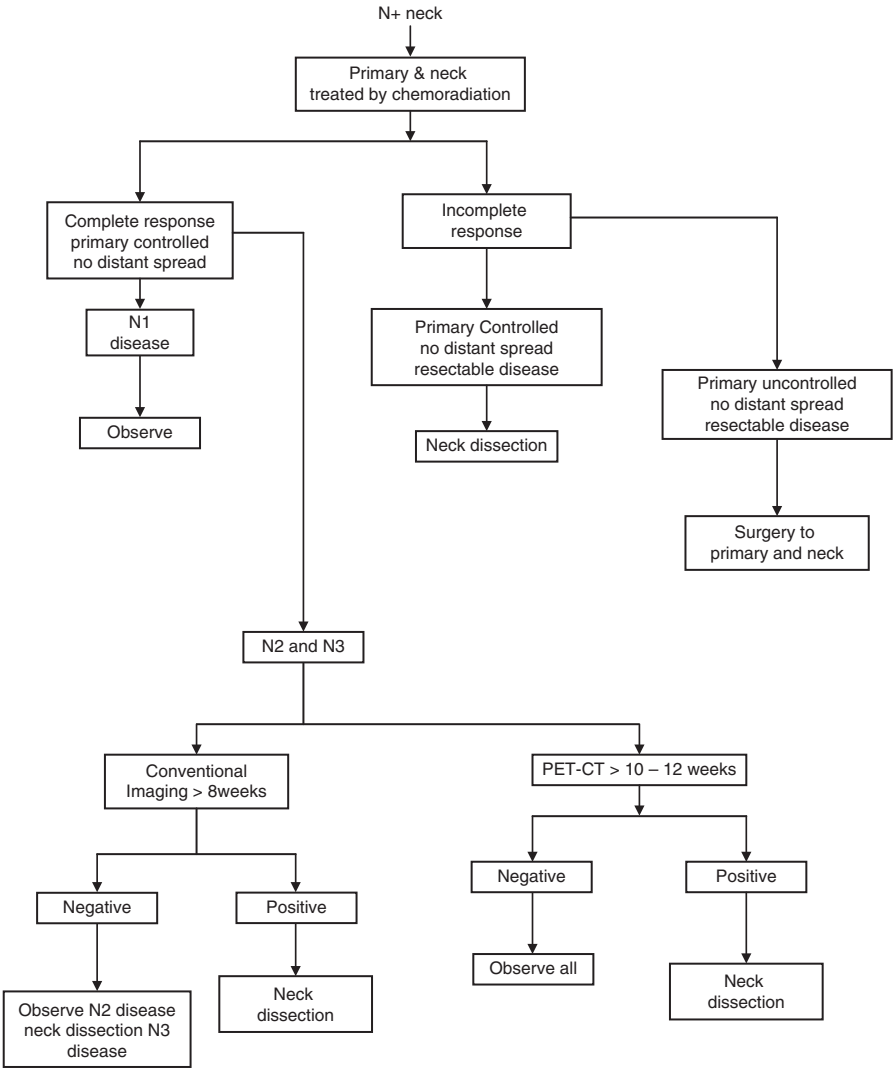

Figure 3: Algorithm for the management of the N+ neck where the initial treatment is concurrrent chemoradiation

require post-operative radiation. Prospective studies have shown that in the absence of bulky disease (N1, N2b), appropriate SND in combination with postoperative radiotherapy result in neck control rates equivalent to those achieved by comprehensive neck dissection. Complete response rates are much higher in patients with nodes less than 3cm in size and regional control rates following radiotherapy alone are best in patients with nodes less than 2cm in size.

4.2.2. N2 and N3 neck disease

Retrospective data suggest an increased risk of regional recurrence following neck dissection alone if histological examination reveals any single node greater than 3cm

in size (N2a and N3) or two or more positive nodes (N2b). 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. Postoperative radiotherapy or chemoradiotherapy reduces the risk of recurrence in the presence of adverse features (see below). If the primary tumour is small but sited where resection is not feasible, and associated with advanced neck disease, an option is to resect the nodal disease prior to treating the primary tumour by radiotherapy (+/- chemotherapy) in addition to delivering postoperative radiotherapy to the involved neck, but consideration must be given to potential delays in the treatment of the primary tumour.

If the primary site is suitable for organ preservation protocols, the neck should be treated at the same time. If involved nodes are fixed and unresectable, non surgical modalities of radiotherapy or chemoradiotherapy may be considered, but a low likelihood of curative outcome should be recognised.

Recommendations

- The treatment choice to the N+ neck should be guided by the treatment to the primary site (Grade D)
- Selective neck dissection alone is adequate treatment for pN1 neck disease without adverse histological features (Grade C)
- Postoperative radiation for adverse histologic features following selective neck dissection confers control rates comparable to more extensive procedures (Grade C)
- Adjuvant radiation following surgery for patients with adverse histological features improves regional control rates (Grade C)
- Salvage surgery can be considered for partial response following chemoradiation (Grade C)
- Postoperative chemoradiation improves regional control in patients with extracapsular spread and/or microscopically involved surgical margins (Grade A)

4.2.3. Adjuvant irradiation and chemoradiation

Retrospective studies suggest that adding irradiation postoperatively increases regional control, 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 concurrent chemoradiation in this setting, especially in the presence of extracapsular spread and/or microscopically involved surgical margins. Patients who had 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.

4.2.4. Planned neck dissection after primary chemoradiation

Retrospective studies suggest that even if a clinical and radiological complete response has been achieved following CRT, around 25% of patients with N2 and N3 necks will have pathological evidence of residual disease. However, the clinical significance of this is not clear as some metastases may be non-viable. There is little support for further surgery to the neck on a planned basis, especially if CT-PET imaging shows no disease. Prospective studies of patients with a complete response as assessed radiologically have mature long-term clinical follow-up and show very low regional relapse rates that are comparable to the regional failure rates reported in planned neck dissections series. Further results from ongoing randomised studies (see below) will provide a robust answer to this scenario.

4.3. Management of the occult primary (see also chapter 30)

Patients with occult primaries comprise less than 5% of all head and neck cancer presentations. The diagnosis is confirmed by FNAC. Open biopsy is best avoided unless absolutely necessary to prevent spillage of tumour into surgical planes, but there is no clear evidence that this affects prognosis. Cytological diagnosis of squamous cell or undifferentiated carcinoma in a neck node in the absence of a visible primary site should instigate further tests. Tests for human papilloma virus status and Epstein Barr virus encoded RNA (EBER) have high positive predictive values and will help point to a primary site. CT or MRI scans may suggest putative primary sites, the commonest being the oropharynx. Adding a PET-CT scan will usually lead to a primary being found in an additional one-third of patients. Workup should ideally include all imaging *prior* to panendoscopy and bilateral tonsillectomy, based on a rare incidence of contralateral or bilateral tonsillar disease.

For adenocarcinomas presenting as unknown primaries, a comprehensive neck dissection is recommended. A parotidectomy may be included with this if the metastatic node is in levels II or III. Primaries arising from outside the head and neck region should be considered.

There is no consensus on the management of squamous cancer arising from occult primaries. Options include primary surgery (comprehensive neck dissection) followed by RT (plus chemotherapy where indicated) to either the ipsilateral involved neck alone or to the bilateral neck and mucosa of the upper aerodigestive tract. Alternatively, primary CRT to the neck or to the neck and all mucosal sites can be delivered, with surgical salvage as discussed below. Extending the radiation field to encompass all possible mucosal primary sites results in lower locoregional failure at 5 years but has no advantage in terms of disease-free survival and emergence of primary cancer but is associated with increased toxicity.

Recommendations

- Imaging should be performed prior to panendoscopy for clinically occult primaries (Grade C)
- In addition to panendoscopy, computed tomographic or magnetic resonance imaging scans must be the minimum imaging done before declaring a primary to be occult (Grade D)
- Co-registered positron emission tomography- computed tomography scans prior to endoscopy and biopsy reduce the incidence of true unknown primaries (Grade C)
- If primary surgery is performed, postoperative chemoradiotherapy for extracapsular spread improves control rates (Grade A)
- Radiotherapy to the neck alone or to the neck and all possible mucosal sites give equivalent disease-free survival rates (Grade D)

5. ASSESSING TREATMENT RESPONSE

Neck node size and fixity predict response rate and local control with radiotherapy alone. In patients with clinical N2 or N3 disease, there is poor correlation between clinical and pathological response following chemoradiotherapy. Co-registered PET-CT scans, performed at least 10 weeks after treatment, have sensitivity and negative predictive values over 90% in this setting as demonstrated using histological examination as gold standard. A negative PET-CT scan following treatment portends a high disease free survival. High standard uptake values are associated with residual disease and this can be used to decide the need for neck dissection following primary CRT.

Recommendation

- Salvage neck dissection may not be required for complete responders who do not show evidence of active disease on co-registered positron emission tomography-computed tomography scans (Grade B)

6. MANAGEMENT OF RECURRENT NECK DISEASE

Prior to planning salvage treatment, the patient should be meticulously evaluated for distant metastases as this group run a higher risk. This group is likely to benefit from PET-CT scans to look for distant metastases. If the recurrence has occurred following RT or CRT and is surgically resectable, surgery should be offered but acknowledging 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 structures at risk make this a realistic option in a larger number of patients. In patients who recur after previous surgical treatment, tumours judged resectable should be offered re-resection followed by postoperative RT or CRT.

7. PALLIATIVE CARE

In incurable nodal disease, an evaluation of best supportive care versus palliative intervention (either palliative chemotherapy or radiotherapy) should be made with the patient to include likely outcome and impact on quality of life. In those wishing to pursue intervention chemotherapeutic regimens include cisplatin, 5 flurouracil and methotrexate (used as single agents or in combination) or palliative radiotherapy administered using simple field arrangements, by lateral parallel pair or a single anterior field. Radiotherapy dosage will be lower than in radical treatment, but up to 45 Gy or occasionally more is needed to impact on disease control.

8. ONGOING RESEARCH

Current NIHR portfolio studies open to recruitment and relevant to neck metastases include:

- The role of selective neck dissection in patients with early oral squamous cell carcinoma (1–3 cm primary size) and no clinical evidence of lymph node metastases in the neck (SEND)
- A multicentre randomised phase III trial comparing PET-CT guided watch and wait policy versus planned neck dissection for the management of locally advanced (N2/N3) nodal metastases in patients with head and neck squamous cancer (PET-NECK)

Key Points

The available level of evidence for managing nodal disease in the neck is poor with a lack of high quality randomised controlled clinical trials.

- Status of cervical lymph nodes is the single most important tumour prognostic factor.
- Prognosis is affected by number of involved nodes, the anatomic level in the neck, tumour load, presence of extracapsular spread, presence of perineural and/or 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 will not be identified on conventional (CT and MR) imaging.

- Incidence of nodal metastases depends on site and size of the primary tumour. This figure may be as low as 1% for early glottic tumours or as high as 80% for nasopharyngeal carcinomas.
- The majority of tumours will metastasise in a predictable manner to certain nodal groups but it should be remembered that certain tumours will fast track to remote sites (i.e. nasopharyngeal cancers to level V, tongue cancers to level IV) and 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.
- Improved control and disease free survival with postoperative concurrent chemoradiation is seen in the presence of extracapsular extension and/or microscopically involved surgical margins.
- Neck dissections should be documented as per the accepted classification system.
- 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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Chapter 30
Unknown Primary

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1. INTRODUCTION

An unknown primary is defined as a squamous cell carcinoma 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 cytology and/or core biopsy under ultrasound guidance. The receipt of a cytological or histological report confirming squamous cell carcinoma initiates the need for further investigation.

2. 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 II, followed by level III, with bilateral involvement and other symptoms (i.e. pain, dysphagia) reported in <10%. The clinical N stage at presentation is usually N2a, N2b, N2c. The presence of cystic malignant metastases is often considered to be a hallmark of human papilloma virus (HPV) related squamous carcinoma, usually with subclinical primaries in the oropharynx. The first echelon lymph node or nodes which are involved in squamous cell carcinoma can act as an indicator of the potential origin of the index primary are shown in table 1.

Table 1. First echelon lymph nodes for various primary sites

level I	oral cavity, oropharynx
level II	oral cavity, oropharynx, larynx, nose, nasopharynx, parotid
level III	oral cavity, oropharynx, larynx, thyroid, nasopharynx
level IV	larynx, thyroid, hypopharynx, oesophagus
level V	nasopharynx, hypopharynx, thyroid, oropharynx
level VI	thyroid, larynx, hypopharynx, cervical oesophagus

It should also be noted that patients presenting with supraclavicular lymphadenopathy may represent a different clinical entity, due to the potential for association with infraclavicular neoplasms, such as lung cancer.

3. 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 outpatient 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:

3.1. Pathology of lymph nodes

The advantage of a core biopsy over fine needle aspiration cytology is that a clearer histological picture can be determined. 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, for example by the use of lung or thyroid markers. More specific investigations such as identification of Epstein Barr Virus (EBV) may correlate highly with a naso-pharyngeal site. HPV has in recent years been shown as a significant aetiological factor in oropharyngeal cancer and so its presence could therefore be suggestive of an oropharyngeal origin.

3.2. Cross-sectional imaging

All patients should have CT scanning from skull base to diaphragm as part of the assessment of a newly diagnosed squamous cell carcinoma of the head and neck. 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. CT 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 II/III lymph node MR imaging 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 a MR imaging of the neck up to skull base.

