Oral Potentially Malignant Disorders and Oral Cancer

This Clinical Dentistry Advisor is an update of an article previously published by EDIC in 2014.

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Background [1,2,3]

Oral potentially malignant disorders* (OPMD) and oral cancer (OC) are alterations of the oral mucosa or conditions that can be encountered by the dentist during routine clinical examination. It is important for the dentist to identify these disorders, appropriately manage the patient and counsel the patient on their significance. These conditions are very complex, with difficulty in fully predicting their behavior. OPMD evolution to cancer is not necessarily linear in progression.

Factors associated with an increased likelihood of malignant transformation (MT) of OPMD include:
- Age (>45 years old)
- Female gender
- Nonsmoking status
- High risk anatomic sites (floor of the mouth, ventrolateral tongue, retromolar area, and soft palate)
- Size (lesions with size >200 mm2 have shown a >5-fold increase in the risk of MT), Clinical phenotype (nonhomogeneous leukoplakia, erythroplakia)
- Higher grade of dysplasia

The dentist also plays an important role in public awareness of these disorders and by doing so, may change the long-term outcomes for patients diagnosed with these conditions.

**Defined by WHO in 2017 as: "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa".*

Oral Potentially Malignant Disorders [2,3]:

We will limit our discussion of OPMD to leukoplakia, erythroplakia, proliferative verrucous leukoplakia, oral submucosal fibrosis, oral lichen planus, actinic cheilitis and dysplasia mindful that other defined disorders have the potential for MT to oral squamous cell carcinoma.

Leukoplakia [2,3,4,5,6,7,8,9]

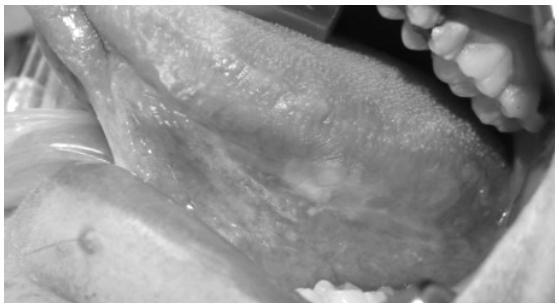

Figure 1. Leukoplakia *Photo courtesy of Dr. Rabie Shanti*

- Clinical diagnosis based on the history and examination findings and not based on histopathologic features
- Defined as a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer
- Most common OMPD
    - Approximately 8% of males over the age 70 will be affected by leukoplakia
- Spontaneous regression is possible
- Risk of malignant transformation (MT) rate is variable
- Two clinical presentations: Homogenous or Non – homogenous
    - Homogenous: thin white plaque with or with out fissures and less likely associated with MT
    - Non-homogenous – 3 subtypes:
        - Erythroleukoplakia a mixed red and white lesion but not predominantly white
        - Speckled leukoplakia/leukoerythroplakia a mixed red and white lesion but predominantly white

        Nodular or verrucous leukoplakia

CONTENTS

• Non homogenous leukoplakia are associated with a greater risk of MT
• Time related progression to MT is not clear and not necessarily linear
• Floor of mouth and posterior lateral tongue sites are more likely to transform

Erythroplakia [4,5]

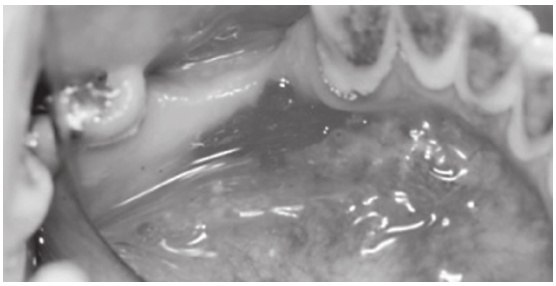

Figure 2. Erythroplakia

• Clinical diagnosis based on the history and examination findings and not based on histopathologic features
• Defined as a bright red, velvety patch that cannot be characterized clinically or pathologically as any other recognizable condition
• Soft palate, floor of the mouth, and buccal mucosa are the most commonly affected sites
• Very high rate of MT; estimated to be 40-50%
• Often diagnosed as severe dysplasia or carcinoma when discovered

