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Oral Potentially Malignant Disorders: Early Detection, Risk Factors, and Management

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Abstract **Review Article**

Oral potentially malignant disorders (OPMDs) represent a diverse group of conditions affecting the oral mucosa that carry an increased risk of malignant transformation to oral squamous cell carcinoma (OSCC). Despite significant advances in understanding their etiology and pathogenesis, OPMDs continue to pose substantial challenges for clinicians, with global oral cancer mortality rates remaining largely unchanged over recent decades. This review synthesises current evidence on the epidemiology, risk factors, early detection modalities, and management strategies for OPMDs. Recent meta-analyses confirm that leukoplakia represents the most common OPMD, with an overall malignant transformation rate of approximately 6%, although proliferative verrucous leukoplakia demonstrates considerably higher transformation rates approaching 48%. Independent risk factors for malignant progression include severe epithelial dysplasia (HR 6.24), high-risk anatomical sites such as the ventral tongue and floor of mouth (HR 3.34), and betel quid chewing history (HR 2.62). Histopathological assessment of epithelial dysplasia remains the gold standard for risk stratification, though emerging evidence supports the potential utility of biomarkers such as DNA aneuploidy. Management has evolved towards risk-stratified approaches incorporating multidisciplinary team collaboration, with risk-adapted surveillance protocols ranging from six-monthly reviews for low-risk lesions to three-monthly monitoring for high-risk cases. This review critically examines contemporary classification systems, debates surrounding overdiagnosis, and novel therapeutic approaches including photodynamic therapy and immune checkpoint inhibition. The evidence underscores the need for standardised screening protocols, improved access to specialist care, and continued research into molecular predictors of malignant transformation to optimise patient outcomes and reduce the global burden of oral cancer..

Keywords: Oral potentially malignant disorders, leukoplakia, malignant transformation, epithelial dysplasia.

1. Introduction

Head and neck squamous cell carcinoma ranks as the sixth most common cancer globally, with approximately 900,000 cases annually, including over 400,000 new cases of oral cavity cancer and 178,000 deaths (Ge *et al*., 2025). Oral squamous cell carcinoma (OSCC) accounts for more than 90% of all oral malignancies and demonstrates a poorer prognosis than many other cancers, with a 5-year survival rate of approximately 50% (Ge *et al*., 2025). The recognition that many OSCCs arise from pre-existing mucosal abnormalities has focused attention on oral potentially malignant disorders (OPMDs) as critical targets for early intervention.

The terminology used to describe these conditions has evolved considerably over time. The World Health Organization (WHO) initially introduced the term "oral potentially malignant disorders" in 2007, a designation recently reaffirmed in a consensus report from the WHO Collaborating Centre for Oral Cancer (Celentano & Cirillo, 2024). This terminology is significant: the word "disorder" conveys the concept of mucosal field change, signalling an elevated risk of developing OSCC either at the same site as the original OPMD or elsewhere in the oral cavity. The deliberate selection of "potentially malignant" over "premalignant" acknowledges that while these conditions carry an increased statistical risk of evolving into OSCC, such progression is not inevitable (Celentano & Cirillo, 2024).

Early screening and intervention for OPMDs are widely recognised as the "golden window" for blocking progression to cancer and improving outcomes (Ge *et al*., 2025). However, current OPMD management faces three core challenges: weak screening awareness and lack of standardisation, ambiguous risk stratification leading to either overtreatment or inadequate follow-up, and the absence of multidisciplinary team (MDT) mechanisms in many healthcare settings (Ge *et al*., 2025). This review aims to synthesise current evidence on OPMDs, examining their epidemiology, risk factors, early detection methods, and contemporary management approaches to inform clinical practice and future research directions.

