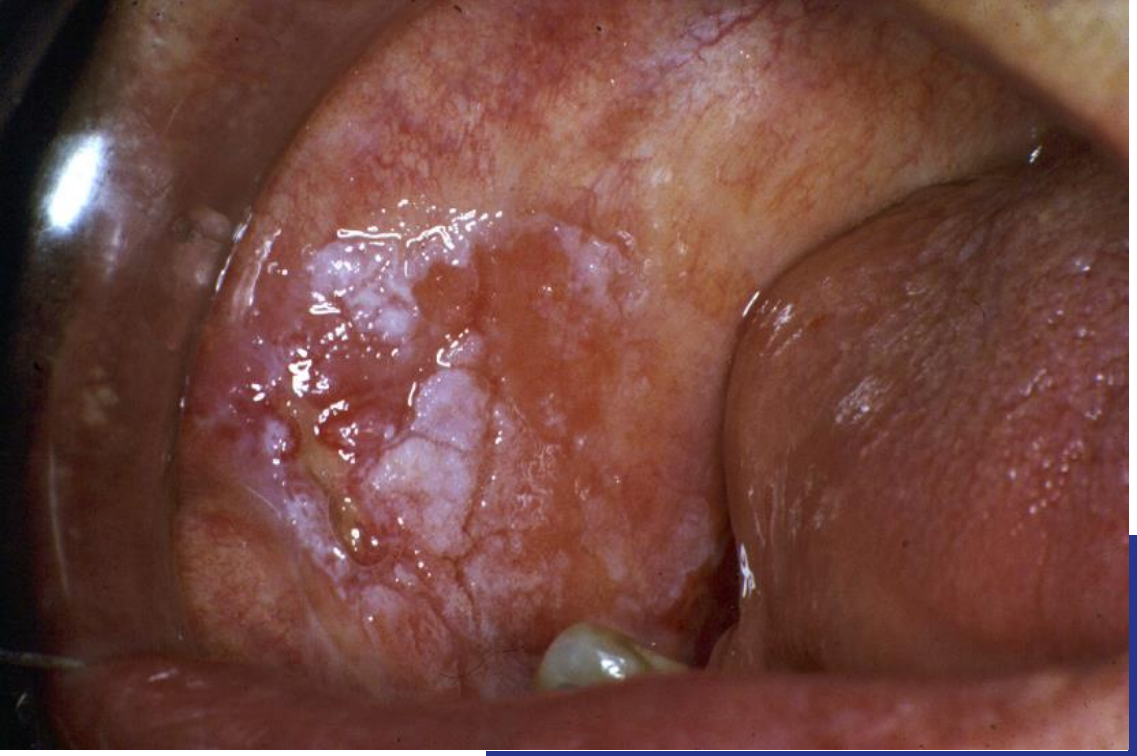

THE UNIVERSITY OF WESTERN AUSTRALIA

Oral Potentially Malignant Disorders

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BDS DipOPath MDSc MFDS RCPS FHEA FRCPath PhD FFOMP(RCPA)

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Review > Dent Clin North Am. 2025 Jul;69(3):327-346. doi: 10.1016/j.cden.2025.03.001. Epub 2025 Apr 23.

Oral Potentially Malignant Disorders: Current Knowledge and Future Directions

Omar Kujan [1]

Affiliations + expand

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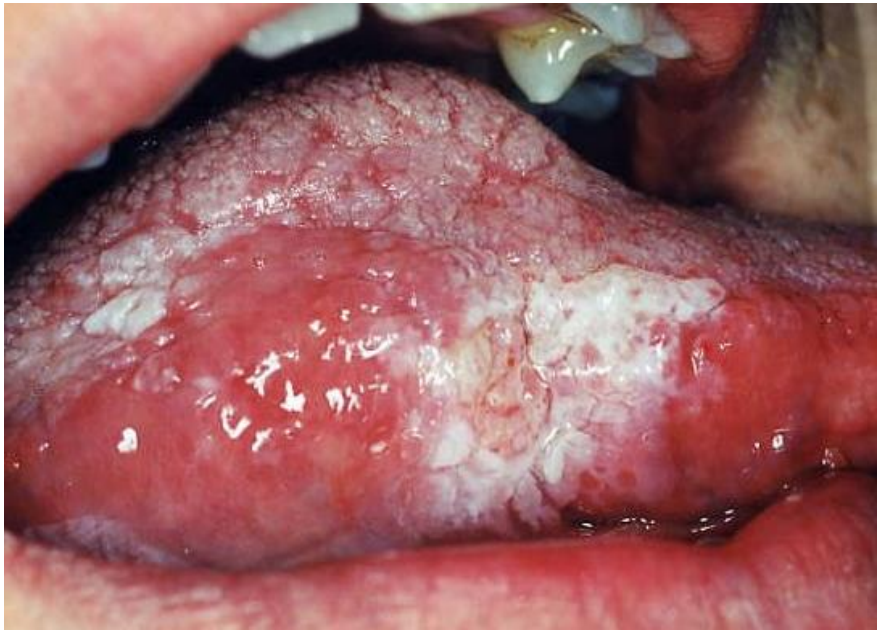
Abstract

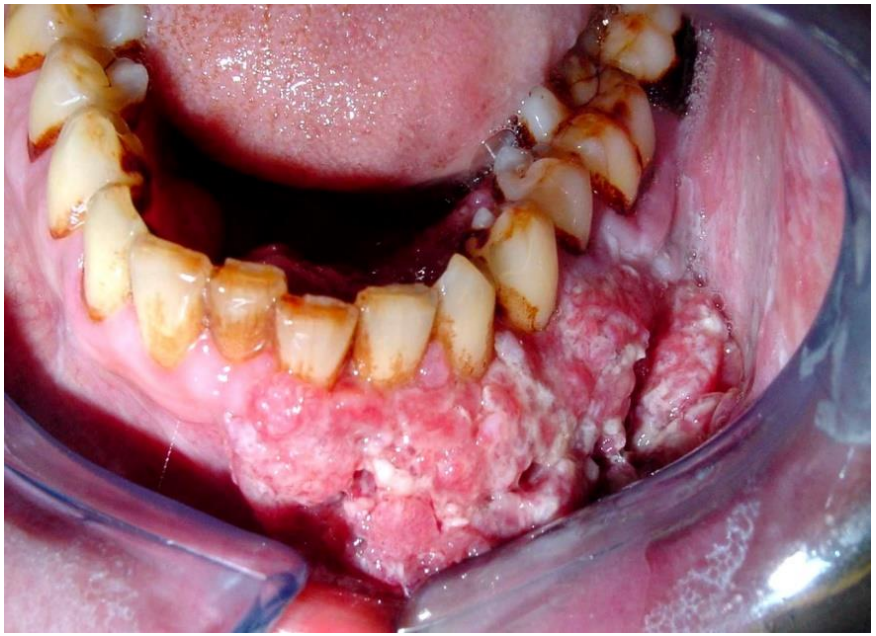
Oral potentially malignant disorders (OPMDs) include a range of oral mucosal lesions and conditions that carry an increased risk of progressing to oral squamous cell carcinoma. This review compiles current knowledge on the changing definition and terminology of OPMDs. It also examines the factors associated with malignant transformation, the usefulness of diagnostic adjuncts for general dental practitioners, and current and emerging management strategies. This study draws from consensus reports, clinical reviews, recent findings, and future directions to provide a comprehensive understanding of OPMDs, aiming to assist both specialists and general practitioners in effectively identifying, diagnosing, and managing these conditions.

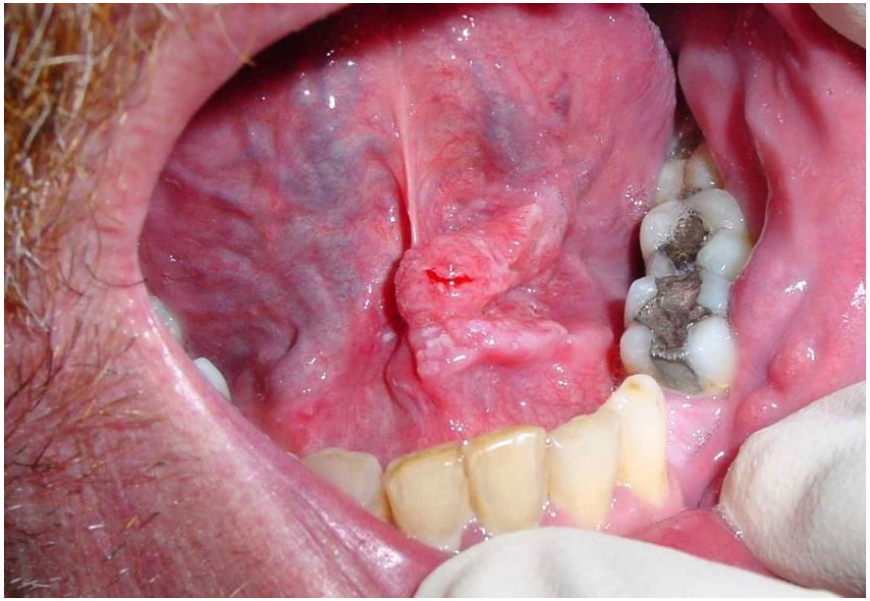
Keywords: Diagnostic adjuncts; Malignant transformation; Management; OPMDs; Oral cancer; Oral potentially malignant disorders.

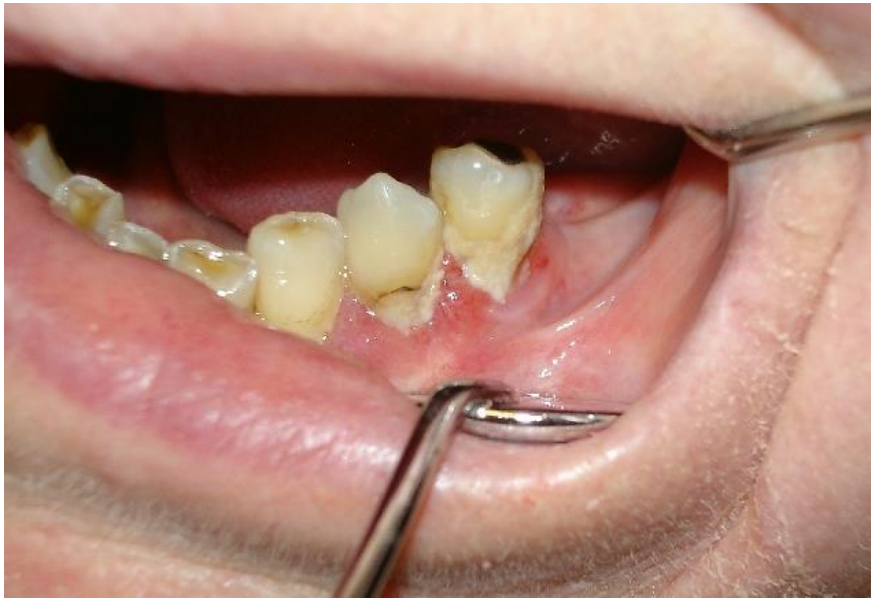
Agenda

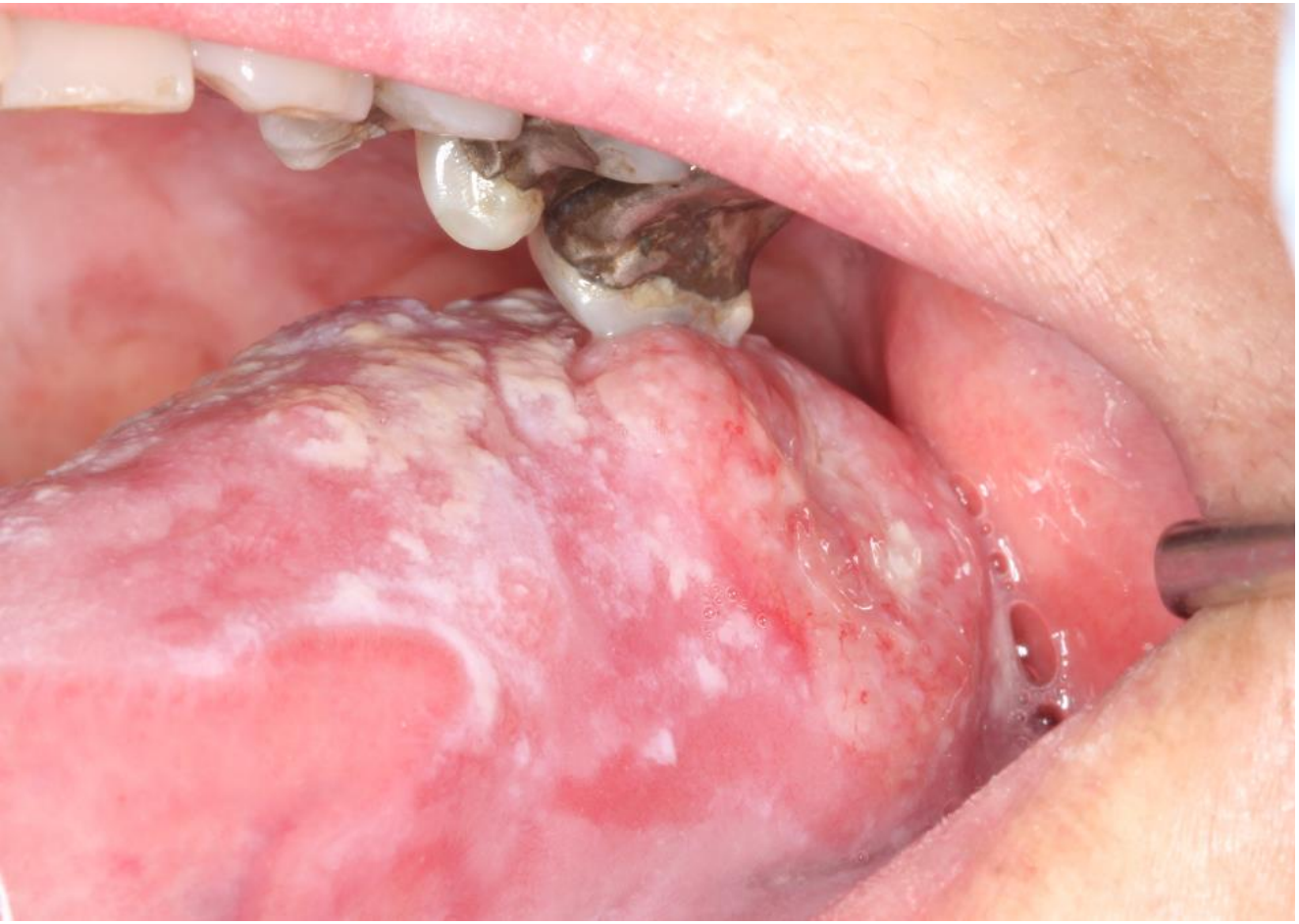
- Nomenclature and classification
- Historical changes
- Epidemiology, risk factors and clinical types
- Malignant transformation
- Clinical Tips