3.3. Positron emission tomography-computerised tomography fusion scan (PET-CT)

PET-CT scanning is the recognised investigation of choice in the assessment of the unknown primary and has been reported to contribute to accurate identification in at least one-third of the cases. The evidence in support of this

modality is level 3 and is based on observational series. It should be noted that there is a significant false positive identification rate associated with PET-CT scan. A recent metanalysis showed an overall 84% sensitivity and 84% specificity of primary tumour detection using PET-CT. Although evidence in support of PET-CT varies, in general it would appear that it increases the identification rate when compared with the other more standard imaging techniques.

3.4. Panendoscopy

Following each of the clinical and radiological assessments it is necessary to carry out panendoscopy of the upper aero-digestive 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 sub-sites 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 sub-sites which should be examined are the nose, paranasal sinuses, nasopharynx, oral cavity, hard and soft palate, 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 then the question of random biopsies arises. Although there is little evidence in support of this longstanding 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.

It is now recognised that in the absence of any lesion that an ipsilateral tonsillectomy should be performed. Consideration should be given to bilateral tonsillectomy, as there have been significant reports of this yielding squamous cell carcinoma which may not be clinically obvious on direct examination. It has been reported that patients subsequently diagnosed by tonsillectomy have better outcomes than other unknown primary patients. Although this could theoretically be attributed to the treatment being better directed in the tonsillectomy group it should be noted, in the series described, that there was a lower volume of cervical metastases in the tonsillectomy group.

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. 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.

3.5. Staging

The neck is staged as set out in Chapter 29. It should be noted that the correct T stage for an unknown primary is T0 and not Tx.

Recommendations

All patients presenting with confirmed cervical lymph node metastatic squamous cell carcinoma and no apparent primary site should undergo:

1. PET-CT whole body scan (Grade D)
2. Panendoscopy and directed biopsies (Grade D)
3. Bilateral tonsillectomy (Grade D)

4. TREATMENT

The aim of the treatment of the majority of patients with a 'true' unknown primary should be curative with the least morbidity to the upper aero-digestive 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 regimes will therefore involve combined modality treatment but on occasions, (chemo) radiotherapy, and even more rarely surgery, will be used as single modality treatment. The rate of emergence of the primary tumour is approximately 3% 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 loco-regional control. However, the rarity of unknown primaries (approximately 1–2% 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.

Surgery on its own may be sufficient treatment for N1 necks demonstrating no extracapsular spread, but in all other scenarios, it needs to be supplemented by adjuvant (chemo) radiation. For more advanced neck disease intensive combined treatment is required. This could be either a combination of neck dissection and radiotherapy, 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.

4.1. Surgery as primary modality

4.1.1. T0N1

4.1.1.1. 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 I-V, 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 radiotherapy and clearly avoids the potential side effects of radiotherapy. There are no randomised data to support MRND over selective neck dissection (SND). However, in the absence of other adjunctive therapies for the N1 neck, a MRND is preferred as its extent and subsequent radiological assessment may avoid the need for radiation.

4.1.1.2. With extracapsular spread

When extracapsular spread is found, however, then radiotherapy to at least the involved nodal levels is necessary, although it is more usual to irradiate the entire ipsilateral post-operative neck, and boost the involved levels. The addition of chemotherapy to radiotherapy 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. There are no robust data to support the additional use of total mucosal irradiation with ipsilateral neck radiation following neck dissection for T0pN1 disease.

There are also some reports that locoregional tumour control is up to 40% 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.

4.1.2. T0N2a, T0N2b, 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. Radical radiotherapy 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 and overall survival rates. The chemotherapy protocols used were heterogenous, and included concomitant cisplatin, concomitant 5-fluorouracil (5FU) 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.

4.1.3. 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 chemoradiotherapy will usually be necessary.

Table 2. Treatment recommendations for the various stages of neck disease

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

4.2. Radiotherapy

4.2.1. Primary treatment

For N1 disease with extracapsular spread, N2 and N3 disease, initial chemoradiation with neck dissection only for those patients not achieving a clinical or metabolic complete response on post-treatment imaging is a valid management strategy. The extent of the radiotherapy 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 total mucosal irradiation. The latter is practised more commonly in the UK.

4.2.2. Adjuvant treatment

There is a lack of consensus on the radiotherapy target volumes that should be treated after neck dissection. Treatment of the ipsilateral hemi-neck alone is of low toxicity and may achieve local control in the cervical nodes. 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 radiotherapy for treatment of head and neck cancer, an absolute survival benefit of 6.5% is seen at 5 years. Investigating concomitant chemoradiation in the post-operative setting, the RTOG group

demonstrated a 10% improvement in locoregional control rate, and a 22% risk reduction of disease recurrence and death at 2 years, while the EORTC group showed a 13% improvement in locoregional control, 25% risk reduction of disease progression, and 30% risk reduction of death at 5 years. 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.

4.2.3. Total mucosal irradiation (TMI)

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 total mucosal irradiation for occult primary head and neck cancer patients, claiming improved local control, but no overall survival benefit. There is no conclusive evidence to support the routine use of TMI.

What is clear, however, is that with conventional radiotherapy 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. 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 2-year loco-regional control (85%-88%) and overall survival (74%-85%). The MD Anderson group, however, have most recently reported the most mature data, with 5 year actuarial locoregional control of 94% and overall survival of 89%. The TMI in all reports was well tolerated, and with significantly reduced xerostomia and mucositis. Because of the lack of randomised evidence, the post-operative radiotherapy volume treated should therefore be at the discretion of the treating clinician. If TMI is advocated the use of IMRT is recommended.

Recommendations

- Post-operative neck: 60 Gy in 30 fractions or equivalent (Grade D)
- Post-operative neck with extracapsular spread: 64 Gy in 34 fractions or equivalent (Grade D)
- Gross macroscopic disease still present: 70 Gy in 30 fractions or equivalent (Grade D)
- Putative mucosal sites and the uninvolved neck: 50 Gy in 25 fractions or equivalent (Grade D)

4.3. 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 radiotherapy should be as for treatment

of patients with detectable head and neck squamous cell carcinomas. 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.

4.3.1. Neoadjuvant chemotherapy

While the MACH-NC meta-analysis failed to demonstrate a significant benefit for the use of induction chemotherapy, many of the historical trials included pre-dated the use of taxanes. Both the EORTC 24971/ TAX 323 study and the TAX 324 trial found that the addition of docetaxel (T) to cisplatin (P) and 5-fluorouracil (F) resulted in improved progression-free survival, overall survival 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 cyto-reductive measure prior to definitive concomitant chemoradiation, even for occult primary disease. The caveat remains that the outcome of such cases/ series' should be reported in the literature where possible, for this rare group.

4.3.2. Concomitant chemotherapy

The addition of postoperative adjuvant chemotherapy concurrently with radiation has transformed with the publication of two trials from EORTC and RTOG. See section 4.2.2 above for detailed discussion.

4.3.3. Adjuvant chemotherapy

There are no convincing data that chemotherapy given after radiation or surgery is of benefit in terms of either disease-free or overall survival for patients with detectable primaries. This approach cannot therefore be recommended for patients with occult primary head and neck cancer.

Recommendations

- Concomitant chemotherapy with radiation should be considered in patients with an unknown primary (Grade D)
- Concomitant chemotherapy with radiation should be offered to suitable patients in the postoperative setting, where indicated (Grade A)
- Neo-adjuvant chemotherapy can be used in gross "unresectable" disease (Grade D)

5. 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 squamous cell carcinoma with cervical metastasis (see chapter 35). The highest risk period for relapse of squamous carcinoma following treatment occurs in the first 2 years. A frequent follow-up programme of monitoring every four 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%), and a negative scan undertaken 3–4 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.

Recommendations

- Patients should be followed up at least 2 monthly in the first 2 years and 3 to 6 monthly in the subsequent years (Grade C)
- Patients should be followed up to a minimum of 5 years with a prolonged follow up for selected patients (Grade B).
- PET-CT scan at 3–4 months after treatment is a useful follow up strategy (Grade D)

Key Points

- All patients with a clinical unknown primary should have comprehensive imaging, including PET-CT 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, IMRT should be used.
- Follow up should be similar to that employed in patients who have received treatment for an identified tumour of the head and neck.

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Chapter 31
Rehabilitation/Speech Therapy

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1. INTRODUCTION

Most head and neck cancers and their treatments affect speech and swallowing and this section concentrates on rehabilitation of these functions. Allied Health Professional (AHP) head and neck cancer rehabilitation pathways are required as part of the implementation of the IOG 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 and dental implantologists should also be considered.

The stages of the pathways and the allied health professionals interventions appropriate to each stage are detailed along with an extensive evidence review in the National Cancer Rehabilitation Pathway for Head and Neck Cancer (http://www.cancer.nhs.uk/rehabilitation/index.htm).

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 (SLT) within this team. SLTs 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 preference and lifestyle.

Recommendations

- All MDTs should have rehabilitation patient pathways covering all stages of the patient's journey (Grade D)
- Clinicians treating head and neck cancer patients should consult the National Cancer Rehabilitation Pathway for Head and Neck Cancer (Grade D)

2. REHABILITATION OF VOICE, SPEECH AND SWALLOW

2.1. Goals of rehabilitation

1. Achieve the best possible functional outcome and quality of life.
2. Identify and carry out interventions which are most effective for both the specific treatment and the individual patient at the optimal time.
3. Provide support and rehabilitation to the patient and their carers.

2.2. Assessment

All head and neck cancer patients should have a pre treatment assessment of speech and swallowing. Baseline assessments should be undertaken by the SLT 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 (FEES) and videofluoroscopy/modified barium swallow. 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.

2.3. Therapy/Interventions

2.3.1. Pre-treatment

Pre-treatment counselling should be provided to advise on the anticipated effects of the cancer as well as subsequent treatments (chemoradiation, radiotherapy, surgery and palliation) on functions and that the SLT will assist with rehabilitation.

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. For those undergoing surgery the teaching of swallow strategies beforehand can reduce risk and maximise function.

2.3.2. Post Treatment

2.3.2.1. 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 radiotherapy to the larynx.

2.3.2.2. Speech

For those undergoing oral surgery a programme of compensations, articulation and intelligibility can be started once suture lines have healed.

2.3.2.3. 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 impove quality of life. These interventions include:

- 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.

2.3.2.4. Oral rehabilitation

Intraoral prostheses providing palatal lift, obturation and augmentation can improve speech and swallow function after oral resections and the SLT and restorative dental surgeon 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.

Recommendations

- All head and neck cancer patients should have a pre-treatment assessment of speech and swallowing (Grade D)
- A programme of prophylactic exercises and the teaching of swallowing manoeuvres can reduce impairments, maintain functions and enable a speedier recovery (Grade D)
- Continued SLT input is important in maintaining voice and safe and effective swallow function following head and neck cancer treatment (Grade D)

3. MANAGEMENT OF STENOSIS/STRICTURE

3.1. Prevention, assessment and diagnosis

Stenosis of the (hypo)pharynx and neopharynx is common following treatment for laryngeal and pharyngeal cancer. After treatment of cervical oesophageal cancer some degree of stenosis is almost inevitable in this region especially following chemoradiotherapy. Reported rates vary from 8% following primary chemoradiotherapy to 40% or more

following salvage surgery after (chemo)radiotherapy, particularly if preceded by a pharyngocutaneous fistula. Additional dysphagia occurs in extended surgery, particularly with posterior tongue resection and with extended neck surgery with sacrifice of glossopharyngeal and hypoglossal nerves (minor), and vagus nerve (major).

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 3cm (unstretched) to 8cm (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 repaired 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 versus non-peristaltic flaps have yet to be quantified in maintaining a functional postoperative voice and swallow.

3.2. Treatment

This depends on the type (functional versus anatomical, scar versus recurrence), site and comorbid factors such as fitness for further reconstructive surgery. Median tube placement times following all forms of treatment for head and neck cancer are in the region of 20 to 26 weeks, and up to 50% of patients reconstructed with free or pedicle flaps are tube feed dependent at one year post surgery. Reported rates of complication with gastrostomy tubes vary considerably with up to 3% mortality rates reported in some series and 0% 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. Continuous radial expansion balloons allow dilation up to 20mm diameter and may be safer and more effective than traditional bougies. They can also be utilised without general anaesthesia.

Sternomastoid flaps can be useful in the non irradiated patient, but is less reliable than pectoralis major, radial forearm (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 versus cosmesis. Reported case series for RFF, jejunum or ALT describe similar complication rates (<5% flap failure, up to 50% pharyngocutaneous fistula) and success rates (speech intelligibility and swallow performance).

3.3. Cricopharyngeal myotomy

CP myotomy appears to have little value per se for improvement of dysphagia following surgical treatment of cancers of the oropharynx.

Recommendations

- Disease recurrence must be ruled out in the management of stricture/stenosis (Grade D)
- Continuous radial expansion balloons offer a safe, effective dilation method with advantages over gum elastic bougies (Grade D)

4. REHABILITATION AFTER LARYNGECTOMY

4.1. Speech

Laryngectomy results in significant alteration of anatomy and often complex rehabilitation. A range of voice prostheses are now available including Blom Singer and Provox. 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.

SLTs with appropriate training and expertise in the management of the stoma and tracheo-oesphageal puncture (TEP) 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. SLTs should be aware of the need for and rationale behind, amongst others, videoflouroscopy for troubleshooting, 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 Voice Restoration (SVR): The role of the speech and language therapist".

