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# Oral potentially malignant disorders: nomenclature and classification

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**Abstract**

Oral potentially malignant disorders (OPMDs) are associated with an increased risk of occurrence of cancers of the lip or oral cavity. This paper presents an updated report on the nomenclature and the classification of OPMDs, based predominantly on their clinical features, following discussions by an expert group at a workshop held by the World Health Organisation (WHO) Collaborating Centre for Oral Cancer in the UK. The first workshop held in London in 2005 considered a wide spectrum of disorders under the term 'potentially malignant disorders of the oral mucosa' (PMD) (now referred to as oral potentially malignant disorders: OPMD) including leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral lichen planus, oral submucous fibrosis, palatal lesions in reverse smokers, lupus erythematosus, epidermolysis bullosa and dyskeratosis congenita. Any new evidence published in the intervening period was considered to make essential changes to the 2007 classification. In the current update, most entities were retained with minor changes to their definition. There is sufficient evidence for an increased risk of oral cancer among patients diagnosed with "oral lichenoid lesions" and among those diagnosed with oral manifestations of chronic graft-versus-host disease. These have now been added to the list of OPMDs. There is, to date, insufficient evidence concerning the malignant potential of chronic hyperplastic candidosis and of oral exophytic verrucous hyperplasia to consider these conditions as OPMDs. Furthermore, due to lack of clear evidence of an OPMD in epidermolysis bullosa this was moved to the category with limited evidence. We recommend the establishment of a global research consortium to further study the natural history of OPMDs based on the classification and nomenclature proposed here. This will require multi-centre longitudinal studies with uniform diagnostic criteria to improve the identification and cancer risk stratification of patients with OPMDs, link them to evidence-based interventions, with a goal to facilitate the prevention and management of lip and oral cavity cancer.

## 1. INTRODUCTION

In March 2020, the WHO Collaborating Centre for Oral Cancer in the UK convened a workshop attended by invited experts to discuss the advances in knowledge and recent changes in the understanding of oral potentially malignant disorders (OPMDs). OPMDs are a significant group of mucosal disorders that may precede the diagnosis of oral squamous cell carcinoma (OSCC) (Warnakulasuriya, Johnson, & van der Waal, 2007). Since the introduction of this terminology, *'potentially malignant disorders of the oral mucosa' (*PMD) (later OPMD), health care providers and researchers over the globe have enthusiastically adopted this term and the classification of entities therein, and this has resulted in better reporting of this important group of disorders. A recent review identified over 750 publications on the topic of OPMDs published since 2007 (Liu, Wu, Zhang, Shi, & Yang, 2020). However, discrepancies in describing these disorders are still found in the published literature leading to inconsistency and a degree of confusion. The terminology for disorders that precede development of cancers has evolved over the years to align with greater scientific evidence and to reflect temporal advances in understanding of the natural history of these disorders. OPMDs refer to a group of lesions and conditions characterised by a variably increased risk of developing cancers of the lip (C00) and the oral cavity (C02-C06) (Warnakulasuriya et al., 2007). The terminology has been endorsed by the latest WHO classification on Head and Neck Tumours (Reibel, Gale, & Hille, 2017).

The concept of 'pre-cancer' was introduced in 1805 when a European panel of physicians suggested that there are benign diseases that may develop into invasive malignancy if followed for a long time (Baillie, Simms, et al., 1806). The thinking behind the concept of OPMDs as reported by the 2005 workshop and re-affirmed by the Working Group (2020) is that OPMDs represent tissue "fields" with more or less distinctive clinical appearances at initial assessment, and where a proportion within each clinical category have been documented to have subsequently developed a cancer during follow-up; Viz: tissues within these categories have enhanced malignant potential. Some of these clinical alterations, red and white patches in particular, are seen to co-exist at the margins of overt OSCCs; they possess similar morphological and cytological changes observed in superficially invasive carcinomas; and, some of the chromosomal, genomic and molecular alterations detected in early invasive OSCCs are also found in OPMDs (presented in later chapters in this supplement). It is also important to recognise that OSCC can present without the patient or a clinician having been aware of a preceding clinically altered mucosa at the site. Thus, expert opinion at the 2005 workshop

(published in 2007) proposed a shift from previously used terms "*precancer*", "*epithelial precursor lesions*", "*premalignant*", "*precancerous*", and "*intra-epithelial lesion"* to OPMD. Lesions and conditions were combined into one category of "*disorders*", in recognition of the fact that field change usually exists due to exposure to environmental carcinogens across much of the upper aero-digestive tract, and that the whole person may have changes which influence the risk of cancer development (Johnson, 2017; 2020). *"Potentially malignant"* implies that not all patients diagnosed with any of these mucosal abnormalities will develop an oral malignancy. Nor does it imply that a carcinoma will arise exactly at the site where an OPMD was previously diagnosed. The observed clinical and biological course of these disorders has been discussed recently by Speight, Khurram, & Kujan (2018). The concept that the mere presence of OPMDs is but one of several factors increasing the risk for cancer development is important.

Patients diagnosed with OPMDs may have an increased susceptibility to develop cancer anywhere in their mouth during their lifetime. The majority of these OPMDs may not progress to carcinoma, but rather they provide a field of abnormality in which cancer development is more likely than in their clinically normal mucosa, and more likely than in patients without such disorders. "Clinically normal mucosa" can by molecularly abnormal. As alluded to earlier, the cancer does not necessarily occur in the site of the visibly altered mucosa. An important challenge faced by clinicians managing patients with OPMDs is to be able to identify the small proportion of patients most likely to develop a future malignancy.

Updating the classification of OPMDs is not just an academic endeavour, but necessity for clinicians as they make evidence-based management decisions for patients diagnosed with these disorders. Such decisions have the potential for serious consequences and can impact the patient's quality of life, and need to be carefully considered to minimize the risks for both under- or over-management. In the ICD-11 classification of diseases, the World Health Organisation has proposed revisions for the following purposes; 1) increasing usability, 2) updating scientific content, 3) integrating with eHealth, and 4) accommodating the needs for multi-users in recording, reporting, and analysis (World Health Organisation, 2019). The 2020 workshop on OPMDs adheres to this rationale. The collective expert opinion favours perpetuation of the existing OPMD nomenclature to describe oral mucosal disorders that indicate an increased risk for cancer development, and consideration of new evidence from both basic science and clinical studies. With these objectives in mind, inclusion of some additional disorders has been proposed (Warnakulasuriya, 2018; 2020): oral lichenoid lesions

and reactions, oral chronic graft-versus-host disease, chronic hyperplastic candidosis, and oral exophytic verrucous hyperplasia. We discuss the available evidence on these disorders in section 4 of this report.

This paper lays out the updated classification, provides or endorses definitions of each disorder and highlights areas of uncertainty that warrant further investigation. The objective is to present a consensus on a revised classification of OPMDs, recommended nomenclature and definitions for each disorder. Such classification is predominantly, albeit not exclusively, based on clinical features.

## 2. DEFINITION AND GENERAL FEATURES

The working group has defined OPMD as "*any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer.*"

The presence of an OPMD does indicate an increased risk for cancer of the lip or the oral cavity during the lifetime of the patient, but only a minority progress to cancer. On the other hand, in some patients with an OPMD, microinvasive carcinoma may be discovered on biopsy at the initial assessment. Patients presenting with overt clinical signs and symptoms suggestive of the presence of a "frank carcinoma", (ie deeply ulcerated, exophytic, or indurated) would not be designated as having an OPMD. Table 1 provides definitions for the disorders listed as OPMDs.

OPMDs have a wide range of clinical features including colour variations (white, red, and mixed white and red), topographic changes (plaque/plateau, smooth, corrugated, verrucous, granular, atrophic), and may be of variable size (Williams, Poh, Hovan, Ng, & Rosin, 2008; Speight, Khurram, & Kujan, 2018). Some OPMDs, particularly oral leukoplakia may superficially ulcerate due to abrasion of the surface by trauma from teeth or appliances. OPMDs can involve any anatomical site in the oral cavity and may be uni- or multifocal (Farah et al., 2014). Extraoral sites (eg pharynx, larynx, esophageal, and genital) may demonstrate analogous PMDs. OPMDs have an unpredictable clinical course - remaining static, or may demonstrate progression or regression (Gupta et al., 1980; Holmstrup, Vedtofte, Reibel, & Stoltze, 2006; Speight et al., 2018; Farah, Kujan, Prime, & Zain, 2019).

The majority of patients with OPMDs are diagnosed in middle-aged or elderly patients, predominantly males (Napier & Speight, 2008; Speight et al., 2018). In western populations, elderly females with long-standing leukoplakia and without obvious risk factors have,

paradoxically, a significant risk of progression to cancer. These individuals could carry an endogenous risk factor, rather than being exposed to an environmental factor. Ethnicity and associated dominance of particular cultural risk factors have influenced the type and pattern of OPMDs reported in specific populations. For example, betel quid/areca nut chewing habits are widely prevalent in South Asian populations resulting in a greater prevalence of OPMDs (Lee et al., 2012a; Lee, et al., 2012b, Mello et al., 2018). Reverse smoking habit is also known to induce specific mucosal changes on the palate in some geographic regions (see section 3.7)

## 3. DETAILED DESCRIPTIONS OF THE ORAL POTENTIALLY MALIGNANT DISORDERS

### 3.1 Leukoplakia

Leukoplakia is amongst the most common and most studied OPMD encountered in clinical practice and in population surveys. A bibliometric study of the most-cited articles on oral leukoplakia that provide a historical perspective on scientific evolution of our understanding of this disorder was published recently (Liu, Zhang, Wu, Yang, & Shi, 2019). Historically, several definitions have been proposed for leukoplakia (Supplementary Table 1). The most recent definition by the WHO Collaborating Centre, published in 2007, was "*A predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer*" (Warnakulasuriya et al., 2007). The present Working Group found no reason to change this definition which is now being reported widely in the global literature.

The following criteria should be considered when making a clinical diagnosis of oral leukoplakia:

- A predominantly white patch/plaque that cannot be rubbed off
- Most homogeneous leukoplakias affect a circumscribed area and have well-demarcated borders. A smaller subset can present with diffuse borders.
- Non-homogeneous leukoplakias typically present with more diffuse borders and may have red or nodular components.

- No evidence of chronic traumatic irritation to the area (e.g. a sharp tooth rubbing on the tongue, a white patch on the alveolar ridge or retromolar pad from masticatory friction, a white patch on gingiva from overzealous tooth-brushing)
- Is not reversible on elimination of apparent traumatic causes, i.e. demonstrates a persistence feature
- Does not disappear or fade away on stretching (retracting) the tissue
- Exclusion of other white or white/red lesions outlined in Table 2.

It is emphasised that the term leukoplakia is used as a clinical diagnosis having excluded other clinically recognisable white or white/red lesions (Warnakulasuriya, 2019) (Table 2). The term "persistent" has been used under inclusion criteria but it must be noted that a history of persistence cannot always be ascertained at baseline. When the clinical features are clear it is not always important to definitively establish persistence. During clinical examination of a white patch it is important to first look for a local traumatic cause. If this is evident, the white patch should not be considered a leukoplakia, but rather be designated as a frictional keratosis. Frictional keratoses are typically diffuse and upon removal of the putative frictional source, they should resolve. It is important they are not regarded as an OPMD and must be distinguished from leukoplakia because the latter indicates a future cancer risk.

Leukoplakia can be sub-classified clinically into homogenous and non-homogenous types using distinct features based on colour and surface texture (Table 3). Homogenous leukoplakias are typically asymptomatic and present as a uniformly thin white plaque/patch. They have a smooth surface with a consistent surface topography throughout, are usually sharply demarcated and often exhibit shallow surface cracks/fissures.

On the other hand, non-homogenous leukoplakias may present with diverse clinical presentations including speckled (also referred to as erythroleukoplakia; ie mixed white and red), nodular (small polypoid projections, rounded red or white excrescences) and verrucous (wrinkled or corrugated surface). Leukoplakias, predominantly non-homogeneous leukoplakias, may show focal superficial ulceration. Non-homogenous leukoplakias carry a higher risk of transformation than homogeneous leukoplakias (Diz et al., 2011; Speight et al., 2018), and it is not uncommon for non-homogeneous leukoplakia to exhibit severe dysplasia or even superficially invasive SCC following biopsy at baseline detection (Pentenero et al., 2003; Lee et al., 2006). Lee et al., (2006) reported carcinomas in 12% of incisional biopsies

taken from oral leukoplakia samples in Taiwan. The variable and often severe histopathology within the field of non-homogeneous leukoplakias raises the importance of selecting the correct biopsy site (or sites) to avoid underdiagnosis: indeed, multiple mapping biopsies may be indicated.

