Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders

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Abstract

After more than a decade, the World Health Organization (WHO) published the revised grading system for oral epithelial dysplasia in 2017. The revised classification has changes reflecting our evolution of understanding of the dysplastic process. Although the WHO 2017 three-tier grading system is the gold standard for histological diagnosis of oral potentially malignant disorders, it has certain limitations. Suggestions to overcome these limitations include the use of clinical determinants and molecular markers to supplement the grading system. It has also been suggested that a two-tier system may be more reproducible and clinically translatable for better management. These advances in the understanding of epithelial dysplasia are very important globally and for us in the Indian subcontinent, given the prevalence of habits (tobacco/areca nut) and burden of oral cancer in this part of the world. The following review traces the evolution of the grading system of dysplasia, its relevance and clinical utility.

Keywords: Cancer, epithelial, grading, histopathology, oral dysplasia, potentially malignant, precancer

INTRODUCTION

Oral cancer is the 11th most common cancer in the world, with an estimated 300,000 new cases and 145,000 deaths in 2012.[1,2] In India, 20/100,000 population are affected by oral cancer, which accounts for around 30% of all types of cancer.[3] Most cases of oral cancer are associated with habits (tobacco/areca nut) and are preceded by asymptomatic clinical lesions collectively referred to as oral potentially malignant disorder (OPMD).[4] OPMDs include leukoplakia, erythroplakia, reverse smoker's palate, erosive lichen planus, oral submucous fibrosis, lupus erythematosus and actinic keratosis.[5,6]

The worldwide prevalence rate of OPMDs ranges from 1% to 5%. Estimates provided by individual studies vary depending on the country, the population under investigation, the pattern of tobacco use and the clinical definition used for leukoplakia. One of the early epidemiological studies assessing the risk of OPMDs in India reported that 80% of oral cancers were preceded by OPMDs.[7] The global prevalence (1986 to 2002) of leukoplakia was estimated to be 1.49% to 2.60%.[8,9] The prevalence of erythroplakia among populations in India and Malaysia is estimated to be 0.02%.[10-13] Reported incidence rates of OPMDs in the Indian subcontinent

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have ranged between 0.6/1000 and 30.2/1000 with a regional variation in prevalence from 0.2% in Bihar state in the north to 4.9% in Andhra Pradesh in the east. This difference in the range is attributed to the prevalence and type of tobacco use.[14,15]

OPMD is a clinical diagnosis for which the histological diagnosis may be hyperplasia, hyperkeratosis, oral epithelial dysplasia (OED) or oral squamous cell carcinoma (OSCC). OED is characterized by cytological and architectural alterations reflecting the loss of normal maturation and stratification pattern of surface epithelium.[16,17]

This review aims to discuss the different classifications of OED, their limitations and relevance in determining the risk of malignant transformation. Understanding this relation between the clinical diagnosis of OPMD and histopathological diagnosis of OED is essential for early diagnosis and clinical management.

MALIGNANT TRANSFORMATION OF ORAL POTENTIALLY MALIGNANT DISORDER/ORAL EPITHELIAL DYSPLASIA TO ORAL SQUAMOUS CELL CARCINOMA

Oral leukoplakia is reported to carry up to 2-fold increased risk of developing oral cancer depending on the site and habits.[18] The MTR of leukoplakia varies from 1.4% to 7%.[19-22] A recent systematic review of the observational studies in OPMD reported an MTR of 0.13%–34% across 24 studies.[23] MTR of epithelial dysplasia ranges between 1.4% and 36% (Ho *et al.*: 1.4%–7.62% per year; Lumerman *et al.* 6.6%–36%).[16,21] The variation in rates between studies is attributed to differences in follow-up times, study group definition and selection and tobacco habits.[24]

Oral epithelial dysplasia – Terminology

The word dysplasia denotes abnormal growth.[25] The dysplastic alterations may revert to normal when the underlying inciting stimulus is removed. Dysplastic features in stratified squamous epithelium are characterized by cellular atypia and loss of normal maturation and stratification.[17] The World Health Organization (WHO) monograph on head and neck tumors (2005) uses the term "epithelial precursor lesions" and defines it as "altered epithelium with an increased likelihood for progression to squamous cell carcinoma."[26]

Grading of oral epithelial dysplasia

The current evidence recognizes carcinogenesis of the epithelium as a multistep, progressive, cumulative process of genetic mutations which culminate in tumor formation, and ultimately invasion and metastasis.[27] In this model,

simple epithelial hyperplasia progresses through mild OED, to more severe dysplastic changes with increasing genetic aberrations.[27,28] Grading of OED is used to assess the probability of malignant transformation. OED is observed in nearly all cases of erythroplakia and 1%–30% of oral leukoplakia cases at the time of diagnosis.[4,29]

The criteria used for diagnosing dysplasia include architectural changes (tissue changes) and cytological changes (individual cell changes/cytological atypia). The WHO three-tier grading of oral dysplasia is traditionally used by pathologists, in which OED is graded as mild, moderate and severe.

