



## Oral Mucosal Dysplasia

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Oral potentially malignant disorders (OPMDs) of the oral mucosa include leukoplakia, erythroplakia, erythroleukoplakia, lichen planus and oral lichenoid lesions – each with varying incidences of dysplastic disease at the time of presentation and each with observed incidences of malignant transformation over time. The primary goal of the management of dysplasia, therefore, includes its early detection and treatment prior to malignant transformation. The recognition and management of these OPMDs and an understanding of their potential progression to oral squamous cell carcinoma will reduce the morbidity and mortality associated with these lesions with expedient and properly executed treatment strategies that will have a positive effect on patient survival. It is the purpose of this position paper to discuss oral mucosal dysplasia in terms of its nomenclature, epidemiology, types, natural history and treatment to acquaint clinicians regarding the timing of biopsy, type of biopsy and follow-up of patients with these lesions of the oral mucosa. This position paper represents a synthesis of existing literature on this topic with the intention of closing gaps in our understanding of oral mucosal dysplasia while also stimulating new thinking to guide clinicians in the proper diagnosis and management of OPMDs. The fifth edition of the World Health Organization classification of head and neck tumors published in 2022 represents new information regarding this topic and a construct for this position paper.

In 2005, the World Health Organization (WHO) introduced the term potentially premalignant oral epithelial lesion (PPOEL). It is important today to differentiate PPOEL (that represents a broad term to define a wide variety of clinical lesions) from oral epithelial dysplasia (OED), a term that should be reserved specifically for lesions with microscopic evidence of dysplasia.<sup>1</sup> 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 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.<sup>2</sup> In 2023, OPMDs 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 expedient and 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 to 55 percent.<sup>3,4</sup> 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 leads 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.<sup>5,6,7</sup> 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 (CIS), and frank invasive carcinoma. It is the purpose of this position paper to inform the clinician about the diagnosis and management of oral mucosal dysplasia as well as its epidemiology, type, management and outcomes. To this end, a PubMed search was conducted with the search terms oral mucosal dysplasia, OPMDs, leukoplakia, erythroplakia and erythroleukoplakia to identify published literature regarding these search terms. A review of relevant published literature from 2012 to 2022 resulted in 35 papers deemed to provide reasonable evidence and appropriate for final review. This literature review permitted members of the AAOMS Committee on Oral, Head and Neck Oncologic and Reconstructive Surgery the opportunity to create a position paper represented by a synthesis of evidence and consensus expert opinion regarding the diagnosis and treatment of oral mucosal dysplasia.

## Epidemiology

Oral mucosal dysplasia is a condition that is commonly evaluated and treated by oral and maxillofacial surgeons and 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.<sup>8,9</sup> 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.<sup>10</sup> Patients with OSCC are typically males aged greater than 40 years 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 oropharyngeal squamous cell carcinoma. These early-onset OSCCs or oropharyngeal squamous cell carcinomas 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.<sup>5,11</sup> Current trends show an increase in the incidence of oral cancer among several populations, including younger patients below the age of 40 years 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.<sup>9,12</sup> 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 improve 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 OED 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 may be in selected situations is appropriate. It should be recognized that premalignant or malignant changes can often be subtle and overlooked even with meticulous follow-up. Histological changes indicative of dysplasia can be found in clinically normal mucosa. The advantage for biopsy of lesions that persist over time is the ability to definitively match a clinical diagnosis with histopathology. It is a reality that patients do present with late-stage OSCC who have been followed closely. 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 United States, it is currently recommended that patients undergo annual screening for oral and head and neck cancer.<sup>3,5</sup> 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.<sup>13</sup> Several benign conditions mimic oral malignancies and in converse dysplasia may be found in clinically normal mucosa.

## Types of 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.<sup>2</sup> 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.<sup>2</sup> The estimated international prevalence of leukoplakia is 2 percent.<sup>14</sup> Leukoplakia does not designate 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.<sup>14,15</sup> 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.”<sup>14</sup> 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.<sup>14</sup> The prevalence of erythroplakia varies between 0.02 percent and 0.83 percent, and it occurs primarily in middle-aged and elderly people.<sup>16</sup>

Histologically, erythroplakia typically demonstrates at least moderate or severe dysplasia, or CIS, and the vast majority of erythroplakic lesions will undergo malignant transformation.<sup>14,16</sup> Erythroleukoplakia (Figure 3) is a variant of nonhomogenous leukoplakia. These lesions are mixed red and white lesions and are often referred to as speckled leukoplakia. In a sample of 684 cases of oral premalignant epithelial disorders, Pires et al<sup>17</sup> found