2. Definitions and Classification

2.1 Evolution of Terminology

The terminology for OPMDs has undergone substantial refinement over recent decades. Initially, terms such as "precancer," "premalignant," "precancerous lesions," or "precancerous conditions" were commonly used to describe oral mucosal changes with malignant potential (Kostandini *et al*., 2025). However, these terms proved restrictive and potentially misleading, as not all lesions inevitably progress to cancer, and some conditions affecting oral tissues contribute to carcinogenesis without presenting as specific lesions (Kostandini *et al*., 2025).

An OPMD is now defined as "any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer" (Celentano & Cirillo, 2024). The conditions described in the literature as potentially malignant disorders include erythroplakia, leukoplakia, lichen planus, oral submucous fibrosis, and actinic cheilitis (Kostandini *et al*., 2025).

2.2 Current Classification Systems and Controversies

Despite consensus on the core concept, significant inconsistencies persist in the classification of OPMDs. The list of disorders enumerated in the latest WHO Classification of Head and Neck Tumours differs from that presented in recent consensus documents, creating challenges for researchers and clinicians (Celentano & Cirillo, 2024). For instance, actinic cheilitis demonstrates a relatively well-established malignant transformation rate of approximately 14%, yet it has been earmarked for removal in the latest WHO classification, presumably due to its extraneous location outside the oral cavity and distinct pathogenesis (Celentano & Cirillo, 2024).

These inconsistencies extend to systemic diseases presenting with oral manifestations. Oral graft-versus-host disease, Fanconi anaemia, xeroderma pigmentosum, and other inherited cancer syndromes are variably included or excluded from OPMD lists, despite evidence that patients with these conditions face elevated risks of developing OSCC (Celentano & Cirillo, 2024). Notably, for some of these syndromes, no reports demonstrate a direct association with OSCC, and it remains unclear whether they should be classified alongside disorders with visible precursor lesions.

2.3 Proposed Refinements

Given these challenges, Celentano and Cirillo (2024) have proposed a revised classification framework that more accurately reflects the varying malignancy risks associated with different disorders. They suggest categorising diseases with oral malignant potential into three groups:

1. **Oral Precancerous Diseases**: Encompassing high-risk lesions and conditions such as erythroplakia, non-homogeneous leukoplakia, proliferative leukoplakia, and actinic keratosis.
2. **Oral Potentially Premalignant Diseases**: Covering lesions, conditions, and systemic diseases with distinct oral manifestations harbouring a limited or undefined risk of transformation, such as homogeneous leukoplakia, oral submucous fibrosis, oral lichenoid diseases, chronic hyperplastic candidosis, and keratosis of known aetiology.
3. **Systemic Conditions with Oral Malignant Potential**: Including Fanconi's anaemia, xeroderma pigmentosum, and chronic immunosuppression (including patients post-bone marrow transplantation), which are associated with an increased risk of oral cancer without necessarily presenting preceding precursor lesions.

This framework aims to mitigate overdiagnosis and alleviate patient burdens by more accurately reflecting the probability of malignant progression for different disorders (Celentano & Cirillo, 2024). The distinction is clinically important, as the diagnosis and subsequent management of OPMD can engender substantial out-of-pocket expenditures, precipitating catastrophic health-related financial burdens for households, while the psychological toll on patients manifesting as depression, anxiety, and stress is increasingly recognised (Celentano & Cirillo, 2024).

3. Epidemiology and Global Burden

3.1 Prevalence and Incidence

OPMDs exhibit considerable global variations in prevalence and types, heavily influenced by cultural, lifestyle, and environmental factors. The global prevalence of OPMDs is estimated at 4.47%, ranging from 1% to 5%, with higher rates in regions where risk factors such as tobacco, alcohol, and areca nut use are prevalent (Khodadadi *et al*., 2025). Males demonstrate higher prevalence rates than females, consistent with the gender distribution observed in oral cancer (Ge *et al*., 2025).

A recent epidemiological study of 58 patients with oral premalignant lesions found that males accounted for 62.06% of cases compared to 37.93% in females, corresponding to a 1.63:1 male-to-female ratio

(Kostandini *et al*., 2025). The majority of patients (77.57%) were aged between 50 and 79 years, with a tendency for lesions to appear earlier in men than in women.