Classification systems for grading oral epithelial dysplasia

The main purpose of a classification and grading system is to promote uniform reporting and management. It should also serve as a means for assessing lesions in epidemiological studies. More than 20 classification systems have been proposed in the past two decades in an attempt to standardize OED grading systems. For any grading system to be clinically useful, it should be reproducible, and the histological assessment should reflect the malignant potential of the lesion. Many of these systems are based on the classification of precursor lesion in other sites, including Squamous Intraepithelial Neoplasia (SIN) of the cervix and the Ljubljana classification of larynx.[24,30] A comparison of important classification systems is given in Table 1 and discussed below:[24]

Smith and Pindborg photographic methods (1969)

Smith and Pindborg described the first system for grading epithelial dysplasia of oral mucosa in the year 1969. They evaluated 13 histologic features, which were standardized by a set of photographs. Each feature was graded as absent, slight and marked. A grading of absent was scored as zero, whereas grading of slight or marked was allocated a score between 1 and 10 [Table 2].[31] The scores are added to give the epithelial atypia index (EAI) (0 to 75).[31]

In this system, the diagnosis of epithelial dysplasia is objective and semi-quantitative as the microscopic features are allocated a weighted score. However, the accuracy of weightage given to each of the histologic characteristics was subjective, and it was found to be difficult for routine use.

Ljubljana classification (2003)

The Ljubljana classification was first described by laryngeal pathologists Kambic and Lenart in 1971 for laryngeal hyperplastic lesions. Zerdoner in 2003 proposed the use of Ljubljana classification of laryngeal precancer for grading

Table 1: Comparison of Classification Systems for Histopathological Diagnosis of Oral Epithelial Dysplasia

WHO 1978 classification	WHO 2005 classification	WHO 2017 classification	SIN 2005		Ljubljana classification 2003	SIL 1988	OIN/CIS (JSOP) system 2010	Binary system 2006
Mild dysplasia	Squamous hyperplasia	Mild dysplasia	SIN 1	Low grade dysplasia	Squamous cell (simple) hyperplasia	Hyperplasia/ keratosis	Reactive atypical epithelium	Low risk
	Mild dysplasia				Basal/parabasal cell hyperplasia*	SIL I (low grade)	Oral epithelial dysplasia	
Moderate dysplasia	Moderate dysplasia	Moderate dysplasia	SIN 2	High grade dysplasia	Atypical hyperplasia**		OIN/CIS (JSOP)¹	High risk
Severe dysplasia	Severe dysplasia	Severe dysplasia	SIN 3***			SIL II (high grade)		
	Carcinoma *in situ*				Carcinoma *in situ*			

*Basal/parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter is the lower grade of precursor lesions, **lesions that represent 'risky epithelium' require close follow up and repeated histologic assessment to recognize any progression; approximate analogy to moderate and severe dysplasia, ***SIN 3 includes severe dysplasia and carcinoma *in situ*, ¹classified as differentiated and basaloid types, with transitional variations between the two (several variations are not mentioned in the WHO classification definition). SIL: Squamous Intraepithelial Lesion, SIN: Squamous Intraepithelial Neoplasia, OIN: Oral Intraepithelial Neoplasia, CIS: Carcinoma *in situ*, JSOP: Japanese Society for Oral Pathology

hyperplastic epithelial lesions of the oral cavity in four grades [Tables 1 and 3].[24,32]

The Ljubljana classification includes all histopathological changes that progress to squamous cell carcinoma each of which entails different treatment options. In this system, carcinoma *in situ* (CIS) is distinct from atypical hyperplasia, as these two entities differ in morphology and their progression to invasive carcinoma.[24]

Gale and Warnakulasuriya observe that the Ljubljana classification cannot categorize certain oral lesions such as oral submucous fibrosis and oral lichen planus, which have atrophic epithelium and are without significant atypia. Furthermore, this system is considered complex and time-consuming and needs to be validated for oral lesions.[24,26,30,33,34]

Squamous Intraepithelial Neoplasia/dysplasia (SIN/dysplasia) classification (2005)

SIN is a concept derived from cervical intraepithelial neoplasia. It has been extended with some modification of the WHO classification as "oral intraepithelial neoplasia." It is also used for all sites of the upper aerodigestive tract (UADT). This system proposed
- Unifying all the histological changes as "Oral Intra-epithelial Neoplasm"
- Grading lesions as high grade and low grade.