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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 and 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 may also possess the homogenous fissured and erythroplakic patterns such that the more accurate and inclusive term, proliferative leukoplakia has been proposed.<sup>18</sup> 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, LOH, cytokeratin expression, DNA aneuploidy, matrix metalloproteinase-9 positivity and survivin positivity.<sup>19</sup> 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/ $\beta$ -catenin, PI3K/AKT/mTOR, JAK/STAT, RAS/RAF/MAPK, or TGF $\beta$ .<sup>20</sup>

Dysplasia of the oral mucosa has historically been graded as mild (Figure 4), moderate (Figure 5), severe (Figure 6), and CIS (Figure 7). Odell et al<sup>20</sup> indicated that all OED 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.<sup>21</sup> The fifth edition of WHO classification of head and neck tumors published in 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.<sup>21</sup> For example,

there are instances where OED is limited to the lower third of the epithelium, yet severe dysplasia is diagnosed due to 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.<sup>20,21</sup> Despite great controversy associated with the grading of OED, these designations possess clinical utility and therefore remain the standard regarding management of OED.<sup>20</sup>

Subjectivity in histological interpretation and grading of dysplasia remains a challenge with the 3-tier method of classification of mild dysplasia, moderate dysplasia, and severe dysplasia/CIS. Substantial differences in the interpretations of OED have historically existed among oral and maxillofacial pathologists.<sup>22</sup> Compounding the confusion of grading is the unpredictability of the development of invasive carcinoma from all grades of dysplasia.<sup>23</sup> There are many variables involved in metabolic soft tissue changes, including but not limited to molecular alterations, features of histologic atypia, co-existence of other disease states such as herpes simplex virus, and chromosomal derangements. As many of these entities often coexist with dysplastic change, it is extremely difficult if not impossible to determine with any degree of certainty the likelihood of progression of OED.

A binary (two-stage) system of OED grading, low-grade and high-grade, has recently come into use in many centers. It is based on the appearance of several cytologically identifiable cellular changes seen in OED. Various studies have concluded that this method is easily reproducible with better interobserver agreements when compared to the present three-tier classification system in use today. These visual changes can then be scored and the dysplasia can be graded as either high-grade or low-grade. While the treatment algorithm proposed in this paper continues to use the more standard three-tier classification system of dysplasia, it is acknowledged that the binary staging system also has utility in the management of oral mucosal dysplasia. In fact, the combination of both systems could be of great value to the clinician in planning treatment and follow-up of patients with oral mucosal dysplasia.

Human papillomavirus (HPV)-associated dysplasia of the oral mucosa has gained significant attention due to its distinction from conventional OED. HPV-associated dysplasia is mostly seen in males (M:F = 6:1) and with a

peak incidence in the sixth decade.<sup>21</sup> The ventral/lateral tongue and floor of mouth are most affected, although the gingiva and buccal mucosa also can be affected. These dysplastic lesions usually 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.<sup>24</sup> Gonzalez-Moles et al<sup>25</sup> 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 fifth edition of the WHO classification of head and neck tumors continues to designate oral lichen planus as an OPMD, yet authors report that this designation was a contentious issue.<sup>21</sup> Furthermore, numerous publications have refined the clinical and microscopic features of 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. OSCC arising from lichen planus has been reported to be distinct related to their clinical characteristics and outcomes with higher rates of survival but also higher rates of relapse.<sup>26</sup>

## Summary of available evidence

An annual rate of malignant transformation for all types of leukoplakia collectively is estimated at 1 percent.<sup>14</sup> According to van der Wall,<sup>14</sup> risk factors for malignant transformation include leukoplakia in nonsmokers, nonhomogeneous type, long duration of the leukoplakic lesion, female gender, the presence of epithelial dysplasia, and size more than 200 m<sup>2</sup>. 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<sup>19</sup> 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 mouth accounted for 27 sites that collectively were designated by the authors as high risk after analysis while 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) patients. After exclusion of the first year, in which no malignant transformation occurred, the annual malignant transformation rate remained relatively stable between 4.5 percent and 6.3 percent annually over the 11 years of the study. These data indicate the need to provide long-term, and possibly, life-time clinical surveillance of patients with oral leukoplakia because the rate of malignant transformation remains clinically significant over time. Furthermore, the authors and their panel recommend the need to provide a new biopsy of oral leukoplakia when clinical change is demonstrated.

Aguirre-Urizar et al<sup>27</sup> 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 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 nonhomogenous 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% confidence interval [CI]: 1.39 to 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% CI: 9.5 to 38.2). Furthermore, high-grade dysplasia demonstrated a 4.90-fold increased risk of malignant transformation compared to low-risk epithelial dysplasia (95% CI: 3.02 to 7.96).

