Improving Outcomes in Oral Cancer

A Clinical and Translational Update

Deepak Kademani
Editor

Springer

Improving Outcomes in Oral Cancer

Deepak Kademani
Editor

Improving Outcomes in Oral Cancer

A Clinical and Translational Update

Springer

Editor
Deepak Kademani
Department of Oral and Maxillofacial Surgery
North Memorial Medical Center
Minneapolis, MN
USA

ISBN 978-3-030-30093-7 ISBN 978-3-030-30094-4 (eBook)
https://doi.org/10.1007/978-3-030-30094-4

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my patients who have given me the privilege to care for them and taught me so much about the human spirit

Contents

Oral Epithelial Dysplasia

1

Kenneth Wan and Deepak Kademani

1.1 Introduction

In general histopathology terms, dysplasia is a disordered growth that encompasses an abnormality in the maturation of cells within tissues and the development of cytological atypia within cells. When dysplasia occurs in the epithelium of the oral cavity, the WHO have termed it oral epithelial dysplasia (OED), defining it as a precancerous lesion of stratified squamous epithelium, characterized by cellular atypia and loss of normal maturation and stratification short of carcinoma in situ. It is a histologically proven oral premalignant lesion that is associated with a significant higher risk of malignant transformation. An OED may be part of a clinically apparent lesion, such as leukoplakia, eythroplakia, erytholeukoplakia, lichen planus and submucosal fibrosis, actinic chelitis, and chronic hyperplastic candidiasis. These lesions are termed "oral potentially malignant disorders" (OPMD) by the 2005 WHO workshop and are referred to a variety of clinical lesions, conditions, or systemic disorders, which result in an increased risk of cancer development in the oral cavity compared to normal mucosa in a healthy patient. Recently, the term, "potentially premalignant oral epithelial lesions" (PPOEL), has been described in the literature to replace OPMD. For a lesion to be described as an oral epithelial dysplasia, there must be a biopsied and histopathologically reported foci of dysplasia.

1.2 Grading and Classification of OED

OED is a condition comprising of a spectrum of tissue changes, with several grading systems established to classify into arbitrary levels of severity, hence diagnosis is extremely subjective [1, 2]. The relevant diagnostic criteria have been revised several times and many systems of classification exist, each with their own biases [3]. These are generally based on the histopathological classification of premalignant lesions of other mucosal sites, which frequently develop SCC.

For example, squamous intraepithelial neoplasia (SIN) is an oral adaptation of a system used for classifying precursor lesions of the uterine cervix and have been used for grading OED in the older literature [3]. While the SIN system has its advantages, it has been rejected for use in the oral cavity and oropharynx due to the emphasis placed on tissue thickness due to hyperkeratinization, which is not considered to carry a higher risk of malignancy than normal tissue in the oral cavity [4, 5]. Furthermore, the SIN system suggests an

K. Wan
Department of Oral and Maxillifacial Surgery, North Memorial Health, Robbinsdale, MN, USA

D. Kademani (✉)
Oral and Maxillofacial Surgery and Hospital Dentistry, Head and Neck Oncologic and Reconstructive Surgery, North Memorial Medical Center, Minneapolis, MN, USA
e-mail: Deepak.Kademani@northmemorial.com

D. Kademani (ed.), *Improving Outcomes in Oral Cancer*,
https://doi.org/10.1007/978-3-030-30094-4_1

inevitable progression to malignancy, which is not the case of OEDs in the oral cavity [6].

In the Ljubljana grading system, lesions are categorized into simple hyperplasia, basal/parabasal hyperplasia, atypical hyperplasia, or carcinoma in situ. It is an alternative system based on another anatomical site but adapted for the oral cavity and oropharynx [7]. Originally utilized in the context of laryngeal precursor lesions, it is considered beyond the scope of the histopathological changes which occur in the oral cavity and oropharynx [3].

Another grading systems include the Smith and Pindborg, which utilizes 13 histological features that are standardized by a set of photographs. After comparing with the photographic standard, the feature is graded as none, slight, or marked and given a score. The scores are added to achieve the epithelial atypia index (EAI) score (maximum possible is 75), and depending upon the EAI, the dysplasia is graded as no dysplasia, mild, moderate, or severe.

