Review Article

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Dentistry Section

Oral Epithelial Dysplasia: A Narrative Review on Histological Grading, Computer-aided Diagnostics and Treatment Approaches

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ABSTRACT

Head and Neck (H&N) cancer represents a significant global health burden, ranking sixth among all cancer types worldwide, with a particularly high prevalence in developing countries. Oral cancer, a subset of H&N cancer, encompasses malignant growths within the oral cavity region. Oral Epithelial Dysplasia (OED) serves as a precursor lesion to oral cancer and is identifiable through histological examination by pathologists. While histological grading correlates with progression cancer risk, accurately predicting lesion advancement remains challenging due to limited research and study. Despite established grading criteria based on architectural and cytological changes in the oral cavity histological images, variability exists among pathologists in assessing OED presence and grade. The present article explores OED as a precancerous lesion, delving into various histological grading systems based on architectural and cytological changes. Additionally, it examines the role of Computer-aided Diagnostics (CAD) leveraging Artificial Intelligence (AI) in OED detection. Lastly, the paper discusses treatment modalities for oral cavity cancers.

Keywords: Artificial intelligence, Cancer prevention, Dysplasia grading, Oral cancer, Treatments

INTRODUCTION

A healthy mouth is a one-of-a-kind and priceless asset that is also an integral part of overall health and quality of life; it can even be considered a basic human right. In reality, oral health is frequently compromised every day by various types of diseases, including dental caries, periodontal disease, and, in rare cases, oral cancer, lesions caused by Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), conditions of the mucosa and salivary glands, as well as a variety of pains and clefts [1]. Currently, oral diseases are recognised as a worldwide epidemic and a major public health issue that affects almost every individual throughout their lives [2]. Oral cancer ranks as the 11th most common cancer worldwide. One of the leading causes of death in India is oral cancer, which affects a large segment of the population [3]. The United States projects 2,001,140 new cancer cases and 611,720 cancer-related deaths for 2024 [4], with a sustained decline in mortality attributed to factors such as reduced smoking rates, advancements in early detection, and enhanced treatment options. The overall cancer mortality rate has dropped by 31% since 1991, resulting in 3.2 million fewer cancer deaths. Men are more than twice as likely as women to develop oral and oropharyngeal cancers. White people are slightly more likely than Black people to be affected. Overall, men have a one in 60 (1.7%) lifetime risk of developing oral cavity and oropharyngeal cancer, while women have a one in 140 (0.71%) lifetime risk of developing oral cavity and oropharyngeal cancer. Men's cancer rates are more than twice as high as women's [5].

In the present article, the author discusses the risk factors of oral cancer, the statistics relating to oral cancer incidence in India according to various socio-economic positions, and the different diagnostic techniques routinely used to detect oral cancer [6]. Most of the sources for oral cavity cancers are associated with tobacco, areca nuts, Human Papillomavirus (HPV), and excessive alcohol habits. Good oral health begins with good oral hygiene, such as using fluoride toothpaste, flossing daily, and seeking professional help if necessary. Oral health is also affected by social determinants. Ideally, the dentist-to-population ratio should be 1:7500 according to the World Health Organisation (WHO), but in India, it is 1:22,500, which is shocking. Higher disease rates occur in racial/ethnic groups and people with lower education and income [7]. Reagon coined the term "dysplasia" to describe the cells exfoliated from uterine cervix lesions in 1958 [8]. Once upon a time, epithelial dysplasia, epithelial atypia, and dyskeratosis were all interchangeable terms. The term dysplasia is used to describe the presence of abnormality within a tissue. Truly, Dysplasia is not cancer, but it may sometimes become cancer. Dysplasia of the oral cavity is a potentially precancerous lump diagnosed histologically [9]. In oral dysplasia, significant changes in tissue layers and cells can be observed under the microscope, representing a premalignant stage for epithelial carcinomas, for example, Oral Squamous Cell Carcinoma (OSCC). OSCC consists of the oral cavity, nasal cavity, oropharynx, paranasal sinus, larynx, hypopharynx, nasopharynx, tonsils, tongue, salivary glands, parotid glands, and lip [10]. In medical terms, dysplasia is used to describe the premalignant or precancerous stage of epithelial malignancies, such as OSCC, which is caused by a variety of hereditary and environmental variables that result in the proliferation of atypical epithelium. A study [9], discussed various imaging methods for the detection of dysplasia in the oral epithelium of the oral cavity region, which is examined here using the cytological and architectural changes in the epithelium. OED is often a precancerous lesion, and it can be classified into mild, moderate, and severe forms [11]. More recently, a two-tier grading system has been developed [12]. However, this two-tier grading system is done for a better understanding of histopathology OED by the clinician in a practical approach. Histopathology has long been thought to be incongruent in the diagnosis and classification of OED, with low inter- and intraobserver agreement and reproducibility [13]. OED is not hereditary, so it can affect anyone at any stage who is exposed to tobacco and heavy alcohol. A precancerous lesion called OED is an element of potential cancer development within the oral mucosa [14]. A cellular and morphological change found in OED remains a significant risk factor for invasive neoplasia later in life. Precancer lesions cause cancer cells to grow in their immediate surroundings.

