Principles of management in oral cancer

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Squamous cell carcinoma is the most common oral malignancy, with a relatively poor prognosis. Treatment of oral cancer has a major impact on afflicted patients because it affects speech, swallowing and mastication. Surgery is the main treatment of oral cancer, as a single modality or combined with radiotherapy. Vigilance is vital for early diagnosis and better overall prognosis.

Cancer of the head and neck presents as the sixth most common cancer worldwide. Oral cancer rates in the UK have been quoted between 2.5 and 6.9 per 100 000, accounting for 2% of all malignancies (Johnson et al, 1993). This approximates to 2000 new cases per annum in the UK (Park et al, 1998). Large geographical variations exist with figures as high as 19 per 100 000 reported in India and high rates also being reported in Singapore, Hungary and Southern France.

Approximately 94% of all oral malignancies are squamous cell carcinomas, the remainder being salivary gland malignancies, sarcomas, lymphomas, melanomas and metastatic deposits.

The peak incidence is in the 6th and 7th decades but there is a dramatic increase in the incidence in men under 45 years, especially in tongue tumours. The survival rates for this disease are poor, with an overall 5-year survival rate of approximately 45% (Johnson et al, 1993).

Like many cancers, the prognosis is improved the earlier the disease is diagnosed and treatment commenced. Both general dental and medical practitioners are ideally placed to carry out regular surveillance and therefore knowledge of signs and symptoms of oral cancer are vital to facilitate early diagnosis of the disease (*Figure 1*).

AETIOLOGY

Oral squamous cell carcinomas are of multifactorial aetiology, with no single causative agent having been identified.

The commonest risk factor globally is tobacco smoking, although chewing tobacco and snuff dipping occurs in developing countries. Benzopyrene in inhaled smoke is the potential carcinogen. This has been shown to affect the p53 gene, which usually offers protection (Partridge, 2000).

Heavy smokers (>20/day) have a six-fold increased risk of developing oral squamous cell carcinoma than non-smokers, with even light smokers having an increased risk (Cawson et al, 1996). The risk returns to normal after 10 years of abstinence (Franceschi et al, 1990).

Alcohol acts as a risk factor both alone and synergistically with tobacco. People who smoke heavily and have a high alcohol consumption (>30 units/week) have a 24 times greater risk of developing oral cancer (McCoy and Wynder, 1979).

Areca (betel) nut chewing in the Indian subcontinent has been implicated in potentially malignant lesions, of which the majority are squamous cell carcinomas. In developed countries most carcinomas arise de novo (Daftary et al, 1992).

Dietary deficiencies have been implicated in oral cancer and both beta-carotene and vitamin E have been shown to regress oral leucoplakia (Garewal et al, 1999).

Oral carcinogenesis is a multistep accumulation of events affecting cell proliferation, involving at least four groups of genes – oncogenes, tumour suppressor and DNA repair genes, and genes controlling cell death. It has been suggested that 6–10 'hits' are required for the development of oral cancer (Renan, 1993).

PRESENTATION

Oral cancer usually presents as a painless lesion in the form of a non-healing ulcer, an exophytic growth or an area of induration. Pain resulting from infiltration of local nerves is a late symptom indicative of an advanced stage. Bleeding from the site can also be an associated feature. In advanced disease, swallowing may be difficult and painful and a significant number of patients present with a lump in the neck as a first sign. Otalgia is also well associated with tongue base tumours.

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The oral cavity is well recognized as a site of mucosal 'field change', where multiple primary tumours may exist. Synchronous tumours are classified as occurring at or within 6 months of diagnosis of the primary tumour, while tumours arising later are known as metachronous. Incidences of 10–17% for synchronous tumours and 2–11% for metachronous tumours have been cited (Langdon et al, 1977).

Oral squamous cell carcinoma may present de novo in a previously normal area of epithelium or as a transformation of an existing pre-malignant lesion. This is morphologically altered tissue in which cancer is more likely to occur than in the normal tissue. Leucoplakia and erythroplakia (white and red patches respectively) are typical examples. The presence of these lesions should warrant prompt referral to a head and neck cancer unit where they should be biopsied to establish a diagnosis. A pre-malignant condition is a generalized state associated with a significantly increased risk of developing malignancy. Oral submucous fibrosis is the most common (McIntyre and Oliver, 1999). Other conditions that should alert the clinician to possible malignant change include smokers' keratosis, actinic keratosis, chronic hyperplastic candidiasis and erosive lichen planus.