Proliferative Verrucous Leukoplakia[2]

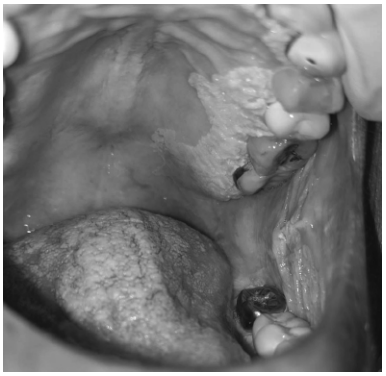

Figure 3. Proliferative verrucous leukoplakia
Photo courtesy of Dr. Rabie Shanti

• Multifocal presentation of leukoplakia which can have homogeneous and nonhomogenous features
• More commomnly seen in women
• Early diagnosis of PVLis difficult as it can start as unifocal and resemble homogenous leukoplakia or plaque like lichen planus
• Lesions often exhibit verrucal texture
• Very difficult to manage
• High risk for MT

Oral Submucosal Fibrosis [10]

• Associated with Betel/Areca nut usage seen in higher prevalence in Southeast Asian populations
• Clinically associated with trismus from mucosal scarring
• High risk of malignant transformation

Oral Lichen Planus [2,11,12,13]

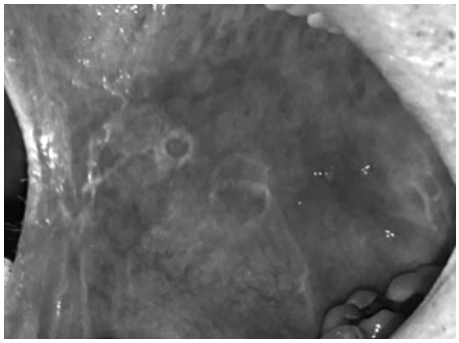

Figure 4. Oral Lichen Planus

• Very common mucocutaneous disease affects 1%-4% of the population
• Various appearances including ulcerative/erosive, plaque - like, atrophic, and reticular
• Plaque like and ulcerative may have higher transformation rate
• Rate of malignant transformation estimated at 0.44% -1.37%

Actinic Cheilitis [14]

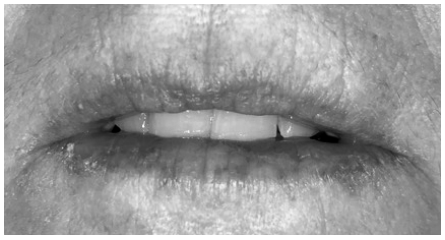

Figure 5. Actinic cheilitis

• Associated with UV light from sun exposure to lip
• Clinically resembles non-healing, chapped lips often associated with ulceration, erythema and a thickened texture
• Usually involves the lower lip
• Loss of the vermillion border is a common finding seen with this condition.

Dysplasia [3,4,7,9]

• Histologic description of the epithelium
• Diagnosis/grading of oral epithelial dysplasia are based on a combination of architectural and cytologic changes using a 3-tiered grading classification: mild, moderate, and severe, with severe dysplasia and carcinoma in situ considered synonymous (2005 World Health Organization Classification)
  ◦ Mild dysplasia
    - Dysplastic cells are limited to the basal layer of the epithelium
  ◦ Moderate
    - Increasing cellular changes in cellular morphology involving the lower two thirds of epithelium
  ◦ Severe dysplasia/Carcinoma in situ (CIS)
    - Changes that extend beyond the lower two thirds are regarded as severe dysplasia/CIS without invasion through the basement membrane
  ◦ Carcinoma
    - Disruption of the basement membrane and

invasion into connective tissue
- Presence of dysplasia implies an increased risk of MT
- Not all dysplastic lesions become malignant; not all non - dysplastic lesions will remain benign
- Severe dysplasia has a high potential to transform to invasive oral cancer

