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Oral potentially malignant disorders: risk of progression to malignancy

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Oral potentially malignant disorders (OPMDs) have a statistically increased risk of progressing to cancer, but the risk varies according to a range of patient- or lesion-related factors. It is difficult to predict the risk of progression in any individual patient, and the clinician must make a judgment based on assessment of each case. The most commonly encountered OPMD is leukoplakia, but others, including lichen planus, oral submucous fibrosis, and erythroplakia, may also be seen. Factors associated with an increased risk of malignant transformation include sex; site and type of lesion; habits, such as smoking and alcohol consumption; and the presence of epithelial dysplasia on histologic examination. In this review, we attempt to identify important risk factors and present a simple algorithm that can be used as a guide for risk assessment at each stage of the clinical evaluation of a patient. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:612–627)

The terminology for oral lesions that may have the potential to progress to malignancy has varied over the years. The term *premalignant* is commonly used and is widely understood, but it implies that an individual lesion may inevitably become malignant. However, the risk is only statistically increased, and therefore the term *potentially malignant*, which suggests that the progression to malignancy is only a potential risk, has become more widely accepted.[1] *Potentially premalignant* is an alternative term that is in keeping with the concept that not all lesions—for example, leukoplakia—will have any potential to progress to malignancy and that the clinician is faced with a mucosal change that is only a potentially premalignant lesion. However, this may add confusion because the sentence may be tautologic and conceptually difficult to understand for nonexperts. At a World Health Organization (WHO) workshop in 2007, it was also recommended that the distinction between potentially malignant lesions and conditions be abandoned in favor of a common term, o*ral potentially malignant disorders* (OPMDs),[1,2] and this has now been accepted in the latest WHO classification.[3]

The term OPMD recognizes the fact that even in patients with a defined lesion, such as leukoplakia, malignancy may arise elsewhere in the oral cavity as a result of field change, even in clinically normal mucosa.[4,5] Numerous disorders have been associated with an increased risk of squamous cell carcinoma (SCC), including leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, actinic cheilitis, palatal lesions of reverse cigar smoking, discoid lupus erythematosus, and some inherited disorders, such as dyskeratosis congenita and Fanconi anemia.

From a clinical perspective, the vast majority of lesions of concern present as white patches, with or without a speckled or red component. Many patients with these lesions will not have a specific diagnosis, and the lesions must be managed as leukoplakia. Although these disorders have an increased statistical risk of malignant change, it is very difficult to predict the outcome for an individual patient. This review will focus on leukoplakia, but other disorders will be mentioned where there is evidence of any defined risk factors.

PROGNOSIS OF ORAL POTENTIALLY MALIGNANT DISORDERS

The definition of *leukoplakia* remains unsatisfactory, but essentially, it refers to a white lesion of the oral mucosa that cannot be defined as a known disease or disorder and carries an increased risk of progressing to cancer.[1-6] However, leukoplakia is a dynamic lesion that may vary in texture or color over time and is not always "white." Indeed, leukoplakias deemed to be at highest risk are often speckled red and white lesions. Pure red lesions, or *erythroplakia*, are much rarer but have the greatest risk for malignant change.[7] Although progression to cancer is the most significant outcome, only relatively few lesions

Statement of Clinical Relevance

Oral potentially malignant disorders may progress to oral cancer, but assessment of an individual patient's risk is difficult. This review describes the most important risk factors and presents an approach to risk assessment at each stage of the clinical evaluation of a patient.

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Table I. Features associated with an increased risk of malignant progression of OPMDs

	Feature	*Parameter*	*Association*
Clinical features	Size of lesion	>200 mm^2	Strong
	Texture	Nonhomogeneous	Strong
	Color	Red (or speckled)	Strong
	Site	Tongue and floor of mouth	Strong
	Sex	Female	Medium
	Age	>50 years	Medium
	Habits	Nonsmoker	Weak
Histologic features	Dysplasia	Severe	Strong
		High-risk	Strong
	HPV	HPV-16 +	Medium
	DNA content	Aneuploidy	Medium
	LOH	Many genes involved	Medium

See text for discussion and references.
HPV, human papillomavirus; LOH, loss of heterozygosity; OPMD, oral potentially malignant disorder.

progress to that stage; the remainder may persist unchanged, may enlarge or reduce in size, or may even resolve completely. Features that may be associated with increased risk of progression to malignancy, along with our estimate of the strength of the association, are listed in Table I. Explanatory notes and relevant references are found in the following sections.

CLINICAL PROGNOSTIC FACTORS FOR PROGRESSION TO CANCER

Site

The location of a lesion within the mouth may influence the risk of malignant transformation, but this is almost certainly related to etiologic factors and therefore may vary by geographic location and local habits. For example, in betel quid chewers, the buccal mucosa is likely to be the most affected site, whereas in reverse smokers, it may be the palate. The lateral border of the tongue and the floor of the mouth are anatomically contiguous and, together, are the most common site for OPMDs and oral cancer in the developed world, where smoking of tobacco and alcohol consumption are the most important etiologic factors. In a UK study of 630 patients with dysplastic lesions, over 95% were leukoplakias; the most common sites (42% of lesions) were the lateral and ventral tongue and the floor of mouth.[8] In addition, lesions at this site were more likely to show severe epithelial dysplasia. Conversely, only 21% of lesions arose on the buccal mucosa, and these were mostly mild dysplasia. In a similar study in Australia, Dost et al.[9] found that 40% of lesions arose on the tongue and the floor of mouth and that these were more likely to be dysplastic or malignant (odds ratio [OR] 2.6; $P = .005$). Thirty-one percent of lesions were on the buccal mucosa, but these were less likely to be dysplastic, and none progressed to malignancy. In a cross-sectional study of 3256 leukoplakias in the United States, the highest prevalence of severe dysplasia or carcinoma in situ (CIS) was in the floor of mouth (13.5%) and tongue (5%).[10] These data suggest that these sites are at the highest risk, but studies of actual malignant transformation have shown variable findings.

In Hungary, although only 8.2% of leukoplakias arose on the tongue, these accounted for 37.5% of the lesions that underwent malignant transformation, equivalent to a transformation rate of 27% for tongue leukoplakias.[11] The floor of mouth also had a high transformation rate, with 13% of lesions developing into cancer. In contrast, although most of the leukoplakias (63%) were found on the buccal mucosa, only 4% of these lesions progressed.[11] Similar data have been reported in England, where 2 studies showed high transformation rates of 24%[12] and 16%[13] for leukoplakias in the floor of the mouth (sublingual keratosis).

In contrast, some studies have been unable to establish a strong correlation between site and malignant transformation. Schepman et al.[14] studied 101 patients with lesions on the tongue or the floor of mouth; 15 (14.9%) developed oral cancer, compared with 5 of 65 (7.7%) whose lesions were located elsewhere, but this was not statistically significant. In a second study by Dost et al.,[15] the malignant potential of 383 dysplastic lesions in 368 patients was determined. Although the tongue (48.8% of lesions) and the floor of mouth (11.5%) together were the most common sites and the tongue had the highest transformation rate of 1.4% per year, the relationship between site and transformation was not significant. Holmstrup et al.[16] followed up 236 patients with 269 lesions and found a malignant transformation rate of 12% for lesions treated surgically and 4% for lesions only observed. The only significant prognostic factors were size and type of lesion (homogeneous vs nonhomogeneous). The site of the lesions was not significant.

In summary, most studies and clinical papers do emphasize the lateral and ventral tongue and the floor of