Figure 1. Oral squamous cell carcinoma affecting the lower alveolus and floor of mouth in an edentulous patient.

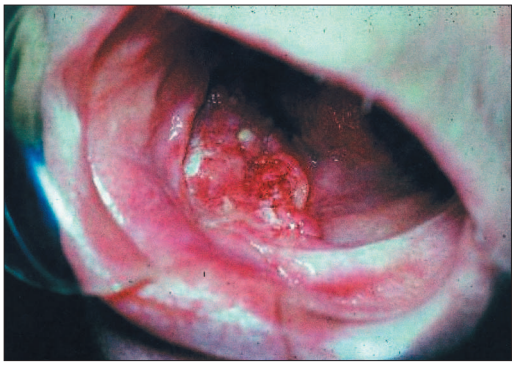


Figure 2. Large squamous cell carcinoma affecting the right lateral border of tongue. These tend to invade the extrinsic muscles of the tongue and so present as T4 lesions.

In general, any ulcer or new oral lesion that persists for longer than 3 weeks should be referred for an urgent specialist opinion and possible biopsy (*Figure 2*).

ASSESSMENT

History

Demographic data such as age, sex and race are required, but a detailed history should also aim to establish potential contributing factors.

Cigarette smoking, or any tobacco intake such as snuff dipping and tobacco chewing, should be noted. Alcohol consumption and type of alcohol is also relevant. Ultraviolet light exposure in outdoor workers is linked to the development of lip cancers whereas nutritional deficiencies are implicated in post-cricoid cancer (Plummer–Vinson syndrome).

Clinical examination

The main role of the clinical examination is to stage the disease as accurately as possible. TNM is the most commonly used staging system (International Union against Cancer, 1997) (*Tables 1* and *2*). T represents the size of the pri-

TABLE 1.
Staging of tumour

T: Primary tumour	Tx	Primary tumour cannot be assessed.
	T0	No evidence of primary tumour
	Tis	Carcinoma-in-situ
	T1	<2 cm
	T2	2–4 cm
	T3	>4 cm
	T4	Invades adjacent structures, i.e. bone, extrinsic tongue muscles, sinuses, facial skin
N: Regional lymph nodes	Nx	Lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	One ipsilateral lymph node <3 cm
	N2a	Ipsilateral lymph node >3 cm but <6 cm
	N2b	Multiple ipsilateral lymph nodes <6 cm
	N2c	Bilateral or contralateral lymph nodes <6 cm
	N3	Lymph node metastasis >6 cm
M: Distant metastasis	Mx	Distant mets cannot be assessed
	M0	No distant mets
	M1	Distant mets present
G: Histological grade of tumour	Gx	Cannot be assessed
	G1	Well differentiated tumour
	G2	Moderately differentiated
	G3	Poorly differentiated
	G4	Undifferentiated

The TNM (tumour-node-metastasis) system is the most commonly used staging system in this disease and involves: T = tumour size; N = involvement of local nodes; M = distant metastasis. Once each sub-classification has been established, the disease can be staged with stage IV lesions having a worse prognosis than stage I

mary tumour, N the presence of nodal metastasis and M evidence of distant metastasis. Staging of the disease ranges from I to IV with corresponding prognostic implications (*Table 3*).

Careful assessment of the primary site aims to establish the T stage. Deep induration of underlying structures may change the classification of a small T1 into a T4 and careful palpation is required to accurately stage the primary. Examination of the entire oral cavity and oropharynx is mandatory to detect mucosal field change or a synchronous tumour. Flexible nasendoscopy is often carried out in the outpatient department, with examination under anaesthesia also used to assess the extent of the lesion or any potential second primary. Of all patients with a squamous cell carcinoma of the oral cavity, 10–30% will develop a second primary of the aerodigestive tract (Day and Blot, 1992).

Oral cancer usually metastasizes in the regional neck lymph nodes. Lymph nodal involvement decreases the survival rate by 50% and is the single most important prognostic factor. Thorough palpation of all nodal groups in the neck should be performed and assessed for site (level), size, consistency, mobility and fixation to surrounding structures. The reliability of this assessment depends on operator experience, with 70% accuracy being commonly stated (Woolgar, 1997). Clinical examination is more difficult in the presence of previous surgery or radiotherapy, so computed tomography (CT), ultrasound and magnetic resonance imaging (MRI) are commonly used to assess the status of the cervical lymph nodes.