Diagnosis of OPMD/Oral Cancer [15,16,17] :
- Clinicians should review the patient's full medical, social, and dental history and then perform a conventional visual and tactile intraoral and extraoral examination
- If a suspicious lesion is detected referral to a specialist or a biopsy of suspicious lesion should be performed resulting in a tissue diagnosis
- Currently the gold standard for predicting the malignant potential of OPMD is the presence and degree of dysplasia
- Various techniques to identify genetic/molecular markers associated with a higher risk of MT are emerging

Adjunctive Diagnostic Techniques [6,15,16]:
- Designed to aid in lesion detection/discrimination, lesion assessment and risk assessment
- In general, evidence supporting the use of adjunctive devices to improve the general practitioner's ability to screen for and identify OPMD and oral cancer at their earliest stages remains unproven, insufficient or low.
- No available adjuncts demonstrate sufficient diagnostic test accuracy to support their routine use as triage tools during the evaluation of lesions in the oral cavity
- Tissue/Salivary Biomarkers
  - Future patterning of genetic/epigenetic and molecular profiling may result in improved predictive capabilities

Management of OPMD [2,6,15] :
- Eliminate risk factors
  - Return in 2-4 weeks
- Biopsy if lesion still present for definitive diagnosis
- Lifelong follow-up
- Clinical studies failed to provide evidence-based recommendations on medical treatment of dysplastic lesions
- If lesion is determined to be severe dysplasia or frank oral cancer, immediate referral to a head and neck cancer specialist is recommended

Oral Cancer

Epidemiology of Oral Cancer [18] :
- Over 53,000 new cases of oral and oropharyngeal cancer annually (projected 2020) in the United States
- Oral cavity cancer has a slight decline in incidence while oropharyngeal cancer there is an increase in incidence
- Accounts for 2.9% of the new cancers diagnosed per year in the U.S.
- Majority of cases diagnosed between ages 55-64 with a median age of diagnosis at age 63
- Male : Female 3:1
- Approximately 10,750 deaths annually (projected 2020)
- Overall 5 year survival rate 66.2% (2011-2016)

Etiology [19] :
- Accumulation of genetic and epigenetic changes from exposure to initiators and promoters without adequate DNA repair.
- Risk Factors include:
  - Tobacco
  - Using smokeless tobacco, including snuff and chewing tobacco
  - Alcohol
    - Combined use of tobacco and alcohol are associated with an increased risk of more than 30-fold
  - Human Papilloma Virus (HPV)(especially HPV Type 16)
  - Immunosuppression/Being immunologically compromised (e.g., after bone-marrow transplantation, long term medication induced immunosuppression)
  - Chewing betel quid, areca nut and paan
  - Fanconi's anemia/dyskeratosis congenita/Li-Fraumeni syndrome
  - History of prior oral cavity cancer or oropharyngeal cancer

Clinical Presentation [9,20,21]

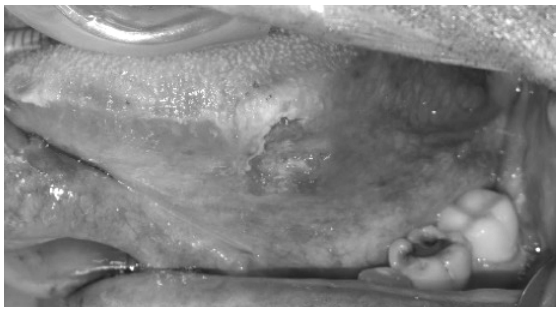

Figure 6. Oral Cancer *Photo courtesy of Dr. Rabie Shanti*

- Majority of oral and oropharyngeal cancers are squamous cell carcinoma and involve the following sites:
  - Tongue
  - Oropharynx
  - Floor of mouth
- Dysplasia more prevalent:
  - Tongue
  - Lips
  - Floor of mouth
- Symptoms
  - Precancerous & early cancerous lesions are not often associated with symptoms
  - Late stage cancer might be associated with dysphagia, pain, speech alteration or an oral/neck swelling
- Prognosis
  - TNM system of cancer classification used for staging
    - Recently updated in 2017 to include depth of invasion, local invasiveness, HPV status and in corporation of extracapsular nodal extension findings
    - Higher the stage - prognosis decreases*
    *(Note: HPV positive tumors have a better overall prognosis compared to HPV negative tumors)
  - Localized tumors of the oral cavity and pharynx have an overall survival rate of 87%
  - Patients with distant metastases demonstrated an over all survival rate of 37%

