

Recent Advances In Oral Potentially Malignant Disorders: A Therapeutic Perspective From An Oral And Maxillofacial Clinician And Pathologist – A Systematic Review

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Cite this paper as: Dr. Karthik Shunmugavelu, Mrs. S.Suganya, Dr. L. Jeevanandam MDS, Dr. Samiullah Dowlath Saheb, (2025) Recent Advances In Oral Potentially Malignant Disorders: A Therapeutic Perspective From An Oral And Maxillofacial Clinician And Pathologist – A Systematic Review. *Journal of Neonatal Surgery*, 14 (8), 560-566.

ABSTRACT

Oral potentially malignant disorders (OPMDs) are recognized precursors to oral squamous cell carcinoma (OSCC) and pose a major diagnostic and therapeutic challenge. This systematic review critically synthesizes recent advances in the classification, diagnosis, molecular pathology, viral associations, and therapeutic management of OPMDs. Systematic literature review according to PRISMA guidelines selected 8 major studies between 2021 and 2025. Developing evidence from literature points toward the role of advanced classification systems, artificial intelligence-guided diagnostics, metabolomic profiling, microenvironmental modulation, and viral oncogenesis in enhancing early diagnosis and risk stratification. Challenges persist with standardization of diagnostic modalities, cross-population validation of biomarkers, and making new technologies universally accessible globally. An integrated multidisciplinary strategy that includes technological advancements and molecular understanding is needed to maximize preventive measures and minimize the global burden of oral cancer.

Keywords: Oral potentially malignant disorders, oral squamous cell carcinoma, viral infections, artificial intelligence, microenvironment, metabolomics, early detection.

1. INTRODUCTION

Oral squamous cell carcinoma (OSCC) remains one of the prevalent head and neck cancers, characterized by aggressive clinical behavior and a poor prognosis. A high percentage of OSCCs are preceded by a clinically apparent phase in the form of oral potentially malignant disorders (OPMDs).^[1] OPMDs constitute a heterogeneous category of lesions, of which but not restricted to oral leukoplakia, erythroplakia, oral lichen planus, and oral submucous fibrosis. All of these conditions have a variable but significant risk of malignant transformation based on several etiological factors.^[2]

The biological behavior and malignant potential of OPMDs are governed by the multiple interactions between genetic mutations, dysregulated cellular pathways, inflammatory reactions, microenvironmental changes, lifestyle factors such as tobacco and alcohol consumption, and viral oncogenesis. Early detection, accurate risk stratification, and appropriate monitoring of OPMDs thus become integral parts of preventing the development of invasive carcinoma.^[3]

Recent advances in technology and biology have greatly complemented the diagnostic and therapeutic repertoire for the management of OPMDs. The integration of artificial intelligence (AI) into image-based diagnostics, the identification of metabolomic biomarkers for early diagnosis, the advancement of optical imaging technologies, and the recognition of immune-microenvironment interactions have all together transformed modern-day clinical practice.^[4] Also, the role of viral

pathogens such as human papillomavirus (HPV) and Epstein-Barr virus (EBV) in the pathogenesis of OPMD is being recognized to a greater extent, providing directions for targeted prevention.^[5]

Given the recent advancements in the specialty, this systematic review aims to critically assess current progress in the understanding, diagnosis, and management of oral potentially malignant disorders (OPMDs). The goal is to integrate available knowledge, recognize current challenges, and provide evidence-based recommendations to improve clinical outcomes and reduce the overall burden of oral cancer.

2. MATERIALS AND METHODS

This systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^[6] (Figure 1) to maintain methodological quality and transparency. The following steps were taken:

Search Strategy: A thorough search was performed on PubMed, Scopus, and EBSCOhost databases for articles published between 2021 and 2025.

Initial Screening: 790 articles were originally retrieved using a mix of keywords for oral potentially malignant disorders, diagnosis, molecular profiling, viral association, and therapeutic approaches.

