

Precancerous Oral Lesions: A Review

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ABSTRACT

This article reviews the different types of oral lesions and factors associated with the development of premalignant (leukoplakia and erythroplakia) and actual cancerous lesions. Diagnostic tools and aids to diagnosis are discussed, as are treatment modalities. Early detections of these lesions could save lives.

Keywords: Oral lesions; premalignant; lesions; diagnostic tool

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INTRODUCTION

The idea of precancer has been a slowly changing and often confusing concept, beginning with the 1805 suggestion by an European panel of physicians that there are benign diseases which will always develop into invasive malignancy if followed long enough (1). With today's definition, a precancer is considered to only hold an increased risk of cancer transformation (2).

Oral precancers, in particular, have a rich and fascinating literature extending as far

back as the 1870s, when Sir James Paget, one of England's most renowned surgeons, proposed that "leukokeratosis" or "smoker's patch" of the hard palate (nicotine palatinus), or the tongue, in inveterate pipe smokers carried an increased risk of eventual cancer transformation (3). He mentioned that he saw his first cancer transformation in this disease in 1851. Ironically, we no longer consider nicotine palatinus to be a precancer, preferring rather to think of it as a response to the heat of tobacco smoke, not the carcinogens (3, 4). The heavily keratinized, i.e. "protected"

Table 1: Precancerous Lesions of the Oral, Pharyngeal and Laryngeal Mucosa, as Suggested in the Literature; Clinical Terms only

Disease Name	Malignant Transformation Potential
Proliferative verrucous leukoplakia (PVC)	*****
Nicotine palatinus in reverse smokers ^a	*****
Erythroplakia	*****
Oral submucous Fibrosis, with leukoplakia	*****
Erythroleukoplakia	****
Granular leukoplakia	****
Laryngeal keratosis	***
Actinic cheilosis	***
Syphilitic glossitis, with dorsal leukoplakia	***
Smooth, thick leukoplakia	**
Smokeless tobacco keratosis	**
Plummer-Vinson disease (sideropenic dysphagia, smooth tongue)	*
Lichen planus, erosive forms ^b	*
Smooth, thin leukoplakia	+/-
Lupus erythematosus, with oral ulcers/keratosis	?
Dyskeratosis congenita, with oral leukoplakia	?
Epidermolysis bullosa, with oral leukoplakia	?
Clarke-Howel-Evans syndrome, with oral leukoplakia	?

a. reverse smoking: smoking with the lit end of the cigarette in one's mouth
b. designated by the 2005 WHO Workshop on Oral Premalignancies as not a precancer^{8,10}

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mucosa of the hard palate is, in fact, one of the least likely sites for oral cancer development (2).

Oral precancer consists of oral precancerous lesions and oral precancerous conditions. The definition of oral precancerous lesion is 'a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart' (5). Oral precancerous lesions have been further subcategorised by the World Health Organisation (1997) into the clinical and histological classification. This sub-categorisation seemed necessary to avoid the misconception that certain oral precancerous lesions can be histologically confirmed and is considered by some to be synonymous with squamous epithelial dysplasia. The clinically recognised oral precancerous lesions are leukoplakia, erythroplakia and 'palatal keratosis associated with reverse smoking' (WHO, 1997). The term 'potentially malignant lesions or conditions' (6) has more currently been preferred as the clinically recognised lesions above, in the majority of cases, do not become malignant. Any of the above clinical diagnoses will be further accepted as oral precancerous lesions histologically, if they are squamous epithelial dysplasia, squamous cell carcinoma-in-situ and solar keratosis (5). These definitions and criteria are especially important in gaining valid epidemiological data, which can be compared globally between one study and another. The oral precancerous condition has been defined as 'a generalised state associated with a significantly increased risk of cancer' (5). The oral precancerous conditions recognised are sideropenic dysphagia, lichen planus, oral submucous fibrosis, syphilis, discoid lupus erythematosus, xeroderma pigmentosum and epidermolysis bullosa (WHO, 1997).

Oral cavity cancer accounts for approximately 3% of all malignancies and is a significant worldwide health problem (7, 8). Most oral malignancies occur as squamous cell carcinomas (SCCs); despite remarkable advances in treatment modalities, the 5-year survival rate has not significantly improved over the past several decades and

still hovers at about 50-60% (9).