In conclusion the general health of the patient should be assessed before any decision can be made regarding surgical management. Not uncommonly cancer patients are malnourished and suffering concomitant severe diseases. Nutritional status should be assessed, with most patients receiving a percutaneous gastrostomy before surgery to help their perioperative feeding.

TABLE 2.
TNM staging of oral cancer

Stage	T	N	M
0	is	0	0
1	1	0	0
2	2	0	0
3	3	0	0
	1	1	0
	2	1	0
	3	1	0
4a	4	0	0
	4	1	0
	Any T	2	0
4b	Any T	3	0
4c	Any T	Any N	1

T = tumour size; N = involvement of local nodes; M = distant metastasis.

TABLE 3.
Five-year survival statistics for oral squamous cell carcinoma

Disease stage	Five-year survival
Stage I	85%
Stage II	66%
Stage III	41%
Stage IV	9%

IMAGING

The need to accurately assess the size of the primary tumour but also to demonstrate cervical metastasis and jaw involvement has led to the use of several imaging investigations.

Plain radiographs

An orthopantomograph will demonstrate the state of the dentition and potential bony infiltration.

Computed tomography

CT is most commonly used to assess the extent of oral cancers and delineate bone involvement. Addition of a contrast agent increases the definition of the primary tumour and demonstrates rim enhancement in pathologically involved nodes. Spiral CT offers rapid scanning and allows multiplanar reformatting but all CT scanning suffers from scatter artefact from dental amalgam, which adversely affects image quality. CT is superior for imaging bone detail and, because of it's faster acquisition times, suffers less motion artefact from breathing and swallowing.

Magnetic resonance imaging

While MRI has superior soft tissue contrast and improved bone marrow imaging than CT, it shows cortical bone and hence invasion poorly. Addition of gadolinium contrast can be used to highlight the primary tumour and demonstrate pathologically involved nodes. Perineural and intracranial extension is more accurately demonstrated by MRI than CT (Parker and Harnsberger, 1991), while MR angiography may provide information about the relation of the tumour to major vascular structures (*Figure 3*).

Ultrasound

Ultrasound is used in the evaluation of cervical lymphadenopathy and has been shown to be

more accurate than palpation in the detection of enlarged nodes (Hajek et al, 1986). Its main role is in ultrasound-guided fine needle aspiration cytology of suspected cervical lymph nodes. This can be used to stage the cervical lymph nodes, improving the specificity of the assessment.

Bone scanning

Bone scanning has been used for the early detection of bone involvement by oral cancer. It has been also used for detection of potential distant bone metastatic deposits, assessment of osteoradionecrosis following radiotherapy and monitoring of bone flaps (Kalavrezos et al, 1996).

Positron emission tomography

Positron emission tomography is a nuclear medicine imaging technique based on increased uptake and metabolism of a glucose analogue (18F-fluorodeoxyglucose) within tumour cells. Fused images with CT and MRI have been used to improve anatomical accuracy. The increased sensitivity may improve the monitoring of metastatic or recurrent disease of patients already treated with surgery and radiotherapy.

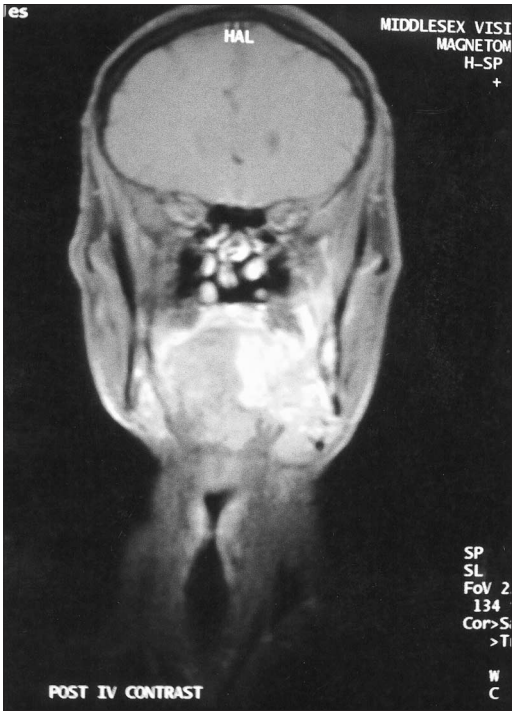
SURGICAL TREATMENT

The management of patients with oral cancer requires a truly multidisciplinary approach involving surgeons, oncologists, radiotherapists, prosthodontists, palliative care physicians, dietitians, speech and language therapists and specialist nurses.