In the past, Oral Potentially Malignant Disorders (OPMD) were referred to as potentially malignant lesions or conditions. These disorders mostly involve leukoplakia and erythroplakia [15,16].

A comprehensive search was conducted across multiple databases, including PubMed, Web of Science, IEEE, Embase, Cochrane Library, Wiley Online Library, and Europe PMC. The search terms encompassed various aspects of oral cavity cancer, oral dysplasia, OED, classification or grading of OED, potentially malignant disorders, CAD, and their combinations. After eliminating duplicates, a total of 1080 papers were identified, of which 153 were deemed relevant while 927 were considered irrelevant. Among the relevant papers, 110 were available in full text. From there, the author selected 11 papers specifically related to OED. The review encompassed studies on oral cancer histological grading by different authors, oral cancer epidemiology, CAD, Artificial Intelligence (AI) and cancer treatments.

DISCUSSION

Histological Grading

The term dysplasia was coined in the 1950s to describe uterine cervix pathology [17]. In 1968, the Cervical Intraepithelial Neoplasia (CIN) grading system was established as the first widely used histological grading system for dysplasia by the WHO in 2014. It consists of three grades- CIN1 (mild), CIN2 (moderate), and CIN3 (severe). The successful implementation of this system influenced the grading of dysplasia in various tissues, including the oral mucosa, for decades [17,18]. Pathologists grade OED by assessing the dysplastic features of the lesions. In the grading system, numerous dysplastic features are utilised, making it challenging to determine the degree of epithelial dysplasia. The most common change to the oral mucosa is squamous cell carcinoma of the mouth [19]. Among potentially malignant disorders, leukoplakia is the most prevalent [20]. Various dysplastic features are employed in grading systems, which complicates rating the degree of dysplasia accurately. Some grading systems suggest assessing mild, moderate, and severe dysplastic features [9]. Recently, efforts have been made to define more precise grading criteria for OED [21,22]. According to the author, no research has revealed any natural prognostic groups or characteristic clustering to establish unique OED patterns [23]. The main goal of this work, as per the article, is to implement a transfer learning method for classifying images as “suspicious” or “normal” using Inception-ResNet-V2. Heat maps are then generated to highlight the regions of the images that are most likely to be involved in decision-making. Their developed approaches are also tested with two independent clinical photographic image datasets of 30 and 24 patients from the UK and Brazil, respectively [24].