Many oral SCCs develop from premalignant conditions of the oral cavity (10, 11). A wide array of conditions have been implicated in the development of oral cancer, including leukoplakia, erythroplakia, palatal lesion of reverse cigar smoking, oral lichen planus, oral submucous fibrosis, discoid lupus erythematosus, and hereditary disorders such as dyskeratosis congenital and epidermolysis bullosa (12).

Among them, white keratotic lesion, leukoplakia, has demonstrated a far greater risk of malignant transformation, a risk which has been discussed since before 1876, when the Hungarian dermatologist, Schwimmer, first coined the term (3). Because of the continuing challenge and confusion surrounding oral precancer concepts, the World Health Organization has periodically convened international workshops to redefine the term "precancer" and the various oral precancerous lesions. Workshop, held in London in 2005, actually recommended the elimination of the term "precancer" and the use of the presumably more illuminating term "potentially malignant lesion" for oral lesions (13). This panel tried to completely eliminate the term "leukoplakia" because of its progressively changing definition over time. At the end of the day, no better diagnostic term could be found. Once applied to any and all white mucosal plaques of the mouth, leukoplakia today is defined as a "white patch or plaque that cannot be characterized clinically or pathologically as any other disease" and is not associated with an obvious etiologic agent except tobacco use (2, 13). This definition excludes lichen planus, frictional keratosis, smokeless tobacco keratosis, nicotine palatines and alveolar keratosis, all diseases which were once included in the diagnosis of leukoplakia. The term is now used in a strictly clinical sense and does not imply a specific microscopic tissue alteration except, of course, the excess surface keratin which is responsible for the white color change. While certain clinical alterations in leukoplakia are known to increase the risk of cancer transformation, it is the microscopic features of

leukoplakia and its less common but more serious red counterpart, erythroplakia which are the most significant prognostic indicators. For example, the clinical entity called leukoplakia is generally thought to carry a malignant transformation rate of approximately 4% (presumably a lifetime risk, although few have been followed for an entire lifetime) (2, 14, 15). The transformation rate for lesions with epithelial dysplasia is much higher, approximating 4-11% for moderately severe dysplasia and 20-35% for severe dysplasia, with malignant transformation usually occurring within 3 years of the dysplasia diagnosis (12-16). Less dysplastic epithelium is much less worrisome in this regard and so the most significant of the oral dysplasia follow-up investigations have confined themselves to severe dysplasias or carcinoma in situ, often combining the two, since both appear to have similar biological behaviours (14, 15, 17).

Despite the general accessibility of the oral cavity during physical examination, many malignancies are not diagnosed until late stages of disease. In order to prevent malignant transformation of these precursor lesions, multiple screening and detection techniques have been developed to address this problem. The early detection of cancer is of critical importance because survival rates markedly improve when the oral lesion is identified at an early stage (9).

COMMON PRECANCEROUS ORAL LESIONS

Common Precancerous oral lesions include Oral leukoplakia, Submucous Fibrosis, Oral erythroplakia and lichen planus (18). Recognition and diagnosis require taking a thorough history and performing a complete oral examination (Table 2).

Oral leukoplakia

Oral leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion" (19). Such a definition, also adopted by the World Health Organization (WHO), is the result of the effort of an international group of experts, who met in Uppsala in 1994 in order to review leukoplakia defini-

