Crispian Scully

Laurence Newman

Jose Vicente Bagan

The Role of the Dental Team in Preventing and Diagnosing Cancer: 3. Oral Cancer Diagnosis and Screening

Abstract: Oral cancer is among the ten most common cancers world-wide, and is especially seen in disadvantaged elderly males. Members of the dental profession have a duty to detect both potentially malignant and malignant oral lesions. Early detection and prompt treatment offer the best hope to the patient with oral cancer, providing the best chance of a cure. As patient awareness regarding the danger of oral cancer increases, the demand for oral cancer 'screening' is also expected to increase significantly.

The signs and symptoms of cancer often resemble less serious conditions more commonly found in the mouth and similarly presenting as a lump, red or white patch or ulcer. If any such lesion does not heal normally within 3 weeks, a malignancy or some other serious disorder must be excluded. A biopsy is indicated. Prompt referral to an appropriate specialist usually allows for the best management but, if this is not feasible, the dental practitioner should take the biopsy which should be sent to a specialist oral pathologist for histological evaluation.

Clinical Relevance: Early detection and prompt treatment offer the best hope to the patient with oral cancer, providing the best chance of a cure. As patient awareness regarding the danger of oral cancer increases, the demand for oral cancer 'screening' is expected to increase significantly as well.

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Professor Crispian Scully, CBE, PhD, MD, MDS, MRCS, FDS RCPS, FFD RCSI, FDS RCS, FDS RCSE, FRCPath, FMedSci, Eastman Dental Institute for Oral Health Care Sciences, 256 Gray's Inn Road, University College London, London WC1X 8LD, **Mr Laurence Newman**, FRCS FFD FDS RCS, Maxillofacial Unit, UCLH NHS Trust, Mortimer Market, London WC1E 6AU and **Professor Jose Vicente Bagan**, DDS, PhD, MD, Hospital General Universitario de Valencia, Avenida 3 Cruces, 46014 Valencia, Spain.

Detection of cancer and potentially malignant lesions

Leukoplakia is the main potentially malignant oral lesion seen but erythroplakia, though much less often seen, has a far higher malignant potential.[1] Most cancers of the oral cavity are oral squamous cell carcinomas (OSCCs), and tobacco and alcohol use are the main risk factors.[2,3]

Many OSCCs are preceded by clinically evident *potentially malignant oral mucosal lesions*, particularly erythroplakia, some leukoplakias and occasional lichen planus lesions. In one series of patients from the Netherlands with a histologically proven OSCC, there were coexistent white lesions detectable clinically in 48% of the patients. In societies where the incidence of OSCC is particularly high, such as in people from South Asia, clinically recognizable potentially malignant lesions are even more common. In either case, there are clearly changes in the DNA and at the molecular level that precede the clinical appearance of a cancer.

A thorough examination is therefore indicated for all dental patients, paying particular attention to the high incidence sites. These include the lip (Figure 1), floor of the mouth, lingual vestibule and lateral margin of the tongue. The

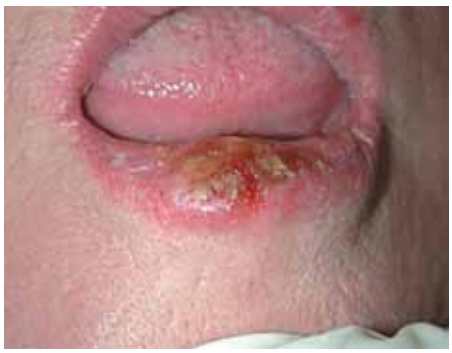

Figure 1. Lip cancer.

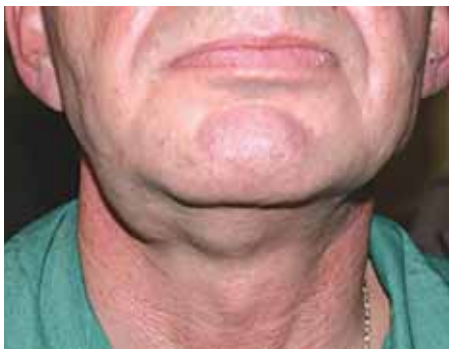

Figure 2. Neck metastases.

Figure 3. Erythroplasia in a patient who also has leukoplakia.

