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Position Paper

American Association of Oral and Maxillofacial Surgeons

Oral Mucosal Dysplasia

Eric R. Carlson, DMD, MD, EdM, FACS

Deepak Kademani, DMD, MD, FACS

Brent B. Ward, DDS, MD, FACS

Daniel Oreadi, DMD, FACS

In 2005, the World Health Organization (WHO) introduced the term "potentially premalignant oral epithelial lesion" (PPOEL). In 2022, it is important to differentiate PPOEL – which represents a broad term to define a wide variety of clinical lesions– from oral epithelial dysplasia, a term that should be reserved specifically for lesions with microscopic evidence of dysplasia.[1] Unfortunately, the nomenclature is not universally consistent and the terms PPOEL and dysplasia have frequently been used interchangeably in the past, thereby creating confusion in the international literature. The 2017 WHO definition of oral potentially malignant disorders (OPMD) is a group of conditions that have clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal mucosa.[2] In 2022, OPMD encompass lesions that include leukoplakia, erythroplakia, erythroleukoplakia, lichen planus and oral lichenoid lesions. The primary goal of management of oral mucosal dysplasia, therefore, includes its early detection, concerted surveillance as appropriate, and treatment as required, prior to malignant transformation. The recognition and management of these OPMDs – and an understanding of their potential progression to oral squamous cell carcinoma (OSCC) – will reduce the morbidity and mortality associated with these lesions with proper treatment that will have a positive effect on patient survival.

There has been marginal improvement in the five-year survival rate of patients with OSCC treated with multimodality contemporary therapy over the last 30 years. Current survival rates for all stages of OSCC range from 50 percent to 55 percent.[3,4] The emphasis of early detection, diagnosis and treatment of premalignant lesions is primarily directed to prevent their transformation to OSCC. Early detection is pivotal to increasing the five-year survival rate because it is directly correlated with stage de-escalation of the lesion at initial presentation. It is important to understand that progression to OSCC is not a singular event but a gradual process of genetic and histologic changes that lead to malignant transformation. The current oral cancer progression model results from genetic changes leading to the accumulation and progression of molecular damage translating to a functional and/or phenotypic change of the normal oral mucosa. This molecular damage often includes inactivation of tumor suppressor genes, most notably p53 and p16, loss of heterozygosity (LOH) at the 3p and 9p locations and unregulated expression of regulatory molecules such as epidermal growth factor (EGFR).[5,6,7] Subclinical changes may accumulate sufficiently to become clinically and/or microscopically apparent as a phenotypically distinct lesion from the remaining oral mucosa. These entities include oral dysplasia, carcinoma in situ and frank invasive carcinoma. It is the purpose of this position paper to update the clinician about the diagnosis and management of oral mucosal dysplasia as well as its epidemiology, types and outcomes.

Epidemiology

Oral mucosal dysplasia is a condition that is commonly evaluated and treated by oral and maxillofacial surgeons as well as other medical and dental specialists. It is estimated the international incidence of oral dysplasia is 2.5 percent of the population, with high-risk groups being as high as 10 percent.[8,9] The recognition and management of oral dysplastic lesions is critical to mitigate progression to malignancy. In 2020, oral cancer accounted for 377,713 new cases and 177,757 deaths reported worldwide.[10] Patients with OSCC are typically males over 40 years of age with a history of regular exposure to etiological risk factors such as tobacco products, alcohol or betel quid; however, younger patients with lower cumulative tobacco or alcohol exposure are increasingly presenting with OSCC or OPSCC (oropharyngeal squamous cell carcinoma). These early-onset OSCCs – or OPSCCs located at the base of the tongue, tonsils and oropharynx – are most

frequently associated with the human papillomavirus infection. Alcohol and tobacco have a synergistic effect, with heavy alcohol consumption and tobacco use having 38 times the risk of developing oral cancer compared to those who refrain from both.[5,11] Current trends show an increase in the incidence of oral cancer among several populations, including younger patients below the age of 40 regardless of an increase in knowledge about etiological risk factors for OSCC. Despite technological advances in cancer therapies, the five-year survival rate for oral cancer remains at approximately 50 percent for most populations and has not changed significantly for the past three decades.[9,12] Squamous cell carcinoma is often preceded by lesions such as leukoplakia or erythroplakia that have the potential to be dysplastic and progress to malignancy. The primary objective to improved patient prognosis is through early detection of these lesions. Detecting dysplastic changes at an early stage allows for active intervention before lesions progress to malignancy. Current practices for the detection of malignant or potentially malignant lesions involve a conventional oral examination (COE) with visual and tactile examination – with leukoplakic or erythroplakic lesions considered suspicious for oral epithelial dysplasia or OSCC. Induration and fixation are tactile signs that might suggest oral malignancy. To confirm clinical findings, patients are usually referred to a specialist for biopsy of lesions for a definitive diagnosis and management. A biopsy is considered the gold standard for the diagnosis of dysplasia as it allows for a thorough evaluation of the epithelial architecture of the lesion.

Observation of oral lesions without biopsy is highly clinician-dependent and, even with meticulous follow-up, early malignant changes may be overlooked. Specifically, poor practice of routine examination of the oral mucosa during dental and medical visits is reported by almost all patients whose oral cancer was diagnosed at a late stage. In addition, histological changes indicative of dysplasia can be found even in clinically normal mucosa. While screening programs to identify malignant lesions have been trialed, their cost-effectiveness in the general population is uncertain and the onus has fallen on primary care providers to screen patients for such lesions. In the U.S., it is currently recommended that patients undergo an annual screening for oral and head and neck cancer.[3,5] Of concern, a meta-analysis has indicated that a COE, while having a relatively high sensitivity at 93 percent, has a poor specificity at 31 percent and cannot reliably differentiate between benign and dysplastic lesions.[13] Analysis states that several benign conditions mimic oral malignancies, and dysplasia may be found in clinically normal mucosa.