Early lesions (T1/early T2) may be treated effectively by a single modality, either surgery or radiotherapy (external beam or interstitial). The use of trans-oral carbon dioxide laser resection without reconstruction is gaining popularity, while trials with photodynamic therapy are underway for superficial lesions and sites of mucosal field change (Hopper, 2000).

Larger T2 lesions (>3 cm) may need combined modality treatment. Current protocols favour surgery followed by radiotherapy (*Figure 4*).

Figure 3. Magnetic resonance imaging of a cancer involving the left tongue, floor of mouth and upper cervical lymph node chain.



THE NECK IN THE SURGICAL MANAGEMENT OF ORAL CANCER

The management of the neck plays a pivotal role in the treatment of oral carcinoma and still causes much debate among head and neck oncologists. The status of the cervical lymph nodes at presentation is the single most important prognostic factor, with even one involved node halving the prognosis for any stage. The incidence of nodal metastasis depends on both the site and size of the primary tumour, with the tongue and floor of mouth having a high chance of spread compared to the maxilla. Tumour thickness greater than 4 mm has been shown to increase the likelihood of nodal metastasis (Zatterstrom et al, 1991).

An understanding of the patterns of lymphatic drainage from all sites in the head and neck is essential as most cervical metastatic spread occurs in a predictable manner, although certain tumours may 'fast track' to more distant nodal groups (Woolgar et al, 1995). This pattern of disease spread will be altered in the presence of previous surgery or radiotherapy. Treatment of cervical lymph nodes can be either elective (no evidence of involvement) or therapeutic (neck metastasis) (*Figure 5*).

Any patient with palpable neck nodes requires surgery to the neck. The gold standard treatment for these cases is the radical neck dissection encompassing removal of all neck nodes en bloc

Figure 4. Orthopantomogram revealing squamous cell carcinoma invading the left side of the mandible requiring segmental resection.

with the internal jugular vein, the sternomastoid muscle and the spinal accessory nerve. High morbidity has led to selective neck dissections mainly applied as an elective staging procedure in the clinically negative (N0) (Persky and Lagmay, 1999). The advantage of performing a selective neck dissection is that prognostic information can be obtained from the histology, allowing accurate staging of the disease. In addition, access can be provided to the great vessels of the neck when microvascular anastomosis for free-tissue transfer reconstruction is anticipated.

In most instances patients with more than one histologically proven positive neck node will progress to radiotherapy.

RECONSTRUCTION

Surgical ablation of oral carcinoma can lead to physical disfigurement, which has a profound functional, psychological and social effect on the patient. This, coupled with changes to speech and swallowing, makes reconstruction after surgical ablation a significant challenge. Resection of the primary tumour should be complete and should not be compromised to facilitate reconstruction.

Principles of reconstruction

The principle behind reconstruction is to replace similar tissue in equal volume to restore function. This is a challenge in the oral cavity because of its complex function and anatomy. Smaller defects can be reconstructed with local tissue, but larger defects require more distant flaps, in the form of regional flaps or free-tissue transfer. Obturation of the defect with a prosthesis is also an option and can be used in defects of the maxilla.

Occasionally primary closure may be possible, although this is usually at the expense of some functional or cosmetic defect. Today the majority of reconstruction in head and neck surgery involves microvascular free-tissue transfer, enabling the reconstruction of composite defects with tissues amenable to complex spatial orientation and increased functional demands.

Reconstruction alone is no longer acceptable and rehabilitation, as close as possible to the premorbid state, is the treatment of choice. Osseointegrated implants are now widely used to carry a prosthetic superstructure that will restore the dentition and aid mastication. These implants can also be placed in the bone, containing free flaps used for the reconstruction.

RECONSTRUCTIVE LADDER

Primary closure

This is the simplest option although distortion of structures may pose a problem.

Skin graft

Split or full thickness grafts are adequate to replace small areas of mucosa. They require a suitable vascularized bed for 'take' and so exposed bare bone, tendon or cartilage are unsuitable. Graft contracture also occurs with split skin contracting more than full thickness. Split-skin grafts may be used to line maxillectomy cavities before obturation.