Table 2: Common Precancerous Oral Lesions

Condition	Clinical presentation	Treatment	Comments
Oral leukoplakia (Axell 1996)	a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion	Since most leukoplakias are asymptomatic, the need for treatment is primarily based on the precancerous nature of the lesion.	Prevention of malignant transformation is particularly important in view of the poor prognosis associated with oral squamous cell carcinoma, with only 30% to 40% of patients still alive 5 years after the diagnosis (37)
Lichen planus (Chan <i>et al.</i> , 1999)	<i>Reticular</i> : white, lacy striae <i>Erosive</i> : erythema and ulcers with peripheral radiating striae, erythematous and ulcerated gingiva	Asymptomatic cases do not require treatment. Symptomatic cases may be treated with a topical corticosteroid gel or mouth rinse	Buccal lesions typical in reticular form; other sites (e.g., tongue, gingiva) may be involved
Oral erythroplakia	Erythroplakia is an uncommon and subtly innocuous change of the oral mucosa, but it has very specific and identifiable clinical characteristics, therapies, and prognostic features	Surgical excision is the treatment of choice. A clear understanding of this lesion may save lives by identifying oral cancers prior to invasion or at an early stage, thereby avoiding extensive surgery and spread of the disease to other parts of the body.	Histopathologically, it has been documented that in oral erythroplakia of the homogenous type, 51% showed invasive carcinoma, 40% carcinoma in situ and 9% mild or moderate dysplasia. Recently, genomic aberrations with DNA aneuploidy have been demonstrated. p53 mutations with different degrees of dysplasia may play a role in some cases of oral erythroplakia.
Submucous Fibrosis	It is characterized by epithelial atrophy, progressive hyalinization of the lamina propria, and later subepithelial and submucosal myofibrosis	Temporary relief from the symptoms and improvement in the oral opening with medicinal treatment such as local injections of cortisone and placentex, has been observed. In view of the lack of availability of curative treatment, and the precancerous nature of this disease, it is essential to follow-up the patients regularly. Prominent environmental causative factors appear to be areca nut chewing and capsaicin the active irritant in chilly peppers (43). The transformation of these lesions clinically into frank carcinomas has been demonstrated repeatedly in incidences of 2% - 8% of all oral cancers (44).	Prominent environmental causative factors appear to be areca nut chewing and capsaicin the active irritant in chilly peppers (43). The transformation of these lesions clinically into frank carcinomas has been demonstrated repeatedly in incidences of 2% - 8% of all oral cancers (44).

tions and classifications on the basis of previously published work (20, 21) and new scientific acquisitions. Thus, leukoplakia is a clinical term used when any other white oral lesion has been excluded. Leukoplakia is often associated with tobacco smoking,

although idiopathic forms are not rare (22). The role of alcohol, viruses and systemic conditions need further investigations (23, 24).

Clinical variants of leukoplakia are classi-

fied into two groups: (1) homogeneous leukoplakia, a lesion of uniform flat appearance that may exhibit superficial irregularities, but with consistent texture throughout; (2) non-homogeneous leukoplakia, a predominantly white or white and red le-

sion (erythroleukoplakia) with an irregular texture that may be characterised by a flat, nodular or exophytic aspect. Histological features of both forms of leukoplakia are quite variable and may include ortho- or para-keratosis of various degrees, mild inflammation and dysplastic changes of various degrees.

Leukoplakia is not uncommon. Although highly variable among geographical areas and demographical groups, the prevalence of leukoplakia in the general population varies from less than 1% to more than 5% (20, 22, 25, 26). According to a study, in which more than 1000 individuals were included, prevalence varied between 0.50% and 3.46%, and the pooled prevalence estimated was between 1.49% and 4.27% (27). Incidence data were observed to be very scarce, a recent study from Japan reported an age-adjusted incidence rate per 100,000 persons-years of 409.2 among males and 70 among females (28), while an Indian study, conducted in a population with distinctive risk factors for oral cancer, reported lower figures: 240 among males and 3 among females (29).

Leukoplakia is a precancerous lesion, i.e. "a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart" (19). The rate of malignant transformation into squamous cell carcinoma varies from almost 0% to about 20% in 1 to 30 years (10, 30, 31). Recently, a study investigating the natural limit of leukoplakia malignant transformation on the basis of European epidemiological data, concluded that the upper limit of the annual transformation rate of oral leukoplakia is unlikely to exceed 1% (32).

Non-homogeneous leukoplakias carry a higher degree of risk of transformation when compared with the homogeneous variants. Patients with signs of dysplasia, about 1/10 of the total, may be at a higher risk. However, studies investigating biomarkers and histological features have found no reliable method to identify which lesion will undergo malignant transformation and which will not (33). Clinical (34),

histological (35) and molecular markers (36) may contribute in assessing the risk of a single patient to develop cancer, however a single, evidence-based and clinically useful predictor of malignant transformation for dysplastic and non-dysplastic leukoplakias, is not available at the moment.