3.2 Most Common OPMD Types

Oral leukoplakia represents the most common OPMD globally, comprising over half of all cases examined in recent studies (Naara *et al*., 2024; Ge *et al*., 2025). It presents as a white patch that cannot be scraped off or attributed to any other diagnosable condition (Khodadadi *et al*., 2025). The global prevalence of leukoplakia is estimated at 4.11% (95% CI: 1.98%–6.97%) (Khodadadi *et al*., 2025). In the study by Ge *et al*. (2025) involving 312 OPMD patients, oral leukoplakia accounted for 52.9% of cases, followed by lichen planus (10.3%).

Homogeneous leukoplakia was identified as the most common subtype in a recent epidemiological analysis, present in 44.8% of patients, followed by lichen planus (25.8%), erythroleukoplakia (6.8%), and nodular leukoplakia (1.7%) (Kostandini *et al*., 2025). Other lesions identified included palatal lesions of reverse cigar smoking (3.4%), nicotine stomatitis (8.6%), and keratosis from tobacco use (5.1%).

3.3 Anatomical Distribution

The anatomical location of OPMDs varies considerably and carries prognostic significance. Buccal mucosa represents the most common site, accounting for 31.03% of lesions in one series, followed by the floor of the mouth (22.4%), gingiva (17.2%), and lateral tongue (7.75%) (Kostandini *et al*., 2025). In younger patients, lesions more frequently involve the palate (median age 51) and lips (median age 40), while older patients more commonly present with lesions on the buccal mucosa (median age 70), floor of mouth (median age 64), and tongue (median age 59) (Kostandini *et al*., 2025).

The location of lesions also demonstrates gender variation: in men, the most common sites are the buccal mucosa and floor of the mouth, while in women, lesions more frequently involve the tongue and commissural areas (Kostandini *et al*., 2025). These distribution patterns have important implications for malignant transformation risk, as certain anatomical sites particularly the ventrolateral tongue and floor of mouth are associated with significantly higher progression rates (Ge *et al*., 2025).

3.4 Malignant Transformation Rates

Quantifying the risk of malignant transformation in OPMDs has been the subject of extensive investigation. A recent systematic review and meta-analysis by Khodadadi *et al*. (2025), encompassing 29 studies, demonstrated an elevated risk of oral cancer associated with OPMDs, with a summary odds ratio (SOR) of 2.5 (95% CI: 2.43-2.58). The highest risks were observed for leukoplakia (SOR 3.35, 95% CI: 3.21-3.50), erythroplakia (SOR 3.3, 95% CI: 3.21-3.50), and oral submucous fibrosis (SOR 2.9, 95% CI: 2.70-3.12). Subgroup and meta-regression analyses demonstrated a significant positive association between the development risk of oral cancer and both age and duration of follow-up.

An umbrella review specifically examining leukoplakia by Fatih *et al*. (2025) reported an overall malignant transformation rate of approximately 6% for conventional oral leukoplakia. However, considerably higher rates were observed for proliferative verrucous leukoplakia (PVL), which demonstrated a transformation rate of 48%, underscoring the importance of accurate subtyping in clinical practice. Females exhibited almost twice the malignant transformation rate of males (64% vs. 35%), while tongue lesions showed the highest site-specific risk (39%) (Fatih *et al*., 2025).

In the prospective cohort study by Ge *et al*. (2025), 21 of 312 patients (6.7%) underwent malignant transformation during a mean follow-up of 28.6 months. The transformation rate was significantly higher in the high-risk group (12.5%) compared to the intermediate-risk (3.5%) and low-risk groups (0%, $P<0.001$). Lesions located in the ventral tongue or floor of mouth demonstrated the highest transformation rate (11.2%), followed by those with severe dysplasia (10.0%). The median time to transformation was significantly shorter in the high-risk group (23.4 months, 95% CI: 18.6-28.2) compared to the intermediate-risk group.