Local flaps

These are relatively reliable flaps and can be used to replace small amounts of tissue. However, because of the limited availability of tissue that can be spared both aesthetically and functionally in the head and neck region, few tend to be used today.

The nasolabial flap can be based superiorly or, more commonly, inferiorly and can be tunnelled into the mouth to reconstruct defects of the anterior floor of mouth.

The temporalis muscle flap, based on the deep temporal vessels, can be rotated into the oral cavity via a zygomatic osteotomy to restore maxillary defects. A galeal flap, based on the galeal aponeurosis, can also be used without the need for an osteotomy. Tongue flaps and fore-

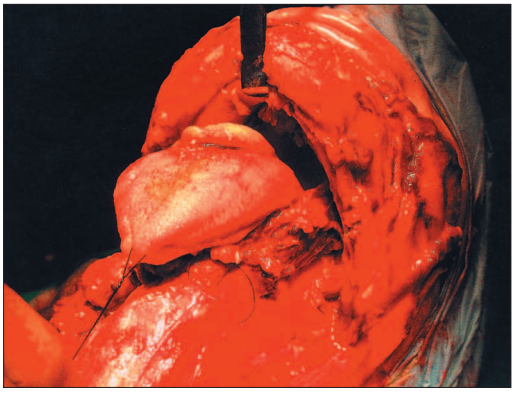
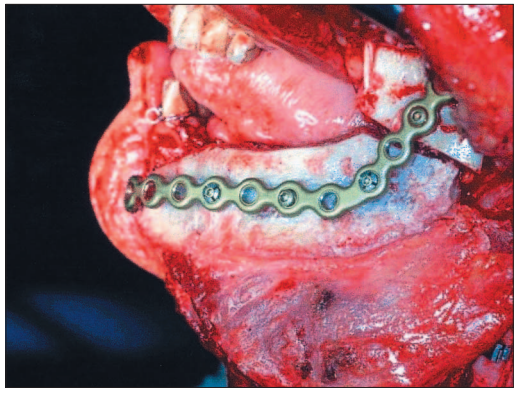


Figure 5. Specimen of a bilateral neck dissection and visor approach to the mandible to provide good access for a total glossectomy, before reconstruction.

Figure 6. Iliac crest free flap based on the deep circumflex iliac artery used to reconstruct the mandible.



head flaps, based on the superficial temporal vessels, are now being used less frequently.

Regional flaps

The pectoralis flap, based on the pectoral branch of the thoraco-acromial vessels, can be used as a myocutaneous, muscle-only or de-epithelialized flap and is commonly used in head and neck reconstruction because of its versatility. This flap is tunnelled under the cervical skin and can be used to provide bulk for the reconstruction of large soft tissue defects in the oral cavity. It is also used as a means of protecting the carotid artery following neck dissection or wound dehiscence. Primary closure of the donor site can usually be achieved.

The deltopectoral flap is a fasciocutaneous option, based on perforators of the internal thoracic artery, and can extend to defects as high as the zygoma, although it requires a planned fistula and pedicle division some weeks later. It was the first described axial flap in head and neck surgery but now has largely been superseded by other techniques.

Pedicled latissimus dorsi flaps may be used when a large area of tissue is needed and again can be used as either a myocutaneous or muscle-only option. Other flaps described include trapezius, sternomastoid and platysma but are now rarely undertaken.

Free-tissue transfer

The development of microvascular anastomosis and free-tissue transfer techniques have revolutionized the reconstructive options available for head and neck oncology, and now offers the gold standard reconstruction of difficult head and neck defects.

Bone, fascia, muscle and skin, or any combination can be used which overcomes the problems of local tissue availability and importing tissue into an irradiated field. The technique offers immediate reconstruction although success tends to be an 'all or nothing' phenomenon with recognized failure rates. These failure rates (approximately 4–5%) can be minimized by flap selection, operator experience and meticulous surgical technique.

The radial forearm free flap is the most commonly used in head and neck reconstruction and is based on the radial artery and its venae commitans. It is a thin and robust fasciocutaneous flap used for mucosal defects, and can also incorporate bone as a composite reconstruction for mandibular defects. Allen's test, which sequentially occludes the radial and ulnar arteries to assess collateral flow if one is sacrificed, along with ultrasound, should be undertaken preoperatively.