Since most leukoplakias are asymptomatic, the need for treatment is primarily based on the precancerous nature of the lesion. Prevention of malignant transformation is particularly important in view of the poor prognosis associated with oral squamous cell carcinoma, with only 30% to 40% of patients still alive 5 years after the diagnosis (37). Many treatments have been proposed for oral leukoplakias (including medical and surgical therapies).

Oral erythroplakia (OE)

Oral erythroplakia is considered a rare potentially malignant lesion of the oral mucosa. It is the most dangerous of all the oral cancer precursor lesions, and a search for erythroplakia should be a part of every oral soft tissue examination in persons aged 35 years and older. No erythroplakia lesions should ever be left untreated. Much has been written about the malignant potential of oral leukoplakia, but too often the dental profession has ignored the more dangerous discoloration, erythroplakia, which carries a much greater cancer risk than the white lesions (17). Reports entirely devoted to oral erythroplakia are very few, and only two reviews none of which are of recent date have been published. Only the true, velvety, red homogeneous oral erythroplakia has been clearly defined while the terminology for mixed red and white lesions is complex, ill-defined and confusing. A recent case control study of oral erythroplakia from India reported a prevalence of 0.2%. A range of prevalences between 0.02% and 0.83% from different geographical areas has been documented. Oral erythroplakia is predominantly seen in the middle aged and elderly (38). One study from India showed a female:male ratio of 1:1.04. The soft palate, the floor of the mouth and the buccal mucosa is commonly affected. A specific type of oral erythroplakia occurs in chutta smokers in

India. Lesions of oral erythroplakia are typically less than 1.5 cm in diameter. The etiology of oral erythroplakia reveals a strong association with tobacco consumption and the use of alcohol.

Histopathologically, it has been documented that in oral erythroplakia of the homogenous type, 51% showed invasive carcinoma, 40% carcinoma in situ and 9% mild or moderate dysplasia. Recently, genomic aberrations with DNA aneuploidy have been demonstrated. p53 mutations with different degrees of dysplasia may play a role in some cases of oral erythroplakia. Transformation rates are considered to be the highest among all precancerous oral lesions and conditions. Surgical excision is the treatment of choice. A clear understanding of this lesion may save lives by identifying oral cancers prior to invasion or at an early stage, thereby avoiding extensive surgery and spread of the disease to other parts of the body.

Lichen Planus

Oral lichen planus is a chronic waxing and waning inflammatory condition that affects an estimated 1 to 2 percent of adults. Although the etiology is uncertain, evidence suggests an immune-mediated mechanism involving CD8⁺ cytotoxic T-cell-induced apoptosis of epithelial cells (39). All age groups may be affected, but it predominates in adults older than 40 years, with a female-to-male ratio of 1.4:1 (40).

Two major clinical forms of oral lichen planus exist: reticular and erosive. The reticular form can appear as bilateral asymptomatic, white, lacy striations (Wickham's striae) or papules on the posterior buccal mucosa. The erosive form manifests as zones of tender erythema and painful ulcers surrounded by peripheral white, radiating striae. It may also manifest as generalized erythema and ulceration of the gingiva, known as desquamative gingivitis.

Classic lesions of reticular form often are readily identified clinically. However, lesions that do not exhibit classic features may require biopsy for diagnosis. Asymptomatic patients do not require treatment. For

symptomatic patients, topical corticosteroid gels, such as fluocinonide and corticosteroid mouth rinses, may be prescribed (41).

Submucous fibrosis

Oral submucous fibrosis is a high risk precancerous condition that predominantly occurs amongst Indians, Indians settled outside India, to a lesser extent in other Asiatics, and sporadically in Europeans. This condition was first reported in India in 1953. It is a severely debilitating oral affliction which is most commonly seen in Indian subcontinent. It is characterized by epithelial atrophy, progressive hyalinization of the lamina propria, and later subepithelial and submucosal myofibrosis (42). The resultant inelasticity of the oral tissues result in often severe restriction in mouth opening, with consequences related to hygiene, nutrition, speech and swallowing. Prominent environmental causative factors appear to be areca nut chewing and capsaicin the active irritant in chilli peppers (43). The transformation of these lesions clinically into frank carcinomas has been demonstrated repeatedly in incidences of 2% - 8% of all oral cancers (44).