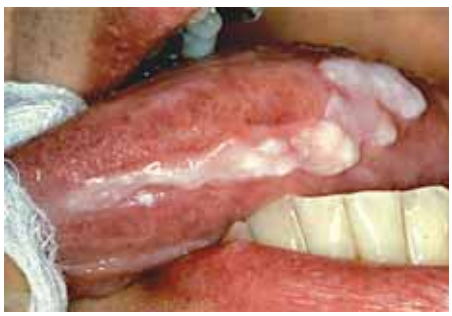

Figure 4. Proliferative verrucous leukoplakia.

posterolateral tongue, posterior tongue and lingual vestibule/floor of the mouth should be especially carefully inspected and examined; it is only too easy to miss hidden OSCCs, and there are almost endless case reports emphasizing this, as well as celebrities who have suffered in this way, making media headlines. This truly is a 'coffin area'.

The cervical lymph nodes must be palpated for swelling that may be caused by metastases (Figure 2).

Nevertheless, the future goal should surely be to detect not only potentially malignant and malignant clinical lesions, but ideally also to reveal epithelial molecular or DNA changes indicative of early carcinogenesis. Early detection and prompt treatment offer the best hope to the patient with oral cancer, providing the best chance of a cure. Sadly, around 50% of patients still present very late for care, largely because the tumour has been painless or ignored.

Potentially malignant states

Some potentially malignant (precancerous) clinical lesions which can progress to OSCCs include especially:

Approximate malignant potential	Lesion	Known aetiological factors	Main clinical features
Very high (85%+)	**Erythroplasia**	Tobacco/alcohol	Red plaque
High in some instances (30%+)	**Actinic cheilitis**	Sunlight	White plaque/ erosions
	Chronic candidosis (candidal leukoplakia)	*Candida albicans*	White or speckled white and red plaque
	Dyskeratosis congenita	Genetic	White plaques
	Leukoplakia (non-homogeneous)	Tobacco/alcohol	Speckled white and red plaque or nodular plaque
	Proliferative verrucous leukoplakia	Tobacco/alcohol /human papillo-mavirus (HPV)	White or speckled white and red or nodular plaque
	Sublingual keratosis	Tobacco/alcohol	White plaque
	Submucous fibrosis	Areca nut	Immobile pale mucosa
	Syphilitic leukoplakia	Syphilis	White plaque
Low (<5%)	**Atypia in immunocompromised patients**	?HPV	White or speckled white and red plaque
	Leukoplakia (homogeneous)	Friction/ tobacco/alcohol	White plaque
	Discoid lupus erythematosus	Autoimmune	White plaque/ erosions
	Lichen planus	Idiopathic	White plaque/ erosions
	Paterson-Kelly-Brown syndrome (sideropenic dysphagia; Plummer-Vinson syndrome)	Iron deficiency	Post-cricoid web

Table 1. Potentially malignant oral lesions and conditions.

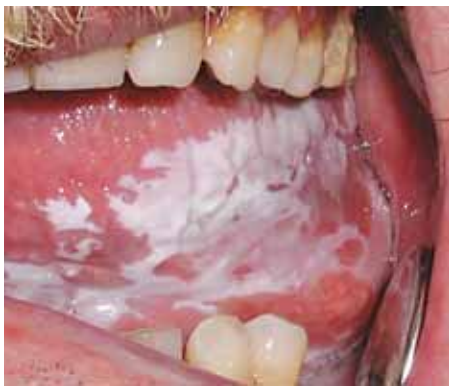
Figure 5. Sublingual keratosis.

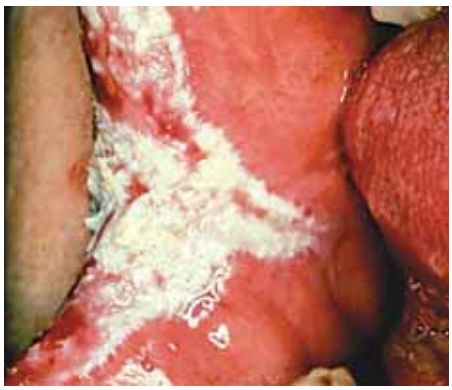
Figure 6. Candidal leukoplakia.


Figure 7. Homogeneous leukoplakia.