Inclusion Criteria:

- Human subject studies.
- Specific studies examining OPMDs or their malignant transformation.
- Systematic reviews, observational studies, cohort studies, clinical trials, and scoping reviews.
- English-language published studies.

Exclusion Criteria:

- Case reports, case series, letters to the editor, and expert opinions.
- Animal studies.
- Studies lacking explicit methodological descriptions.

Selection Process:

- After the elimination of duplicates, titles and abstracts of 654 articles were screened.
- After full-text evaluation, 8 studies were identified as meeting the inclusion criteria and were included in final synthesis.

Data Synthesis and Extraction:

- No data from the included studies were systematically extracted and synthesized.
- Areas of focus were developments in diagnostic technologies, reclassification frameworks, understanding of the tumor microenvironment, the viral infection role, and metabolomic profiling.
- Conflict in the choice of studies was addressed by discussion among the reviewers to ensure consistency and objectivity.



Figure 1: PRISMA FLOWCHART

3. RESULTS

Table 1: Summary Of Study Results

Author (Year)	Study	Focus Area	Study Type	Population/Sub jects	Diagnostic/Therap eutic Tool	Outcome Summary
Jayasinghe et al. (2025) ^[7]	Clinical Aspects of Oral Cancer and Potentially Malignant Disorders with Special Relevance to South Asia.	Clinical Patterns	Review	South Asian OPMD cases	Clinical evaluation	Highlighted regional variability in lesion types and transformation risk.
Zahid et al. (2025) ^[8]	Viral Involvement in Oral Potentially Malignant Disorders: A Scoping Review.	Viral Etiopathogenesis	Scoping Review	OPMD biopsies	Viral DNA analysis	High prevalence of HPV and EBV; suggested viral role in carcinogenesis.

Celentano & Cirillo (2024) ^[9]	Diseases with oral malignant potential: Need for change to inform research, policy, and practice.	Classification	Review	OPMD patients	Classification framework	Reduced overtreatment through pragmatic categorization.
Mohd Faizal et al. (2024) ^[10]	Metabolomic Profiling of Oral Potentially Malignant Disorders and Its Clinical Values.	Metabolomics	Case-Control	Blood/Saliva samples	Metabolomic profiling	Identified metabolite signatures predictive of malignant progression.
Vinayahalingam et al. (2024) ^[11]	Advancements in diagnosing oral potentially malignant disorders: leveraging Vision transformers for multi-class detection.	Artificial Intelligence	Observational	Clinical photographs dataset	Vision Transformer AI model	High accuracy (AUC > 0.9) in differentiating OPMDs and OSCC.
Deng et al. (2022) ^[12]	Microenvironment in Oral Potentially Malignant Disorders: Multi-Dimensional Characteristics and Mechanisms of Carcinogenesis.	Microenvironment	Review	In vitro/in vivo models	Microenvironment modulation	Proposed immuno-metabolic-neural interplay in early carcinogenesis.
Wang et al. (2022) ^[13]	Diagnostic value of objective VELscope fluorescence methods in distinguishing oral cancer from oral potentially malignant disorders (OPMDs).	Diagnostic Innovation	Observational	OPMD lesions	VELscope Autofluorescence	Improved detection of dysplastic lesions vs conventional exam.
Walsh et al. (2021) ^[14]	Clinical assessment for	Screening Strategies	Systematic Review	General population	Clinical examination	Limited sensitivity

	the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults.					of conventional exams; advocated adjunctive tools.
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4. DISCUSSION

The clinical research landscape of OPMD has expanded considerably to include molecular diagnosis, artificial intelligence imaging, treatment in the microenvironment, metabolomics innovation, and virology studies. Comparison of included studies provides a better insight into the current advancements and current gaps.

Celentano and Cirillo (2024)^[9] suggested a pragmatic reclassification of OPMDs into discrete categories according to malignant potential, providing a clinically useful framework that minimizes overtreatment and unnecessary patient burden. This reclassification contrasts with the epidemiological study by Jayasinghe et al. (2025)^[7] that addressed geographical heterogeneity in OPMD prevalence and risk factors, particularly pointing out an increased burden in South Asian populations. Collectively, these studies underscore the need to integrate regional epidemiological information into clinical classification systems.