4.2. Swallow

There has been a growing appreciation in recent years that swallowing also requires rehabilitation in laryngectomy patients. 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% of laryngectomy patients have a degree of dysphagia three years post surgery. Higher levels of depression and anxiety have also been documented in laryngectomees who have dysphagia. 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 utilizing the "polite yawn" has been proposed to help correct this.

4.3. 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 laryngectomy can be significant. Tools such as the EORTC Core Quality of Life Questionnaire can be useful in identifying not only those at risk of psychosocial problems but also to help plan and focus rehabilitation.

Recommendations

- Primary surgical voice restoration should be offered to all patients undergoing laryngectomy (Grade D)
- Attention to surgical detail and long term SLT input is required to optimize speech and swallowing after laryngectomy (Grade D)
- Patients should commence wearing heat and moisture exchange devices as soon as possible after laryngectomy (Grade D)

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Chapter 32
Recurrent cancer

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1. INTRODUCTION

Despite recent advances in the treatment of head and neck cancer, there is no particular therapy which affords a cure for all patients and locoregional tumour recurrence remains a common problem, which is still difficult to manage. All members of the multidisciplinary head and neck team will encounter patients with residual carcinoma shortly after treatment and recurrent disease for many years afterwards.

It is necessary for the team to be aware of the wide variety of options which are available to treat recurrent head and neck cancer, but the starting point must be a thorough understanding of the initial stage of the cancer and complete details of the primary treatment. These details should be obtained and carefully reviewed if the patient is to be treated in a centre other than that which provided the initial treatment. It may be necessary to reassess the initial pathology and staging.

Over half of all patients who die from head and neck cancer have active locoregional disease and whilst a small proportion of patients die from disseminated metastatic disease, over 70% of these patients also have locoregional recurrence.

The reasons for failure to cure are many and are still far from completely understood, but include:

i) understaging of the initial disease, either the primary or nodal disease
ii) inadequate surgery with positive margins post primary resection
iii) geographical miss when applying radiotherapy fields
iv) field cancerisation with synchronous malignant or pre-malignant lesions
v) radio-resistant tumours, relative hypoxia within the tumour mass
vi) drug resistance
vii) second primary tumours and distant metastases

Recurrences are particularly seen in those patients with poor general factors such as inadequate nutrition and the continuation of smoking and excessive alcohol. These general factors, combined with the site and size of the tumour recurrence and the time interval following the initial therapy make it necessary to consider all factors carefully to tailor any proposed further treatment to the individual patient.

2. EVALUATION OF RECURRENT HEAD AND NECK CANCER

Locoregional failure rates of early head and neck cancer to surgery and radiotherapy vary between 10–25% in the sub-sites. Recurrence rates of advanced stage head and neck tumours are in the order of 25–50%. Unfortunately, distinguishing between recurrent carcinoma and changes following surgery and radiotherapy can be a difficult clinical problem. Both surgery and radiotherapy produce changes which include fibrosis, oedema, inflammation and cartilage necrosis. These post-treatment changes are greater with modern chemoradiation regimes, but it is important to remember that severe oedema, inflammation and chondro/osteoradionecrosis are still most often associated with recurrent disease with reports suggesting around a 60% incidence rate.

2.1. Biopsy

Biopsy of heavily irradiated tissues may give rise to further significant infection, chondritis, osteitis and persistent ulceration and pain, which further complicate the decision making process. Biopsies in previously treated areas may also be falsely negative due to sampling error and the fact that there may be interrupted dispersed areas of microscopic residual tumour. If biopsies of suspicious areas taken in the first 3 months after treatment show any areas of microscopic residual tumour, these may indeed not be viable, giving rise to a false positive result. It is only natural that as physicians we feel that we should aggressively pursue possible recurrence, but this can lead to unwanted anaesthetics and surgical procedures, and is not a good use of healthcare resources.

2.2. Imaging

Unfortunately, conventional imaging techniques such as CT and MRI may be misleading when used to search for persistent or recurrent tumour, particularly after partial surgery or chemo-radiation. These modalities are, of course, constantly improving in terms of machinery and experience. In using these modalities, it is important that each multidisciplinary team has a clear view of when imaging should be undertaken post-treatment and serial images should always be available to compare and contrast.

Most recent studies using FDG PET/CT have shown improved detection for both local and regional recurrence in head and neck cancer after both surgery and chemo-radiotherapy. The studies differ in their recommendations for specific tumour sites and generally detection of recurrent tumour in the larynx and hypopharynx are more difficult than in the oral cavity, oropharynx and skull base. Obviously the possibilities of salvage surgery or re-irradiation differ amongst these sites.

It is to be hoped that studies in the future will concentrate on the more specific assessment of the separate sub-sites. Pre- and post-treatment serial imaging with CT, MRI and/or PET should be considered 3 months post completion of treatment,

although radiological studies show that negative scanning beyond 6 months and particularly by one year have a far greater predictive value than in the earlier post treatment periods.

2.2.1. Larynx and hypopharynx

The irradiated larynx and hypopharynx (+/- concomitant chemotherapy) are the most difficult head and neck areas to evaluate post treatment. In the past, surgeons have used direct laryngoscopy under general anaesthesia with additional evaluation by microscope and Hopkin's rods and the taking of biopsies in cases of suspected recurrence. Debate has continued for many years as to whether these biopsies should be deep biopsies and how many should be taken. Multiple studies have frequently shown false negatives and the difficulty of obtaining representative biopsies. Indeed, recurrence may not be proven until up to 12 months after the treatment. Unfortunately, clinical signs and symptoms such as voice deterioration, pain, dyspnoea or dysphagia are neither very sensitive nor specific, although recurrence or persistence of referred otalgia is probably the most useful of these.

In contrast, at present neither CT nor conventional MRI offer highly reliable differentiation between cancer, oedema, irradiation fibrosis or necrosis within the larynx and hypopharynx but recent results for FDG PET and diffusion-weighted MRI are showing a sensitivity of around 90% and a specificity of 95% and may allow for a better choice of patients on whom to perform direct laryngoscopy, and more direction with regard to the site and depth of any necessary biopsies. Diffusion-weighted MRI yields fewer false positive results with residual primary site disease and persistent lymphadenopathy and aids in the detection of sub-centimetre nodal metastases.

Obviously early detection of a recurrence in both the larynx and hypopharynx is important in regard to directing the type and extent of any salvage surgery or re-irradiation. It is to be hoped that the improved accuracy of FDG PET will promote a prospective randomised trial in this area to negate the number of futile examinations under general anaesthesia.

2.2.2. Oral cavity and oropharynx

It is obviously easier to clinically examine both the oral cavity and oropharynx post treatment for the detection of residual or recurrent disease, and indeed, adequate biopsy material can be more easily obtained without the possible increased side effects of necrosis, unless the disease is involving the mandible or deep within the tongue base. The most favoured technique for follow-up in this area in recent times has been serial MRI scans, although CT has its proponents for mandibular evaluation.

Again, however, recent studies with FDG PET imaging in patients who underwent chemo-radiation for oral and oropharyngeal carcinoma have shown an increased sensitivity and specificity, and a negative predictive value of close to 100% for the

detection of regional recurrent disease with serial FDG PET imaging. Further larger prospective studies are required to confirm these early investigations, and again it is to be hoped that these techniques can avoid unnecessary examinations under general anaesthesia with or without biopsy.

2.2.3. Nasopharynx and skull base

Whilst MRI and CT are undoubtedly the modalities of choice for the accurate primary assessment of disease in these areas, FDG PET scanning has been shown to be the most reliable long-term evaluation for recurrent and metastatic disease. The overall accuracy of the FDG PET scan becomes greater 4 months post treatment and by one year, the negative predictive value is almost 100%.

2.2.4. Neck

The neck has long been known to be of major prognostic significance both in primary disease and as a consequence of recurrence. In many patients, surgical treatment is an option following complications or failure of previous surgical or chemo-radiation therapy, and in recent years, some institutes have advocated planned neck dissection following chemo-radiotherapy. Unfortunately, extensive fibrosis and soft tissue changes are more likely to occur after the recently introduced chemo-radiation protocols than after radiation alone. The potential for delayed wound healing and catastrophic breakdown with or without associated flap necrosis and great vessel exposure remains a dangerous situation for head and neck cancer patients.

Studies using FDG PET to predict the necessity for post radiation therapy neck dissection have been increasingly reported over the last decade and it would appear that provided the time interval between the completion of chemo-radiotherapy and the PET evaluation is greater than 12 weeks, the negative predictive value exceeds 92% and beyond 6 months, the negative predictive value improves to almost 100%. The difficulties come when concern exists that there is persistent disease at an earlier period and that delaying neck dissection allows more time for cancer progression and post treatment fibrosis, which makes the neck dissection more difficult. Further evaluation of the optimal timing of imaging post chemo-radiotherapy continues to be debated, but it is to be hoped that planned neck dissection with complication rates as high as 35% will become a thing of the past.

Recommendation

- Positron emission tomography has high negative predictive values in diagnosing residual and recurrent head and neck cancer, especially those of the neck and nasopharynx (Grade A)

2.3. Patient factors and considerations

Patients with recurrent head and neck cancer have often been seriously compromised by their prior therapy and exhibit poor nutritional parameters and functional impairments such as swallowing. With further salvage treatment, they are at a high risk of treatment related complications and these have been substantially documented for surgical salvage, re-irradiation or further chemotherapy with or without radiotherapy. It is paramount that general medical issues and the patients overall performance status are thoroughly evaluated prior to attempting salvage therapy.

2.3.1. Medical issues

In patients previously treated, poor nutrition, low blood indices, hypothyroidism, pulmonary compromise from aspiration, and impaired wound healing may all be present. Recurrent oropharyngeal, hypopharyngeal and laryngeal cancers are particularly associated with pulmonary complications which may be related to long-term silent sub-clinical aspiration, pneumonitis or even frank pneumonia. The patient's pulmonary function and reserve must be evaluated in particular before commencing on any form of tongue base surgery or partial laryngectomy.

Formal nutritional assessment should be carried out by a senior dietitian and pre treatment nutrition by means of fine bore nasogastric tube or PEG placement may be absolutely essential. Re-feeding syndrome and its serious consequences may be a possibility in cachectic patients and so improvement of nutritional status may take a minimum of three weeks before considering new treatment.

Impaired thyroid and parathyroid function may have occurred as a consequence of previous resection of all or part of the thyroid gland or as the result of previous radical radiotherapy. Total laryngectomy following radiation or chemoradiation failure is associated with hypothyroidism in up to 70% of patients and may additionally be associated with hypocalcaemia and post-operative pharyngocutaneous fistula. Such serious co-morbidities may affect the ability of patients already severely compromised to heal and progress post-operatively.

2.3.2. Clinical nurse specialist, speech therapy, dietetics, dentistry, general practice and psychology

Whilst the importance of these members of the multidisciplinary team cannot be overemphasised when treating primary disease, their input is essential prior to considering salvage treatment for residual/recurrent disease. The clinical nurse specialist is frequently the key worker and along with colleagues from speech therapy, dietetics and the patient's primary care general practice may have a more accurate overall assessment of the patient and other family members/carers who are frequently devastated by the news that the disease has not been cured by the primary treatment.

Full dental assessment is essential prior to primary radiotherapy treatment in the head and neck, but a further review may also be of paramount importance before any form of salvage treatment is undertaken for recurrence. On occasions,

additional help from psychology may be indicated and clearly an important factor within this mix is whether the patient has continued to either drink or smoke during their primary treatment. Even well informed patients and their families frequently do not comprehend the possible increased morbidity, mortality and length of time required for salvage treatment.

3. MANAGEMENT PRINCIPLES

Locoregional recurrence following previous inadequate surgery or radiotherapy is a difficult and controversial problem. The literature is confusing, full of inadequate retrospective studies, and what one unit may consider to be unresectable recurrent disease, will be felt to be suitable for radical surgery at another unit. The term "inoperable disease" is commonly used in the chemo-radiotherapeutic literature when all the surgical options have not been considered. Likewise, re-irradiation has been shown to be a good therapeutic option for a number of patients, but has been an unpopular option in many units because of concerns about normal tissue toxicity. Many surgical units are unaware of the success which can be achieved with this form of treatment.

Salvage surgery may be the treatment of choice in patients with disease that is considered suitable for radical resection. The choice is more difficult in patients in whom radical resection with clear margins is unlikely, but this is often difficult to establish because of the limitations of imaging assessment referred to in the previous section.

In some circumstances, surgery may provide useful palliation, particularly in those patients who have necrotic, fungating wounds, fistulae, severe dyspnoea due to airway compromise, or severe difficulties with swallowing amounting even to total dysphagia.

Palliative chemotherapy may be an option, but in a significant number of patients, the most appropriate treatment may be supportive care with the aim of maximal symptom palliation.

3.1. Salvage surgery

Salvage surgery is the most effective form of treatment for recurrent head and neck cancer when it is applicable. Unfortunately, many patients with recurrent disease present with a situation which is inoperable owing to a variety of factors. The extent and location of the tumour are the most important, but additional medical co-morbidities often associated with smoking and alcohol may make any proposed treatment untenable. The patients themselves may decline further surgical options because of concerns about the functional outcome and the immediate risk of morbidity and mortality as a consequence of the surgery.

The figures vary widely within the literature, depending on the preferences of different units, but between 25% and 50% of patients do not proceed to salvage surgery because of perceived unresectable disease, their overall medical condition, distant metastases, or patient refusal.

