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Current challenges and the diagnostic pitfalls in the grading of epithelial dysplasia in oral potentially malignant disorders: A review

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ABSTRACT

Oral cancer is one of the common cancers in the world causing high morbidity. Development of cancer is preceded by certain asymptomatic clinical lesions and conditions all together known as 'oral potentially malignant disorders'. Histologically they are represented by the term 'oral epithelial dysplasia'. The degree of severity of dysplasia is determined in the form of 'grade'. Despite the existence of several grading systems proposed by various scholars, it is still a challenging task for the Pathologists to grade dysplasia accurately for the proper diagnosis of the disease and to follow preferable treatment plans. This review aims to focus on the current challenges and the diagnostic pitfalls in the grading of oral epithelial dysplasia in various oral potentially malignant disorders.

1. Introduction

Oral cancer is one of the common cancers in the world with a high morbidity rate.[1] In India, oral cancer represents as one of the major causes of death affecting a wide range of the population.[2] The most predominant type of oral cancer manifests as oral squamous cell carcinoma (OSCC). Various risk factors related to oral cancer include habits such as tobacco or areca nut chewing, smoking, and alcohol consumption. Oral cancer is preceded by certain asymptomatic clinical manifestations all together known as ***'oral potentially malignant disorders (OPMDs)'***.[3]

World health organization (WHO) in 2017 defined OPMDs as *'clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal mucosa'*.[4]

OPMDs include Leukoplakia (LP), Erythroplakia (EP), Erythroleukoplakia (ELP), Oral submucous fibrosis (OSMF), Palatal changes associated with reverse smoking, and, less commonly, Oral lichen planus (OLP). OPMD is a clinical term used in general practice by the clinicians.[5] Histologically, these disorders are described in term of ***oral epithelial dysplasia (OED)***.

The term ***'Dysplasia'*** could be a Greek acceptation meaning *'abnormal atypical proliferation of tissues'*. ***In 1958, Reagon*** introduced this term related to the pathological changes occurring in the exfoliated cells from the uterine cervix.[6] Dysplasia is mainly a feature of epithelium and is the predecessor of cancer. In course of the progression of cancer visible physical changes take place at the cellular level known as ***'Atypia'*** and at the tissue level called ***'Dysplasia'***. Dysplasia is characterized by distortion of cellular uniformity as well as architectural structure in a particular tissue.[7]

2. Definitions of dysplasia

Dysplasia has been defined by various scholars in different ways.[3,4,6-9] A few of the popular definitions of dysplasia have been summarized in Table 1.

3. Historical background

The phenomenon of progressive changes from a normal epithelium towards dysplastic features and finally, the carcinoma was first termed as ***'dysplasia'*** and ***'carcinoma in situ' (CIS),*** and at present known as

Abbreviations: CIN, Cervical Intraepithelial Neoplasia; CIS, Carcinoma in situ; EAI, Epithelial atypia index; ED, Epithelial dysplasia; EP, Erythroplakia; ELP, Erythroleukoplakia; HPV, Human Papilloma Virus; JSOP, Japanese Society for Oral Pathology; LP, Leukoplakia; N:C, Nuclear cytoplasmic ratio; OED, Oral epithelial dysplasia; OIN, Oral intraepithelial neoplasia; OLP, Oral lichen planus; OPMDs, Oral potentially malignant disorders; OSCC, Oral squamous cell carcinoma; OSMF, Oral submucous fibrosis; SIL, Squamous intraepithelial lesions; SIN, Squamous intraepithelial neoplasia; WHO, World health organization

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Table 1
Definitions of dysplasia.

Author (Year)	Definition	Reference No.
Pindborg (1977)	'The term used for a lesion in which part of thickness of the epithelium is replaced by cells showing varying degree of atypia'.	7
Kumar (1992)	'It is a disturbance in maturational sequence of stratified squamous epithelium and disturbance in cell kinetics of the proliferative compartment with cytological changes'.	7
Freedmen & Stanley Kerpel (1995)	'Oral epithelial dysplasia is the diagnostic term used to describe the histopathological changes seen in chronic, progressive and premalignant disorders of oral mucosa'.	8
Jesper Reibel (2003)	'Epithelial dysplasia is defined as "histological changes in which the risk for development of a carcinoma is higher than in non-dysplastic epithelium'.	3
Sharma N et al., (2010)	'Dysplasia means abnormal, atypical proliferation encountered principally in the epithelium'.	7
Pereira JDS et al., (2011)	'Oral epithelial dysplasias are potentially malignant disorders characterized by diverse degrees of cellular atypia'.	9
Goyal P et al., (2012)	'Oral epithelial dysplasia is the diagnostic term used to describe the histopathological changes seen in a chronic, progressive and a premalignant disorder of oral mucosa'.	9
Rastogi V et al., (2013)	'Dysplasia refers to a series of subtle in cells signifies that anaplasia will develop soon'.	6
WHO (2017)	'Oral epithelial dysplasia as a spectrum of architectural and cytological epithelial changes caused by accumulation of genetic changes, associated with an increased risk of progression to squamous cell carcinoma.'	4