4. Risk Factors for Development and Malignant Transformation

4.1 Established Risk Factors

Tobacco use remains the predominant risk factor for both the development of OPMDs and their subsequent malignant transformation. The International Agency for Research on Cancer (IARC) has consistently identified tobacco smoking and smokeless tobacco products as causal agents in oral carcinogenesis (Oral Health Foundation, 2026). In the study by Kostandini *et al*. (2025), 46.55% of patients with OPMDs were current smokers, and 13.79% were former smokers. Among smokers, 18.51% used hand-rolled tobacco, with most consuming 10-20 cigarettes daily over periods exceeding 10 years.

Alcohol consumption acts synergistically with tobacco to increase risk. In the same series, 34.48% of patients were moderate alcohol drinkers and 22.4% were heavy alcohol drinkers, with a strong association observed between smoking and regular alcohol consumption (Kostandini *et al*., 2025).

Betel quid chewing represents a major risk factor, particularly in South and Southeast Asian populations. Ge *et al*. (2025) identified betel quid chewing history as an independent risk factor for

malignant transformation (HR 2.62) in their multivariate Cox regression analysis. The study identified a specific high-risk subgroup: patients with a history of betel quid chewing, lesions located in the ventral tongue or floor of mouth, and a pathological diagnosis of mild dysplasia demonstrated a cumulative transformation rate of 9.1% despite their low pathological grade, leading the authors to recommend including all such patients in high-risk management categories.

Human papillomavirus (HPV) infection has been increasingly recognised as a risk factor for oropharyngeal cancers, though its role in OPMDs affecting the oral cavity proper remains less clearly defined (Australian Dental Association, 2025). The Australian Dental Association (2025) advocates for HPV vaccination as an essential measure to reduce the incidence of HPV-related oral and oropharyngeal cancers.

4.2 Histopathological Risk Factors

Epithelial dysplasia represents the most important predictor of malignant transformation. Histopathological examination of OPMDs typically reveals a spectrum of changes ranging from hyperkeratosis through various grades of dysplasia to carcinoma in situ. According to the 2017 WHO criteria, oral epithelial dysplasia is classified as low-grade (including mild and moderate dysplasia) when cytomorphological changes are confined to the lower half of the epithelium, and as high-grade (severe dysplasia) when changes involve more than half of the epithelial thickness (Kostandini *et al*., 2025).

Ge *et al*. (2025) identified severe epithelial dysplasia as the strongest independent predictor of malignant transformation, with a hazard ratio of 6.24 in their multivariate analysis. In their cohort, pathological biopsy revealed moderate to severe epithelial dysplasia in 23.1% of cases. Similarly, Kostandini *et al*. (2025) found that among lesions exhibiting dysplastic features, 11.76% demonstrated moderate to severe characteristics.

The grading of dysplasia, however, is not without controversy. Recent studies have challenged the ability of the current classification system to predict risks consistently, leading to proposals for alternative grading systems (Kostandini *et al*., 2025). Despite these limitations, histological assessment remains the cornerstone of risk stratification in clinical practice.

4.3 Anatomical Site as a Risk Factor

The anatomical location of OPMDs significantly influences malignant transformation risk. Ge *et al*. (2025) identified lesions located in the ventral tongue or floor of mouth as independent risk factors for progression, with a hazard ratio of 3.34. This finding aligns with the known high-risk nature of these sites in oral cancer epidemiology, likely reflecting differences in epithelial thickness, vascular supply, and exposure to carcinogens retained in saliva.

The umbrella review by Fatih *et al*. (2025) confirmed that tongue lesions show the highest site-specific risk for malignant transformation, with 39% of transformed lesions originating at this site. This finding has important implications for surveillance protocols and patient counselling.