Gilveti, et al<sup>28</sup> 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 nonhomogenous leukoplakia (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 underwent malignant transformation who had high-grade dysplasia who were originally diagnosed with moderate 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 less) 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<sup>29</sup> reviewed 5,071 patients, 4,299 males and 772 females, with OPMDs 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 86 patients (5.81 percent) with severe epithelial dysplasia progressed to oral cancer. Of particular interest is that 49 of the 1,684 patients with benign epithelial hyperplasia/hyperkeratosis experienced malignant transformation to 37 squamous cell carcinomas and 12 verrucous carcinomas.

Gonzalez-Moles et al<sup>24</sup> 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 that 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, the history of organ transplantation, and the presence of skin lesions or systemic disorders suggestive of lupus erythematosus.<sup>24</sup>

## Treatment of dysplasia

The status of evidence related to the treatment of oral leukoplakia and dysplasia is summarized by a 2016 Cochrane review.<sup>30</sup> “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 trials demonstrating value that would suggest broad application. The available data for evidence-based decision-making related to surgical therapies are therefore extremely limited and significant controversy exists regarding treatment protocols.<sup>31,32,33</sup> The views expressed in this section are therefore based primarily on consensus expert opinion related to this disease process noting that the authors of this position paper have significant individual and vast collective experience. The concepts suggested should be considered as general gestalt that requires application to

the specific clinical situation of each patient. In no way are the authors’ 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 that 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. It is also acknowledged that some patients present with an unresectable burden of disease or disease that is technically resectable, but for which the morbidity associated with resection may not warrant treatment. Furthermore, the algorithms do not intend to address all clinical situations surrounding the surgical treatment of dysplasia, for example, whether or not to “chase” surgical margins of dysplasia beyond the treatment of clinical disease. Finally, patients should be made aware that recurrence even after successful treatment is common and no treatment, including surgical interventions, has been scientifically proven to prevent progression to cancer; thus, careful follow-up with providers trained in COE is warranted.

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 OED, the malignant transformation rate was <sup>28</sup>.6 percent in untreated patients and 12.3 percent in patients who underwent treatment using scalpel excision, laser excision, or laser ablation.<sup>28</sup> Older age, nonhomogenous clinical appearance and incomplete excision all demonstrated a worse prognosis.<sup>28</sup> A prior study of 118 patients with severe dysplasia reached similar conclusions where treated patients had a risk of transformation of 6 percent compared to 29 percent in untreated patients ( $P = .004$ ). Likewise, a retrospective study of 136 patients of all grades of dysplasia demonstrated a significant reduction in malignant transformation rate with both scalpel excision and laser ablation.<sup>34</sup> These data are collectively stronger, but in contrast to the report by Holmstrup et al,<sup>9</sup> noting a higher transformation rate to cancer in patients who underwent intervention for their premalignant lesions. As mentioned previously, none of these studies were RCTs and conclusions are therefore limited. Nevertheless, the data serve a basis for the reasonable recommendations

of surgical 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 reliability 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 has shown significant variability in the literature.<sup>9</sup> As such, while the recommendations below use 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. It is again emphasized that 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. While some patients present with truly unresectable disease or unresectable due to morbidity, 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. On the other hand, ablation involves vaporization of the lesion, typically with a CO<sub>2</sub> 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 the 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 or margin assessment, and therefore requires the surgeon's judgment regarding the appropriateness of ablation of any oral mucosal lesion without first performing an incisional biopsy. The authors

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of this paper do not recommend the use of laser ablation for high-grade dysplasia, including severe or CIS 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 1.0-1.5 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 that difficulty can exist for 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. Our treatment algorithm proposes treatment combining the two features with variable treatment options based on availability as well as surgeon and patient shared decision-making.

## **Follow-up of patients with dysplasia of the oral mucosa**

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. The potential for all grades of dysplasia to undergo malignant transformation should not be dismissed. Clinical surveillance 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.<sup>34,35</sup> Follow-up may appropriately be delegated to any provider adequately trained in COE.

## Research regarding oral mucosal dysplasia

As more questions than answers currently exist in the understanding of etiology, progression, treatment and prevention of OED, ongoing research is critical. While what is included below is not applicable to current practice and only briefly summarized, it is intended to point readers toward areas of research that may impact the future understanding and inform future treatments.