Cervical Intraepithelial Neoplasia (CIN).[10] CIN was further classified by ***Reichart in 1973*** as CIN I, CIN II, CIN III, and CIS.[11] Later, in ***1988,*** the National cancer institute workshop gave ***Bethesda classification*** and introduced the term ***Squamous Intraepithelial Lesions (SIL***) dividing it further into low and high-grade. Low-grade SIL had features same as CIN I, whereas the high-grade represented the features similar to CIN II & III.[12] ***Reichart in 1990*** also added a new terminology; 'Borderline CIN' or 'CIN associated with Human papillomavirus (HPV) related changes' to differentiate CIN I from condylomas related to HPV and to avoid misdiagnosis of CIN.[13]

4. Relationship of OED and malignant transformation

Not all the OPMDs get transformed into oral cancer. Some of them possess specific morphological alterations making them more prone to malignant transformation. Moreover, it has been observed that some clinically normal-appearing sites are also associated with the risk factors leading to their carcinomatous potential.

LP is one of the most common OPMDs having a high risk of developing carcinomatous changes. The frequency of ED in LP varies between < 1 and $> 30\%$.[3] According to ***Neville,*** 5–25% of biopsy samples of the LP showed evidence of dysplasia.[9]

EP is rarer than LP but shows more evidence of dysplastic changes. ***Mehta et al., (1971)*** described that 4 out of 9 cases of EP, showed the features of ED. According to ***Shafer and Waldron (1975),*** 51% of lesions of EP were diagnosed as OSCC and 40% as CIS.[9]

Pindborg and Zachariah in 1965 *and* ***Ramanathan and Dharmalingam in 1975*** described the precancerous nature of OSMF.[14,15] OSMF Patients are more prone to malignant transformation as compared to other OPMDs. In a study reported in 1970, it was found that 7.6% of OSMF cases progressed into OSCC which was increased up to 9% in later studies.[16]

5. What is grading of dysplasia and why is the need for grading?

The severity of the degree of dysplastic features is termed as the ***Grade*** of epithelial dysplasia.[7] It is a challenging task for the pathologists to assess the degree of ED in the OPMDs, and grade it with accuracy so that the risk of malignant transformation can be predicted in an early time to reach a proper diagnosis for implementing an appropriate treatment plan.[7]

Till today, many grading systems have been proposed for OED by various scholars but every system is enclosed with few limitations raising a need to discover some ideal system. In this context, many studies have been conducted to establish a reliable and reproducible method of grading of OED and over time various changes have been introduced in these grading systems but large scale research is required to discover a perfect system.

6. Requirements of an ideal grading system

An ideal grading system must possess some of the basic requirements which are as follows:

- It should be easy to follow with minimal inter and intra-observer variability.[17]
- It should demarcate between the cases that require treatment or not.[7]
- It must include appropriate parameters, should be biologically purposeful, and must signify the malignant potential of the involved site.[17]

7. Various grading systems

Many grading systems of OED have been proposed by various scholars with their specific criteria and features which are summarized in Table 2.

7.1. SMITH and PINDBORG (1969)

They proposed the first system for grading OED in 1969 based on a set of photographs.[18] They considered two major factors for providing the scores.

- Concentrating on a single histopathological feature at a time paying full attention to its details.
- Allowing individual assessment of each character by the observer allotting a particular score to each one.

They included 13 histologic features grading them further as absent, slight, and marked and assigned specific scores (Table 2).

7.1.1. Advantages

- This system provides an objective and semi-quantitative diagnosis of dysplasia.
- Numerical values added in this system help to provide statistical analysis.

7.1.2. Disadvantages

- It cannot answer the question that why some non-neoplastic lesions also show the evidence of dysplasia.[19]
- This method is monotonous and time consuming.

Katz et al., in 1985 used this system in 214 cases of OED and observed that the system could prove to be a standard method to grade

Table 2
Various grading systems proposed for oral epithelial dysplasia.