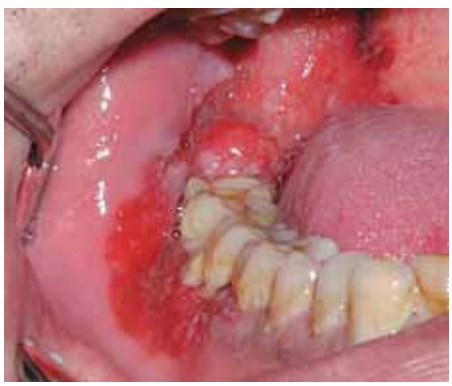
Figure 8. Ulceration due to a carcinoma.


Figure 9. Ulceration caused by a carcinoma.

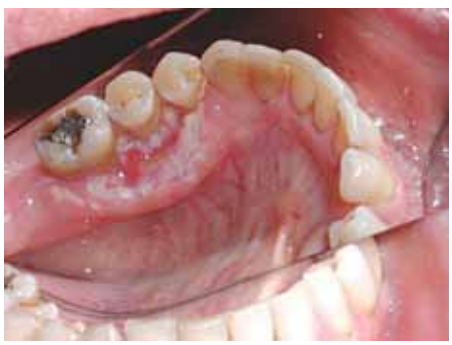
Figure 10. Carcinoma presenting as a white lesion.

■ Erythroplasia (erythroplakia) – the most likely lesion to progress to severe dysplasia or carcinoma. Erythroplastic lesions are velvety red plaques (Figure 3), which in at least 85% of cases show frank malignancy or severe dysplasia. Carcinomas are seen 17 times more frequently in erythroplakia than in leukoplakia (but leukoplakias are far more common).
■ Leukoplakia, particularly where admixed with red lesions as in speckled leukoplakia, and:
■ Proliferative verrucous leukoplakia (Figure 4);
■ Sublingual leukoplakia (Figure 5);
■ Candidal leukoplakia (Figure 6);
■ Syphilitic leukoplakia (exceptionally rare now).

The prevalence of malignant transformation in leukoplakia ranges from 3–33% over 10 years:[1,2] some leukoplakias appear to have a high malignant potential, but in others it is low. Most white lesions, particularly homogeneous leukoplakias (Figure 7), are not malignant or potentially malignant. Verrucous or speckled leukoplakias are much more likely to be premalignant. Epithelial dysplasia has conventionally been the marker used to predict malignant potential.[4-6]

Apart from these leukoplakias, actinic cheilitis, oral submucous fibrosis and some lichen planus, most other potentially malignant lesions or conditions have only a very low incidence of dysplasia or malignant change (Table 1).

Malignant transformation of leukoplakias or other potentially malignant lesions cannot be accurately predicted based solely upon clinical characteristics.[1] Therefore, all red, white and mixed lesions persisting for 3 or more weeks require evaluation by biopsy examination.

Diagnosing oral cancer

Early OSCCs are often asymptomatic, appear innocuous, and can be easily overlooked[5-7] though, in theory, they are relatively easy to detect by examination[6] when classic features of malignancy such as ulceration, nodularity and fixation are clinically evident.[6,7] OSCC may present in a number of guises such as:
■ An indurated lump/ulcer, or a firm infiltration beneath the mucosa (Figure 8);
■ A granular ulcer with fissuring or raised exophytic margins (Figure 9);
■ A white or mixed white and red lesion (Figure 10);
■ A red lesion (erythroplasia);
■ A lump sometimes with abnormal supplying blood vessels;
■ A non-healing extraction socket (Figure 11);
■ A lesion fixed to deeper tissues or to overlying skin or mucosa;
■ Cervical lymph node enlargement, especially if there is hardness in a lymph node or fixation.

Enlarged nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumour, or metastatic disease. Occasionally (about 5%), a cervical lymph node enlargement is detected in the absence of any obvious primary tumour – when the likely site for the primary in order of predilection is the tongue base, tonsil or nasopharynx.

The problem is that OSCCs can resemble not only oral potentially malignant lesions but also some common benign oral lesions. Thus, the differentiation

Figure 11. Carcinoma arising at an extraction site.