3.1.1. Larynx

The larynx is the most successful site in terms of overall cure rate from salvage surgery, and indeed, it is outstanding amongst cancer in general for allowing substantial success with a second treatment following previous failure. Multiple reports detail 5-year survival figures of 60–85% for salvage treatment in early laryngeal cancers and 40–56% for laryngeal cancer overall.

3.1.1.1. Partial laryngectomy

Most of the cases which may be amenable to either open or endoscopic partial laryngectomy are those who have failed radiotherapy for early glottic or occasionally supraglottic tumours. Whether using endoscopic or open partial procedures, it is important to know the precise details of the original tumour and in the majority of cases, this will have been a T1 or T2 lesion. All forms of endoscopic evaluation and imaging are less reliable following previous radiation therapy or previous partial laryngeal surgery in comparison to the evaluation of a primary tumour, particularly when there is notable oedema.

Endoscopic transoral laser microsurgery

Endoscopic treatment of laryngeal recurrence has been increasingly used in recent years following radiation failure, mainly for early glottic recurrence. More than one endoscopic resection may be required in order to be certain that all residual or recurrent disease is thoroughly removed, and as in all operative procedures post radiotherapy, the pathological evaluation of the extent of residual tumour is more difficult. If there is any degree of doubt, the patient should proceed to total laryngectomy. Chondronecrosis has only been reported in rare instances following the use of endoscopic partial laryngectomy techniques, and it is rare for patients to require a tracheostomy in association with the procedure. However, patients suitable for this procedure need careful selection. Recent meta- analysis suggests control rates for endoscopic procedures to be inferior to open partial laryngectomy (local control at 24 months 53.9%; n=239)

Open partial laryngectomy

In contrast to the endoscopic procedures, partial laryngectomy for the treatment of radiation failure disease has been advocated for more than 5 decades. It is once again uncommon to consider this treatment following modern combined synchronous chemo-radiotherapeutic regimes. These procedures do carry a significant risk of chondroradionecrosis and oedema which necessitates some patients remaining with a tracheostomy.

Post-operative dysfunction, notably swallowing problems and aspiration, still remain a problem within this group of patients, even when only treated with prior radiation. The most common techniques used are those of vertical partial laryngectomy and supra-cricoid laryngectomy, and whilst there are no absolute criteria for these patients, it is important that these procedures are undertaken by experienced teams with a thorough understanding of the techniques and post-operative problems.

Recent meta-analyses indicate very good control rates with partial laryngectomy in this setting. The local control rate at 24 months for 560 patients was 86.9% (95% CI, 84%–89.5%), the disease-free survival rate for 352 patients was 91.2% (95% CI, 88.2%–93.9%). Total laryngectomy can be used for failure of salvage vertical partial laryngectomy or supra-cricoid laryngectomy, and for those results published, does not seem to be associated with a substantial decrease in survival if close follow-up is continued. Outcomes were more consistent and superior with supracricoid laryngectomy (local control at 24 months 94.1%). Whilst supraglottic laryngectomy has been used for radiation failure of supraglottic tumours, the literature is sparse on this group of patients and indicates significant problems with laryngeal oedema, airway and dysphagia.

Recommendation

- Open partial laryngectomy, for appropriate indications, can lead to high local control rates for recurrent laryngeal tumours (Grade A)

3.1.1.2. Total laryngectomy

This procedure is a very good salvage procedure for patients treated initially by combined synchronous chemo-radiotherapy or who have residual or recurrent disease which is evaluated to be T3 or T4. It is also important to remember that it is often the best procedure for those patients whose general condition and medical co-morbidities are poor. It rapidly produces a safe airway and return to normal swallowing in many of these patients, rather than the more protracted route, which can be a particular problem with open partial laryngeal procedures.

Many units still employ total laryngectomy to treat all cases of recurrent laryngeal carcinoma and this often depends on the individual preference of the local team, patient factors and choice, and the overall experience of the team. Published control rates following total laryngectomy are lower than the previously reported control rates for endoscopic and open partial procedures, but that is a reflection of the fact that they include many more patients and those with more extensive disease. Patients undergoing total laryngectomy for salvage frequently have tumour extension into the soft tissues and the presence of a wide variety of adverse features such as associated neck nodes and adverse histology.

The literature therefore varies widely with regard to 5-year published control rates following total laryngectomy, with results between 40 and 70%, depending on whether the tumours are glottic and supraglottic and associated with neck disease. A proportion of these patients will also develop either a primary carcinoma of the lung or distant metastases. Even so, these control rates are exceptional in cancer terms for a second major treatment, and with the advances in vocal rehabilitation and our improved understanding of swallowing and quality of life issues, total laryngectomy still remains an important and successful procedure.

Evidence suggests that there is increased risk of wound complications following initial treatment with synchronous combined chemo-radiation, and a number of UK units currently cover the pharyngeal repair and adjacent carotid arteries by means of a simple pedicled muscle or free flaps, particularly when the total laryngectomy is

undertaken in association with a neck dissection. This prophylactic measure lessens the risk of serious wound complications post-operatively, stenosis of the neopharynx and potential carotid blow-out. The same procedure may accompany salvage surgery in other areas of the head and neck.

Recommendation

- Total laryngectomy is a dependable salvage procedure with predictable outcomes (Grade C)

3.1.2 Oral cavity and oropharynx

Whilst clinical examination of the oral cavity may more easily result in detection of residual or recurrent disease, the extent of the disease in the deeper tissues and possible invasion of the mandible remain difficult. Residual or recurrent disease within the deep aspects of the tongue base and tonsil tissues may be extremely difficult to evaluate and as stated previously, whilst MRI and CT are common primary assessments, diffusion MRI and PET CT may be more useful in tumours in these areas.

3.1.2.1. Surgical options

The type and extent of the salvage surgery in these areas often ranges from simple excision such as partial glossectomy by a variety of means, or more major resection such as hemiglossectomy and floor of mouth excision with or without additional resection of the mandible and accompanying neck dissection. Involvement of the mandible by both tumour and radionecrosis may necessitate considerable segmental resection or even hemi-mandibulectomy. More conservative marginal resections are less commonly undertaken.

Advanced recurrent disease in the tongue base or lateral pharyngeal wall may require additional laryngectomy or pharyngectomy in order to clear the disease, and such combinations as total glossectomy and total laryngectomy require considerable discussion between the patient and the multidisciplinary team, and are generally only undertaken in younger, fitter and highly motivated patients. Whilst a wide variety of reconstruction techniques are frequently the cause of considerable discussion, it is essential to remember that clearance of all disease is the primary aim.

Unfortunately, despite long discussions and multiple reports involving extensive numbers of patients, there are no adequate randomised trials with agreed outcome measures comparing the early and long-term results of the varying resections and reconstructive options.

3.1.2.2. Reconstructive options

There is a vast literature on this subject, ranging from no reconstruction in association with partial glossectomy or even hemi-glossectomy, through local flaps, pedicled flaps and a wide variety of free flaps ranging from fascio-cutaneous through a spectrum of osseomyocutaneous techniques. These may be supplemented by the

use of osseointegration to restore dentition and, indeed, this is the ultimate goal of rehabilitation as mastication, swallowing and speech are frequently the most important issues in this group of patients.

The exact reconstruction technique will depend on patient variables and the preference and experience of the multidisciplinary team involved with an individual patient. The larger reconstructions frequently require the combined efforts of two or more teams, involving maxillo-facial, plastic and ENT surgeons.

3.1.3. Hypopharynx

In attempting to differentiate between post treatment changes and recurrent tumour, the irradiated hypopharynx is arguably the most difficult head and neck site. This is unfortunate as this area of disease has the poorest prognosis from the primary treatment. Signs and symptoms such as voice deterioration, pain, dyspnoea and dysphagia are neither very sensitive nor specific, although otalgia may be the most useful of these. As with the larynx, direct laryngoscopy under general anaesthesia and multiple biopsies may still not obtain representative tissue and multiple futile pharyngolaryngoscopies add to morbidity. From recently reported results assessing the oral cavity, oropharynx and larynx after chemo-radiotherapy, it is likely that FDG PET and diffusion MRI will prove to be the most useful radiological assessments and hopefully decrease the need for recurrent procedures under general anaesthesia.

3.1.3.1. Surgery

Partial surgery for limited recurrence in the posterior pharyngeal wall and the lateral wall of the pyriform fossa is occasionally possible with primary or limited reconstruction repair. However, the majority of patients with recurrent pyriform fossa disease will require at least vertical, near total, or total laryngectomy with substantial pharyngectomy and flap repair.

Squamous carcinoma of the hypopharynx has a well-known propensity for submucosal spread which may increase considerably following radiation failure. Postcricoid disease in particular often involves the cervical oesophagus. Obtaining clear margins, both superiorly and inferiorly are of utmost importance.

Total laryngopharyngectomy is therefore the commonest procedure and the principle of reconstruction is to establish continuity of the pharynx. Options include jejunal graft, radial forearm or anterolateral thigh flap, with or without subsequent tracheo-oesophageal puncture for attempted restoration of speech. Patients with extensive cervical oesophageal disease making the inferior limit of resection difficult may require a gastric pull-up procedure. Other tubed pedicled flaps (e.g., pectoralis major tubed flap) have fallen into disfavour.

3.1.4. Nasopharynx

This disease is rare in the UK, but has been 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% at 5 years.

3.1.5. Nose, paranasal sinuses and skull base

Despite the rarity of these tumours and the tremendous diversity of pathology in these areas, salvage treatment, most notably surgical, can achieve good long-term cure rates in selected pathologies and patients. Patients who recur after primary radiotherapy or limited nasal, sinus or lateral skull base surgery may be cured by craniofacial resection +/- orbital resection or petrosectomy.

Anterior and antero-lateral craniofacial resection carries a relatively low morbidity despite previous failed primary treatment, and, aside from complete cure, can produce many years of disease free survival in pathologies such as adenoid cystic carcinoma,chondrosarcoma,low-grade adenocarcinoma and olfactory neuroblastoma. This latter pathology is frequently controlled long term by re-irradiation. These procedures should be confined to treatment centres specialising in these rare cases.

3.2. Re-irradiation of head and neck cancer

Treatment for salvage using further radiotherapy with or without chemotherapy requires the same careful considerations as salvage surgery, but in select cases, there is a significant body of literature showing a good probability of achieving local control. Indeed, re-irradiation has a long history, but is rarely used in the UK because of concerns about treatment related toxicity and the lack of significant response in many patients. Experience and clinical judgement are vital in assessing the possibilities of serious toxicity but balancing this against the indisputable fact that otherwise this patient group of patients will all die from their recurrent disease or its sequelae. Persistent or recurrent head and neck cancer in a patient treated with previous high dose radiotherapy usually relates to one of three main factors:

1. relative radiation resistant tumours
2. geographical miss
3. development of a second primary malignancy

These main factors are further added to by the degree of hypoxia within the tumour volume and patient factors such as persistent smoking, alcohol consumption, poor attendance and often considerable social deprivation.

The potential high incidence of severe late normal tissue complications remains a concern amongst radiation oncologists, but in those colleagues who have undertaken re-irradiation and published their work, the extent of complications is generally less than that theoretically proposed by radiobiology studies. This is almost

certainly due to repair of radiation induced injury between initial radiation and subsequent re-irradiation. This would explain why the longer the disease free interval between the initial radiotherapy and the disease recurrence, the better the chance of survival after treatment with re-irradiation and the lower the incidence of serious complications.

Much of the literature on the subject relates to re-irradiation for residual/recurrent nasopharyngeal carcinoma. Clearly the problem at this site is the higher complication rate due to the proximity of important structures within the skull base and brain. The overall incidence of late complications at this site is around 25% and as at other head and neck sites, the most common complications are soft tissue or bone necrosis. With the advent of modern reconstructive surgical techniques, a number of these complications can be successfully dealt with.

Clearly, most re-irradiation for head and neck cancer is planned to exclude important neurological anatomy, such as cranial nerves (notably the optic nerve), brain stem, brain and spinal cord. Data on re-irradiation of recurrent disease or second primary tumours remain extremely variable in the literature, emanating from individual therapists or centres. Five year survival rates published within the literature vary from 10–90% depending on whether the series are unselected or highly selected. However, local control rates around about 40% are commonly reported, although severe, subsequently fatal complication rates rise continuously over the following years to levels of around 25–30%. There are no phase 3 trials reported in the literature to date.

Recommendation

- In carefully selected patients, re-irradiation is a worthwhile procedure that offers substantial local control (Grade C)

3.2.1. Re-irradiation with external beam radiotherapy alone

This technique has most commonly been employed for recurrent nasopharyngeal carcinoma. Whilst altered fractionation schedules showing increased local control in the primary treatment of head and neck cancer have been widely reported in the last 20 years, data on re-irradiation with accelerated or hyperfractionated radiotherapy is minimal.

3.2.2. Re-irrradiation with brachytherapy

This has been reported for recurrent tumours of the oropharynx and nasopharynx, particularly using iridium[192] after loading techniques, with and without additional surgical resection. Reported local control rates are often between 40–60%, but the 5-year overall survival between 15–30% due to a high incidence of second primaries, metastases and death from intercurrent disease.

3.2.3. Re-irradiation with IMRT

IMRT has potential therapeutic advantages in the treatment of localised recurrent disease in that delivery of a high intensive dose of re-irradiation can be given to the disease whilst sparing the surrounding tissues. The literature remains limited at present but the initial prospective studies on recurrent nasopharyngeal carcinoma reported from China show excellent initial tumour response with reasonable acute toxicity profiles.