It was seen that in submucous fibrosis there is a tendency toward epithelial atrophy associated with hyperorthokeratosis and pyknotic changes in the nuclei of the basal-cell layer. Hyperplasia of the epithelium usually associated with hyperparakeratosis was also noticed. Vacuolization of prickle-cell layer, increased mitotic activity, and epithelial atypia were also noticed in a few cases (45).

Oral submucous fibrosis has a characteristic clinical appearance and there are very few conditions that need to be differentiated from it. One is oral manifestation of scleroderma. Compared still is the oral involvement in scleroderma. More often, pale mucosa, coupled with pigmentation seen in anemic conditions, may be mistaken for blanching in submucous fibrosis.

Several therapeutic and surgical methods have been tried in the treatment of submucous fibrosis. Following therapy the oral mucosa should regain and retain its

normalcy, and there should be a reduction in the risk for oral cancer. However, no such definitive and widely accepted treatment is currently available for this condition. Some temporary relief from the symptoms and improvement in the oral opening with medicinal treatment such as local injections of cortisone and placentex, has been observed. In view of the lack of availability of curative treatment, and the precancerous nature of this disease, it is essential to follow-up the patients regularly. Furthermore, they must be educated to discontinue the use of areca nut and tobacco in any form, with the aim of preventing further progress of the disease and perhaps reducing the risk of oral cancer. Encouragingly, submucous fibrosis is amenable to primary prevention. Intervention studies have demonstrated a reduction in the development of new cases of submucous fibrosis (incidence cases) when areca-nut chewing habits are discontinued.

FACTORS RESPONSIBLE

In the developing world, low socio-economic status, literacy, access to health services and the availability of treatment affect the pattern of oral and peri-oral lesions. Behavioral factors related to the patients are also important determinants (46, 47). Oral health is part of total health and essential for quality of life. The ubiquity of oral HIV lesions emphasizes its clinical importance. In many developing countries access to oral health care is limited.

Study found no relationship between current smoking and presence of any oral disease (48). The effect of medications like anti-fungal or anti-viral agents on the prevalence of oral diseases has been documented (49). Oral lesions were also found to be significantly associated with low CD4 counts below 300 cells/mm³ among Italian patients as reported by (23). Cobos-Fuentes *et al.* (51) Studied that oral lichenoid lesions might also be result of contact with dental materials. According to report of Su *et al.* (52) incidence of oral malignancies are related to nickel and arsenic concentrations in farm soils.

Thus lesion prevalence differed significantly

by age, sex, and tobacco use. Individual demographic details such as age, gender, occupation, food habits, other deleterious oral habits, religion and oral hygiene measures should have a provision in biopsy request sheet and should be duly filled which will help in identifying risk-groups. Community programmes should be taken for public health to get them screened for any oral-mucosal lesions by availing pathological lab facilities.

WORK-UP AND THE EARLY DETECTION OF ORAL CANCER

With the development and success of screening programs for breast, cervical, and colon cancer, the potential to reduce the morbidity and mortality of oral cancer through early detection modalities is of critical importance. Data indicates that the diagnosis of oral squamous cell carcinoma (SCC) at an early stage of disease allows for less aggressive treatment, improves quality of life, and improves the overall 5-year survival rate when compared with SCCs diagnosed at late stages (9).

The criterion standard for diagnosis and identification of oral lesions is histopathologic analysis via the procurement of a tissue sample by surgical biopsy. Because of the invasive nature of surgical biopsy, early detection techniques are designed to provide a minimally invasive assessment of the malignant potential of the lesion that guides the approach to diagnosis and treatment of these lesions.

The approaches to the screening and detection of malignant and potentially malignant conditions have the potential to drastically alter the course of oral cavity disease but have yet to effectively reduce the overall morbidity and mortality of oral cancer. The major modalities designed to reduce this burden include oral cavity examination, supravital staining, oral cytology, chemoluminescent technique, and optical detection systems.

Oral cavity examination

The examination of the oral cavity has traditionally been the preferred approach for the detection of oral mucosal abnormali-

ties. As a noninvasive technique, the oral cavity examination can be performed quickly, is without additional diagnostic expense to the patient, and may be performed by health care professionals across a multitude of disciplines.