Red lesion (erythroplasia)
White lesion
Lump
Ulcer with fissuring or raised exophytic margins
Pain or numbness
Abnormal blood vessels supplying a lump
Loose tooth
Extraction socket not healing
Induration beneath a lesion, ie a firm infiltration beneath the mucosa
Fixation of lesion to deeper tissues or to overlying skin or mucosa
Lymph node enlargement
Dysphagia
Weight loss

Table 2. Warning features suggestive of carcinoma.

of malignant lesions from benign lesions by clinical inspection alone can be difficult if not impossible.[8] Even highly trained professionals with wide experience cannot always adequately identify precancers and early stage OSCC by visual inspection alone.[9] Since the oral examination has undetermined sensitivity and specificity,[10-13] there is an indisputable need for a more accurate tool that can determine the nature of oral lesions. Furthermore, the recognized classic features of OSCC (Table 2), such as ulceration, induration, elevation, bleeding and cervical lymphadenopathy are features of advanced rather than of early disease.[14] Given the difficulty in clinically differentiating potentially malignant and malignant oral lesions from some that are benign, it would seem clear that the solution would be to biopsy and this should be done. However, despite this, there is often a substantial delay in biopsy, even when oral lesions display characteristics of frank cancers,[15,16] and few leukoplakias (the most common potentially malignant lesions) are ever biopsied.[17]

The golden rule should surely be to biopsy any persistent mucosal lesion where there is not absolute confidence that the diagnosis is of a benign lesion. There should be a high index of suspicion, especially of a solitary lesion present for longer than 3 weeks. The whole oral mucosa should also be examined as there may be widespread dysplastic mucosa ('field change') or even a second primary neoplasm – and the cervical lymph nodes must always be examined.

Biopsy

An incisional biopsy is invariably indicated and should be sufficiently large to include enough suspect and apparently normal tissue to give the pathologist a chance to make a diagnosis and not to have to request a further specimen. Most patients tolerate (physically and psychologically) one biopsy session, although it is never a particularly pleasant experience. Most biopsy wounds, whether 0.5 cm (too small) or 1.5 cm long (usually adequate) heal within 7 to 10 days. Therefore it is better to take at least one ample specimen. Some authorities take several biopsies at the first visit in order to avoid the delay and aggravation resulting from a negative pathology report in a patient who is strongly suspected as suffering from a malignant neoplasm.

An excisional biopsy should be avoided, unless the lesion is extremely small, since this is unlikely to excise an adequately wide margin of tissue if the lesion is malignant, but will destroy for the surgeon or radiotherapist clinical evidence of the site and character of the lesion.

Since red rather than white areas are most likely to show any dysplasia present in the lesion, a biopsy should be taken of the red areas. Various attempts to highlight clinically probably dysplastic areas before biopsy, for example by the use of toluidine blue dye, have not proven to be reliable, but may be of some help where there is widespread 'field change'. It tends to highlight clinically red areas.

False negative results are occasionally possible from incisional biopsy and, even where dysplasia has been excluded by incisional biopsy, studies have shown that the excised lesion may prove to contain OSCC in up to 10%.[18]

Carcinoma is diagnosed histopathologically when there is:

- Dysplasia extending through the full thickness of the epithelium;
- Extension of the rete pegs into the underlying lamina propria, ie invasion across the basement membrane.

It is generally accepted that prognosis is best in early carcinomas, especially those that are well-differentiated and not metastasized (Tables 3 and 4); fortunately, most OSCCs are well- or moderately-differentiated, but many OSCCs are diagnosed at a late stage.

If the pathology report denies malignancy, and yet clinically that is still the diagnosis, then discussion with the pathologist, and a re-biopsy are invariably indicated.

Developments in prognostication in potentially malignant lesions

The only method currently widely available to determine the prognosis fairly reliably depends on the laboratory examination of a tissue sample by biopsy, since it is accepted that dysplasia may precede malignant change.[19] Malignant change may be as high as 36% when moderate or severe epithelial dysplasia is present, and up to 50% with severe dysplasia. However, the histological finding of dysplasia cannot be used for confident prediction of malignant change in any individual case as it is subjective, and pathologists vary between each other in their opinion. Even the same pathologist will sometimes give a different opinion on different occasions if faced with the same specimen.

Clearly, studies of potential biomarkers are needed in order to introduce

Primary tumour size (T)	
Tx	No available information
T0	No evidence of primary tumour
Tis	Only carcinoma *in situ*
T1, T2, T3, T4	Increasing size of tumour
Regional lymph node involvement (N)	
Nx	Nodes could not be or were not assessed
N0	No clinically positive nodes
N1	Single ipsilateral node less than 3 cm in diameter
N2a	Single ipsilateral node 3 – 6 cm
N2b	Multiple ipsilateral nodes less than 6 cm
N2c	Bilateral or contralateral nodes less than 6 cm
N3	Any node greater than 6 cm
Involvement by distant metastases(M)	
Mx	Distant metastasis was not assessed
M0	No evidence of distant metastasis
M1	Distant metastasis is present

Several other classifications are available, eg STNM (S = site).
T1 maximum diameter of 2 cm; T2 maximum diameter of 4 cm; T3 maximum diameter over 4 cm; T4 massive tumour greater than 4 cm diameter, with involvement of adjacent anatomical structures.