4.4 Emerging Risk Factors and Controversies

Recent research has identified additional factors that may influence OPMD progression. Chronic mucosal injuries have been associated with an increased relative risk of OSCC in large retrospective studies, and a retrospective analysis of real-world data from approximately 150,000 patients revealed a significantly elevated risk of developing OSCC in individuals with recurrent aphthous stomatitis (Celentano & Cirillo, 2024). However, the inclusion of such conditions within the OPMD classification remains controversial, as the evidence base for their malignant potential varies considerably.

The concept of field cancerisation, originally described by Slaughter in the 1950s, has gained renewed attention in understanding OPMD progression. Field cancerisation describes a broad area of tissue that has undergone precancerous changes, extending beyond a single tumour or lesion (Celentano & Cirillo, 2024). While evidence of field cancerisation exists in clinically normal oral mucosa, evidence for field defects in OPMDs is limited, and this remains an active area of investigation.

5. Early Detection and Diagnosis

5.1 Clinical Examination

Conventional oral examination (COE) remains the current standard for OPMD detection (Khodadadi *et al*., 2025). The Australian Dental Association (2025) recommends that inspection for oral cancer should include direct visualisation and palpation of the mucosa of the oral cavity and external lip, as well as palpation of the head and neck lymph nodes, and should occur annually as part of comprehensive examination. All individuals, including the edentulous, should be encouraged to have annual oral cancer screening.

Ge *et al*. (2025) emphasise that traditional reliance on "visual and tactile examination" is highly subjective, necessitating standardised procedures and supportive technologies. They propose a screening pathway comprising initial screening (questionnaire plus visual/tactile examination) followed by refined screening (pathological biopsy). The questionnaire should record history of smoking, alcohol consumption, betel quid chewing, HPV exposure, systemic diseases, and symptom duration. Visual and tactile examination should include standardised recording of lesion location, size, colour, texture, borders, and bleeding tendency.

Preliminary risk assessment using a simple checklist (e.g., red or white patch exceeding 1 cm combined with risk factors) triggers referral to a specialist.

5.2 Histopathological Assessment: The Gold Standard

Biopsy remains the gold standard for differentiating OPMDs and grading epithelial dysplasia (Khodadadi *et al*., 2025; Naara *et al*., 2024). The biopsy principle requires sampling from the most abnormal area including the border zone (Ge *et al*., 2025). Histopathological examination provides not only diagnostic confirmation but also critical prognostic information through the assessment of dysplasia grade.

Naara *et al*. (2024) highlight that advances in histological grading, specifically the WHO's three-tier system (mild, moderate, and severe dysplasia), have significantly enhanced the accuracy of risk assessment for malignant transformation. However, they acknowledge that the management of OPMDs remains challenging due to the lack of standardised screening protocols and varied clinical management approaches.

Kostandini *et al*. (2025) found that 75% of lesions in their series showed no dysplastic characteristics, while 76.4% of those with dysplastic features exhibited moderate to severe changes. The degree of dysplasia was associated with the type of oral premalignant lesion but not significantly with lesion size. Dysplasia was significantly more common in patients with a family history of cancer and those with a personal history of cancer, with a slight increase observed in older patients and women.

5.3 Adjunctive Diagnostic Tools

Studies have shown that adjunctive tools can assist in the detection and risk evaluation of OPMDs (Khodadadi *et al*., 2025). These include:

Chemiluminescence and tissue autofluorescence: These technologies enhance visualisation of mucosal abnormalities by highlighting changes in tissue reflectance or fluorescence. However, they support but do not replace conventional oral examination and biopsy (Khodadadi *et al*., 2025).

Vital staining: Toluidine blue staining has been used to identify areas of increased nucleic acid content, potentially indicating dysplasia or malignancy. The technique is inexpensive and provides immediate results but suffers from variable sensitivity and specificity.

Cytology techniques: Oral brush biopsy with computer-assisted analysis offers a non-invasive sampling method, particularly useful for large or multiple lesions where multiple biopsies might be impractical. However, histopathology remains necessary for definitive diagnosis of lesions with positive or atypical cytology findings.

