Michael Lewis

Mouth Cancer – Risk Factors and Potentially Malignant Disorders

Abstract: The incidence of mouth cancer in the UK has increased more than 30% during the past decade and the overall 5-year survival remains poor, at approximately 55%. A number of risk factors for mouth cancer has been identified, and all dental professionals should be aware of these, and, where possible, provide intervention. Some cases of mouth cancer arise in a pre-existing mucosal condition, known as an oral potentially malignant disorder (OPMD). Awareness of the presence of an OPMD, or any mucosal changes that fulfil the criteria for urgent suspected cancer (USC) in primary care, should lead to an appropriate referral to specialist services.
CPD/Clinical Relevance: This paper provides a review of the risk factors for mouth cancer and potentially malignant disorders.
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The majority (90%) of malignant tumours that occur in the mouth represent squamous cell carcinoma arising within the mucosal epithelium. The incidence of mouth cancer is increasing in many countries, including the United Kingdom. Unfortunately, despite improvements in treatment, the 5-year survival following diagnosis remains poor, at approximately 55%.[1] The single most important factor that can improve the individual outcome is detection of the tumour whilst small, specifically 2 cm or less in diameter with no regional node involvement or distant metastases (stage I). Patients with a tumour detected at stage I are associated with an 85% 5-year survival, compared to those with stage IV (greater than 4 cm in diameter with regional node involvement and possible distant metastasis), for whom the 5-year survival is only 10%.[1,2]

Squamous cell carcinoma represents epithelial cell turnover that is out of normal control (Figure 1).

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Although to date no single factor as to why the epithelium undergoes malignant transformation has been identified, a number of factors associated with the development of mouth cancer has been described (Table 1). It is essential to investigate the presence of potential risk factors and, where possible, eliminate them. The dental practice setting provides an ideal environment for the provision of brief preventive intervention for mouth cancer.

It is also important to recognize that certain mucosal abnormalities in the mouth, referred to as oral potentially malignant disorders (OPMDs), are known to have an increased incidence of malignant transformation. These OPMDs, and any other mucosal abnormality noted during a routine oral soft tissue examination, require full assessment and management. It is essential that an appropriate referral is made if the clinical findings fulfil the criteria for urgent suspected cancer (USC).

Risk factors

Tobacco

Tobacco usage has traditionally been regarded as a prime risk factor for mouth cancer.[3] Whilst predominantly used in the form of cigarettes, the oral mucosa can be directly exposed to tobacco in chewing products, either alone or in combination with other substances. More than 300 carcinogens have been identified in tobacco smoke, in particular aromatic hydrocarbons, which when absorbed into the mucosa cause damage to replicating epithelial cells. Tobacco smoke and associated heat can also stimulate melanocytes in the oral mucosa and result in areas of increased pigmentation, especially in the soft palate (Figure 2).

Heat-not-burn (HNB) cigarette products have recently been developed by tobacco companies and promoted as an alternative to traditional smoking, with a reduction in the intake of carcinogenic substances. In these devices, the tobacco is warmed enough to produce a vapour but not actually burnt. The health risks of HNB products remain uncertain, but are known to still deliver harmful carcinogens to the user.

Details of any tobacco habit, such as number of cigarettes smoked daily or number of grams of tobacco used in 'roll-ups' per week, should be recorded as part of the patient's social history. All patients with a tobacco habit should be advised on the increased risk of developing mouth cancer. Smokers who do not drink alcohol have a two-fold risk of developing mouth

Tobacco smoking
Smokeless tobacco
Betel quid
Alcohol
Genetics
Immunosuppression
Ultraviolet light
Human papilloma virus
Previous mouth cancer

Table 1. Risk factors associated with mouth cancer.

Figure 1. Squamous cell carcinoma on the lateral margin of the tongue.