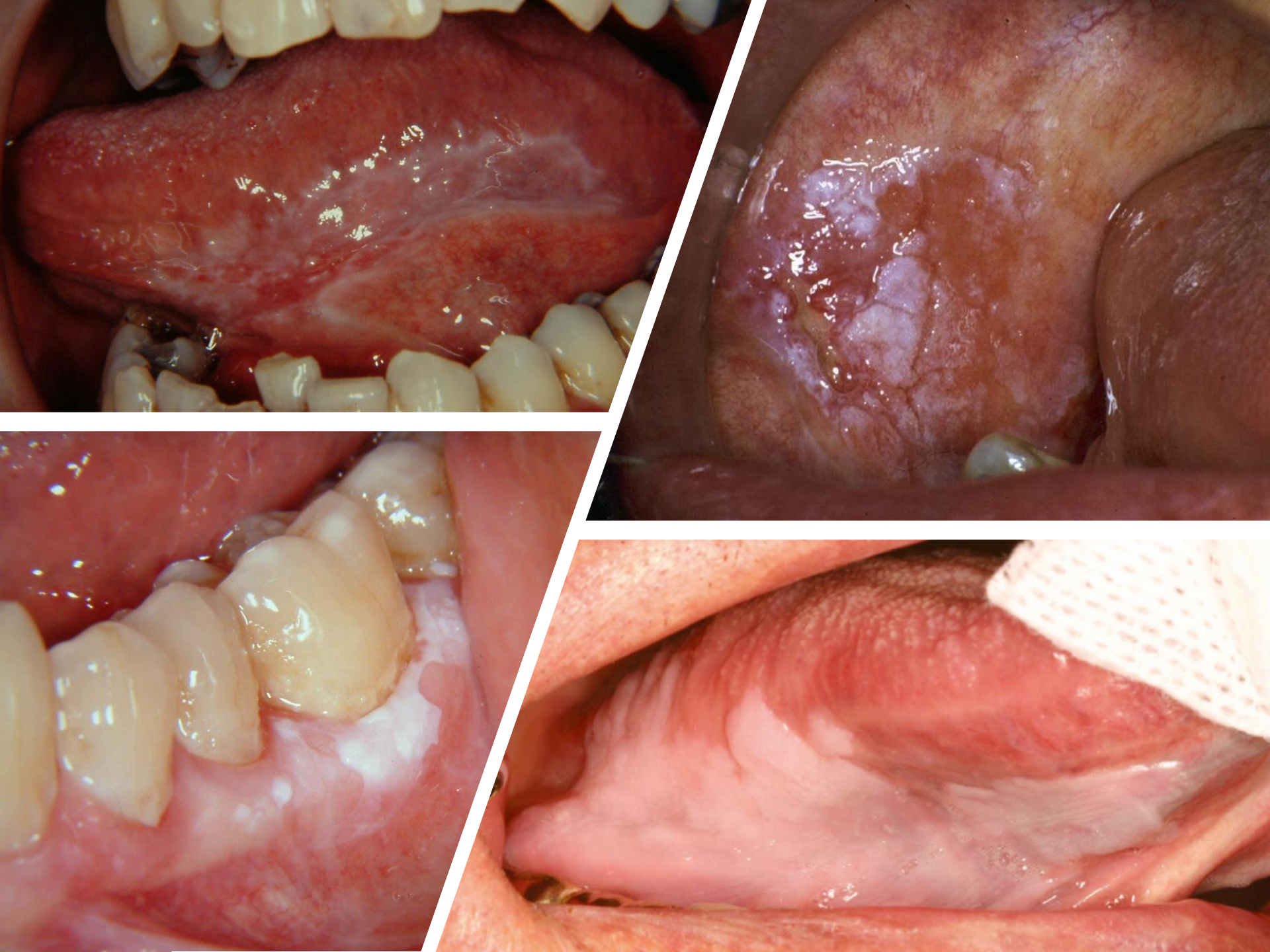


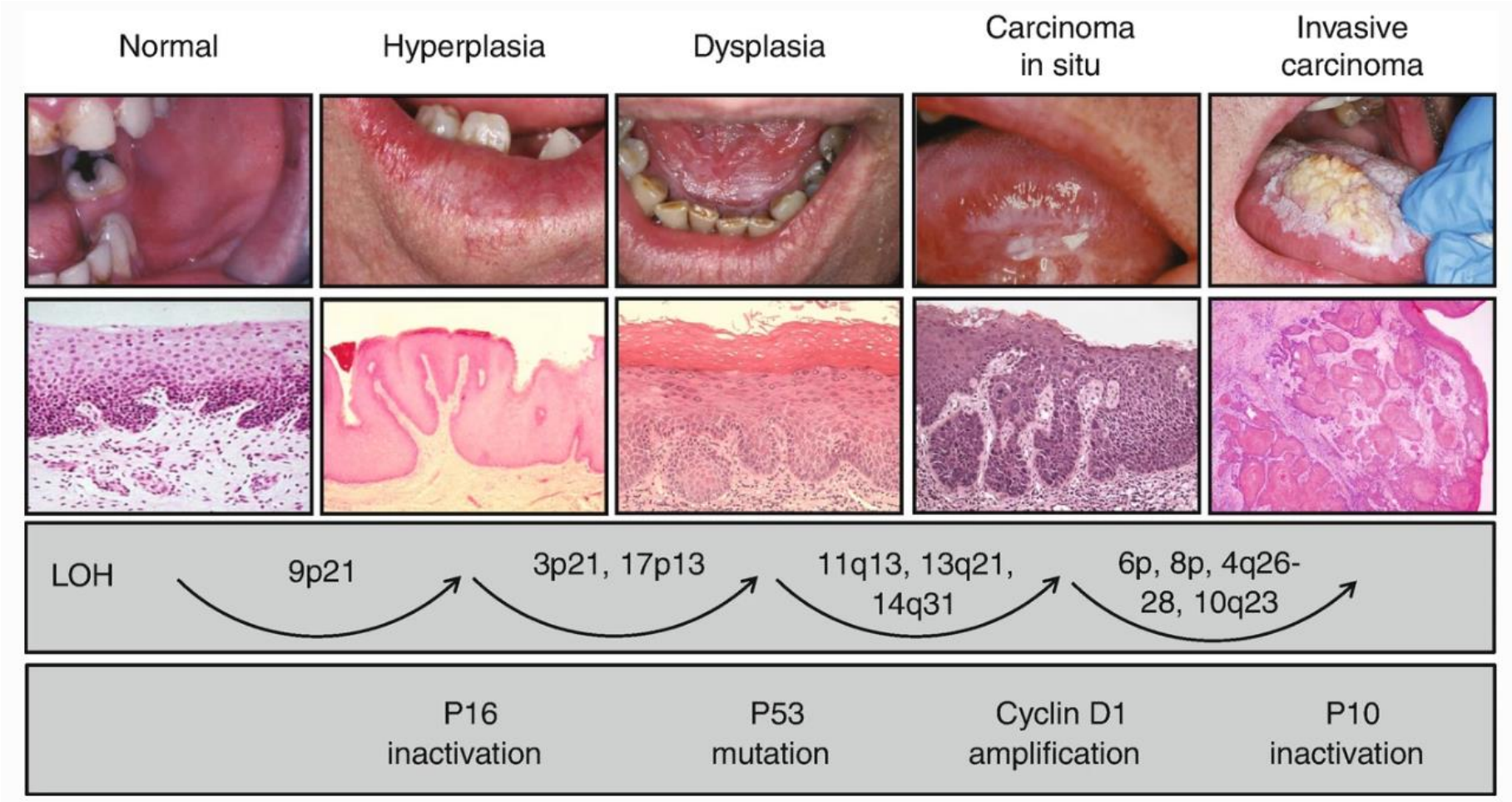






- 2/3 of oral cancers are detected at advanced stage
- 5-year survival rate is 50%
- Early detection can lead to high survival rate





Farah, C.S., Shearston, K., Nguyen, A.P., Kujan, O. (2019). Oral Carcinogenesis and Malignant Transformation. In: Brennan, P., Aldridge, T., Dwivedi, R. (eds) Premalignant Conditions of the Oral Cavity. Head and Neck Cancer Clinics. Springer, Singapore. https://doi.org/10.1007/978-981-13-2931-9_3

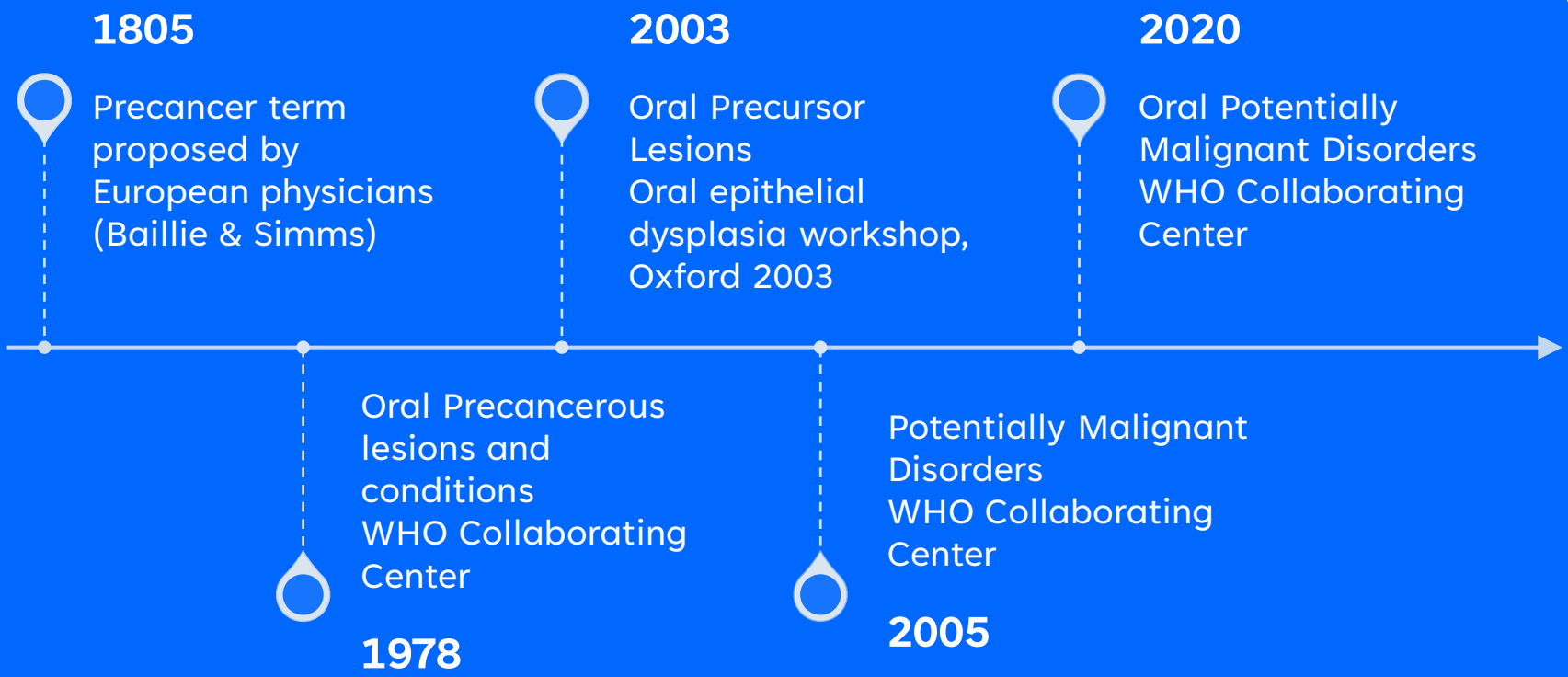
Agenda

Nomenclature and classification

- **Definition**
- 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)

- 'pre-cancer', 'precursor lesions', 'pre-malignant', 'intra epithelial neoplasia' and 'potentially malignant' have been used in the international literature to broadly describe clinical presentations that may potentially become cancer.

History of terminology



J Oral Pathol Med. 2007 Nov;36(10):575-80. doi: 10.1111/j.1600-0714.2007.00582.x.

Nomenclature and classification of potentially malignant disorders of the oral mucosa

S Warnakulasuriya [1], Newell W Johnson, I van der Waal

Affiliations + expand

PMID: 17944749 DOI: 10.1111/j.1600-0714.2007.00582.x

Abstract

At a workshop coordinated by the WHO Collaborating Centre for Oral Cancer and Precancer in the UK issues related to terminology, definitions and classification of oral precancer were discussed by an expert group. The consensus views of the Working Group are presented here. The term, 'potentially malignant disorders', was recommended to refer to precancer as it conveys that not all disorders described under this term may transform into cancer. Critically evaluating all definitions proposed so far for oral leukoplakia, the Working Group agreed that the term leukoplakia should be used to recognize 'white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer'. An outline was proposed for diagnosing oral leukoplakia that will prevent other oral white disorders being misclassified as leukoplakia. The Working Group discussed the caveats involved in the current use of terminology and classification of oral potentially malignant disorders, deficiencies of these complex systems, and how they have evolved over the past several decades. The terminology presented in this report reflects our best understanding of multi-step carcinogenesis in the oral mucosa, and aspires to engender consistency in use.