Emerging technologies: Recent developments have introduced new methods for diagnosis, including immunocytochemistry, fluorescence imaging, and laser confocal microscopy, which may prove more accurate and cost-effective than traditional methods (Kostandini *et al*., 2025). Confocal microscopy can provide real-time histological information without tissue removal, though its clinical utility requires further validation.

5.4 Biomarkers and Molecular Predictors

The identification of biomarkers that predict malignant transformation could allow for more personalised management strategies focusing on high-risk individuals (Khodadadi *et al*., 2025). The umbrella review by Fatih *et al*. (2025) evaluated multiple potential biomarkers and identified DNA aneuploidy as the most promising predictor with a moderate level of evidence quality for clinical application.

Other molecular markers under investigation include loss of heterozygosity, p53 mutations, and various microRNA expression profiles (Khodadadi *et al*., 2025). Advances in molecular biology are paving the way for more targeted approaches to diagnosing, staging, and managing OPMDs, though further research is needed before these tools enter routine clinical practice.

6. Risk Stratification and Management

6.1 Principles of Risk-Stratified Management

Contemporary OPMD management has evolved towards risk-stratified approaches that tailor intervention intensity to individual patient risk profiles. The goal is to optimise outcomes by focusing resources on high-risk individuals while avoiding overtreatment and unnecessary anxiety in low-risk patients.

Ge *et al*. (2025) developed and validated a risk stratification system based on a modified scoring system incorporating features associated with proliferative verrucous leukoplakia. Patients are stratified into three groups:

- Low-risk (0-4 points): 6-month review
- Intermediate-risk (5-8 points): 3-month review with clinical and photographic documentation
- High-risk (≥9 points): 3-month review with MDT consultation and consideration of active intervention

This approach successfully identified significant differences in malignant transformation rates between groups (12.5% in high-risk vs. 3.5% in intermediate-risk vs. 0% in low-risk, $P<0.001$), validating its clinical utility.

6.2 Surveillance Protocols

Regular follow-up is essential for all patients with OPMDs, regardless of initial risk stratification. The optimal frequency of review depends on individual risk factors, lesion characteristics, and previous history.

For low-risk lesions (homogeneous leukoplakia without dysplasia in low-risk anatomical sites), 6 to 12-month review is generally considered adequate (Ge *et al*., 2025; Khodadadi *et al*., 2025). For intermediate and high-risk lesions, 3-month review is recommended, with careful documentation of lesion characteristics using clinical photography to detect subtle changes over time (Ge *et al*., 2025).

Indications for repeat biopsy include lesion enlargement, change in colour or texture, development of symptoms (pain, bleeding, ulceration), or failure to respond to cessation of risk factors (Ge *et al*., 2025). Annual review of all OPMD patients, with repeat biopsy as indicated by clinical changes, represents a prudent approach.

6.3 Multidisciplinary Team Approach

The complexity of OPMD management, particularly for high-risk lesions, necessitates a multidisciplinary team (MDT) approach. Ge *et al*. (2025) implemented an MDT model involving collaboration between Oral Pathology, Head and Neck Surgery, Oncology, and Otolaryngology departments. The process follows: initial diagnosis in Oral Medicine with biopsy confirmation, MDT consultation for high-risk cases to determine treatment plan, treatment implementation by Oral Medicine or Surgery, oncology follow-up if malignant transformation occurs, and shared data platform for ongoing monitoring.

The MDT model achieved a 2-year cancer-free survival rate of 91.4% in high-risk patients and improved follow-up compliance to 83.3% (Ge *et al*., 2025). These findings support the of MDT-based approaches in OPMD management, particularly for high-risk cases where treatment decisions are complex and require multidisciplinary input.

6.4 Therapeutic Interventions

Surgical management remains the mainstay of treatment for localised OPMDs with dysplasia or high-risk features. Complete excision with clear margins is the goal, though this may be challenging for extensive or multifocal lesions. The evidence base for surgical intervention preventing malignant transformation is limited by the absence of randomised controlled trials, but observational data support excision of high-risk lesions where feasible.