Table 3. TNM classification of malignant neoplasms.

Stage	TNM	Approximate % survival at 5 years
1	T1 N0 M0	85
11	T2 N0 M0	65
111	T3 N0 M0 T1, T2 or T3 N1 M0	40
1V	Any T4, N2, N3 or M1	10

Adapted from Woolgar 1995[21] and Sciubba 2001.[22]

Table 4. Prognosis for intra-oral carcinoma.

more objectivity into prognostication. New techniques are appearing, particularly molecular methods such as examining for genetic changes such as abnormal tumour suppressor genes (TSGs).

As a surrogate for individual molecular markers, measurement of gross genomic damage may be a realistic option for accurate prognostication of oral potentially malignant lesions. One approach is the measurement of nuclear DNA content (DNA ploidy), a surrogate measure of gross genetic damage. Normally, a non-dividing somatic cell contains a *diploid* amount of DNA in 23 pairs or 46 chromosomes. Just before cell division, the DNA is doubled and, in mitosis, the 23 pairs of chromosomes are evenly distributed to two daughter cells. In somatic cells, if a doubling of the DNA during S-phase occurs without a subsequent cell division, the nucleus will then contain quadruples of the DNA, making the cell *tetraploid*. A further doubling without cell division yields eight copies of DNA, termed *octaploidy*. Multiple copies of DNA in excess of diploidy is termed *polyploidy*. If the chromosomes are not uniformly distributed to the daughter cells, or if parts of chromosomes become detached, the chromosomal segregation during mitosis is termed *unbalanced* – a situation termed *aneuploidy* and commonly observed in many cancers.

The method for measuring DNA ploidy uses automated image cytometry of nuclei obtained from routinely processed tissue samples, needs little additional expertise over that currently available in most pathology laboratories, and appears to have prognostic value in potentially malignant oral lesions.[20] Changes in DNA ploidy have been shown to predict subsequent transformation to OSCC – even in some lesions that have been classified by experts histopathologically as lacking dysplasia.

There is also enormous attraction in the possibility of identifying molecular changes in exfoliated cells such as in saliva. For example, clonal genetic changes in exfoliated cells identical to those found in the primary OSCC were found in 80% of saliva samples using microsatellite markers, suggesting that this may be useful for early diagnosis.

The most predictive of the molecular markers thus far available and assessed in OSCC development include chromosomal polysomy, p53 protein expression, and changes in chromosomes 3p or 9p. The use of these markers as an adjunct to routine histopathological examination can help prognostication and effective management of these lesions, but routine use is hampered by the complexity of the tests and the frequent lack of such facilities in routine laboratories.

Management of the patient with cancer or possible cancer

One of the most difficult clinical situations in which clinicians can find themselves is with the patient in whom serious disease such as cancer is suspected. Cancer to many, if not most, patients is a term that forebodes disaster – not unreasonably, since most have had relatives or friends who have died of the disease. Patient communication and information are then crucial aspects in management.

If the patient is to be referred to a specialist for confirmation of a diagnosis and insists (rightly) on a full explanation as to why there is a need to refer for a second opinion, it is unwise for you to suggest a serious diagnosis to the patient. Better that you admit ignorance about the field and say that you are trained more to be suspicious but doubt the lesion is anything to worry about, though you would be failing in your duty if you did not ask for a second opinion. That is what you would do for a member of your family – why should the patient be treated any the less?