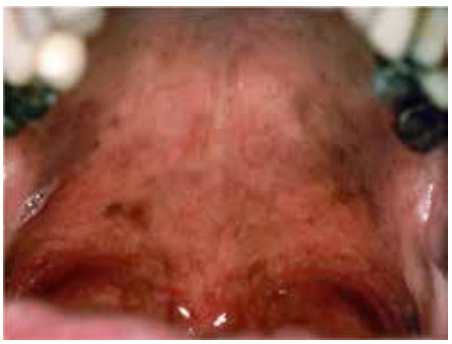

Figure 2. Pigmentation in the palate associated with smoking habit.

cancer, which increases with frequency and duration.[4] The use of smokeless products, such as powdered snuff or chewing tobacco, also carry similar risks.

All patients should be advised on the association of a tobacco habit with a negative impact on health. Advice on contact details of a local cessation service should be provided, in particular to those patients who express a wish to quit. A risk reduction has been demonstrated within one year of quitting.[5] The use of conventional cigarettes is declining in developed countries due to public health measures, which should hopefully lead to a reduction in tobacco-related mouth cancer.

Most forms of smoking cessation are based on nicotine replacement therapy. Nicotine-containing products are available as chewing gum, oral and nasal sprays, sub-lingual lozenges, inhalators and transdermal patches. More recently, electronic cigarettes have become popular as a method of nicotine replacement, and the associated 95% reduction in harm compared to cigarette smoking has gained professional support. However, it is important to advise patients that the preferred option is to quit completely.

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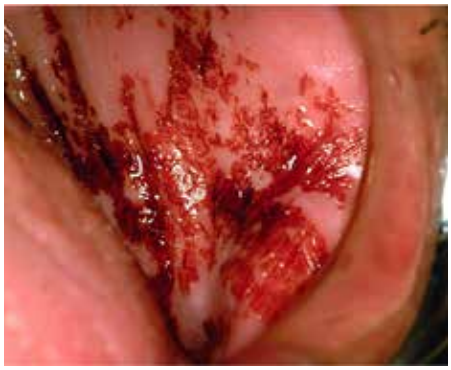

Figure 3. (a, b) Mucosal pigmentation associated with chewing of betel quid.

Betel quid

The chewing of betel quid, which is a mixture of areca nut with other substances, such as lime and tobacco, wrapped in a betel leaf, is popular in south and south-east Asia. It is also used by communities from these regions in other parts of the world, including the UK. The placement of the betel quid in direct contact with the oral mucosa produces characteristic pigmentation changes (Figure 3). The habit is associated with a three-fold increase in mouth cancer.[6] It has also been implicated in the development of oral submucous fibrosis, a condition also associated with mouth cancer. All patients with a betel chewing habit should be given advice to quit.

Alcohol

Alcohol is a well recognized risk factor for mouth cancer.[7] Consumption of alcohol in the UK is increasing. Although ethanol is not regarded as carcinogenic, its implication in mouth cancer is due to its metabolism by alcohol dehydrogenase to acetaldehyde (ACH). A number of mechanisms by which ACH causes carcinogenesis in the oral epithelium have been proposed, including disruption of DNA synthesis and repair.[7] There is a two-fold increased risk of mouth cancer in individuals who drink but do not smoke tobacco.[4] However, it is also known that ethanol can act as a solvent and increase absorption of carcinogens into the mucosa. This in part explains the five-fold increase in mouth cancer in individuals who smoke tobacco and consume more than three alcoholic drinks per day.[4]

Details of alcohol consumption should be taken as part of the social history. Traditionally, this has comprised recording the number of units of alcohol drunk per week. The advice is that there should be a maximum of 14 units per week with at least two alcohol-free days in that period. It has been proposed that a Modified Single Alcohol Screening Question (M-SASQ) is more useful than asking the number of units per week.[8] The M-SASQ consists of the following question, '*How often do you have six or more standard drinks on one occasion*?' *Never, less than monthly, monthly, weekly, or daily or almost daily.* A positive score is any option other than *never* or *less than monthly*. Patients with a positive score should be advised to contact local support services to help with alcohol addiction.