WHO classification 2005

Classification of precancerous lesions and conditions

Precancerous lesions	Precancerous conditions
Leukoplakia	Submucous fibrosis
Erythroplakia	Actinic keratosis
Palatal lesions in reverse smokers	Lichen planus
	Discoid lupus erythematosus
	Hereditary disorders with increased risk: dyskeratosis congenita and epidermolysis bullosa

J Oral Pathology Medicine, Volume: 36, Issue: 10, Pages: 575-580, First published: 26 July 2007, DOI: (10.1111/j.1600-0714.2007.00582.x)

WHO Collaborating Centre for Oral Cancer-Expert Symposium on Oral Potentially Malignant Disorders: 04-05 March 2020

Review > Oral Dis. 2021 Nov;27(8):1862-1880. doi: 10.1111/odi.13704. Epub 2020 Nov 26.

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

Saman Warnakulasuriya [1], Omar Kujan [2], José M Aguirre-Urizar [3], José V Bagan [4 5], Miguel Ángel González-Moles [6 7], Alexander R Kerr [8], Giovanni Lodi [9], Fernanda Weber Mello [10], Luis Monteiro [11], Graham R Ogden [12], Philip Sloan [13], Newell W Johnson [14 15]

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PMID: 33128420 DOI: 10.1111/odi.13704

Free article

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 Organization (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

WHO classification 2020

Classification of oral potentially malignant disorders	Newly included in 2021 classification
Leukoplakia	Oral Lichenoid Lesion
Proliferative verrucous leukoplakia	Oral Graft versus Host Disease
Erythroplakia	**Remove from the 2021 classification due to limited evidence**
Oral submucous fibrosis	Oral Epidermolysis Bullosa
Oral lichen planus	Chronic hyperplastic candidosis
Actinic Keratosis (Actinic Cheilitis)	Exophytic verrucous hyperplasia/verrucous hyperplasia
Palatal changes in reverse smoking	
Oral Lupus Erythematosus	
Dyskeratosis Congenita	

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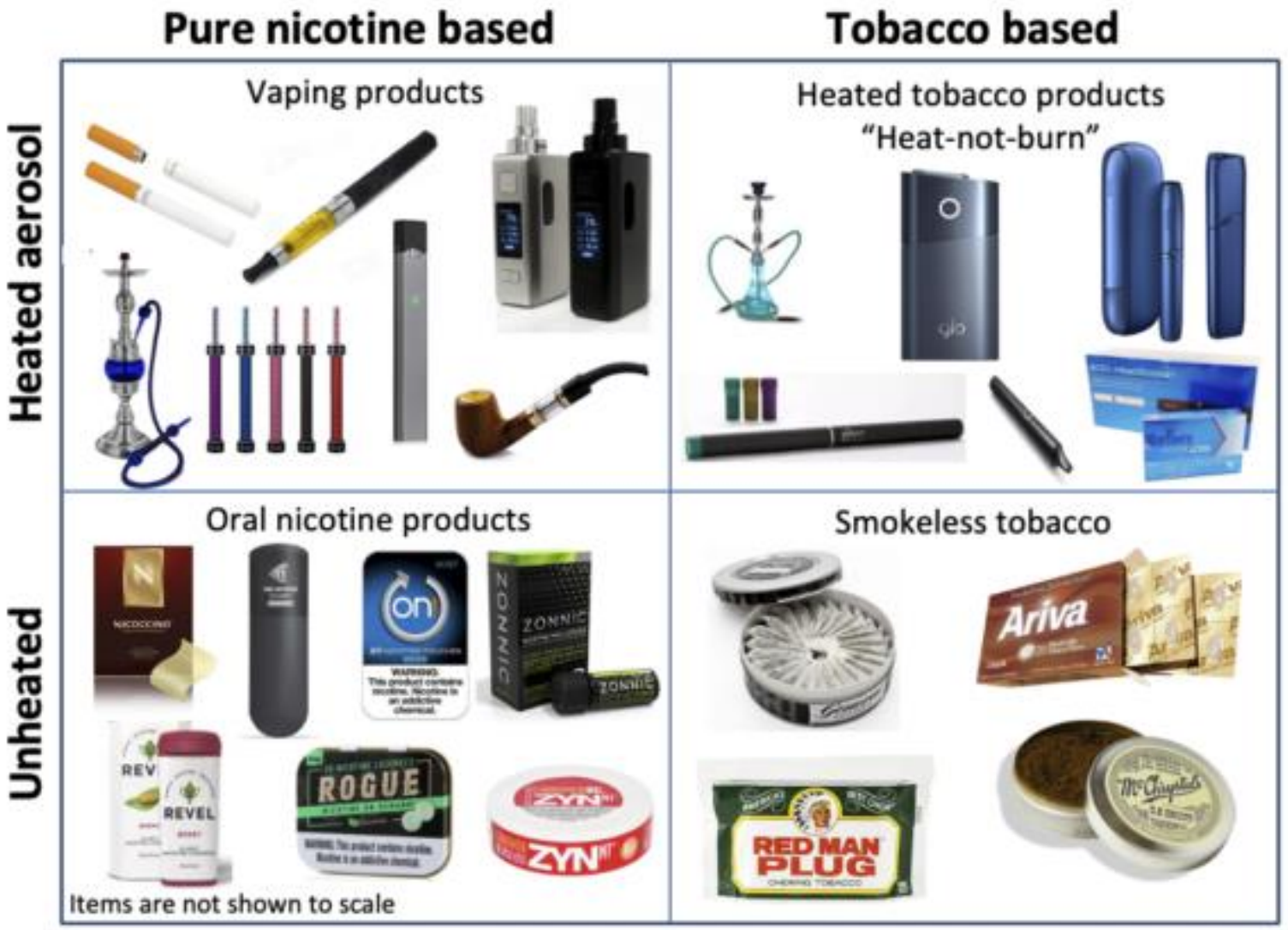
OPMD Epidemiology

- A recent systematic review included 22 epidemiological surveys that estimated a global prevalence of OPMDs at **4.47%** (95% CI = 2.43–7.08).

- It was noted that prevalence may vary between populations and was generally higher in Asians and males.

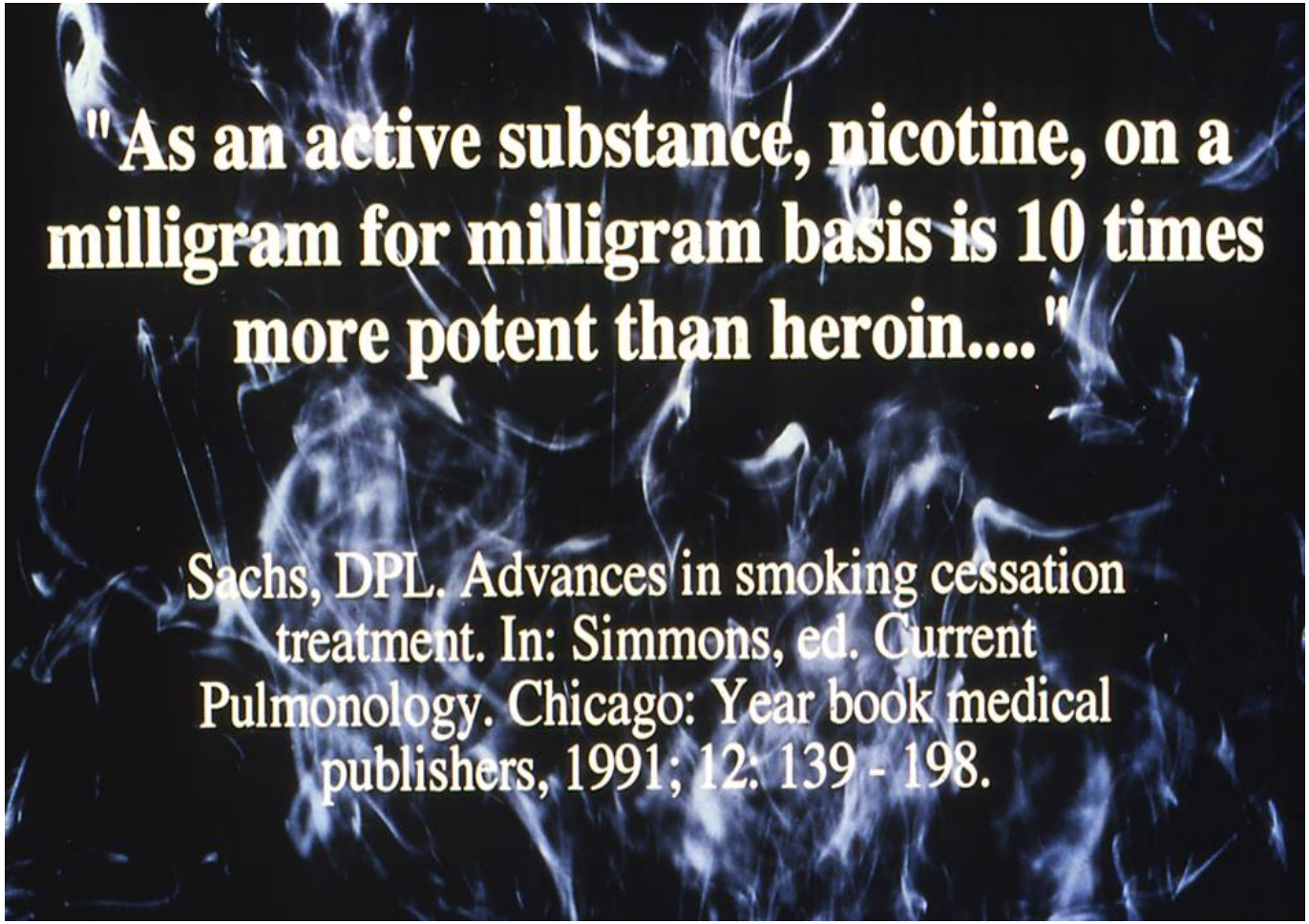
Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. J Oral Pathol Med 2018 Aug; 47: pp. 633-640.

Risk factors



Kujan, O. (2017). Human Oral Cancer (Epidemiology and Characteristic). In: Al Moustafa, AE. (eds) Development of Oral Cancer. Springer, Cham. https://doi.org/10.1007/978-3-319-48054-1_1

Smokers are also at **10 times** higher risk for oral cancer compared to non-smokers.



Risk factors

Moderate drinkers have 1.8-fold higher risks of oral cavity and pharynx cancers and 1.4-fold higher risks of larynx cancers than non-drinkers, and heavy drinkers have 5-fold higher risks of oral cavity and pharynx cancers and 2.6-fold higher risks of larynx cancers

Kujan, O. (2017). Human Oral Cancer (Epidemiology and Characteristic). In: Al Moustafa, AE. (eds) Development of Oral Cancer. Springer, Cham. https://doi.org/10.1007/978-3-319-48054-1_1

Risk factors

- **The combination of smoking and drinking is the most important aetiological factor for oral cancer and OPMDs**
- Many patients smoke and drink heavily (>5 standard drinks/day)
- Both of these account for up to 75% of all OPMD cases

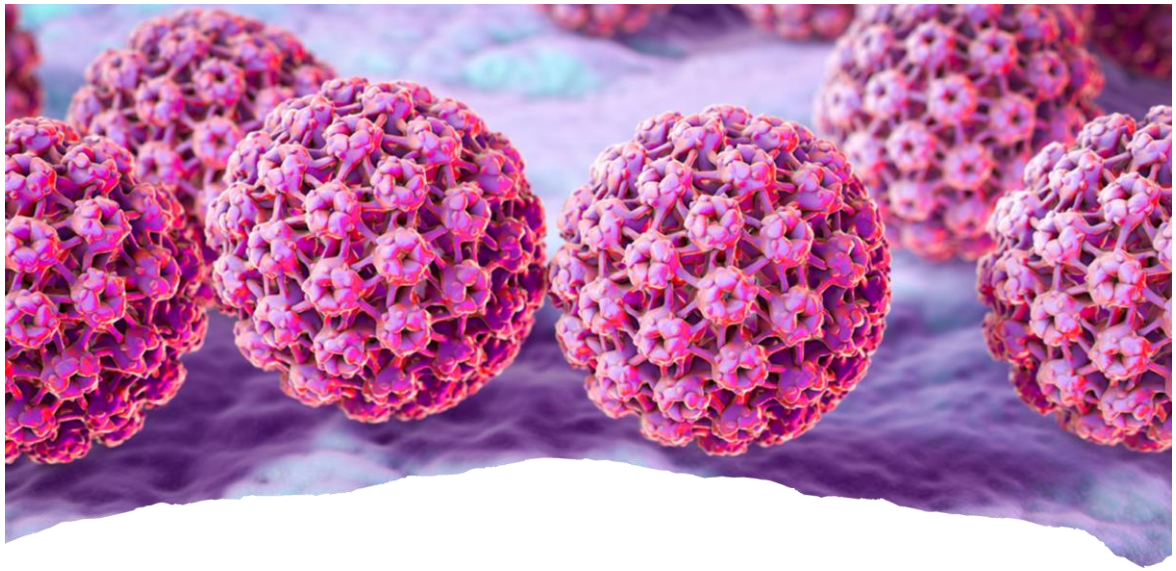
Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO Collaborating Centre for Oral Cancer. Oral Dis. 2021 Nov;27(8):1862-1880. doi: 10.1111/odi.13704.