Early cancers in otherwise healthy patients, especially those in sites

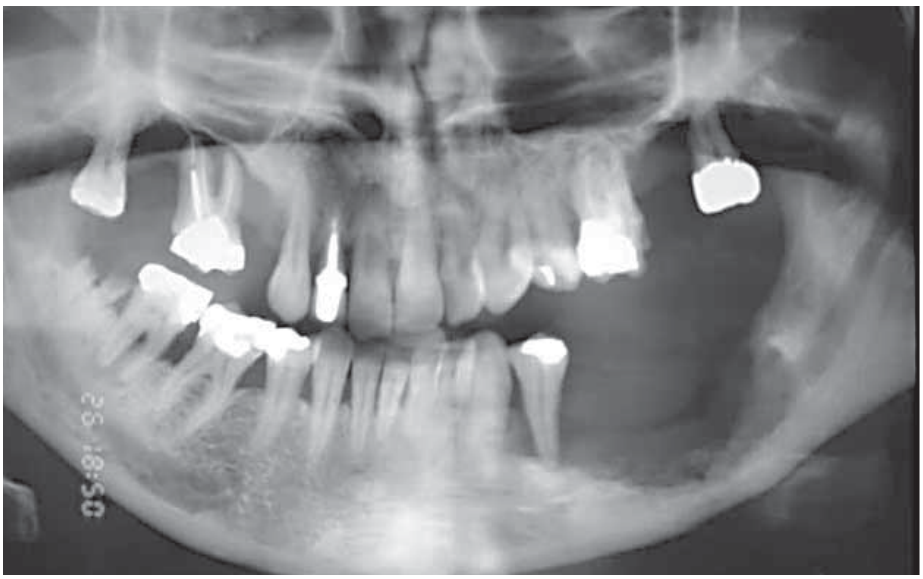

Figure 12. Bone erosion from a carcinoma.

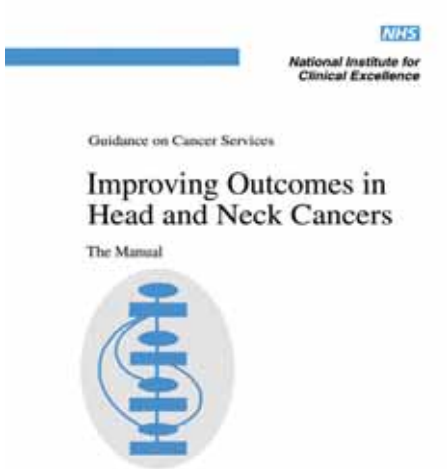

Figure 13. NICE Guidelines; Improving Outcomes in Head and Neck Cancers (2004).

such as the lip, have such a good prognosis that they can be said to be 'curable'. On the other hand, the prognosis of intra-oral carcinoma is not as good, but little is gained by expressing this to the patient or relative. If you *are* concerned, phone or write for an *urgent* opinion.

Once a cancer diagnosis has been firmly established, it is reasonable to discuss with the patient and, if they agree, the partner and relatives that:

- Tumours differ in their degree of malignancy;
- Patients differ in their defences;
- Their tumour has been detected at an early stage (hopefully);
- The prognosis is good for early cancer;
- Treatment efficacy is continually improving;
- Reconstruction is continually improving;
- Medical and anaesthetic care are continually improving;
- You have referred them to the best possible centre for treatment;
- The oncological team will provide fuller details of treatment options.

You must leave discussion of prognosis and actual treatment to the surgeon/oncologist concerned, as only they are in a position to give accurate facts to the patient concerned.

What the specialist team does

The team will undertake a history and examination, to determine not only the size of the cancer, but also local invasions, nodal and other metastases, and will stage the tumour, usually according to the TNM staging (Table 3). They will also consider the medical history and fitness of the patient for anaesthesia and surgery. For this, investigations are invariably necessary.

Investigations

The principles are to confirm the diagnosis histopathologically and, to determine whether there is malignant disease elsewhere, whether:

- Bone, muscles or cervical lymph nodes are involved;
- There are other primary tumours (typically in the upper aerodigestive tract – mouth, nares, pharynx, larynx, oesophagus, bronchus); there is controversy as to the need for endoscopy in all cases to detect such tumours but, ideally, nasendoscopy, oesophagoscopy and bronchoscopy should be carried out.
- There are metastases – which initially are to regional lymph nodes and later to the lungs and bone and, rarely, to the liver or brain. Imaging may detect abnormalities that escape clinical examination.

