

Head and neck cancer—Part 2: Treatment and prognostic factors

H Mehanna,¹ C M L West,² C Nutting,³ V Paleri⁴

¹Institute of Head and Neck Studies and Education, University Hospitals Coventry, Coventry CV2 2DX

²University of Manchester, Manchester

³Head and Neck Unit, Royal Marsden NHS Foundation Trust, London

⁴Otolaryngology-Head and Neck Surgery, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne

Correspondence to: H Mehanna hishammehanna@aol.com

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In this second of a two part series, we discuss recent advances in the management of cancers of the head and neck. We also discuss the important prognostic factors, including the importance of human papillomavirus (HPV) positivity in the newly discovered HPV related cancers of the head and neck. As before, we have used evidence from national guidelines, randomised trials, and level II-III studies. We have also limited our discussions to squamous cell carcinoma of the head and neck, which constitutes more than 85% of head and neck cancers.

What determines prognosis in head and neck cancer?

Site and TNM stage

The most important prognostic factors are site and TNM (tumour, node, metastasis) stage. The table details the survival rates of patients diagnosed with head and neck cancer at different sites. Patients with tumours that are larger and have spread to nodes and other tissues have poorer survival. Guidelines for head and neck carcinomas from the Royal College of Pathologists state that other accepted features related to clinical outcome are grade, pattern of invasion, proximity of carcinoma to resection margins, and the presence of extranodal spread. A large meta-analysis showed that extranodal spread more than halved the chances of surviving for five years (odds ratio 2.7, 95% confidence interval 2.1 to 3.7).^{1 w1}

Comorbid illness

The results of large meta-analyses of clinical trial data show that poor performance status (poor fitness and presence of comorbidities) is associated with an adverse prognosis.^{2 3} A systematic review of the effect of comorbidity on survival from head and neck cancer found that for laryngeal cancer, for example, the risk of death is significantly related to comorbidity (hazard ratio 1.5-13.5, depending on

SOURCES AND SELECTION CRITERIA

We used the terms “head and neck”, “larynx”, “oral”, and “oropharynx”—with each limited by “cancer”, “diagnosis”, and “treatment” separately—to search the Medline, Embase, PubMed, Cochrane, CINAHL, and AMED databases. We also used them to cross check national guidelines, reference lists, textbooks, and personal reference lists. We assessed over 1000 identified abstracts for relevance.

Five year survival rates for patients diagnosed with head and neck cancer in 1996-9 in England and Wales²³

Site	5 year survival rate (%)
Lip	93
Larynx	65
Oral cavity	51
Tongue	49
Oropharynx	44
Hypopharynx	19

the comorbidity).⁴ A systematic quantitative review of the association of anaemia and survival in patients with cancer showed that anaemia increased the relative risk of death in patients with head and neck cancer by 47%.^{w2} Meta-analyses of clinical trial data show that advancing age is associated with a decreased probability of survival.^{2 3 w3}

Molecular markers

Molecular markers of prognosis have been studied but none has yet entered routine clinical reporting. A systematic review and meta-analysis found no conclusive value for p53 as a prognostic factor because of heterogeneity across studies.^{w4} Another meta-analysis of tumour expression of the angiogenic vascular endothelial growth factor in 1002 patients found that patients who were positive for this growth factor had nearly double the risk of death (relative risk 1.88, 1.43 to 2.45) at two years.^{w5} A large body of evidence associates tumour hypoxia with adverse prognosis, and hypoxia associated markers have shown promising results, in particular hypoxia inducible factor 1 α and carbonic anhydrase 9.⁵ High tumour expression of the epidermal growth factor receptor was linked with a poor prognosis in several studies, and also predicted benefit from accelerated radiotherapy.^{w6 w7}

How to treat cancers of the head and neck

Management is increasingly being delivered by specialists, whose main interest is cancers of the head and neck. Multidisciplinary care has now become the standard of care, often

SUMMARY POINTS

The main prognostic factors are stage, site of disease, and comorbidities
Treatment decisions should involve a multidisciplinary team of health professionals and the patient, and must balance efficacy and survival with potential functional and quality of life outcomes
Early stage cancers are usually treated by either surgery or radiotherapy
More advanced tumours usually require both surgery and chemoradiotherapy
The disease and its treatments can cause substantial functional impairment and reduced quality of life
Patients and their carers need considerable support during and after treatment

A PATIENT'S PERSPECTIVE

When I first saw the ulcer under my tongue, I thought that I just hadn't noticed it before. At that time I was smoking around 35-40 cigarettes a day. My busy life meant that it was three months before I visited my general practitioner and was referred to the specialist. The penny dropped, and I realised that this could be cancer.