There is a considerable increase in terms of both labour and expense over standard radiotherapy techniques.

3.2.4. Cyberknife – stereotactic radiotherapy

This new form of radiation delivery awaits further evaluation but has the potential to treat localised residual or recurrent disease and patients whose locoregional disease is controlled but who have developed isolated, or minimal lung metastases.

3.2.5. Re-irradiation combined with salvage surgery

If the residual/recurrent tumour is due essentially to intrinsic radio-resistance, perhaps coupled with hypoxia, then in theory maximal surgical resection to remove the radio-resistant clonogens may then be more successfully treated by radiation, perhaps combined with chemotherapy to reduce proliferation or increase tumour DNA damage. These are the most common methods currently employed for the full range of head and neck cancers, but again with widely varying control rates and survival figures as a consequence of the many variables.

3.2.6. Re-irradiation with concomitant chemotherapy

In order to try and improve outcomes in salvaging patients with recurrent disease, a wide variety of radiosensitising agents, including Hydroxyurea, Cisplatin, Paclitaxel and Docetaxel have been given concomitantly with re-irradiation. There are multiple phase 1 and 2 studies giving variable locoregional control rates of up to 30%, but 5-year survival of around 15% in patients who had been previously treated by radiotherapy. The survival rates for patients with a second primary tumour are notably better than for those with recurrent disease. Whilst the approach is feasible in selected patients, all the literature reports significant acute and late treatment related toxicity occurring in approximately one third of all patients.

Significant survival improvement remains a somewhat unfulfilled goal, and there is limited data at present in these patients regarding the effects of the chemotherapy and their subsequent performance status and quality of life. There is need for further trials with end points other than overall survival or tumour response in this patient population.

3.3. Palliative chemotherapy

Despite the recent advances made in the treatment of patients with squamous carcinoma of the head and neck confined to the primary site and neck region, many patients still relapse locally and are not candidates for salvage surgery or re-irradiation with or without chemotherapy. The majority of these patients die as a result of complications of their cancer and additionally a smaller group present with metastatic disease and are therefore not appropriate for attempts at radical curative treatment.

Patients with recurrent or metastatic disease require different goals in terms of their treatment and the palliation of existing symptoms, and hopefully the prevention of new cancer related problems. At this time, no single agent chemotherapy has been convincingly demonstrated to prolong survival and tumour shrinkage does not necessarily produce benefit in patients' symptoms or quality of life.

Multivariable analysis from palliative chemotherapy clinical trials have shown that the time to progression of disease and ultimate death is significantly influenced by general factors rather than the particular chemotherapy regime. These factors once again have been shown to be closely related to poor performance status, stage of disease and the prior treatment. There is no adequately powered randomised controlled clinical trial comparing chemotherapy treatment with supportive care. Table 1 shows some of the widely accepted factors associated with worse outcomes in patients with recurrent or metastatic squamous carcinoma of the head and neck treated by systemic chemotherapy:

Table 1. Factors associated with adverse outcome after chemotherapy in recurrent and metastatic disease

Patient related factors
• Poor performance status
• Presence of co-morbidity
• Poor cognitive function
• Lack of social support
• Ongoing tobacco, alcohol or beetle quid use
Disease related factors
• Advanced stage bulky locoregional or metastatic disease
• Previous history of aggressive disease
• Hypercalcaemia of malignancy
Treatment related factors
• Prior treatment
• Lack of or minimal response to treatment

Methotrexate and bleomycin used to be the most widely used chemotherapeutic agents, but since the 1980's, cisplatin has gained wide acceptance, but the considerable number of RCTs which have now been published comparing various combinations of platinums and other chemotherapeutics can be briefly summarised as follows. The evidence for cisplatin as a single agent is not superior to methotrexate in terms of response or median survival. The combination of cisplatin and methotrexate is not superior to methotrexate alone.

Whilst cisplatin and multi agent containing regimes are associated with higher response rates than single agent treatments, they are also associated with higher grade toxicity. Platinum containing combination regimes have been shown to have response rates approaching 50% in randomised controlled trials, but none of these trials have demonstrated a survival superiority of a particular regime. Indeed, there are trials which show that the median survival trend favours single agents over combinations. The survival information and meta-analysis of these trials has shown the difference in median survival in all comparisons to be less than one month. These factors have to be considered in relation to the morbidity of these regimes.

3.3.1. Cetuximab

As recurrent squamous carcinoma tends to be rich in epidermal growth factor receptors there has recently been considerable interest in the use of Cetuximab as several phase 2 and 3 studies have shown that the EGFR targeting monoclonal antibody, cetuximab, offers clinical benefit for patients with squamous head and neck cancer. In these trials, both tumour response and patient survival are in excess of that achieved by the conventional chemotherapeutic regimes. However, the addition of a platinum regime to cetuximab in this group of patients seems to confer no further benefit over cetuximab alone, particularly if those patients received platinum during their initial treatment prior to the recurrent disease.

Unfortunately, the limited superior survival that cetuximab provides in patients with recurrent or metastatic disease has again to be balanced against significant morbidity. Any survival advantage seems to be related to the development of rash. The integration of this targeted treatment therapy into treatment plans is associated with considerable cost and CRC studies show the costs per life year gain to be relatively high for cetuximab compared to other healthcare interventions. As such, NICE have recently declined to recommend this approach.

4. CAROTID ARTERY BLOW-OUT SYNDROME

Bleeding from the carotid artery or its branches (carotid blow-out) is a much feared and well-recognised complication following treatment for recurrence of head and neck cancer. The majority of patients require end of life supporting measures and often particular attention needs to be given to their close relatives who may experience this awful event.

Traditionally, surgical treatment has a high morbidity and mortality, and can be technically extremely challenging. However, with the continuing improvements in interventional radiology, recent publications have confirmed that endovascular techniques are now a definite low morbidity and viable treatment option in a selected group of patients. This can be particularly useful if there is a herald bleed and the situation can be stabilised by means of oropharyngolaryngeal packing whilst interventional radiology is mobilised. Control of the haemorrhage is more likely if the bleeding arises from the external carotid artery and its branches.

Early reports involve the use of permanent balloon occlusion, usually without serious neurological complications, but recently whilst temporary balloon occlusion may be used initially to try and ascertain the risk of cerebral ischaemia, subsequent super-selective embolisation or the placement of covered or uncovered endovascular stents have been increasingly reported in significant series of patients.

Unfortunately, the use of endovascular intervention has led to the emergence of a new group of patients who are those with recurrent carotid artery bleeding and some authors have advocated returning to the use of permanent carotid occlusion whenever possible. Clearly, the multidisciplinary team must address the ethical issues involved in deciding whether patients undergo this active treatment rather than having end of life conservative measures.

Key Points

- Recurrent disease is the major cause of mortality in patients who die from head and neck cancer.
- Recurrent tumours should undergo comprehensive evaluation and imaging, as for new primaries, before planning management.
- Patients with recurrent cancer need multi-disciplinary input in treatment planning
- Management options will vary based on the primary site, time since previous treatment, patient's general health and the expertise available at the treating centre.
- The outcome is dependent on the primary site, with higher chance of local control for some favourable sites.

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Chapter 33
Reconstruction in Head and Neck Surgical Oncology

Authors: James S. Brown (Maxilla, midface and oropharynx), Hisham Mehanna (Pharyngolarynx), Stephen Morley (Oral soft tissue and mandible)

1. INTRODUCTION

The problems of reconstructive surgery for the head and neck are variable and can be very complex. This chapter deals with the management of the loss of skin, the maxilla, the mandible including the associated soft tissues, the oropharynx and the laryngopharynx. It is not possible to fully discuss the anatomy and how that relates to the reconstruction and there is very little scientific evidence relating to the reconstruction of head and neck defects. Mandible 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.

2. ORAL SOFT TISSUES AND MANDIBLE

Most reconstructions are undertaken primarily following tumour extirpation, but secondary reconstructions are also undertaken to treat problems such as fistulae or as treatment for osteoradionecrosis. Modern techniques aim for one stage reconstruction utilising flap 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 factors relating to the surgical defect and any future possible treatments including radiotherapy. No appropriately powered RCT's exist to determine flap selection in most instances and this is usually determined by individual surgeons. Important patient factors include prior treatments, especially surgery and radiotherapy and the patients overall health including medical and tobacco history. Multiple tissue types often require to be reconstructed.

2.1. Soft tissues

Oral soft tissues include tongue, floor of mouth, buccal mucosa and the tonsil, retro-molar trigone and tonsillar area. It is rare that only one of these tissue types is involved. Reconstructive access is usually determined by the extent of surgical resection and may involve a mandibular split for posterior lesions.

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); anterolateral thigh flap (ALT); latissimus dorsi; rectus abdominus and flaps based on the scapular/para-scapular axis. 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. Multiple skin paddles can be designed and the flap can be raised as a cutaneous, fasciocutaneous, fascial or osseo-cutaneous flap (see below). The principle disadvantage of this flap is the poor donor site if a large flap which requires skin grafting to the donor is required.

The ALT flap allows for importation of very large tissue volumes and is versatile. Fascio-cutaneous and fascial flaps can be raised, along with muscle and fascia-lata if required. The flap has a long pedicle but is technically challenging to raise. It is a relatively thick flap but can be thinned. If multiple perforating vessels are available 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 fistulae. Regional flaps such as pectoralis major and deltopectoral can be effective in importing tissue but are not generally considered as a first choice.

2.2. Mandible reconstruction

Reconstruction of the mandible must address the size of bony defect; the site of the defect; associated soft tissue loss and the desirability of dental rehabilitation. Free tissue transfer is the mainstay of mandible 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, including the fibula flap, deep circumflex iliac artery flap (DCIA), scapular flap and RFF.

The fibular flap allows harvest of a long piece of bone which is of adequate height for osseointegration and can be osteotomized several times for contouring. It is relatively easy to harvest as an osseus or osteoseptocutaneous flap, with or without muscle. This versatility means it is the workhorse of mandible reconstruction in most centres. Drawbacks of the flap include its relative lack of height and difficulty in incorporating an external skin paddle.

The DCIA flap provides for a high bony segment and the natural curve of the ileum means that for lateral defects 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.

RFF 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.

Dental rehabilitation is a key part on mandible reconstruction and pre-operative liaison with an appropriate team including consideration of osseo-integrated implants is mandatory.

3. MAXILLA AND MIDFACE RECONSTRUCTION

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 involvment.

Throughout this section it is necessary to refer to the classification suggested in figure 1. The choice of a prosthetic option or reconstruction depends on the nature of the defect so that in the 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 (ClassIV) 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 Class 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 between the ablative, reconstructive team and the prosthodontist, maxillofacial technician, and the patient. 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.

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 and which generally do not require rehabilitation.

Class II

This is the standard hemimaxillaectomy 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 (Class 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 will give better support to the perinasal area such as the deep circumflex iliac artery (DCIA) flap which includes the iliac crest and internal oblique. The scapula flap can be supplied by the circumflex scapula artery which supplies the lateral scapula (scapula flap) through periosteal perforators along its

length or the angular branch of the thoracodorsal artery (thoracodorsal angular artery (TDAA)) which supplies the scapula tip. The advantage of the TDAA 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 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 TDAA 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 has been popularised by Cordeiro but the ectropinon rate is high and there is a risk of bone loss if radiotherapy is required.

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 TAA 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 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 TDAA flap is also a good option.

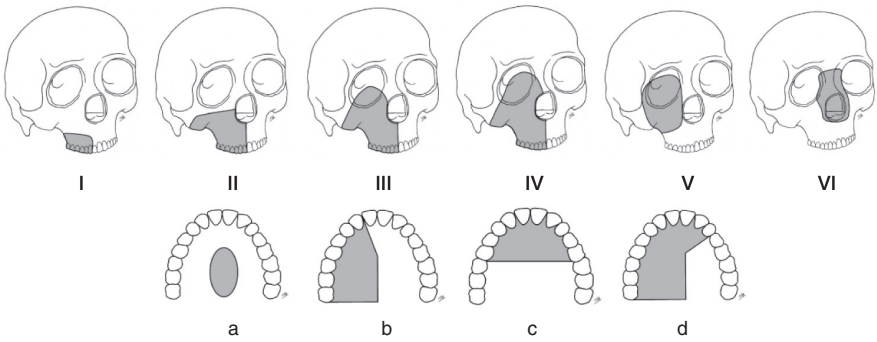

Fig 1. Classification of the Maxillary and Midface defect
Class I-VI relates to the vertical component of the defect including orbitomaxillary (Class V) and nasomaxillary (Class VI) when often the palate and dental alveolus are intact. Class a-d relates to the increasing size of the palatal and dento-alveolar part of the defect indicating increasing difficulty in obtaining good results with obturation

Class V

In the orbitomaxillary defect the main aim is not to obdurate the orbital space with too much soft tissue so as to allow space for an orbital prosthesis. The temporalis or temproparietal 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 and nasal bones then free tissue transfer is probably essential. The composite radial forearm flap can be ideal if harvested with fascia to line the nasal side of the radial strut and the skin to restore the face. The composite radial can be augmented with a glabella or forehead flap. In this defect attention must be paid to the restoration of the nasal bones with vascularised tissue to prevent complications during and following radiotherapy.