Risk factors

Betel quid/Areca nut

- Areca nut
  - Abundant copper and flavonoids
    - Stabilize and enhance cross-linking of collagen
      - Fibrosis
  - Alkaloids (arecoline)
    - Stimulate collagen synthesis and reduce collagen degradation
    - Can be converted to carcinogenic nitrosamines
- Gutka
  - Powdered tobacco, slaked lime, and spices wrapped in *Piper betle* leaf, also referred to as "betel leaf"
    - more rapid development of oral lesions

Risk factors



HPV is thought to cause 70% of oropharyngeal cancers in the United States.

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Agenda

Clinical types

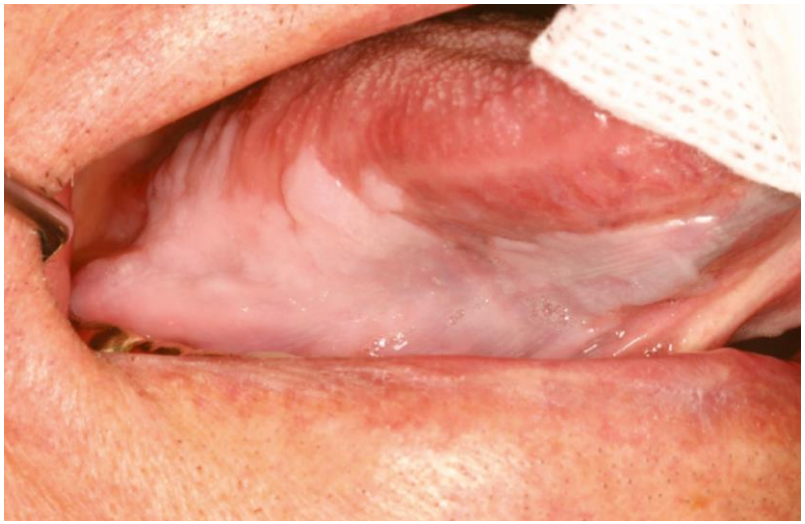
Leukoplakia
Persistent white patch that cannot be rubbed off. Generally asymptomatic

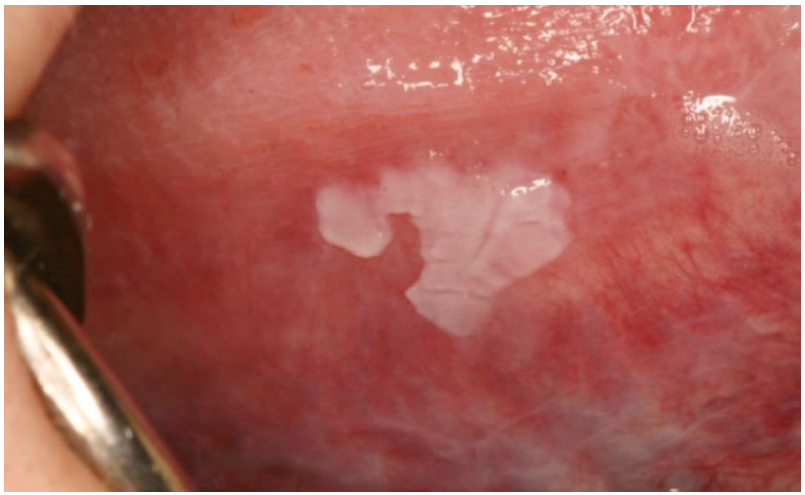
- 1-4% in Western countries
- Higher prevalence in SE Asia
- Global prevalence: 2-3%

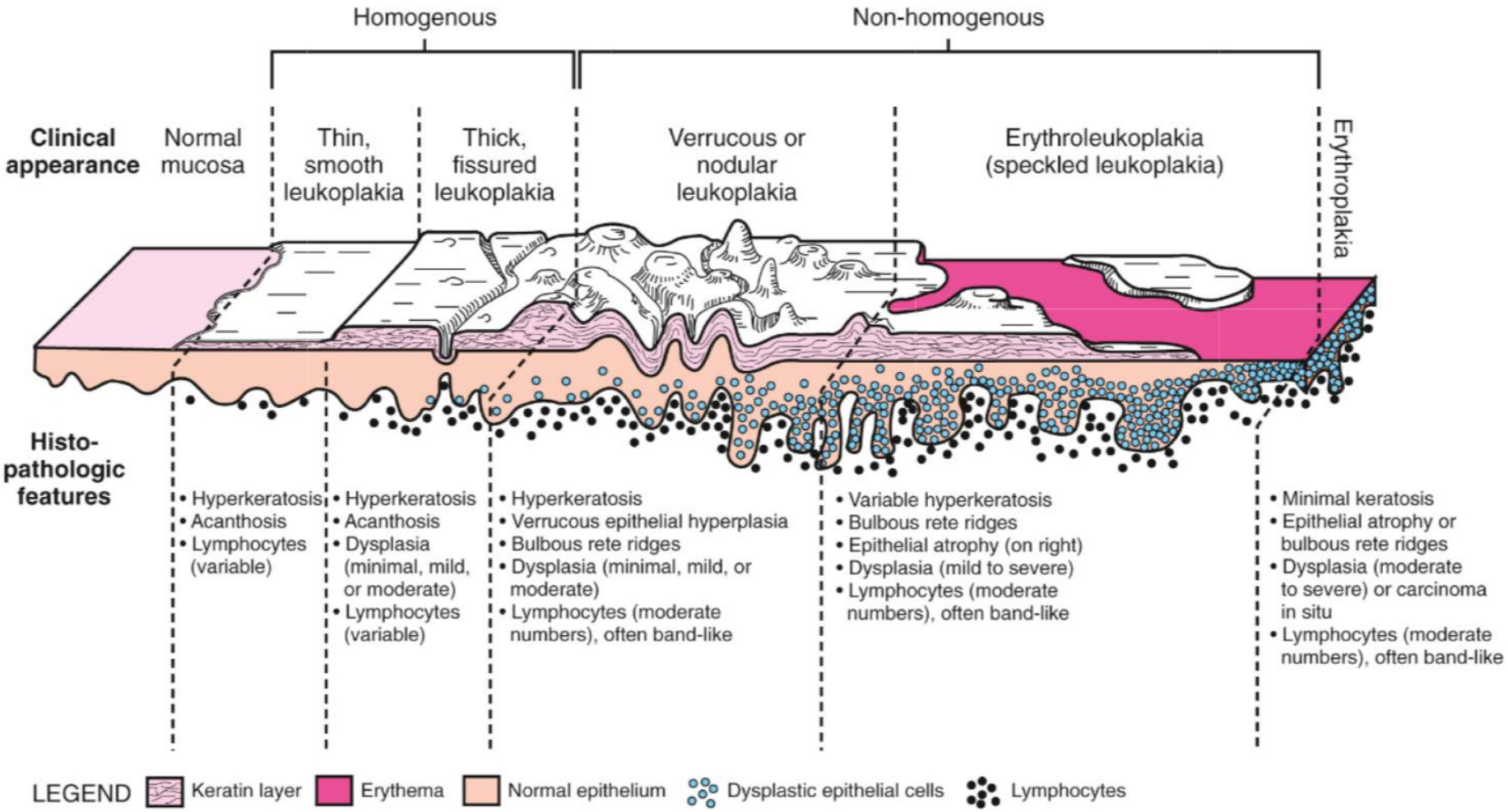
Homogeneous leukoplakia : Uniformly white, flat and thin, have a smooth surface and may exhibit shallow cracks.

Nodular leukoplakia : Small polypoid or rounded outgrowths, red or white excrescences.

Verrucous leukoplakia : The surface is raised, exophytic, wrinkled or corrugated

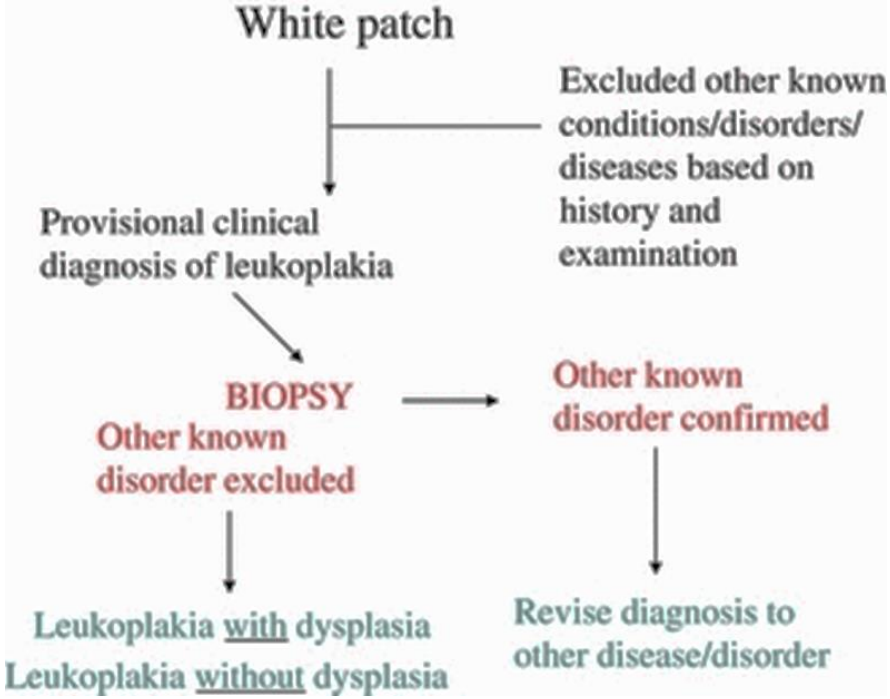






Bouquot JE, Gnepp DR. Laryngeal precancer: a review of the literature, commentary, and comparison with oral leukoplakia. Head Neck. 1991;13:488–497.

Leukoplakia



- White sponge naevus,
- Frictional keratosis,
- Alveolar ridge keratosis,
- Chemical injury,
- Acute pseudomembranous candidosis,
- Leukoedema,
- Fordyce's spots/ condition,
- Skin graft,
- Hairy leukoplakia,
- Leukokeratosis nicotina palate (Smoker's palate)

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J Oral Pathology Medicine, Volume: 36, Issue: 10, Pages: 575-580, First published: 26 July 2007, DOI: (10.1111/j.1600-0714.2007.00582.x)

Agenda

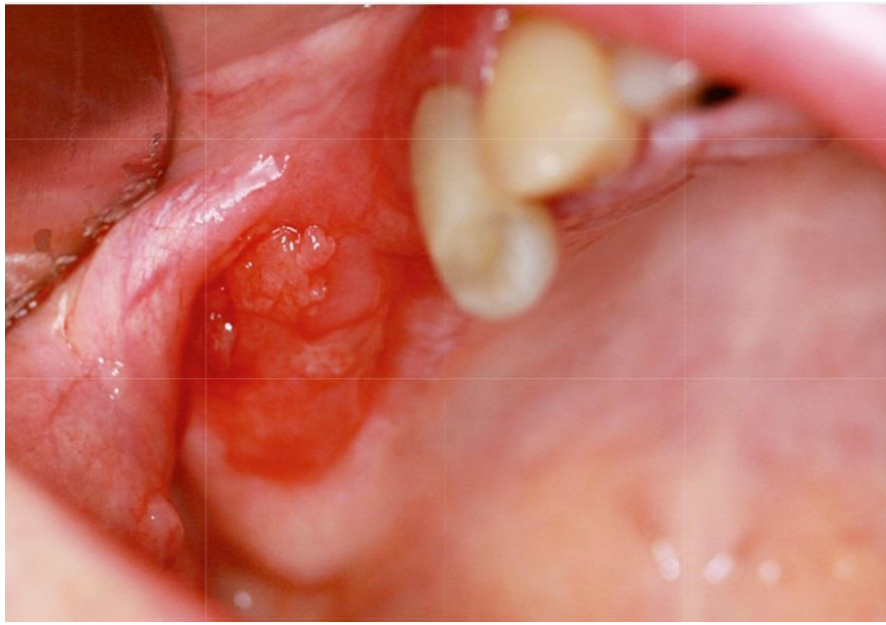
Clinical types

Erythroplakia

Defined as "A predominantly fiery red patch that cannot be characterised clinically or pathologically as any other definable disease"

Discomfort, tingling and sensitivity to touch, hot beverages or spicy foods

- Velvety
- Granular
- Red plaque
- Usually painless
- Flat or indurated



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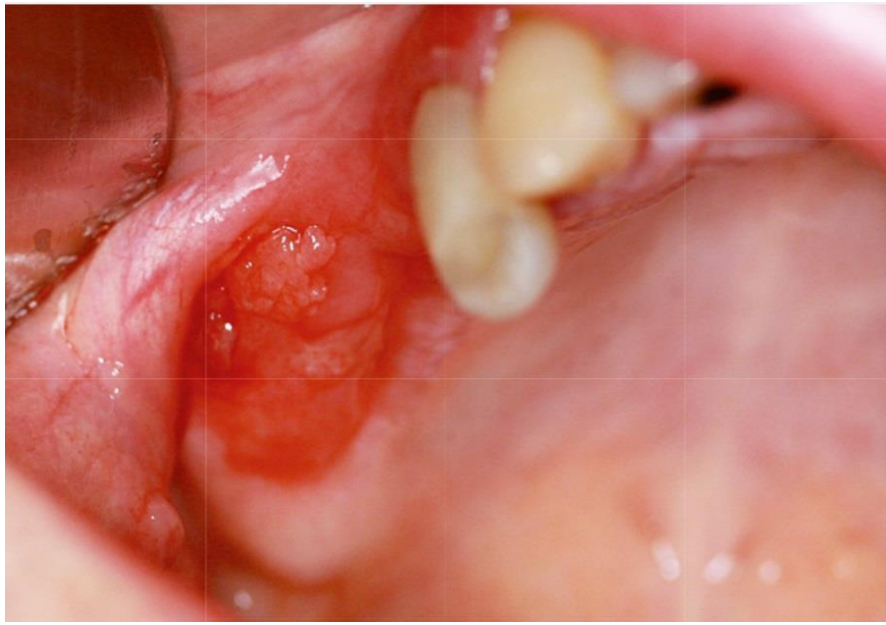
Agenda