GRADING SYSTEM	CRITERIA USED	GRADES	ADVANTAGES	DISADVANTAGES	REFERENCE NUMBER
SMITH and PINDBORG (1969)	1. Drop shaped rete ridges. 2. Loss of stratification regularity. 3. Keratin formation by individual cells. 4. Hyperplasia of basal layer 5. Loss of intercellular adherence. 6. Loss of basal cell polarity. 7. Nuclear hyperchromatism. 8. Increased N:C ratio. 9. Anisocytosis, Anisonucleosis. 10. Cellular and nuclear pleomorphism. 11. Increased mitotic activity. 12. Presence of mitotic figures in superficial half of epithelium. 13. Abnormal mitosis.	Criteria were categorized as absent, slight and marked. **Scoring:** Absent = zero, Slight or marked = 1 and 10. The scores were cumulated = ***EAI*** *varied from 0-75. **Total score:** 0-10 **(No dysplasia)** 11-25 **(Mild dysplasia)** 26-45 **(Moderate dysplasia)** 45-75 **(Severe dysplasia)**	• Objective and semiquantitative. • Numerical values help in providing statistical analysis.	• Monotonous. • Time consuming. • Can't explain the reason for evidence of dysplasia in non-neoplastic lesions.	18
BANOCZY and CSIBA (1976)	1. Loss of epithelial stratification. 2. Hyperplasia of basal / spinous cell layer or both. 3. More number of mitotic figures. 4. Increased N:C ratio. 5. Loss of polarity of basal cells. 6. Pleomorphic nuclei. 7. Hyperchromasia. 8. Keratinization of single cells. 9. Loss of intercellular adherence.	**Mild** : When 2 of the listed histological changes are observed. **Moderate**: When 2 -4 of the listed histological changes are observed. **Severe :** When 5 or more of the listed histological changes are observed.	• Simple. • Less time consuming.	• Only subjective interpretation. • Can't explain the associated risk factors.	23
WHO (1978)	1. Loss of basal cell polarity. 2. Multiple layers of cells having basaloid appearance. 3. Increased N:C ratio. 4. Drop shaped epithelial ridges. 5. Loss of stratification. 6. More number of mitotic figures. 7. Mitotic figures in the superficial layers. 8. Cellular polymorphism. 9. Nuclear hyperchromatism. 10. Enlarged nucleoli. 11. Reduction of cellular cohesion. 12. Keratin pearls in spinous cell layer.	**Mild: D**ysplastic features in the lower 1/3rd of epithelium. **Moderate**: Dysplastic features in the lower 2/3rd of epithelium. **Severe** : Dysplastic features involving > 2/3rds of epithelium.	• Simple. • Less time consuming. • Includes both cellular and architectural features.	• Lack of providing associated risk factors. • Observer agreement variability.	24
KRAMER (1980)	1. Drop shaped epithelial ridges. 2. Disturbed polarity of the basal cells. 3. Basal cell hyperplasia. 4. Loss of stratification. 5. Anisocytosis. 6. Nuclear hyperchromasia. 7. Prominent nucleoli. 8. Increase N:C ratio. 9. Cell crowding. 10. More mitosis. 11. Mitosis in upper layers. 12. Abnormal mitosis.	No grading system. The epithelium is dysplastic when ≥2 criteria are present.		• Provides no specific grade. • Just a subjective interpretation.	25

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Table 2 (*continued*)

GRADING SYSTEM	CRITERIA USED	GRADES	ADVANTAGES	DISADVANTAGES	REFERENCE NUMBER
	13. Loss of cellular adhesion. 14. Intraepithelial keratinization.				
BURKHARDT and MAERKAR (1981)	1. Basal cell hyperplasia. 2. Loss of basal cell polarity. 3. Cellular pleomorphism. 4. More mitotic figures. 5. Dyskeratosis. 6. Abnormal and lack of epithelial stratification. Additional indicators for dysplasia: 1. Increase in subepithelial lymphocytes, plasma cells and interepithelial cells. 2. Candida species.	**Low:** Presence of only first 2 criteria. **Medium**: Presence of first 5 criteria. **High:** All 6 criteria are present **CIS:** More marked features of high degree dysplasia seen.	• Also signifies some other associated risk factors.	• Suffers inter and intra-observer variability. • Not a reliable and accurate method.	26
SHAFER (1983)	1.More and abnormal mitosis. 2. Keratin formation by single cell. 3. Epithelial pearls within spinous layer. 4.Altered N:C ratio. 5. Loss of polarity. 6. Large prominent nucleoli. 7. Dyskeratosis. 8. Poikilocytosis. 9. Basilar cell hyperplasia.	**Mild (Grade I dysplasia**): Proliferation of atypical or immature basal cells above the parabasal region. **Moderate (Grade II dysplasia):** Proliferation into the middle one-third of the epithelium. **Severe (Grade III dysplasia**): Abnormal proliferation from the basal layer into the upper third of the epithelium.	• Simple. • Involves both cellular and tissue alterations.	• No evidence of associated risk factors. • Lack of numerical values leading to failure in providing statistical analysis. • Observer disagreement.	28
LUMERMANN et al. (1995)	1. Basal cell hyperplasia. 2. Nuclear enlargement and hyperchromatism. 3. Drop-shaped epithelial ridges.	***Mild***: 'Minimal' dysplastic alterations confined to the lower third of the epithelium. ***Moderate***: Dysplastic changes confined up to 2/3rds of the thickness of the epithelium. ***Severe:*** Dysplastic changes found in more than 2/3rds but less than the entire thickness of the epithelium. ***CIS***: Dysplastic changes are seen throughout the entire thickness of the epithelium with no invasion into the sub-mucosa. ***Verrucous hyperplasia with dysplasia***: The epithelium exhibits considerable thickening with surface papillations, hyper-parakeratosis and para-keratin plugging and occasional dysplastic cells confined to the lower 1/3rd of the epithelium.	• Introduced new category as "verrucous hyperplasia with dysplasia".	• Can't determine dysplasia accurately. • Lack of numerical values leading to failure in providing statistical analysis. • Observer disagreement.	8
NEVILLE (1995)	1. Enlarged nuclei. 2. Large and prominent nucleoli. 3. Increased N:C ratio. 4. Hyperchromatic nuclei. 5. Cellular and nuclear pleomorphism. Dyskeratosis. 6. Increased mitotic activity. 7. Abnormal mitotic figures. Additional criteria – 1. Teardrop-shaped or bulbous ridges., 2. Loss of polarity, 3. Keratin or epithelial pearls. 4. Loss of epithelial cell cohesiveness	**Mild:** Pleomorphic and hyperchromatic nuclei are seen in basal and parabasal cell layers. **Moderate:** Dysplasia extends to middle of the spinous cell layer. **Severe** : Disordered arrangement with cellular crowding is seen throughout the cell layers. Slight maturation and flattening of cells are seen at epithelial surface. **CIS:** Entire thickness of the epithelium contains dysplastic features.	• Simple. • Involves both cellular and tissue alterations.	• No evidence of associated risk factors. • Lack of numerical values leading to failure in providing statistical analysis. • Observer disagreement.	29