Types of dysplasia

Oral epithelial dysplasia (OED) is a collective term for lesions of the oral mucosa that possess changes in color, histology and molecular characteristics compared to surrounding oral soft tissues. From a clinical perspective, OED can be described as white (leukoplakia), red (erythroplakia), or mixed red and white (erythroleukoplakia). Leukoplakia (Figure 1) is defined as a white plaque of equivocal risk whereby other known diseases or disorders are excluded that are associated with no increased risk of cancer.[2] Therein, the evaluation of a white lesion of the oral cavity, and the proclamation of the term leukoplakia, requires that otherwise innocuous lesions are excluded in the lesion's differential diagnosis – including those that are developmental (hereditary benign intraepithelial dyskeratosis), reactive (hairy tongue, leukoedema, smokeless tobacco keratosis), infectious (candidiasis, oral hairy leukoplakia), immune-mediated and autoimmune (idiopathic lichen planus, chronic graft vs. host disease, migratory glossitis), and metabolic (uremic stomatitis). Aside from its mere white color, leukoplakia is subcategorized as either homogenous or nonhomogenous. Homogenous leukoplakia is most frequently well-demarcated and fissured while nonhomogenous leukoplakia is most commonly verrucous or nodular.[2] The estimated international prevalence of leukoplakia is 2 percent.[14] Leukoplakia does not denote the presence or absence of any specific grade of dysplasia, as the term represents a clinical definition and is not linked to any specific microscopic pattern.[14,15] Stated differently, leukoplakia can be dysplastic or nondysplastic in terms of its histologic character.

Erythroplakia (Figure 2) is defined as a "fiery red patch that cannot be characterized clinically or pathologically as any other definable disease."[14] Rather than a patch, the clinical presentation of erythroplakia is a symptomatic flat or occasionally depressed change of the mucosa such that erythroplasia might be a more appropriate term.[14] The prevalence of erythroplakia varies between 0.02 – 0.83 percent, and it occurs primarily in middle-aged and elderly people.[16] Histologically, erythroplakia typically demonstrates at least moderate or severe dysplasia, or

carcinoma in situ, and the vast majority of erythroplakic lesions will undergo malignant transformation.[14,16] Erythroleukoplakia (Figure 3) is a variant of nonhomogenous leukoplakia. These mixed red and white lesions are often referred to as speckled leukoplakia. In a sample of 684 cases of oral premalignant epithelial disorders, Pires et al.[17] (2020) found that leukoplakia represented 82 percent of the sample (564 cases), erythroleukoplakia, referred to as speckled leukoplakia, represented 6 percent of the sample (42 cases), and pure erythroplakias were not found in the sample.

Proliferative verrucous leukoplakia is another variant of nonhomogenous leukoplakia. It is characterized by unremitting, multifocal and progressive disease at a single site or at contiguous sites in the oral mucosa that are refractory to conventional treatment. Proliferative verrucous leukoplakia may not only possess the classic verrucous and nodular pattern, typical of nonhomogenous leukoplakia, but also may possess the homogenous fissured and erythroplakic patterns such that the more accurate and inclusive term, proliferative leukoplakia, has been proposed.[18] A comparison of solitary leukoplakia and proliferative leukoplakia is noted in Table 1.

Numerous molecular factors have been associated with the malignant transformation of oral leukoplakia. These include DNA methylation, loss of heterozygosity (LOH), cytokeratin expression, DNA aneuploidy, matrix metalloproteinase-nine positivity and survivin positivity.[19] In most studies, the presence and grade of dysplastic change represents the primary risk factor for malignant transformation of leukoplakia, although 3p and/or 9p LOH are the most significant predictors of progression. Most cancers possess dysregulated activation of a few cancer pathways, including WNT/β-catenin, PI3K/AKT/mTOR, JAK/STAT, RAS/RAF/MAPK or TGFβ.[20]

Dysplasia of the oral mucosa has historically been graded as mild (Figure 4), moderate (Figure 5), severe (Figure 6) and carcinoma in situ (CIS) (Figure 7). Odell et al.[20] indicated that all oral epithelial dysplasia grading systems represent artificial constructs that are subjective estimates of a spectrum of changes. Grading of OED, therefore, exists as a highly contentious practice and international consensus is difficult to obtain due to varying grading schemes in different regions of the world.[21] The 5th edition of the World Health Organization Classification of Head and Neck Tumours (2022) maintains the three-tiered OED grading system, although it is emphasized that defining oral mucosal dysplasia by thirds of the oral epithelium oversimplifies its complexity.[21] For example, there are instances where OED is limited to the lower third of the epithelium; yet, severe dysplasia is diagnosed because of numerous architectural and cytologic features that upgrade the dysplasia (Table 2). The designation of CIS was merged with severe dysplasia in the 2017 WHO classification due to the inability to differentiate these types of dysplasia on histologic grounds as well as the inability to differentiate their risk of malignant transformation.[20,21] Despite great controversy associated with the grading of oral epithelial dysplasia, these designations possess clinical utility and remain the standard of care regarding management of oral epithelial dysplasia.[20]

Human papillomavirus (HPV)-associated dysplasia of the oral mucosa has gained significant attention due to its distinction from conventional oral epithelial dysplasia. HPV-associated dysplasia is most commonly seen in males (M:F = 6:1) and with a peak incidence in the sixth decade.[21] The ventral/lateral tongue and floor of the mouth are most commonly affected, although the gingiva and buccal mucosa also can be affected. These dysplastic lesions generally present as a flat and well-demarcated white to red patch that is indistinguishable from other types of oral leukoplakia. Distinguishing histologic findings of HPV-associated oral dysplasia are noted in Table 3.

Lichen planus of the oral mucosa is a chronic inflammatory autoimmune disease that is characteristically identified by lacy white lesions with or without erosive or atrophic areas. The disease has been estimated to affect 1.32 percent of the European population, and the disease increases in its incidence after the age of 40 years.[22] Gonzalez-Moles et al.[23] performed a systematic review and meta-analysis of studies investigating the risk of malignant transformation of oral lichen planus and identified a cancer incidence of 1.14 percent among these cases. The 5th edition of the World Health Organization Classification of Head and Neck Tumours continues to designate oral lichen planus as an oral potentially malignant disorder; yet, authors report that this designation was a contentious issue.[21] Further, numerous publications have refined the clinical and microscopic features or oral lichenoid lesions

to distinguish them from oral lichen planus. However, these distinctions were believed to be insufficient to remove oral lichen planus as a potentially malignant disorder.