Currently, the 2005 WHO Classification is most widely used for classification of tissue dysplasia. A range of cellular and architectural changes in the tissue is assessed and classified into a specific grade of dysplasia (Tables 1.1 and 1.2).

Issues with intraobserver reproducibility and interobserver agreement plagues all the aforementioned grading system, with the Ljubljana and Smith & Pindborg system faring worse than the WHO system. Merely determining the presence of OED appears to be a challenge, with one US study reporting a Kappa value of 0.51 (moderate strength of agreement) between three oral pathologists when asked to assess OED presence and absence [8]. Intraexaminer reliability varied greatly among the pathologists, with one scoring a Kappa value as low as 0.22 (slight strength of agreement) [8]. Another study reported Kappa agreement scores of 0.15 and 0.41 between six pathologists in determining the presence of OED among 120 slides [9]. Lumerman et al. reports an interexaminer reliability of only 54% [10].

Considering the low consistency between diagnoses, it is expected that this would be a major limitation among most studies, and this has resulted in remaining controversy surrounding the predictive value of OED.

Table 1.1 List of architectural and cytological changes associated with oral epithelia dysplasia, 2005 WHO Classification

Architecture	Cytology
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 mitoses	Increased nuclear-cytoplasmic ratio
Dyskeratosis	Increase nuclear size
Keratin pearls within rete pegs	Atypical mitotic figures
	Increase number and size of nucleoli
	Hyperchromasia

Table 1.2 Classification of oral epithelial dysplasia, 2005 WHO classification

Hyperplasia	Increased cell number; the architecture shows regular stratification without cellular atypia
Mild epithelial dysplasia	Architectural disturbance limited to the lower third of the epithelium accompanied by cytological atypia
Moderate epithelial dysplasia	Architectural disturbance extending into the middle third of the epithelium with consideration of the degree of cytologic atypia
Severe epithelial dysplasia	Greater than two-thirds of the epithelium showing architectural disturbance with associated cytologic atypia or architectural disturbance extended into the middle-third of the epithelium with sufficient cytologic atypia
Carcinoma in situ	Full-thickness architectural abnormalities in the viable cellular layer accompanied by pronounced cytologic atypia; atypical mitotic figures and abnormal superficial mitoses

1.3 Clinical Presentation of OED

OED within the oral cavity may present in a range of clinical lesions, rendering it not possible to diagnose without invasive biopsy. Clinically, OEDs may appear as homogenous lesion (clinically provisionally diagnosed as homogenous

leukoplakia or keratosis), nonhomogenous (clinically provisionally diagnosed as nonhomogenous leukoplakia, eythroplakia, speckled leukoplakia), lichenoid (clinically provisionally diagnosed as oral lichen planus or oral lichenoid tissue reaction), or others (lesions which are diagnosed as nonspecific ulcerations/erosions/atrophies, angiogranuoloma, frictional keratosis, leukoedema). In several studies, nonhomogenous clinical appearance was highly associated with dysplasia, and over 80% of provisional nonhomogenous lesions were dysplastic or malignant on biopsy.

Lesions that display redness or surface irregularity are more likely to be dysplastic [11]. Erythroplakia is reported to carry the greatest rate of OED of any oral mucosal lesion, with greater than 90% exhibiting dysplastic characteristics on biopsy [12], and a vast majority of these undergo malignant transformation [2]. In a study of 166 leukoplakias, a nonhomogeneous clinical appearance was found to be associated with presence of OED on histopathological assessment, and they were more likely to develop oral SCC on follow-up [13].

In respect to the clinical features of OED, one study has found that all lesions that displays any degree of OED were associated with some form of leukoplakic appearance [14]. In the same study, severe dysplasia was diagnosed mostly in mixed red and white lesions; however, this was not statistically significant. Comparably, lesions which exhibited redness had a greater tendency to present with moderate dysplasia in contrast to clinically white lesions; however, the rate of severe dysplasia was equal between white and mixed red and white lesions, indicating that these findings may be due to sample variation [11]. Tissue redness as a feature of malignant progression can also be appreciated in relation to OLP, where it has been reported that erosive and ulcerative types are at risk of malignancy [15].