The evidence regarding oral examination as an effective screening technique, however, remains controversial. In a recently published randomized clinical trial with nearly 130,000 participants, investigators concluded that the evidence to support or refute the use of oral examination as a screening program was insufficient. However, this study, performed by the "Kerala" group in India, demonstrated improved survival rates at 9 years among males with high-risk habits (tobacco use) (53). Although an increase in survival for the overall population was not seen, this study was the first to clearly support the efficacy of an oral cancer screening program in a high-risk population.

Supravital staining

Toluidine blue (TB) is an acidophilic dye designed to stain acidic cellular components such as DNA and RNA. Its use in the detection of precancerous/cancerous tissue is based on the fact that dysplastic tissue contains quantitatively more DNA and RNA than nondysplastic tissue. To perform the staining, a 1% solution is placed on the oral mucosa and removed after 1-2 minutes with 2% acetic acid. The clinician then examines the oral mucosa for areas of increased cellular staining (54).

In the evaluation of potentially malignant oral lesions, TB staining may provide better demarcation of lesion margins, may guide biopsy site selection, and may be valuable in the identification and visualization of lesions in high-risk patients (55, 56, 57). Although useful as an adjunct to clinical examination, the specificity of TB staining is limited because cells undergoing inflammatory changes and benign hyperplasia may also retain dye leading to false-positive results. Overall, the sensitivity of TB staining ranges from 0.78 to 1.00, and the specificity ranges from 0.31 to 1.00 (58).

Oral cytology

Oral cytology describes a diagnostic technique used to sample oral tissue for histomorphological analysis. To obtain a tissue sample, the clinician applies a stiff brush to the oral mucosa with enough pressure to induce pinpoint bleeding, which ensures a full-thickness or trans-epithelial tissue sample. These cellular samples can then be analyzed by a variety of unique diagnostic measures, including cytomorphometry, DNA cytometry, and immunocytochemical analysis (54, 57).

Computerized image analysis of brush biopsy samples (OralCDx) uses a computer program to perform morphological and cytological analysis of tissue samples. The computerized analysis ranks cells based on the amount of abnormal morphology, which are then presented to a pathologist for further distinction and classification. The sensitivity of the OralCDx ranges from 0.71 to 1.00, and the specificity is as low as 0.32 (54).

DNA cytometry uses a DNA-specific Feulgen dye to quantify and identify deviations in DNA content in sampled tissue. Although data are still limited, the addition of DNA measurements to cytological analysis has been shown to increase the sensitivity and specificity of brush biopsies (54).

The use of oral cytology in the detection of dysplastic lesions shows considerable promise but has been limited thus far by variable false-positive and false-negative results (56, 57).

Chemiluminescent light

Chemiluminescent light based systems (ViziLite Plus, MicroLux DL) use the application of a diffuse chemiluminescent light source to visualize abnormal oral mucosa not visible under normal incandescent light. A 1% acetic acid oral rinse is used to remove surface debris and slightly desiccate the oral mucosa before direct examination with the light source. Under illumination, normal epithelium absorbs the light (appearing light blue) while abnormal tissue reflects the light (appearing

white, with sharper, distinct margins). The ViziLite system then uses a toluidine blue stain to aid in further lesion assessment. As of 2008, insufficient evidence supports the use of chemiluminescent light modalities in discovering pathology that would not have been identified using incandescent light alone. However, the potential ability to identify pathologic tissue not visible under conventional examination may support the use of chemiluminescent light as a screening technique (56).

TISSUE AUTOFLUORESCENCE

Tissue autofluorescence describes the exposure of epithelial tissue to specific wavelengths of light that results in the excitation of cellular fluorophores and emission of energy in the form of fluorescence. With the disruption of normal tissue morphology in dysplastic lesions, tissue fluorescence is scattered and absorbed, resulting in characteristic alterations in color that can be visually interpreted (58).

The VEL scope is an early detection device based on these principles. Under excitation with the VEL scope device, normal mucosa emits a pale green light, whereas abnormal mucosa appears dark. The initial evidence suggests that the VEL scope may be useful as both an adjuvant method of margin determination during surgical procedures as well as a screening technique to identify premalignant lesions not visualized during conventional examination (56).

CONCLUSION

This review described about different types of pre-cancerous oral lesions and their diagnosis and treatment. It is very important to diagnose these lesions earlier so that it can be prevented to turning into a cancerous growth.

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