Summary of evidence

An annual rate of malignant transformation for all types of leukoplakia collectively is estimated at 1 percent.[14] According to van der Wall,[14] risk factors for malignant transformation include leukoplakia in nonsmokers, nonhomogeneous type, long duration of the leukoplakic lesion, female gender, the presence of epithelial dysplasia, DNA aneuploidy, and size greater than 200 m^2. The various clinical presentations for oral leukoplakia permit discretion on the part of the clinician regarding the performance of an incisional biopsy. Small, innocuous appearing homogenous leukoplakic lesions might be subjected to clinical follow-up while larger and multifocal lesions might warrant incisional biopsy at the time of consultation. An expedient incisional biopsy of an erythroplakic lesion is typically indicated due to the likelihood of high-grade dysplasia or frank carcinoma being present in an erythroplakic lesion, as well as the high rate of malignant transformation of these lesions over time.

Evren et al.[19] reported a retrospective study of 170 patients with leukoplakia of the oral mucosa, including 117 women and 53 men. The age range of these patients was 26 to 98 years with a mean of 59 years. Ninety-one patients (54 percent) presented with a homogenous leukoplakia while 79 patients presented with a nonhomogenous leukoplakia that was described as erythroplakia, nodular or verrucous. The tongue accounted for 59 sites of leukoplakia and the floor of the mouth accounted for 27 sites that collectively were designated by the authors as high-risk. All remaining anatomic sites of leukoplakia were categorized as low risk. Ninety-one patients underwent observation as initial treatment, while 69 patients underwent excision of their leukoplakia. Malignant transformation of the leukoplakia to squamous cell carcinoma occurred in 39 of 170 (22.9 percent) of patients. Calculated from the patient's first clinical visit, the rate of annual malignant transformation was 4 percent (95 percent CI: 2.9 – 5.5). The annual rate of malignant transformation was constant over follow-up time with a rate of 5 percent (95 percent CI: 3.3 – 7.1) at one year, 4.5 percent (95 percent CI 2.0 – 8.7) at six years, and 6.3 percent (95 percent CI: 1.7 – 15.2) at 11 years. These figures indicate the need to provide long-term and possibly lifetime clinical surveillance of patients with oral leukoplakia since the rate of malignant transformation remains stable over time. Further, these authors indicated the need to provide a new biopsy of oral leukoplakia when clinical change is demonstrated.

Aguirre-Urizar et al.[24] performed a systematic review and meta-analysis of malignant transformation of oral leukoplakia. Twenty-four studies were selected that reported a total of 16,604 patients. The rate of malignant transformation ranged from 1.1 percent to 40.8 percent. Following meta-analysis, the pooled proportion of malignant transformation was 9.8 percent. The time from first diagnosis of leukoplakia to the onset of carcinoma was determined in 10 studies and ranged from 1.8 to 5.1 years. The clinical type of leukoplakia that transformed into squamous cell carcinoma was determined in 13 studies. Two-thirds of 525 lesions that underwent malignant transformation were non-homogenous leukoplakia, and one-third of the 525 lesions were homogenous leukoplakia. The meta-analysis showed a 4.06-fold increased risk of malignant transformation for nonhomogeneous leukoplakia (95 percent CI: 1.39 – 11.89). In terms of grade of the dysplasia of the leukoplakic lesion, the presence of dysplasia showed a 23.8-fold increased risk of malignant transformation (95 percent CI: 9.5 – 38.2). Further, high-grade dysplasia demonstrated a 4.9-fold increased risk of malignant transformation compared to low-risk (95 percent CI: 3.02 – 7.96).

Gilvetti et al.[25] provided a retrospective review of the outcomes of 95 patients with high-grade dysplasia of the oral mucosa. In all cases, the lesions appeared as homogenous or non-homogenous leukoplakia (i.e., erythroleukoplakia, verrucous, nodular or other exophytic features) or erythroplakia. For inclusion in the study, a histopathologic diagnosis of severe dysplasia was required, but cases of moderate dysplasia were included if they showed sufficient cytologic and/or architectural atypia to be regarded as high-grade dysplasia. Seventeen patients (17.8 percent) developed a squamous cell carcinoma at the same site as the high-grade dysplasia, with a mean time for malignant transformation of 50 months. None of the 20 patients who were originally diagnosed with moderate dysplasia underwent malignant transformation who had high-grade dysplasia. The authors reported that some patients with high-grade dysplasia of the oral mucosa may develop recurrence and/or malignant transformation

of their lesions eight to 10 years following effective excisional biopsy, such that these patients also should undergo indefinite clinical surveillance. A young age (50 years or younger) at the time of diagnosis, homogenous appearance of the lesion and complete excision of the lesion with negative margins improved the patient's prognosis.

Wang et al.[26] reviewed 5,071 patients (4,299 males and 772 females) with oral, potentially malignant disorders over a 10-year period. These disorders included 186 patients with dysplastic oral submucous fibrosis, 957 patients with epithelial dysplasia, 869 patients with verrucous hyperplasia and 1,684 patients with hyperkeratosis/epithelial hyperplasia. Malignant transformation was noted in nine of 186 patients with dysplastic oral submucous fibrosis and 63 of the 957 patients with epithelial dysplasia. Sixty-one of the 949 patients (6.43 percent) with mild epithelial dysplasia progressed to cancer; six of the 108 patients (5.56 percent) with moderate epithelial dysplasia progressed to cancer, and five of the eighty-six patients (5.81 percent) with severe epithelial dysplasia progressed to oral cancer. Of particular interest is that 49 of the 1684 patients with benign epithelial hyperplasia/hyperkeratosis experienced malignant transformation to 37 squamous cell carcinomas and 12 verrucous carcinomas.