Clinical types

Erythroplakia

Clinical conditions to exclude in the diagnosis

- Erythematous candidiasis,
- Denture-associated stomatitis on palate,
- Erythema migrans.
- Erosive and inflammatory / infective disorders, Desquamative gingivitis,
- Discoid lupus,
- Erosive lichen planus,
- Pemphigoid



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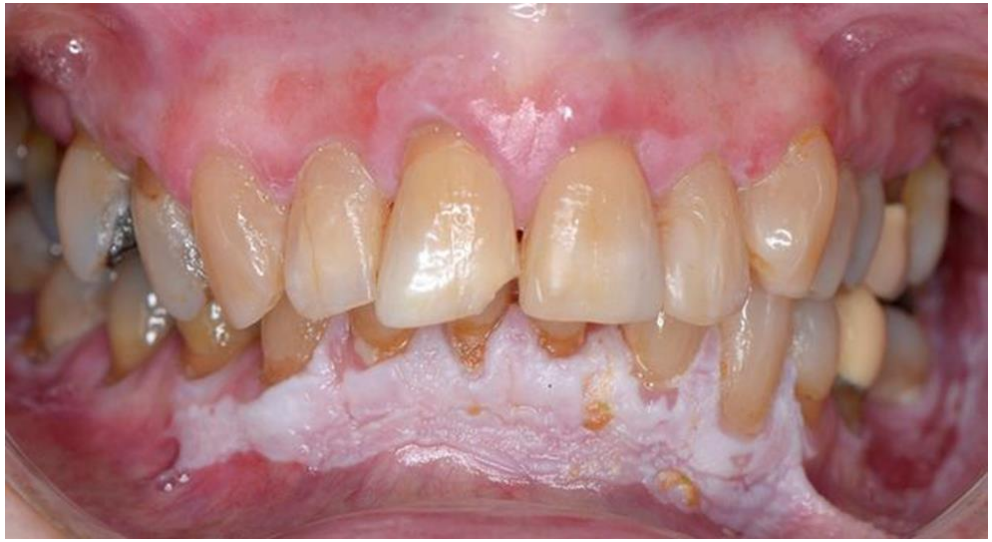
Proliferative verrucous leukoplakia

- 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



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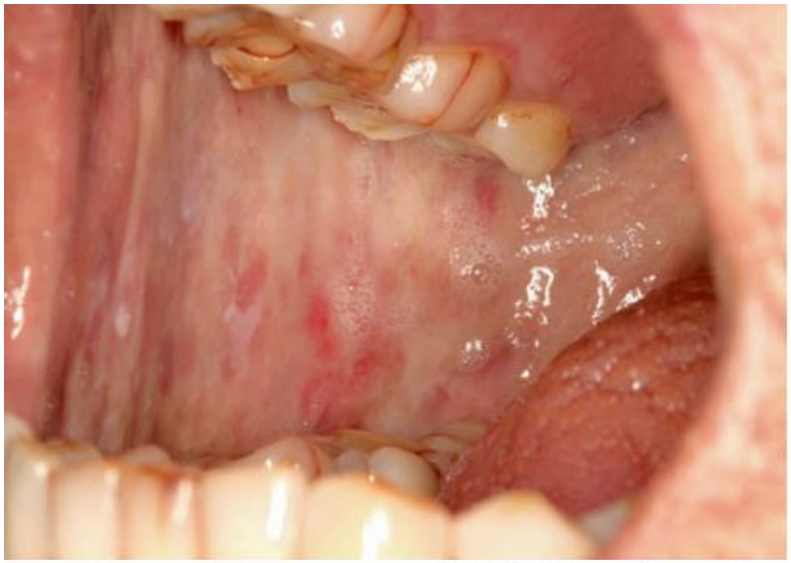
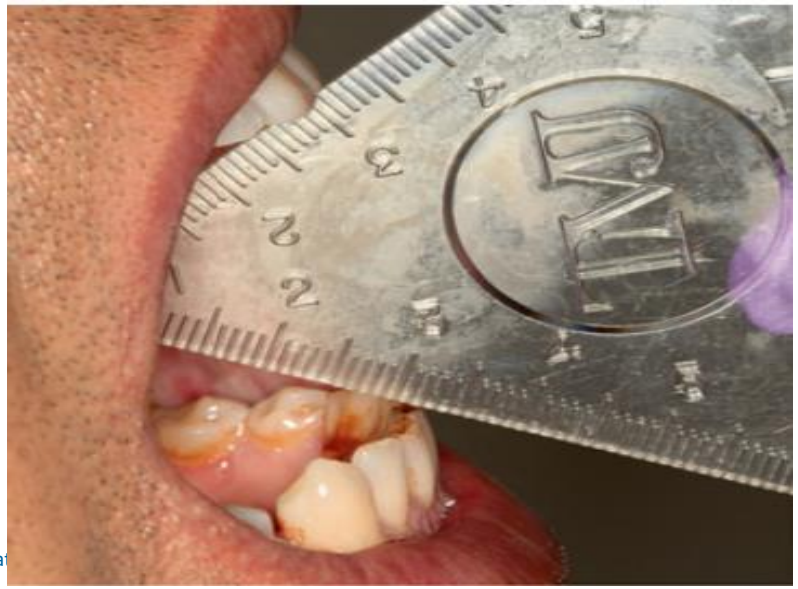
Oral submucous fibrosis

- Diffuse, pale, marble-like, and keratotic areas
- Sites
  - Buccal mucosa
  - Soft palate
  - Tongue
- Symptoms
  - Burning
  - Increasing trismus
- Clinical presentation
  - Blanching of oral mucosa
  - Marked loss of tongue papillae
  - Leathery mucosa
  - Fibrous bands
  - Limited mobility of tongue (rigidity)
  - Shrunken or deformed uvula
  - Limitation of mouth opening
  - Sunken cheeks





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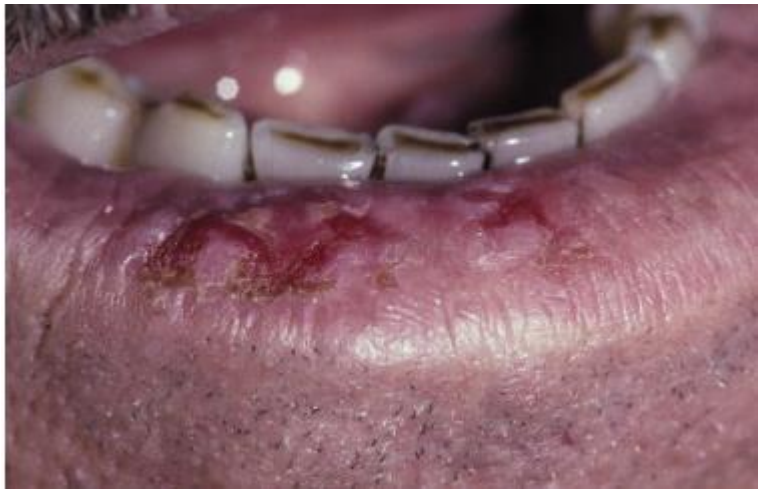
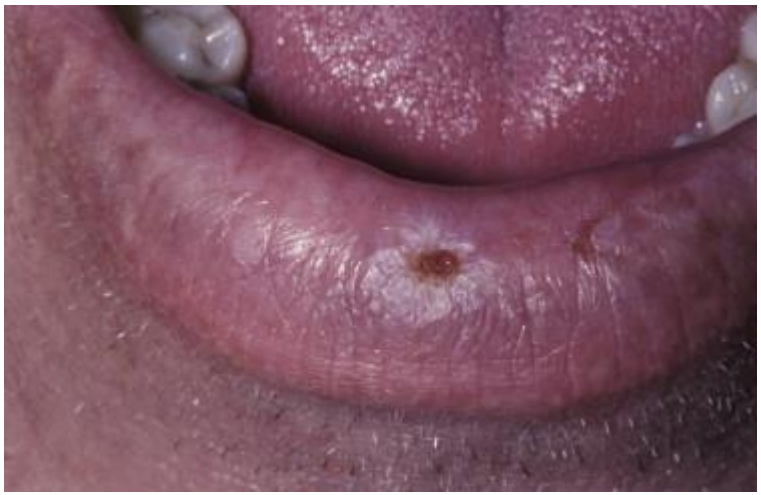
Actinic cheilitis

- UV light exposure
- Aetiopathogenesis similar to that of actinic keratosis of the skin
- Early
  - –Atrophy (smooth, blotchy, pale areas)
  - –Dryness
  - –Fissuring
  - –Blurring of the vermilion border
- Late
  - –Rough, scaly areas
  - –May develop leukoplakia





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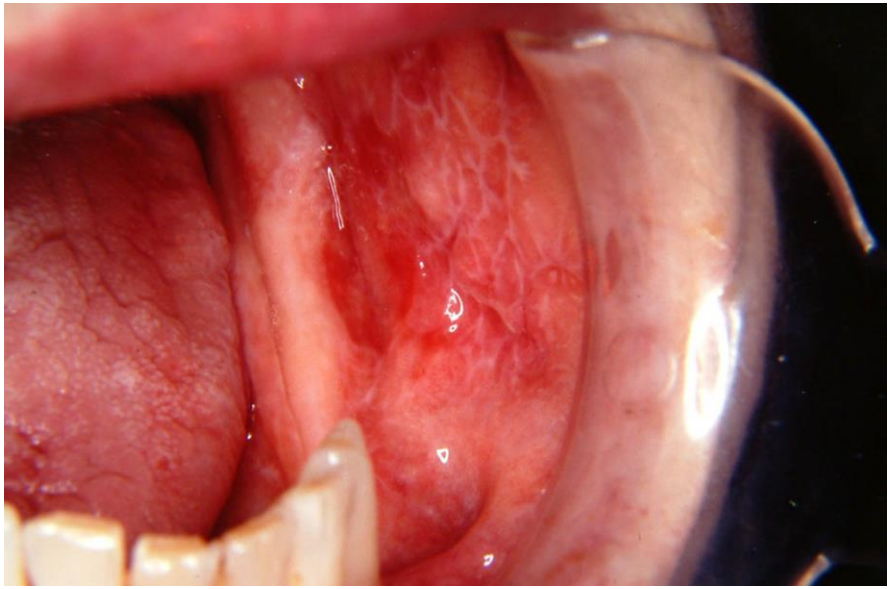
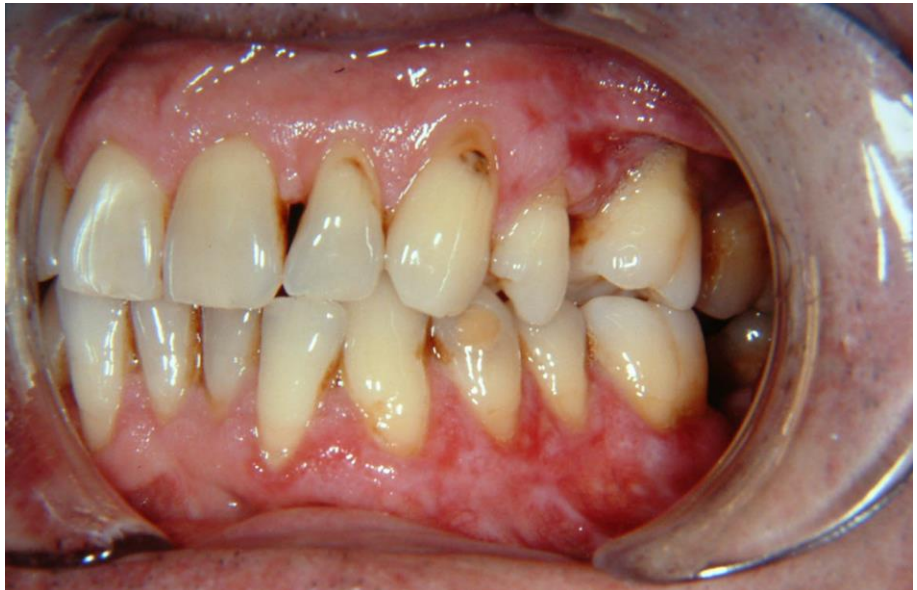
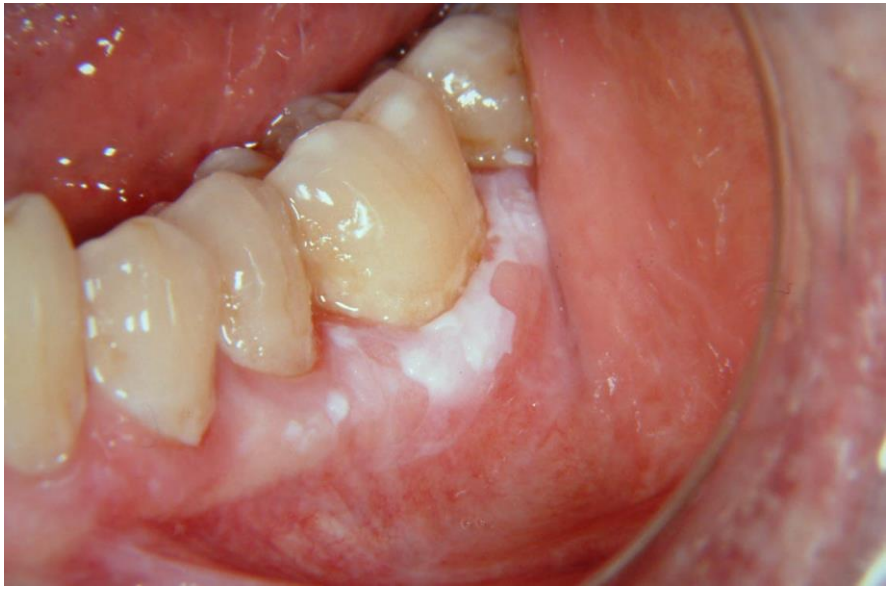
Lichen Planus