Pathogenesis [17,22] :
- Multistage process that does not necessarily follow a linear progression
- Transformation from a benign to a malignant disease is a genetic/epigenetic process that occurs at the cellular/

molecular level, which later becomes histologically evident at the tissue level and becomes clinically evident on examination.

- Studies have identified a molecular (genetic) profile model regarding the risk of progression to cancer:
  - **Low** when no genetic change is seen
  - **Intermediate** if there is genetic loss on the short arms of chromosome at sites 3p & 9p
  - **High** if there is 3p & 9p loss accompanied by genetic loss on additional chromosome arms (including 4q,8p,11q,13q,and 17p)
- Several potential additional changes in molecular markers of oral cancer and OPMD have been studied and may be helpful to understand the behavior of the neoplasia in the future.

Management of Oral Cancer [22,23]:

- Usually treated by surgery, and/or radiation with or without chemotherapy, solely or in combination
- Surgical excision is often the treatment of choice for accessible well defined tumors
- Transoral robotic surgery TORS is a novel surgical approach resulting in fewer side effects
- Radiotherapy could be an effective alternative to surgery but most often is an adjunct in regional control
- Chemotherapy (adjuvant) has been shown to improve regional control and long term survival
- Complications to surgery include disfigurement, dysphagia, trismus and speech impairment
- Complications to radiotherapy include both immediate effects (mucositis, dysphagia/odynophagia) and delayed effects (salivary dysfunction, trismus, dysgeusia, dental disease, potential for osteoradionecrosis)
- Complications to chemotherapy include mucositis, pain, neuropathy and dysgeusia
- Since patient's that have had a history of prior oral cavity cancer or oropharyngeal cancer are at high risk for developing another, lifelong follow up with particular attention to the clinical oral and head and neck exam is warranted

Summary:

Oral potentially malignant disorders and oral cancer are alterations of the oral mucosa that will be encountered by the dentist during routine clinical examination. The dentist maybe the first healthcare provider to identify these abnormalities and initially manage/counsel the patient regarding the significance of the finding. It is important to have an understanding of the risk factors associated with these disorders and an understanding regarding the detection of them as well. At this time, predicting the behavior of these lesions is difficult and incomplete. In the future, as the understanding of genetic/molecular signatures found in the patient's tissue or saliva improves, so will our ability to predict the potential for malignant transformation and our ability to better manage the patient's disease. The dentist plays an important role in changing the long term outcomes for patients diagnosed with these conditions as well as maintaining the oral health in those who have been treated for oral cancer.

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Dr. Sollecito graduated from the University of Pennsylvania, School of Dental Medicine in 1989. He completed a general practice residency and a fellowship in oral medicine at the University of Pennsylvania Health System. He is board certified by the American Board of Oral Medicine and the American Board of Special Care Dentistry.He is a Fellow in Dental Surgery, Royal College of Surgeons of Edinburgh and a Fellow of the International College of Dentists, USA Section. He is currently Professor and Chair of Oral Medicine at the University of Pennsylvania, School of Dental Medicine and Professor of Oral Medicine in Otolaryngology: Head and Neck Surgery, University of Pennsylvania School of Medicine. He is also an Attending in Oral Medicine at the Hospital of the University of Pennsylvania and a University Associate at the Children's Hospital of Philadelphia. Dr. Sollecito is an expert in oral mucosal diseases, facial pain as well as in the dental treatment of the medically complex patient. He is a Past President of the American Academy of Oral Medicine. His research interests include oral cancer and pre-cancer. Dr. Sollecito has authored numerous papers and chapters related to various topics in Oral Medicine.

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