ROUTINE CANCER SCREENING - WHAT IT CAN DO FOR YOUR PATIENT AND YOUR PRACTICE

Ashley Clark, DDS, FACD, FAAOMP
Associate Professor and Division Chief
Diplomate, American Board of Oral and Maxillofacial Pathology

Conflicts of interest & disclaimers

- Neither I nor members of my immediate family have any financial relationship with commercial entities that my be relevant to this presentation.
- The opinions expressed in this presentation are those of the speaker and not necessarily those of my employer.
- The opinions expressed in this course should not be construed as advice to care for specific patients.

Objectives

- Upon completion of this course, the participant should be able to:
  - Discuss potentially malignant disorders of the oral cavity, specifically leukoplakia
  - Recognize how leukoplakia presents and how it may progress
  - Determine an appropriate treatment plan for patients with leukoplakia
  - Discuss how to help prevent squamous cell carcinoma in your patient population

Introduction

- Around ~54K people in the United States will be diagnosed with oral or oropharyngeal cancer this year
  - Around 11K patients will succumb to disease this year
- Men are twice as likely as women to be diagnosed with oral cancer
- 62 is the average age of all patients, though 25% occur in people younger than 55 years old
- Squamous cell carcinoma (SCCa) is the most common type of oral cancer by far

https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/about/key-statistics.html

Dhanuthai K, Rojanawatsirivej S, Thosaporn W, et al. Oral cancer: A multicenter study. *Med Oral Patol Oral Cir Bucal.* 2018;23(1):e23-e29.

Introduction

- Though HPV-negative oral cancer is most common in older males, there is a rising incidence of SCCa affecting the tongue in young white women (ages 18-44)
  - From 1973-2012, there was a 0.6% annual increase
  - These tongue SCCas are HPV-negative and the etiology is not known (tobacco and alcohol are not considered etiologic factors in this increase)
    - Even in patients under 30 who smoke or drink, the duration of exposure is insufficient to account for SCCa development
    - It has been suggested in the literature that the risk for oral cancer increases after 21 years of smoking

Llewellyn CD, Linklater K, Bell J, et al. An analysis of risk factors for oral cancer in young people: a case-control study. *Oral Oncol.* 2004;40:304-313.

Tota JE, Anderson WF, Coffey C, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. *Oral Oncology.* 2017;67:146-152.

Introduction

- There are two molecularly and epidemiologically distinct types of oral and oropharyngeal squamous cell carcinoma:
  - 1. Those that are positive for high-risk human papillomavirus (HPV)
  - 2. Those that are negative for high-risk HPV
- Each warrants their own discussion, as they have different etiologic factors, tend to occur in different locations, affect different demographics, and have different survival rates
- We will focus on HPV-negative SCCa, as there is no known dysplastic phase for HPV-positive SCCa

Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol*. 2014;50:380-386.

Etiology

- The etiology of HPV-negative oral squamous cell carcinoma is multifactorial; extrinsic and intrinsic factors are involved
- Extrinsic factors include tobacco smoke, alcohol, and sunlight (sunlight only for lower lip vermilion)
- Intrinsic factors include systemic conditions or generalized states; examples include malnutrition and iron-deficiency anemia
- Aside from a handful of rare, heritable conditions such as dyskeratosis congenita or Fanconi anemia, heredity does not appear to play a major causative role

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

POTENTIALLY MALIGNANT DISEASES

Focus on leukoplakia

Screening for SCCa

- Clinicians should perform conventional visual and tactile examinations (CVTE) intra- and extraorally on dental patients – every patient, every time
- I follow the same pattern to ensure I've looked everywhere
  - Upper labial mucosa, lower labial mucosa
  - Right buccal mucosa, left buccal mucosa
  - Maxillary facial gingiva, mandibular facial gingiva
  - Maxillary lingual gingiva, mandibular lingual gingiva
  - Right lateral tongue, left lateral tongue
  - Ventral tongue, floor of mouth, dorsal tongue
  - Hard and soft palate
  - Oropharyngeal area if possible

Lingen MW, Abt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. *JADA*. 2017;148(10):712-727.

Screening for SCCa

- Oral diagnostic aids?
  - Light-based detection systems including autofluorescence

Lingen MW, Abt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. *JADA*. 2017;148(10):712-727.

Oral dysplasia

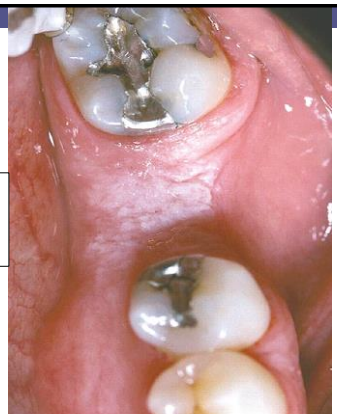
- Oral dysplasia is present in up to 1 in 200 patients
- The most common presentation is leukoplakia, something that affects up to 2.5% of Americans

Leukoplakia

- Leukoplakia is defined by the World Health Organization as “a white plaque of questionable risk having excluded other known diseases or disorders that carry no risk”
  - This means tobacco pouch keratosis, leukoedema and etc. are not leukoplakias
- A clinical term; leukoplakia is never a diagnosis
- True leukoplakia should always be considered a potentially malignant disease