In the CIN grading system, mild dysplasia is characterised by cytological changes limited to the basal third of the epithelial thickness, while CIN2 and CIN3 are associated with the middle and upper thirds, respectively [18,25]. However, according to molecular analysis of cervical disease, CIN1 is biologically distinct from CIN2 and CIN3 [26]. The following are the most commonly used grading systems proposed for OED by various authors and organizations, with the grading system criteria and grades presented chronologically in [Table-1] [12,22,27-34]. A study conducted by Shubhasini AR et al. [35], evaluated the degree of agreement between two pathologists in grading the inter and intraobserver variability of dysplasia in the

Year	Author/grading system	Grading Criteria Used	Grades
1969	Smith C and Pindborg JJ [27]	1. Drop-shaped rete ridge 2. Basal cell hyperplasia 3. Irregular epithelial stratification 4. Loss of intercellular adherence 5. Keratinisation of cells below keratinised layer 6. Loss of polarity 7. Hyperchromatic nuclei 8. Anisocytosis and asinonucleosis 9. Increased nucleocytoplasmic ratio in basal and prickle cell layer 10. Mitotic activity 11. Level of mitotic activity 12. Pleomorphic cells and nuclei 13. Presence of Bizarre mitoses	The scoring is given based on the Epithelial Atypia Index (EAI). Min EAI=0 Max EAI=75 Scoring: Absent=0, Slight or Marked=1 and 10 Grading: 0-10: No dysplasia 11-25: Mild 26-45: Moderate 46-75: Severe
1975	Waldron CA and Shafer WG [28]	1. More and abnormal mitosis. 2. Keratin formation by a single cell. 3. Loss of polarity. 4. Basilar cell hyperplasia. 5. Epithelial pearls within the spinous layer. 6. Altered N:C ratio. 7. Large prominent nucleoli. 8. Dyskeratosis. 9. Poikilocytosis.	Grade IDysplasia: Proliferation of atypical or immature basal cells above the parabasal region. Grade IIDysplasia: Proliferation into the middle 1/3rd of the epithelium Grade IIIDysplasia: Abnormal proliferation from the basal layer into the upper 3rd of the epithelium.
1978	Kramer IR et al., [29]	1. Loss of polarity of basal cells 2. Drop-shaped rete pegs 3. An increased nuclear-cytoplasmic ratio 4. Irregular epithelial stratification 5. The presence of mitotic figures in the superficial half of the epithelium 6. Increased number of mitotic figures 7. Reduction of cellular cohesion 8. Nuclear hyperchromatism 9. Cellular polymorphism 10. Enlarged nucleoli 11. The presence of more than one layer of cells having the basaloid appearance 12. Keratinisation of single cells or cell groups in the prickle cell layer	Mild: Dysplastic features observed in the lower 1/3rd of the epithelium. Moderate: Dysplastic features were observed in the lower 2/3rd of the epithelium. Severe: Dysplastic features observed greater than 2/3rd of the epithelium.
1995	Lumerman H et al., [30]	1. Basal cell hyperplasia 2. Drop-shaped rete ridges 3. Nuclear enlargement and hyperchromatic	Mild: Dysplastic alternation is seen in the lower 1/3rd of the epithelium Moderate: Dysplastic features are seen till the 2/3rd thickness of the epithelium Severe: Dysplastic features changes are seen in more than 2/3rd but less than the entire thickness of the epithelial Carcinoma in-situ (CIS): Dysplastic changes are found in the entire thickness of the epithelium without invading the submucosa. Verrucous hyperplasia with dysplasia: The epithelium exhibits thickening along with surface papillations, parakeratin plugging, and hyperkeratosis cell is seen in the lower third of the epithelium