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Table 2 (*continued*)

GRADING SYSTEM	CRITERIA USED	GRADES	ADVANTAGES	DISADVANTAGES	REFERENCE NUMBER
SPEIGHT et al. (1996)	WHO 1978 criteria	**Mild:** Dysplasia present in parabasal cells. **Moderate**: Dysplastic features extending up to middle 1/3rd layer. **Severe:** Dysplastic features extending to upper layer.(similar to the WHO grading except for the absence of Carcinoma-in-situ)	• Simple. • Involves both cellular and tissue alterations.	• Observer disagreement. • Variability in thickness of oral epithelial lining leads to inaccurate grading.	30
SOAMES (1998)	WHO 1978 criteria	**Mild:** Dysplasia involving the lower third of epithelium showing pleomorphism, suprabasal mitosis and loss of stratification. **Moderate:** Dysplasia involving the 2/3rd of epithelium. **Severe:** Marked cellular atypia with disturbed stratification.	• Simple. • Involves both cellular and tissue changes.	• Variation in observer agreement. • Variability in thickness of oral epithelial lining leads to inaccurate grading.	31
KUFFER and LOMBARDI (2002)	WHO 1978 criteria	**Risk lesions**: Lesions without dysplasia. **Precursors of oral squamous cell carcinoma:** Lesions with dysplasia.	• Introduced new terminologies.	• Lack of evidence of malignant transformation in both categories. • Observer disagreement.	32
LJUBLJANA (2003)	1.Increased prickle cell layer without changes in of basal and parabasal layers. 2.Proliferation of basal and parabasal cell layers extending up to one half of total epithelial thickness, containing cells with moderately enlarged nuclei, show occasional normal mitosis, and contains $< 5\%$ of dyskeratotic cells. 3.Stratification is preserved, Nuclear atypia (enlarged nuclei containing irregular nuclear contours, with marked variations in staining intensity), increased prominent nucleoli increased N:C, increased mitoses, more dyskeratotic cells. 4. Loss of stratification of epithelium, marked cellular alteration, increased mitosis with abnormal pattern, extending up to high levels of epithelium	**Simple hyperplasia**: Criteria 1 **Abnormal hyperplasia**: Criteria 2 **Atypical hyperplasia:** Criteria 3 **Carcinoma in situ:** Criteria 4	• Focuses on important associated risk factors. • Provides an indication to identify the lesions accurately for implementing proper treatment plan.	• Can't categorize dysplasia in atrophied epithelium. • Lack of numerical values. • Complex. • Time consuming.	36
BROTHWELL et al. (2003)	1. Basal and parabasal cell hyperplasia. 2. Nuclear hyperchromatism. 3. Nuclear pleomorphism. 4. Bulbous retes.	**0. No dysplasia.** **1.Mild dysplasia:** Increase in number of cells in basal and parabasal cells showing nuclear hyperchromatism and pleomorphism. **2.Moderate dysplasia:** Features of Grade 1 also involving prickle layer and Presence of bulbous rete pegs. **3.Severe dysplasia:** Features of grade 2 throughout the epithelium. **4 CIS:** Atypical changes in the full thickness of the epithelium indicating early invasion without any clinical evidence.	• Good inter and intra-observer variability. • Numerical values help to provide statistical analysis.	• Time consuming. • Tedious. • Does not indicate associated risk factors. • Does not include all the cellular and tissue changes.	37

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Table 2 (*continued*)