After investigations, I had an operation to remove the cancerous ulcer. The tumour had spread to my lymph glands and had attached itself to a nerve that worked my tongue, which had to be cut to remove the tumour. This troubled me because I knew it would affect my speech and possibly, in the long term, my career. I coped well after the operation and was allowed home after a week. Unknowingly, this had been a stroll in the park compared with what was to come. I started chemoradiotherapy and was offered the option to participate in clinical trials for a new drug. For the next six weeks, every weekday I made a 50 mile round trip to the hospital for treatment. At first I went on my own as I thought that I coped better this way. However, 15 days into the treatment, I had to be driven. I had by now become unable to eat or even drink and had a tube inserted in my stomach. I felt very down, for the first time in many years. I would come home from the treatment and go straight to bed after a five minute battle with the stairs. This period was the lowest part of my life. I said to myself, could this have been avoided?

When I look back on this journey, I tend to forget the bad things and think of the positive ones; the people who helped me, my family, my friends, and my partner who was my rock throughout my treatment. I now enjoy good health and have my life back on track.

Tony, Newcastle upon Tyne



Fig 1 | A cancer of the left vocal cord before resection (left) and immediately after resection with a carbon dioxide laser (right)

encouraged by national guidelines and protocols.⁶ The complexities of combined surgery and radiotherapy, as well as rehabilitation, mean that a team of health professionals is needed to deliver high quality care to patients treated for head and neck cancer. An ideal team usually includes head and neck surgeons from different disciplines, clinical and medical oncologists, clinical nurse specialists, speech and language therapists, dietitians, psychologists, restorative dentists, prosthodontists, and social workers. Although we have no data to prove that multidisciplinary treatment has improved care, intuitively and anecdotally that seems to be the case.

Radiotherapy and surgery are the two most common treatments for cancers of the head and neck. The choice of treatment modality depends on individual factors related to the site of the tumour and stage, but also patient preference.

Early stage tumours

Case series, often retrospective and from single centres, have shown that for early stage tumours in many sites surgical excision or radiotherapy have similar cure rates but a different side effect profile.⁷⁻⁸ Radiotherapy may offer better 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 tongue base. A recent advance in surgical treatment, transoral carbon dioxide laser (fig 1), reduces morbidity with improved organ preservation com-

pared with open surgery. Prospective and retrospective case series have shown good outcomes for organ preservation in certain cancers, such as early glottic cancers and tonsillar cancers, because this technique causes less tissue damage than open surgery.⁹⁻¹⁰ However, there have been no randomised comparisons of radiotherapy and carbon dioxide laser surgery. For some sites (such as the oral cavity), mainly retrospective single centre case series have shown that surgical excision alone may be curative,⁷ and that it is associated with a highly satisfactory functional outcome.¹¹

Advanced tumours

For advanced squamous cell carcinoma of the head and neck, single modality treatment (surgery or radiotherapy) is associated with poorer outcomes,⁸ and randomised studies have shown that combined use of surgery and postoperative radiotherapy, or combined chemotherapy and radiotherapy, offer the highest chance of achieving a cure.⁸⁻⁹

Primary reconstruction, using microvascular free flaps, of large defects after surgical resection of oral tumours especially, and laryngopharyngectomy (removal of the larynx and pharynx), is now a standard treatment that improves functional abilities and quality of life.¹²⁻¹³

Patients with HPV related cancer

Retrospective analyses of samples from patients recruited in large randomised trials and retrospective case series show that patients with HPV related oropharyngeal carcinoma seem to respond better to a variety of treatments, including chemoradiotherapy or surgery and radiotherapy,¹⁰⁻¹² than those with non-HPV related head and neck tumours. Because these patients are generally younger, they may survive for several decades with substantial side effects and functional impairment as a consequence of the treatment they receive, and this may have implications for carers, the health system, and social care.