## Quantitative tissue phenotyping

Of potential future value in predicting malignant transformation of oral mucosal dysplasia is the use of quantitative tissue phenotype.<sup>36,37</sup> The gradual development of genomic instability of cells predicts changes in phenotype that can distinguish malignant cells from normal cells. Changes can occasionally be detected with hematoxylin and eosin-stained tissue. A subset of premalignant cells at risk for malignant transformation might be phenotypically distinct. To this end, quantitative tissue pathology permits the profiling of numerous microscopic characteristics at the cellular and subcellular levels that are not apparent at the conventional microscopic level.<sup>36</sup> Guillaud et al<sup>37</sup> studied the utility of quantitative tissue phenotype as measured by high-resolution image analysis to predict malignant transformation of hyperplasia, mild and moderate dysplasia, and severe dysplasia and CIS. A nuclear phenotype score (NPS) was established as an aggregate of five nuclear morphometric characteristics that distinguished 4,027 normal nuclei in 29 normal oral mucosal biopsy specimens from 4,298 abnormal nuclei in 30 specimens of squamous cell carcinoma. These five features included the maximum radius of the nucleus (Max\_radius), the amount of the nuclear boundary explained by 3 lobes (Harm003\_fft), the relative spatial distribution of high and low absorbance variations in the nucleus (Fractal\_area1), the presence of a dark nucleus with light areas of a light nucleus with

dark areas (Absorbance\_skewness), and the fraction of the nuclear diameter one can travel prior to an intensity change (Long90\_runs). A cell-by-cell phenotypic analysis was performed whereby a score was assigned to each nucleus indicating similarity to normal or cancer cells in 10 regions of interest within each tissue sample. The NPS represented the weighed sum of the 10 regions. An NPS with a value of 1 corresponded to a tissue sample with 100 percent normal cells, while an NPS with a value of 10 corresponded to a tissue sample with 100 percent cancer-like cells. The NPS was defined for 69 cases of oral premalignant lesions. A significant increase in NPS was noted in cases of severe dysplasia and CIS compared to hyperplasia, mild dysplasia and moderate dysplasia. Within the former group, an elevated NPS was significantly correlated with the presence of high-risk LOH patterns. In addition, there was a statistically significant difference between cases of hyperplasia, mild dysplasia, and moderate dysplasia that progressed to cancer compared to those that did not progress to cancer. The authors selected a cutoff value of 4.5 for the NPS to distinguish those cases that would undergo malignant transformation versus those cases that would not progress. Cases with an NPS more than 4.5 had a 10-fold increase in progression to cancer within five years.

## Prevention of malignant transformation of oral mucosal dysplasia

Chemoprevention represents a strategy that delays, reverses or prevents the development of invasive cancer from premalignant disease. Numerous compounds and pharmacologic agents have been administered and studied to determine their ability to interfere with progression of dysplasia to invasive cancer of the oral cavity. These entities are antimutagens, including desmutagens and bioantimutagens; N-acetyl-L-cysteine; topical bleomycin; polyphenols such as green tea extract and curcumin; antiproliferatives such as retinoids, carotenoids, and nonsteroidal anti-inflammatory drugs; and ligands of peroxisome proliferator-activated receptor gamma.<sup>38</sup> McCarthy et al<sup>39</sup> reviewed early-phase trials in the chemoprevention of oral cancer in terms of their evidence and methodology. They point out that no trial has realized uniform acceptance due to toxicity or lack of efficacy, as





well as problems related to the study's size and end points. A common problem is that studies do not properly select the patients at high risk for progression of dysplasia to invasive cancer versus those patients with nonprogressive disease.<sup>38</sup> Lodi et al<sup>30</sup> reviewed 14 RCTs involving 909 patients undergoing medical and other treatments for oral mucosal leukoplakia in terms of preventing its progression to invasive cancer. The development of invasive cancer, clinical resolution of the leukoplakia and improvement of histologic features were assessed with three treatment interventions: topical bleomycin versus placebo, systemic beta carotene versus placebo, and systemic vitamin A versus placebo. None of these treatments were effective in preventing the development of invasive cancer as measured up to two years for beta carotene and vitamin A, and up to seven years for topical bleomycin therapy. Most treatments caused side effects of varying severity in a high proportion of participants. While no chemoprevention protocols are currently advocated, a new RCT “Metformin for the Prevention of Oral Cancer in Patients with Oral Leukoplakia or Erythroplakia” is underway and enrolling subjects.

In the final analysis, there are currently no validated mechanisms to prevent the progression of oral mucosal dysplasia to cancer. Surgical intervention remains unstudied in a randomized prospective clinical trial that would have the power to delineate its benefits. This position paper is intended to assist clinicians with available evidence and expert opinion to best serve the significant numbers of patients impacted by this complex disease process.

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The authors recognize the contributions of Dr J. Michael McCoy regarding histopathological analysis of oral mucosal dysplasia.

