INTRODUCTION

- Diagnosing and treating lesions of the mouth and gums is a challenging problem for many care providers.
- Wide variety of disease processes that can present with similar appearing lesions.
INTRODUCTION

- In a study of identification of oral lesions in older adult patients, almost all clinicians felt that it was important to examine older patients' oral cavities; however, less than one-fifth routinely did so.
- Almost 4 out of 5 did not correctly diagnose a clinical picture of an early squamous cell carcinoma.

EPIDEMIOLOGY

- Prevalence of potentially malignant conditions varies by geographic region and ranges from 1-5%.
- Most affected patients are middle-aged or older males.
- Potentially malignant lesions are most commonly observed on the buccal mucosa, gingiva, tongue and floor of mouth.
ORAL CANCER

- Accounts for 3% of all cancers in the United States, with approximately 25-30,000 cases diagnosed each year.
- One of the most common malignancies in Southeast Asia, accounting for 30-40% of all cases in India.
- Surveillance Epidemiology and End Results (SEER) data indicate an increased prevalence of cases in the younger (<40) population. Increasing from 3% in 1973 to 6% in 1993, and many are without the traditional risk factors and less male predominance.

RISK FACTORS AND PATHOPHYSIOLOGY

- Tobacco is a well-known risk factor for oral squamous cell carcinoma and premalignant lesions. Up to 80% of those with oral cancer have used tobacco products.
- Alcohol also has been linked to these lesions, and the combination of heavy alcohol use combined with tobacco may convey 100 times greater risk than the general population.
ROLE OF HPV IN OC CANCER AND PREMALIGNANT LESIONS

- Continues to be under debate. Not as clear a risk factor as seen in the oropharynx.
- HPV DNA has been demonstrated in 17.6% of oral leukoplakia lesions and 19.7% of oral lichen planus lesions.
- Clarification on whether the presence of HPV in these lesions leads to carcinomatous change continues to be investigated.

TERMINOLOGY AND DEFINITIONS

- The World Health Organization classifies premalignant oral cavity disorders into 2 general categories:
  - A precancerous lesion is “a morphologically altered tissue in which oral cancer is more likely to occur than in its apparently normal counterpart.” These include leukoplakia, proliferative verrucous leukoplakia, and erythroplakia.
  - A precancerous condition is “a generalized state associated with significantly increased risk of cancer.” These include oral submucous fibrosis and lichen planus.
Precancerous lesions

LEUKOPLAKIA

- WHO: A white patch or plaque that cannot be scraped off or stripped off easily, and moreover, which cannot be characterized clinically or pathologically as any other disease.
- 85% of all oral premalignancies, and occurs in 3-4% of the population.
- Seen most often in middle-aged and older men and arises most frequently on the buccal mucosa, alveolar mucosa and the lower lip.
LEUKOPLAKIA

- Lesions arising on the floor of mouth, lateral/ventral tongue, and lower lip are most likely to harbor dysplasia or progress to malignancy.
- Rate of conversion has been reported from 3.6 and 17.5%, and as many as 19.9% of lesions may harbor some degree of dysplasia, with 3.1% demonstrating frank carcinoma.

LEUKOPLAKIA RISK FACTORS

- Include advanced age, female sex, lesions greater than 200 mm², and non-homogenous lesions.
**PROLIFERATIVE VERRUCOUS LEUKOPLAKIA (PVL)**

- Unique form of aggressive disease considered to be in the continuum of leukoplakia as either a subtype of non-homogenous OL or a distinct clinical entity.
- Most patients are women without a history of tobacco use.

**PVL**

- Generally appears as an irregular white patch or plaque with a varying surface.
- Difficult to treat, often recurs, multifocal proliferation, and progression to verrucous or squamous cell carcinoma in 60-70%, much higher than in other leukoplakic lesions.
ERYTHROPLAKIA

• WHO: Fiery red patch that cannot be clinically or pathologically distinguished from another definable disease.

• Clinical appearance is a red macule or patch with a soft, velvety texture most often occurring on the floor of mouth, lateral tongue, retromolar trigone, or soft palate.

ERYTHROPLAKIA, A CONCERNING PREMALIGNANT LESION

• Worrisome clinical condition that often harbors dysplasia.

• 51% of lesions have been shown to demonstrate invasive squamous cell carcinoma, with 40% demonstrating carcinoma in situ, and 9% mild-to-moderate dysplasia.
Precancerous Conditions

ORAL SUBMUCOUS FIBROSIS (OSF)

- Chronic progressive condition found predominantly in persons of Asian descent.
- Considered to be a result of the use of the Areca, or betel nut with resultant disruption of the extracellular matrix.
OSF

- Often manifests with diffuse involvement of the oral cavity, pharynx, and upper esophagus.
- Clinically appears as whitish mucosa lacking elasticity.
- Epithelial dysplasia has been reported in 7-26% of OSF tissues, and long-term studies suggest a 7% progression to malignancy.

