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This series aims to enhance the healthcare team's awareness of the importance of early detection by recognizing signs and symptoms of orofacial cancers and their management, and of prevention. It discusses treatment complications from surgery, radiotherapy (RT) and chemotherapy (CTX), summarizing the outcomes of a meeting on 'Oral Healthcare in People Living with Cancer' held in 2010, attended by 300 delegates from 33 countries – dentists, specialists, and Dental Care Professionals (DCPs), and the cancer support team. There is a considerable body of literature on oral cancer but very little is written on healthcare aspects of people living with cancer and a particular focus of this meeting was caring for survivors. The Faculty included European leaders in the field who have authored the series. The full peer-reviewed papers from the meeting are published in *Oral Oncology* 2010; **46**; 485–570.

Oral Cancer: Comprehending the Condition, Causes, Controversies, Control and Consequences

4. Potentially Malignant Disorders of the Oral and Oropharyngeal Mucosa

A range of potentially malignant disorders is recognized but erythroplakia (erythroplasia), leukoplakia and lichenoid lesions are the most important. Others, such as actinic cheilitis, discoid lupus erythematosus, submucous fibrosis, Fanconi anaemia (syndrome) and other lesions are important but generally less common (Table 1).

Our inability to be able to define the risk of malignant transformation of a potentially malignant oral lesion for an individual patient is one of the biggest challenges in the field, as is the inability to reliably predict the effects of any treatments. Sadly, the evidence base is missing.

It is even more crucial, therefore, to ensure that the patient gives fully informed consent to the management decided after full discussion with the clinician.

This article focuses on erythroplakia, leukoplakia and lichenoid lesions/lichen planus.

Erythroplakia

Erythroplakia is rare (<1.0%), typically related to tobacco and alcohol use, and seen in the middle-aged and the older patient. It is usually a solitary lesion defined as a 'fiery red patch that cannot be characterized clinically or pathologically as any other definable disease'. The clinical appearance is often of a flat or even depressed erythematous area of mucosa and for that reason the term 'erythroplasia' may be more appropriate (Figure 1). In some, there is a mixture of red and white changes – when the lesion is termed 'erythroleukoplakia' or non-homogeneous leukoplakia.

Histopathologically, erythroplakia frequently shows at least moderate or severe dysplasia and the majority will undergo malignant transformation. Erythroplakia needs to be removed by surgery, usually either by cold knife (scalpel) or by laser excision, and the specimen sent for

histopathological examination, but there are no reliable data about the recurrence rate.

Leukoplakia

Leukoplakia is more common than erythroplakia (~2%) and is associated with tobacco, alcohol and possibly papillomavirus. Defined as 'A white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer', it can be confused with other white lesions, such as amalgam-associated leukoplakic or lichenoid lesions. By definition, the term excludes entities such as frictional keratosis, smokers keratosis and lichenoid lesions.

Leukoplakia can appear clinically as:

- a homogeneous type (flat, thin, uniform white in colour) (Figure 2)
- a non-homogeneous type, either as a white-and-red lesion

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	Malignant potential		
	Very high	High	Low
Main entities	Erythroplakia	Leukoplakia (non-homogeneous), Candidal leukoplakia	Leukoplakia (homogeneous), Lichen planus
Uncommon entities		Actinic cheilitis, Submucous fibrosis, Dyskeratosis congenita	Discoid lupus erythematosus, Fanconi syndrome

Table 1. Potentially malignant disorders.



Figure 1. Erythroplasia (From Scully *et al* Oral and Maxillofacial Diseases. 3rd ed Informa).



Figure 2. Leukoplakia; homogeneous type (From Scully *et al* Oral and Maxillofacial Diseases. 3rd ed Informa).



Figure 3. Erythroleukoplakia.



Figure 4. Carcinomatous transformation in leukoplakia.

(‘erythroleukoplakia’), that may be either irregularly flat (speckled) (Figure 3) or nodular, or as verrucous leukoplakia (usually has a uniform white verrucous texture). Proliferative verrucous leukoplakia (PVL) is a subtype of verrucous leukoplakia, being characterized by multifocal presentation, resistance to treatment and a high malignant transformation rate.