2003	Žerdoner D [31]	1. Increased prickle cell layer without changes in basal and parabasal layers. 2. The 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, and more dyskeratotic cells. 4. Loss of stratification of epithelium, marked cellular alteration, increased mitosis with an abnormal pattern, extending up to high levels of epithelium	Simple hyperplasia: Criteria 1 Abnormal hyperplasia: Criteria 2 Atypical hyperplasia: Criteria 3 CIS: Criteria 4
2003	Brothwell DJ et al., [22]	1. Bulbous retes 2. Basal and parabasal cell hyperplasia 3. Nuclear hyperchromatism 4. Nuclear pleomorphism	0. No dysplasia. 1. Mild dysplasia: Increase in the number of cells in basal and parabasal cells, showing nuclear hyperchromatism and pleomorphism. 2. Moderate dysplasia: Features of Grade 1 also involve basal, parabasal, prickle layer, and the presence of bulbous rete processes. 3. Severe dysplasia: Features of grade 2 throughout the entire epithelium thickness. 4 CIS: Atypical changes in the full thickness of the epithelium indicate early superficial connective tissue invasion without any clinical evidence.
2005	Barnes L et al. [32]	Architecture criteria 1. Irregular epithelial stratification 2. Loss of polarity of basal cells 3. Drop-shaped rete ridges 4. Increased number of mitotic figures 5. Abnormally superficial mitoses 6. Premature keratinisation in single cells 7. Keratin pearls within rete ridges Cytology criteria 1. Abnormal variation in nuclear size 2. Abnormal variation in nuclear shape 3. Abnormal variation in cell size 4. Abnormal variation in cell shape 5. Increased nuclear-cytoplasmic ratio 6. Increased nuclear size 7. Atypical mitotic figures 8. Increased number and size of nucleoli 9. Hyperchromatism	Hyperplasia: Hyperplasia of basal/parabasal cell layers without cellular atypia Mild: Architectural changes limited only to the lower third of the epithelium accompanied by cytological atypia Moderate: Architectural changes are limited to the 2/3rd of the epithelium. Severe: Architectural disturbances extending greater than 2/3rd of the epithelium and the cytological atypia number increased CIS: Architectural disturbances are seen throughout the epithelium
2005	Gale N et al. [33]	WHO (2005) criteria	SIN1: Similar to mild dysplasia SIN2: Similar to moderate dysplasia SIN3: Combination of severe dysplasia and CIS
2006	Kujan O et al [12]	WHO (2005) criteria	Low-risk: Lesions presenting with less than 4 architectural changes or less than 5 cytological changes. High-risk: Lesions presenting with at least 4 architectural changes and 5 cytological changes.
2017	Sloan P et al [34]	Architectural changes: 1. Irregular epithelial stratification. 2. Drop-shaped rete ridges. 3. Keratin pearls within rete ridges. 4. Loss of polarity of basal cells. 5. Increased number of mitotic figures. 6. Abnormal superficial mitosis. 7. Dyskeratosis. 8. Loss of epithelial cell cohesion** Cytological changes: 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: Confined to the lower 1/3rd of the epithelium exhibiting cytological and/or architectural alterations. Moderate: Changes from 1/3rd- middle 3rd of the epithelium Severe/CIS: Changes up to the upper 2/3rd to the entire thickness of the epithelium.

[Table/Fig-1]: Various OED grading systems [12,22,27-34]

same patients. They also reviewed the existing grading systems, including the WHO Classification 2005 [32]) and the binary system of classification (low-risk and high-risk) (suggested by Kujan et al. [12]) of oral dysplasia, both of which were blinded to the clinical diagnosis for their histological diagnosis. Statistical analysis revealed poor intraobserver variability with a p-value of 0.8 using the WHO classification and 0.3 using the binary classification. The binary classification, which is more likely to have higher concordance among pathologists, is recommended by the authors based on the results from the clinical standpoint. As pointed out by Nankiveli P et al. [36] and Jain A. et al. [37], the binary system potentially aids clinicians in decision-making regarding management strategies.