LICHEN PLANUS

- Lichen planus is a disease that can affect the skin and any mucosal lining. It is often only found in the oral cavity.
- Affects approximately 2% of the population all ages, primarily women over the age of 50.
- Characterized as a chronic immunologic mucocutaneous disorder, but is not completely understood.
- Varies in appearance. The reticular pattern is commonly seen on the buccal mucosa as lacy web-like, white threads that are slightly raised, often termed Wickham’s striae.
EROSIVE AND ULCERATIVE LICHEN PLANUS

- An erosive or ulcerative pattern can affect any mucosal surface. This form often appears as bright red due to the loss of the top layer of the affected mucosa.
- Often painful with exposure to extremes of temperature, acidic, coarse, or spicy food.
- Treatment of these lesions is topical or systemic steroid therapy in an effort to convert to the asymptomatic reticular form.
- Malignant transformation has reported in up to 10% of patients, with greater risk of transformation in erosive lesions and in cases of lesions of lateral border of the tongue.

MANAGEMENT OF PRECANCEROUS LESIONS

- Standard options range from watchful waiting to biopsy, laser surgery, and aggressive resection.
- Other approaches work to decrease the incidence of invasive tumor growth in patients with recognizable premalignant lesions.
PREVENTATIVE MEASURES

• Avoidance of further carcinogenic exposures (eg, tobacco, alcohol). While important, but may not be sufficient as many or most of the critical genetic alterations leading to transformation have already occurred in early premalignant lesions.

• Chemoprevention to reverse or inhibit carcinogenic progression.

• Screening individuals known to be high risk for the development of invasive cancer, based upon the presence of risk factors or risk factors or premalignant lesions in a target population.

RATIONALE FOR CHEMOPREVENTION

• Field Cancerization - Implies that oral cancer does not arise as an isolated cellular phenomenon, but rather as an anaplastic tendency involving many cells at once that results into a multifocal development of cancer at various rates within the entire field.

• Multistep carcinogenesis - SCCHN result from a multi-step process with defined intermediate stages, leading to fully transformed, invasive, and metastatic disease.
CHEMOPREVENTION

- If the size of the lesion, its location, or the medical status of the patient makes the surgical removal difficult, use of antioxidant supplement can be considered as a tool to potentially prevent progression to carcinoma.

- Vitamin A, vitamin E, and beta carotene are the most commonly used.

CHEMOPREVENTION

- 13-cis-retinoic acid (aka isotretinoin or Accutane) most well studied.

- MD Anderson study of 44 patients with oral leukoplakia were treated with 1-2mg/kg/day 13-cRa for 3 months: 32 (67%) had more than 50% reduction in lesion size; however, toxicity (cheilitis, facial erythema, dryness and peeling of skin) was particularly severe in patients at the higher dose with 47% requiring dose reduction. Patients treated at the lower dose had less toxicity and better tolerance, although most noted xeroderma and 29% developed conjunctivitis. Furthermore 50% of responders relapsed after 3 months of treatment cessation.
CHEMOPREVENTION

- In a second trial, 70 patients with leukoplakia underwent indication with high dose isotretinoin (1.5mg/kg/day for 3 months) and were then randomized to “maintenance” with low dose isotretinoin (0.5mg/kg/day for 9 months) or beta carotene (30mg/day). Of the 53 evaluable patients, those in the retinol group saw a response to maintenance therapy or continuation of stable lesions over those in the beta carotene group (92 vs 45%, p<0.001). Side effects were generally mild, but more prominent with isotretinoin.

NEW ADVANCES IN CHEMOPREVENTION

- An array of natural compounds such as green tea extract, curcuminoids (found in turmeric), resveratrol, pomegranate juice, and soybeans are under investigation in head and neck chemoprevention trials.

- These compounds contain high levels of polyphenols which have antioxidant properties and inhibit carcinogenesis mediated by downstream signaling pathways.
WORKUP AND EARLY DETECTION OF ORAL CANCER

- Diagnosis of early squamous cell carcinoma allows for less aggressive treatment, improves quality of life, and improves overall 5-year survival rate.
- Gold standard is clinical inspection and histopathologic analysis with biopsy.
- Because of the invasive nature of biopsy, early detection techniques are utilized as a way to provide a minimally invasive assessment of the malignant potential of the lesion that guides the approach to diagnosis and treatment.

NON-INVASIVE TOOLS FOR EARLY DETECTION

- Supravital staining with toluidine blue dye
- Oral CDx brush biopsy kits
- Optical imaging systems. Most common: ViziLite, ViziLite Plus, and VELscope.
SUPRAVITAL STAINING: TOLUIDINE BLUE

- Member of the thiazine group of metachromatic dyes, which binds to DNA and is partially soluble both in water and alcohol.
- In theory, dysplastic and malignant cells have a higher nucleic acid content than normal tissue, thus staining of suspicious lesions with this dye can aid in the recognition of mucosal changes.

