Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer

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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 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) (Warnakulasuriya et al, 2007) (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. We recommend the term "proliferative multifocal leukoplakia" in place of "proliferative verrucous leukoplakia". 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 OPMDs based on the

classification and nomenclature proposed here. This requires multi-centre longitudinal studies with uniform clinical diagnostic criteria that can answer critical questions, ultimately to improve the prevention, early detection and management of oral cancer by the identification of OPMDs and through evidence-based interventions.

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 et al., 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, et al., 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, 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 oral squamous cell carcinomas 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).

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. An important challenge faced by clinicians managing patients with OPMDs is to be able to recognise the small proportion of subjects (or cases) that is likely to develop a future malignancy.

Updating the classification of OPMDs is not just an academic endeavour, but a clinically mandated need to provide best management to patients diagnosed with these disorders with potential serious consequences, using an evidence-based approach aiming to enhance the patient's quality of life. 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 expert opinion favours continuation of the OPMD nomenclature to describe oral mucosal disorders that indicate an increased risk for cancer development, considering new evidence from both basic science and clinical studies. Under this umbrella, inclusion of some additional disorders has been proposed by various researchers: 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 investigations. The objective is to present a consensus on a revised classification of OPMDs, recommended nomenclature and definitions for each disorder, using current evidence and predominantly based on their 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 an 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 clinical signs suggestive of the presence of an invasive 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.

Table 1. Recommended definitions for OPMDs

Commonly encountered		
Disorder	**Definition**	**Source**
Oral Leukoplakia (OL)	"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)
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 Cheilitis (Actinic Keratosis) (AC/AK)	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
Less commonly encountered		
Oral Erythroplakia (OE)	'A predominantly fiery red patch that cannot be characterized clinically or pathologically as any other definable disease'.	WHO Collaborating Centre, 2007
Oral Proliferative Multifocal Leukoplakia (OPML)	Progressive, persistent, and irreversible disorder characterized by the presence of multiple leukoplakias that frequently become warty.	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
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 Dyskeratosis Congenita (ODC)	'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

The clinical manifestations of OPMDs have a wide range of features including colour variations (white, red, and mixed white and red), topographic changes (plaque/plateau, smooth, corrugated, verrucous, granular, atrophic), and variable sizes (Williams, Poh, Hovan, Ng, & Rosin, 2008; Speight et al., 2018). Some OPMDs, particularly oral leukoplakia may superficially ulcerate due to abrasion of the surface by trauma from teeth or appliances. OPMD can involve any anatomical site in the oral cavity and can present in single or multiple sites (Farah et al., 2014). Other head and neck sites (eg pharynx and larynx) may demonstrate analogous PMDs, as may genital mucosae. OPMDs have an unpredictable clinical course - remaining static, or may demonstrate progression or regression (Holmstrup et al., 2006; Speight et al., 2018; Farah, Kujan, Prime, & Zain, 2019).

The majority of OPMD cases are diagnosed in middle-aged or elderly patients, predominantly males (Napier & Speight, 2008; Speight et al., 2018). In western populations, elderly females with a 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 cultural habits have influenced the type and pattern of OPMDs reported in specific populations due to the dominance of particular risk factors. For example, betel quid/areca nut chewing habits are widely prevalent in South Asian populations resulting in a greater prevalence of OPMDs (Lee, Ko, Warnakulasuriya, et al., 2012; Lee, Ko, Yen, et al., 2012, 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 definition by the WHO Collaborating Centre 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 used widely in the global literature.

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

- A persistent white patch/plaque that cannot be rubbed off
- Most homogeneous leukoplakias affect a circumscribed area with demarcated borders. A smaller subset can present with diffuse borders, and non-homogeneous leukoplakias are often more diffuse.
- 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
- Does not disappear or fade away on stretching (retracting) the tissue
- Exclusion of other white lesions outlined in Table 2.