Non-surgical approaches are increasingly being evaluated. Photodynamic therapy (PDT) involves application of a photosensitising agent followed by light activation to destroy abnormal cells. Naara *et al*. (2024) note that PDT is being evaluated for safety and efficacy in OPMD management, with promising early results for certain lesion types.

Chemoprevention aims to reverse or arrest the progression of OPMDs using pharmacological agents. Retinoids, cyclooxygenase inhibitors, and other agents have been investigated, though results have been mixed and toxicity concerns limit long-term use. Naara *et al*. (2024) report that chemopreventive and molecularly targeted agents are being evaluated for their safety and efficacy in preventing OPMD progression.

Immune checkpoint inhibitors represent a novel approach being evaluated as potential preventive strategies to halt the progression of OPMDs (Naara *et al*., 2024). While currently in early stages of investigation, immunotherapy may offer new options for patients with high-risk lesions not amenable to surgical management.

6.5 Lifestyle Modification and Patient Education

Cessation of risk factors is fundamental to OPMD management. All patients should be counselled regarding tobacco cessation, alcohol reduction, and cessation of betel quid use where applicable. The Australian Dental Association (2025) supports education and programs aiming to reduce high-risk behaviours and advocates for HPV vaccination as an essential measure to reduce the incidence of HPV-related oral and oropharyngeal cancers.

Patient education should address the rationale for surveillance, the significance of symptoms requiring prompt review, and the importance of regular dental examinations. The psychological impact of OPMD diagnosis should not be underestimated; Celentano and Cirillo (2024) note that the anxiety stemming from a pre-cancer diagnosis, the necessity for rigorous follow-ups, and the prospect of invasive treatments can assume notable proportions when extended to a broad demographic.

7. Challenges and Controversies

7.1 Overdiagnosis and Overtreatment

A significant controversy in OPMD management concerns the potential for overdiagnosis and overtreatment. Celentano and Cirillo (2024) question the practicality and implications of labelling such a large population as precancerous, given that the actual progression to oral cancer is significantly low for most disorders. Globally, close to half a billion individuals are afflicted by oral diseases earmarked as potential precursors to cancer a designation that raises significant concerns, especially given that only a minute fraction may derive actual benefits.

The detriments associated with anxiety from a pre-cancer diagnosis, the necessity for rigorous follow-ups, and the prospect of invasive treatments can be substantial (Celentano & Cirillo, 2024). Recent research suggests that the diagnosis and subsequent management of OPMD can engender substantial out-of-pocket expenditures, precipitating catastrophic health-related financial burdens for households. Furthermore, the

psychological toll on these patients, manifesting as depression, anxiety, and stress, is noteworthy.

7.2 Inconsistencies in Classification

The evidence supporting the inclusion or exclusion of certain conditions from the OPMD list lacks clarity, as does the methodology and consensus-building process (Celentano & Cirillo, 2024). Significant inconsistencies manifest in systemic diseases presenting with OPMDs. For example, specific evidence indicating a distinct increased risk associated with oral lesions in graft-versus-host disease remains inconclusive. Similarly, for inherited cancer syndromes including Fanconi anaemia and xeroderma pigmentosum, the statistically heightened risk of developing oral cancer for all these rare familial syndromes is yet to be firmly established.

Without greater consistency in classification, it becomes difficult to argue against the consideration of other diseases that clinically present as ulcers and are sporadically linked to malignancy, such as aphthous stomatitis and trauma. Excluding diseases with weak or uncertain associations from the OPMD list would be a prudent decision (Celentano & Cirillo, 2024).

7.3 Health System and Access Issues

Access to specialist care for OPMD management varies considerably across healthcare systems and geographical regions. Primary care institutions often lack systematic screening training, resulting in high missed diagnosis rates (Ge *et al*., 2025). The absence of MDT mechanisms in many settings limits the ability to provide comprehensive, coordinated care for high-risk patients.