Lichenoid dysplasia is a term to describe lesions that on histopathology are primarily dysplastic in nature but exhibit some features of OLP [16]. Oral lichen planus is assumed to be potentially malignant and may of undertaking malignant transformation; however, controversy does exist. Up to 3% of OLP cases have been reported to undergo malignant transformation [17]. Krutchkoff et al. argue that OLP in itself is not potentially malignant, and that associations with transformation are due to inaccurate and overdiagnosis [16].

1.4 Risk Factors for OED

OED has a high association with the male gender [18–21]. Studies have demonstrated that males are more at risk because of greater levels of exposure to risk habits such as alcohol and tobacco consumption [4].

[I]It is well established in the literature that smoking is highly associated with the development of PPOELs and malignancies in the oral cavity [4]. In respect to the development of OED, the exposure and the level of exposure of tobacco to the oral epithelium is significantly associated with the development of dysplastic tissue changes. In one study, those who were identified as current smokers had an odds ratio of 4.1 for developing OED when compared to those who never smoked [22]. Of 173 OED cases in a retrospective study, the author found that half of the patients who reported tobacco usage presented with some degree of OED on biopsy [14]. Another study reported that severe and moderate dysplasia in particular arose at a higher rate among smokers, with approximately 77% of severe dysplasia occurring in tobacco users [23].

It is recognized in the literature that alcohol and tobacco act synergistically as a risk factor for oral SCC [24–26], but conflicting evidence exists to support alcohol's role in the development of OED. A paper by Morse et al. reported that they did not find any significant association between alcohol consumption and development of OED [27] while a previous study by the same groups of authors observed that consumption of seven or more alcoholic beverages a week increased the risk of detecting OED on biopsy of a PPOEL by two times [27]. In another study, 50% the PPOELs presenting with dysplasia occurred in individuals who reported regular consumption [28]. The carcinogenicity of alcohol is thought to

be due to the metabolism of ethanol to mutogenic acetaladehyde in the oral cavity.

The most high-risk area for development of oral SCC and OED, as agreed on by many authors, is the floor of the mouth and the tongue, particularly the lateral border [1, 29, 30]. This is owing to the fact that a greater level of carcinogenic exposure is present as tobacco, and alcoholic products dissolve in the saliva and settle on the floor of the oral cavity [29]. In addition, due to the thinner and nonkeratinized epithelium of these sites, tissue penetration and a more potent level of carcinogenic exposure is possible. Also contributing may be the differing embryonic origins of these site and response to carcinogens [29]. In a study by Barnes et al. that examined the clinical features of OED, it was reported that severe dysplasia was more likely to form on the lateral tongue and floor of the mouth, compared to the rest of the oral cavity [4]. Pereira et al. also has a similar finding, with severe dysplasia occurring most often on the floor of mouth and tongue.

1.5 Relationship Between OED and PPOEL

Leukoplakia, erythroplakia, oral lichen planus, oral submucosa fibrosis, and actinic chelitis are recognized potential premalignant oral epithelial lesion.

Leukoplakia is defined as any "white plaque of questionable risk having excluded other known disease and disorders that carry no increased risk of cancer". The can be grouped in to homogenous or nonhomogenous (erythro-leukoplakia). A subtype of leukoplakia, proliferative verrucous leukoplakia has the highest rate of malignant transformation of any oral white patch lesion. The proportion of biopsied leukoplakia cases positive for OED has been reported as 15%, and the proportion of cases that will undergo malignant transformation is 1% [2, 4].

Erythroplakia is defined as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. The proportion of biopsied erythroplakia cases positive for OED is reported as 91%, and the proportion of cases that will undergo malignant transformation is 100% [2, 4, 12].

Oral lichen planus (OLP) is considered by some authors to be a PPOEL; however, controversy does exist about this inclusion [13]. OLP is a chronic inflammatory disease thought to be immune-mediated and have some genetic predisposition; however, the exact etiology is not known. The proportion of biopsied OLP cases positive for OED that will undergo malignant transformation has been reported as 1–3.2% [2, 4].