Gonzalez-Moles et al.[22] have provided a critical review of 89 published papers in the international literature that specifically comment on the potential for malignant transformation of oral lichen planus. Their meta-analysis indicated a rate of malignant transformation of 2.28 percent, and the authors therefore proclaimed lichen planus as a potentially malignant disorder. The authors also proposed to establish recommendations to researchers and clinicians regarding the criteria for performing future studies whose results will be scientifically valid. The samples should be representative of the general population, including patients derived from hospitals, dental schools and private offices. The authors pointed out the primary confounding factor in the study of the malignant transformation of oral lichen planus is the lack of widely accepted diagnostic criteria of lichen planus. Their clinical diagnostic criteria included the presence of white reticular lesions at any location of the oral mucosa without the requirement for symmetry or bilaterality. Exclusion criteria were intimate contact of the lesion with dental restorative materials, lesions in close temporal relationship with the use of a drug, history of organ transplantation, and the presence of skin lesions or systemic disorders suggestive of lupus erythematosus.[22]

Treatment of dysplasia

The status of evidence related to the treatment of oral leukoplakia and dysplasia is summarized by a 2016 Cochrane Review.[27] "Surgical interventions, including laser therapy and cryotherapy, have never been studied by means of a randomized controlled trial (RCT) that included a no treatment or placebo arm." Most trials in the Cochrane review were chemoprevention, rather than surgical intervention, with none of these demonstrating value that would suggest broad application. The available data for evidence-based decision-making related to surgical therapies is therefore extremely limited, and significant controversy exists regarding treatment protocols.[28,29,30] Therefore, the views expressed in this section are based primarily on consensus expert opinion related to this disease process, noting the authors of this AAOMS position paper have significant individual and vast collective experience. The concepts suggested should be considered as general gestalt that require application to the specific clinical situation of each patient. In no way are these recommendations intended to create a standard of care related to any specific patient condition. In addition, given the lack of unambiguous evidence, it is important patients be given the opportunity for shared decision-making related to their care since multiple modalities, including observation, remain viable alternatives in many cases, especially in cases of persistent and recurrent disease.

While limited in magnitude, some evidence exists that treatment of dysplasia is, in fact, cancer protective. In a recent retrospective study of 120 patients with high-grade oral epithelial dysplasia, the malignant transformation rate was 28.6 percent in untreated patients and 12.3 percent in patients who underwent treatment either using scalpel, laser excision or laser ablation. Older age, non-homogenous clinical appearance and incomplete excision all demonstrated a worse prognosis.[25] A prior study of 118 patients with severe dysplasia reached similar conclusions where treated patients had a transformation risk of 6 percent compared to 29 percent in untreated patients ($P = 0.004$). Likewise, a retrospective study of 136 patients of all grades of dysplasia demonstrated a

significant reduction in malignant transformation rate with both scalpel and laser ablation.[31] These data are collectively stronger but in contrast to the report by Holmstrup et al.[9] noting a higher transformation rate to cancer in patients who underwent intervention for their premalignant lesions. As mentioned previously, none of these studies were randomized controlled trials and conclusions are therefore limited. Nevertheless, the data serve as a basis for the reasonable recommendations of observation or treatment based on patient and clinical lesion factors.

As histopathology is a prominent consideration in a proposed decision-making process, it should be noted that controversy exists regarding the reliably of histopathology related to multiple factors – including those in control of both surgeons and pathologists. From a surgical standpoint, incisional biopsy may not be representative of the most aggressive location of any given lesion, and multiple biopsies of larger lesions are certainly a reasonable but not required consideration. In addition, concordance of histopathologic reads by pathologists have shown significant variability in the literature.[32] As such, while the recommendations below utilize mild, moderate and severe dysplasia, it is acknowledged that some investigators have advocated for a two-grade system of low-grade and high-grade dysplasia.

Decision-making for treatment of dysplasia consists of the combination of patient, clinical lesion and histopathologic factors in a shared decision-making model where patients understand potential risks and benefits. All patients should be informed that progression – despite treatment – occurs, and recurrence is common such that long-term and, at times, lifelong follow-up is indicated. Finally, it should be noted some patients present with truly unresectable disease and in all patients the morbidity of removal is an important consideration. However, in many circumstances, a justifiable and beneficial role for surgery exists. Surgery for dysplasia has two distinct forms: either excision or ablation. Excision refers to removal of a lesion with the generation of a specimen for pathologic assessment. Ablation involves vaporization of the lesion, typically with a C02 laser, and does not produce tissue for a histologic assessment. Therein, three procedures may be performed, including scalpel excision, laser ablation and laser excision. Scalpel excision and laser excision of oral mucosal dysplasia incorporate a linear margin surrounding the lesion, the magnitude of which is based on the discretion of the surgeon as well as the grade of the dysplastic lesion. Both procedures provide tissue for thorough lesion diagnosis, assignment of the most advanced grade of dysplasia and complete margin assessment. There are no reliable data at present for distinguishing outcomes between laser excision and scalpel excision. Laser ablation, as occurs with a carbon dioxide laser, does not provide tissue to a pathologist for a microscopic diagnosis of the lesion nor margin assessment, and therefore requires the surgeon's judgement regarding the appropriateness of ablation of any oral mucosal lesion without first performing an incisional biopsy. This position paper does not recommend the use of laser ablation for high-grade dysplasia, including severe or carcinoma in situ of the oral mucosa that has been diagnosed on incisional biopsy or any lesion that is clinically suspicious for malignant transformation. Specimens from laser excision may be assessed for margins; however, cauterization creates complexity in histopathologic interpretation of those margins, especially for the smaller excisions and smaller margins for dysplastic lesions compared to the 1.0 to 1.5 cm margins routinely taken for cancer. Margin assessment is important in cases where surgeons and patients plan to continue excision beyond the clinical lesion for histopathologic evidence of disease either on frozen or permanent sections. It is important to recognize the occasional difficulty in interpreting dysplasia and its precise grade on frozen sections.

Treatment of oral mucosal dysplasia is multidimensional and based on individual patient and lesion characteristics and clinical observation. Many patients ultimately require surgery with effective provider communication and shared decision-making with patients representing the hallmark of treatment. Comprehensive and flexible treatment planning is especially important given that oral mucosal dysplasia is a disease process that is unpredictable – frequently unremitting or recurrent – and whose treatment can result in significant morbidity, with the ultimate outcome being progression to cancer regardless of treatment. For simplicity, patient and clinical lesion features are combined with histopathology as the primary consideration in the algorithm presented (Figure 8). Table 4 outlines general high-risk features for consideration in both patients and clinical lesions. The treatment algorithm proposes treatment combining the two features with variable treatment options based on availability as well as surgeon and patient shared decision-making.

The follow-up of patients with oral mucosal dysplasia is dependent on clinician preferences, as standardized guidelines on the recommended surveillance of these patients do not exist. This notwithstanding, clinical follow-up of patients should be frequent, particularly in patients with severe dysplasia/CIS for concern for malignant transformation. Clinical surveillance also should be based on the site of the lesion, the grade of dysplasia, and the patient's presence or absence of risk factors. In the final analysis, long-term follow-up of patients with oral mucosal dysplasia – and possible lifelong follow-up – can certainly be justified with principles of self-examination reviewed with the patient at each follow-up visit.