Another study was conducted by Manchanda A and Shetty DC [38], assessing inter- and intraobserver variability using the Smith C and Pindborg JJ [27] and WHO grading systems 1978 [29], along with the Brothwell grading system [22]. A total of 45 histological tissues of dysplasia were examined, 15 each of mild, moderate, and severe dysplasia, and blindly graded by three observers using the three grading systems mentioned. The authors noted that the Brothwell system had significantly higher interobserver agreement than the WHO 1978 and Smith C and Pindborg JJ systems. Intraobserver agreement was similarly much greater in the Smith C and Pindborg JJ system, but predictability and the likelihood index were dispersed across a wider range in this system.

Every grading system has advantages, as well as disadvantages and limitations. Research teams continually improve their methods over time. For example, Smith C and Pindborg JJ (1969) is the oldest grading system for OED [27]. Its disadvantage is that it is time-consuming and monotonous. It cannot explain why some non neoplastic lesions exhibit dysplasia signs. The WHO (1978) grading

system [29] has limitations as it does not consider factors that determine malignant potential. The clinical relevance of distinguishing severe dysplasia from CIS remains unclear. Different observers may reach different conclusions. A study by Warnakulasuriya S. [39] highlights the need for more objective clinical and molecular biomarkers as histological grading of oral precancer's epithelial dysplasia in this system is subjective and may not reliably predict malignant potential. The WHO (2005) grading system also has limitations such as variations in oral epithelium thickness, the need for numeric values for statistical analyses, and the absence of malignant transformation risk factors.

Currently, the most widely used grading systems for OED are the Binary Grading System (2006) [12,40] and WHO (2017). Most pathologists utilise both systems for dysplasia grading, but overall, pathologists tend to prefer the WHO (2017) grading system [34] due to its simplicity and ease of use. WHO (2017) also enhances the WHO (2005) classifications [32,41]. The main drawback of the Binary Grading system (2006) is that a large-scale study is necessary to verify the system's reliability and reproducibility

Computer-aided Diagnosis (CAD) of OED

The CAD is a system designed to assist doctors in interpreting medical images. The CAD system analyses digital images to identify typical features, such as diseases, and to highlight conspicuous sections to aid in making professional decisions. Now-a-days, CAD is considered the future application in digital pathology for examining Whole Slide Imaging (WSI) images and utilising Machine Learning (ML) algorithms. CAD is an interdisciplinary technique that combines AI and Computer Vision (CV) with image processing in pathology and radiology. Through CAD, tumours, polyps in the colon, dysplastic changes, and other abnormalities can be easily detected. CAD has been used clinically for over 40 years, but it does not substitute for doctors or professionals; instead, it plays a supportive role in medical diagnosis. In general, radiologists are responsible for interpreting medical images [42].

In the age of algorithms and AI, where computers can perform human-level tasks, defining risk may be far more significant based on how much human oversight is required [42]. AI may play a key role in accurately predicting the development of oral cancer, but several methodological issues must be addressed concurrently with advances in AI algorithms for the latter to be applied to population-based detection protocols on a large scale [43]. ML is a branch of AI [44] that focuses on using algorithms to solve various problems, such as data classification or regression, and is a growing area of interest for researchers looking to turn large amounts of data into knowledge that can be used in clinical decision-making. A recent advancement in ML is Deep Learning (DL) [45], which may more appropriately be referred to as a sub-part of ML [46]. DL is suited to handling large data sets, making it capable of processing decision-making. DL systems find patterns that are useful for tasks other than those for which they were designed. DL-based pattern recognition software has successfully detected objects and classified images of various cancer diseases in medical image analysis. A diagnostic DL system should include information that can help it localise and explain its decision, just like a human can diagnose a disease based on the image features that inform the diagnosis.