Oral submucous fibrosis (OSF) is a chronic mucosa disease of the upper digestive tract [11, 20]. Fibrosis of the lamina propria and submucosal layers of the mucosal lining of the oral cavity, oropharynx, and, at times, the esophagus, resulting in loss of tissue mobility and limited oral opening, is its histopathological characteristic. The proportion of biopsied OSF cases positive for OED is 7–25%, and the proportion of cases that will undergo malignant transformation is 1–8% [2, 4, 31].

Actinic cheilitis is a keratotic condition of the lip vermillion which is considered to be potentially malignant. Patients may present with various clinical signs and symptoms, the most commonly reported being dryness of the lip, atrophy, erythema, ulceration, edema, and blurring of the vermillion border. Proportion of biopsied OSF cases positive for OED is 100% [4, 32].

1.6 Detection and Diagnosis

The gold standard test for diagnosis of OED is histopathological from specimens taken from a formal tissue biopsy [33–35]. There are no reported chairside adjunctive tests currently that have reported higher sensitivity and specificity numbers that trumps the combination of clinical examination and tissue biopsy [33]. There is a myriad of adjunctive tests available for the clinician's armamentarium, with the pros of being non/minimally invasive and causing little to no morbidity but with a tradeoff for giving appreciable levels of false positives and negatives. These adjunctive tests should only be used in situations where the clinician is unsure after clinical examination whether to go ahead with a tissue biopsy

or to find areas within a large homogenous lesion to incisional biopsy that will yield a specimen with more advanced atypia or dysplasia. They should not be used when the lesion is clinically frankly dysplastic or cancerous where a formal biopsy would be indicated. We describe several more common adjunctive tests below.

Metachromatic dyes that have high affinity for nucleic acids, such as toluidine blue can be used as an aid to detect high-grade dysplasia and malignant lesion based on the premise that they produce higher levels of nucleic acids compared with normal tissue. The intention is to guide the clinician to areas for biopsy, but overall, toludine blue has poor sensitivity and specificity (57–81% and 56–67%, respectively) [33, 36]. The figures are better with increasing severity of dysplasia, such as severe dysplasia/carcinoma in situ but are poor in mild and moderate dysplasia.

Another minimally invasive detection technique is brush cytology/biopsy that required the clinician to use a dedicated brush to collect a transepithelial and exfoliated cell sample, which is then fixed on a histology slide and submitted for specialized computer-aided scanning analysis. As the transepithelial array of cells are architecturally disordered, it can only detect the presence of cellular atypia and not able to differentiate invasive carcinoma from carcinoma in situ. Apart from its high cost, it is in limited use in clinical practice owing to inconsistent sensitivity and specificity figures in the literature (range 73–100% and 32–94%, respectively) [37, 38].

There is evidence to suggest that light-reflecting properties of oral mucosal changes in a progressive and predictable manner from the spectrum of normal to frankly malignant oral epithelial tissue. Autofluorescence and chemiluminescence diagnostic/screening tools take advantage of this assumption for them to be marketed to clinicians for use, with a myriad of commercial brands available for sale. The tools' specificity and sensitivity functioning statistics are generally not promising with one systemic review's reporting rates of 0–100% and 0–75% for chemiluminescence and 30–100% and 15.3–100% for autofluorescence, respectively [33, 39]. It was purported that sensitivities of 100% published in some of the papers where owing to lesions that were clinically obvious by routine visual examination [40, 41]. From a specificity standpoint, both autofluorescence and chemiluminescence performed suboptimally in differentiating dysplasia/malignancy, inflammation, and reactive from each other. An alternative, modified chemilumninescence method that takes advantage of dysplastic and malignant cells expressing a different glycan residue, which can then be conjugated with a proprietary fluorescent lectin has shown promising results, with an in vivo study yielding sensitivity and specificity of 89% and 82%, respectively [42–44].

Dysplastic and malignant cells generally have depleted or negligible glycogen content compared to healthy mucosa. Lugol's iodine solution, which contains iodine and potassium iodide in an aqueous solvent will bind to normal mucosa and have low affinity for dysplastic/malignant tissue. The literature has shown that it is a useful adjunct in obtaining clear margins for dysplasia/intraepithelial neoplasm during tumor resections (32% clear margins in the control group versus 4% in the Lugol's solution group) [45].