Recent advances in surgery

Transoral surgery using the carbon dioxide laser under microscope guidance is now a widely accepted technique that can help in organ preservation, mainly in early disease.¹⁰ More recently, robotic surgery (fig 2) has been used and evaluated,



Fig 2 | Surgical robot. Intuitive Surgical, with permission

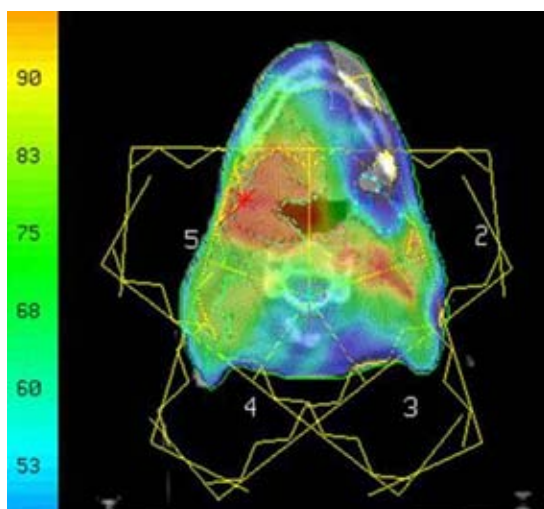


Fig 3 | Dosimetry planning for a patient being treated with intensity modulated radiotherapy. The diagram shows the doses of radiotherapy delivered to each organ. It shows that through the use of sophisticated planning and delivery methods this technique enables the one parotid gland to be spared high doses of radiotherapy

especially for transoral resection of cancers of the base of the tongue and the tonsils. The high definition stereoscopic view, with three dimensional input, and the manoeuvrability of the robotic grasper provide improved access and visualisation. This technique allows resection of more extensive tumours located in difficult to reach areas than is possible using traditional transoral resection with microscopic guidance.^{w14} Reports of early outcomes using robotic surgery, usually in combination with postoperative radiotherapy, show functional outcomes comparable to other treatment modalities.^{w14} A recent prospective feasibility study of 45 patients reported no involved margins, but 56% and 17.8% patients needed postoperative chemoradiotherapy or radiotherapy respectively.^{w14} No data on long term outcomes are available yet.

Reconstruction of large defects using microvascular free flaps comes at a considerable economic cost through substantial investment in microvascular expertise and postoperative care, as well as rehabilitation and support services. Newer techniques that result in less donor site morbidity and may have better functional outcomes, such as anterolateral thigh free flaps, circumflex iliac flaps, and scapular flaps, are increasingly used in preference to other more established flaps.

Patients undergoing bony reconstruction may now have osseo-integrated implants placed at the same time to allow dental and prosthetic rehabilitation after treatment has been completed. This has improved functional and aesthetic outcomes and increased patient satisfaction in retrospective and prospective case series.^{w15}

Recent advances in radiotherapy

In recent years radiotherapy has benefited from advances in cancer imaging, high speed computer software that optimises treatment planning (intelligently selecting the most appropriate beam direction and shape), and developments in radiation delivery technology. It is now one of the most technology driven branches of medicine. A tightly fitted moulded perspex

mask, which is custom made for the patient, is used to immobilise the patient in the same specific orientation and position on the table during the delivery of the daily radiotherapy on an outpatient basis. Radiation treatment is delivered by computer driven linear accelerators with sub-millimetre accuracy, so that radiation is focused on the tumour bearing tissues and radiation of normal tissue structures is minimised.

A recent UK randomised trial of 88 patients found that intensity modulated radiotherapy, a new form of radiotherapy that allows better control of radiation dose delivery to the head and neck, reduced radiation induced xerostomia (the main long term side effect of standard radiotherapy) from 75% to 39% ($P=0.004$) at 12 months after treatment (fig 3).¹³ A similar improvement in side effects was seen in a randomised controlled study for patients with nasopharyngeal cancer.¹⁴

Large randomised controlled studies have shown improvements in local tumour control with accelerated radiotherapy (radiation delivered over a shorter time period) or hyperfractionated radiotherapy (delivery of a higher dose of radiation in two to three low dose fractions a day).¹⁵ These treatments have not shown consistent improvements in overall survival, but have resulted in increased short term mucosal toxicity; they have therefore not been adopted widely outside of North America.

Newer developments using particle therapy, such as proton therapy or stereotactic radiotherapy, may spare particularly radiosensitive organs close to tumours (such as the brain and spinal cord). However, these new technologies, especially proton therapy, are not yet widely available, their benefits have not been proved, and they cost considerably more than standard radiotherapy techniques.