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### 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**

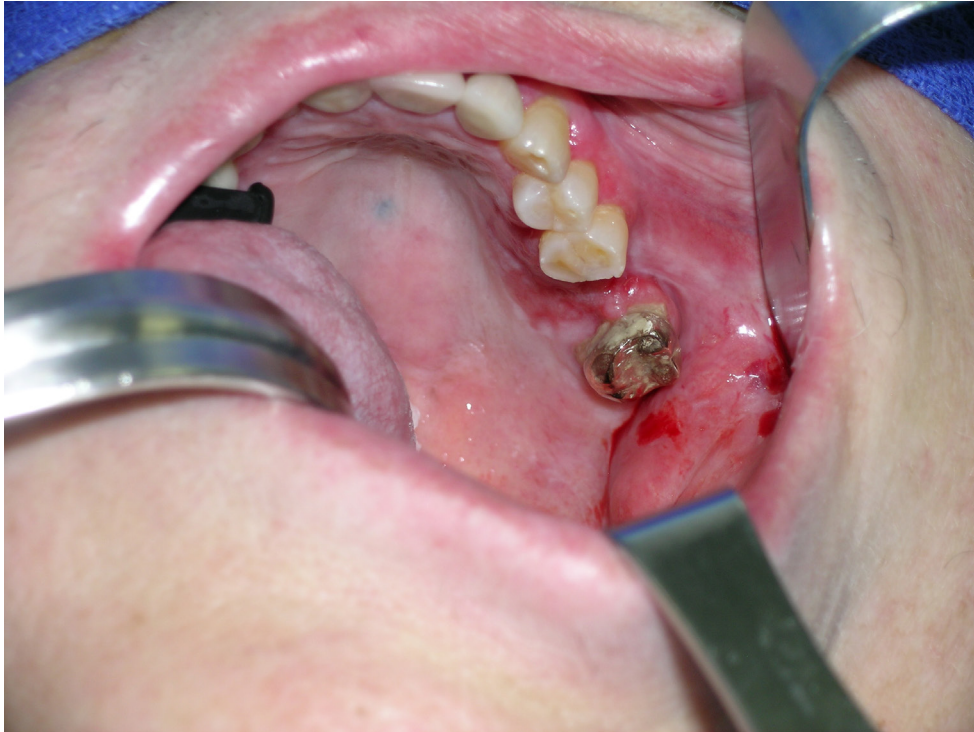


Figure 2. An example of erythroplakia of the left palatal mucosa. The histopathology pertaining to incisional biopsy of this lesion identified microinvasive squamous cell carcinoma.