It is important to document whether the patient with a leukoplakia is a never smoker because these patients may experience a more aggressive natural history.

In the 2007 classification, mixed white and red lesions were considered as a separate entity under the term erythroleukoplakia. The consensus of the current Working Group was to classify erythroleukoplakia under non-homogeneous leukoplakia (Table 3).

The current expert group emphasises that at the time of baseline detection, oral leukoplakia is a provisional clinical diagnosis made by exclusion of other white disorders. A diagnostic biopsy is indicated to confirm this clinical diagnosis or modify it (ie. oral lichen planus, or hyperplastic candidosis). One or more underlying histopathologic diagnoses ranging from simple epithelial hyperplasia with hyperparakeratosis or hyper(ortho)keratosis, varying severity of epithelial dysplasia are consistent with oral leukoplakia (Reibel et al., 2017; Ranganathan and Loganathan, 2019). It is customary that the pathologist mentions whether the histology is compatible with the clinical diagnosis of leukoplakia or not, indicates the presence or absence of dysplasia and if present, provides the grade(s) of dysplasia. To achieve uniformity in reporting we recommend a pathology report to state "keratosis with no/mild/moderate/severe dysplasia, consistent with oral leukoplakia". A biopsy may on occasion demonstrate superficially invasive carcinoma, then the diagnosis of leukoplakia is revised to carcinoma. These pathological aspects of leukoplakia are presented in detail by Kujan et al., in this volume.

Any field surveys that have not included a protocol for biopsy should clarify that the diagnosis was based on clinical features without histopathological confirmation

Misdiagnosis and misclassification of leukoplakias have led to confusion and inaccurate reporting of prevalence (Auluck & Pai, 2005), also thereby under-reporting malignant transformation in cases of oral leukoplakia. One source of confusion is conflating the many different situations in which "frictional keratosis" is misclassified under the umbrella of "leukoplakia". Keratosis" is unfortunately misused by some clinicians to clinically describe a white lesion. We discourage keratosis as a clinical term unless it is part of a specific name such as frictional keratosis. The published literature refers to other disorders which include keratosis in their name, and that need to be better defined:

- Tobacco pouch keratosis - this is a white patch found on the lower buccal grooves among smokeless tobacco users who retain their tobacco quid at the site (Müller, 2019). Most of them will resolve following discontinuation of the habit but those that persist should be included within the group leukoplakia. A biopsy is indicated at baseline and further study is needed to assess their natural history.
- Sublingual keratosis- A white patch when found of the floor of the mouth or inferior surface of the tongue was termed *sublingual keratosis* by Kramer's group (Kramer, El-Labban, & Lee, 1978a). The authors attributed high significance to these, having noted that a large proportion of their patients with such white patches developed squamous cell carcinomas in that area. Subsequent studies have not confirmed the extremely high risk of transformation noted in early studies, but the floor of mouth remains a high-risk site and leukoplakias at this site merit careful follow-up. The Working Group recommends that any white patch on floor of mouth - having excluded other known conditions - should be clinically considered a leukoplakia.
- Sanguinaria-associated keratosis- Damm et al., (1999), Eversole et al., (2000) and Mascarenha et al., (2002) described a unique form of a white patch that could be attributed to the use of a dentifrice and/or mouthrinse containing the herbal additive sanguinaria. Sanguinarine is the principal alkaloid in an extract from the Indian bloodroot plant (Sanguinuriu canadensis L.). Sanguinaria-associated keratosis is rarely reported these days since the product was banned. This condition should not be considered a leukoplakia, as it has an established cause, and would generally resolve on removal of the cause.
- Palatal keratosis in reverse smokers- This has a very specific appearance and is classified as a separate entity in the OPMD literature and is not considered as a leukoplakia. Reverse smokers' keratosis is considered a disorder with a comparatively high risk of malignant transformation (Gupta et al., 1980) (see section 3.7)
- Keratosis of unknown significance (KUS)- This term was introduced by Woo, Grammar, & Lerman, (2014) and refers to the histologic entity of hyperkeratosis with minimal to no epithelial dysplasia or cellular atypia (Woo et al., 2014; Villa et al., 2019). There is no rationale to apply this term in the clinical context. In fact, over 50% of leukoplakias will be in this histologic category. The Working Group does not recommend use of the term "keratosis of unknown significance".

### 3.2 Proliferative verrucous leukoplakia

This condition is defined as a distinct form of multifocal oral leukoplakia characterised by having a progressive clinical course, changing clinical and histopathologic features, and is associated with the highest proportion of oral cavity cancer development compared with other OPMDs (Cabay, Morton, & Epstein, 2007; Iocca et al., 2019). Other terms proposed in the literature are Proliferative Multifocal Leukoplakia (Aguirre-Urizar et al., 2011) and Proliferative leukoplakia (Villa et al., 2018). From a clinical perspective, the evolution of this type of OPMD often begins as one or more leukoplakias, later presenting in multiple locations due to gradual spread of an individual focus or resulting from fusion over time of several adjacent foci (Villa et al., 2018). The original report by Hansen et al., (1985) coining the term Proliferative Verrucous Leukoplakia proposed that the diagnosis be made by a combination of clinical and histological features (Hansen, Olson, & Silverman, 1985). Specific clinical diagnostic criteria were later proposed by Cerero-Lapiedra et al., (2010) and Carrard et al., (2013). Their criteria included the disorder affecting more than two different oral sites, and the existence of a verrucous area. Initial clinical presentation could be flat white lesions (without any verrucous component) (Batsakis, Suarez, & El-Naggar, 1999; Villa et al., 2018), and may also sometimes have a lichenoid clinical appearance (Garcia-Pola et al ., 2016) and be signed out as being lichenoid by the pathologist. In the latter situation it is possible that a case could be erroneously treated as OLP for many years, with the risk of missing, or of accelerating, subsequent malignancy. Despite the imperfection of the term PVL to capture an expanded group of patients with multifocal disease, the term is widely reported, and the Working Group recommended retaining this term.

A high proportion of patients diagnosed with PVL eventually develops oral cancer. A recent systematic review estimated the proportion to be 49.5% (CI 26.7%-72.4%) (Iocca et al., 2019). Patients with a diagnosis of PVL may subsequently develop either conventional squamous cell carcinomas or verrucous carcinomas. Multiple primary carcinomas were documented in a case-series mostly affecting gingival sites (Bagan, Murillo-Cortes, Poveda-Roda, Leopoldo-Rodado, & Bagan, 2019).

### 3.3 Erythroplakia

Erythroplakia is a solitary lesion defined (Table 1) as ‘a predominantly fiery red patch that

cannot be characterised clinically or pathologically as any other definable disease'

Erythroplakia exhibits a clinical appearance of a sharply demarcated, flat or depressed, erythematous area of mucosa with a matt appearance. Inflammatory conditions that may result in a red clinical appearance are excluded prior to arriving at this diagnosis (see Table 3) (Kramer et al., 1978b; van der Waal & Scully, 2011; Warnakulasuriya, 2019) The solitary presentation of erythroplakia helps to distinguish it from other more widespread conditions such as erosive lichen planus, lupus erythematosus and erythematous candidiasis which present more often in multiple sites (van der Waal, 2010). Other conditions include autoimmune disorders, infections, and vascular hamartomas/vascular neoplasms that may exhibit similar clinical features and should be considered in the differential diagnosis (Reichart & Philipson, 2005). Most oral erythroplakias, at the time of diagnosis, are either histopathologically a squamous cell carcinoma or show high-grade epithelial dysplasia.

### 3.4 Oral Submucous Fibrosis (OSF)

Oral submucous fibrosis is a well-recognised OPMD characterised by fibrosis of the oral mucosa (and submucosa) and there is a higher risk for oral cancer development in patients with OSF. In moderate to advanced cases fibrosis may also involve the oropharynx and the upper third of the oesophagus (Maher, Ahmed, Qureshi, Zuberi, & Syed, 1991; Misra, Misra, Dwivedi, & Gupta, 1998., Tilakaratne, Ekanayaka, & Warnakulasuriya, 2016). The definition proposed by Kerr et al., (2011) following the World Workshop of Oral Medicine V that has gained acceptance was slightly modified by the Working Group; *'A chronic, insidious disease that affects the oral mucosa, initially resulting in loss of fibroelasticity of the lamina propria and as the disease advances, results in fibrosis of the lamina propria and the submucosa of the oral cavity along with epithelial atrophy'*. The clinical diagnostic features are described in Table 3. The clinical features at the time of presentation of oral submucous fibrosis depend on the stage of the disease. It is generally characterised by patients reporting a burning sensation of the oral mucosa and intolerance to spicy foods. Initial signs include a leathery mucosa, pallor, loss of tongue papillae, petechiae and occasionally vesicles. As the disease progresses fibrous bands develop in lips, cheek mucosa and soft palate and this hallmark feature leads to a limited mouth opening (Kerr et al., 2011). There is growing evidence to support the role of genetic susceptibility and family history in the pathogenesis and clinical presentation of OSF (Ray, Chatterjee, & Chaudhuri, 2019). Several grading systems have been proposed. Based on

objective criteria a 5-grade system was proposed by Kerr et al., (2011). The working group endorses this for clinical use.

### 3.5 Oral lichen planus

Carrozzo et al., (2019) characterised oral lichen planus (OLP) as a disease with bilateral white reticular patches affecting buccal mucosae, tongue, and gingivae. More severe presentations include erosions/areas of atrophy and ulceration. Despite being a common non-infectious disorder in the oral cavity (Roopashree et al., 2010), oral lichen planus (OLP) continues to be a disorder without clear causative factors (Krutchkoff, Cutler, & Laskowski, 1978; van der Meij et al., 1999; Cheng, Gould, Kurago, Fantasia, & Muller 2016; Aghbari et al., 2017). Cancer development in patients with a diagnosis of OLP was recently reviewed by Gonzalez-Moles et al., (2019). OLP should be diagnosed using both clinical and histopathological characteristics (Table 4) (van der Meij & van der Waal, 2003; Al-Hashimi et al., 2007; Cheng et al., 2016), and should be clearly distinguished from disorders with similar clinical appearances but due to other causes including oral lichenoid lesions (van der Meij & van der Waal, 2003), oral lichenoid drug reactions (Scully & Bagan, 2004), oral lichenoid contact hypersensitivity reactions (Al-Hashimi et al., 2007), lichen planus pemphigoides, chronic ulcerative stomatitis, acute and chronic graft-versus host disease, lichen sclerosus, lupus erythematosus, and the early stages of PVL (Cheng et al., 2016; Carrozzo et al., 2019). When defining cancer development in patients with OLP authors should follow strict criteria in diagnosing OLP that incorporate clinical, histopathological and patient characteristics (Idrees, Kujan, Shearston, & Farah, 2020). Diagnostic criteria of oral lichen planus endorsed by the Working Group based on previous proposals are listed in Table 4.

### 3.6 Actinic Keratosis/Actinic Cheilitis

Actinic Keratosis (AK) is produced by the effect of actinic (solar, predominantly ultraviolet) radiation to exposed areas of the face, and therefore predominantly the skin and vermilion of the (lower) lip. The precise areas affected are important in clinical assessment (Savage, McKay, & Faulkner, 2010). AK occurs predominantly in middle-aged and light-skinned men with outdoor occupations (Dancyger et al., 2018). There may be localised or diffuse lesions of white flaking plaques or scaly lesions with interspersed red areas (Markopoulos, Albanidou-Farmaki, & Kayavis, 2004). In very mild cases, patients may present simply with dryness of lips (Savage et al., 2010).The white surface is due to hyperkeratosis whilst the red colour results from

epithelial atrophy or even erosion allowing the vasculature to shine through. It is not possible to predict which AKs will progress, regardless of the histological grade (AK I-AK III) (Fernandez Figueras, 2017).