1.7 Human Papillomavirus and Dysplasia

There are over 160 genotypes of human papilloma virus and some subtypes are risk factors for development of oropharyngeal and oral squamous cell carcinoma. Specifically, 16 and 18 have been described as high risk for the development of oropharyngeal carcinoma [46, 47]. HPV-derived oncogenes, E6 and E7, causes epithelial malignant transformation by repressing p53 and Rb tumor suppressor gene functions [46]. The prevalence of HPV is 0.9–12% in clinical normal mucosa, and in an immunocompetent host, the infection is usually cleared within 2 years [48]. Perseverance of the virus past the 2 year mark augments the likelihood of malignant genetic mutation and transformation. Controversy exist on the association and prevalence of HPV in PPOELs. A systematic review described an overall odds ratio of 3.87 between all PPOELs and aggregate HPV-DNA, and when dysplasia was the specific variable, the OR raised to 5.10 [46].

The prevalence of HPV subtypes 16 and 18 was reported to be 25% in oral and oropharyngeal dysplasia in one meta-analysis [49]. HPV-driven dysplasia have been described as being unique in histopathological studies as they are characterized by karyorrhexis and apoptosis [47]. Chemoprevention and HPV vaccination is anticipated to reduce the prevalence and incidence of oropharyngeal/oral squamous cell carcinoma.

1.8 Field Cancerization and OED

OED presents the initial steps of field cancerization, when early cellular and architectural changes affect the mucosal epithelium. Field cancerization describes the multistep and sequential process of carcinogenesis of epithelial tumors. This process was first described by Slaughter et al. after microscopic examination of almost 800 oral and pharyngeal cancers revealed that tissue abnormalities extended beyond the clinically obvious tumor [50]. This suggested that cancers arise from patches or fields of genetically abnormal cells which display features of malignancy but remain noninvasive. These fields develop from a single mutated stem cell which divides and differentiates to produce similarly abnormal daughter cells. Uncontrolled cell division allows for the growth and development of this field which replaces the overlying normal tissue [51]. Histopathologically, this field is diagnosed as OED and is considered potentially malignant.

1.9 Malignant Transformation

There is a myriad of widely varying figures in the literature relating to the malignant transformation rate of OED to OSCC; this may be owing to when effect of confounding factors such as exposure to risk factors not considered, classification of clinical lesions being varied between studies, and, as previously outlined, the classification of dysplasia is not an exact science. The malignant transformation rate of OED varies vastly in the literature, with a range of 6–36% [52]. Current variables in the literature that affect the MTR are the site of the lesion; tongue and FOM being at the higher end of the MTR spectrum along with the grade of the dysplasia [1]. There are conflicting reports with respect to grading severity being correlated with MTR [23, 53, 54]. A predominance of the contemporary literature supports the hypothesis that MTR is correlated with the presence of OED and it severity [1]. On the other-hand, there are some studies not supporting the relationship between MTR and grade of dysplasia, such as Dost et al.'s paper, involving biopsy-proven OED in 368 individuals, which came to a conclusion that the severity of dysplasia, graded according the 2005 WHO classification and the Kujan et al. binary system, was not correlated with the risk of malignant transformation [23].

In a retrospective study of biopsy specimens collected over 20 years, Cowen et al. [55] demonstrated that a relationship existed between the presence of OED and malignancy. However, the authors failed to undertake a statistical analysis of their findings. A similar retrospective study was conducted in the UK, and a significant relationship between OED grading and oral SCC development was found [56]. The annual transformation rate of severe dysplasia was 5.6%, compared with 0.3% of nondysplastic PMDs. This is further corroborated by Schepman et al. [13], who concluded that leukoplakia which presented with moderate to severe OED, had a significantly higher predisposition to developing a malignancy. Silverman et al. [17] reported a malignant transformation rate of 36% for lesions which present with OED. Small sample size however is a shortcoming of this study, which puts into doubt the validity of these results; only 22 lesions which presented with some degree of OED were included in the aforementioned study. Another study from Australia has reported that 4.7% of OEDs progressed to oral cancer in a mean time of 3.3 years, and it also suggested that mild grades of OED were just as likely to transform into OSCC as severe-grade OEDs. This is in stark contrast to Mehanna's meta-analysis that showed mild/moderate OEDs had a malignant transformation of 10% versus severe OED/CIS which has a rate of 24%.