Recent advances in chemotherapy

In a large meta-analysis of 93 trials and more than 17 000 patients, concomitant chemotherapy (given during radiotherapy) was shown to improve locoregional 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 in the adjuvant or neoadjuvant setting. In addition, combining chemotherapy with radiation improves the rates of organ conservation. Cisplatin chemotherapy schedules were the most effective.^{16 w16 w17}

Two randomised controlled trials have shown that concomitant use of cisplatin and radiotherapy after surgery increases tumour control and overall survival in high risk patients with positive resection margins or extracapsular lymph node spread.^{17 18}

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 patients with squamous cell carcinoma of the head and neck in a large randomised controlled trial.^{19 w18} This was the first time that a biologically targeted treatment was shown to be effective in the treatment of head and neck cancer.

Although concomitant chemotherapy has been shown to improve outcomes for head and neck cancer, the role of neoadjuvant chemotherapy (chemotherapy given before start of radiotherapy) remains controversial. Two recent phase II and phase III randomised studies suggested that the addition of docetaxel to cisplatin and fluorouracil given

TIPS FOR NON-SPECIALISTS

When following up patients with head and neck cancer who have been treated, watch out for:

- Recurrence of pretreatment symptoms, such as hoarseness
- New pain in head and neck
- Persistent cough or haemoptysis
- New ulcers, bleeding, or neck lumps
- Hypothyroidism after radiotherapy

before definitive radiotherapy improved survival. However, the use of non-standard radiotherapy and chemoradiation schedules in these trials has led to uncertainty about the benefits of this approach when standard chemoradiotherapy is prescribed.^{20 21}

What are the complications of treatment?**Surgical complications**

Surgical procedure times vary from one to 12 hours, and patients often have a high burden of concurrent medical illness. These patients are prone to complications arising from prolonged anaesthesia, such as pulmonary consolidation and deep venous thrombosis. Depending on the nature of the procedure, patients may also be at increased risk of postoperative aspiration and its consequences. Although it is not a complication, the end stoma resulting from laryngectomy may affect patients' activities of daily living because of problems with body image and the need for daily tracheo-oesophageal valve care to maintain speech through the valve.

Because most surgical procedures are of the clean-contaminated variety, where the oral or pharyngeal lumen is opened at some point in the procedure, case series report postoperative surgical site infection rates of 20-40%.^{w19 w20}

Other early complications include haemorrhage from major vessels and wound breakdown, the last of which is especially common in patients who have had radiation before surgery. In a prospective study of the outcome of surgical salvage of failed chemoradiotherapy for laryngeal cancer in patients from a randomised controlled trial, a third of patients developed a salivary fistula into the neck.²² Rarely, injury to the lymphatic duct on the left side of the neck can lead to a lymph leak that can take up to a few weeks to settle.

Surgery can injure or require sacrifice of important neuromuscular structures to ensure tumour clearance. Injury to the spinal accessory nerve, which leads to shoulder dysfunction, and removal of the sternocleidomastoid muscle, which causes loss of contour to the neck, may also occur. Other cranial nerves (VII, X, and XII) and the sympathetic chain are also prone to injury depending on the extent of the tumour. Although microvascular free flap reconstructions have a consistently high success rate (>95%), failure of a flap can have considerable complications that can lead to prolonged hospital stay and a delay in any planned postoperative radiotherapy.

In the longer term, patients present with functional problems such as impaired swallowing and speech and voice problems, or weak shoulder. They may have to care for an end stoma. These sequelae will require input from various health professionals to achieve rehabilitation.

Complications of chemoradiotherapy

Acute complications of radiotherapy to the head and neck region include radiation dermatitis, xerostomia, excessive mucus production, and painful mucositis. Consequently, patients often reduce their intake of food and liquids and some may require nasogastric feeding or percutaneous gastrostomy to maintain adequate nutrition. The addition of concomitant chemotherapy may exacerbate the severity and duration of these acute effects. The acute effects of

radiation typically settle four to six weeks after treatment is completed.

Serious late radiation toxicity is seen in as many as 82% of patients at five years,²³ and it may include xerostomia, fibrosis of soft tissues, dysphagia, and osteo-radionecrosis of the mandible.²³ These complications are important because they are usually permanent. Some, like xerostomia, improve over time,¹³ but others, such as pharyngeal stenosis, are occasionally progressive and sometimes resistant to treatment. Minimising the volume of the tissues receiving radiotherapy (for example, by sparing salivary glands or bone) can reduce the rate of these complications, as shown in the PARSPORT trial.¹³

What quality of life do treated patients have?