It is emphasised that the term leukoplakia is used as a clinical diagnosis having excluded other clinically recognisable white lesions (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. 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. Frictional keratoses should not be 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 leukoplakia presents as a white lesion of uniformly flat, thin appearance and has a smooth surface with a constant texture throughout the affected area, is sharply demarcated and often exhibits shallow cracks/fissures of the surface. Such disorders are often asymptomatic and carry a low risk of cancer.
On the other hand, non-homogenous leukoplakias may present with many clinical varieties including speckled (also referred to as erythroleukoplakia; mixed, white and red), nodular

(small polypoid projections, rounded red or white excrescences) and verrucous (wrinkled or corrugated surface). Leukoplakia patches may show focal superficial ulceration. Non-homogenous leukoplakias carry a higher risk of transformation than homogeneous leukoplakias (Speight et al 2018), and it is not uncommon for non-homogeneous leukoplakia to exhibit severe dysplasia or even superficially invasive SCC at first biopsy (Pentenero et al., 2003; Lee et al., 2016). Lee et al., (2016) reported carcinomas in 12% of incisional biopsies taken from oral leukoplakia samples in Taiwan. This raises the importance of selecting the correct biopsy site (or sites) to avoid underdiagnosis: indeed, multiple biopsies are usually wise.

When describing a leukoplakia, it is important to comment whether it is a smoking-associated leukoplakias or a leukoplakia in a never smoker as they may behave differently in their 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).

Once a clinical diagnosis of oral leukoplakia has been designated, a diagnostic biopsy is indicated. Histopathology may either confirm this clinical diagnosis or modify it (ie. oral lichen planus, or hyperplastic candidosis). In cases where the histopathologic diagnosis rendered is “epithelial hyperplasia”, “hyperkeratosis”, or “epithelial dysplasia” the clinical diagnosis of leukoplakia is retained.

It is preferable to confirm the diagnosis by biopsy and histopathology to exclude other disorders. When a diagnostic biopsy is undertaken it is customary that the pathologist mentions whether the histology is compatible with leukoplakia or not, indicates the presence or absence of dysplasia and if present, provides the grade(s) of dysplasia. The current expert group emphasises that at the time of first consultation, leukoplakia is a provisional clinical diagnosis made by exclusion of other white disorders. A diagnostic biopsy is indicated to characterise the disorder which may demonstrate one or more underlying histopathologic diagnoses ranging from simple epithelial hyperplasia with hyperparakeratosis or hyper(ortho)keratosis, varying severity of epithelial dysplasia, (Reibel et al., 2017; Ranganathan and Loganathan, 2019). A biopsy may on occasion demonstrate superficially invasive carcinoma, then the diagnosis of leukoplakia is revised to carcinoma. When dysplasia is present it should be graded. These pathological aspects of leukoplakia are presented in detail by Kujan et al., in this volume. The clinical diagnosis of leukoplakia is confirmed following a diagnostic biopsy that allows the exclusion of a carcinoma or any other known benign disorder that may affect the oral mucosa.

To achieve uniformity in reporting we recommend a pathology report to state "keratosis with no/mild/moderate/severe dysplasia, consistent with oral leukoplakia".

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

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 (eg an aspirin tablet or a caustic agent eg 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. 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. Positive history of immunosuppression from HIV disease or drugs – the latter often following organ transplantation.
Nicotinic stomatitis (leukokeratosis nicotina palati or smokers' palate)	Greyish white palate with red spots (inflamed minor mucous glands). Smoking history,
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.

Misdiagnosis and misclassification of leukoplakias have led to confusion and inaccurate reporting of prevalence (Auluck and 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 miscoded under the umbrella of "leukoplakia". Keratosis/hyperkeratosis, and parakeratosis are histopathological terms to refer to an increased thickness of the keratin and/or parakeratin layers of stratified squamous epithelia that can be triggered by several factors including simple friction, regular mechanical trauma, and chemical damage. Keratosis (in areas of normally non-keratinised mucosa) hyperparakeratosis or hyperkeratosis are histopathological features of many dysplasias and carcinomas. 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 also refers to other forms of keratosis 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).

As this is a tobacco-induced lesion it is consistent with a clinical diagnosis of oral leukoplakia and is included within the group leukoplakia

- 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 and Lee, 1978b). 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, no dysplasia and resolves 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 et al. (2014) and refers to the histologic entity of hyperkeratosis with minimal to no epithelial dysplasia or cellular atypia (Woo, Grammer and Lerman, 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 Oral proliferative multifocal leukoplakia (Oral p**roliferative verrucous leukoplakia)**

Aguirre-Urizar et al., proposed the term Proliferative Multifocal Leukoplakia in place of Proliferative Verrucous Leukoplakia (PVL) in 2011. This condition is defined as a distinct clinical form of 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 (Table 3) (Cabay, Morton, & Epstein, 2007; Iocca et al., 2019). Another term proposed in the literature is 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 and 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, and 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.