Histologically, the epithelium may show hyperplasia or atrophy, disordered maturation, varying degrees of keratinisation or parakeratinisation, cytological atypia and increased mitotic activity. The lamina propria often shows basophilic degeneration of collagen, elastosis and vasodilatation (de Santana Sarmento, Miguel, Queiroz & da Silveira, 2014; Cavalcante, Anbinder & Carvalho, 2008; Mello, Melo, Modolo, & Rivero, 2019). Lichenoid inflammation is often present and a histopathological diagnosis of lichenoid actinic keratosis should then be rendered. Benign lichenoid keratosis (lichen planus-like keratosis) is an important differential diagnosis in facial skin, including vermillion border. In a case series (n= 124) reported from Brazil, 25% displayed early SCC in the biopsy specimens (Mello et al., 2019). A systematic review on AK found no reliable estimates concerning the frequency of AK developing into invasive carcinoma (Werner et al., 2013).

### 3.7 Palatal lesions in reverse smokers

In reverse smoking, the burning end of a cigarette or cigar is held inside the mouth. Where this is practiced, as many as 50% of all oral malignancies are found on the hard palate, a site usually spared other OPMDs, except among pipe smokers. Reverse smoking is an endemic tobacco habit practised in the coastal rural Andhra Pradesh, India. The habit is also prevalent among the people of the Caribbean Islands, in Latin America (Colombia, Panama, Venezuela), Sardinia, and among some Pacific Islanders, for example, the Philippines, but there are no follow up studies published, outside India. Field research undertaken by the Tata Institute of Fundamental Research (TIFR), India, (Gupta et al., 1980) first described palatal changes in reverse smokers in several Indian cohorts as “thickened white plaques of palate, mucosal nodularity, excrescences around orifices of palatal (minor) mucosal glands, yellowish brown staining, erythema and ulceration. Lesions can present as red, white or mixed red and white, in a background of tobacco staining”. In a later Indian study of reverse smokers, 32% were found white and red patches on their palates (Bharath et al., 2015).

### 3.8 Oral lupus erythematosus

Lupus erythematosus is a chronic auto-immune disease which can be principally subdivided into 3 forms: (1) systemic, (2) drug-induced, and (3) discoid. Oral lesions may manifest in approximately 20% patients with systemic lupus. Oral lesions of lupus erythematosus (OLE) exhibit similar clinical presentations as found in OLP. Typically, OLE presents as a central circular zone of atrophic mucosa, with superficial ulceration surrounded by whitish striae (Odell, 2017). Buccal mucosae, palate and lips are most commonly affected. Histopathologic criteria for the diagnosis of (discoid) lupus erythematosus are described by Schiødt, (1984). Carcinomas developing within lesions OLE are rare intra-orally, and most arise on the lips (Arvanitidou et al., 2018). It is not always possible to confidently distinguish OLP from OLE intra-orally, so that in the absence of systemic features it is quite possible that malignancy arising in LE would be misclassified as a malignancy arising in OLP.

### 3.9 Dyskeratosis congenita

Dyskeratosis Congenita (DKC) (also called Zinsser-Cole-Engman syndrome), is a rare hereditary condition of dysfunctional telomere maintenance that is regarded as a potentially malignant disorder. A higher frequency of oral cancers is noted among patients affected by this condition (Bongiorno, Rivard, Hammer, & Kentosh, 2017). The pathogenesis is attributed to mutations of several genes that help maintain telomere structure and function, such as the DKC1 gene. DKC1 gene encodes for the ribonucleoprotein dyskerin (Abdel-Karim et al., 2009; Ballew & Savage, 2013). Most cases are inherited, and may be X-linked, autosomal dominant or autosomal recessive, with variable penetrance (Handley & Ogden, 2006). The condition often arises early and should always be considered and excluded in a child presenting with oral leukoplakia. It consists of the triad of oral leukoplakias (usually on the dorsal tongue but can arise in any mucous membranes within the body), hyperpigmentation of the skin (usually with a reticular pattern on the neck) and nail dystrophy (Ogden, Connor, & Chisholm, 1988). Lichenoid like lesions have also been reported (Handley & Ogden, 2006). The prognosis is often poor, due to either malignant change within the oral lesions or bone marrow failure resulting in overwhelming infection and death. Attempts have been made to identify potential markers for future cancerous change within these oral lesions. Evidence for disturbed cytokeratin, abnormal p53 expression and changes at an ultrastructural level (foetal/neonatal features) have been reported some 10 years before malignant change (McKay, Ogden, & Chisholm, 1991; Ogden, Chisholm, Hopwood, & Lane, 1993).

## 4. CONDITIONS NEWLY ADDED IN 2020 CLASSIFICATION

### 4.1 Oral lichenoid Lesions (OLL)

Oral lichenoid lesions (OLL) lack the typical clinical or histological appearance of OLP ie they may not be symmetrical and could be unilateral. According to van der Meij & van der Waal, (2003), OLL would be those disorders that do not present the clinical and / or histopathological characteristics considered typical (but compatible) with OLP. Oral lichenoid lesions include (a) atypical OLP and unilateral lichenoid lesions (as characterised by van der Meij et al 1999; van der Meij & van der Waal, 2003; van der Meij , Mast , van der Waal, 2007), (b) those in close contact relationship to a dental restoration, often amalgam, referred to as oral lichenoid contact reactions (OLCR) (Al-Hashimi et al., 2007; McParland & Warnakulasuriya, 2012), (c) lichenoid drug- reactions (LDR) (Al-Hashimi et al., 2007), (e) oral lesions following intake of food or some substances, like cinnamon, and (f) oral lesions of graft versus host disease. Furthermore, lichenoid contact reactions to betel quid (BQ) are reported among BQ users (Reichart & Warnakulasuriya, 2012).

It is a diagnostic challenge to clinically distinguish OLL from OLP. Recently, Aguirre-Urizar et al., (2020) proposed grouping OLP and OLLs under the term “oral lichenoid disease”, which they define as a potentially malignant disorder of the oral mucosa that cannot be clinically or histopathologically diagnosed as any other specific oral disease. Oral lichenoid diseases encompass both OLP and OLL and characteristically show white papules (and reticular formation) and are sometimes accompanied by other types (erosive-ulcerative, atrophic, plaque, and bullous). Gonzalez Moles et al., (2019) also argues for abandoning the term OLL as defined by van der Meij & van der Waal, (2003). The evidence from their systematic review suggests that patients with OLL, have more or less similar malignant potential to OLP (Gonzalez-Moles et al., 2019).

Importantly, the current Working Group recommends health professionals refrain from using the term ‘oral lichenoid dysplasia’ to describe an entity amongst OLP or lichenoid disorders which show dysplastic changes. If dysplasia is present, the diagnosis should be oral epithelial dysplasia with lichenoid features (ie if the latter features are indeed evident) or OLP with dysplasia. Additional details regarding this topic are reported by Kujan et al., (2021) in this volume.

### 4.2 Oral graft versus host disease (OGVHD)

OGVHD is reported in patients with haematologic malignancies receiving allogeneic stem cell transplants (Elad, Zadik, Caton, & Epstein, 2019). They present in acute and chronic forms that

usually involve several organs (Flowers, Kansu, & Sullivan, 1999). Oral lesions with a lichenoid appearance, erythema, atrophy, and ulceration were reported in more than 90% of patients who suffered from GVHD (Schubert et al., 1984; Fricain et al., 2005). Since our previous Workshop Report on OPMDs (Warnakulasuriya et al., 2007), progression to cancer in OGVHD-related oral lichenoid lesions has subsequently been reported in several case studies (Demarosi, 2005; Mawardi et al., 2011; Frydrych, Kujan, & Farah, 2019; Hashimoto, Nagao, Koie, Miyabe & Saito, 2019). Atsuta et al., (2014) analysed a data base of 17,545 adult recipients of an allogeneic stem cell transplantation between 1990 and 2007 in Japan. Multi-system chronic graft-versus-host disease (GVHD) was a significant risk factor for the development of all solid tumours (RR=1.8, P<0.001), significantly higher for oral cancer (RR=2.9, P<0.001) among patients after 1-year post-transplant. The possible role of immunosuppressant therapy for chronic graft-versus-host disease on the development of oral squamous cell carcinoma needs consideration (de Araújo et al., 2014).

## 5. DISORDERS WITH LIMITED OR INSUFFICIENT EPIDEMIOLOGICAL EVIDENCE FOR MALIGNANT POTENTIAL.

The current literature refers to three other disorders that are probably associated with an increased frequency of oral cancers; epidermolysis bullosa, chronic hyperplastic candidosis and exophytic verrucous hyperplasia

We describe here the available evidence and highlight the controversies surrounding these disorders:

### a. Disorders with limited epidemiological evidence of malignant potential.

*5.1 Oral epidermolysis bullosa*

Epidermolysis bullosa was included as a potentially malignant disorder in our 2007 classification of OPMDs. A specific potentially malignant oral lesion associated with epidermolysis bullosa is not well characterized in the literature. Squamous cell carcinomas are common in sun exposed areas among patients with recessive dystrophic type of epidermolysis bullosa (RDEB). A review by Wright, (2010) includes case reports of oral SCCs, particularly among individuals with severe generalized RDEB.

### b. Disorders with insufficient epidemiological evidence

The Working Group reviewed the available evidence on the following disorders and found insufficient evidence for their malignant potential. At present, these are not recommended for inclusion within the OPMD group of disorders.

*5.2 Chronic hyperplastic candidosis (CHC)*

CHC presents as an adherent white patch caused by a chronic fungal infection, usually *Candida albicans* (Farah et al., 2019). The clinical presentation is thick white plaques, or mixed red and nodular non-homogenous white patches most commonly involving the anterior buccal mucosae and commissures or on the dorsum of the tongue (Dilhari et al., 2016). There is some experimental evidence that *Candida* causes epithelial hyperproliferation (Sitheeque & Samaranayake, 2003; Rast, Kullas, Southern, & Davis, 2016). It is known that *C. albicans* dramatically modifies the clinical and histological aspects of oral white plaques commonly referred to as candida leukoplakia. *Candida* is frequently present in the biopsies of moderate and severe dysplasia and significant dysplastic changes are noted in the epithelium of candida leukoplakias harbouring *Candida* species (McCullough et al., 2002; Shukla et al., 2019). It is postulated that *Candida*-related oral carcinogenesis could arise from acetaldehyde production from alcoholic beverages by specific *Candida* isoforms (Alnuaimi et al., 2016). Candidalysin - a cytolytic peptide toxin secreted by C. albicans – by interacting with Epithelial Growth Factor Receptors (EGFR) could activate human EGF pathways to produce increased cell proliferation (Ho et al., 2019).

The distinction between candida leukoplakia and chronic hyperplastic candidosis is not clear and most authors consider these two terms synonymous. The first description of candidal leukoplakia was published by Cawson & Lehner, (1968) and reviewed by Sitheeque & Samaranayake, (2003). Both sets of authors emphasize that the lesions responded readily to antifungal treatment, which supports a causal relationship. Nevertheless, it must be noted that whilst many cases improve with antifungal treatment, they do not disappear completely. The current Working Group noted that it is important to have consistency in the way we use these two terms and that antifungal treatment should be part of the diagnostic process.

A recent systematic review on “candida leukoplakia” (Shukla et al., 2019) identified 3 studies quoting malignant transformation ratios of 2.5%, 6.5% and 28.7%: such a wide range implies inconsistent diagnostic criteria. The definition of leukoplakia excludes specific causes and the Working Group noted that candidal leukoplakia was now a deprecated term.

*5.3 Exophytic verrucous hyperplasia)/Oral verrucous hyperplasia*

Verrucous hyperplasia of the oral mucosa - a relatively unrecognized entity that may resemble verrucous carcinoma both clinically and histologically was first described by Shear and Pindborg, (1980). VH was considered a precurser of verrucous carcinoma (Batsakis et al., 1999). A new entity was proposed by a group of South Asian pathologists to describe a "mass type" lesion with an exophytic and verrucous appearance specifically recognised among areca nut and betel quid users (Zain et al., 2016; Patil, Warnakulasuriya, Raj, Sanketh, & Rao, 2016). This disorder was first noted in Taiwanese patients diagnosed with OPMDs (Wang et al., 2009) and the name proposed by these authors was *oral verrucous hyperplasia*. A second cohort was described later by the same group amongst which 6 (10%) developed an oral cancer (Wu et al., 2018). This disorder can present in two forms: 1) as an exophytic, fleshy verruco-papillary outgrowth with a white and/or pink surface colour or 2) as a white, plaque-like exophytic verrucous lesion. It typically manifests as a discrete or solitary lesion and may co-exist in patient presenting with oral submucous fibrosis. The clinical presentation could masquerade as a squamous cell carcinoma or verrucous carcinoma. Absence of deep induration is a cardinal feature.