These findings differ from those from Asian countries such as Taiwan and India, which tend to conclude that OED does not affect malig-

nant potential. Prospective evaluation of 1458 Taiwanese patients presenting with a PPOEL revealed that in over 10 years of follow-up, no cases of severe OED developed a malignancy [57]. While results show that those patients presenting with OED transformed at a higher rate than those without, this was not statistically significant, indicating SCC development is unaffected by dysplastic features. The estimated annual malignant transformation rate of 3.02% is considered particularly low in light of other research; however, the authors suggest this to be due to broader inclusion criteria, incorporating a wider variety of PPOELs. Comparative studies tend to limit analysis to a particular type of lesion, such as leukoplakia [13, 17, 29, 58]. A smaller scale study also conducted in Taiwan found similar results [59].

Difficulty arises when comparing the results of these studies, as differing study design, inclusion criteria, and statistical analyses affect the findings. Several studies restrict inclusion criteria to certain types of PPOELs, most commonly leukoplakias [13, 17, 58], which limit the generalisability of malignant transformation rates, which themselves are calculated via differing means. Varying definitions of PPOELs also affect selection criteria, particularly those with a focus on leukoplakia, the diagnostic criteria of which has been revised several times. Older studies tend to follow the classification of the time, so conditions such as frictional keratosis, which have no risk of malignancy above normal healthy mucosa, were included as leukoplakias, affecting overall study outcomes [2].

1.10 Molecular Markers Associated with Development and Progression of OED/PPOEL

Research of complex molecular mechanisms underpinning oral behavior, development, and progression of oral cancers has been vast and progressing at a rapid pace in the past several decades.

Despite this, our current cognizance of the critical molecular process that heralds and drives dysplastic or potentially premalignant epithelial lesions' progression to oral squamous cell carcinoma is still lacking [60]. As such, the development of clinically applicable prognostic and diagnostic markers and targeted therapies that eventuate in improved prognosis and survival of head and neck cancer patients has not been fruitful to date.

A comprehensive description of all molecules studied is beyond the scope of this chapter. The majority of the molecules explored are associated with critical cellular and molecular oncogenic processes or the term "hallmarks of cancer" coined by Hanahan and Weinberg [61]. These processes involve sustained cell proliferation, evasion of growth suppression, resistance to apoptosis, replicative immortality, angiogenesis, invasion, and metastasis as well as emerging "hallmarks" such as evasion of immune system surveillance, reprogramming of cellular metabolism, and enabling molecular characteristics (genomic instability and tumor-promoting inflammation) [61].

Of note are markers relating to epigentetic events, which is an emerging area in research. These epigenetic events include histone sumoylation and acetylation, microRNA and long encoding RNA post-transcriptional regulation (upregulation, downregulation, or overprogression or underexpression) and DNA methylation [60].

DNA Hypermethylation. In approximately 40% of OED cases, p16 gene hypermethylation is detected and a corresponding proportion progresses to OSCC. In addition, during the progression of mild to severe OED, hypermethylation of the p15 and 16 gene has been documented. MGMT gene methylation is described to be greater than 50–80% of OL. Oral lichen planus without dysplastic features can be distinguished from those with dysplasia by detection of methylation of TSPYLS5, NKX2-3, RBP4, TRPC4, CMTM3, CLDN11, and MAP6 genes. Methylated HOXA9, EDNRB, and DCC (deleted in colorectal cancer) were correlated with malignant or premalignant oral lesions. Methylated zinc finger protein 582 (ZNF582, transcription factor on chromosome 19) has also been suggested as a biomarker for oral dysplasia and cancer [60].