**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**

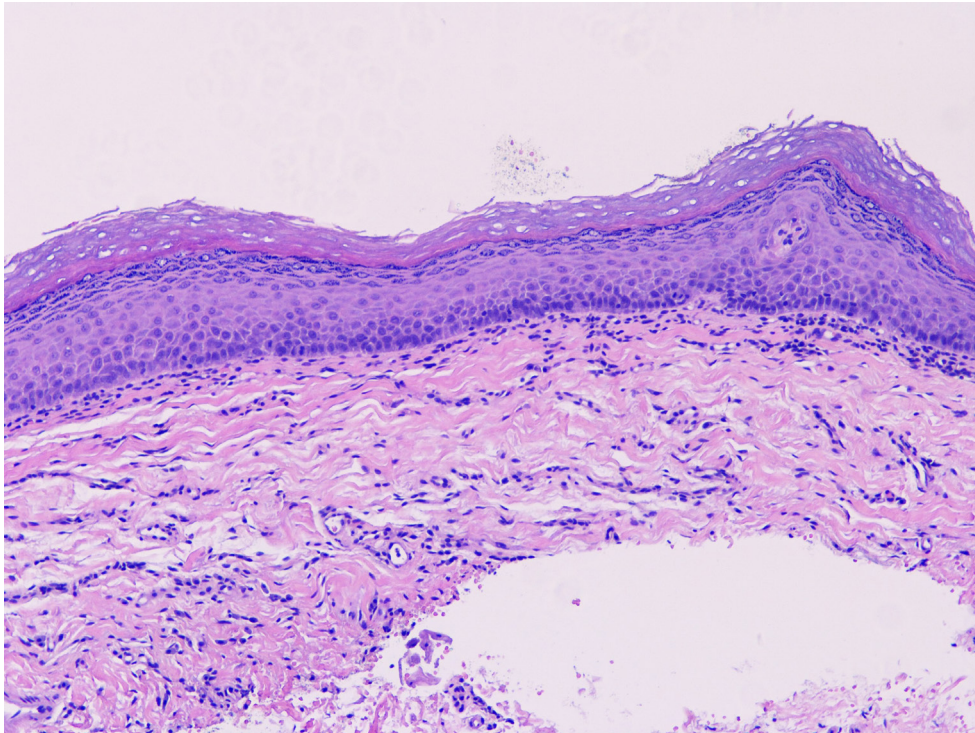


Figure 4. Mild dysplasia of the oral mucosa based on the classic three-tier system. With the minimal number of ominous cytologic changes seen, including the lack of abnormal variation in nuclear size and shape, this is an example of low-grade dysplasia using the binary system. Such an example of mild dysplasia might be observed under specific circumstances rather than excised (Figure courtesy of Kitrina Cordell, DDS, MS).



**Figure 5**

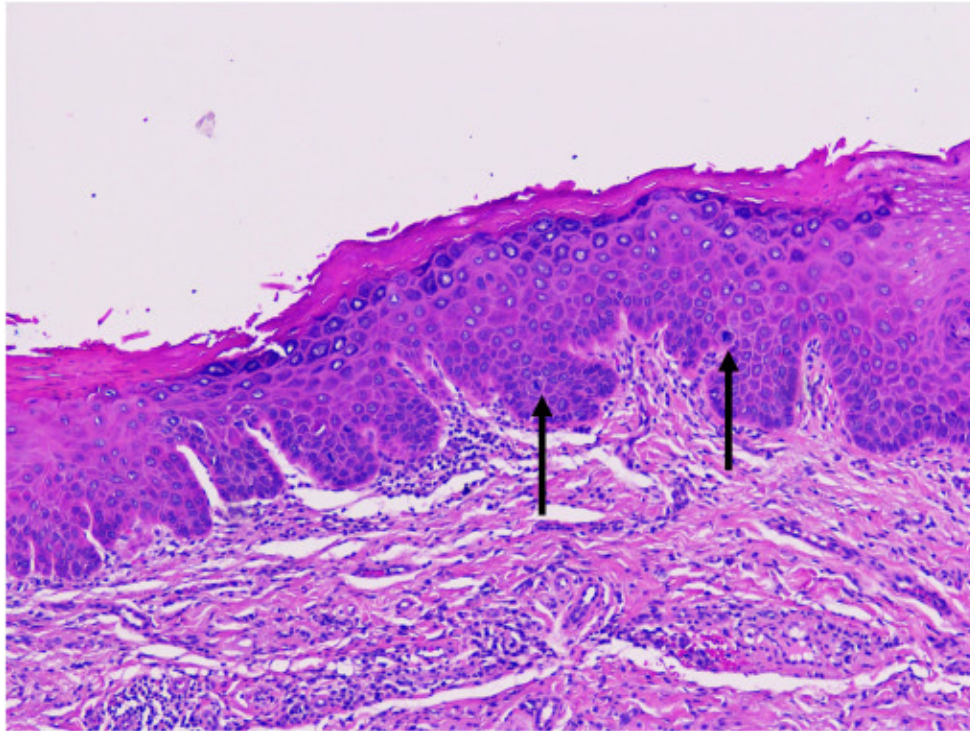


Figure 5. Moderate dysplasia of the oral mucosa. With the blunted and budding rete ridges, as well as atypical mitotic figures and abnormal variation in cell size and shape (arrows), this dysplasia is termed high-grade using the binary system. While some cases of moderate dysplasia are observed, the high-grade nature of this histopathology dictates excision of this lesion (Figure courtesy of Kitrina Cordell, DDS, MS).