The Working Group noted that a verrucous area may not appear during evolution of Oral Proliferative Verrucous Leukoplakia and recommended the term "Oral Proliferative Multifocal Leukoplakia" (PML).

A high proportion of patients diagnosed with OPML eventually develops oral cancer. A recent systematic review estimated the malignant transformation proportion at 49.5% (CI 26.7%-72.4%) (Iocca et al., 2019). Patients with a diagnosis of OPML 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).

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 Frictional keratoses, including Alveolar Ridge Keratosis Chemical injury Chronic candidal infection Leukoedema Fordyce's spots/condition Skin graft Oral Hairy Leukoplakia (OHL) Leukokeratosis Nicotina Palati (Smoker's palate)
		Non homogeneous leukoplakias: **(sub types**) *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:* Mixed, white and red (speckled) but retaining predominantly white character. Margins may be irregular	Geographic tongue/Erythema Migrans 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 Denture-associated stomatitis

	hot beverages or spicy foods.		Erythema migrans Erosive and inflammatory/infective disorders Desquamative gingivitis Discoid lupus erythematosus Erosive lichen planus Pemphigoid Pemphigus vulgaris Vascular hamartomas 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. **Reticular**: lace-like white lines, **Linear, annular**; various presentations as lines or, rings **Papula**r: White dots **plaque-type**: white patch **Atrophic, erosive and ulcerative**: red and ulcerated. **Bullous**: vesicular	Oral lichenoid contact hypersensitivity reactions Oral lichenoid drug reactions Oral lichenoid lesions (see below) Lichenoid lesions in a betel quid user Mucous Membrane Pemphigoid Lichen planus pemphigoides Chronic ulcerative stomatitis Chronic graft-versus host disease Lichen sclerosus Oral lupus erythematosus Oral proliferative multifocal leukoplakia
Oral Submucous Fibrosis (OSF)	Burning sensation to spicy food.	Blanching of oral mucosa Marked loss of tongue papillae Leathery mucosa	Scleroderma

	Later, restricted mouth opening	Fibrous bands Limited mobility of tongue (rigidity) Shrunken or deformed uvula Limitation of mouth opening Sunken cheeks	
New in 2020 Classification			
Oral Lichenoid Lesion (OLL)	Asymptomatic. 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. Asymmetrical	Oral lichen planus
Oral Graft vs host disease (OGVHD)	Red and atrophic areas could be sore	As above. A history of allogenic haematopoietic cell transplantation.	Oral lichen planus Oral lichenoid contact reaction Oral lichenoid drug reaction

3.3 Oral 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’ (Kramer et al., 1978a; van der Waal & Scully, 2011): Other conditions include autoimmune disorders, infections, and vascular hamartomas and vascular neoplasms that may exhibit similar clinical features and should be considered differential diagnoses to erythroplakia (Reichart and Philipson, 2005).

The solitary presentation of erythroplakia distinguishes it from other more widespread conditions in the list of differential diagnoses mentioned in Table 4, including erosive lichen planus, lupus erythematosus and erythematous candidiasis which present more often in multiple sites (van der Waal, 2010). Most oral erythroplakia, 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 a patient who has OSF. In moderate to advanced cases fibrosis may also involve the oropharynx and the upper third of the oesophagus (Maher et al.,1991; Misra et al.,1998.,Tilakaratne et al., 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 the development of fibrous bands in lips, cheek mucosa and soft palate becomes the hallmark feature leading 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, not always symmetrical white reticular patches usually affecting buccal mucosae, the borders of the tongue with erosions and areas of atrophy sometimes being present. 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 et al., 2016; Aghbari et al., 2017). Cancer development in patients with a diagnosis of OLP is discussed in this volume by Gonzalez-Moles et al. 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, Gould, Kurago, Fantasia, & Muller, 2016), and should be clearly distinguished from similar clinical appearances due to other causes including oral lichenoid drug reactions (Scully and Bagan, 2004) and oral lichenoid contact hypersensitivity reactions, which taken together we have termed Oral Lichenoid Lesions (OLL), lichen planus pemphigoides, chronic ulcerative stomatitis, acute and chronic graft-versus host disease, lichen sclerosus, lupus erythematosus, and the early stages of proliferative multifocal leukoplakia (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).

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 - 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. - Sometimes presents as desquamative gingivitis.