Genetic factors

There is some evidence that genetic variants involving alcohol metabolism

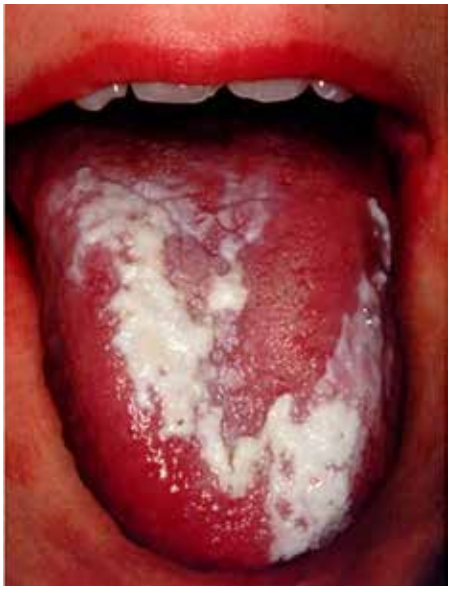

Figure 4. Leukoplakia in dyskeratosis congenita (Courtesy of Professor G Ogden).

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Figure 5. Renal transplant patient with a leukoplakia **(a)** that underwent malignant transformation **(b)**.

and DNA repair pathways are risk factors for mouth cancer and a hereditary family history has been described.[5] In addition, some genetic conditions, for example dyskeratosis congenita, are known to be associated with increased incidence of cancer and should be managed as an OPMD (Figure 4).

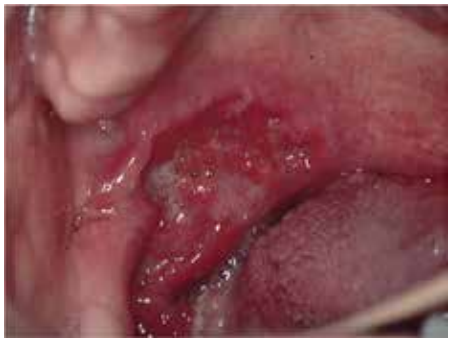

Figure 6. HPV-positive oropharyngeal squamous cell carcinoma.

Leukoplakia
Erythroplakia
Palatal changes in reverse smokers
Oral submucous fibrosis
Actinic keratosis
Lichen planus
Discoid lupus erythematosus
Hereditary disorders with increased risk

Table 2. Potentially malignant disorders of the oral mucosa.[12]

Immunosuppression

The development of mouth cancer has been described in association with the use of immunosuppressive drugs, in particular as an aspect of solid organ transplantation.[9] Renal transplant patients may develop a leukoplakia, some of which develop into mouth cancer (Figure 5). Reduction in the immunosuppressive therapy can lead to reduced incidence of cancer.[10]

Human papilloma virus

There are more than 100 types of human papilloma virus (HPV), some of which are associated with the development of malignancy at different body sites. In recent years, it has been recognized that HPV 16 is involved in oropharyngeal cancer. It is important to appreciate that HPV is implicated in oropharyngeal cancer rather than mouth cancer (Figure 6). The virus is sexually transmitted and, although the natural history of oral HPV infection is not well understood, there is increased oral carriage of the virus in individuals who have four or more oral sex partners. Interestingly, HPV-associated squamous cell carcinoma in the oropharynx has a better prognosis than conventional non-HPV-infected cancer.[11] It is thought that HPV-positive tumours have less genomic damage and field change and, as such, respond better to a combination of radiotherapy and chemotherapy.[11]

Vaccination programmes for HPV-16 and HPV-18 are now available in many countries and this should be given to both boys and girls at the age of 11–12 years.

Ultraviolet light

Chronic exposure to ultraviolet (UV, mainly UVB) in sunlight, often as part of an outdoor occupation, increases the risk of developing actinic (solar) keratosis and cancer of the lower lip. Protective sun-blocking agents (SPF 15 or greater) should be recommended.

Previous mouth cancer

A patient who has been diagnosed and successfully treated for mouth cancer needs close review, since such an individual is at an increased risk of developing a further (new primary) mouth cancer.