In the assessment and quantification of epithelial dysplasia, a distinction is commonly made between dysplastic and non-dysplastic leukoplakias, although there may be considerable intra- and inter-observer variation among histopathologists. An annual malignant transformation rate of about 1–2% is probably a realistic figure for all types of leukoplakia together. Epithelial dysplasia – often correlating with a non-homogeneous, erythroleukoplakic clinical appearance – is in general regarded as the most important indicator of malignant potential. In dysplastic leukoplakias, the malignant transformation may reach 30% (Figure 4).

In any potentially malignant lesion such as a leukoplakia, however, there might be a range of cells present of different malignant potential, including some that cross the epithelial basement membrane – defining the lesion as cancer (Figure 5).

- Cells with green nuclei = normal
- Cells with orange nuclei = dysplastic
- Cells with red nuclei = severely dysplastic/malignant

Thus the histopathological interpretation of a biopsy from such a lesion could vary from benign to malignant, depending on the site biopsied, the histopathologists acumen, and other factors. Total reliance on a biopsy result, therefore, could be fraught. Indeed, more than 25 years ago, one study showed that oral leukoplakias which were non-dysplastic upon incisional biopsy proved, in around 10% of cases, to contain cancers on excision of the leukoplakias. Similar findings were reported more recently by a different group of investigators.

It is also not possible at present to predict which dysplastic lesions will progress to carcinoma reliably, nor to be absolutely certain that a clinical lesion has malignant potential or not. Over the past few years, much effort has gone into identifying genetic changes that may underlie oral carcinoma and to find biomarkers, such as DNA ploidy, and changes in p53, and chromosomes 3 and 9 that might predict neoplastic change. Unfortunately, none has yet been shown to be absolutely reliable – but these or other markers will, in the future, surely not only add to our understanding of the pathobiology of malignant transformation, but help diagnostically and prognostically.

We can conclude therefore that, at least at present, there are no signs or symptoms which reliably predict whether a leukoplakia will undergo malignant change, though

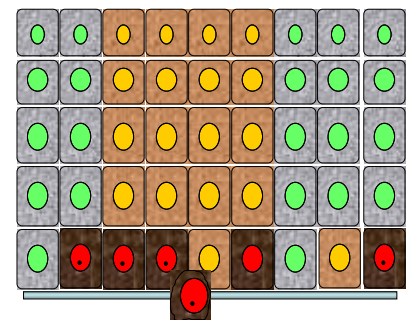


Figure 5. Diagrammatic representation of composition of a clinical mucosal lesion considered potentially malignant.

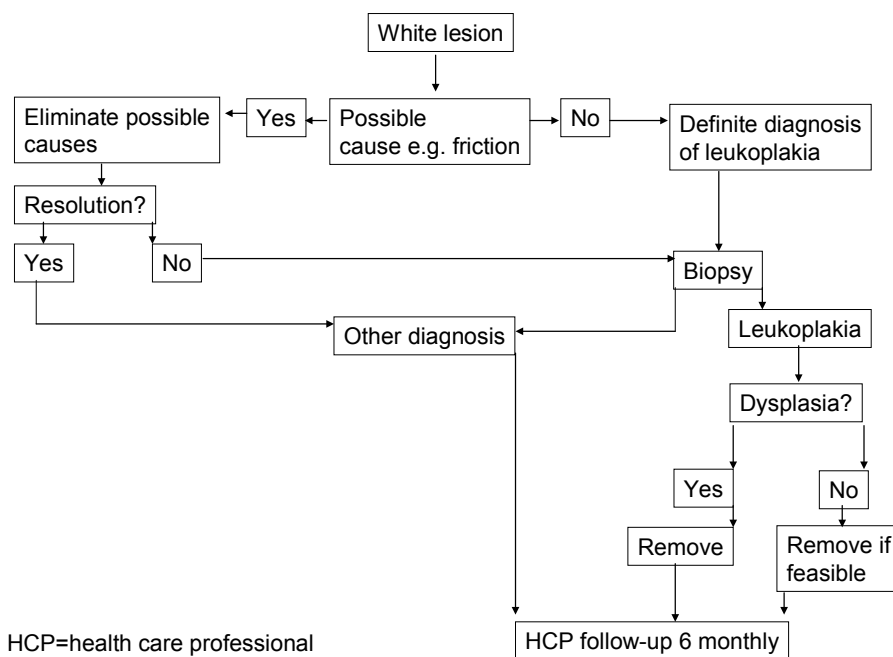
suggestive features are the presence of:

- Erythroplasia;
- Dysplasia;
- Genetic changes.