**Figure 6**

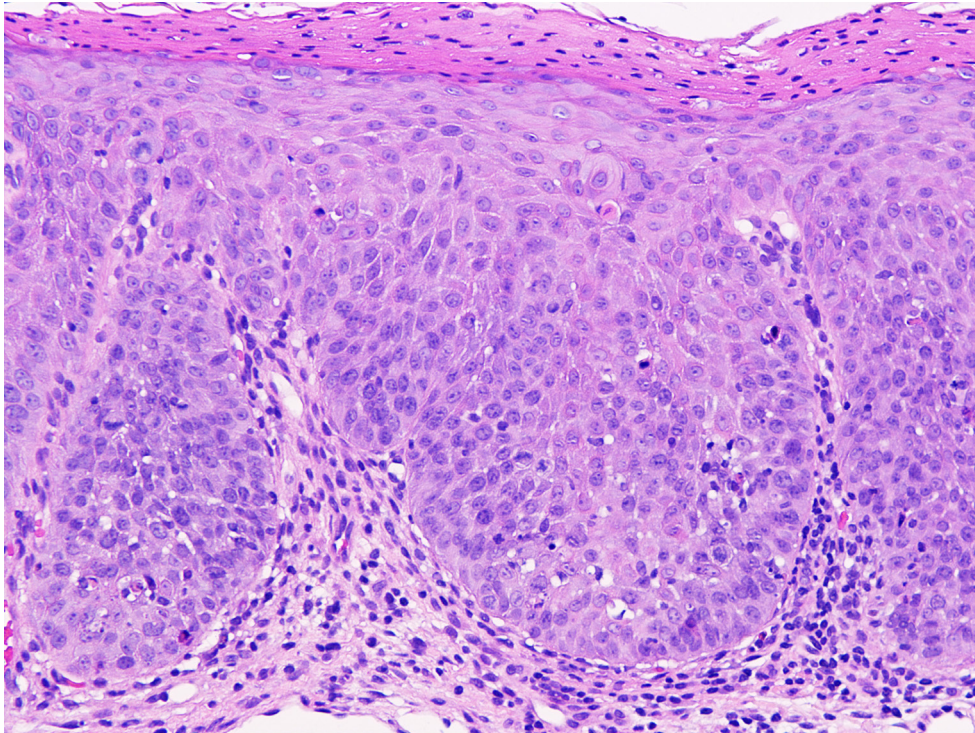


Figure 6. Severe dysplasia of the oral mucosa. Severe dysplasia and carcinoma in situ are used interchangeably based on the WHO 2017 and 2022 classifications. The classification equivalence supports treatment recommendations as severe dysplasia and CIS are treated identically with wide local excision. (Figure courtesy of Kitrina Cordell, DDS, MS).



**Figure 7**

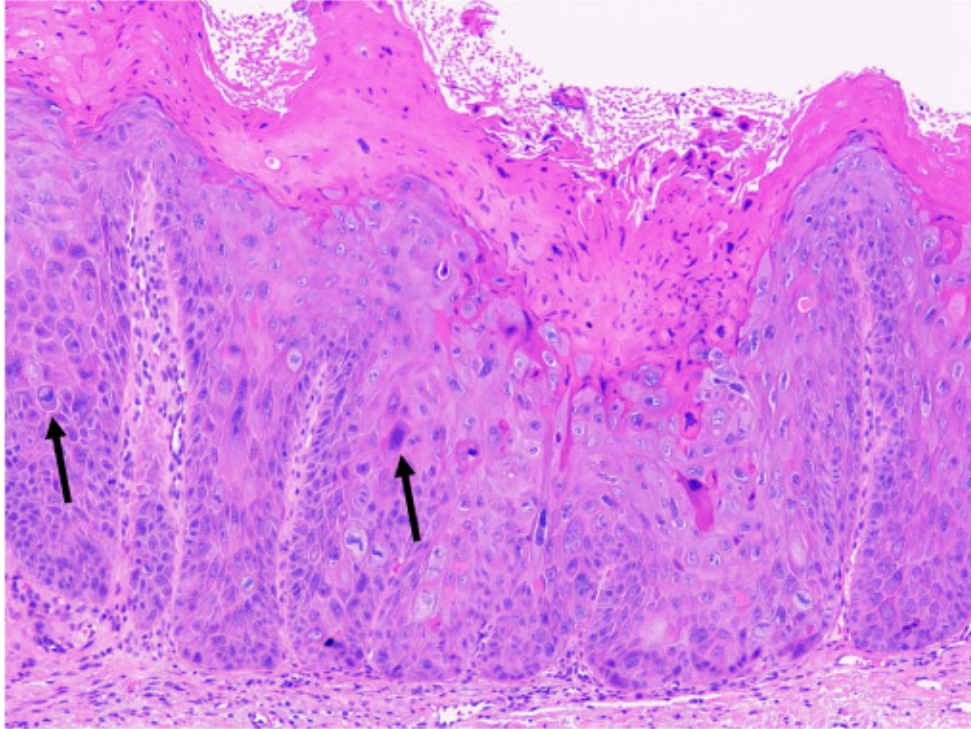


Figure 7. Carcinoma in situ of the oral mucosa. Carcinoma in situ is no longer the preferred term in grading OED and is replaced with the term severe dysplasia. This notwithstanding, cytologic differences are appreciated between this example of CIS that demonstrates abnormal variation in nuclear size and shape, abnormal variations in cell size, and atypical mitotic figures (arrows), and Figure 6 that demonstrates severe dysplasia without a similar magnitude of cellular atypia (Figure courtesy of Kitrina Cordell, DDS, MS).