Potentially malignant conditions

The majority of cases of SSC in the mouth arise in what was previously clinically normal tissue. However, some cancers are known to develop within a pre-existing mucosal abnormality and a list of such conditions was published in 2007 (Table 2).[12]

Leukoplakia

The most frequently recognized OPMD is leukoplakia (Figure 7), which was first defined by the WHO in 1978 as '*a white patch or plaque that cannot be characterised clinically or pathologically as any other disease*'.[13] The term has subsequently been refined following various international workshops and is now used to describe '*white plaques of questionable risk having excluded (other) known diseases and disorders that carry no increased risk for cancer*'.[14] It is essential to remember that leukoplakia is a clinical term and not a diagnosis. A biopsy is required to exclude

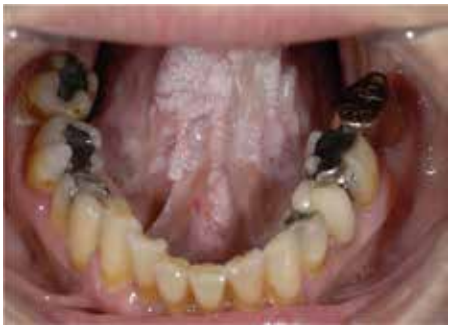

Figure 7. Leukoplakia in the floor of the mouth.

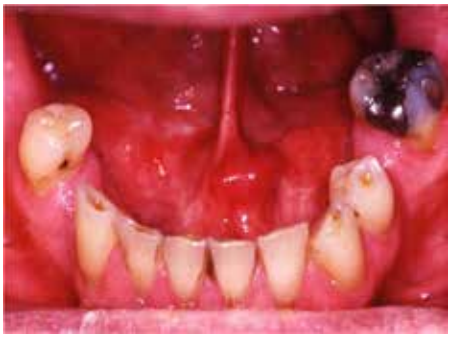

Figure 8. Erthroplakia in the floor of the mouth.

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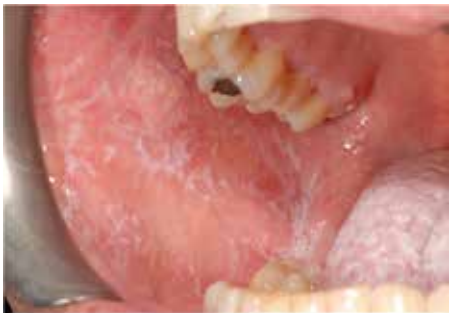

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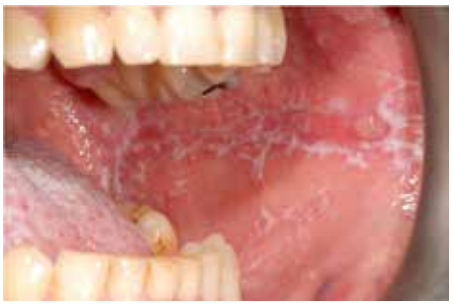

Figure 9. (a , b) Bilateral lichen planus in the buccal mucosae.

known mucosal disorders that may present as a white patch. Although often associated with the presence of epithelial dysplasia, leukoplakia itself has no specific histopathological features. The reported malignant transformation rate for oral leukoplakia has ranged from low levels of 0.13% in India[15] and 2.6 % in the UK,[16] to high levels of 17.5% in USA.[17] These findings are undoubtedly influenced by the geographical site, population studied, number of patients and length of follow-up observation period. The global malignant transformation rate of leukoplakia is generally accepted to be 1.36% per year.[18]

There is a rare form of leukoplakia, termed proliferative verrucous carcinoma (PVL), which has a reported transformation rate as high as 70%.[19] The presentation of PVL is characterized by an initial white patch that develops into multiple areas of exophytic/wart-like changes within the mucosa. The aetiology of PVL is unknown and treatment is difficult due to progressive recurrence following surgical removal.