- Immune mediated
  - –T lymphocytes mainly
- Idiopathic vs drug induced
- Prevalence
  - –0.22-5% worldwide
  - –30-80 year
  - –Approximately 15% have cutaneous disease as well
- Females > Males

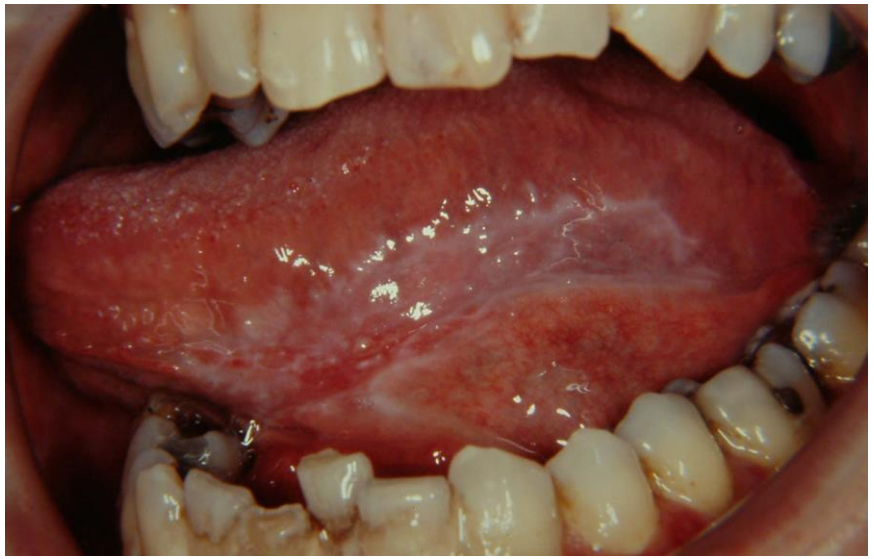


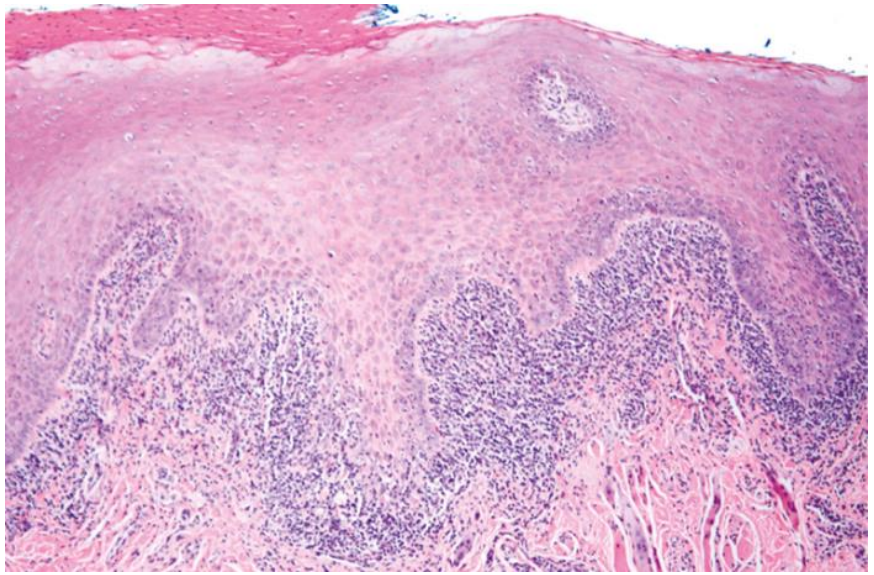




Lichen Planus

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
Histopathological 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

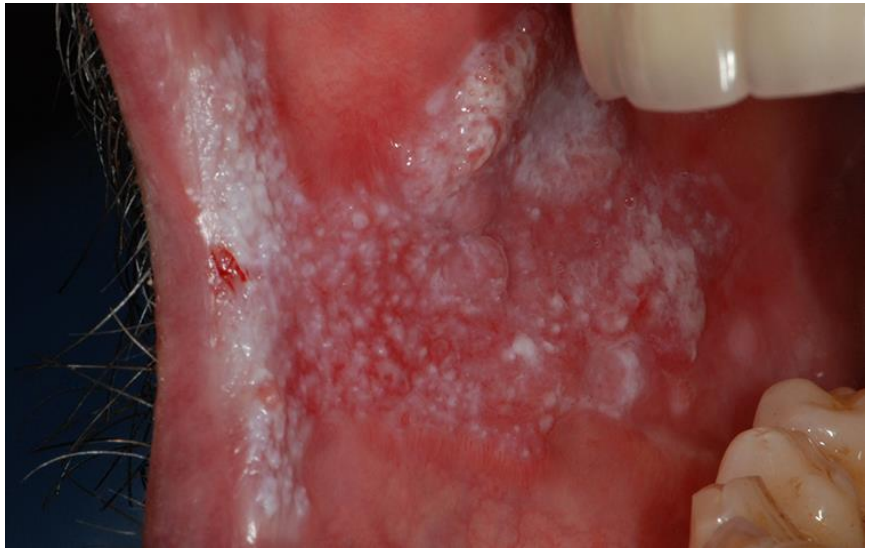




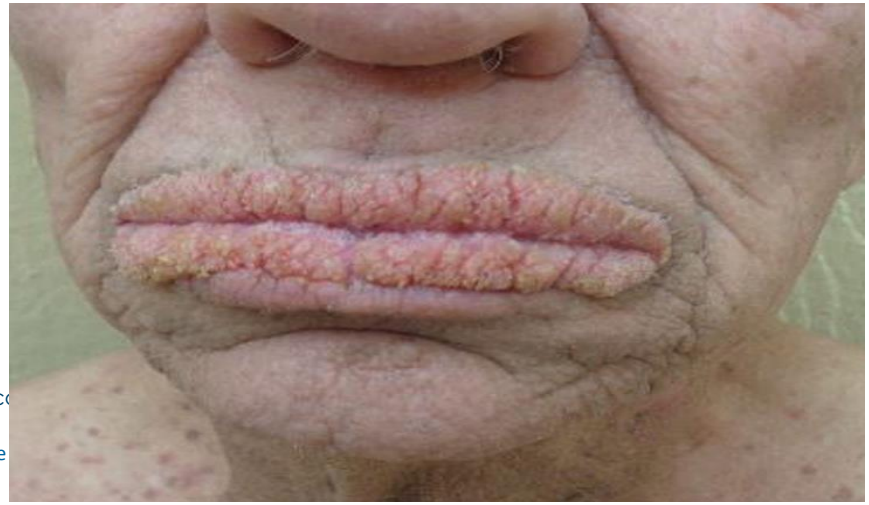
Agenda

Disorders with insufficient epidemiological evidence

- Chronic hyperplastic candidosis



- Exophytic verrucous hyperplasia/Oral verrucous hyperplasia



https://www.mdedge.com/dermatology/article/241469/dermatopathology/oral-verruc

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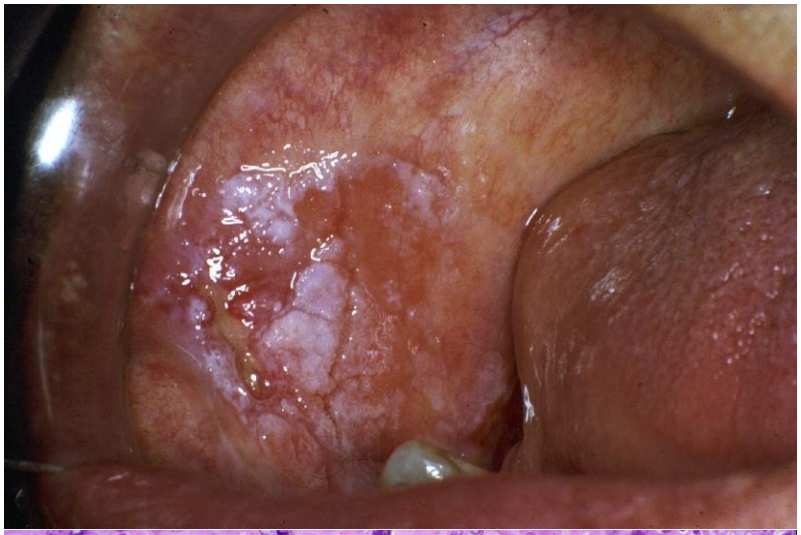

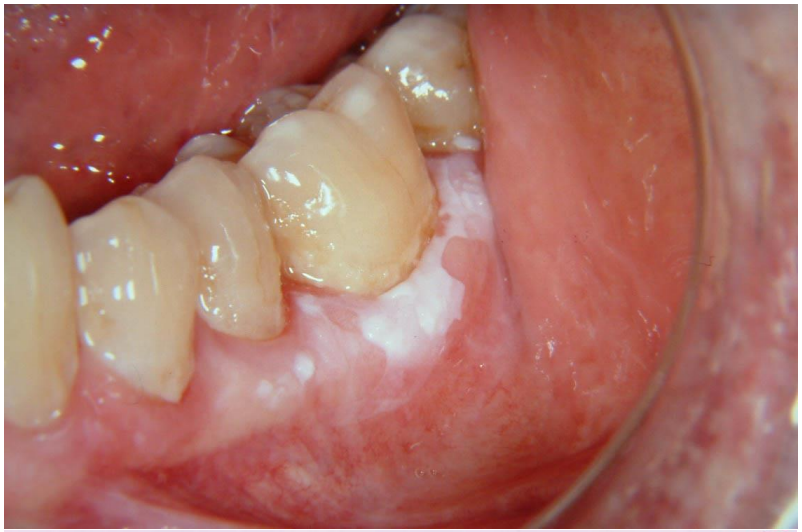

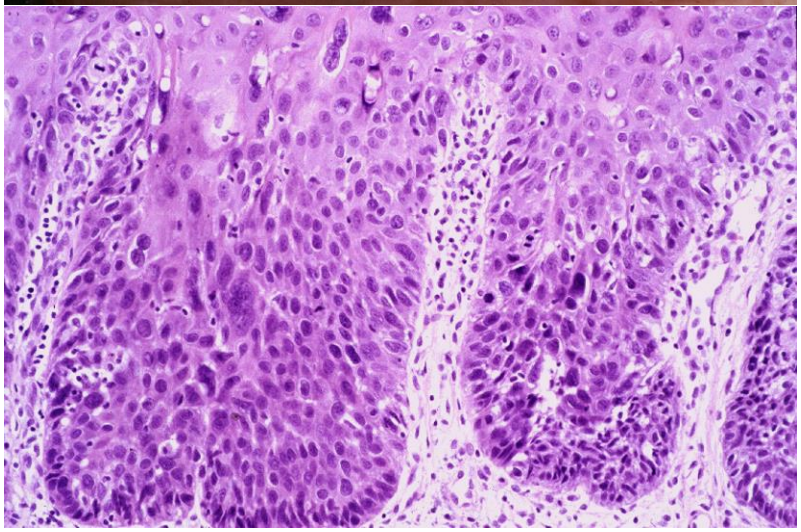

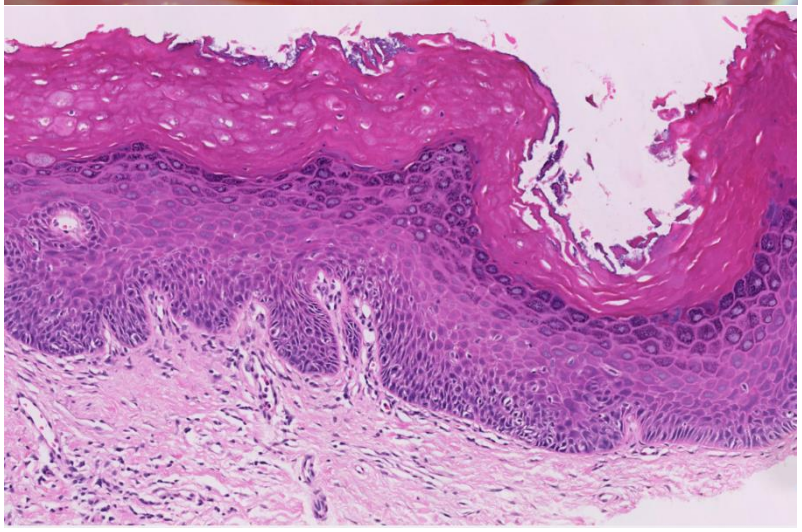

ORAL DISEASES
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REVIEW ARTICLE | Full Access

Oral epithelial dysplasia: Recognition, grading and clinical significance

Edward Odell, Omar Kujan, Saman Warnakulasuriya, Philip Sloan

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Abstract

Histopathological grading of epithelial dysplasia remains the principal laboratory method for assessing the risk of malignant transformation in oral potentially malignant disorders (OPMDs). Current views on the molecular pathogenesis and histological interpretation of the features of epithelial dysplasia are described, and the use of grading systems for epithelial dysplasia is discussed. Changes to the current 2017 WHO criteria for diagnosis are proposed with emphasis on the architectural features of epithelial dysplasia. The predictive values of three-grade and binary systems are summarised, and categories of epithelial dysplasia are reviewed, including lichenoid and verrucous lesions, keratosis of unknown significance, HPV-associated dysplasia, differentiated and basaloid epithelial dysplasia. The implications of finding epithelial dysplasia in an oral biopsy for clinical management are discussed from the pathologists' viewpoint.