Figures and Tables

Figure 1

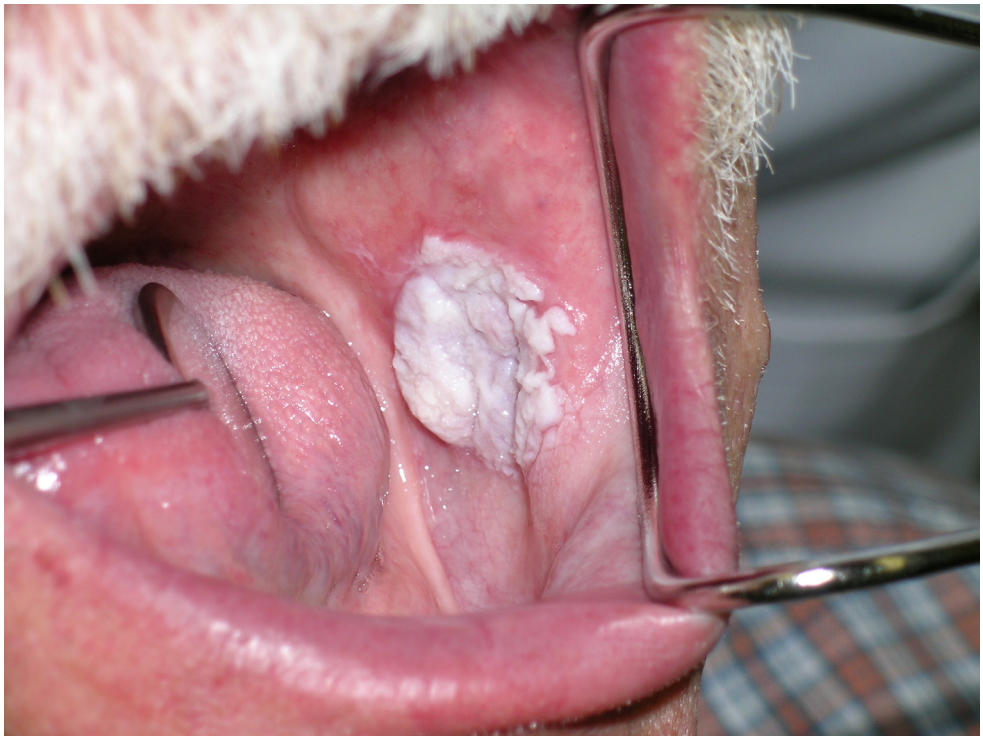

Figure 1: An example of homogenous leukoplakia of the left buccal mucosa. The histopathology pertaining to incisional biopsy of this lesion identified verrucous carcinoma.

Figure 2

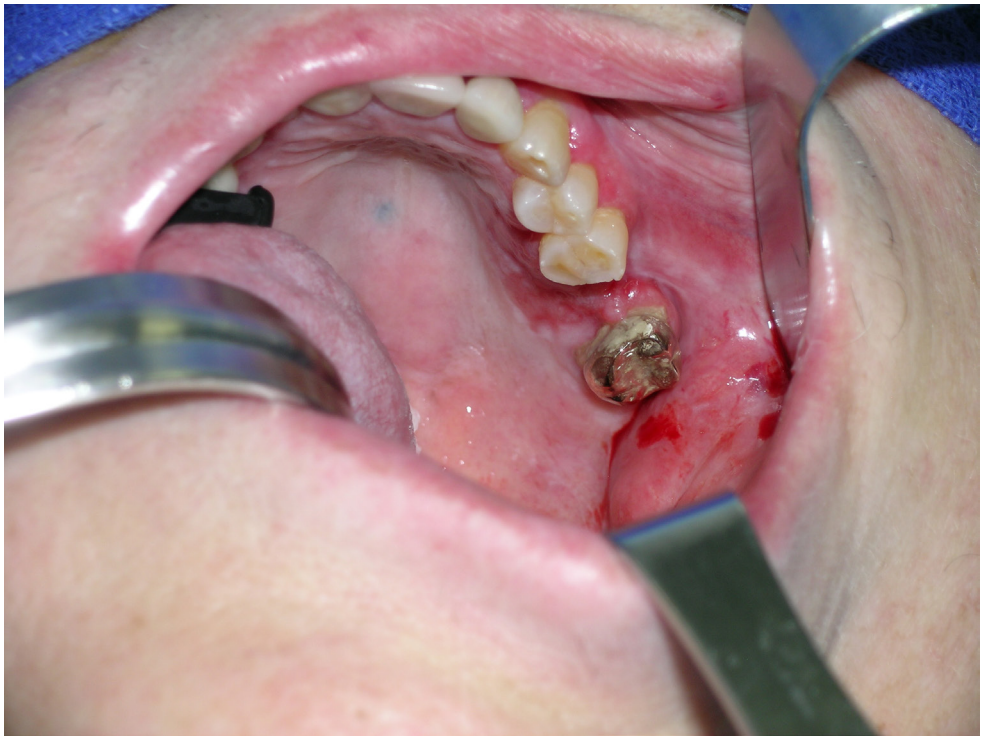

Figure 2: An example of erythroplakia of the left palatal mucosa. The histopathology pertaining to incisional biopsy of this lesion identified micro-invasive squamous cell carcinoma.