Microscopic Images

Histology is the gold standard for confirming the detection and diagnosis of oral dysplasia. AI may assist pathologists in grading oral dysplasia [47]. OED is predominantly diagnosed and graded based on architectural alterations and specific histologic features. Although AI has recently gained popularity in medical image analysis, only a few studies use traditional ML algorithms to diagnose oral precancerous and cancerous lesions [48]. Deep Convolutional Neural Networks (CNNs), which are modern AI algorithms, have recently been the focus of research in digital pathology for CAD [49]. The potential of these AI architectures in oral histological image analysis was demonstrated in some studies using CNNs and feature-based ML strategies [50]. The image-based ML method is appropriate for grading oral dysplasia because the task is primarily based on distinguishing an object's texture from the texture of its surroundings in an image. CNNs like Visual Geometry Group 16 (VGG16) [51], Residual Network (RestNet50) [52], and Inception-v3 [53] are helpful in several digital pathology studies [54], focusing on both feature extraction and image-based approaches.

Comparisons between two neural network architectures for distinguishing normal mucosa and unhealthy cells observed that VGG (80.66%) was more accurate in classifying tumour cells as opposed to healthy cells, and that ResNet (78.34%) was less accurate. The precision scores were as follows: VGG - 75.0%, ResNet - 72.4%, and F-Score - 77.6% and 75.5%, respectively [55].

Optical and Hyperspectral Images

The study of oral images using AI provides a method for the early and initial detection/diagnosis of certain abnormalities, offering ample scope for research. A study [56] on clinically annotated photographic images discovered that pre-processing with the VGG19 model significantly increased the classification accuracy of benign and precancerous tongue lesions to 98%.

In another study that applied a probabilistic Neural Network (NN), researchers were able to distinguish lichen planus from leukoplakia and normal tissues, achieving specificities of 81%, 74%, and 88%, respectively [57].

A Convolutional NN (CNN) strategy was employed to differentiate between normal and dysplastic tissue, followed by the use of a partitioned deep CNN that achieved 94.5% accuracy [58,59]. The latter work was conducted on hyperspectral images from the BioGPS University of California, Irvine (UCI) repository. Another study on hyperspectral images was carried out by Halicek M et al., who utilised tensor flow for classification and concluded that CNN (96.4%) had the highest accuracy in distinguishing between healthy tissue and cancerous tissue, followed by Support Vector Machine (SVM), Reinforcement Learning (RL), Differentiated Thyroid Carcinoma (DTC), Linear Discriminant Analysis (LDA) (67.4%) [60].

In their study [61], researchers explored the potential of CV and DL technology in photographic images of oral cancer. They investigated and identified OPMD using a 2-stage pipeline (oral lesion detection and oral lesion classification) through an automated system. In their preliminary real-time results, the authors achieved DL-based methods for automated detection and classification of oral cancer. The proposed model shows promise as a low-cost, non invasive tool to aid in OPMD screening and detection. The authors observed that U-Net models performed well in pixel-wise semantic segmentation, with the EfficientNet-b7 model receiving the highest dice score of 92.9%. YOLOv5l analyses the entire image for lesion regions and detects the lesion location within, while EfficientNet-b4 is used to classify the detected oral cancer lesions into multiple classes (Benign, OPMD, Carcinoma).

A study was conducted by Song B et al., to develop a low-cost, portable, easy-to-use system for the classification of oral dysplasia and malignancy images using various DL algorithms on a smartphone [62]. Researchers in this study took photographs of the oral mucosa, gingiva, soft palate, vestibule, tongue, and floor of the mouth. A variety of DL methods were employed, including VGG-CNN-M, VGG-CNN-S, and VGG-16, with VGG-CNN-M achieving the highest average accuracy of 86.9% in 4-fold cross-validation when compared to the other two. The author proposed a two-stage method for computing oral histological images, utilising 12 layers deep CNN for the segmentation of their constituent layers. Random forests were trained on texture-based features (such as the Gabor

filter) to detect keratin pearls from segmented keratin regions during both stages of the procedure.

A recent study by Rahman T and Mahanta LB focused on the precise segmentation of OED in oral cavity histopathological images, which is crucial for early diagnosis and treatment planning [63]. They utilised DL-based methods such as U-Net and other transfer learning models like VGG16, VGG19, MobileNet, and DeepLabV3+ as backbones with U-Net for segmenting the oral cavity epithelium. The study compared the performance of these transfer learning models for accurate and precise segmentation of histopathology images. The vanilla U-Net model achieved the highest Intersection over Union (IoU) at 93.73% for oral epithelial segmentation.