WHO Classification 2017

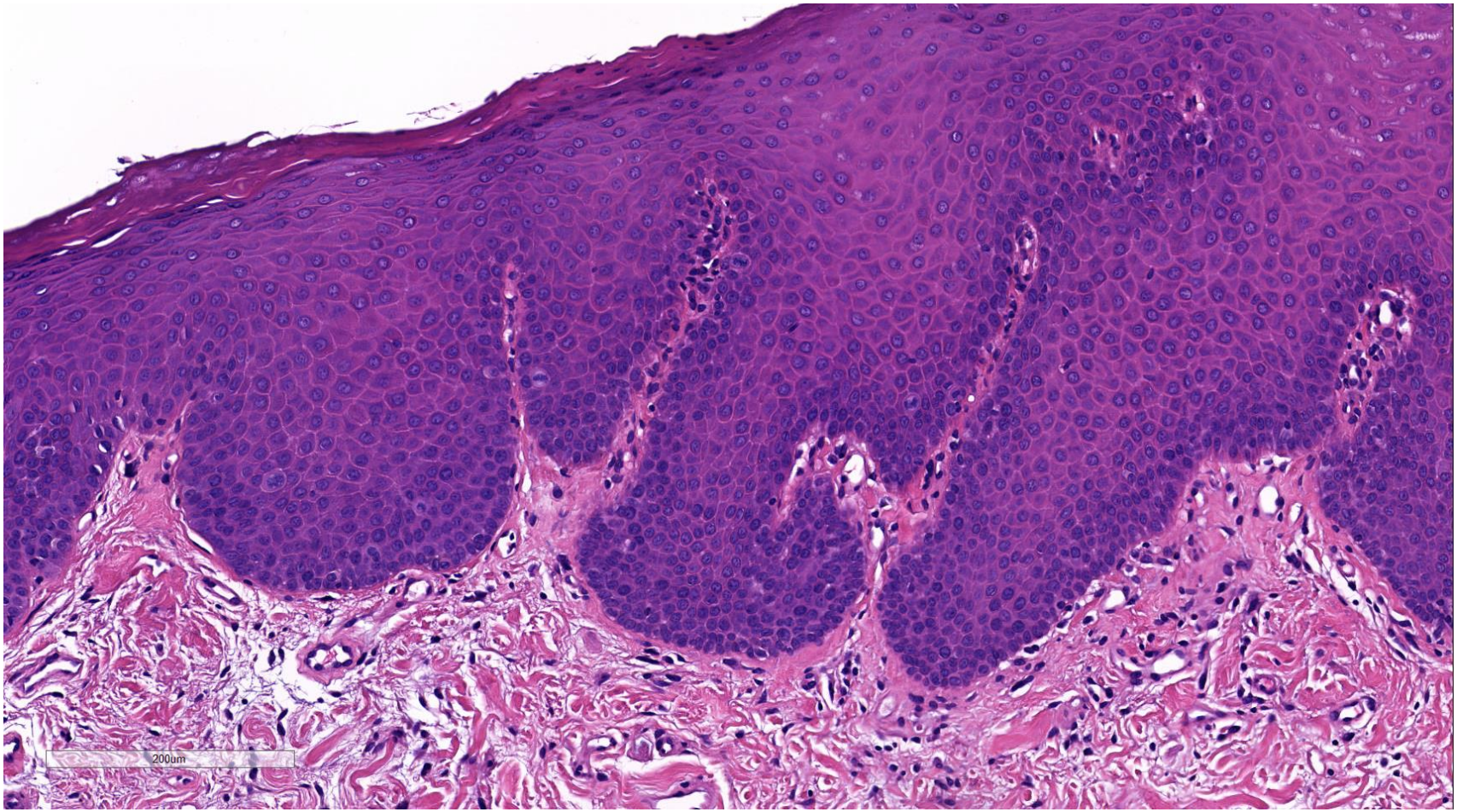
diagnostic criteria

Architectural changes	Cytological changes
Irregular epithelial stratification	Abnormal variation in nuclear size (anisonucleosis)
Loss of polarity of basal cells	Abnormal variation in nuclear shape (nuclear pleomorphism)
Drop-shaped rete ridges	Abnormal variation in cell size (anisocytosis)
Increased number of mitotic figures	Abnormal variation in cell shape (cellular pleomorphism)
Abnormally superficial mitotic figures	Increased nuclear-cytoplasmic ratio
Pre-mature keratinization in single cells (dyskeratosis)	Atypical mitotic figures
Keratin pearls within rete ridges	Increased number and size of nucleoli
Loss of epithelial cell cohesion	Hyperchromasia

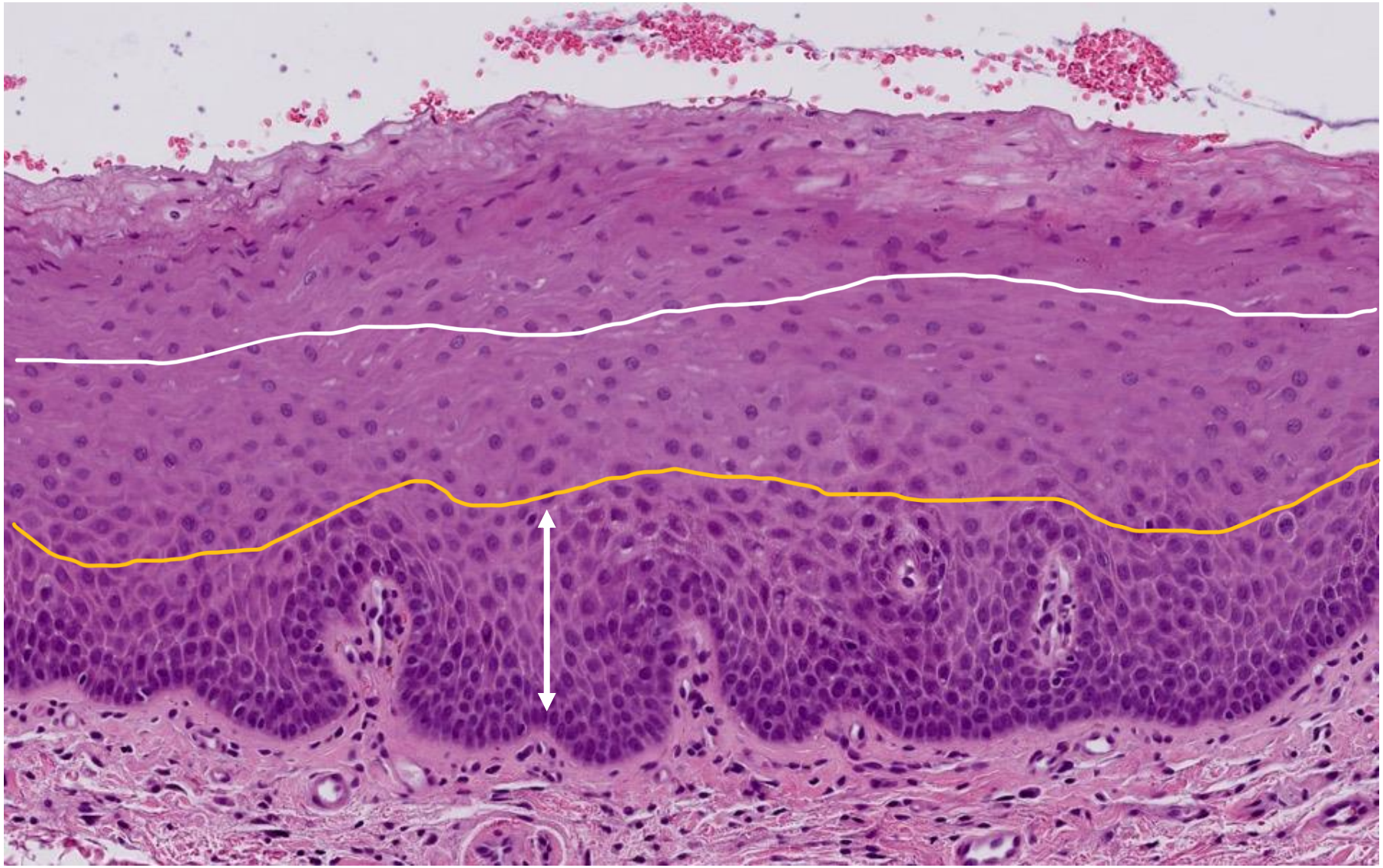
WHO Classification 2022

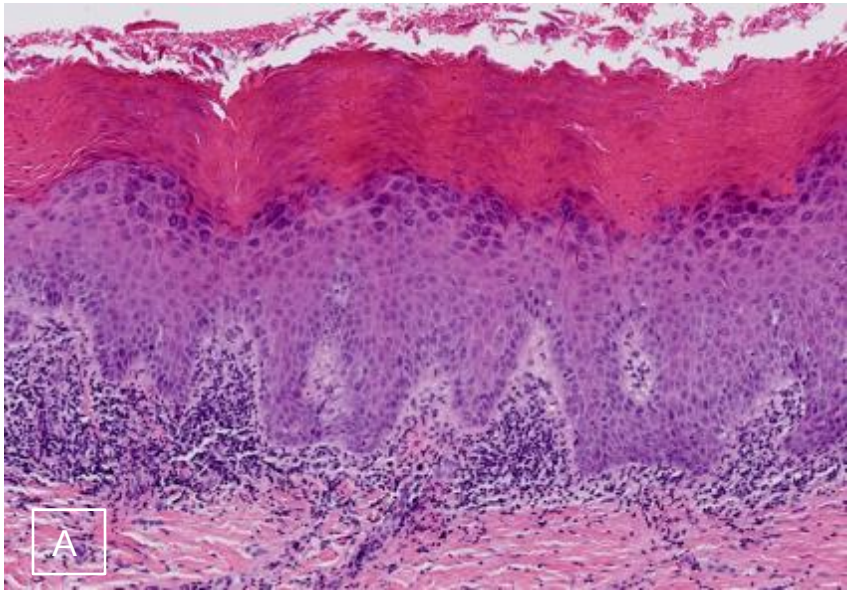
diagnostic criteria

Architectural Features	Cytological Features
Irregular stratification	Abnormal variation in nuclear size
Loss of polarity or disorganisation of basal cells	Abnormal variation in nuclear shape
Drop shaped rete processes	Abnormal variation in cell size
Basal cell clustering/nesting	Abnormal variation in cell shape
Expanded proliferative compartment	Increased mitotic activity
Mitoses high in epithelium	Increased nuclear size
Mitoses in maturing cells	Increased nucleus:cytoplasm ratio
Generalized premature keratinization	Atypical mitotic figures
Keratin pearls in rete processes	Increased number and size of nucleoli
Reduced keratinocyte cohesion	Single cell keratinisation
Altered keratin pattern for oral sub-site	Nuclear hyperchromasia
Verrucous or papillary architecture	Apoptotic mitoses
Extension of changes along minor gland ducts	
Sharply defined margin to changes	
Multiple different patterns of dysplasia	
Multifocal or skip lesions	



Hyperkeratosis and epithelial hyperplasia with no dysplasia (x100).

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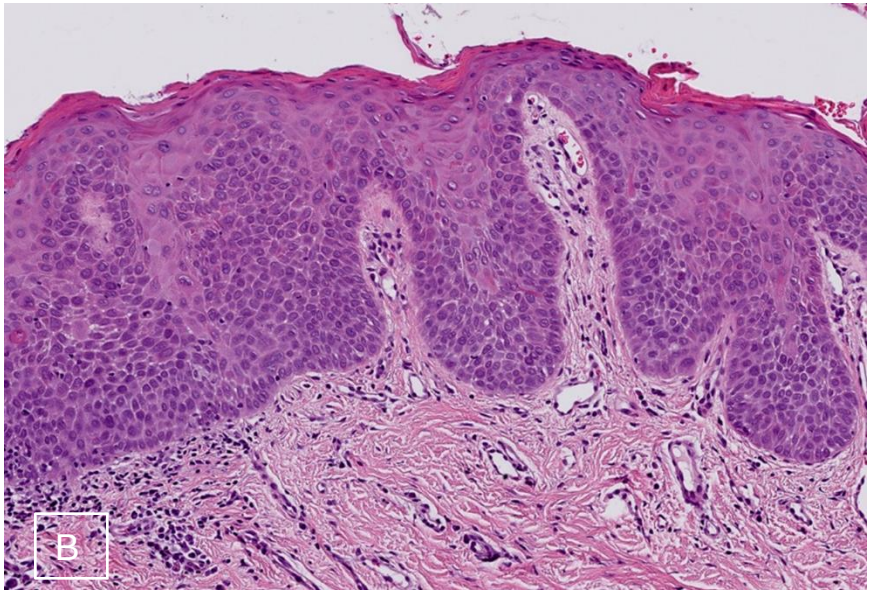
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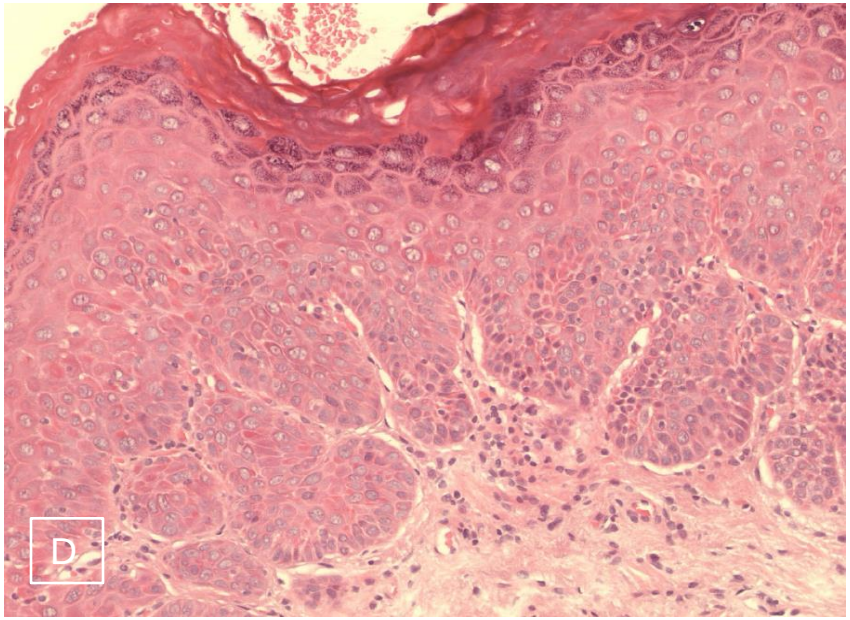
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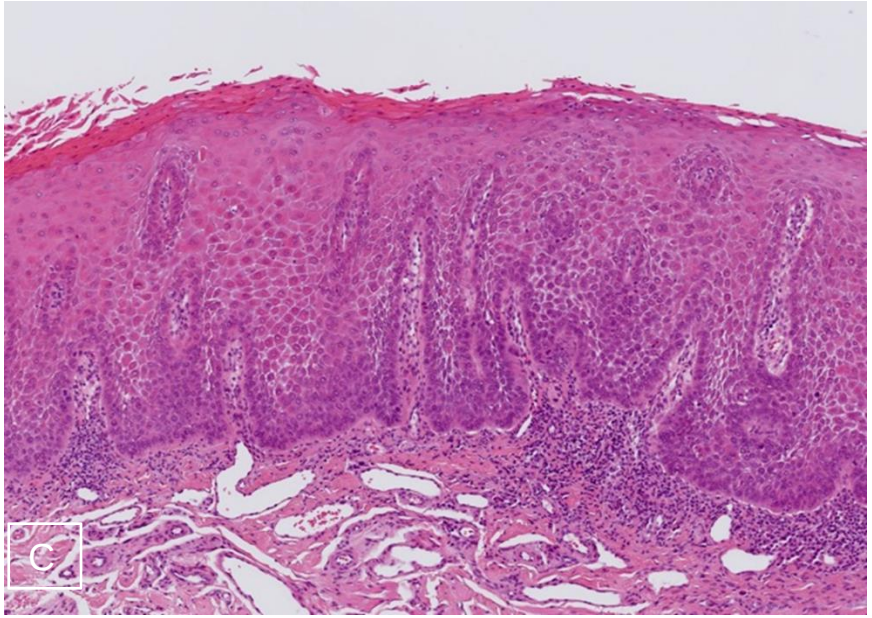
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ORAL ONCOLOGY

Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation

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OPMD Malignant transformation

- A systematic review of 92 studies indicated the overall malignant transformation rate across all OPMD groups was **7.9%** (99% CI = 4.9%-11.5%).
- Proliferative verrucous leukoplakia **49.5%** (99% CI 26.7%-72.4%).
- Erythroplakia **33.1%** (99% CI 13.6%-56.1%)
- Leukoplakia **9.5** (5.9%-14.00%)
- Oral Submucous Fibrosis **5.2%** (99% CI 2.9%-8.00%)
- Oral Lichenoid Lesions **3.8%** (99% CI 1.6%-7.00%)
- Lichen planus **1.4%** (99% CI 0.9%-1.9%)

Potentially malignant disorders of the oral cavity and oral dysplasia: A systematic review and meta-analysis of malignant transformation rate by subtype. Head Neck. 2020 Mar;42(3):539-555.

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Oral and Maxillofacial Pathology

Oral potentially malignant disorders: risk of progression to malignancy

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https://doi.org/10.1016/j.oooo.2017.12.011

Oral potentially malignant disorders (OPMDs) have a statistically increased risk of progressing to cancer, but the risk varies according to a range of patient- or lesion-related factors. It is difficult to predict the risk of progression in any individual patient, and the clinician must make a judgment based on assessment of each case. The most commonly encountered OPMD is leukoplakia, but others, including

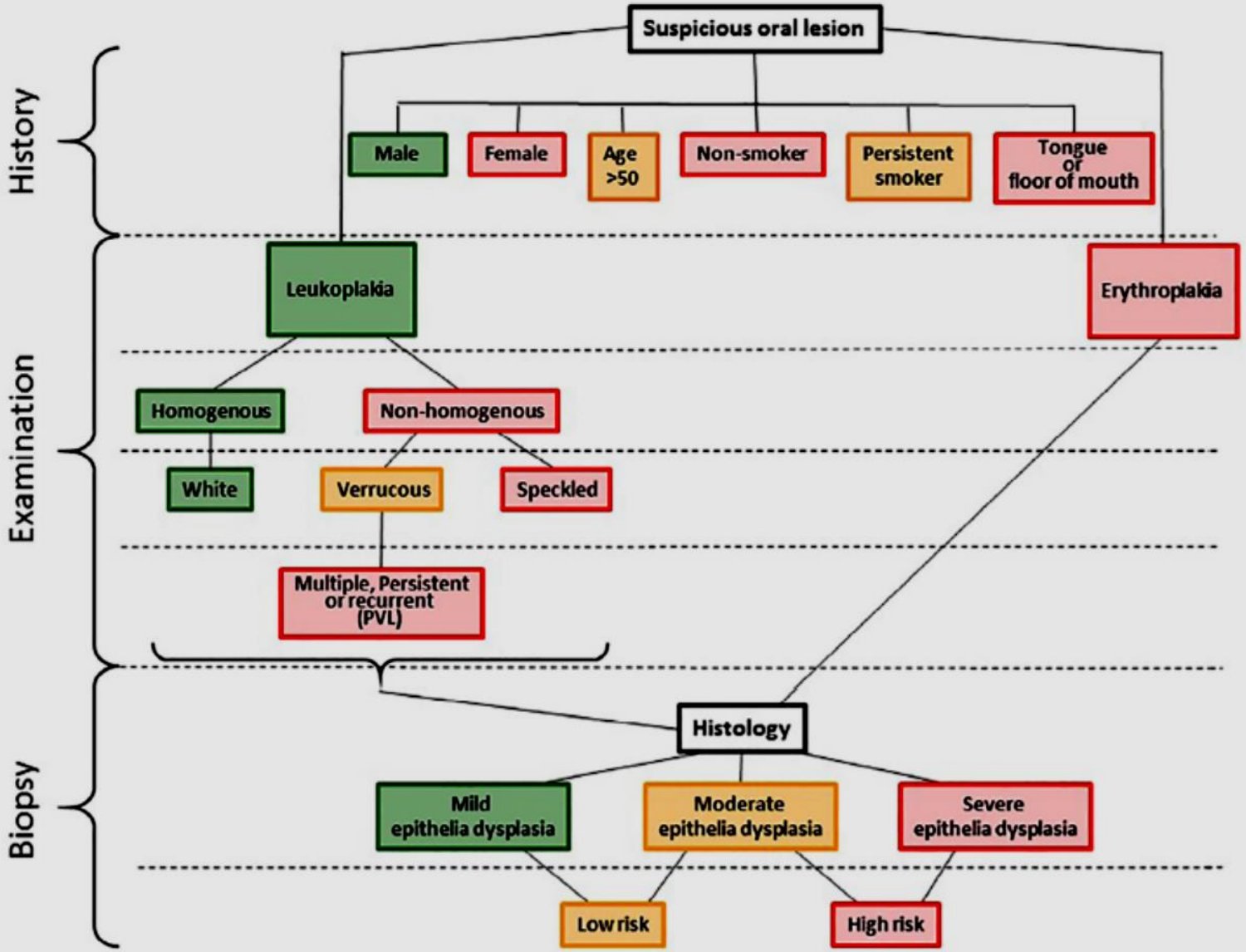

Fig. 3. A simple algorithm for clinical risk assessment of oral potentially malignant disorders (OPMDs). The clinician is faced with a suspicious oral lesion, and at each stage of the assessment process the risk of individual features are illustrated as green (low risk), amber (medium risk), or red (high risk). The levels of risk and explanations are given in the text.

OPMD Malignant transformation

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Features associated with an increased risk of malignant transformation of OPMDs

	Feature	Parameter	Association
Clinical features	Size of lesion	>200mm^2	Strong
	Texture	Nonhomogeneous	Strong
	Colour	Red (Speckled)	Strong
	Site	Tongue or floor of mouth	Strong
	Sex	Female	Medium
	Age	>50 years	Medium
	Habits	Nonsmoker	weak
Histological and molecular features	Dysplasia	Severe	Strong
		High-grade	Strong
	HPV	HPV +16	Medium
	DNA content	Aneuploidy	Medium
	LOH	Many genes involved	Medium

OPMD Malignant transformation

A recent systematic review revealed

- a higher rate of MT for non-homogeneous OL, affecting the tongue or the FOM, measuring >200mm^2, in patients without smoking habits.
- non-homogeneous OL have a higher chance of recurrence after treatment compared with homogeneous ones.
- PVL, we found a significantly higher risk of MT associated with the female sex.

Clinical predictors of malignant transformation and recurrence in oral potentially malignant disorders: A systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Nov;134(5):573-587.

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Differential diagnosis of mucosal lesions in the mouth

1.	**History of current illness** • **Onset, location, intensity, frequency, duration** • **Aggravating and/or relieving variables** • **Better, unchanged or worse over time**
2.	Medical, tobacco and alcohol history • Medical conditions • Medications and allergies • Tobacco and alcohol (type, frequency, duration)
3.	Clinical examination • Extraoral • Intraoral • Lesion inspection (adjunct tools)
4.	Differential diagnosis
5.	Diagnostic tests • biopsy
6.	Definitive diagnosis
7.	Suggested management

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Differential diagnosis of mucosal lesions in the mouth

- Number of possibilities
- High frequency of insignificant lesions
- Occasional very significant lesions

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Differential diagnosis of mucosal lesions in the mouth

- Not really an OPMD
- Normal
- Developmental
- Traumatic
- Infectious

- Idiopathic

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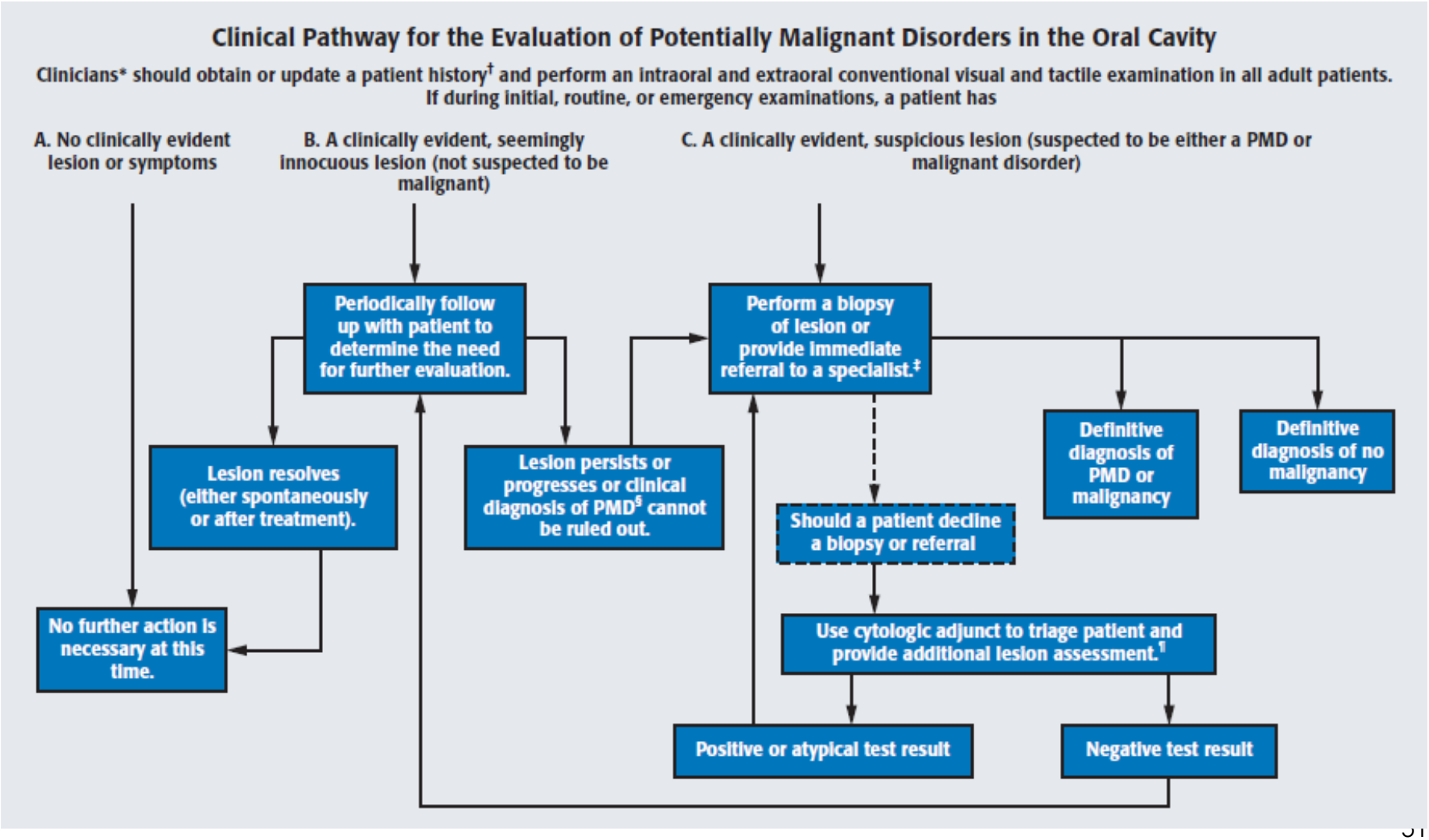
How to differentiate lesions

- Carcinoma?
- Is it normal?
- Evidence for a developmental condition?
- Habits and causes of friction?
- Does site help - CHC, OHL, SN
- Any striae?
- Risk features for dysplasia or malignancy?
- Smear it
- Biopsy it

Clinical tips



Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: A report of the American Dental Association. J Am Dent Assoc. 2017 Oct;148(10):712-727.e10.

Summary

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Oral cancer is a preventable disease
Early detection can improve survival rates and quality of life

Dentists and other dental team members play a significant role in detecting OPMDs

For patients with a clinically evident oral mucosal lesion considered to be suspicious of an OPMD, clinicians should perform a biopsy of the lesion or provide immediate referral to a specialist.

Cancer may arise during the natural history of an OPMD, patient follow-up at appropriate intervals is strongly recommended. The follow-up interval should be decided based on the individual's risk assessment and patient compliance

Quiz

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