Histone Modification. Tumor invasion and oncological transformation can be the result of histone modification that has triggered deregulation of chromatic-based process. An example of this is lysine modification on H3 histone at

specific position Lys9, Lys4, Lys18, and Lys27 that become methylated and/or acetylated as is observed in some oral squamous cell carcinoma lesion. Papillon-Cavanagh et al. [62] have demonstrated diminished H3-K36 methylation characterizes a subset of head and neck SCC, but all studies have thus far addressed only SCCs, and data on PPOELs or dysplasia are deficient.

Micro-RNA. Cellular noncoding mirco-RNA, in concert with other factors, regulates the cellular protein expression and functions. Reports of association between miRNA profiles and oral premalignant/dysplasia are few. MiR-31 was reported as being augmented in some potentially premalignant oral epithelial lesions, such as hyperkeratotic and hyperplastic lesions, which are deemed less likely to progress to SCC compared to OED. Cervigne et al. have reported that overexpression of miRNA-345, miRNA-21, and miRNA-181b was essential to malignant transformation. Increase in lesion severity during progression was associated with elevated expression of miRNA-345, miR-181b, and miR-21 [63].

1.11 Management

1.11.1 Prevention

In the management of premalignancy, primary prevention should be the first armamentarium utilized, and any modifiable risk factors for OED should be eliminated in order to prevent and arrest the progression of premalignancy to malignancy. Patients should be counseled on tobacco use cessation and limit alcohol intake. Risk stratifying is extremely important in order to identify high-risk individuals and then to provide appropriate screening and counseling. From a systemic review, the predicted attributable lifetime risk for developing oral squamous cell carcinoma if an individual smoked solely, consumed alcohol solely, or in used tobacco and alcohol in combination was 25%, 18%, and 40%, respectively [64]. The correlation between development of OED that may progress to oral squamous cell carcinoma with tobacco use and alcohol consumption risk is dose-dependent and cumulative over an individual's lifetime. A meta-analysis study involving 5338 patients who received surgical excision/resection of oral squamous cell carcinoma, 30% were found positive for all HPV subtypes, 18% for HPV18, and 25% for HPV16 [65]. Although the link between HPV as a causative factor in oral squamous cell carcinoma is not as strong as for oropharyngeal carcinoma, the HPV vaccine may play a role in secondary prevention. Other prevention strategies include early detection of PPOELs and prevention of malignant transformation [33].

1.11.2 Surgical Management

Surgery management of OED involving excision using scalpel, excision, or ablation using laser or cryosurgery is reported. There are no RCTs comparing the efficacies of these in respect to recurrence, progression to malignancy. Surgery in the form of excision and/or laser ablation is at present, the most accepted mode of treatment [54, 66–68].

Cryosurgery have limited use in treatment of OED and have been reported to yield higher rates of recurrence and malignant transformation [69]. Surgical excision with a scalpel blade is a consistent modality and common in surgical practice as it is cost effective, simple to use, and provides a surgical specimen with margins that is undamaged by heat of a laser, which allow for accurate histopathological examination [52]. Excision of large OED lesion with a blade may produce undesirable cicatricial healing, this can be overcome by placing a split thickness skin graft in the surgical bed [69].

CO_2 lasers are used frequently in the surgical management of OED. The mechanism of CO_2 laser involved applied focal, collimated energy that augments the temperature of the target tissue to greater than 100 °C, culminating in the phase change of water to steam. Adjustable power of laser permits its use as a surgical knife or ablative agent (5–25 W). Laser can be used defocused to ablate the tissue and permit hemostasis, and the site is left deepithelialized to heal by secondary intention. CO_2 laser creates a unique wound, in that it is only a few tenth of mm deep with limited removal of healthy tissue. Meltzer suggests recurrence of leukoplakia with laser is only 10% compared with scalpel at 34% [70]. Other advantages

include cellular destruction by ablation minimizes release of inflammatory mediators compared with a scalpel, hence patient is reported to have less pain and swelling; blood vessels with diameter of the lumen less than half of a millimeter are sealed off, producing a less bloody field; and limited wound contracture. The main criticism is that the vaporized tissue is not available for histological exam, but this can be overcome somewhat by taking multiple incision biopsy specimens prior to lasering. Another disadvantage of laser ablation is that epithelial migration is delayed, and the surgical wound may take longer to heal [70].