4. 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 trans-oral laser resection without reconstruction may give better functional results than reconstructing this muscular tube with non-sensate skin such as the radial forearm flap.

4.1. Reconstruction of the soft palate

The most commonly described method of soft palate reconstruction involves the use of the radial forearm flap 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 radial forearm flap which is de-epithelialised in order to be sutured to the de-epithelialised posterior pharyngeal wall, but a superiorly based pharyngeal flap can be utilised to provide the nasal lining with good results. 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.

4.2. Reconstruction of the pharyngeal walls and tonsillar regions

Placing free tissue transfers will disrupt the muscular tube and probably decrease function. The role of trans-oral laser resection is paramount in this region.

4.3. 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. Seikally and associates do report good results but general support for posterior tongue reconstruction is weak.

Table 1. Methods of soft palate reconstruction

No reconstruction	Obturation
Local flaps	Superiorly based pharyngeal flaps Palatoplasty and lateral pharyngeal flap Palatal island mucoperiosteal flap Palatal island and pharyngeal flap Masseter and buccal mucosa transposition flap Masseter, buccal mucosa and pharyngeal flaps Temporalis Superior constrictor advancement flap Velopharyngoplasty or masseter and buccal advancement flap
Pedicled flaps	Temporal osteocutaneous island flap Galeo-pericranial flap
Free flaps	Radial forearm flap Radial forearm and additional local flaps Folded radial forearm flap Lateral arm flap Jejunum Anterolateral thigh flap

5. PHARYNGO-LARYNGECTOMY RECONSTRUCTION

5.1. 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 [less than 1 cm in width], it is often better to excise the remnant and undertake a total circumferential reconstruction.

5.2. Total circumferential pharyngo-laryngectomy defects

5.2.1. Lower anastamosis above clavicles

Where the lower anastamosis of a total circumferential pharyngo-laryngectomy reconstruction would lie above the clavicle, several options exist: Jejunal free flap [JFF],

gastro-omental free flap [GFF], tubed radial forearm free flap [RFF] and tubed anterolateral thigh free flap [ALT]. 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.

5.2.2. 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 and the RFF. Swallowing problems due to hyper-peristalsis and a "wet" sounding voice are common with JFF, which also carries a high morbidity rate due to abdominal complications [30–40%]. RFF carry 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.

5.2.3. Post chemoradiotherapy (salvage) cases

In general, reconstructive free flap surgery post chemoradiotherapy 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 wrapped around the anastamotic site to decrease the possibility of leakage and also improve the overlying skin quality. Any of the other options mentioned previously – JFF, ALT, RFF – may also be used in post chemoradiotherapy cases, although more additional vascularised tissue can be included with the ALT.

5.2.4. Lower anastamosis below clavicles

If the resection extends to below the level of the clavicles, 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%, morbidity of 31–55% and reported fistula rates of 3–23%. 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.

Key Points

A. Mandible and oral cavity

1. The RFF and the ALT are the preferred options for oral soft tissue reconstruction
2. The fibula flap is now considered the workhorse for mandibular reconstruction following ablative surgery

3. The DCIA with internal oblique provides a superior form of the mandible and deeper implant placement and should be considered if implant-retained oral rehabilitation is planned
4. The scapula provides a good option for extensive soft tissue resections including the mandible and an alternative if atheroma precludes the fibula. The donor site is also the best tolerated

B. Midface and maxilla

1. Multidisciplinary decision-making should include the patient, surgeon and dental prosthodontist.
2. 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

C. Oropharynx

1. The oropharynx is a constrictor muscular tube with the soft palate superiorly and the epiglottis inferiorly.
2. Using local tissue only to restore the constrictor tube is essential. Free tissue transfer is best reserved for the reconstruction of the soft palate.
3. Functional results for posterior tongue reconstruction are disappointing.
4. The scapula flap provides a reliable and functional result with a well-tolerated donor site if mandibular resection is required.

D. Pharyngolarynx

1. Partial pharyngeal defects may be closed primarily or using a pedicled myocutaneous, usually a pectoralis major, flap or with a free flap.
2. 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 suggest that gastromental free flaps may have some advantages.
3. Tubing over and use of a salivary bypass tube appears to decrease complication rates with anterolateral thigh and radial forearm free flaps.
4. 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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Chapter 34
Palliative and Supportive Care

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1. INTRODUCTION

Palliative care aims to improve the quality of life of patients and their carers who are facing the problems associated with life threatening illness, through the prevention and relief of suffering, ensuring comfort and dignity, by means of early identification and impeccable assessment of pain and other problems, physical, psychosocial and spiritual.

Patients with head and neck cancer are a group in whom both palliative and supportive care is especially appropriate and particularly specialised, whether curable 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 of when specialist palliative care expertise is needed. This may involve core multidisciplinary team members, social workers, psychologists etc. Levels of intervention may involve inpatient, outpatient, day care, home care and telephone advice, from a single, arm's length intervention to a taking over of care. In turn, specialist palliative care practitioners need to be aware of when and how to use palliative interventions such as surgery, radiotherapy 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.

Recommendation

- Palliative and supportive care must be multidisciplinary (Grade D)

2. APPROACHES

Palliative care approaches can broadly be divided into conventional and holistic / complementary (table 1). Much of this chapter is devoted to conventional treatments

as used in symptom control; hand in hand with this goes the need for assessment of psychosocial issues of both patient and carers.

Table 1. Palliative care approaches.

Conventional Treatments	Holistic/Complementary
• Pain • Hydration/ Nutrition • GI symptom relief • Anxiety • Agitation • Dysphagia • Airway management • Hypercalcaemia	• Breaking bad news • Patient aspirations • Counselling • Psychological support • Emotional support • Support groups • Massage therapy • Aromatherapy

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 quality of life, therefore important decisions need to be made at presentation about which treatment pathway to take. The alternative to primary radical treatment, 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 extending life or no active treatment, but symptom control.

Effective decision-making in the palliative setting is important. The patient and family should adequately understand the diagnosis and prognosis, especially if it is different to before. Evidence suggests it is often the prognostic information which is inadequate (perhaps at times as the clinicians lack or are unfamiliar with available accurate prognostic tools). 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 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 positive manner, and it should not be assumed or conveyed that the 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.

The SPIKES protocol (Setting, Perception, Invitation, Knowledge, Empathy and Strategy) can be a helpful framework for head and neck oncology. This includes taking adequate time to talk to the patient, asking their understanding of the disease and inviting them to express how much they want to know, how they want to be told, and who they want to have with them. Language used should be understandable, with silences to allow news to be taken in. Clinicians should show empathy to the range of emotions presented by the patient and the family, and patient should leave the consultation with a plan of care.

3. SYMPTOM CONTROL

3.1. 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 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 breathing/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.

Recommendations

- Palliative surgery should be considered in selected cases (Grade D)
- For control of bleeding endovascular stenting or embolisation should be considered (Grade D)

3.2. Non-surgical palliation

3.2.1. Radiotherapy

Debate continues around the optimal dosage regimen for palliative radiotherapy. Low-level evidence exists for the use of hypofractionation schedules and short course radiotherapy. Other protocols such as described by the Radiation therapy Oncology Group (RTOG) have also demonstrated benefit. Symptom control can be achieved in up to 80% 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 Cochrane systematic review of radiotherapy for painful bone metastases reports benefit in up to 50% of patients.

3.2.2. Chemotherapy

This includes the use of platinum-based agents, 5 FU and methotrexate, either as monotherapy or in combination with radiotherapy and demonstrates benefit in symptom control and quality of life measures, but may increase toxicity and hence side-effects from 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 selected cases.

3.2.3. Future modalities

Future research will include the role of taxanes e.g., paclitaxel, monoclonal antibodies e.g., cetuximab, newer chemotherapeutic agents, photodynamic therapy (PDT) and interstitial laser therapy (ILT). Descriptive series report some symptom control using these modalities but without evidence of improved survival.

Recommendation

- Hypofractionated or short course radiotherapy should be considered for local pain control (Grade D) and for painful bony metastases (Grade A)

3.3. Palliation of dysphagia

Forty percent of patients with head and neck cancer suffer from dysphagia. This is due to:

- Mechanical obstruction
- Functional obstruction
- Drug induced
- Fistula
- Pain

Assessment of the swallow is essential in most head and neck patients. It is important to establish whether oral intake is possible and whether it is safe. Aspiration is not uncommon and maybe silent in up to 40% 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 different textures and in combination with videofluoroscopy.

Aspiration does not inevitably mean no oral intake. A degree of aspiration maybe well tolerated and methods taught to clear the airway after swallowing can be implemented. Similarly certain textures maybe better tolerated and the used of thickened fluids can help maintain oral intake. It is important to take in to 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 or gastrostomy allows for hydration, nutrition and medication. The type of tube used depends largely on ability to pass a nasogastric tube or fashion a gastrostomy (most commonly performed radiologically), perceived duration of use and patient choice.

Conventional treatments can be helpful in the palliation of swallowing. Surgical debulking either with or without the laser and radiotherapy 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 (Grade D)
- Establishment of enteral feeding must be considered early in patients who are unable to maintain their intake orally (Grade D)

3.4. Palliation of the airway

Where there is airway compromise it is common practice in ENT to consider a tracheostomy. Sometimes the airway can be improved by tumour debulking. However sometimes there is a role for NO surgical intervention. In these instances palliation with sedation and reduction of secretions can support a patient in a terminal event. These situations are difficult and it is unlikely that a rational discussion can be had with someone experiencing acute airway compromise. However, expectation of a future event can be discussed with the patients and their carers. For example in a patient with a tracheal tumour that has been repeatedly debulked, is not a candidate for stenting and who has received palliative radiation. There will come a time when the airway compromise will be life threatening. A tracheostomy may not be an option in this instance, but to have the patient and family prepared for the event is paramount. They must know what will be in place to prevent the anxiety associated with such a situation and the patient must be comfortable to the end.

3.5. Pain

Pain is very common, affecting most patients at any stage. It may be disease or treatment related, either acute/immediate or persistent/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 WHO "Pain Ladder" (table 2) with 3 steps of increasing potency, and used depending on pain severity and response.

Table 2. WHO Pain Ladder

1. Paracetamol +/- non steroidal anti-inflammatory drug +/- adjuvant
2. Weak opioid (codeine or tramadol) + step 1 drugs
3. 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 or gastrostomy tube in situ.

3.5.1. 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 infusion of morphine or diamorphine can be used, with subcutaneous doses for breakthrough. Diamorphine is preferred since it is more soluble and can be used in much smaller volumes. *To convert from oral to injected morphine divide the dose by 2; to convert to injected diamorphine divide by 3.*

Transdermal preparations of fentanyl have theoretical and practical attractions for background pain as an alternative, particularly if there is morphine intolerance (e.g., nausea/vomiting, constipation, and dysphoria) or there is renal failure. For breakthrough morphine solution; or buccal, sublingual or intranasal fentanyl (new preparations with which experience is limited, and not yet widely recommended) can be used.

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.

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.

3.5.2. 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 used for the more constant, burning neuralgic pains; available as tablet and liquid.
- Anticonvulsants are used for stabbing, brief pains. Gabapentin and pregabalin are the most used, available only as tablets/capsules unless through special arrangements with one's pharmacy.
- Carbamazepine is an alternative and is available both as tablet, liquid and even suppositories.

First line would be either antidepressant or anticonvulsant (*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. It is not for chronic or predictably long term pain. Clonazepam is occasionally useful. Methadone and ketamine are useful, but only in specialist settings.

3.5.3. Visceral pain

This may respond poorly to opioids and treatment depends on cause. Pain due to metastatic disease may be eased with Dexamethasone (4–8 mg daily) and some respond to the adjuvants described above.

Judicious use of all these drugs is best achieved by seeking advice from the specialist palliative care service whenever there is concern. Equally, one should also take advice from specialists in pain management, as interventional techniques can be very effective where systemic treatments fail.

3.5.4. 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 lollies.

Recommendations

- Pain relief should be based on the WHO pain ladder (Grade B)
- Specialist pain management service involvement should be considered early for those with refractory pain (Grade D)

3.6. Nausea and vomiting

The approach must take account of the large number of patients who are enterally fed. Even with this there is often a need for injectable – subcutaneous 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 –See appendix 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.

3.7. Constipation

Constipation develops in half of patients who are terminally ill with cancer admitted to a hospice. In 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. 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 and docusate. Movicol (polyethylene glycol) is 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 (Grade D)

3.8. Confusion and agitation

It is important to distinguish anxiety (unsettled, frightened, panic) from confusion, particularly delirium. Confusion is common, affecting up to 75% 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 treatment of anxiety. Diazepam can be given orally, via a tube in liquid form, or by injection, though only intravenously. Lorazepam can be taken as a swallowed tablet, or a tablet dissolved sublingually, dry mouth allowing. If injections/infusions are needed, midazolam is preferred, as it can be given subcutaneously (most common route) or intravenously when almost immediate effect is needed.

Delirium as a cause of confusion can be related to a number of organic causes – infection, dehydration, metabolic disturbance, respiratory failure, urinary retention/constipation 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 one in drug withdrawal, most often delirium is better managed using haloperidol (as tablet, liquid or injection, including subcutaneous), or levomepromazine (as tablet or injection) where sedation is needed in managing paranoia etc.

In some cases, particularly at the end of life – so called terminal agitation/restlessness – benzodiazepines and antipsychotics need to be combined.