Hsue et al., (2007) reported on a group of 1458 Taiwanese patients with OPMDs and based on clinical and histopathologic criteria 324 (22%) were classified as oral verrucous hyperplasia: 10 patients developed malignancies during a mean follow-up time of 43 months. Wang et al., (2014) reporting on 5071 southern Taiwanese patients from Kaohsiung city diagnosed with OPMDs, described the clinical presentation of 869 OVH patients, 59 of whom (6.79%) developed cancer in a follow up period of 33.5 months. Cancers were found mostly on the buccal mucosa, but the lower lip, dorso-lateral surfaces of the tongue, soft palate and gingiva were also affected. The clinical and histological diagnostic criteria for oral verrucous hyperplasia aka oral exophytic verrucous hyperplasia (OEVH) are outlined by Zain et al., (2016). A high proportion of these disorders in Taiwanese subjects demonstrated OED at the initial histopathological investigation and a proportion developed oral cancer at the sites of the presenting lesion. Recent reports on exophytic/oral verrucous hyperplasia proposed that this disorder be regarded as an OPMD (Hsue et al., 2007; Wang et al., 2009; Wang et al., 2014; Zain et al., 2016; Patil et al., 2016; Wu et al., 2018). Several cases presented at a workshop held in Kuala Lumpur (Zain et al., 2016) have provided new evidence that these may arise as a secondary lesion in patients with oral submucous fibrosis (Shah, Bansal, Shirsat, Prasad, & Desai, 2019). Having considered the recent publications describing these disorders the

Working Group was of the opinion that it would be desirable to obtain more follow up data from several countries in regions where betel quid chewing is common. The Working Group recommends the term OEVH rather than OVH for this apparent entity.

## 6. CARCINOMAS ARISING IN PATIENTS WITH OPMDs

The most common histopathological diagnosis reported for a cancer arising in a patient with an OPMD is a conventional squamous cell carcinoma. OPMDs are a heterogeneous and have variability in their ratios of progression to cancer (1.4% - 49.5%) over a follow-up period ranging from 12 months to 20 years) (Iocca et al., 2019). Predicting the risk of transformation remains a significant challenge even in specialist practice. At one end of the spectrum patients diagnosed with PVL and erythroplakia show high frequencies of cancer development (close to 30-50%), and on the other hand, oral lichen planus (OLP) show lower frequencies of cancer development (1-2%). Oral leukoplakia has a variable risk with non-homogeneous forms showing higher risk compared with homogeneous leukoplakia. The presence and grade of epithelial dysplasia has shown prognostic utility in stratifying the risk of cancer development. In a meta-analysis Mehanna et al., (2009) have shown that higher grades of dysplasia have significantly higher frequencies of cancer development. Techniques such as ploidy assessment when combined with dysplasia grading may refine the prediction of risk (Alaizari, Sperandio, Odell, Peruzzo, & Al-Maweri, 2018). Accompanying publications in this volume discuss in greater detail cancer development in patients with OPMDs, pathology tools, biomarkers and how ploidy analysis may assist in stratifying risk. The biomarkers currently investigated for predicting the risk are not in routine clinical use anywhere in the world.

## 7. CARCINOMA ARISING FROM CLINICALLY NORMAL MUCOSA

Malignancy can arise from an area of “normal-looking” mucosa without the patient or a clinician being aware of an OPMD being present earlier at the site. This is consistent with the concept of a field change, that apparently normal mucosa may contain significant molecular aberrations that increase the likelihood of cancer (Nikitakis et al., 2018; Thomson, Goodson, & Smith, 2017; Farah et al., 2018; Farah, Shearston, Nguyen, & Kujan, 2019).

There is a need to further investigate the basic biology associated with the concept of field cancerisation as proposed by Slaughter et al., (1953) - not least in ensuring common terminology (Ogden & Hall, 1997). Field cancerisation is characterized by phenotypic and genetic changes in the neighbouring areas of frank carcinomas, whilst the term “field change” should be reserved for alterations in tissues that show no evidence of disease clinically or

histologically (Ogden, 1998). A proliferating field that gradually displaces the normal mucosa have been detected on the basis of mutations in TP53, whereas they are usually not detected by routine diagnostic techniques (Braakhuis, Tabor, Kummer, Leemans, & Brakenhoff, 2003; Braakhuis, Leemans, & Brakenhoff, 2005). Thus, the identification of a marker usually associated with malignant disease would signify a field change effect in the absence of histomorphological evidence of dysplasia. Such patients may not have yet developed nor indeed may never develop a tumour.

Currently available adjunctive tools (Rashid & Warnakulasuriya, 2015; Kerr, 2020) have not been adequately researched to test whether the new optical devices are able to identify these occult lesions within field changes. However, evidence for field change, based on a variety of markers (eg cytokeratins, p53 and markers of angiogenesis) have been identified within biopsies of clinically normal mucosa from oral cancer patients (Ogden, Chisholm, Hopwood, Lane, 1993, Ogden, Chisholm, Morris & Stevenson , 1997, El Gazzar, Macluskey, & Ogden, 2005), and using exfoliative cytology (eg cytomorphology, cytokeratins (Ogden, 1997). However, a reliable marker that can predict future malignant change in every case has yet to be found. Future molecular techniques might make these invisible changes detectable but further research is needed.

## 8. SYNDROMES THAT MAY POTENTIATE CANCER DEVELOPMENT IN THE ORAL CAVITY

Close to 20 familial cancer syndromes are described and people born with inherited genetic predispositions develop haematological malignancies and solid cancers at a younger age and with a relatively high frequency. Important examples are Fanconi anaemia, xeroderma pigmentosum, Li Fraumeni syndrome, Blooms's syndrome, ataxia-telangiectasia and Cowden syndrome.

Many of these syndromes are caused by alterations in tumour suppressor genes, or DNA repair genes that can be broadly divided into two groups, called gatekeepers and caretakers respectively. Prime et al., (2001) examined whether there is an increase in the incidence of oral cancer in inherited cancer syndromes and whether the genes that are known to be relevant to the pathogenesis of these cancer syndromes also play a role in the development and behaviour of oral cancer. These authors provide a comprehensive list of gatekeeper genes associated with several hereditary cancer syndromes (Prime, Thakker, Pring, Guest, & Paterson, 2001).

Of the many familial cancer syndromes described, Fanconi Anaemia has the strongest evidence for a predisposition for oral cancer and a short description appears below:

### 8.1 Fanconi anaemia (FA)

An increased susceptibility of Fanconi anaemia (FA) patients to early-onset OSCCs - largely in the absence of known life-style risk factors - has been observed for decades. Fanconi anaemia (FA) is a rare autosomal recessive disorder of DNA repair genes in which the defect(s) lie in the repair of DNA crosslinks. It is characterized by physical congenital anomalies (skeletal malformations), aplastic anaemia, and then progressive pancytopenia. FA may lead to bone marrow failure, leukemia, and/or solid tumours, including head and neck cancers, with oral squamous cell carcinoma being the most common type. Recently there has been renewed interest among researchers on development of OSCCs in FA. Masserot et al., (2008) described head and neck squamous cell carcinoma in 13 patients (8 in oral cavity) with Fanconi anemia after hematopoietic stem cell transplantation. In a systematic review Furquim et al., (2018) identified a total of 121 individuals affected by FA and OSCC among 47 published from 1970 to 2016. The tongue was the most affected site. The overall risk was estimated to increase 500 to 700-fold for head and neck cancer in FA patients compared to the general population (Kutler et al., 2003) and the majority developed carcinomas at an early age. Therefore, young people who develop HNSCC must receive FA diagnostic tests. Patients with FA can present with potentially malignant disorders, especially oral leukoplakia (Amenábar, Torres-Pereira ,Tang, & Punyadeera, 2019). Among 138 Brazilian patients with FA who had not undergone hematopoietic stem cell transplantation (HSCT), 16 cases (12%) were diagnosed with oral leukoplakia, with a median age of 16.5 years (Cavalcanti et al., 2015)

### 8.2 Plummer-Vinson syndrome

Plummer-Vinson (Paterson-Kelly) syndrome (PVS) - a constellation of symptoms relating to postcricoid oesophageal webs, atrophic glossitis, koilonychia, and dysphagia considered to be caused by microcytic hypochromic anaemia - was linked to predisposition to upper digestive tract cancer. Barron, (1991) claimed in an analysis of a Welsh cohort that this syndrome no longer existed. Anaemia causes atrophy of the oral epithelium (Rennie et al., 1984; Ranasinghe et al., 1987) and could be a co-factor among people with OPMDs and deserves attention in future research.

## 9. OTHER TERMINOLOGIES

It has recently been suggested to replace the term OPMD with: "potentially premalignant oral epithelial lesion (PPOEL)" (Nikitakis, 2018; van der Waal, 2018). The terminology, *oral potentially malignant disorders,* is now well established in the literature with over 750 publications and the Working Group could not see any reason for change. Both in the 2007 paper, and here, we argue distinction between the terms "potentially malignant" and "premalignant": the former indicates an unknown potential for the later development of a malignant tumour; the latter an inevitability given sufficient time. "Potentially premalignant" may indicate lack of premalignancy. Moreover, changes observed in histology are not limited to epithelium and therefore "epithelial lesion" is inappropriate. Epithelial-connective tissue interactions are fundamental to homeostasis and disease and connective tissue changes are a striking component of many disorders (Vucicevic Boras et al., 2018; Johnson, 2020), including in oral lichen planus and oral submucous fibrosis (OSMF) (Arakeri et al., 2018; Lodi et al., 2005).

## 10. IMPLICATIONS FOR RESEARCH

- The complete natural history of the individual OPMDs is yet to be confirmed
- There is a need for further research to identify the potential risk of cancer in patients with different OPMDs based on strict clinicopathological diagnostic criteria.
- There is a need to better understand the number of oral cancer cases developing from apparently normal oral mucosa.
- There is a need to elucidate the role (if any) of Candida infection in dysplastic tissues.
- The role of immunosuppression in GVHD towards the development of oral cancer needs study.
- There is a need to identify molecular differences between homogenous and non-homogenous leukoplakias, and dysplastic and non-dysplastic leukoplakias.
- There is a need to identify reliable molecular predictive and prognostic biomarkers to guide personalized management of OPMDs as the current model to estimate the risk of malignant transformation is based only on clinical and histopathological features of the observed mucosal changes.
- The Working Group reiterates the need for good quality longitudinal studies, assembling cases by the precise clinicopathological criteria defined here, gathering extensive metadata on demography and risk factors, and analyzing follow-up data appropriately. Studies with inconsistent designs should not be pooled.

## 11. CONCLUSIONS

This paper provides an update on the 2007 WHO Collaborating Centre's classification of oral potentially malignant disorders. The Working Group identified sufficient evidence on oral lichenoid lesions and oral graft versus host disease that merit their addition to the classification proposed in 2007. The natural history and the biological behaviour of many OPMDs remain unknown and there was consensus that further research on these disorders is warranted. A global research consortium to study OPMDs is needed to establish multi-site longitudinal studies with well-defined clinicopathological diagnostic criteria to address questions and characterise their natural history, and possibly to prevent development of oral cancer in patients diagnosed with these disorders.

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## DISCLOSURES

The authors filed detailed disclosure of potential conflicts relevant to the workshop topics, and none were declared.

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## REFERENCES

Abdel-Karim, A., Frezzini, C., Viggor, S., Davidson, L.E., Thornhill, M.H., & Yeoman, C.M. (2009). Dyskeratosis congenita: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*,*108*, e20-e24.

Aghbari, S. M. H., Abushouk, A. I., Attia, A., Elmaraezy, A., Menshawy, A., Ahmed, M. S., & Ahmed, E. M. (2017). Malignant transformation of oral lichen planus and oral lichenoid lesions: A meta-analysis of 20095 patient data. *Oral Oncol, 68*, 92-102.

Aguirre-Urizar, J. M. (2011). Proliferative multifocal leukoplakia better name that proliferative verrucous leukoplakia. *World J Surg Oncol*, 9, 122.