Erythroplakia

Oral erythroplakia (Figure 8) is defined as '*a fiery red patch that cannot be characterised clinically or pathologically as any other definable lesion*'.[20] Erythroplakia, in a similar way to leukoplakia, has no specific histopathological features. The term is used clinically to record the presence of an erythematous mucosal abnormality that does not have a clinical appearance characteristic of known red patches, such as denture-associated candidosis or median rhomboid glossitis. Oral erythroplakia has the highest transformation rate of all of the OPMDs, being reported as between 14% and 50%.[21] Erythroleukoplakia is an alternative clinical term that can be used when the mucosa has a speckled red and white appearance. Importantly, erythroleukoplakia is associated with a high risk of malignant change.

Lichen planus

The aetiology of oral lichen planus (OLP) is unknown but does involve the immune system, since a primary histopathological feature is a sub-epithelial band of T lymphocytes, indicating a cell-mediated reaction. OLP is one of the most frequently occurring mucosal conditions in the population, with a reported prevalence of between 0.5% and 2.2%.[22] Different types of OLP have been described, including reticular, atrophic, erosive, plaque-like and bullous, based on the appearance of the mucosa. However, actual typing in an individual patient is often difficult, since different types may be present simultaneously and also change during the course of disease over months.

Overall, the most characteristic feature is the presence of bilateral white striations in the buccal mucosa (Figure 9). The reported malignant transformation for OLP worldwide has varied between 0.4% and 6.4%, depending on the population studied and length of follow-up period. Two historical UK-based studies revealed yearly transformation rates of 0.07% and 0.27%.[23,24] A recent systematic review revealed an increased transformation risk with erythematous forms on the tongue (Figure 10).[25]

Submucous fibrosis

Submucous fibrosis is a chronic disorder of the upper alimentary tract, which presents most obviously within the mouth as vertical fibrous bands in the buccal mucosa that limit mouth opening. The patient will also complain of an overall burning sensation within the mouth, including the buccal mucosa, which may appear white or erythematous (Figure 11). Oral submucous fibrosis (OSF) has a strong association with the social habit of chewing areca (betel) nut, which is popular in populations living in and originating from the Indian subcontinent and surrounding countries. Alkaloids within the nut stimulate fibroblast proliferation. The malignant transformation rate from a long-term follow-up study of OSF in an Indian population was reported as 7.6%.[26]

Palatal keratosis in reverse smokers

Reverse smoking, in which the lit end of a cigar or cigarette is placed in the mouth, is popular in the rural populations of the Amazon, New Guinea and Indian subcontinent. The physical irritation from heat and tobacco smoke induces hyper-keratinization and erythematous changes

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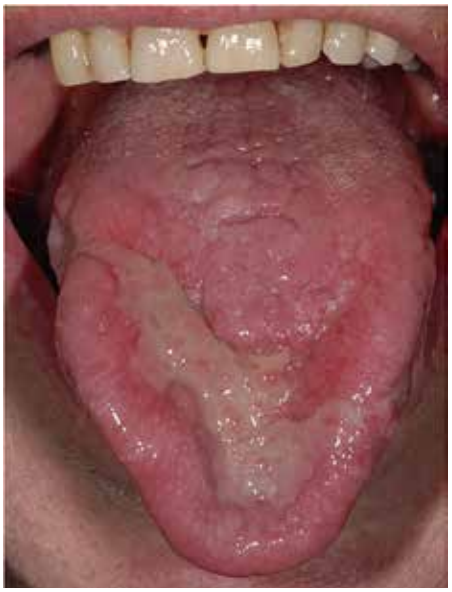

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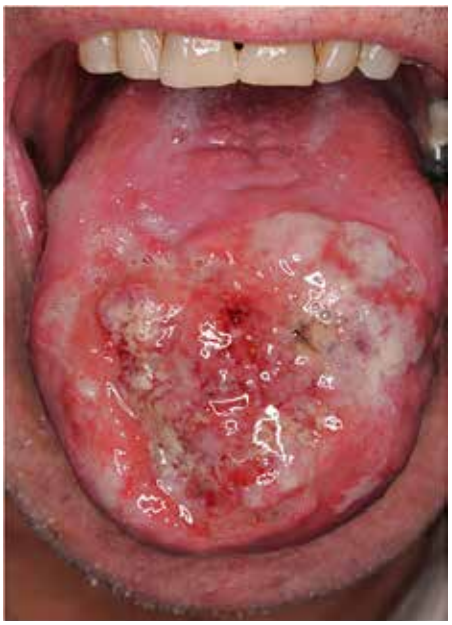