GRADING SYSTEM	CRITERIA USED	GRADES	ADVANTAGES	DISADVANTAGES	REFERENCE NUMBER
TAKASHI SAKU et al., (2004)	Depending on the potential for malignant transformation.	**Mild:** Lesions with atypical features whose potential for malignant transformation is unknown. **Moderate:** Lesions characterized by carcinomatous potential. It is also regarded as true dysplasia. **CIS**: Characterized by true but not invasive neoplasm.	• Provides detailed features of CIS.	• Omitted the term 'severe dysplasia'. • Lack of numerical values leading to failure in providing statistical analysis.	38
WHO (2005)	**Architectural features:** 1. Irregular epithelial stratification. 2. Loss of polarity of basal cells. 3. Basal cell hyperplasia. 4. Drop-shaped rete ridges. 5. Increased number of mitotic figures. 6. Abnormal superficial mitosis. 7. Dyskeratosis. 8. Keratin pearls within rete ridges. **Cytological features:** 1. Anisonucleosis. 2. Nuclear pleomorphism. 3. Anisocytosis. 4. Cellular pleomorphism. 5. Increased N:C ratio. 6. Increase in nuclear size. 7. Atypical mitotic figures. 8. Increased number and size of nucleoli. 9. Hyperchromasia.	**Hyperplasia:** Hyperplasia of basal/parabasal cell layers without cellular atypia. **Mild dysplasia**: Architectural changes limited to lower third of the epithelium accompanied by cytological atypia. **Moderate dysplasia: A**rchitectural changes limited to middle third of the epithelium. **Severe dysplasia**: Architectural disturbances extending above 2/3rds of the epithelium. **CIS** : Architectural abnormalities in full thickness accompanied by cytological atypia.	• Includes both cytological and architectural changes. • Also includes the term 'hyperplasia' providing more details. • Exhibits good observer agreement.	• Variability in thickness of oral epithelial lining leads to inaccurate grading. • Lack of numerical values leading to failure in providing statistical analysis. • Does not provide associated risk factors.	39
SIN DYSPLASIA CLASSIFICATION (2005)	WHO 2005 criteria.	**SIN 1**: Similar to mild dysplasia. **SIN 2**: Similar to moderate dysplasia. **SIN 3**: Combination of severe dysplasia and CIS.	• Simple. • Also involves other regions of upper aerodigestive tract.	• Only subjective interpretation. • Lack of evidence of malignant transformation. • Overlapping of features leads to inaccurate grading.	41
BINARY SYSTEM (2006)	WHO 2005 criteria.	**High-risk lesions**: Lesions presenting with at least 4 architectural changes and 5 cytological changes. **Low-risk lesions: L**esions presenting with < 4 architectural changes or < 5 cytological changes.	• Objective. • Good observer agreement. • Help clinicians to identify the risk potential.	• Large scale studies still needed to investigate its accuracy and reliability.	44
BOUQUOT et al., (2006)	• Cellular atypia or dysplasia similar to squamous cell carcinoma. • No evidence of invasion into underlying stroma. • Epithelium with more number of atypical cells have more risk of becoming malignant. • Epithelium with most extreme atypia of cells has the greatest risk of malignant transformation. • Final grading is based on the most severely involved area of change, even if that area includes no more than a few rete ridges.	**Mild :** Proliferation of atypical or immature basal cells above parabasal region up to lower 3rd of epithelium. **Moderate**: Proliferation into middle 3rd of epithelium. **Severe:** Abnormal proliferation of atypical cells from basal layer into upper 3rd of epithelium.	• Simple.	• Subjective. • Lack of numerical values leading to failure in providing statistical analysis.	46

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Table 2 (*continued*)

GRADING SYSTEM	CRITERIA USED	GRADES	ADVANTAGES	DISADVANTAGES	REFERENCE NUMBER
OIN/CIS (JSOP) SYSTEM (2010)	WHO criteria 2005	**OIN1**: < 1/3rd of epithelium shows dysplastic features. **OIN2:** 1/3rd-2/3rds of epithelium show dysplastic features. **OIN3**: Full thickness of epithelium show dysplasia. *Based on "Bethesda classification" for cervical cancer, the system with 3 grades for OIN was replaced by a 2 grade system later. **Low grade oral intraepithelial neoplasia (loin):** OIN 1 **High grade oral intraepithelial neoplasia (hoin):** OIN2 and OIN3	• Simple. • Less tedious. • Less time consuming. • Can distinguish features of OSCC from cervical cancer.	• Subjective. • Observer variability. • Thickness of epithelium may vary leading to improper grading.	47
WHO (2017)	**Architectural features:** 1. Irregular epithelial stratification. 2. Loss of polarity of basal cells. 3. Drop-shaped rete ridges. 4. Increased number of mitotic figures. 5. Abnormal superficial mitosis. 6. Dyskeratosis. 7. Keratin pearls within rete ridges. 8. Loss of epithelial cell cohesion** **Cytological features:** 1. Anisonucleosis. 2. Nuclear pleomorphism. 3. Anisocytosis. 4. Cellular pleomorphism. 5. Increased N:C ratio. 6. Atypical mitotic figures. 7. Increased number and size of nucleoli. 8. Hyperchromasia.	**Mild dysplasia:** Confined to the lower 1/3rd of the epithelium exhibiting cytologic and/or architectural alterations. **Moderate dysplasia:** Changes from 1/3rd – middle 3rd of the epithelium. **Severe dysplasia/ CIS:** Changes up to upper 2/3rd third to the entire thickness of the epithelium.	• Simple. • Improved WHO 2005 system.	• Subjective. • Does not imply the continuous progression of dysplasia. • Can't predict malignant potential. • Variability in thickness of oral epithelial lining leads to inaccurate grading. • Lack of numerical values leading to failure in providing statistical analysis.	48

CIS- Carcinoma in situ; EAI- Epithelial atypical index; JSOP- Japanese Society for Oral Pathology; N:C- Nuclear cytoplasmic ratio; OIN- Oral intraepithelial neoplasia; OSCC-Oral squamous cell carcinoma; SIN- Squamous intraepithelial neoplasia; WHO-World health organization.

dysplasia minimizing the observer variability with the use of photographic aid. But it could provide just the subjective accuracy of the scores. All these controversies restricted this system's application in routine practice by the pathologists.[20]

Manchanda & Shetty in 2011 observed a good intra-observer agreement in the grading of OED using this system compared with Brothwell and the WHO 2005 system but the inter-observer agreement was poor. Also, this system seemed to be more time consuming and complex because each dysplastic feature was to be to noticed to reach final scoring.[21]

Geetha et al., in 2015 graded 50 cases of histopathologically diagnosed dysplasia using three different systems. And they found Smith and Pindborg system to be less ideal than the WHO and Ljubljana system of grading dysplasia. They found this method to be difficult and time consuming as compared to the other two methods used.[22]

7.2. BANOCZY and CSIBA (1976)

They graded OED into three categories using the parameters suggested by ***Mehta et al., in 1971*** (Table 2). Based on their grading, they described the distribution of leukoplakic lesions by age, sex, clinical types, location, and follow-up results and co-related these factors with the grades of dysplasia.[23]

7.2.1. Advantages

- It seems to be a simple method of grading.
- It is less time consuming.