Aguirre-Urizar, J.M., Alberdi-Navarro, J., Lafuente-Ibáñez de Mendoza, I., Marichalar-Mendia, X., Martínez-Revilla, B., Parra-Pérez. C., Juan-Galíndez, A-D., & Echebarria-Goicouria, M-A. (2020). Clinicopathological and prognostic characterization of oral lichenoid disease and its main subtypes: A series of 384 cases. *Med Oral Patol Oral Cir Bucal, 25*(4), e554-e562.

Alaizari, N.A., Sperandio, M., Odell, E.W., Peruzzo, D.,& Al-Maweri, S.A. (2018). Meta-analysis of the predictive value of DNA aneuploidy in malignant transformation of oral potentially malignant disorders. *J Oral Pathol Med, 47*(2), 97-103. doi:10.1111/jop.12603.

Al-Hashimi, I., Schifter, M., Lockhart, P. B., Wray, D., Brennan, M., Migliorati, C. A., . . . van der Waal, I. (2007). Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 103 Suppl*, S25 e21-12. doi:10.1016/j.tripleo.2006.11.001

Alnuaimi, A. D., Ramdzan, A. N., Wiesenfeld, D., O'Brien-Simpson, N. M., Kolev, S. D., Reynolds, E. C., & McCullough, M. J. (2016). Candida virulence and ethanol-derived acetaldehyde production in oral cancer and non-cancer subjects. *Oral Dis, 22*(8), 805–814.

Amenábar, J.M., Torres-Pereira, C.C, Tang, K.,& Punyadeera, C.(2019). Two enemies, one fight: An update of oral cancer in patients with Fanconi anemia. *Cancer,* 125(22):3936-3946

Arakeri, G., Thomas, D., Aljabab, A. S., Hunasgi, S., Rai, K. K., Hale, B., . . . Brennan, P. A. (2018). TFM classification and staging of oral submucous fibrosis: A new proposal. *J Oral Pathol Med, 47*(4), 403-409.

Arvanitidou, I.E., Nikitakis, N.G., Georgaki, M., Papadogeorgakis, N., Tzioufas, A., & Sklavounou, A. (2018) Multiple primary squamous cell carcinomas of the lower lip and tongue arising in discoid lupus erythematosus: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol*, *125*(2), e22-e30.

Atsuta, Y., Suzuki, R., Yamashita, T., Fukuda, T., Miyamura,K., Taniguchi, S. …..Y Kodera, Japan Society for Hematopoietic Cell Transplantation. (2014). Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease. *Ann Oncol*, *25*(2):435-441.

Axell, T., Holmstrup, P., Kramer, I. R. H., Pindborg, J. J., & Shear, M. (1984). International seminar on oral leukoplakia and associated lesions related to tobacco habits. *Community Dent Oral Epidemiol, 12*(3), 145-154.

Axell, T., Pindborg, J. J., Smith, C. J., & van der Waal, I. (1996). Oral white lesions with special reference to precancerous and tobacco- related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18-21 1994. International Collaborative Group on Oral White Lesions. *J Oral Pathol Med, 25*(2), 49-54.

Auluck, A.,& Pai, K.M. (2005). (Mis)Interpretations of leukoplakia. *J Can Dent Assoc*, *71*(4), 237-238.

Bagan, J., Murillo-Cortes, J., Poveda-Roda, R., Leopoldo-Rodado, M., & Bagan, L. (2019). Second primary tumors in proliferative verrucous leukoplakia: a series of 33 cases. *Clin Oral Investig*, *24*(6), 1963-1969. doi: 10.1007/s00784-019-03059-9.

Baillie,S, Simms,W. (1806) Queries and responses from the Medical Committee of the Society for Investigating the Nature and Cure of Cancer. Edinburgh Med Surg J 1806; 2: 382-389.

Ballew, B.J.& Savage, S.A. (2013) Updates on the biology and management of dyskeratosis congenita and related telomere biology disorders. *Expert Rev Hematol*, *6*(3), 327-337

Baron, J.H. (1991). The Paterson-Brown Kelly syndrome of sideropenic dysphagia does not exist. *J R Coll Physicians Lond, 25*(4), 361.

Batsakis, J.G., Suarez, P., & El-Naggar, A.K. (1999). Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol*, *35*(4), 354-359.

Bharath, T. S., Kumar, N. G., Nagaraja, A., Saraswathi, T. R., Babu, G. S., & Raju, P. R. (2015). Palatal changes of reverse smokers in a rural coastal Andhra population with review of literature. *J Oral Maxillofac Pathol, 19*(2), 182-187.

Bongiorno, M., Rivard, S., Hammer, D., & Kentosh, J. (2017). Malignant transformation of oral leukoplakia in a patient with dyskeratosis congenita. *Oral Surg Oral Med Oral Pathol Oral Radiol, 124*(4):e239-e242.

Braakhuis, B.J., Tabor, M.P., Kummer, J.A., Leemans, C.R., & Brakenhoff, R.H. (2003). A genetic explanation of Slaughter's concept of field cancerization: evidence and clinical implications. *Cancer Res, 63*(8), 1727-1730.

Braakhuis, B. J., Leemans, C. R., & Brakenhoff, R. H. (2005). Expanding fields of genetically altered cells in head and neck squamous carcinogenesis. *Semin Cancer Biol, 15*(2), 113-120. doi:10.1016/j.semcancer.2004.08.004

Cabay, R. J., Morton, T. H., Jr., & Epstein, J. B. (2007). Proliferative verrucous leukoplakia and its progression to oral carcinoma: a review of the literature. *J Oral Pathol Med, 36*(5), 255-261.

Carrard, V.C., Brouns, E.R., & van der Waal, I. (2013). Proliferative verrucous leukoplakia; a critical appraisal of the diagnostic criteria. *Med Oral Patol Oral Cir Bucal*. *18*(3), e411-e413.

Carrozzo, M., Porter, S., Mercadante, V., & Fedele, S. (2019). Oral lichen planus: A disease or a spectrum of tissue reactions? Types, causes, diagnostic algorhythms, prognosis, management strategies. *Periodontol 2000*. *80,* 105– 125. https://doi.org/10.1111/prd.12260

Cavalcanti, L.G., Lyko, K.F., Araújo, R..L, Amenábar, J.M., Bonfim, C., & Torres-Pereira, C.C. (2015). Oral leukoplakia in patients with Fanconi anaemia without hematopoietic stem cell transplantation. *Pediatr Blood Cancer, 62*(6), 1024-1026.

Cavalcante, A.S., Anbinder, A.L., & Carvalho, Y.R. (2008). Actinic cheilitis: clinical and histological features. *J Oral Maxillofac Surg, 66*(3):498-503.

Cawson, R.A., & Lehner, T. (1968). Chronic hyperplastic candidiasis--candidal leukoplakia. *Br J Dermatol, 80*(1), 9-16.

Cerero-Lapiedra, R., Balade-Martinez, D., Moreno-Lopez, L. A., Esparza-Gomez, G., & Bagan, J. V. (2010). Proliferative verrucous leukoplakia: a proposal for diagnostic criteria. *Med Oral Patol Oral Cir Bucal, 15*(6), e839-845.

Cheng, Y. S., Gould, A., Kurago, Z., Fantasia, J., & Muller, S. (2016). Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. *Oral Surg Oral Med Oral Pathol Oral Radiol, 122*(3), 332-354. doi:10.1016/j.oooo.2016.05.004

Damm, D.D., Curran, A., White, D.K., & Drummond, J.F. (1999). Leukoplakia of the maxillary vestibule—an association with Viadent?. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 87,* 61–66.

Dancyger, A., Heard, V., Huang, B., Suley, C., Tang, D., & Ariyawardana, A. (2018). Malignant transformation of actinic cheilitis: A systematic review of observational studies. *J Invest Clin Dent*. *9*, e12343. https://doi.org/10.1111/jicd.12343

de Araújo, R.L., Lyko, K.de F., Funke, V.A., & Torres-Pereira, C.C.(2014). Oral cancer after prolonged immunosuppression for multiorgan chronic graft-versus-host disease. *Rev Bras Hematol Hemoter, 36*(1):65-68. doi:10.5581/1516-8484.20140016

de Santana Sarmento D.J., da Costa Miguel, M.C., Queiroz, L.M., Godoy, G..P, & da Silveira, E.J. (2014). Actinic cheilitis: clinicopathologic profile and association with degree of dysplasia. *Int J Dermatol, 53*(4), 466-72. doi: 10.1111/ijd.12332

Demarosi, F., Soligo, D., Lodi, G., Moneghini, L., Sardella, A., & Carrassi, A. (2005) Squamous cell carcinoma of the oral cavity associated with graft versus host disease: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 100*(1), 63-69.

Dilhari, A., Weerasekera, M. M., Siriwardhana, A., Maheshika, O., Gunasekara, C., Karunathilaka, S., . . . Fernando, N. (2016). Candida infection in oral leukoplakia: an unperceived public health problem. *Acta Odontol Scand, 74*(7), 565-569. doi:10.1080/00016357.2016.1220018

Diz, P., Gorsky, M., Johnson, N.W, Kragelund, C., Manfredi, M., Odell, E., Thongprasom, K., Warnakulasuriya, S.. van der Waal, I. (2011). Oral leukoplakia and erythroplakia: a protocol for diagnosis and management. EAOM– Diagnostic and therapeutic protocols 2011; 1: 1-8. Available from: http://www. Eaomedicine.com/webhtml/002/001/001.pdf.

Elad, S., Zadik, Y., Caton, J.G., & Epstein, J.B.(2019). Oral mucosal changes associated with primary diseases in other body systems. *Periodontol 2000, 80*(1), 28-48.

El-Gazzar, R., Macluskey, M., & Ogden, G.R. (2005). Evidence for a field change effect based on angiogenesis in the oral mucosa? A brief report. *Oral Oncol, 41,* 25-30.

Eversole, L.R., Eversole, G.M., & Kopcik, J. (2000). Sanguinaria-associated oral leukoplakia: comparison with other benign and dysplastic leukoplakic lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 89(4),* 455-64.

Farah, C. S., Jessri, M., John, K., Lalla, Y., Vu, A., & Kujan, O. (2018). Clinical features and diagnosis. In J. P. Shah & N. W. Johnson (Eds.), *Oral and Oropharyngeal Cancer* (2nd Edition ed., pp. 100-112.): CRC Press.

Farah, C. S., Kujan, O., Prime, S., & Zain, R. B. (2019). Oral Mucosal Malignancies. In C. S. Farah, R. Balasubramaniam, & M. J. McCullough (Eds.), *Contemporary Oral Medicine: A Comprehensive Approach to Clinical Practice* (pp. 1249-1436). Cham: Springer International Publishing.

Farah, C. S., Shearston, K., Nguyen, A. P., & Kujan, O. (2019). Oral Carcinogenesis and Malignant Transformation. In P. A. Brennan, T. Aldridge, & R. C. Dwivedi (Eds.),

*Premalignant Conditions of the Oral Cavity* (pp. 27-66). Singapore: Springer Singapore.

Farah, C. S., Woo, S. B., Zain, R. B., Sklavounou, A., McCullough, M. J., & Lingen, M. (2014). Oral cancer and oral potentially malignant disorders. *Int J Dent, 2014*, 853479. doi:10.1155/2014/853479

Fernandez Figueras, M.T.(2017). From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. *J Eur Acad Dermatol Venereol, Suppl 2*, 5-7. doi:10.1111/jdv.14151

Flowers, M. E., Kansu, E., & Sullivan, K. M. (1999). Pathophysiology and treatment of graft-versus-host disease. *Hematol Oncol Clin North Am, 13*(5), 1091-1112, viii-ix. doi:10.1016/s0889-8588(05)70111-8

Fricain, J. C., Sibaud, V., Hafian, H., Deminiere, C., Taieb, A., & Boiron, J. M. (2005). Oral manifestations of chronic graft-versus-host disease. *Ann Dermatol Venereol, 132*(12 Pt 1), 1017-1025. doi:10.1016/s0151-9638(05)79574-0

Fritsch, A., Loeckermann, S., Kern, J. S., Braun, A., Bösl, M. R., Bley, T. A., Schumann, H., ….Bruckner-Tuderman, L. (2008). A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. *J Clin Invest, 118*(5), 1669–1679.