Figure 3

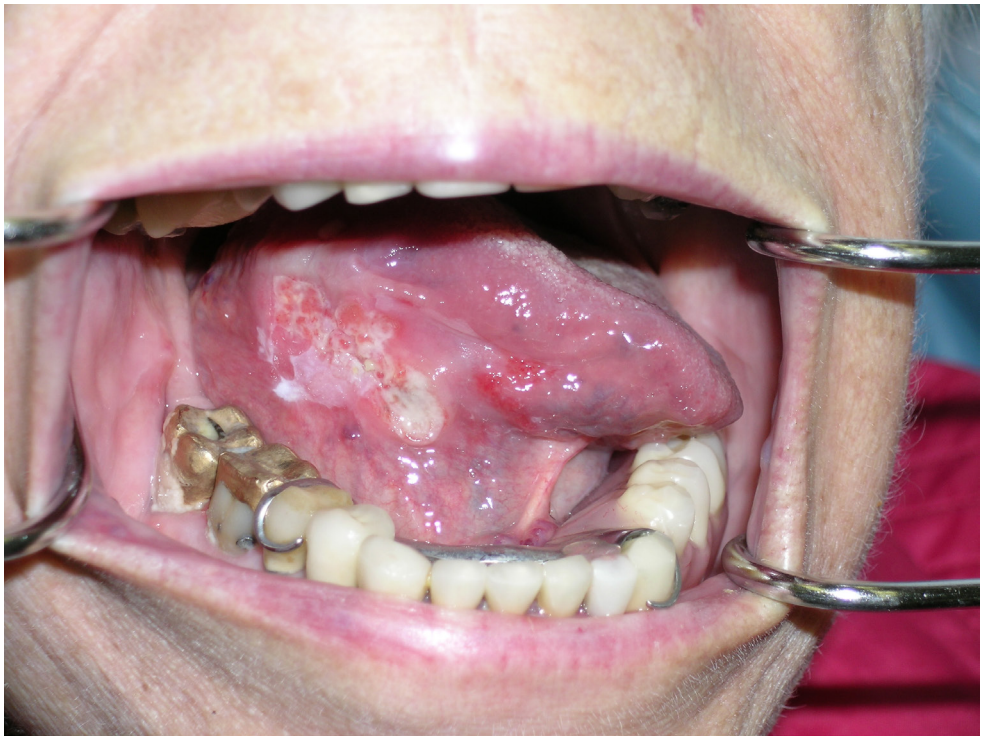

Figure 3: An example of erythroleukoplakia of the right ventral tongue. The histopathology pertaining to incisional biopsy of this lesion identified invasive squamous cell carcinoma.

Figure 4

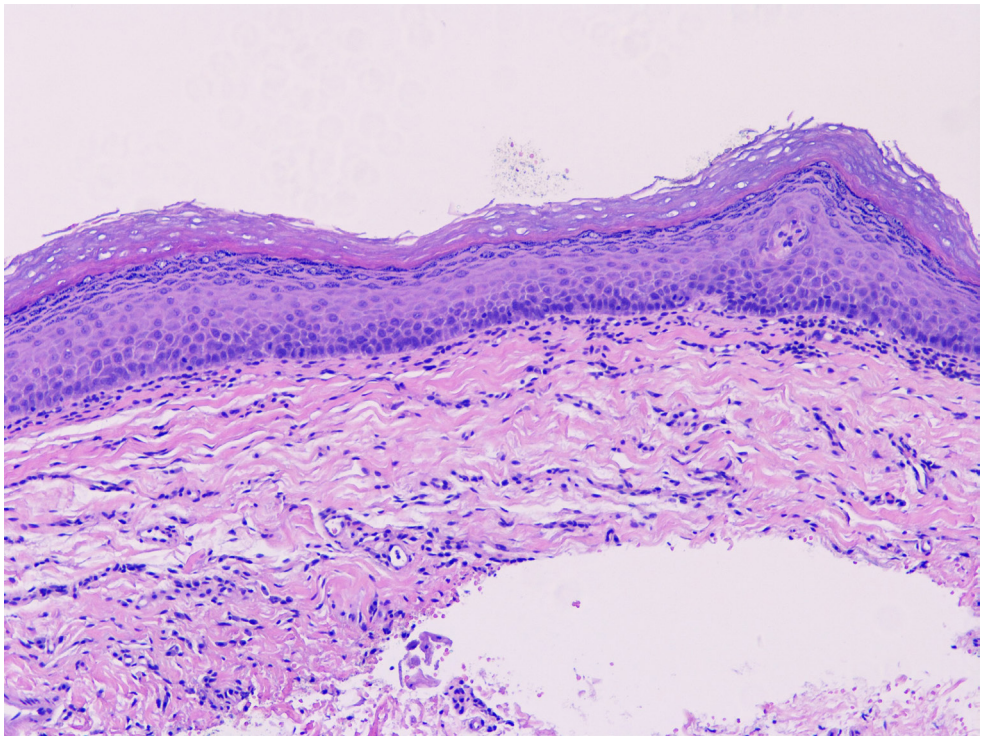

Figure 4: Mild dysplasia of the oral mucosa (Courtesy of Kitrina Cordell, DDS, MS)

Figure 5

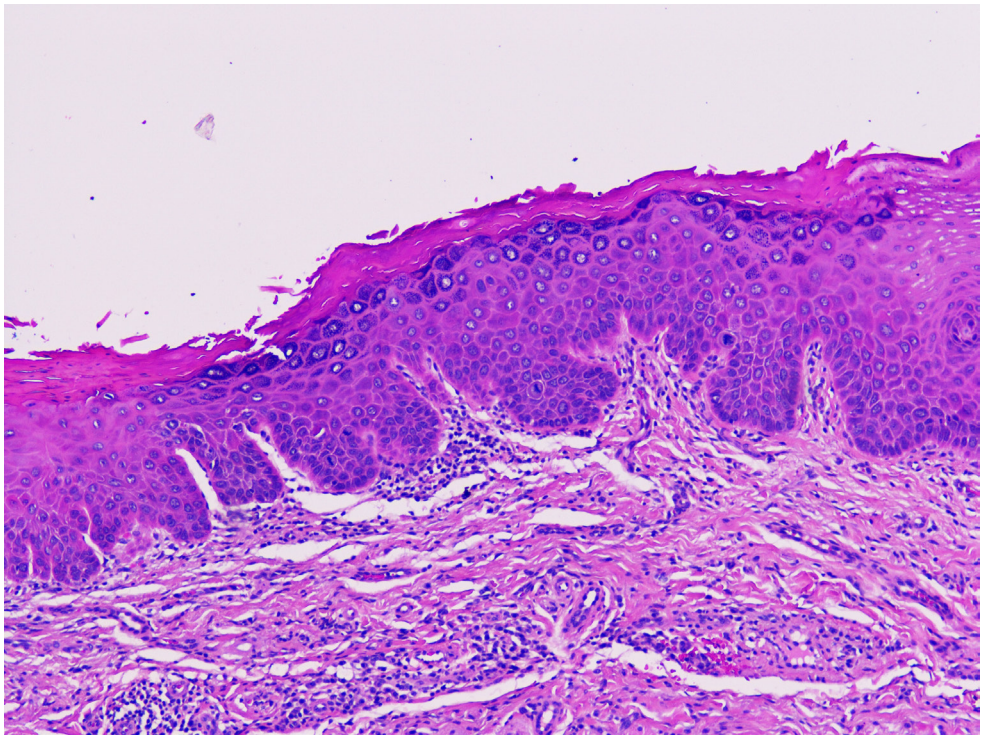

Figure 5: Moderate dysplasia of the oral mucosa (Courtesy of Kitrina Cordell, DDS, MS)