7.2.2. Disadvantages

- The system provides a subjective interpretation of the dysplastic features.
- It cannot recognize the risk factors associated with malignant potential. So, it is not widely accepted.

7.3. WHO (1978)

In context of introducing standard criteria to grade OED, WHO in 1967 established a collaborating reference center aimed to identify the precancerous lesions and their relative risks of transforming into malignancy.[24] Using specific parameters they had graded OED into three types as mild, moderate, and severe in 1978 (Table 2).

The presence of mild dysplasia indicated the no-risk potential for malignant changes, however high-risk sites such as the floor of the mouth and the ventral surface of the tongue needed greater consideration. The presence of moderate dysplasia signified the alerting sign and the severe dysplasia indicated the considerable risk of malignant changes.[7]

7.3.1. Advantages

- This system is easy to use and less time consuming.
- It takes into consideration both cellular and architectural features.

7.3.2. Disadvantages

- It does not take into account which factor was important in determining the malignant potential.
- Severe grades may merge into CIS but the practical value of distinguishing severe dysplasia and CIS was not clarified.
- Observer agreement may vary in different cases.

Geetha et al., (2015) in their study graded 50 cases of histopathologically diagnosed dysplasia using three different systems. And they depicted that WHO 1978 grading system had shown the best results among the three with moderate to good intra-observer agreement and fair inter-observer agreement.[22]

7.4. KRAMER (1980)

This system didn't categorize ED into any grades.[25] They followed the same criteria as used in WHO 1978 system. And they also included two new parameters which were; cellular crowding and abnormal mitosis. According to them, the epithelium may be considered as dysplastic if it involves any two or more of the criteria described in Table 2.

7.5. BURKHARDT and MAERKAR (1981)

They considered six different parameters to classify dysplasia. They graded dysplasia into the four categories (Table 2). In their study, the degree of dysplasia was correlated with the clinical parameters which were associated with relatively poor prognosis such as age, sex, location, dental status, and exogeneous irritants. Cases showing moderate to high degree of dysplasia developed malignancy.[26]

7.5.1. Advantages

- This system also takes into consideration some other risk factors associated with dysplasia such as the presence of candida species and the subepithelial inflammatory component.

7.5.2. Disadvantages

- The system cannot provide specific and accurate grading for OED.
- It may suffer inter and intra-observer variability.

Girod SC et al., in 1998, in their study, classified epithelial dysplastic lesions according to this system and investigated the expression of Ki-67, p53, and PCNA in different degrees of dysplasia and demonstrated a better correlation.[27]

7.6. SHAFER (1983)

Shafer listed a few criteria to grade dysplasia based on the particular histopathological features and the cellular alterations extending from the basal cell layer towards the inner layers of the epithelium.[28] He categorized OED into three grades i.e.; mild, moderate, and severe (Table 2).

7.6.1. Advantages

- It involves both cellular and architectural features.
- It is simple and easy to use.

7.6.2. Disadvantages

- It does not signify which factors are important in determining the malignant potential.
- It may show variability in inter and intra-observer agreement from study to study.

7.7. LUMERMANN et al., (1995)

They followed a few criteria for grading dysplasia such as hyperplasia of the basal layer, hyperchromatic nuclei with an increased size, and drop-shaped rete pegs.[28] They graded dysplasia into five subtypes (Table 2).

7.7.1. Advantages

- They introduced a new category i.e., verrucous hyperplasia with dysplasia.

7.7.2. Disadvantages

- Their study depicted that the dysplastic changes are multicentric with the presence of normal or hyperplastic epithelium in certain missing areas of dysplasia. And in the same biopsy specimen the grades of dysplasia were variable suggesting that it was not always that dysplastic features could be observed in the region including biopsy, to evaluate an accurate extent, it was essential to examine the complete area. Thus new category (verrucous hyperplasia) may create confusion during grading.

7.8. NEVILLE (1995)

This system used 11 parameters to diagnose dysplasia. It graded dysplasia into four subtypes depending on the region of epithelium involved (Table 2).[29]

7.8.1. Advantages

- It involves both cellular and architectural features.
- It is simple and easy to use.

7.8.2. Disadvantages

- It does not signify which factors are important in determining the malignant potential.
- It may suffer inter and intra-observer variability.

7.9. SPEIGHT et al., (1996)

They emphasized that the thickness of the epithelium throughout which dysplastic changes occur, is an important factor in the grading of dysplasia.[30] They used the same criteria as followed by WHO 1978 grading system and categorized dysplasia into three grades (Table 2).

7.9.1. Advantages

- This system involves both cellular and architectural alterations in the epithelium.
- It is simple and easy to apply.

7.9.2. Disadvantages

- The thickness of the oral epithelial lining may vary widely from region to region thus leading to inaccurate grading of OED.
- Variation in observer agreement.