Histopathologic criteria	- Presence of a well-defined band-like predominantly lymphocytic infiltrate that is confined to the superficial part of the connective tissue. - Signs of vacuolar degeneration of the basal and/or supra basal cell layers with keratinocyte apoptosis - 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.

3.6 Oral lichenoid Lesions (OLL)

Oral lichenoid lesions (OLL) lack the typical clinical or histological appearance of OLP ie they may not be symmetrical. OLL include oral lichenoid reactions to dental restorations or are drug-induced

van der Meij et al., (2010) used the term oral lichenoid lesions to refer to atypical forms of OLP with a clinical or histopathological presentation that was not compatible with oral lichen planus. It is a diagnostic challenge to clinically distinguish OLL from OLP under the common term of "oral lichenoid diseases" (Aguirre-Urizar et al, 2020). Gonzalez Moles (2020) in this volume argues for abandoning the term OLL as defined by van der Meij. The evidence from his systematic review suggests that the mouths of patients with lichen planus, whether presenting with typical or atypical appearances, have more or less similar malignant potential (Gonzalez-Moles et al 2019, 2020). His group recommends that both bilateral and unilateral presentations (ie symmetric or not symmetric) be considered in one group as OLP, provided the histological appearances are consistent.

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

The term oral lichenoid lesion is also used for lichenoid reactions. These can be broadly sub-classified into (Al-Hashimi et al., 2007: (1) those in close relationship to a dental restoration, often amalgam, referred to as oral lichenoid contact reactions (OLCR), (2) drug-induced lichenoid reactions (LDR). Furthermore, lichenoid contact reactions to betel quid (BQ) are reported among BQ users (Reichart & Warnakulasuriya, 2012). These are reversible oral lesions that usually recede following removal of the precipitating cause and are, therefore, unlikely to have any significant malignant potential**.**

3.7 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, McKay, & Faulkner, 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: there may also be hyperaemia as part of a true cheilitis. 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). In a case series (n= 124) reported from Brazil, 25% displayed early SCC in the biopsy specimens (Mello, Melo, Modolo, Rivero, 2019). A systematic review on AK found no reliable estimates concerning the frequency of AK developing into invasive carcinoma (Werner et al., 2013).

3.8 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. 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 leukoplakic 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 with palatal lesions in the form of leukoplakia or erythroplakia (Bharath et al., 2015). 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.

3.9 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 and erythroplakia. Typically, OLE presents as a central circular zone of atrophic mucosa, with superficial ulceration surrounded by whitish striae (Odell, 2017). Buccal mucosa, palate and lips are mostly affected. Histopathologic criteria for the diagnosis of (discoid) lupus erythematosus are described by Schiødt (1984). Carcinomas developing in lesions of oral lupus erythematosus (OLE) are rare, most frequently arising on sun-exposed skin but could affect the lips. In a review of the English language literature of 40 years (1978-2018), Arvanitidou et al. (2018) documented 22 reported cases of carcinoma of the vermillion border of the lip arising in OLE lesions. It is not always possible to confidently distinguish lichen planus from lupus erythematosus intra-orally, so that in the absence of systemic features it is quite possible that malignancy arising in lupus would be miscoded as malignancy arising in lichen planus.

3.10 Oral graft versus host disease (OGVHD)

OGVHD is reported in patients with haematologic malignancies receiving allogeneic stem cell transplants (Elad et al., 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 (2005), 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. Extensive-type 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).

3.11 Oral dyskeratosis congenita

Oral Dyskeratosis Congenita (ODKC) is rare hereditary condition that is regarded as a potentially malignant disorder. A higher frequency of oral cancers is noted among patients affected by this condition (Bongiorno et al., 2017).

Dyskeratosis Congenita (DKC), (also called Zinsser-Cole-Engman syndrome), is a rare condition of dysfunctional telomere maintenance. The pathogenesis is attributed to mutations of several genes that help maintain telomeres, such as the DKC1 gene. DKC1 gene encodes for the ribonucleoprotein dyskerin (Abdel-Karim et al., 2009). These genes would normally be responsible for maintaining telomere structure and function. 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 leukoplakic patches (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 et al., 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

et al., 1991; Ogden et al., 1992; Ogden et al.,1993). Family history and young age at presentation would suggest the hereditary nature of this disorder.

4. 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 conditions:

4.1 Disorders with limited epidemiological evidence of malignant potential.

4.1.1 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.

4.2 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.