It is also important to:

- Ensure that the patient is as prepared as possible for the major surgery required, particularly in terms of mental state, and the ability to cope with general anaesthesia, potential blood loss and ability to metabolize drugs.
- Address any potential dental or oral problems pre-operatively, to avoid later complications such as osteoradionecrosis. Therefore, almost invariably indicated are:
- Jaw radiography (often rotating pantomography) (Figure 12);
- Lesional biopsy;
- Fine needle biopsy of equivocal neck lymph nodes with ultrasound control, or sentinel node biopsy (biopsy of the main draining lymph node);
- Chest radiography: important as a pre-anaesthetic check, especially in patients with known pulmonary or airways disease and to demonstrate metastasis to lungs or hilar lymph nodes, ribs or vertebrae;
- MRI or CT scans of the primary site, of the head and neck, and suspected sites of distant metastases, and MRI scans of the neck to delineate the extent of cervical node metastases;
- Electrocardiography;
- Blood tests: full blood picture and haemoglobin grouping and cross-matching; clotting assays; urea and electrolytes; liver function tests; blood gases.

OSCC should be staged according to the TNM classification of the International Union against Cancer (UICC) – tumour size (T), nodal metastases (N) and distant metastases (M) (Table 3) – since this classification relates well to overall survival rate, ie the earlier the tumour, the better the prognosis and the less complicated is the treatment. In one series recently,[23]

Criteria	Are criteria fulfilled with respect to OSCC	Comments
The cancer is an important public health problem.	Yes	
Treatment of small lesions confers a significant survival advantage.	Yes	
Facilities for further diagnosis and treatment are available.	Equivocal	Usually they are, though the costs need to be considered.
There is an identifiable latent stage.	Equivocal	This is less clear cut since many OSCCs do not appear to be preceded by a clinically identifiable precancerous lesion.
The screening test should be effective with few false positive results.	Equivocal	Oral examination may be fairly effective but will produce many false positives and some false negatives: most potentially malignant lesions appear not to progress to cancer. Molecular or cellular biological techniques are required to improve this.
The screening test is well accepted.	Equivocal	It is, but, as discussed above, somewhat limited.
The natural history of cancer is completely defined.	Equivocal	Unfortunately it is not – the same applies to potentially malignant lesions.
The strategy for treatment is well defined.	Equivocal	This criterion is the most contentious since there is no universal agreement on treatment policy for potentially malignant lesions and no randomized controlled trials of note.
The cost should be affordable.	Equivocal	The cost of an oral examination is relatively low, though the financial and other costs of other or further investigation and follow-up are more difficult to define.
Regular observation of potentially malignant lesions should result in early detection of malignant change.	Equivocal	This is not always the case.

Table 5. How criteria for screening are met with respect to OSCC.

the 5-year survival probability was 81% for patients without metastases, 64% for patients with intra-nodal metastases and 21% for patients with metastases showing extra-capsular spread. Management should improve following the introduction of care guidelines, multidisciplinary working, and guidance such as that from the National Institute for Clinical Excellence (NICE; Figure 13).

Screening for oral cancer and potentially malignant lesions

Screening to identify oral cancer and potentially malignant lesions would appear attractive but, though many of the screening criteria are fulfilled at least partially, screening has yet to be widely accepted (Table 5).[24-26] Indeed, the US National Cancer Institute has concluded that 'there is insufficient evidence to establish that screening would result in a decrease in mortality from oral cancer.'[27]

Regular observation of potentially malignant lesions should in theory result in early detection of malignant change but, in reality, this is not always the case. Nevertheless, management of early cancers needs to be less radical and appears to confer survival advantage.

Management of early OSCC appears also to be associated with less morbidity and thus it is important to be suspicious of oral lesions – particularly in patients at high risk, such as older males with habits such as the use of tobacco, alcohol or betel.

Conclusion

Although the efficacy of screening for oral cancer to increase survival and reduce mortality remains unproven, there are examples of apparent incidences of success. For example, it is believed that Cuba's on-going oral cancer screening programme has resulted in a higher proportion of cancers being localized at diagnosis and a comparatively high survival rate.[28] A reduced incidence of oral pre-cancerous lesions has been reported in a primary prevention trial. In addition, the abstinence of tobacco for a six-week period resulted in the reversal of potentially pre-cancerous oral lesions.[29] Nevertheless, even in the health-conscious USA, the number of patients actually screened for oral cancer is remarkably low.[30] Unfortunately, among patients with OSCC referred for secondary care, the uptake of available services varies enormously.[31]

Websites and patient information:
http://www.entnet.org/cancer.html

http://cancer.med.upenn.edu/new/index.html
http://www.oralcancer.org
http://www.cancer.gov

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