In general, studies on the early detection of oral cancer will be greatly enhanced by the intervention of AI, and consequently, clinical practice will be more effective. Due to its ability to detect complex patterns, AI can automate many tasks. Therefore, research is essential to facilitate the interdisciplinary integration of such techniques, and advancements in this field may pave the way for future research.

Treatments

Every year, the American Cancer Society calculates new death and cancer incidence statistics for the US based on population-based data [64]. There are over 500,000 new cases of oral cancer every year, associated with 350,000 deaths worldwide, making it one of the top ten most common cancers globally [24]. Based on individual circumstances and dysplasia grading, treatments are offered. If someone has mild epithelial dysplasia and no urgent treatment is needed, a little bit of care is sufficient. However, in cases of moderate and severe epithelial dysplasia, treatment is recommended, often involving surgical removal of the patch or laser treatment. According to studies and clinician advice, Oral Dysplasia or OED can be managed with active treatment facilities [65,66]. Patients with medically compromised conditions or diffuse lesions may benefit from active treatment. Several methods are available for treating patients with OED that can prevent dysplasia from progressing to cancer [67]. Many types of cancer occur on the floor of the mouth, on the tongue, gums, inside the cheek, and on the hard palate. In addition to more aggressive cancers, there are those that have spread into nearby tissues and those that have spread to nearby lymph nodes in the neck. A common treatment for oral dysplastic lesions is surgical excision with cold steel, laser, or cryosurgery. Surgery is preferred when small lesions progress from moderate to severe dysplasia. In South Asian countries, most people seek treatment late due to remote locations and socio-economic problems. Consequently, many patients' treatments become complicated because they are highly associated with alcohol, smoking, gutka, and poor diets [68]. Malignant transformation rates were higher among patients with untreated lesions (14.6% vs. 5.4%). Another study found that surgery increased the malignant transformation more than in non surgery patients [69]. In their study, 59% of patients who underwent surgery had erythroplakia and non homogeneous leukoplakia, while 15% had non surgical treatment. Additionally, the majority of surgically treated lesions were found in high-risk areas, such as the floor of the mouth, the tongue, and the ventral tongue. Treatments for oral leukoplakia are becoming more accepted using laser surgery. The carbon dioxide laser is the most popular and extensively used for both excision and evaporation [70,71]. Cryosurgery is another method for treating OED patients, but it has some limitations. With or without OED, it plays a crucial role in managing oral leukoplakia. Cryosurgery has no tissue for examination, poor depth control, and significant postoperative pain and swelling [72]. Some advantages of the cryosurgery method are that it is both bloodless and low-risk for infection, as well as relatively pain-free [73,74]. A study was conducted by [75] using cryogun cryotherapy for oral leukoplakia. They treated 72 patients with leukoplakia on the buccal mucosa, including 26 with mild, seven with moderate, and one with severe dysplasia, and eight lesions recurred. However, repeated treatment effectively controlled them at a mean follow-up time of 18 months. Finally, they showed that cryogun cryotherapy is more effective for oral leukoplakia treatments. Chemoprevention is another strategy for treating OPMD where medical therapies are used either topically or systemically. Several medications are considered chemopreventive agents, including genistein, resveratrol, S-allyl cysteine, diallyl sulfide, capsaicin, allicin, lycopene, curcumin, ellagic acid, lactacyl anethol, ursolic acid, silymarin, catechins, anethol, and eugenol [76]. The Cochrane review from 2006 concluded that no chemoprevention agent helped prevent oral malignant transformation [77]. According to Jerjes W et al., in a follow-up study using photodynamic therapy on an oral dysplastic lesion, 100% in mild, 82% in moderate, 81% in severe, and 69% in carcinoma-in-situ showed positive results [78]. Especially for mild dysplasia, photodynamic therapy showed favourable results, but standardisation and formulation are problematic when determining the treatment protocol of photodynamic therapy. Photodynamic therapy is an ablative treatment that employs a photosensitising agent to destroy localised tissue and cells. The most studied chemopreventive agents are vitamins, especially retinoids, which are both natural and synthetic vitamin A derivatives [67,79]. In the area of chemoprevention of oral dysplasia, the use of Cyclooxygenase (COX) inhibitors remains of interest. Both oral dysplasia and H&N cancer are associated with the upregulation of COX-2 and Vascular Endothelial Growth Factor (VEGF) [80].