7.10. SOAMES (1998)

This system followed the same criteria that were used by WHO 1978 grading system.[31] And divided OED into three grades depending upon the thickness of the epithelium (Table 2).

7.10.1. Advantages

- It involves both cellular and architectural features.
- It is simple and easy to use.

7.10.2. Disadvantages

- Variation in the thickness of the oral epithelial lining may lead to inaccurate grading of OED.
- It may show observer variability.

7.11. KUFFER and LOMBARDI (2002)

They stated that the clinical criteria were more significant in the diagnosis and the terminology of precancer.[32] They classified these lesions into two categories.

1. Risk lesions: Oral precancerous lesions which histologically do not show dysplasia.
2. Precursors of OSCC: Lesions with evidence of dysplasia.

7.11.1. Advantages

- This system introduced two new terminologies in association with dysplasia.

7.11.2. Disadvantages

- Because of the difference in malignant transformation rate between three grades of dysplasia, the term “risk lesion” is not feasible to use for the lesions showing no evidence of dysplasia and no risk of malignant transformation. It can mislead a clinician with no knowledge in this specialty in properly diagnosing the severity of dysplasia.
- The terminology “precursor of OSCC” concerning dysplasia suggested that the associated disorders were more prone to malignant transformation. This had no scientific evidence.

Mincer et al., in a study reported that 20% of OED showed regression and 40% revealed no evidence of severity.[33] While ***Gupta et al.***, in another study observed that 13% of cases with OED regressed and 40% showed no progression towards severity.[34]

7.12. LJUBLJANA GRADING SYSTEM (2003)

Laryngeal pathologists, ***Kambic and Lenart in 1971*** proposed this system of classifying dysplasia in laryngeal hyperplastic lesions.[35] ***Zerdoner in 2003*** suggested its use for grading hyperplastic epithelial lesions of the oral cavity and divided them into four grades (Table 2).[36]

7.12.1. Advantages

- It provides vast information to the clinicians regarding accurate diagnosis and management of OED.
- It focuses on important factors that are of the primary concern for the clinicians in identifying the patients with benign lesions, mild to moderate grade, and severe grade, depending on which it is recognized whether they require further follow up for the treatment or not.

7.12.2. Disadvantages

- This classification fails to categorize some oral lesions such as OSMF and OLP which show atrophy of epithelium and absence of significant atypia.
- It is complicated and consumes more time and its application for oral lesions needs to be investigated.
- There is a need to add a numerical values into this grading so that statistical tests for significance can be applied to it.

7.13. BROTHWELL et al., (2003)

Brothwell et al., in 2003, graded 64 sections of OED lesions using only four criteria[37] and graded dysplasia into five subtypes and provided a numerical value to each grade (Table 2).

7.13.1. Advantages

- Using this system, statistical analysis can be made.

- Inter and intra-observer agreement has been found to be consistent.

7.13.2. Disadvantages

- It is time consuming and tedious to use.
- It does not indicate the risk factors involved.
- Not all cellular and tissue alterations have been considered for grading.

7.14. TAKASHI SAKU et al., (2004)

They proposed a new concept for histopathology of oral borderline lesions.[38] They classified dysplasia into three grades as mild, moderate, and CIS (Table 2).

They further grouped CIS histologically into four types.

1. **Basaloid:** Cells replacing the entire thickness of epithelium are mostly basaloid here.
2. **Verrucous:** Characterized by round rete ridges with differentiation towards keratinization, hyperkeratosis, and keratin plugging.
3. **Acantholytic:** It is the most difficult subtype to identify as it resembles simple epithelial hyperplasia. There is distinctive keratinization on the surface, indented rete ridges, dyskeratosis in the lower layers of rete processes.
4. **Atrophic:** The surface is flat with the absence of hyperkeratosis, small rete ridges. There is a loss of cellular cohesion within rete processes with dense lymphocytic band formation.

7.14.1. Advantages

- This system also helps to distinguish other features of CIS by categorizing it into its subtypes.

7.14.2. Disadvantages

- The term 'severe dysplasia' has not been included.
- Numerical values need to be added to provide a statistical analysis.

7.15. WHO (2005)

A working group formulated for a consensus conference in Lyon, France in 2005, put forward some criteria to grade epithelial dysplasia which was published as WHO 2005 classification.[39] They used the combination of cellular and architectural changes, based on which they divided the epithelium into "thirds" and classified the lesions into five categories (Table 2).

7.15.1. Advantages

- They introduced 'squamous hyperplasia' as a new term.
- They considered both cellular and architectural changes in the epithelium.
- This system shows good inter and intra-observer agreement.

7.15.2. Disadvantages

- The thickness of the oral epithelium may vary leading to inaccurate grading.
- Numerical values need to be added to make a statistical analysis.
- It does not provide the risk factors associated with malignant transformation.