Figure 10. Lichen planus **(a)** that underwent malignant transformation **(b)**.

within palatal mucosa. A high incidence of cancer in the hard palate, which is a relatively rare site in non-reverse smokers, has been associated with this habit.[27]

Actinic keratosis

Actinic keratosis is associated with exposure to ultraviolet light and characteristically affects the lower lip presenting as palpable white plaques. Regular review is required and the development of palpable induration would indicate the need for biopsy to exclude transformation into either a squamous cell carcinoma or basal cell carcinoma (Figure 12). The actual transformation rate of actinic keratosis is unknown.

Figure 11. White patches in buccal mucosa and restricted mouth opening in submucous fibrosis.

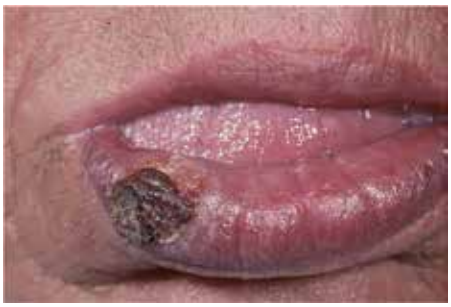

Figure 12. Squamous cell carcinoma arising in previous actinic keratosis.

Discoid lupus erythematous

Discoid lupus erythematosus, which can produce oral mucosal changes that resemble oral lichen planus or erythroplakia, has been reported to transform into squamous cell carcinoma.

Dyskeratosis congenita

Dyskeratosis congenita, which is an inherited genetic-based OMPD, is a bone marrow disorder that is associated with oral leukoplakia and mouth cancer that can cause death in young adulthood.[28]

Other conditions

Although not included in the WHO list of OPMDs, chronic hyperplastic candidosis (CHC) is recognized as having the potential to undergo malignant transformation.[29] CHC characteristically presents as bilateral adherent white patches in the buccal commissure regions of the mouth (Figure 13) or dorsum of the tongue. This type of oral candidosis is seen almost exclusively in smokers. Although the provision of systemic antifungal therapy will produce a dramatic clinical improvement (Figure 14), the mucosal changes will recur if the patient does not stop the tobacco habit.

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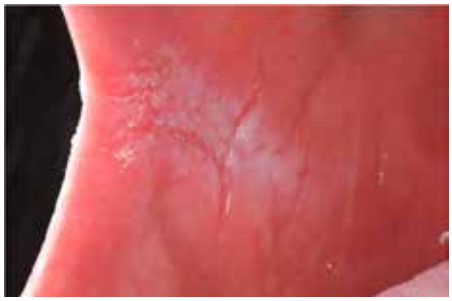

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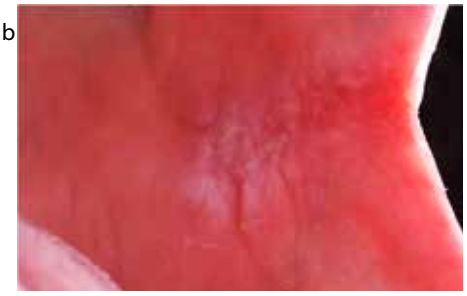

Figure 13. (a, b) Chronic hyperplastic candidosis as bilateral white patches.