Radiation therapy is another method for treating oral cavity cancer. It plays an important role when general anaesthesia is not required, and normal anatomical functions are to be maintained. Radiotherapy treatment can be delivered through external beam radiation (teletherapy) with common side-effects, or through interstitial therapy (e.g., brachytherapy, plesiotherapy). Recent research suggests that new improvements in cancer imaging and radiation technology have allowed for more precise treatment administration, leading to more remarkable survival rates and a reduction in the detrimental effects of radiation [81]. Radiation therapy is referred to as radical radiation therapy when used solely for cancer treatment. Patients with early-stage cancer typically receive only radical radiotherapy; however, patients with unresectable or advanced cancer may receive radiotherapy in combination with chemotherapy or targeted therapy using monoclonal antibodies against the Epidermal Growth Factor Receptor (EGFR) to enhance the cytotoxic effect of radiation. Adjuvant radiation therapy is used following surgery, while palliative radiation therapy is used to alleviate cancer symptoms. A study by Awadallah M et al., discussed the rationale behind radiation therapy to eradicate any microscopic tumour burden that may remain in the surgical field and to prevent recurrence [82]. Radiation therapy involving electromagnetic fields consists of electrons and photons, with the latter treatment being the most popular for treating oral cancers. The most common primary treatment is surgery, which has a high rate of treatment success, with overall survival rates reaching 75-90 percent in early stages [83]. Radiation therapy may include particle therapy, which uses protons, neutrons, or ions with a large electrical charge, such as helium. Intensity-modulated radiation therapy is another form of radiation therapy used for treating oral cancers. Radiation treatment can be used as either a primary treatment or as an adjunct to surgery.

CONCLUSION(S)

The OED is a precancerous lesion, not cancer. It is a condition where abnormal cell growth occurs. The present article broadly discusses various histological grading methods provided by different scholars and authors to propose an ideal system for OED grading. However, each system has constraints that limit its application in everyday situations. Among all these grading systems, the WHO 2017 grading system is the most accepted and utilised by pathologists for OED grading during treatments. Nonetheless, there are still many

limitations to it, making it challenging for oral pathologists to precisely detect the progression of OED and arrive at a proper diagnosis. A deeper understanding of the molecular mechanisms involved in malignant development should help predict which patients are most likely to experience changes. Histopathological assessment of the severity of OED remains the gold standard for predicting the malignant transformation of precancerous lesions. People should be aware of various highly dangerous risk factors that may lead to death. The treatment of OED or oral cancer remains challenging. AI is paving the way for a more streamlined healthcare system and offering virtually endless possibilities for cancer treatment. Pathologists are not to be replaced by AI. Instead, pathologists hope that AI will bring precision to oral oncology and oncologic pathology with rapid recommendations and automated assistance. The article also discusses three main types of treatments: surgery, chemotherapy, and radiation. However, surgery remains the only viable treatment option, despite its significant functional implications. More research is needed to develop a reliable and reproducible method for grading OED using AI and exploring treatment options. The present research should focus on the system's predictive value, relevance, applicability, and feasibility for a better understanding. Finally, it is evident that AI-based studies are lacking in the field of OED, particularly at the microscopic level.

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