However, it was argued that in UADT, surface maturation/keratinization can occur in the presence of dysplastic layers in the lower strata of epithelium, which

Table 2: Scoring in Smith and Pindborg grading system (depending on the epithelial atypia index)

Score	Grade
0-10	No dysplasia
11-25	Mild dysplasia
26-45	Moderate dysplasia
Above 45	Severe dysplasia

EAI: Epithelial atypia index

Table 3: Ljubljana grading system

Ljubljana grading system	Treatment options
Simple hyperplasia	Purely hyperplastic lesions that do not require close follow-up
Abnormal hyperplasia	
Atypical hyperplasia or "risky" epithelium	Mild degrees of atypia that require close follow-up to recognize any progression to severe atypia
Carcinoma *in situ*	Severe atypia that require surgery or radiotherapy

is not a feature of cervical intraepithelial neoplasm. Hence, in UADT, a classification of SIN/dysplasia was introduced. It was a modification of 2005 WHO grading system [Table 1].[24,32,35] The important considerations of this classification are:
1. Dysplasia is a spectrum
2. One end of the spectrum is hyperplastic keratinizing SIN/dysplasia and the other end is atrophic SIN/ dysplasia
3. Hyperplastic keratinizing SIN/dysplasia is called keratinized dysplasia
4. Atrophic SIN/dysplasia is similar to the WHO type dysplasia.

The hyperplastic keratinizing SIN/dysplasia and atrophic SIN/dysplasia clinically correspond to leukoplakia and

erythroplakia, respectively. The disadvantage of this system was the overlap of features between the two ends of the spectrum leading to underdiagnosis of the grade. This system is largely based on subjective interpretation.[30] Crissman and Sakr emphasize that the lesions exhibiting keratinizing dysplasia have a high incidence of local relapse and a high progression rate to invasive SCC.[36-40]

Oral Intraepithelial Neoplasia/ Carcinoma in situ (Japanese Society for Oral Pathology), OIN/CIS (JSOP) system (2010)

In 2010, the Working Group of the Japan Society for Oral Tumours (WG–JSOT) proposed a new entity–oral intraepithelial neoplasia (OIN)–in the first edition of its "General Rules for Clinical and Pathological Studies on Oral Cancer." The term OIN was introduced to avoid confusion with the WHO's term of CIS and to lay emphasis on the characteristics of oral SCC different from those of SCC of the uterine cervix. According to the Working Committee of the Japanese Society for Oral Pathology (JSOP), OIN/CIS system describes oral precursor lesions under three categories: reactive atypical epithelium, OED and OIN/CIS (JSOP) [Table 1].[24] Mucosal resection is recommended for the treatment of OIN/ CIS (JSOP), whereas follow-up is recommended for OED in the OIN system.[24,41,42]

World Health Organization (WHO) classification systems
World Health Organization (WHO) 1978 classification

A collaborating reference center was established by the WHO in the year 1967, to characterize and define those lesions that should be considered as oral precancer and to determine their relative risk of becoming malignant.[17,33] In its report in 1978, the WHO defined and listed 12 characteristics of epithelial dysplasia and graded epithelial dysplasia as mild, moderate and severe and published the same in the "Histopathological typing of cancer and precancer of the oral mucosa," in 1997, the characteristic histologic features were listed:

1. Loss of polarity of basal cells
2. Basaloid appearance in more than one layer of cells
3. An increased nuclear-cytoplasmic ratio
4. Drop-shaped rete pegs
5. Irregular epithelial stratification
6. Increased number of mitotic figures
7. Mitotic figures in the superficial half of the epithelium
8. Cellular polymorphism
9. Nuclear hyperchromatism
10. Enlarged nucleoli
11. Reduction of cellular cohesion
12. Keratinization of single cells or cell groups in the prickle cell layer (Kramer et al., 1978).