If larger volumes of tissue are required, other flaps may be used and re-anastomosed. These include latissimus dorsi and rectus abdominus. Occasionally free jejunum may be used if the defect also involves the oro-pharynx.

Bone may be required to replace mandibular or maxillary defects and the development of several bone-containing free flaps has greatly improved the cosmetic and functional outcome with the ability to incorporate intraosseous implants to support prosthetic dentures or obturators (*Figures 6* and *7*).

Commonly used bone flaps include the fibular flap based on the peroneal artery, scapular flap based on the circumflex scapular artery, the hip bone flap based on the deep circumflex iliac artery and the composite radial flap. These are not without donor site morbidity.

RADIOTHERAPY

Penetrance of radiotherapy into a tumour is inversely proportional to the volume, and the larger the volume of the primary tumour the more likely it is to contain hypoxic cells which are resistant to irradiation. Radiotherapy alone is therefore more effective in eradicating small tumours, i.e. T1 and small T2. Salvage surgery is reserved for local regional recurrence, usually occurring within the first 2 years of treatment. External beam irradiation, occasionally using several fields, or interstitial brachytherapy with implanted radioactive isotopes are most commonly used.

More commonly radiotherapy is used as adjuvant therapy following surgery. If surgery is carried out before radiotherapy this will provide the radiotherapist with valuable information on which to plan the treatment. The indications for such treatment are:

- Any stage with microscopically positive margins
- Close resection margins <5 mm
- More than one metastatic neck node
- Any node with extracapsular spread, perineural or intravascular invasion.

There is little proof that chemotherapy has a role in the primary management of oral cancer but it may have a role in conjunction with radiotherapy if no surgery is contemplated.

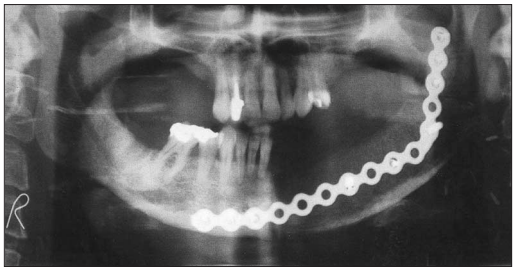


Figure 7. Repeat orthopantomogram showing the segmental resection and reconstruction shown in Figure 6.

REHABILITATION

Rehabilitation of the oral cancer patient should not be an afterthought but planned at the time of diagnosis. There are many teams which contribute to the package and it is important that the patient plays a central role and is fully versed in what it will entail.

As well as the surgical and radiotherapy teams, speech therapists, dieticians, specialist nurses, physiotherapists and hygienists all have a role to play in restoring the patient as close as possible to his/her pre-morbid state. Prosthodontists and restorative dentists provide dental implants which help restore the dentition and have a major influence on the quality of life of the patient.

Excellent back-up is provided by several charities who can offer support and guidance during the whole rehabilitation process.

PALLIATION

Unfortunately a percentage of these cancers will present at such an advanced stage that they are inoperable. In the circumstances the palliative care team and the Macmillan services play a pivotal role in symptom management. Occasionally palliative surgical de-bulking may be required for symptom relief or pain control, with palliative radiotherapy also having a role to play.

PROGNOSIS AND FUTURE DEVELOPMENTS

The prognosis for survival in oral cancer is dependant on tumour stage. Five-year survival rates in the absence of metastasis are 80%, compared to 40% if neck disease is present and even less in the presence of extracapsular lymph nodal spread (Beenken et al, 1999). Photodynamic therapy has been used in several studies in early carcinoma and as adjuvant intra-operative therapy for recurrent tumours and shown favourable response rates. Other interesting therapies being tried at the moment include tumour angiogenesis target therapy, oncolytic virus therapy and apoptosis-inducing therapy. On the reconstructive side, distraction osteogenesis may play a greater role in the future and the use of sensate flaps may prove interesting. HM

KEY POINTS

- Oral squamous cell carcinoma is common, accounting for 2% of all cancers in the UK.
- Early stage disease has a good prognosis but this rapidly deteriorates with advanced disease.
- Smoking and alcohol consumption are the main aetiological factors and act synergistically.
- The optimum management involves input from all the multidisciplinary team.
- Involvement of the cervical lymph nodes is the single most important prognostic factor; decreasing the survival rate by 50%.
- Early surgery, with or without radiotherapy, offers the best chance of cure.
- Quality of life issues should always be borne in mind when planning treatment.

Conflict of interest: none.

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