The general consensus is that the presence of OED predisposes a lesion to undergo malignant transformation; logic would follow that the severity would have an impact, as the more severe the dysplasia is, the more genetically aberrant and therefore histopathologically similar to an SCC. Regardless of this supposed multistep progression model, current practice sees some clinicians forgoing active treatment of milder lesions, which are monitored rather than excised [1, 6]. This is somewhat supported by the literature, which reports the risk of a mildly dysplastic lesion progressing to cancer being less than 5% [6]. More severe tissue changes are reported to progress to SCC in as low as 7% of cases [6]. Distinguishing between these levels of severity in itself presents a challenge, with subjectivity unavoidable in the process of classifying a continuous scale of tissue change. In contrast, there is literature to support the notion that irrespective of the grade of OED, all biopsy-proven OED should be treated by excision or laser ablation, instead of the "wait and watch" approach some clinicians take for mild dysplasia. The management of mild and moderate OED remains controversial, and there is no concrete well-designed RCTs that give support either way. Owing to the higher risk of malignant transformation of severe OEDs and CIS, the accepted convention treatment is surgical excision with or without reconstruction. Diagram 1 depicts our departments protocol in the management of mild, moderate, and severe/CIS OEDs [71] (Fig. 1.1).

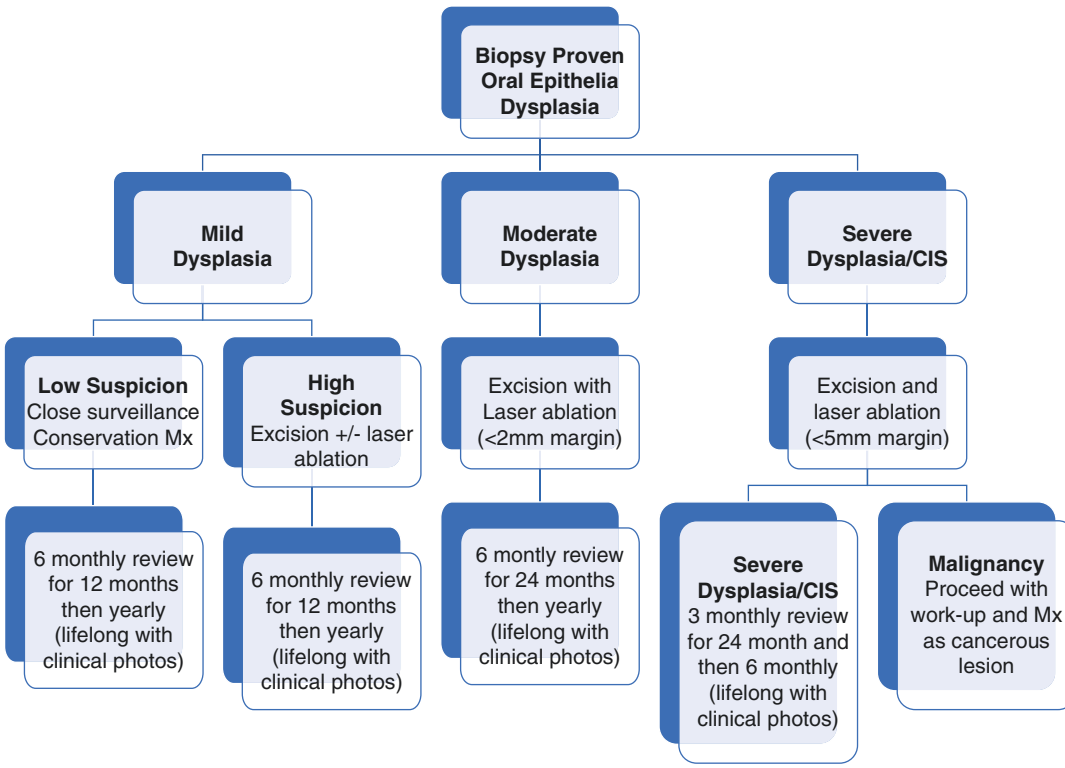

Fig. 1.1 Authors' algorithm for management of oral epithelial dysplasia