Figure 6

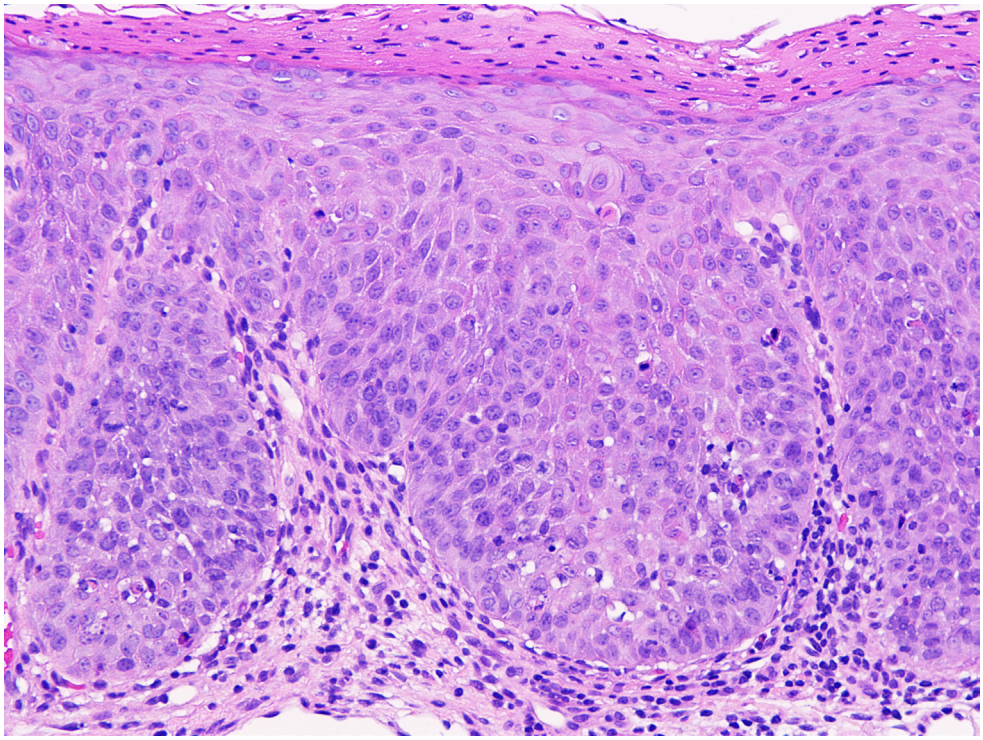

Figure 6: Severe dysplasia of the oral mucosa (Courtesy of Kitrina Cordell, DDS, MS)

Figure 7

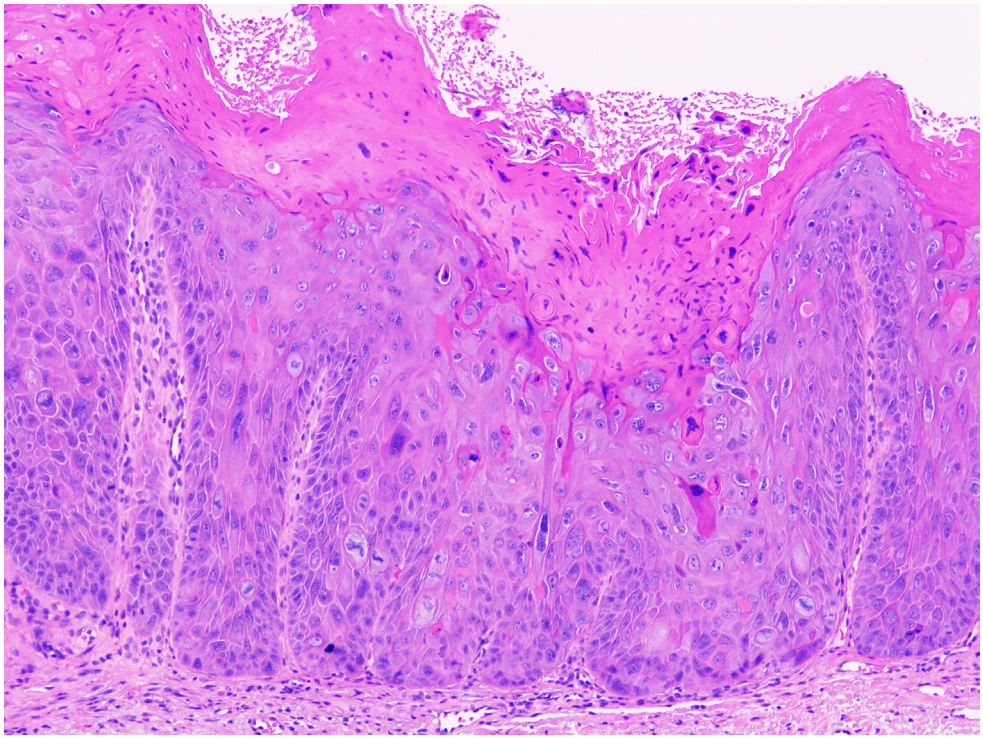

Figure 7: Carcinoma in situ of the oral mucosa (Courtesy of Kitrina Cordell, DDS, MS)