Known risk factors for malignant transformation are listed below:

- Of non-homogeneous type;
- Containing epithelial dysplasia;
- Of long duration;
- In non-smoker;
- In female;
- On the tongue and/or floor of the mouth;
- Of size > 200 mm²;
- With DNA aneuploidy.

The evidence from systematic



HCP=health care professional

Figure 6. Management of leukoplakia.

reviews is that medical therapies are not reliably effective: topical anti-cancer agents or retinoids, though generally well tolerated, have only temporary efficacy, and perhaps their best indication is when the location or extent of the lesion render surgical removal difficult. Topical treatment with podophyllin or bleomycin

has induced some regression or even total resolution, but lesions recur.

An algorithm for the management of leukoplakia is presented in Figure 6. Biopsy confirmation is essential. Possible aetiological factors should be removed, and an observation of 2–4 weeks seems acceptable to observe any possible

regression. The authors are of the opinion that it is best to remove all non-regressing leukoplakias if feasible, irrespective of the reported presence or absence of epithelial dysplasia on biopsy, despite there being no scientific evidence that treatment truly prevents the possible future development of a squamous cell carcinoma. This seems wiser than ‘watchful waiting’.

The most commonly used treatment modalities include surgical or CO₂ laser excision with the specimen sent for histopathological examination. In widespread leukoplakias, photodynamic therapy may be considered. Recurrence rates may be up to 30%, probably mainly depending on the duration of follow-up.

The efficacy of continuous follow-up of oral leukoplakia patients is virtually unknown.

Lichen planus

Oral lichen planus (OLP) is also regarded as a potentially malignant disorder, but with an annual malignant transformation rate less than 0.5%. Transformation may occur in any of the clinical types of OLP.

Unfortunately, there are no strategies that can prevent this malignant transformation and the efficacy of continuous follow-up of OLP patients, although recommended by various authors, is questionable.

Cochrane Synopses

TREATMENT OF PERIODONTAL DISEASE FOR GLYCAEMIC CONTROL IN PEOPLE WITH DIABETES.

Simpson TC, Needleman I, Wild SH, Moles DR, Mills EJ. Treatment of periodontal disease for glycaemic control in people with diabetes. Cochrane Database of Systematic Reviews 2010, Issue 5. Art. No.: CD004714. DOI: 10.1002/14651858.CD004714.pub2.

‘Long-term control of blood sugar levels is considered to be of critical importance in preventing complications associated with diabetes. Research evidence has suggested that treating gum disease in people with diabetes may assist in lowering blood sugar levels. The aim of this review was to investigate the relationship of treating

gum disease on blood sugar control in people with diabetes and suggest a future strategy for research and medical/dental practice. The evidence gathered suggested that there may be small but significant improvement in blood sugar control from treating pre-existing gum disease in people with Type 2 diabetes mellitus.’

HYPNOSIS FOR CHILDREN UNDERGOING DENTAL TREATMENT

Al-Harasi S, Ashley PF, Moles DR, Parekh S, Walters V. Hypnosis for children undergoing dental treatment. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD007154. DOI: 10.1002/14651858.CD007154.pub2.

‘Children are often anxious or non-compliant during dental treatment. Anecdotal evidence as well as published articles indicate hypnosis can be used with great effect in paediatric behavioural management. The aim of this review was therefore to see what evidence there is to support the use of hypnosis with children and adolescents undergoing dental procedures. Only three randomised controlled trials (with 69 participants) fulfilled the inclusion criteria for this review. Two of these three studies reported positive outcomes in favour of hypnosis however statistical analysis and meta-analysis were not possible due to insufficient studies meeting the inclusion criteria.’