4.2.1 Oral Chronic hyperplastic candidosis (OCHC)

Presents as an adherent white patch caused by a chronic fungal infection, usually *Candida albicans* (Farah, Kujan, Prime & Zain, 2019). OCHC can appear at any site within the oral cavity but is mostly seen on the anterior buccal mucosae and commissures or on the dorsum of the tongue with a clinical presentation of thick white plaques, or mixed red and nodular non-homogenous white patches (Dilhari et al., 2016). There is some experimental evidence that *Candida* causes epithelial hyperproliferation (Sitheeque and Samaranayake, 2003; Rast et al., 2016). It is known that C. albicans dramatically modifies the clinical and histological aspects of oral leukoplakia. *Candida* is frequently present in the biopsies of moderate and severe

dysplasia and significant dysplastic changes are noted in the epithelium of oral 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 ethanolic beverages by specific *Candida* isoforms (Alnuaimi et al., 2016). C. albicans and candidalysin - a cytolytic peptide toxin secreted by C. albicans – by interacting with Epithelial Growth Factor Receptors (EGFR) activate human EGF pathways to produce hyper 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 (1968) and reviewed by Sitheeque and 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.

4.2.2 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 in 1980. VH was considered a precurser of verrucous carcinoma (Batsakis, Suarez , el-Naggar, 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 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 can manifest as a discrete or solitary lesion and may co-exist in a 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 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 considered that this lesion could 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 et al., 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.

5. 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.

Iocca et al (2019), in a meta-analysis, reported a cumulative proportion of 7.9% (4.9%-11.5%) diagnosed with oral cancer among cohorts with OPMDs over a time scale ranging from 12 months to 20 years. Predicting the risk of transformation remains a significant challenge even in specialist practice. Some already may have foci of carcinomas at the first consultation. OPMDs are heterogeneous and have variability in their ratios of progression to cancer (Iocca et al., 2019). For example, patients diagnosed with PML (proliferative multifocal leukoplakia)

and erythroplakia later show high frequencies of oral cancer. On the other hand, oral lichen planus (OLP) in most follow up studies show lower frequencies of oral cancer (1-2%). Idrees et al (2020), applying stricter criteria for the selection of OLP cases reported a lower risk ratio of only 0.44%. Oral leukoplakia (OL) 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 et al., 2018). Accompanying publications in this volume discuss in greater detail cancer development in patients with different OPMDs, pathology tools 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.

6. 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 (Ogden and Hall, 1997) 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. Field cancerisation should refer to the identification of changes at a cellular and molecular level in tissues with histomorphological evidence of malignancy, whilst field change should be reserved for alterations in tissues that show no evidence of epithelial dysplasia (Ogden, 1998). 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.

It is possible that normal-looking mucosa may harbour changes that are not visible to the naked eye, with white light, during routine examination. Currently available adjunctive tools (Rashid and 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. Use of these tools to search for "occult lesions" remains a research question.

However, evidence for field change , based on a variety of markers (eg cytokeratins, p53 and angiogenesis) have been identified within biopsies of clinically normal mucosa from oral cancer patients (Ogden et al., 1993,Ogden et al., 1997, El Gazzar et al., 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.

7. 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 (Kinzler and Vogelstein, 2002)

Many of these syndromes are caused by mutations or deletions in tumour suppressor genes, or DNA repair genes that can be broadly divided into two groups, called gatekeepers and caretakers. 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.

Of the many familial cancer syndromes described we found good evidence for predisposition for oral cancer in Fanconi Anaemia and short description appears below:

7.1 Fanconi anaemia (FA)

An increased susceptibility of Fanconi anaemia (FA) patients to early-onset carcinomas of the oral cavity - largely in the absence of known life-style risk factors - has been observed for many 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. Recently there has been renewed interest among researchers on development of

oral cancers in FA. Following hematopoietic stem cell transplantation (HSCT) - the main treatment for bone marrow failure in these patients – there is increased risk for solid tumours, including head and neck cancers, with oral squamous cell carcinoma being the most common type. Young and Alter (1994), reviewing 800 FA patients reported in the literature 17 had been diagnosed with cancers in the oral cavity or pharynx. In a systematic review Furquima et al (2018) identified a total of 121 individuals affected by FA and oral cancer 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.

7.2 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.

8. 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” conflates and confuses. 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; Rao et al., 2020).

9. 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 need better to 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 atowards 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.

10. 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 lichenoid disorders that merit its 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 was warranted on these disorders. 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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