Madhura MG et al., in 2016 used a photographic method and WHO 2005 classification system to grade 50 samples of OED and found significant inter and intra observer agreement using both the methods.[40]

7.16. SQUAMOUS INTRAEPITHELIAL NEOPLASIA / DYSPLASIA CLASSIFICATION (2005)

This is a modification of previously introduced CIN classification which was later opted for other sites also including oral mucosa.[41] It represents the modified WHO classification 2005 as "oral intraepithelial neoplasia" (OIN) and SIN in general, to involve multiple sites of upper aerodigestive tract altogether.[42]

According to this system, dysplasia is a spectrum with hyperplastic keratinizing SIN/dysplasia on one side which is known as keratinized dysplasia and the other side is atrophic SIN/dysplasia which is similar to the WHO type dysplasia.[43]

In this grading system lesions are classified as SIN 1, SIN 2, SIN 3 (Table 2).

7.16.1. Advantages

- This is simple and easy to use.
- This system also involves other regions of the upper aerodigestive tract leading to a wide range of assessment of the severity of dysplasia.

7.16.2. Disadvantages

- There is no evidence that why many of the potentially malignant lesions of the oral mucosa are not transformed into carcinoma.
- Overlapping features between the two sides of the spectrum lead to inaccurate grades.
- This system is based on subjective interpretations mainly.

7.17. BINARY SYSTEM (2006)

In the WHO classification, prognostic evaluation of the grading of moderate dysplasia was problematic. This problem was resolved by the binary system introduced by *Omar Kujan et al.*[44] They categorized the lesions into high and low-risk (Table 2).

7.17.1. Advantages

- This system is more objective.
- Classifying the lesions into high and low risk, this system helps to predict the clinical outcome and guide pathologists to make the proper diagnosis.
- It shows good observer agreement.

7.17.2. Disadvantages

- Large scale studies are still required to investigate the reliability and reproducibility of this system.

Kujan et al., in their study observed that grading of dysplastic lesions using this system showed a higher inter-observer agreement as compared to the WHO system of grading in 2005.

Nankivell et al., demonstrated that the binary system had a better reproducibility as compared to WHO classification in the grading of OED.[45]

7.18. BOUQUOT et al., (2006)

They combined cellular and tissue changes to classify dysplasia.[46] They categorized OED into three subdivisions: mild, moderate, and severe (Table 2).

Regardless of individual characteristics, they used the following grading criteria.

- Cellular atypia or dysplasia similar to SCC.

- Lack of evidence of invasion into underlying stroma.
- Greater risk of malignant changes in the epithelium with more atypical cells and the risk increases with the increase in the number of atypical cells.
- Final grading should be based on the area that shows the most severe dysplastic change, even if that area is limited up to few rete pegs.

7.18.1. Advantages

- This system has simplified the criteria used for grading of dysplasia by providing specific features.

7.18.2. Disadvantages

- This system provides subjective interpretations.
- Large scale studies are still needed to investigate its reliability.

7.19. ORAL INTRAEPITHELIAL NEOPLASIA (OIN) / CARCINOMA IN SITU (CIN); JAPANESE SOCIETY FOR ORAL PATHOLOGY (JSOP) SYSTEM (2010)

In 2010, a new term "OIN" was introduced by the Working Group of the Japanese Society for Oral Tumours (WG–JSOT) to rectify the WHO's terminology of CIS and to highlight the features of OSCC differentiating them from those of SCC of the uterine cervix.[47]

According to this system, the oral precursor lesions are divided into three categories: Reactive atypical epithelium, OED, and OIN/CIS. Three grades of OIN have been introduced: OIN 1, OIN 2, and OIN 3. Based on "Bethesda classification" for cervical cancer, the system with 3- grades for OIN was replaced by a 2-grade system later on (Table 2).

7.19.1. Advantages

- It is simple and easy to use.
- It is less tedious and time taking.
- It helps to distinguish features of OSCC from cervical cancer.

7.19.2. Disadvantages

- It suffers inter and intra-observer variability.
- Its reliability is yet needed to be investigated.

7.20. WHO (2017)

This is the recent classification system of OED grading in which certain changes have been introduced in the criteria used to grade dysplasia by WHO in 2005.[48,49]

- Terms "squamous hyperplasia" and "CIS" are omitted from the WHO 2005 system.
- The term "CIS" corresponds with severe dysplasia.
- The feature, "increase in nuclear size" has also been removed.
- "Loss of epithelial cell cohesion" has been included in this classification.

This system is the most widely in use for the grading of OED. This classification proposed a 3-tiered grading system for OED: Mild, Moderate, and Severe.[50] "CIS" is the same as "severe dysplasia" (Table 2). However, this system also exhibits some limitations.

7.20.1. Advantages

- This system is simple and easy to use.
- It has improved the previously used classification by WHO in 2005.

7.20.2. Disadvantages

- It is based on subjective interpretations.
- It does not imply the continuous progression of dysplasia.
- It can't predict its malignant potential.
- Lack of numerical values lead to failure in providing statistical analysis.

8. Conclusion

Attempts have been taken by many scholars and researchers to propose an ideal system for the grading of OED. But every system has got certain limitations restricting their use in common practice. At present, WHO 2017 grading for OED is the most acceptable system. But it also suffers from many shortcomings which is one of the important factors that has become a challenge for the oral pathologists to detect the accurate progression and stage of OED to reach a proper diagnosis. Robust research on the predictive value, relevance, applicability, and feasibility of this system are warranted and large scale studies are still required to discover a reliable and reproducible method for grading of OED.

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3. Dr Madhushankari GS: Visualization and Formal analysis.

Declaration of competing interest

Nil.

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