Figure 8

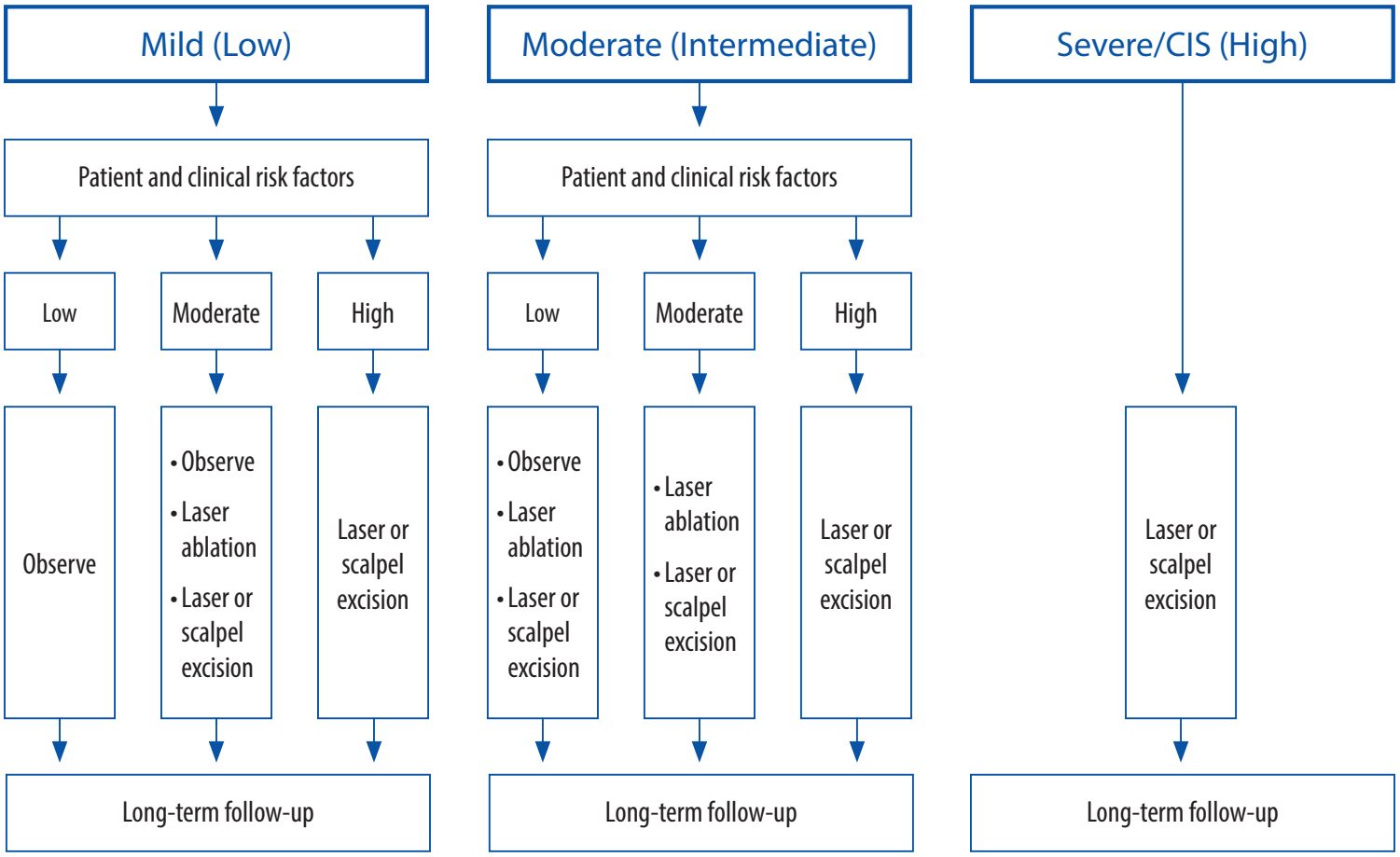

Figure 8: Algorithm for treatment of dysplasia of the oral mucosa

Table 1

Distinguishing features of solitary vs. proliferative leukoplakia of the oral mucosa

Parameter	Solitary leukoplakia	Proliferative leukoplakia
Gender	Mostly men 2-3.5 : 1	Mostly women 2.5-5 : 1
Smoking history	Common (> 60%)	Uncommon (< 30%)
Number of sites	Solitary	Multiple
Most common sites	Lateral/ventral tongue and floor of mouth	Gingiva and buccal mucosa
Malignant transformation	8 – 22%	70 – 100%
Management	Amenable to surgical excision	Serial biopsies due to recurrence and predilection to malignant transformation

Adapted from: Woo SB: Oral epithelial dysplasia and premalignancy. Head and Neck Pathology 13: 423-39, 2019.

Table 2

Architectural and cytologic features of oral epithelial dysplasia (WHO 2022)

Architectural features	Cytologic features
Altered keratin pattern for oral subsite	Abnormal variation in nuclear size
Verrucous or papillary architecture	Abnormal variation in nuclear shape
Extension of changes along minor gland ducts	Abnormal variation in cell size
Sharply defined margin to changes	Abnormal variation in cell shape
Multiple different patterns of dysplasia	Increased nuclear-to-cytoplasmic ratio
Multifocal or skip lesions	Atypical mitotic figures
Expanded proliferative compartment	Increased number and size of nucleoli
Basal cell clustering/nesting	Single cell keratinization
	Apoptotic mitoses
	Increased nuclear size

Adapted from: Woo SB: Oral epithelial dysplasia and premalignancy. Head and Neck Pathology 13: 423-39, 2019; and Muller S, Tilakaratne WM: Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Tumours of the Oral Cavity and Mobile Tongue. Head and Neck Pathology 2022.

Table 3
Histologic features of HPV-associated oral dysplasia

Half to full thickness of epithelium affected
Replacement of most of epithelial thickness by cells of basaloid or lower prickle cell morphology
Loss of demarcation between basal, prickle cell and maturing compartments
Acanthosis
Increased suprabasilar mitoses
Scattered isolated markedly atypical cells at all levels including apoptotic cells, apoptotic mitoses, multinucleated cells and grossly atypical cells with karyorrhexis.
Tendency to vertical orientation of basal and prickle cells
Preserved basal layer of small cuboidal almost normal cells
Brightly eosinophilic parakeratinized surface
Folded epithelial architecture
Focal koilocytic change/vacuolation near surface layer typical of replicative HPV infection
Intense positive reaction for p16 immunoexpression
Positive DNA or RNA in situ hybridization for HPV

Adapted from: Odell E, Kujan O, Warnakulasuriya S, Sloan P: Oral epithelial dysplasia: recognition, grading and clinical significance. Oral Diseases 27: 1947-76, 2021.

Table 4
High risk features

Patient Characteristics	Lesion Characteristics
• Older age • Tobacco/alcohol consumption • Multiple lesions (PVL) • Diagnosis of lichen planus • Unable to engage in routine follow-up	• Erythroleukoplakia or erythroplakia • Size exceeding 200 m^2 • Location • Non-homogenous • Ill-defined margins

References

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