Studies exploring quality of life outcomes in patients with head and neck cancer have shown greater impairment of quality of life for combined than for single modality treatments.^{w21} Several large prospective cohorts studies have shown that patients' quality of life is greatly reduced during treatment but starts to improve about three months after treatment ends and continues to improve for one to two years, with little further improvement thereafter.^{w21} More recently, data suggest a possible deterioration in quality of life in the long term (10 years) in survivors of head and neck cancer, but it is not clear whether this is the result of late sequelae of treatment or the development of other related or unrelated comorbidities.²⁴ Clearly, however, late effects of treatment, especially dry mouth and swallowing problems, are important determinants of long term quality of life.²⁵

Interestingly, quality of life outcomes do not seem to differ significantly between the different treatment modalities, at least in the short to medium term, because several small retrospective and prospective cohort studies have reported similar outcomes for both radiotherapy and transoral laser conservation surgery for early laryngeal tumours.^{w22} Similar quality of life outcomes have been reported for patients who have had laryngectomy (removal of the larynx) compared with those who have had organ sparing chemoradiotherapy for the treatment of advanced laryngeal cancer.^{w23} Of note, qualitative studies have shown that a cure is the primary concern of patients with head and neck cancer, followed by prolongation of survival and then quality of life.²⁶ This is by no means consistent, however, and patients differ in their priorities,²⁶ which highlights the importance of involving patients fully in the decision making and treatment process.

ONGOING RESEARCH QUESTIONS

- To understand the epidemiology, prognosis, and optimum treatment of patients with human papillomavirus induced head and neck cancer
- To understand the optimum schedules for combination of radiotherapy, growth factor receptor inhibition, and chemotherapy
- To delineate the role of robotic surgery in transoral resection of oropharyngeal and laryngeal tumours and other head and neck surgical procedures, such as minimally invasive thyroidectomy
- To individualise the treatment and management of head and neck cancers on the basis of tumour cell biomarkers

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Previous articles in this series

- Head and neck cancer—Part 1 (*BMJ* 2010;341:c4684)
- Diagnosis and management of Barrett's oesophagus (*BMJ* 2010;341:c4551)
- Managing anaemia in critically ill adults (*BMJ* 2010;341:c4551)
- Managing gastro-oesophageal reflux in infants (*BMJ* 2010;341:c4420)
- Evaluating the child who presents with an acute limp (*BMJ* 2010;341:c4250)

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

WHO. The global burden of disease: 2004 update. 2008. www.who.int/evidence/bod

National Cancer Comprehensive Network (www.nccn.org/index.asp)—Guidelines on treatment of cancers including head and neck in US

Scottish Intercollegiate Guidelines Network. Diagnosis and management of head and neck cancer guidelines. Guideline no 90. 2006. www.sign.ac.uk/guidelines/fulltext/90/index.html

National Institute for Health and Clinical Excellence. Improving outcomes in head and neck cancers—the manual. 2004. <http://guidance.nice.org.uk/csgn/guidance/pdf/English>

Fanconi Anaemia Clinical Network. Clinical standards of care in the UK. www.fanconi.org.uk/clinical-network/standards-of-care/

Resources for patients and carers

Cancer Research UK (www.cancerresearchuk.org)—National site that covers all cancers; very easy to navigate with lots of information

Macmillan (www.macmillan.org.uk)—National site that covers all cancers; easy to navigate; need to type larynx into the search engine

Merseyside Head and Neck Cancer Centre (www.headandneckcancer.co.uk)—Suitable for patients and carers in any part of the country, easy to navigate, very clear language and format

Get A-Head (<http://www.getahead.org.uk>)—Easy to navigate, suitable for patients and carers in any part of the country, very informative; click on “patient info” then “helpful information”

National Association of Laryngectomy Clubs (www.laryngectomy.org.uk)—Patient organised site with a wide selection of information for patients and professionals; hard copies are free on request

Guidelines and Audit Implementation Network (<http://www.gain-ni.org>)—Informal learning course of six modules

How can recurrent or metastatic cancer be treated?

In patients with metastatic or locally recurrent head and neck cancer, treatment is usually palliative. If the recurrence occurs in previously untreated tissues of the head and neck then surgery and chemoradiation may be used as local salvage treatments. If not, chemotherapy with cisplatin and fluorouracil may be used to reduce symptoms. A recent randomised controlled trial found that the addition of an epidermal growth factor receptor inhibitor (cetuximab) to the above schedule produced a modest prolongation of overall survival.²⁷

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Patient consent obtained.

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