Recommendation

- Organic causes of confusion should be identified and corrected where appropriate, failing this treatement with benzodiazepines or antipsychotics should be considered (Grade D)

3.9. 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 /confusion can result.
- Hyoscine butyl bromide, which is not CNS 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 subcutaneous use needed.
- 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.

3.10. Steroids

As with other cancers, corticosteroids are widely used. Dexamethasone (table 3) is the most used, because of its potency, relative lack of mineralocorticoid properties, and wide range of formulations (water soluble tablets, solution, and injection, subcutaneous or intravenous).

Dexamethasone 1mg = Prednisolone 7.5mg

Long-term use also requires that attention be paid to bone mineral density, and bisphosphonates, and calcium/vitamin D supplements are indicated (table 4). 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 3 to 4 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.

Table 3. Indications and dosage for steroid use

Appetite, energy and well being	4mg initially
Adjuvant analgesic	8–16mg initially
Antiemetic	see above and oncology guidelines
Spinal cord compression	see NICE guidelines (CG 75)
Tumour oedema (e.g., tracheal compression, SVC obstruction)	8–16mg initially

Table 4. Side effects of steroid use

Insomnia	Cushingoid appearance
Psychiatric disturbance	Osteoporosis
Candidiasis	Proximal myopathy
Dyspepsia and PUD	Avascular necrosis
Loss of glycaemic control	
Drug interactions (especially warfarin and anticonvulsants)	

3.11. Spinal metastases

The incidence of spinal metastases in HNSCC is reported to be less than 2%, however it is more common in thyroid cancer (2–13%). 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 (table 5) and action is essential and consideration that symptoms may be suggestive of spinal metastatic disease is the first step.

Table 5. 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

Neurological symptoms and signs should be assessed and an MRI of the whole spine obtained. Treatment depends on findings and includes steroids, surgical stabilisation and radiotherapy. Clear guidelines on diagnosis and management have been published by NICE and the readers should familiar themselves with these.

Recommendation

- Patients with symptoms suggestive of spinal metastases or metastatic cord compression must be managed in accordance with the NICE Guidance on this (Level C)

4. END OF LIFE CARE – THE LIVERPOOL CARE PATHWAY

This "care plan"/guideline has found wide acceptance in the UK in particular, and is in use in all care settings, including patients' own homes. It has just been revised as a twelfth edition, published in December 2009.

The role of the doctor is to recognise that death is imminent, and the patient's senior clinician is seen as the one to contribute to the multiprofessional decision to sign up to use it. Care is then modified, with unnecessary medication being stopped, and essential medication continued, usually by subcutaneous infusions and boluses. In the head and neck patient the quite frequent presence of nasogastric and gastrostomy tubes allows continued use of some medications which would otherwise be impossible to administer. Similarly, the latest version of the "pathway" document lays more emphasis than hitherto on artificial hydration and nutrition. While nutrition is usually inappropriate in dying patients, neither subcutaneous nor intravenous fluid is necessarily ruled out – although the benefits can be, indeed often are very limited, indeed outweighed by the problems. Tubes provide a further option for those patients. The other point emphasised in the new document is the need for regular multiprofessional review, and the possibility that patients may improve, for whatever reason, and so be "taken off the pathway" and alternative approaches implemented.

The four main symptoms at which "anticipatory prescribing" is aimed at are:

- pain
- nausea/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
- antiemetic–levomepromazine
- agitation–midazolam and/or levomepromazine or haloperidol
- antisecretory–hyoscine, either butyl- or hydrobromide

The choice can be modified if other drugs have an already-established role, not least because the "first choice" has been ineffective or unsuitable, along the lines discussed above. Fortunately, all the commonly needed drugs can be given subcutaneously, and feeding tubes increase the available options.

Recommendation

- All patients at the end of life should be placed on and managed according to the Liverpool Care Pathway (Grade C)

5. DO NOT ATTEMPT RESUSCITATION (DNAR)

This is a subject of such wide clinical and ethical complexity (Tables 6 and 7) 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)

Table 6. Fundamental ethical principles

• Autonomy
• Beneficence
• Non maleficence
• Justice

Table 7. Relevant articles of Human Rights Act

2. The right to life
3. Freedom from inhuman/degrading treatment
8. The right to privacy
10. Freedom of expression and to be informed
14. Freedom from discrimination

Fundamental to the point is the identification that cardiopulmonary resuscitation (CPR) has become inappropriate and to recognise those who competently refuse it, whether that is to be written down, and so to provide a framework for local policies

There exist conflicting issues regarding DNAR. CPR is a treatment, and no doctor is required to offer any treatment that they do not feel to be in their patient's best interests. However the default position in most hospitals is in favour of offering CPR.

5.1. A competent patient

Based on the BMA document many Trusts insist on discussion of a DNAR order. A competent patient can decline CPR and a DNAR can be written, however they cannot insist that CPR be offered. In this situation a DNAR can not be completed – which is *not* to say that CPR will be offered – *the decision is left until the situation arises to consider the issue of whether this CPR treatment is a reasonable one.*

Despite the insistence on discussion it is not always appropriate in that it may cause unnecessary distress. One should be aware of 'defensive discussions' where the real beneficiary is the healthcare team - these may be unethically frightening for the patient. If there is no discussion, the reasons for this must be documented. An increasingly widely employed concept is that of "Allow Natural Death" ie there is no need to burden the patient or others with discussion when there is no question of offering CPR.

Most of the above advice is most easily applied to hospitals, hospices, nursing homes there is little regarding management of the patient at home, where it is

equally important to avoid unnecessary CPR. Here it is necessary to have the written order in the patient's possession, and so discussion is then obligatory. Indeed in many places, the Ambulance Service requires and up-to-date DNAR form before transporting the patient, again placing emphasis on the need for discussion when one's instincts may have been to otherwise avoid it.

What protects us from most of this for most of the time is the essential reasonableness of patients and families and the Law of Averages

5.2. An incompetent patient

5.2.1. Recent incompetence

If the patient has recently become incompetent, some questions need to be asked:

- Have they previously discussed and agreed to a DNAR?
- Or made some other form of advanced decision to refuse treatment/living will?
- Or, increasingly common, been party to "Advanced Care Planning"?
- 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 case this person can be approached, bearing in mind that they, no more than the patient, can insist on treatment, only decline it - *see above*.

5.2.2. Longstanding incompetence

If the patient is incompetent throughout, then the decision is left to the doctor(s) and other members of the team to act in the patient's best interest. Where they exist family, next of kin, carers etc 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.

Occasionally no agreement can be reached between doctor, the team, the patient and those close to the patient, in which case second opinions can be sought, or even legal advice where there is the possibility of more formal measures such as the involvement of the Court of Protection.

Recommendations

- CPR is inappropriate in the palliative patient (Grade D)
- DNAR orders should be completed and discussed with patient and /or family where appropriate. This is absolutely necessary when a patients care is to be managed at home (Grade D)

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Chapter 35
Follow-up of Head and Neck Cancers

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1. 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. 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. 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 2 years when the risk of loco-regional recurrence is known to be high and then reduce frequency, with follow-up often finishing at 5 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.

In order to rationalise follow-up, patients could be divided into low and high risk. This is well recognized in thyroid cancer but it is not the case in all other types of head and neck cancer especially squamous cell carcinoma. It is a belief that, this categorization could help to determine which patients should be followed for more than 5 years. It would also help to establish which screening test may be needed in order to detect recurrence or second primaries.

2. GENERAL CONSIDERATIONS

2.1. Length

The length of follow-up is generally 5 years although there are many clinicians who follow-up patients for longer periods or even for life. Follow up of patients

over 5 years would be justified for the following groups: high-risk patients, specific tumours (eg. adenoid cystic carcinomas), patients who have undergone complex treatments who require on-going rehabilitation and support, and the detection of new primary tumours as well as 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 5 years with a prolonged follow-up for selected patients (Grade B).

2.2. 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 2 years when the risk of loco-regional recurrence is high followed by a decrease in frequency after the second year. This is evidence of the recognition of the importance of this high frequency. The follow-up in the first 2 years should be between 4 to 8 weeks and from 3 months to 6 months thereafter.

Recommendation

- Patients should be followed up at least 2 monthly in the first 2 years and 3 to 6 monthly in the subsequent years (Grade C).

2.3. Setting

At present, 90 % 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 (Grade C).

2.4. Type of health professional

At present patients are followed up by their treating clinicians and their teams. Allied heath professionals including speech and language therapists, dieticians and

clinical nurse specialist may offer specific follow-up in their areas of expertise but this is usually in addition to the clinicians 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 become vital to open lines of communication between the patient and family and the clinical team should any problems arise.

Recommendations

- Patients should be followed-up by dedicated multidisciplinary clinical teams (Grade C).
- The multidisciplinary follow-up team should include. clinical nurse specialists, speech and language therapists, dietitians and other allied health professional in the role of key workers (Grade C).

2.5. 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 rigid or fibre-optic nasopharyngolaryngoscopy. Rigid stroboscopy can also be used in patients who have been treated for laryngeal cancer.

Recommendations

Clinical assessment should include adequate clinical examination including nasopharyngolaryngoscopy (Grade B).

2.6. Screening investigation

Currently there is evidence that MRI and PET-CT scanning are superior at detecting recurrence and second primaries. This is especially true in some tumour sites such as the nasopharynx and following treatment with chemo-radiation. PET-CT has also the advantage of being a systemic evaluation.

Recommendation

MRI and PET-CT should be used when recurrence is suspected (Grade B).

2.7. Second primary tumours

The incidence of second primary tumours varies between 5 to 12% at 5 years. There is good evidence to indicate that patients with head and neck squamous

cell carcinoma have an increased the risk of developing second primary malignant tumours. This risk appears to be constant throughout the follow-up period, with an incidence ranging from 2% to 4% 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 (Grade B).

3. SPECIFIC CONSIDERATIONS

3.1. Second-look microlaryngoscopies

In laryngeal cancer, especially in those patients treated with transoral laser microsurgical excision, it is advisable to perform second-look microlaryngoscopies especially in scenarios where there is uncertainty between the surgeon and pathologist 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.

3.2. 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 squamous cell carcinomas. The use of tumour markers in the follow-up of patients with thyroid cancer is addressed in Chapter 28.

3.3. 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 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 the appearance and detection of recurrences (Grade D).
- Patients should be offered support with tobacco and alcohol cessation services (Grade B).

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Chapter 36
Clinical Research, National Studies and Grant Applications

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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 United Kingdom. The framework for the organisation of clinical cancer research is based upon the National Cancer Research Network (NCRN), which encompasses all 30 UK Cancer Networks as well as Scotland and Wales. The NCRN includes a national executive and regional directors in each of the cancer research networks. At a local level the NCRN is responsible for the provision of research infrastructure including research nurses. The allocation of the NCRN resource is largely determined by a partner organisation – the National Cancer Research Institute (NCRI). The National Cancer Research Institute 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 specialities related to clinical cancer research are represented – e.g. surgical specialities of head and neck surgery, maxillofacial surgery and plastic surgery, clinical oncology, 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. 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 Dr Christopher Nutting at the Royal Marsden Hospital.

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 (www.ncri.org.uk).

For individuals interested in developing clinical research there are a number of sources of funding where grant applications can be submitted. For large randomized phase III trials the 2 main funders at the present time are Cancer Research UK through the clinical trials advisory and awards committee (CTAAC) and also the health technology assessment panel (HTA).

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 (HTA). 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 (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. For smaller research projects in single centre 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/
www.rcr.ac.uk
www.rcseng.ac.uk
www.bahno.org.uk
www.hta.ac.uk

Chapter 37
Education of Trainees, Training and Fellowships

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1. INTRODUCTION

Appropriate and effective training in Head and Neck Surgical Oncology (HNSO) is crucial in order to ensure high quality Head and Neck Oncology services in the future.

The problems encountered by the re-structuring and shortening of training programmes over the last decade have been lessened by the creation of interface and post-specialty dedicated training posts. These changes require more substantial input by trainers which may impact on patient care, but there is no doubt that better structured and dedicated time in sub-specialty training is required.

2. EDUCATIONAL PRINCIPLES

2.1. Training

Training in HNSO, both in the parent speciality and for Interface trainees is governed by a curriculum approved by the GMC. From 2007, all surgical trainees have been required to follow the curriculum for training as set out in the Intercollegiate Surgical Curriculum project. For Clinical Oncology, training is supervised by the Royal College of Radiologists (RCR) and for Medical Oncology by the Royal College of Physicians (RCP).

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 to 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 standards are met and 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 of the Intercollegiate Surgical Curriculum Programme *(*www.iscp.ac.uk). This will identify the gap between what they know or can do compared to 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** (Specific, Measurable, Achievable, Relevant & Timely) objectives 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.

2.2. 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 (eg 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 and professionalism/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 that confirms that the trainee has met his or her targets for the year and is progressing satisfactorily. ARCP 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 (RITA) 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.

3. CAREER STRUCTURE

3.1. Otorhinolaryngology-Head and Neck Surgery (ORL-HNS) and Plastic Surgery (PS)

Training in ORL-HNS 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 MRCS (ENT) or MRCS (GS or PS).

Higher surgical training lasts 6 years and during this time all trainees will develop competence in all aspects of the specialty. Trainees should take their Intercollegiate Exam from ST6 onwards. In the final 2 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.

3.2. Oral and Maxillofacial Surgery (OMFS)

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 GMC register. Registration with the 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 MRCS. Once the MRCS is obtained they are eligible to apply for a post in specialty training in OMFS. Trainees from dentistry as a second degree, need to decide if they are likely to wish to practice dentistry outside of OMFS, in which case they will do dental foundation training, likely to be 1 to 2 years then if they have MRCS already they can apply in to a specialty training post in OMFS.