Furquim, C.P., Pivovar, A., Amenábar, J.M., Bonfim, C., &Torres-Pereira, C.C. (2018). Oral cancer in Fanconi anemia: Review of 121 cases. *Crit Rev Oncol Hematol*, *125*, 35-40. doi:10.1016/j.critrevonc.2018.02.013

Frydrych, A. M., Kujan, O., & Farah, C. S. (2019). Chronic disease comorbidity in patients with oral leukoplakia. *Oral Cancer, 3*(1), 17-26. doi:10.1007/s41548-018-0015-y

Garcia-Pola, M.J., Llorente-Pendás, S., González-Garcia, M., & García-Martín, J.M. (2016). The development of proliferative verrucous leukoplakia in oral lichen planus. A preliminary study. *Med Oral Patol Oral Cir Bucal*, *21*(3), e328-34.

Gonzalez-Moles, M. A., Ruiz-Avila, I., Gonzalez-Ruiz, L., Ayen, A., Gil-Montoya, J. A., & Ramos-Garcia, P. (2019). Malignant transformation risk of oral lichen planus: A systematic review and comprehensive meta-analysis. *Oral Oncol, 96*, 121-130. doi:10.1016/j.oraloncology.2019.07.012

Gupta, P.C., Mehta, F.S., Daftary, D.K., Pindborg, J.J., Bhonsle, R.B., Jalanwalla, P.N.,…..Mehta, M.N. (1980). Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. *Community Dent Oral Epidemiol, 8, 287*–333.

Handley, T. P., & Ogden, G. R. (2006). Dyskeratosis congenita: oral hyperkeratosis in association with lichenoid reaction. *J Oral Pathol Med*, *35*(8), 508–512. https://doi.org/10.1111/j.1600-0714.2006.00434.x

Hansen, L. S., Olson, J. A., & Silverman, S., Jr. (1985). Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol, 60*(3), 285-298. doi:10.1016/0030-4220(85)90313-5

Hashimoto, K., Nagao, T., Koie, S., Miyabe, S., & Saito, T.(2019). Secondary squamous cell carcinoma of the tongue complicated with bronchiolitis obliterans as a manifestation of graft-versus-host disease following peripheral blood stem cell transplantation. *Case Rep Hematol.* 6015803.

Ho, J., Yang, X., Nikou, S.A., Kichik, N., Donkin, A., Ponde, N.O., Richardson, J.P.... Naglik, J.R. (2019). Candidalysin activates innate epithelial immune responses via epidermal growth factor receptor. *Nat Commun, 10*(1):2297

Holmstrup, P., Vedtofte, P., Reibel, J., & Stoltze, K. (2006). Long-term Treatment Outcome of Oral Premalignant Lesions. *Oral Oncol,* 42(5):461-74.

Hsue, S. S., Wang, W. C., Chen, C. H., Lin, C. C., Chen, Y. K., & Lin, L. M. (2007). Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. *J Oral Pathol Med, 36*(1), 25-29. doi:10.1111/j.1600-0714.2006.00491.x

Idrees, M., Kujan, O., Shearston, K., & Farah, C. S. (2020). Oral lichen planus has a very low malignant transformation rate: A systematic review and meta-analysis using strict diagnostic and inclusion criteria. *J Oral Pathol Med*. doi:10.1111/jop.12996

Iocca, O., Sollecito, T. P., Alawi, F., Weinstein, G. S., Newman, J. G., De Virgilio, A., . . . Shanti, R. M. (2020). Potentially malignant disorders of the oral cavity and oral dysplasia: A systematic review and meta-analysis of malignant transformation rate by subtype. *Head Neck. 42*(3), 539-555. doi:10.1002/hed.26006

Johnson, N.W. (2017) The Biology and Pathology of Squamous Cell Carcinomata in the Head and Neck. In. Warnakulasuriya, S. & Khan, Z. (Eds.) *Squamous Cell Carcinoma-Molecular Therapeutic Targets*. pp 1-36, Springer. Berlin

Johnson, N.W. (2020) Cancer Biology and Carcinogenesis: Fundamental Biological Processes and How They Are Deranged in Oral Cancer. In: Warnakulasuriya, S.& Greenspan, J.S. (Eds.) *Textbook of Oral Cancer Prevention, Diagnosis and Management* pp 399-425, Springer; Berlin.

Kerr, A. R. (2020). Diagnostic Adjuncts for Oral Cavity Squamous Cell Carcinoma and Oral Potentially Malignant Disorders. In: Warnakulasuriya, S.& Greenspan, J.S. (Eds.) *Textbook of Oral Cancer Prevention, Diagnosis and Management* pp 99-117, Springer; Berlin.

Kerr, A. R., Warnakulasuriya, S., Mighell, A. J., Dietrich, T., Nasser, M., Rimal, J., . . . Johnson, N. W. (2011). A systematic review of medical interventions for oral submucous fibrosis and future research opportunities. *Oral Dis, 17 Suppl 1*, 42-57. doi:10.1111/j.1601-0825.2011.01791.x

Kramer, I.R., El-Labban, N., & Lee, K.W. (1978a). The clinical features and risk of malignant transformation in sublingual keratosis. *Br Dent J, 144(6),* 171-80.

Kramer, I. R., Lucas, R. B., Pindborg, J. J., & Sobin, L. H. (1978b). Definition of leukoplakia and related lesions: an aid to studies on oral precancer. *Oral Surg, Oral Med, Oral Pathol, 46*(4), 518-539.

Krutchkoff, D. J., Cutler, L., & Laskowski, S. (1978). Oral lichen planus: the evidence regarding potential malignant transformation. *J Oral Pathol, 7*(1), 1-7.

Kutler DI, Auerbach AD, Satagopan J, Giampietro PF, Batish SD, Huvos AG, Goberdhan A, Shah JP, & Singh B. (2003). High incidence of head and neck squamous cellcarcinoma in patients with Fanconi anemia. *Arch Otolaryngol Head Neck Surg*, *129*(1):106-12. doi: 10.1001/archotol.129.1.106. PMID: 12525204.

Lee, J.J., Hung, H.C., Cheng, S.J., Chen, Y.J., Chiang, C.P., Liu, B.Y., Jeng, J.H., … Kok, S.H. (2006). Carcinoma and dysplasia in oral leukoplakias in Taiwan: prevalence and risk factors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 101*(4), 472-80.

Lee, C. H., Ko, A. M., Warnakulasuriya, S., Ling, T. Y., Sunarjo, Rajapakse, P. S., . . . Ko, Y. C. (2012a). Population burden of betel quid abuse and its relation to oral premalignant disorders in South, Southeast, and East Asia: an Asian Betel-quid Consortium Study. *Am J Public Health, 102*(3), e17-24. doi:10.2105/AJPH.2011.300521

Lee, C. H., Ko, A. M., Yen, C. F., Chu, K. S., Gao, Y. J., Warnakulasuriya, S., . . . Ko, Y. C. (2012b). Betel-quid dependence and oral potentially malignant disorders in six Asian countries. *Br J Psychiatry, 201*(5), 383-391. doi:10.1192/bjp.bp.111.107961

Liu, W., Zhan, Y., Wu, L., Yang, X., Shi, L. (2019). Characteristics and trends of oral leukoplakia research: A bibliometric study of the 100 most cited articles. *Medicine (Baltimore)*, *98*(27):e16293. doi: 10.1097/MD.0000000000016293.

Liu, W., Wu, L., Zhang, Y., Shi, L., & Yang, X. (2020). Bibliometric analysis of research trends and characteristics of oral potentially malignant disorders. *Clin Oral Investigation, 24(1)*, 447-454.

Lodi, G., Scully, C., Carrozzo, M., Griffiths, M., Sugerman, P. B., & Thongprasom, K. (2005). Current controversies in oral lichen planus: report of an international consensus meeting. Part 1. Viral infections and etiopathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 100*(1), 40-51. doi:10.1016/j.tripleo.2004.06.077

Markopoulos, A., Albanidou-Farmaki, E., & Kayavis, I. (2004). Actinic cheilitis: clinical and pathologic characteristics in 65 cases. *Oral Dis, 10(4),* 212-6.

Mascarenhas, A.K., Allen, C.M., Melvin L. & Moeschberger, M.L. (2002). The association between Viadent® use and oral leukoplakia-results of a matched case-control study. *J Public Health Dent*, *62*(3), 158-621.

Maher, R., Ahmed, W., Qureshi, H., Zuberi, S.J., & Syed, S. (1991). Oesophageal changes in oral submucous fibrosis using fibreoptic endoscopy- a pilot study. *J Pak Med Assoc, 41*, 312-313.

Masserot, C., de Latour, R., Rocha, V., Thierry Leblanc, T., Arnaud Rigolet A., Francis Pascal, F., ….Socié G. (2008) Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. *Cancer*, *113*(12), 3315-3322.

Mawardi, H., Elad, S., Correa, M. E., Stevenson, K., Woo, S. B., Almazrooa, S., . . . Treister, N. (2011). Oral epithelial dysplasia and squamous cell carcinoma following allogeneic hematopoietic stem cell transplantation: clinical presentation and treatment outcomes. *Bone Marrow Transplant, 46*(6), 884-891. doi:10.1038/bmt.2011.77

McCullough, M., Jaber, M., Barrett, A. W., Bain, L., Speight, P. M., & Porter, S. R. (2002). Oral yeast carriage correlates with presence of oral epithelial dysplasia. *Oral Oncol, 38*(4), 391-393.

McKay, G. S., Ogden, G. R., & Chisholm, D. M. (1991). Lingual hyperkeratosis in dyskeratosis congenita: ultrastructural findings. *J Oral Pathol Med, 20*(4), 196–199. https://doi.org/10.1111/j.1600-0714.1991.tb00921.x

McParland, H., Warnakulasuriya, S.(2012). Oral lichenoid contact lesions to mercury and dental amalgam--a review. *J Biomed Biotechnol,* 589569. doi: 10.1155/2012/589569.

Mehanna, H.M., Rattay, T., Smith, J., & McConkey, C.C. (2009). Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. *Head Neck, 31(12),* 1600-9. doi: 10.1002/hed.21131.

Mello, F.W., Melo, G., Modolo, F., & Rivero, E.R.C. (2019). Actinic cheilitis and lip squamous cell carcinoma: Literature review and new data from Brazil. *J Clin Exp Dent*, *11*(1), e62-9.

Mello, F. W., Miguel, A. F. P., Dutra, K. L., Porporatti, A. L., Warnakulasuriya, S., Guerra, E. N. S., & Rivero, E. R. C. (2018). Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. *J Oral Pathol Med, 47*(7), 633-640.

Misra, S.P., Misra, V., Dwivedi, M., & Gupta, S.C. (1998). Oesophageal subepithelial fibrosis; an extension of oral submucous fibrosis. *Postgrad Med J*, 74: 733-736.

Müller S. (2019). Frictional Keratosis, Contact Keratosis and Smokeless Tobacco Keratosis: Features of Reactive White Lesions of the Oral Mucosa. *Head and neck pathology*, *13*(1), 16–24. https://doi.org/10.1007/s12105-018-0986-3

Napier, S. S., & Speight, P. M. (2008). Natural history of potentially malignant oral lesions and conditions: an overview of the literature. *J Oral Pathol Med, 37*(1), 1-10. doi:10.1111/j.1600-0714.2007.00579.x

Nikitakis, N. G. (2018). Special focus issue on potentially premalignant oral epithelial lesions: introduction and perspective. *Oral Surg Oral Med Oral Pathol Oral Radiol, 125*(6), 575-576. doi:10.1016/j.oooo.2018.03.013

Nikitakis, N. G., Pentenero, M., Georgaki, M., Poh, C. F., Peterson, D. E., Edwards, P., . . . Sauk, J. J. (2018). Molecular markers associated with development and progression of potentially premalignant oral epithelial lesions: Current knowledge and future implications. *Oral Surg Oral Med Oral Pathol Oral Radiol, 125*(6), 650-669. doi:10.1016/j.oooo.2018.03.012

Odell E.W. (2017). Cawson's Essentials of Oral Pathology and Oral Medicine. Elsevier; 9 edition.