OED is graded as mild, moderate and severe based on whether dysplastic features were restricted to the lower third, middle third and the upper third of the epithelium, respectively [Table 1].[17,43,44]

World Health Organization (WHO) 2005 classification

The WHO 2005 classification recognizes five histopathological stages in epithelial precursor lesions: Squamous hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia and CIS. The criteria for diagnosing epithelial dysplasia are architectural and cytological/cellular changes [Table 4].[26]

Based on the architectural and cytological alterations, the epithelium is divided into "thirds," and the lesions are classified into five categories [Table 1]:[5,26]

1. Hyperplasia (Squamous hyperplasia): Lesions with an increase in cell number in the spinous layer and/or in the basal/parabasal cell layers. There is presence of regular stratification and no cellular atypia
2. Mild dysplasia: Architectural disturbance present only in the lower third of the epithelium with cytological atypia
3. Moderate dysplasia: The criteria postulate that architectural disturbance extending into the middle third of the epithelium, but the degree of cytological atypia may require upgrading it to "severe dysplasia"
4. Severe dysplasia: Architectural disturbance observed in greater than two thirds of the epithelium, with cytological atypia
5. Carcinoma in situ (CIS): Is a noninvasive carcinoma, classified as a precursor lesion of OSCC. CIS is characterized by full thickness or almost full thickness of epithelial architectural disturbance in the viable cell layers accompanied by pronounced cytological atypia.

Table 4: World Health Organization (WHO) criteria for epithelial dysplasia (2005)

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

*Present in 2005 WHO classification; has been removed in 2017 WHO classification. WHO: World Health Organization

World Health Organization (WHO) 2017 classification

In the recently published 2017 WHO grading system, features of "squamous hyperplasia (acanthosis and basal cell hyperplasia)" and "carcinoma *in situ* (CIS)" present in the 2005 WHO classification has been dropped from the OED grading [Table 1]. The term CIS is removed from the 2017 WHO classification and used synonymously with severe dysplasia. The cytological/cellular feature, "increase in nuclear size" in the 2005 WHO classification has also been dropped from 2017 WHO diagnostic criteria of OED. The architectural feature "loss of epithelial cell cohesion" has been included in 2017 WHO diagnostic criteria [Table 5].[45]

Binary system (2006)

Warnakulasuriya *et al.* in their review on OED classification system report that in the workshop conducted on issues related to OPMD in the United Kingdom, the WHO Collaborating Centre for Oral Cancer and Precancer (2005), the working group emphasized the need for two-tier classification – low risk (no / questionable / mild); high risk (moderate / severe) for better reproducibility and clinical utility. However, they added that further studies are needed before the two-tier system can be adopted [Table 1].[30,46]

The binary system for grading epithelial dysplasia categorizes OED into low risk and high risk for undergoing malignant transformation.[46] Kujan *et al.* in their study show that the binary system that uses four architectural and five cytological features had an increased inter-observer agreement ($\kappa = 0.5$) as compared to the WHO ($\kappa = 0.22$).[46] Nankivell *et al.* also contend that the binary system has a superior reproducibility, and a similar prognostic ability when compared to the three-tier WHO system.[47] They showed that the binary

Table 5: World Health Organization (WHO) criteria for epithelial dysplasia (2017)

Architectural changes	Cellular 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)
Abnormal superficial mitosis	Increased nuclear-cytoplasmic ratio
Premature 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

**Included in the 2017 WHO classification. WHO: World Health Organization

system with the use of four architectural features and four cytological features has a higher multi-observer kappa ($\kappa = 0.59$) compared with the WHO system ($\kappa = 0.49$).[47]

Although the three-tier grading systems (mild, moderate and severe) is widely used, the binary system complements the WHO classification systems, and it has merit as it helps clinicians to make critical clinical decisions particularly in cases with moderate dysplasia. It also facilitates a standardized approach to overcome some difficulty in subjectivity in reporting of epithelial dysplasia. However, the biological significance of this system needs to be validated in longitudinal studies to explore its value in the prediction of malignant transformation risk of OPMDs.

Oral epithelial dysplasia in the clinical context

The histopathologic assessment for the presence of OED is considered the current gold standard for predicting malignant transformation of OPMDs.[30] The presence of epithelial dysplasia is an indicator of the malignant potential of OPMDs, and the risk of these lesions to progress to carcinoma increases with the increasing grades of epithelial dysplasia.[48-51]

The efficacy and usefulness of histopathological grading of precursor lesions as an indicator of malignant transformation have long been debated in the literatures as malignant transformation of OPMDs can also occur in the absence of OED.[6,27,52-54] Furthermore, wide intra- and inter-observer variability in grading epithelial dysplasia raises the concern of reproducibility.[55-58]

Accurate clinical classification, supported by objective histopathological examination, will aid follow-up studies that aim to predict malignant transformation of OPMDs. In this context, prospective studies on OPMD/OED with longitudinal follow-up of patients are the need of the hour for clinical validation of the revised three-tier or binary system. Given the difficulty of conducting a longitudinal study, cases pooled from multiple sources are an alternative that needs to be considered.