**Figure 8**

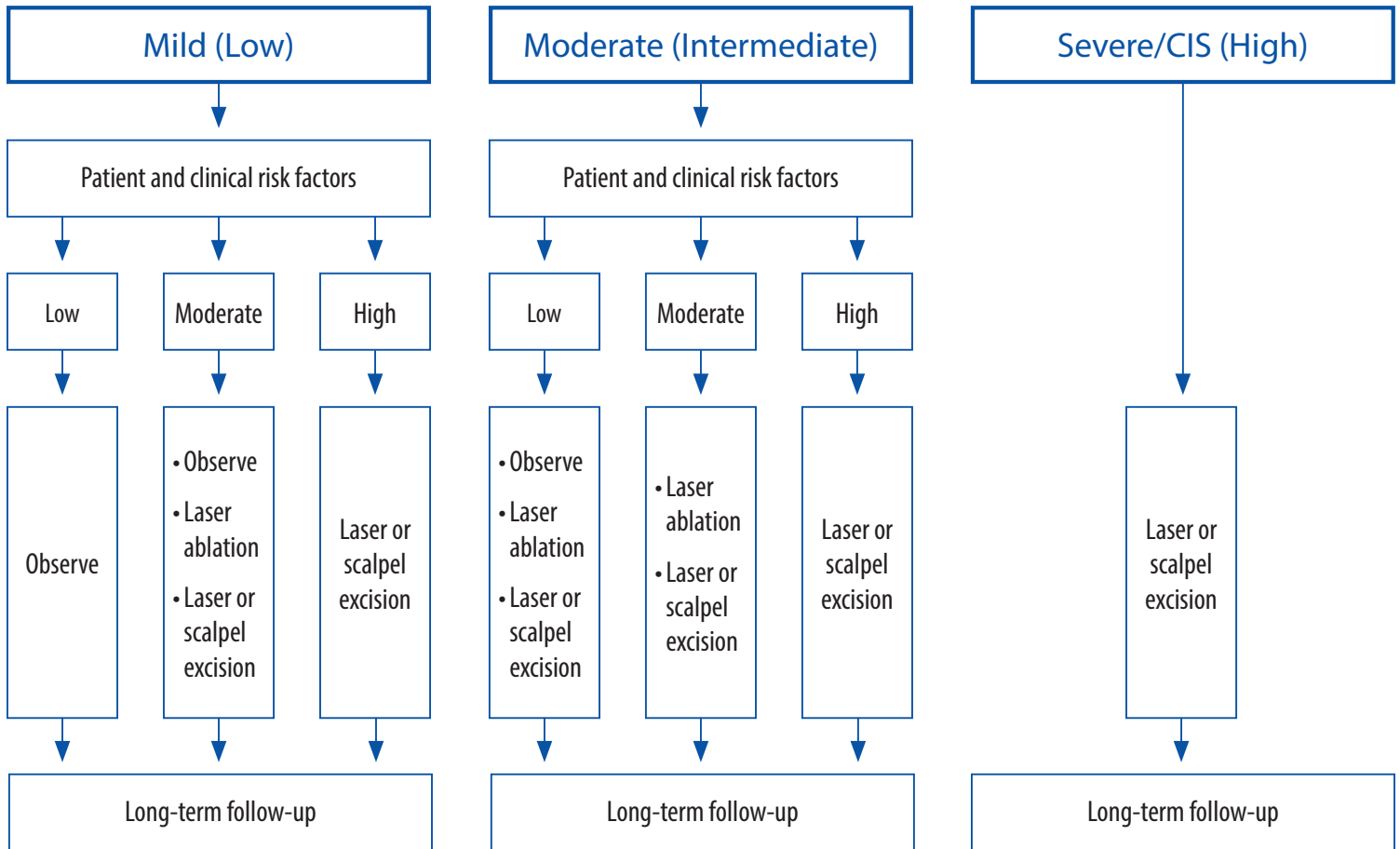


Figure 8: Algorithm for treatment of dysplasia of the oral mucosa



**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: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 fifth 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 for oral mucosal dysplasia**

Patient Characteristics	Lesion Characteristics
<ul style="list-style-type: none"> <li>• Older age (&gt; 60 years)</li> <li>• Tobacco/Alcohol consumption</li> <li>• Multiple lesions (PVL)</li> <li>• Diagnosis of lichen planus</li> <li>• Unable to engage in routine follow-up</li> </ul>	<ul style="list-style-type: none"> <li>• Erythroleukoplakia or erythroplakia</li> <li>• Size exceeding 200 mm</li> <li>• Location</li> <li>• Nonhomogenous</li> <li>• Ill-defined margins</li> </ul>

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