Ogden, G.R., Connor, E., & Chisholm, D.M.(1988). Dyskeratosis congenita: report of a case and review of the literature. *Oral Surg Oral Med Oral Pathol, 65*(5), 586–91

Ogden, G.R., Chisholm, D.M., Hopwood D., & Lane, E.B. (1993). Evidence for field change in oral cancer based on cytokeratin expression. *Brit J Cancer, 67*, 1324-1330.

Ogden, G.R.,& Hall, P.A. (1997). Field change, clonality and early epithelial cancer: possible lessons from p53. *J Pathol, 181,* 127-129.

Ogden, G.R., Chisholm, D.M., Morris, A.M., & Stevenson, J.H. (1997). Overexpression of p53 in normal oral mucosa of oral cancer patients does not necessarily predict further malignant disease. *J Pathol, 182,* 180-184.

Ogden, G.R. (1997). Potential early markers of carcinogenesis in the mucosa of the head and neck using exfoliative cytology. *J Pathol, 181,* 347.

Ogden, G.R. (1998). Field cancerisation in the head and neck. Oral Diseases. 4: 1-3.

Ogden, G. R., Cowpe, J. G., & Green, M. W. (1990). Evidence of field change in oral cancer. *Br J Oral Maxillofac Surg, 28*(6), 390-392.

Patil, S., Warnakulasuriya, S., Raj, T., Sanketh, D. S., & Rao, R. S. (2016). Exophytic oral verrucous hyperplasia: a new entity. *J Investig Clin Dent, 7*(4), 417-423. doi:10.1111/jicd.12166

Pentenero M, Carrozzo M, Pagano M, Galliano D, Broccoletti R, Scully C, & Gandolfo S. (2003). Oral mucosal dysplastic lesions and early squamous cell carcinomas:underdiagnosis from incisional biopsy. *Oral Dis*, *9*(2), 68-72.

Prime, S.S., Thakker, N.S., Pring, M., Guest, P.G., & Paterson, I.C. (2001). A review of inherited cancer syndromes and their relevance to oral squamous cell carcinoma. *Oral Oncol, 37*(1), 1-16. doi:10.1016/s1368-8375(00)00055-5

Ranasinghe, A.W., Johnson, N.W., & Scragg, M.A. (1987). Iron deficiency depresses cell proliferation in hamster cheek pouch epithelium. *Cell and Tissue Kinetics*, *20*(4), 403-412.

Ranganathan, K.,& Loganathan, K. (2019). Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. *J Oral Maxillofac Pathol, 23*(1), 19–27.

Rashid, A., & Warnakulasuriya, S. (2015). The use of light-based (optical) detection systems as adjuncts in the detection of oral cancer and oral potentially malignant disorders: a systematic review. *J Oral Pathol Med, 44,* 307-328.

Rast, T.J., Kullas, A.L., Southern, P.J., & Davis, D.A. (2016). Human Epithelial Cells Discriminate between Commensal and Pathogenic Interactions with Candida albicans. *PLoS ONE, 11(4)*, e0153165. https://doi.org/10.1371/journal.pone.0153165

Ray, J.G, Chatterjee, R, & Chaudhuri, K.(2019). Oral submucous fibrosis: A global challenge. Rising incidence, risk factors, management, and research priorities. *Periodontol 2000*, *80*, 200- 212.

Reibel J, Gale N, & Hille J. (2017). Oral potentially malignant disorders and oral epithelial dysplasia. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PPJ, eds.

*WHO Classification of Head and Neck Tumours*. p.112-115, 4th ed. Lyon, France, IARC.

Reichart, P.A.,& Phillipsen, H.P. (2005). Oral erythroplakia- a review. *Oral Oncol, 41*, 551-61.

Reichart, P.A,, & Warnakulasuriya, S. (2012) Oral lichenoid contact lesions induced by areca nut and betel quid chewing: a mini review. *J Investig Clin Dent, 3*(3), 163-166.

Rennie, J.S., MacDonald, D.G., & Dagg, J.H. (1984). Iron and the oral epithelium: a review. *J R Soc Med*, *77*(7), 602-607. doi:10.1177/014107688407700714

Roopashree, M. R., Gondhalekar, R. V., Shashikanth, M. C., George, J., Thippeswamy, S. H., & Shukla, A. (2010). Pathogenesis of oral lichen planus--a review. *J Oral Pathol Med, 39*(10), 729-734. doi:10.1111/j.1600-0714.2010.00946.x

Savage, N. W., McKay, C., & Faulkner, C. (2010). Actinic cheilitis in dental practice. *Australian Dent J, 55 Suppl 1*, 78-84. doi:http://dx.doi.org/10.1111/j.1834-7819.2010.01202.x

Schiødt, M. (1984). Oral discoid lupus erythematosus. III. A histopathologic study of sixty-six patients. *Oral Surg Oral Med Oral Pathol,* 57(3), 281-293.

Schubert, M. M., Sullivan, K. M., Morton, T. H., Izutsu, K. T., Peterson, D. E., Flournoy, N., … R. Strob (1984). Oral manifestations of chronic graft-v-host disease. *Arch Intern Med, 144*(8), 1591-1595.

Scully C, & Bagan JV. (2004). Adverse drug reactions in the orofacial region. *Crit Rev Oral Biol Med, 15*, 221-39.

Shah, A.M., Bansal, S., Shirsat, P.M., Prasad, P., & Desai, R.S.(2019). Exophytic verrucous hyperplasia in oral submucous fibrosis: A single-center study. *J Oral Maxillofac Pathol, 23*(3):393-399.

Shear, M., Pindborg, J.J. (1980). Verrucous hyperplasia of the oral mucosa. Cancer 46(8):1855-1862

Shukla, K., Vun, I., Lov, I., Laparidis, G., McCamley, C., & Ariyawardana, A. (2019). Role of Candida infection in the malignant transformation of oral leukoplakia: A systematic review of observational studies. *Trans Res in Oral Oncol, 4*, 2057178X19828229. doi:10.1177/2057178x19828229

Sitheeque, M.A., & Samaranayake, L.P. (2003). Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). *Crit Rev Oral Biol Med, 14(4),* 253-67.

Slaughter, D. P., Southwick, H. W., & Smejkal, W. (1953). Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer, 6*(5), 963-968.

Speight, P. M., Khurram, S. A., & Kujan, O. (2018). Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol, 125*(6), 612-627. doi:10.1016/j.oooo.2017.12.011

Thomson, P. J., Goodson, M. L., & Smith, D. R. (2017). Profiling cancer risk in oral potentially malignant disorders-A patient cohort study. *J Oral Pathol Med, 46*(10), 888-895. doi:10.1111/jop.12625

Tilakaratne, W.M., Ekanayaka, R.P., & Warnakulasuriya, S.(2016). Oral submucous fibrosis: a historical perspective and a review on etiology and pathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol, 122*(2),178-191. doi:10.1016/j.oooo.2016.04.003

van der Meij, E.H., Mast, H., van der Waal, I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. Oral Oncol. 2007 Sep;43(8):742-8. doi: 10.1016/ j.oraloncology.2006.09.006.

van der Meij, E. H., & van der Waal, I. (2003). Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. *J Oral Pathol Med, 32*(9), 507-512.

van der Meij, E. H., Schepman, K. P., Smeele, L. E., van der Wal, J. E., Bezemer, P. D., & van der Waal, I. (1999). A review of the recent literature regarding malignant transformation of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 88*(3), 307-310.

van der Waal, I. (2010). Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. *Oral Oncology, 46*(6), 423-425. doi:http://dx.doi.org/10.1016/j.oraloncology.2010.02.016

van der Waal, I. (2015). Oral leukoplakia, the ongoing discussion on definition and terminology. *Med Oral Patol Oral Cir Bucal, 20*(6), e685-692. doi:10.4317/medoral.21007

van der Waal, I. (2018). Historical perspective and nomenclature of potentially malignant or potentially premalignant oral epithelial lesions with emphasis on leukoplakia-some suggestions for modifications. *Oral Surg Oral Med Oral Pathol Oral Radiol, 125*(6), 577-581. doi:10.1016/j.oooo.2017.11.023

van der Waal, I., & Scully, C. (2011). Oral cancer: comprehending the condition, causes, controversies, control and consequences. 4. Potentially malignant disorders of the oral and oropharyngeal mucosa. *Dental Update, 38*(2), 138-140.

Villa, A., Hanna, G. J., Kacew, A., Frustino, J., Hammerman, P. S., & Woo, S. B. (2019). Oral keratosis of unknown significance shares genomic overlap with oral dysplasia. *Oral Dis, 25*(7), 1707-1714. doi:10.1111/odi.13155

Villa, A., Menon, R. S., Kerr, A. R., De Abreu Alves, F., Guollo, A., Ojeda, D., & Woo, S. B. (2018). Proliferative leukoplakia: Proposed new clinical diagnostic criteria. *Oral Dis, 24*(5), 749-760. doi:10.1111/odi.12830

Vucicevic Boras, V., Fucic, A., Virag, M., Gabric, D., Blivajs, I., Tomasovic-Loncaric, C., . . . Velimir Vrdoljak, D. (2018). Significance of stroma in biology of oral squamous cell carcinoma. *Tumori, 104*(1), 9-14. doi:10.5301/tj.5000673

Wang YP1, Chen HM, Kuo RC, Yu CH, Sun A, Liu BY, Kuo YS, & Chiang CP. (2009). Oral verrucous hyperplasia: histologic classification, prognosis, and clinical implications. *J Oral Pathol Med, 38*(8), 651-6. doi: 10.1111/j.1600-0714.2009.00790.x..

Wang YY, Tail YH, Wang WC, Chen CY, Kao YH, Chen YK, & Chen CH. (2014). Malignant transformation in 5071 southern Taiwanese patients with potentially malignant oral mucosal disorders. *BMC Oral Health, 14*,99. doi: 10.1186/1472-6831-14-99.

Warnakulasuriya, S., Johnson, N. W., & van der Waal, I. (2007). Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med, 36*(10), 575-580. doi:10.1111/j.1600-0714.2007.00582.x

Warnakulasuriya, S.(2018) Clinical features and presentation of oral potentially malignant disorders.*Oral Surg Oral Med Oral Pathol Oral Radiol.* 125(6):582-590.

Warnakulasuriya, S. (2019). White, red, and mixed lesions of oral mucosa: A clinicopathologic approach to diagnosis. *Periodontol 2000.* 80(1):89-104.

Warnakulasuriya S.(2020). Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. *Oral Oncol.* 22; 102:104550.

Werner, R.N., Sammain, A., Erdmann, R., Hartmann, V., Stockfleth, E.,& Nast, A. (2013). The natural history of actinic keratosis: a systematic review. *Br J Dermatol. 169*(3), 502-518. doi:10.1111/bjd.12420

Williams, P. M., Poh, C. F., Hovan, A. J., Ng, S., & Rosin, M. P. (2008). Evaluation of a suspicious oral mucosal lesion. *J Can Dent Assoc, 74*(3), 275-280.

Woo, S.B., Grammer, R.L.,& Lerman, M.A. (2014) Keratosis of unknown significance and leukoplakia: a preliminary study. *Oral Surg Oral Med Oral Pathol Oral Radiol, 118(6),* 713-24. doi: 10.1016/j.oooo.2014.09.016.

World Health Organisation. (2019). International Classification of Diseases (ICD-11). https://www.who.int/classifications/icd/en/.

Wright, J.T.(2010). Oral manifestations in the epidermolysis bullosa spectrum. *Dermatol Clin*, *28*, 159-164.