Urgent suspected cancer referral

The outcome of mouth cancer is significantly improved if the tumour is detected and treated when it is less than 2 cm in diameter with no local metastasis. On this basis, any patient suspected to have cancer should be referred as a USC for specialist assessment rapidly with an expectation that they will be seen within 14 days (2-week wait, 2WW) or 10 working days (10-day rule).[1] The 2WW system for cancer, including head and neck cancer, was introduced in the UK in 2000. The National Institute for Health and Clinical Excellence (NICE)[30] and Healthcare Improvement Scotland (HIS)[31] have published referral guidelines to help clinicians decide which patients should be referred as USC. These guidelines focus on the presenting clinical

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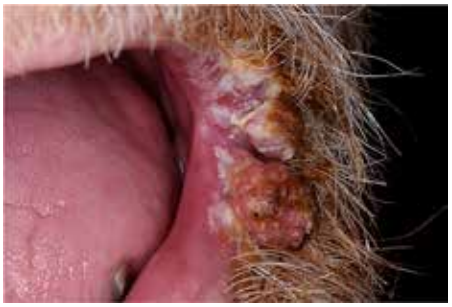

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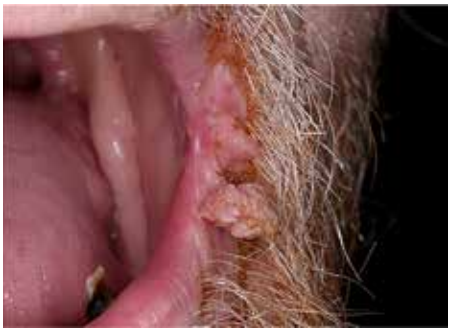

Figure 14. Chronic hyperplastic candidosis at presentation **(a)** and improvement after 7 days of systemic fluconazole **(b)**.

■ Unexplained ulceration in the oral cavity lasting more than 3 weeks
■ A persistent and unexplained lump in the neck
■ A lump on the lip or in the oral cavity consistent with oral cancer
■ A red or red and white patch in the oral cavity consistent with erythroplakia or erythroleukoplakia

Table 3. Potentially malignant disorders of the mucosa.[12]

symptoms (Table 3).

An audit of the 2WW rule in the Oral and Maxillofacial Surgery department at the Newcastle General Hospital, and then subsequently in the Oral Surgery and Oral Medicine departments at Newcastle Dental Hospital, revealed positive head and neck cancer detection rates of 11% and 7%, respectively, in the cohorts of patients examined.[32] A similar study at the Oral Medicine department in King's College, London, reported that 8% of urgent referrals were found to have oral cancer.[33] Both audits concluded that further education of referring practitioners and refinement of the referral guidelines were required to ensure a more efficient service.

One aspect of referral that can be improved is avoidance of the term 'lesion'. The word lesion derives from the Latin term *laesio* meaning injury and, as such, is non-specific. It is far more helpful to use the descriptive words such as ulcer, swelling or red patch in the clinical records and any referral communication.[34] In addition, the inclusion of clinical photographs, in not only USC but routine referrals, has to be recommended, since this is extremely useful to the clinician in vetting the urgency of any referral.

Methods of referral from primary care to specialist secondary care vary widely. Historically, referrals have been made in the form of a written letter with inevitable risk of delay within a postal system. Electronic record management and referral systems within managed clinical networks (MCNs) are being introduced and these have a range of advantages, including an assurance of rapid and safe delivery of the referral request. In addition, some electronic systems ensure that all relevant information is provided by the referring practitioner, since the referral will not be accepted until this is completed online. Individual practitioners must be aware of their local referral system.

One unfortunate impact of early lockdown restrictions of the COVID-19 pandemic was the significant reduction in the number of USC referrals from both dental and medical primary care.[35] Although the referrals are coming through the system again now, there has undoubtedly been a delay in diagnosis for some patients with an inevitable adverse impact on their outcome.

Conclusion

Although the aetiology of mouth cancer remains unknown, a number of risk factors have been found for the development of this form of malignancy. Some of these factors are modifiable and patients should be provided with appropriate advice in primary dental care. In addition, all members of the dental team should be aware of mucosal changes that are associated with the potential for malignant change. Knowledge and application of the USC referral pathway is an essential aspect of primary care dentistry.

Compliance with ethical standards

Informed consent was obtained from all patients for the clinical images used in this article.

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CPD ANSWERS September 2020

1. B	**6.** C
2. A	**7.** C
3. D	**8.** C
4. C	**9.** A
5. D	**10.** C