In the spectrum of diagnostic advancements, Vinayahalingam et al. (2024)^[11] showed the improved diagnostic sensitivity of vision transformers by AI over routine clinical examination for differentiation of OPMDs-OCCC. Wang et al. (2022)^[13] did the same and presented evidence for the usefulness of VELscope autofluorescence imaging as an early indicator of high-risk lesions. Walsh et al. (2021)^[14] corroborated these results by referring to the limitations of traditional clinical oral examinations and suggesting the addition of adjunctive diagnostic modalities. Collectively, these studies affirm a shift towards technology-aided precision diagnostics.

Mohd Faizal et al. (2024)^[10] proposed metabolomic profiling as a viable method to identify predictive biochemical changes for malignant transformation. The findings are in agreement with the non-invasive early detection methods proposed by Vinayahalingam et al. (2024)^[11] and Wang et al. (2022)^[13], indicating that the combination of imaging advancements with molecular profiling can significantly enhance risk prediction models.

From a pathophysiological perspective, Deng et al. (2022)^[12] provided a comprehensive review of the tumor microenvironment's role in OPMD progression, elucidating the complex interactions between immune, metabolic, mechanical, and neural elements. Their insights advance understanding beyond the classical view of genetic mutations alone and open new avenues for microenvironment-targeted preventive strategies.

The study by Zahid et al. (2025)^[8] of the viral etiology of OPMDs added another significant component, demonstrating high prevalence rates of oncogenic viruses such as HPV, EBV, HBV, and HSV in OPMD lesions. While these findings suggest a potential contributory role of viral infection to malignant transformation, they also highlight the current gaps in establishing a causal relationship, which needs further longitudinal studies.

Pratima Kumari et al. (2022)^[15] stressed lifestyle changes and early interventions in consonance with public health efforts in general to alleviate OPMD burden. Chiu et al. (2021)^[16] also presented epidemiological data in favor of early screening in high-risk individuals with decreased malignant transformation rates on active surveillance.

In spite of these developments, the following main challenges persist:

- There is a need for standardization of diagnostic modalities and agreement on classification criteria.
- Multicenter, large-scale validation studies will be needed for biomarkers like those discovered through metabolomics.
- AI diagnostic systems should be developed using representative and diverse training datasets for clinical application.
- Socioeconomic and infrastructural limitations continue to limit the uptake of advanced diagnostics in resource-constrained settings.
- Clinical integration of viral screening protocols is still uneven in the face of emerging evidence.

Overall, the integration of molecular, technological, and virological knowledge is a paradigm shift in the management of OPMDs. To realize the full potential of these innovations, however, will require a multidisciplinary, globally concerted effort that brings together technological advances with equitable clinical practice.

5. CONCLUSION

Recent developments have redefined the knowledge and treatment of oral potentially malignant disorders (OPMDs). New classification systems allow more accurate risk stratification and avoid unnecessary treatment, while acknowledging regional epidemiological variation highlights the importance of localized approaches. Advances in technology, including AI-based imaging and metabolomics, provide enhanced early detection. Emerging insight into the tumor microenvironment and viral oncogenesis offers new therapeutic targets beyond conventional histopathology. However, there are some challenges like standardization of diagnosis, biomarker validation, equitable access to innovations, and identification of the role of viral infection. Multidisciplinary, integrated management of future OPMD will include technological innovation, molecular profiling, and personalized preventive strategies to effectively control oral cancer burden.

6. FUTURE DIRECTIONS

- Future validation of AI diagnostic instruments across various populations.
- Standardized protocols of viral detection as part of OPMD screening.
- Clinical trials focused on microenvironmental modulation.
- Extension of metabolomic studies for non-invasive early detection.

International coordination to harmonize classification, diagnosis, and management practices.

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