Specialty training in OMFS lasts 5 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.

3.3. Oncology (O)

Currently, in the UK, there are two main types of oncologist concerned with the management of patients with cancer: Medical Oncologists (MO) and Clinical Oncologists (CO). Both see and assess patients with cancer and both specialities are part of the core membership of cancer MDTs.

Medical Oncologists are physicians trained in the use of systemic drug therapies for cancer, either alone or in combination with other treatments. Cos are trained in both systemic drug therapy and in the use of radiotherapy.

Training for MOs is supervised by the RCP. Entry is at ST3 level (entrants must have passed Part 1 MRCP and are expected to pass Part 2 within the first year of their specialist training). There is a 4 year training programme leading after passing the Specialty Certificate Examination (SCE), to a CCT in MO.

Specialist training in CO also begins at ST3 level and also demands MRCP Part1 for entry and that MRCP Part 2 be passed by the end of ST3. The training is supervised by the RCR and there is a two-part examination leading to Fellowship of the RCR (FRCR). The training takes 5 years. The part 1 examination, usually passed by the end of ST4, covers the basic sciences of oncology and radiotherapy the Part 2 examination, usually passed during the 4th 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.

4. INTEGRATED AND ADVANCED FELLOWSHIPS

Although HNSO is yet to become a recognized specialty, the SACs in OMS, ORL-HNS and PS, through the JCST Tumour Interface Group (TIG), 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 recognized training post and have completed successfully their Intercollegiate Examination. The recognized fellowships are shown in table 1.

Additionally, there are several hospitals that offer further advanced independent Post-CCT HNSO Fellowships although these are yet to be recognized by accredited bodies. These programmes are currently available in University Hospital Coventry, Addenbrooks Hospital Cambridge, Nottingham University Hospital, Guy's and St Thomas' Hospital and St George's Hospital in London.

In the European Union sub-specialty training in HNSO remains diverse. However the UEMS has initiated steps to standardize sub-specialty 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 consultant head and neck surgical oncology posts have the required additional and adequate training in this sub-specialty. This is often an essential or a desired requirement in the job descriptions.

Table 1 Interface head and neck oncology fellowships in the United Kingdom

Region	Lead Hospital
Kent & Sussex	Queen Victoria Hospital
Mersey	Aintree Hospital
North Trent	Royal Hallamshire Hospital
Northern	Freeman Hospital
Northwest 1	Manchester Royal Infirmary
Northwest 2	North Manchester General Hospital
Oxford	John Radcliffe Hospital
South East Thames	Guy's and St Thomas Hospital
West Midlands	Queen Elizabeth Hospital
West of Scotland	Glasgow Royal Infirmary
Yorkshire	Hull Royal Infirmary

Recommendation

- Trainees applying for consultant head and neck surgical oncology posts should have completed additional training in the sub-specialty

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Chapter 38
Future Perspectives

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1. OTOLARYNGOLOGY PERSPECTIVE

We are entering a period of profound change in healthcare delivery due to changing therapeutic options and financial imperatives. The socialised, lean nature of the NHS makes it, in theory, an ideal place in which to embed new treatments, processes and business models for population and individual benefit. The over-riding trends in the immediate future organisation of head and neck oncology must be towards very few centres performing surgery and radiotherapy, as only in this way will the full benefits of costly new technologies be realised, the full range of options be presented to patients and costs offset by maximum possible gains in quantity and quality of life (QALY balancing). As *quid pro quo*, it is essential that a new type of specialist is born to apply the best of screening, diagnostic, rehabilitation and palliative care tools in smaller, 'spoke' units also, for example using telemedicine and high resolution endoscopy.

Following on from phase II trials in the 1990's, the addition of chemotherapy to radiotherapy for loco-regionally advanced squamous cell carcinoma of the head and neck has probably led to improvements in loco-regional disease control and survival, but is associated with substantial acute and late toxicities. Although standard chemotherapeutic regimens have been manipulated and supplemented by the introduction of newer cytotoxic agents, still there have been no real improvements in survival for patients with recurrent or metastatic disease. Combination with targeted agents is starting to reduce this toxicity, with epidermal growth factor receptor (EGFR) inhibitors (e.g., cetuximab) and tyrosine kinase inhibitors (e.g., erlotinib) the most used. Inhibition of angiogenesis (e.g., bevacizumab, VEGF inhibitor) will improve as our understanding of the subtleties of VEGF variants grows. Phase III trial data for apoptosis and COX-2 inhibitors and immunotherapies are also awaited, and likely will reduce toxicities further.

However, the dominance of toxic chemotherapeutic regimens will be seriously challenged if the bar can be lowered for the performance of surgery with curative intent. Robots already permit extension of endoscopic surgery around corners, making 2D into 3D. Newer lasers can be passed via endoscopes in the outpatients for early lesions, or to activate photodynamic agents. The advent of regenerative medicine, including stem cells and tissue engineering may hold the most promise, however: it will permit the functional and cosmetic regeneration of head and neck tissues in a functional manner that will facilitate wider and more effective resection of margins, tissues and organs with dramatically improved quality of life for recipients.

These paradigm shifts demand a new look at how we train the head and neck surgical and medical oncologists of the future, for it has to be and will be radically different from the past.

Recommendations

1. Head and neck cancer services need to centralise into units dealing with a minimum of 100 new cases of squamous mucosal cancer per annum
2. This requires an exciting new approach to 'spoke' units with advanced imaging, diagnostics, telemedicine and palliative care introduced as surgery and chemoradiation is centralised
3. More dedicated fellowships for advanced training in head and neck surgery are required
4. Research is a necessary future-proofing skill for these trainees, who will face major changes throughout their working lives

2. MEDICAL AND RADIATION ONCOLOGY PERSPECTIVE

In the last ten years, the non-surgical management of head and neck cancer has seen a number of significant advances. These include: (i) technological advances in radiation delivery that can be employed as a means of reducing normal tissue toxicity and potentially increasing dose to tumour tissues; (ii) proof of the superiority of concomitant chemoradiotherapy over radiotherapy alone in both definitive and adjuvant treatment settings; and (iii) identification of some of the molecular biological processes underlying disease causation and behaviour and, as a direct result, the development of novel targeted therapies that modulate these processes.

(i) In the first of these areas, the value of normal tissue-sparing radiotherapy techniques has been confirmed in data from the PARSPORT Phase III study and the CR-UK-sponsored COSTAR Phase III study of cochlea-sparing radiotherapy in patients with parotid tumours has opened to recruitment. It is likely that other studies of intensity-modulated radiotherapy (IMRT) will also test the ability of this technique to reduce treatment-related morbidity. A further CR-UK-funded dose-escalation Phase III study (ART-DECO) of concomitant chemotherapy with either intensity-modulated radiotherapy or conventional radiotherapy will recruit patients with laryngo-pharyngeal tumours over the next 4 years.

(ii) In the area of concomitant chemoradiotherapy, research effort will focus on two major themes: the addition of epidermal growth factor receptor targeted therapies (cetuximab, panitumumab, zalutumumab, lapatinib) to cisplatin during concomitant chemoradiotherapy; and the use of new agents (e.g., taxanes, growth factor receptor inhibitors) during induction/neoadjuvant chemotherapy. The findings of the RTOG 0522 study on adding cetuximab to chemoradiotherapy concluded that the addition of cetuximab to the radiation-cisplatin platform did not improve progression-free or overall survival. However, the triplet regimen was associated with higher rates of mucositis and CET-induced skin reactions.

(iii) The area of identifying novel molecular targets for therapy in head and neck cancer is likely to be a particularly fruitful area of research activity in the next decade. The original proof-of-principle data for EGFR-targeted drugs combined with radiotherapy were derived in patients with head and neck cancers and a recent phase III study showed that these agents also improve outcome in the palliative setting. These models will also be used for a range of new agents, including those targeting insulin-like growth factor 1 receptor, vascular endothelial growth factors and receptors, DNA repair inhibitors (eg PARP inhibitors). As a result, it is likely that clinical trial activity will continue to increase rapidly for patients with newly-diagnosed, relapsed and metastatic head and neck cancers.

3. ORAL AND MAXILLOFACIAL SURGERY PERSPECTIVE

The past decades have witnessed dramatic advances in anaesthetic techniques enabling longer and safer operations; imaging modalities such as MRI and ultrasound leading to improvements in preoperative planning and staging; pathological understanding of bone invasion and neck disease leading to conservative mandibular surgery and more frequent but less radical neck dissection; nutrition and dietetics with endoscopic and radiologically inserted gastrostomies; and speech and swallowing therapies.

Surgical tools such as the Colorado needle and Harmonic scalpel have reduced operative blood loss. Electrically powered saws and titanium plating systems have allowed more precise bone surgery and re-popularisation of Henry Butlin's original mandibulotomy. Access surgical techniques have allowed easier and safer approaches to deep structures whilst, conversely, endoscopic and laser advances have popularized non-invasive surgery. The greatest surgical advances have probably come though from the advent of the surgical microscope and microsurgical equipment and sutures coupled with increased understanding of the blood supply of reconstructive tissues by luminaries such as MacGregor, Bakamjian and Taylor. The ability to use composite distant tissue to microsurgically reconstruct the defect has led to an increased ability to perform successful ablative cancer surgery without harm. The patients recover more quickly from these complex operations incorporating primary reconstruction and their appearance, speech and swallowing are often not significantly adversely affected.

All these advances have combined to alter the management of head and neck cancer. Oral squamous cell cancer (OSCC) in particular has changed from primary radiotherapy with surgical salvage in the 1970s to primary surgery with adjuvant radiotherapy or chemoradiotherapy now. These alterations in OSCC treatment protocols have translated into improvements in 5-year survival figures and local and regional disease control. Unfortunately, these improvements have only been recorded from a few centres, such as Memorial Sloan Kettering, New York and University Hospital Aintree, Liverpool, where data collection is scrupulously maintained.

Despite these successes, there are many areas where improvement is needed. Malignant salivary diseases such as adenoid cystic and adenocarcinoma stubbornly

resist radiotherapy or chemotherapy solutions and disease control has barely improved. The improved local and regional control of OSCC has highlighted our inability to reduce distant metastatic spread of OSCC and metachronous aerodigestive tract primaries. Radiation normal tissue damage continues to cause morbidity despite advances with radiotherapy planning such as IMRT. This could be because these advances are frequently used to increase total radiotherapy dosage to control disease. An increasing number of patients surviving OSCC are presenting with problems related to carotid artery stenosis and osteoradionecrosis cases still occur.

Now, and in the immediate future, CADCAM (computer-aided design and computer-aided manufacturing) techniques will increasingly be used to plan jaw reconstruction, possibly with the incorporation of better restoration of missing teeth. Cosmetic techniques may be used to further improve patients' appearance following treatment. The increased use of novel agents such as epidermal growth factor receptor antibodies, and studies on the timing of adjuvant chemotherapy treatment will lead to improvements in disease control.

In the future, we must improve data collection in all units to determine outcomes. With this in place we can initiate prospective surgical studies to determine the evidence base for current treatment. These "gold standards" can then serve as comparators for future innovations. Finally, tumour tissue banks, if accurately maintained so that tissue can be compared to clinical outcomes in the patients from whom it is harvested, will provide answers on prognostic factors and future therapies, especially when allied to tissue culture and chemosensitivity studies.

Key Points

- The future will see an increasingly rapid pace of change.
- There will be a shift towards personalized medicine, with treatments possibly decided using molecular methods in a 'one-stop—shop' setting.
- These changes demand that we rapidly address the organization of head and neck oncology services, with far greater centralization of care into major centres that can apply advances more quickly.
- Regenerative medicine will permit restoration of function to ever-higher standards
- All of these advances will come at a financial price, so careful business planning and clinical pathway development is necessary to ensure the UK population will be able to benefit as early as possible, with the immense survival and quality of life gains that will surely follow.

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Useful websites

Professional organisations:

British Association of Endocrine and Thyroid Surgeons (www.baets.org.uk/)
British Association of Head & Neck Oncologists (http://www.bahno.org.uk)
British Association of Head and Neck Oncology Nurses (http://www.bahnon.org.uk)
British Association of Oral and Maxillofacial Surgeons (http://www.baoms.org.uk)
British Association of Otorhinolaryngology – Head and Neck Surgery (http://www.entuk.org)
British Association of Plastic, Reconstructive and Aesthetic Surgeons (www.bapras.org.uk)
Head and Neck Section, The British Association of Otorhinolaryngology – Head and Neck Surgery (http://www.entuk.org/head_and_neck)
The Royal College of Pathologists (http://www.rcpath.org)
The Royal College of Radiologists (http://www.rcr.ac.uk)
The Royal College of Speech and Language Therapists (http://www.rcslt.org)

Cancer information:

Cancer Patient Information Pathways (http://www.cancerinfo.nhs.uk/cancer-patient-information-pathways)
Cancer Research UK (www.cancerresearchuk.org)
Macmillan Cancer Support (http://www.macmillan.org.uk)
National Cancer Institute (www.cancer.gov)
National Cancer Intelligence Network (http://www.ncin.org.uk)
National Head and Neck Cancer Audit reports (http://www.ic.nhs.uk/headandneck)
NHS Choices Cancer (www.nhs.uk/conditions/cancer)