Wu, M. H., Luo, J. D., Wang, W. C., Chang, T. H., Hwang, W. L., Lee, K. H., . . . Chiang, W. F. (2018). Risk analysis of malignant potential of oral verrucous hyperplasia: A follow-up study of 269 patients and copy number variation analysis. *Head Neck, 40*(5), 1046-1056. doi:10.1002/hed.25076

Zain, R. B., Kallarakkal, T. G., Ramanathan, A., Kim, J., Tilakaratne, W. M., Takata, T., . . . Jalil, A. (2016). Exophytic Verrucous Hyperplasia of the Oral Cavity - Application of Standardized Criteria for Diagnosis from a Consensus Report. *Asian Pac J Cancer Prev, 17*(9), 4491. doi:10.7314/APJCP.2016.17.(9).4491

**Table 1. Recommended definitions for OPMDs**

| Disorder | Definition | Source |
|---|---|---|
| Leukoplakia | "A predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" | WHO Collaborating Centre (2007) |
| Proliferative Verrucous Leukoplakia (PVL) | Progressive, persistent, and irreversible disorder characterized by the presence of multiple leukoplakias that frequently become warty. | WHO Collaborating Centre 2020 |
| Erythroplakia | 'A predominantly fiery red patch that cannot be characterized clinically or pathologically as any other definable disease'. | WHO Collaborating Centre, 2007 |
| Oral Submucous Fibrosis (OSF) | 'A chronic, insidious disease that affects the oral mucosa, initially resulting in loss of fibroelasticity of the lamina propria and as the disease advances, results in fibrosis of the lamina propria and the submucosa of the oral cavity along with epithelial atrophy'. | Modified from: World Workshop on Oral Medicine V (Kerr et al., 2011) |
| Oral Lichen Planus (OLP) | A chronic inflammatory disorder of unknown aetiology with characteristic relapses and remissions, displaying white reticular lesions, accompanied or not by atrophic, erosive and ulcerative and/or plaque type areas. Lesions are frequently bilaterally symmetrical. Desquamative gingivitis may be a feature. | WHO Collaborating Centre 2020 |
| Actinic Keratosis (Actinic Cheilitis) (AK/AC) | A disorder that results from sun damage and affects exposed areas of the lips, most commonly the vermilion border of the lower lip with a variable presentation of atrophic and erosive areas and white plaques. | WHO Collaborating Centre 2020 |
| Palatal Lesions in Reverse Smokers | White and/or red patches affecting the hard palate in reverse smokers, frequently stained with nicotine. | WHO Collaborating Centre 2020 |
| Oral Lupus Erythematosus (OLE) | An autoimmune connective tissue disease which may affect the lip and oral cavity, where it presents as an erythematous area surrounded by whitish striae, frequently with a "target" configuration. | WHO Collaborating Centre 2020 |
| Dyskeratosis Congenita (DC) | 'A rare cancer-prone inherited bone marrow failure syndrome caused by aberrant telomere biology. It is characterized clinically by the presence of the diagnostic triad of dysplastic nails, lacy reticular skin pigmentation and oral leukoplakia' | Ballew & Savage 2013 |

| | | |
|---|---|---|
| **Newly included in 2020 classification** | | |
| Oral Lichenoid Lesion (OLL) | Oral lesions with lichenoid features but lacking the typical clinical or histopathological appearances of OLP ie may show asymmetry or are reactions to dental restorations or are drug-induced. | WHO Collaborating Centre 2020 |
| Oral Graft vs Host Disease (OGVHD) | Clinical and histopathological presentations similar to oral lichen planus in a patient developing an autoimmune, multi-organ complication after allogenic hematopoietic cell transplantation. | WHO Collaborating Centre 2020 |
| **Removed from the 2020 classification due to limited evidence** | | |
| Oral Epidermolysis Bullosa (OEB) | 'A severe epidermal fragility disorder associated with trauma-induced blistering, progressive soft tissue scarring, and increased risk of epidermal cancer' | Fritsch et al., 2008 |

**Table 2: Other white lesions and disorders to be excluded based on clinical features alone before considering a clinical diagnosis of oral leukoplakia**

| Normal and pathological entities | Diagnostic features |
|---|---|
| White sponge naevus | Noted in early life, family history, lesions are throughout the mouth; Genital mucosa may be affected. |
| Frictional keratosis* | History of friction or other mechanical trauma, mostly along the occlusal plane, an etiological cause apparent, mostly reversible upon removal of the cause |
| Biting of lip, commissures or cheeks (morsicatio buccorum) | Habit of lip &/or cheek biting known; irregular whitish flakes with jagged out line |
| Chemical injury | Known history of exposure to a chemical (e.g. an aspirin tablet or a caustic agent e.g. sodium hypochlorite). The site of lesion corresponds to chemical injury, painful, resolves rapidly |
| Oral lichen planus | White papules joined up with lines to form a reticular appearance on the surface of variably inflamed mucosa. It can also present as desquamative gingivitis. Plaque type may be difficult to distinguish from oral leukoplakia |
| Acute pseudomembranous Candidiasis** | Generally widespread. The white membrane can be scraped off sometimes revealing an erythematous/raw footprint.<br>Associated with local or systemic (e.g. immunodeficiency) underlying causes. |
| Chronic hyperplastic candidosis | An adherent white or white and red patch caused by a chronic fungal infection, usually *Candida albicans* |
| Leukoedema | Bilateral on buccal mucosae, and disappears upon stretching (retracting). Predilection among some racial groups. |
| Fordyce's spots/condition | <1mm diameter, elevated, circular buff-coloured spots/ papules distinctly demarcated from the normal surrounding lining mucosa |
| Skin graft | Known history of a skin graft |
| Oral hairy leukoplakia | Bilateral keratosis with vertical streaking, most common on the lateral borders of the tongue, but can focally affect other mucosal sites, especially in non-keratinised areas.<br>Positive history of immunosuppression from HIV disease or drugs – the latter often following organ transplantation or the use of high potency steroid inhalers. |
| Nicotinic stomatitis | Greyish white palate with red spots (inflamed minor mucous glands). Smoking history, |

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| (leukokeratosis nicotina palati or smokers' palate) | |
| Uremic stomatitis | White, sharply demarcated, adherent plaques made of fibrinous exudate with some desquamated epithelial cells. History of renal disease |

* Several terms are used for white patches induced by trauma: Frictional keratosis typically appears as a patch with diffuse borders; when found on alveolar ridges these are referred to as alveolar ridge keratosis (ARK); a white line along the occlusal plane is referred to as linea alba buccalis; Morsicatio buccarum is a condition characterized by chronic irritation or injury to the buccal mucosa, caused by repetitive chewing, biting or nibbling; None of these should be characterised as oral leukoplakia.

** Acute pseudomembranous candidiasis is usually a widespread and distinctive infection of oral, and sometimes oropharyngeal mucosa and should be easily differentiated from oral leukoplakia.

**Table 3. Clinical presentations and differential diagnosis of some common OPMDs**

| Disorder | Symptoms | Clinical presentation | Clinical conditions to exclude in the diagnosis |
|---|---|---|---|
| Oral Leukoplakia (OL) | Generally asymptomatic | **Homogeneous leukoplakia**: Uniformly white, flat and thin, with a smooth surface which may exhibit shallow cracks. Cannot be rubbed off. | White Sponge Naevus<br>Frictional keratoses, including Alveolar Ridge Keratosis<br>Chemical injury<br>Chronic candidal infection<br>Leukoedema<br>Fordyce's spots/condition<br>Skin graft<br>Oral Hairy Leukoplakia (OHL)<br>Leukokeratosis Nicotina Palati (Smoker's palate) |
| | | **Non homogeneous leukoplakias: (sub types)**<br>*Nodular leukoplakia*: Small polypoid or rounded outgrowths, red or white excrescences. | |
| | | *Verrucous leukoplakia*: The surface is raised, exophytic, wrinkled or corrugated | HPV Lesions eg Condylomata/Warts |
| | Some discomfort | *Erythroleukoplakia:*<br>Mixed, white and red (speckled) but retaining predominantly white character. Margins may be irregular | Geographic tongue/Erythema Migrans<br>Erosive lichen planus or lichenoid lesions |
| Oral Erythroplakia | Discomfort, tingling and sensitivity to touch, | A localized red patch with well-defined margins and a matt surface. | Erythematous candidiasis<br>Denture-associated stomatitis |

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|---|---|---|---|
| | hot beverages or spicy foods. | | Erythema migrans<br>Erosive and inflammatory/infective disorders<br>Desquamative gingivitis<br>Discoid lupus erythematosus<br>Erosive lichen planus<br>Pemphigoid<br>Pemphigus vulgaris<br>Vascular hamartomas<br>Vascular neoplasms |
| Oral Proliferative Multifocal Leukoplakia (OPML) | Some discomfort | Multiple, thick, white patches in more than two different oral sites, frequently found on the gingiva, alveolar processes and palate. Majority present with a verrucous pattern. Lesions spread and coalesce during development. Recurrence in a previously treated area. | Lichen planus (particularly in early stages of OPML) |
| Oral Lichen Planus (OLP) | Asymptomatic. Erosive/ulcerative variety is sore | Mostly white lines or as a white plaque.<br>*Reticular*: lace-like white lines,<br>*Linear, annular*; various presentations as lines or, rings<br>*Papular:* White dots<br>*plaque-type*: white patch<br>*Atrophic, erosive and ulcerative*: red and ulcerated.<br>*Bullous*: vesicular | Oral lichenoid contact hypersensitivity reactions<br>Oral lichenoid drug reactions<br>Oral lichenoid lesions (see below)<br>Lichenoid lesions in a betel quid user<br>Mucous Membrane Pemphigoid<br>Lichen planus pemphigoides<br>Chronic ulcerative stomatitis<br>Chronic graft-versus host disease<br>Lichen sclerosus<br>Oral lupus erythematosus<br>Oral proliferative multifocal leukoplakia |
| Oral Submucous Fibrosis (OSF) | Burning sensation to spicy food. | Blanching of oral mucosa<br>Marked loss of tongue papillae<br>Leathery mucosa | Scleroderma |

| | | | |
|---|---|---|---|
| | Later, restricted mouth opening | Fibrous bands<br>Limited mobility of tongue (rigidity)<br>Shrunken or deformed uvula<br>Limitation of mouth opening<br>Sunken cheeks | |
| **New in 2020 Classification** | | | |
| Oral Lichenoid Lesion (OLL) | Asymptomatic.<br>Red and atrophic areas could be sore | White lines (reticular: lace-like, linear or annular), papular, sometimes plaque-type. Red and erosive with white striae.<br>Asymmetrical | Oral lichen planus |
| Oral Graft vs host disease (OGVHD) | Red and atrophic areas could be sore | As above.<br>A history of allogenic haematopoietic cell transplantation. | Oral lichen planus<br>Oral lichenoid contact reaction<br>Oral lichenoid drug reaction |

**Table 4: Diagnostic criteria of oral lichen planus based on previous proposals (Al-Hashimi et al., 2007; Cheng et al., 2016; van der Meij & van der Waal, 2003; and Aguirre-Urizar et al., 2020).**

| | |
|---|---|
| **Clinical criteria** | - Presence of bilateral, more or less symmetrical white lesions affecting buccal mucosa, and/or tongue, and/or lip, and/or gingiva<br>- Presence of a white papular lesions and lace-like network of slightly raised white lines (reticular, annular or linear pattern) with or without erosions and ulcerations.<br>- Sometimes presents as desquamative gingivitis. |
| **Histopathological criteria** | - Presence of a well-defined band-like predominantly lymphocytic infiltrate that is confined to the superficial part of the connective tissue.<br>- Signs of vacuolar degeneration of the basal and/or supra basal cell layers with keratinocyte apoptosis<br>- In the atrophic type there is epithelial thinning and sometimes ulceration caused by failure of epithelial regeneration as a result of basal cell destruction. A mixed inflammatory infiltrate may be found. |

**Supplementary Table 1: Historical Definitions of Oral Leukoplakia and Proliferative Verrucous Leukoplakia**

| **Oral Leukoplakia** | |
|---|---|
| **Definition** | **Source** |
| 'A white patch or plaque that cannot be characterized clinically or pathologically as any other disease' | WHO (1978) (Kramer, Lucas, Pindborg, & Sobin, 1978b) |
| 'A white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except use of tobacco' | Malmo Conference (1983) (Axéll, Holmstrup, Kramer, Pindborg, & Shear, 1984) |
| 'Leukoplakia is a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease and it is not associated with any physical or chemical causative agent except the use of tobacco.' | Uppsala international symposium (1994)<br>(Axéll et al., 1996) |
| 'White plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer'. | WHO Collaborating Centre 2007 |
| 'A predominantly white patch or plaque that cannot be characterized clinically or pathologically as any other disorder; oral leukoplakia carries an increased risk of cancer development either in or close to the area of the leukoplakia or elsewhere in the oral cavity.' | van der Waal, 2015 |
| 'White plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer' | WHO Collaborating Centre 2020 |
| **Proliferative Verrucous Leukoplakia** | |
| 'Leukoplakias that spread and become multifocal. PVL is slow-growing, persistent, and irreversible, and in time areas become exophytic and wart like' | Hansen, Olson, & Silverman, 1985 |