TOLUIDINE BLUE

- A positive staining of TB appears as a royal blue.
- Highly sensitive (97.8-93.5%) but less specific (92.9-73.3%).
- High false positive rate.
ORAL CDX BRUSH BIOPSY

- Uses the concept of exfoliative cytology to provide a cytological evaluation of cellular dysplastic changes.
- Provides a complete transepithelial sample as the brush extends deep in the epithelial layers.
- Samples are fixed onto a glass slide, stained and analyzed microscopically via a computer-based imaging system.
- No value in lesions that are not visible.
- Incisional biopsy still suggested if there is clinical suspicion of a lesion regardless of the Oral CDx result.

CHEMILUMINESCENCE: VIZILITE

- Application of a diffuse chemiluminescent light source to visualize abnormal oral mucosa not visible under normal incandescent light.
- 1% acetic acid oral rinse is used to remove surface debris and slightly desiccate the oral mucosa before direct examination with the light source.
- Normal epithelium will absorb light and appear light blue whereas hyperkeratinized or dysplastic lesions will reflect the light and appear white with sharper, distinct margins.
- The ViziLite Plus system then uses a toluidine blue stain to aid in further lesion assessment.
TISSUE AUTOFLUORESCENCE

- Exposure of epithelial tissue to specific wavelengths of light 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.

VELSCOPE

- Under excitation with the VELScope device, normal mucosa emits a pale green light, whereas abnormal mucosa appears dark.

- Rely on qualitative observations to detect and delineate neoplastic oral lesions, so reliable screening requires well-defined and standardized image interpretation criteria, and high-level training.

- May not be useful in the primary care setting.
TREATMENT

- First line treatment of lesions with a biopsy or testing indicative of high-grade dysplasia, carcinoma in situ or squamous cell carcinoma, if amenable, is surgical excision with at least 1 cm margins.
- CO2 laser allows for improved healing times and better functional outcomes.

AUTOFLUORESCENCE AS AN INTRAOPERATIVE TOOL

- Several promising studies showing the use of autofluorescence intraoperatively to more accurately determine extent of disease and better approximate surgical margins.
- Early study (2006) by Poh et al demonstrates how the surgical margin can be affected with the use of the VELscope.
Fig. 1. Stepwise protocol used for assessing surgical field. 
A. In the operating room, initial assessment under white light of an ill-defined SCC at right ventrolateral tongue; B. clinically apparent tumor outlined in blue; C. assessment of field using FV in the dark; D. FVL area outlined in green in the dark; E. boundary of surgical specimen (red). F. Blocking of surgical specimen, showing location of punch biopsy site from clinically visible tumor (red circle), from tissue showing FVL, placed directly abutting FVL boundary (green circle), and, from tissue showing FVR, placed directly abutting the boundary of surgical specimen (blue circle).

MARGIN RESULTS

Study design showing results of analysis for 122 biopsies. Each biopsy is described with respect to location (tumors, margin), FV status (FVR, FVL), histology (SCC, CIS, high-grade dysplasia (HGD), low-grade dysplasia (LGD); no dysplasia), and LOH analysis (presence of patterns previously associated with recurrence; ref. 22). MR1, no LOH at 3p and 5p. MR2, LOH at 3p and/or 5p. *, 12 cases were randomly selected from FVR margins without dysplasia for LOH analysis.
CONTINUED STUDY

- Poh et al recently (March 2016) published a retrospective observational study of 246 patients undergoing surgery for high-grade dysplasia or oral carcinoma. 154 patients underwent surgery with fluorescent visualization of intraoperative tumor margins, and 92 undergoing traditional surgery serving as controls.

- Patients who underwent intraoperative fluorescence visualization had a dramatic reduction in the 3-year recurrence rate (6.5% compared to 40.6%).

- Currently the group is finalizing the results in a multi center, phase 3 trial to validate their results.

SUMMARY

- Oral premalignant lesions are highly variable and can harbor a large range of histopathology.

- Field cancerization proves to be a difficult problem to manage.

- Early detection of high risk lesions is key.

- No good long-term chemoprevention agent at this time.

- Clinical inspection with incisional biopsy remains the gold standard.
SUMMARY

- Screening is important especially in higher risk groups.
- Non-invasive screening tools still with high false positive rates and rely on a higher level of training and qualitative measurements.
- Surgical resection first line treatment for high-risk lesions.
- Autofluorescence shows promise intraoperatively to better delineate resection margins.

MOST IMPORTANTLY: DON’T FORGET TO LOOK
HISTOPATHOLOGIC FEATURES OF LEUKOPLAKIA

LEGEND
- Normal epithelium
- Dysplastic epithelial cells
- Lymphocytes
- Candida hyphae
- Keratin layer
- Irregular hyperkeratosis
- Hyperkeratosis
- Acanthosis
- Dysplasia (mild/moderate)
- Moderate/severe dysplasia
- Unerupted teeth
- Congenital vessels
- Carcinoma in situ
- Erythroplakia (speckled leukoplakia)