Besides grading of OED, these studies also need to address clinical determinants and molecular diagnostic aids, which are briefly discussed below.

Clinical determinants of malignant transformation

The risk factors to predict the malignant transformation of OPMDs remains challenging.[59] van der Waal I[5,60] and Lee JJ[61] reported major risk factors for the malignant transformation include
- Female gender
- Long duration of leukoplakia
- Leukoplakia in non-smokers (idiopathic leukoplakia)

- Site predilection for tongue and/or floor of the mouth
- Size ≥200 mm^2
- Non-homogenous type.

Gender predilection

In India, MTRs of leukoplakia are greater in men than in women, possibly because of the association with chewing tobacco and smoking habits[21,62,63] whereas in Europe and other western countries, it is greater in women than men.[4,5,15,64-66]

Duration

Cancers from dysplastic lesions usually develop over a period of 2–5 years, but can occur much later.[50,67,68] Time frame for this process varies, but it is thought to be a relatively slow process, with malignant transformation occurring over a period of few years.[69]

Smokers versus non-smokers

Lesions in non-smokers are 7.1 times more likely to undergo malignant transformation compared to heavy smokers.[16,19,20,64]

Anatomical location

The floor of the mouth and/or on the lateral tongue has a high risk for malignant transformation.[21,64,70-72]

Homogenous versus non-homogenous leukoplakia

Reibel and Holmstrup considered non-homogenous appearance as an important marker for malignant transformation.[73] Although the most common clinical type of leukoplakia is homogenous, a higher malignant transformation (13.1%) occurs among the non-homogenous clinical types.[23,64,73,74] Speckled and erosive leukoplakia have the highest MTR.[66,75] Homogenous, thick leukoplakia undergoes malignant transformation in 1%–7% of cases. Once the surface becomes granular or verruciform, the malignant transformation potential becomes 4%–15%. Erythroleukoplakia carries an average transformation potential of 28%, but the rates vary from 18% to 47% in different studies.[68]

Other clinical determinants

Large lesions (≥200 mm^2),[64,76,77] multifocal or multiple leukoplakia,[62,63] and proliferative verrucous leukoplakia[20,77-80] are also associated with increased risk of malignant transformation. Advancing age is also shown be an important determinant of malignant transformation.[19,75,78,81,82] The presence of aneuploidy has been found to signify a high risk of malignant transformation in leukoplakia.[83-86]

Other prognostic indicators

It has been suggested that the use of molecular markers along with clinical and histological grading can better predict disease progression. Alterations and mutations in the genetic content of oral epithelium are an integral part of "premalignancy."[87,88] Many genes and signaling pathways have been shown to be involved in the development of OSCC. Molecular markers that correlate OED with malignant transformation[89] include:

a. Overexpression of EGFR,[90] c-Jun,[91] Ki67/Mcm2,[92] Cyclins D and E,[93] p53,[94-96] p63,[97] survivin, MMP-9,[98] TGF alpha,[99,90] COX-1 and-2[100-102]
b. Amplification of Cyclin D1[103,104]
c. Loss of c-erbB2,[105] pRB[106]
d. Upregulation of telomerase (human telomerase reverse transcriptase; hTERT)[107-109]
e. Aneuploidy[84]
f. Loss of heterozygosity (Chromosome loci 3p, 8p, 9p, 4q, 11q, 13q, 17p)[110-112]
g. Cytokeratins (CK 1, CK 8 and CK 18)[113,114]
h. High-risk Human papillomavirus, p16.[115]

Progress in molecular oncology has significantly advanced the knowledge on tumorigenesis; however, the clinical utility of these genetic markers in OPMD/OED need to be defined.

CONCLUSION

Oral squamous cell carcinoma is often diagnosed in the late stages of the disease. Delayed diagnosis precludes successful treatment and favorable outcomes. Oral potentially malignant disorders are associated with the variable rate of malignant progression, with the finding of oral epithelial dysplasia on tissue biopsy remaining the gold standard in guiding management.

Long-term prospective studies are imperative to understand the natural history of oral potentially malignant disorders and oral squamous cell carcinoma, to facilitate diagnosis of at an early stage and render appropriate treatment, thereby reducing the morbidity and the mortality associated with advanced stage of oral cancer.

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Conflicts of interest
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