The Australian Dental Association (2025) recommends that the Australian Government ensure that survivors of head, neck, and oral cancers have access to rehabilitative and restorative oral health services consistent with the standards of survivorship care available for other cancers. Similar advocacy is needed globally to address disparities in access to OPMD care.

8. Future Directions

8.1 Molecular Biomarkers and Personalised Medicine

Continued research into the molecular and cellular mechanisms driving the development and progression of OPMDs is essential (Naara *et al*., 2024). Identifying biomarkers that predict malignant transformation could allow for more personalised management strategies focusing on high-risk individuals (Khodadadi *et al*., 2025). DNA aneuploidy shows promise for clinical application, while other markers including loss of heterozygosity, microRNA profiles, and epigenetic changes require further validation.

Advances in molecular biology are paving the way for more targeted approaches to diagnosing, staging, and managing OPMDs (Khodadadi *et al*., 2025). Integration of molecular risk stratification with clinical and histopathological assessment could significantly improve the accuracy of predicting malignant progression.

8.2 Novel Therapeutic Approaches

Immunotherapy and other novel treatments are being explored as potential options for preventing the progression of OPMDs to OSCC (Khodadadi *et al*., 2025). Immune checkpoint inhibitors are being evaluated as potential preventive strategies, though they remain in early stages of investigation (Naara *et al*., 2024).

New imaging technologies, such as confocal microscopy that can provide real-time histological information, offer the potential for more accurate diagnosis and monitoring without repeated biopsies (Khodadadi *et al*., 2025). Machine learning and artificial intelligence applications are being developed to assist in risk prediction and management decisions (Khodadadi *et al*., 2025).

8.3 Implementation Science and Health Policy

Developing OPMD management models that are sensitive, operable, and align with the practical resource constraints of primary and tertiary hospitals holds significant practical importance (Ge *et al*., 2025). The model based on risk stratification and MDT collaboration, validated by Ge *et al*. (2025), is suitable for promotion in primary care hospitals and could serve as a template for wider implementation.

Public health strategies should focus on primary prevention through risk factor modification, secondary prevention through early detection, and tertiary prevention through optimal management of established OPMDs. The IARC guidance provides evidence-based recommendations for oral cancer prevention and early detection, identifying major risk factors and promoting opportunistic screening in dental settings (Oral Health Foundation, 2026).

9. Conclusion

Oral potentially malignant disorders represent a diverse group of conditions with varying potential for malignant transformation to oral squamous cell carcinoma. Early identification and appropriate management are crucial to reducing the burden of oral cancer, which continues to cause significant morbidity and mortality worldwide despite advances in treatment.

Current evidence confirms that leukoplakia is the most common OPMD, with an overall malignant transformation rate of approximately 6%, though proliferative verrucous leukoplakia demonstrates considerably higher rates approaching 48%. Independent risk factors for malignant progression include severe epithelial dysplasia, high-risk anatomical sites (ventral tongue and floor of mouth), and betel quid chewing

history. Histopathological assessment of epithelial dysplasia remains the gold standard for risk stratification, though emerging evidence supports the potential utility of biomarkers such as DNA aneuploidy.

Management has evolved towards risk-stratified approaches incorporating multidisciplinary team collaboration, with risk-adapted surveillance protocols tailored to individual patient risk profiles. The MDT model has demonstrated improved outcomes, including higher cancer-free survival rates and better follow-up compliance.

However, significant challenges remain, including inconsistencies in classification, the potential for overdiagnosis and overtreatment, and variable access to specialist care. Continued research into molecular predictors of malignant transformation, novel therapeutic approaches including immunotherapy, and implementation science to optimise care delivery across diverse healthcare settings is essential.

General dental practitioners, equipped with knowledge of diagnostic adjuncts and risk factors, are uniquely positioned to identify OPMDs early and initiate appropriate management or referral. With appropriate training and resources, the dental profession can make a substantial contribution to reducing the global burden of oral cancer through improved detection and management of oral potentially malignant disorders.

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