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Frictional keratosis, not leukoplakia



© Photo(s): Dr. Jerry Bouquot, Morgantown, WV

Leukoplakia

- Clinical features:
  - Most commonly found in patients over 40 years old; the prevalence increases rapidly with age
    - 10% of men over age 70 are affected
  - Most leukoplakias with dysplasia are found on the lateral/ventral tongue or floor of mouth

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Leukoplakia

- Thin leukoplakia represents the earliest lesions and it presents as slightly elevated gray or white plaques
  - Most have sharply demarcated borders
  - The lesions may appear fissured or wrinkled
- Thin leukoplakia seldom shows dysplasia on biopsy
- The malignant potential is probably less than 5%
  - Exception: If the lesion is positive for a high-risk strain of HPV

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

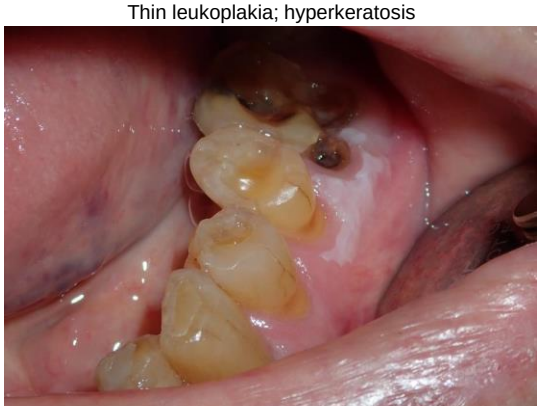
Thin leukoplakia; hyperkeratosis

© Photo(s): Dr. Ashley Clark, University of Kentucky College of Dentistry

Thin leukoplakia; hyperkeratosis

© Photo(s): Dr. Eugene Ko, Penn Dental Medicine

Thin leukoplakia; hyperkeratosis



Thin leukoplakia; mild dysplasia

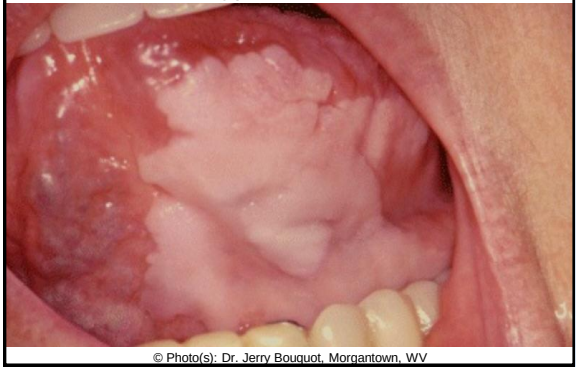
Thin leukoplakia; carcinoma-in-situ (HPV-16)

Leukoplakia

- Thin leukoplakia can progress to become thicker, more distinctly white, and fissured
  - This is termed homogeneous or thick leukoplakia
- Most leukoplakias remain at this stage; up to 1/3 may regress

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Thick leukoplakia; mild dysplasia with hyperkeratosis



Leukoplakia

- Some lesions of thick leukoplakia can progress to develop increased surface irregularities
  - This is called granular or nodular leukoplakia; those with wartlike projections are termed verruciform leukoplakia

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Verruciform leukoplakia; severe dysplasia

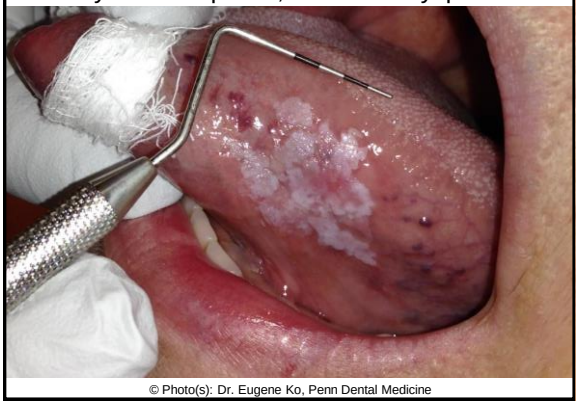
© Photo(s): Dr. Jerry Bouquot, University of Texas School of Dentistry Houston, Texas

Leukoplakia

- If granular, nodular, or verruciform leukoplakia progresses, the lesion begins to demonstrate scattered red patches (erythroplakia)
- The erythroplakia found in areas of leukoplakia represents sites in which epithelial cells are so immature they can no longer produce keratin
- Red and white intermixed lesions are termed erythroleukoplakia
- Erythroplakia and erythroleukoplakia frequently reveal advanced dysplasia on biopsy

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Erythroleukoplakia; moderate dysplasia



© Photo(s): Dr. Eugene Ko, Penn Dental Medicine

Leukoplakia - PVL

- Proliferative verrucous leukoplakia (PVL) is a special high-risk form of leukoplakia
- It is characterized by multiple keratotic plaques with roughened surface projections
- Lesions slowly spread throughout the mouth; the gingiva is typically involved
- Lesions nearly always transform into verrucous carcinoma or SCCa if left untreated; the average time of transformation is 8 years after initial diagnosis

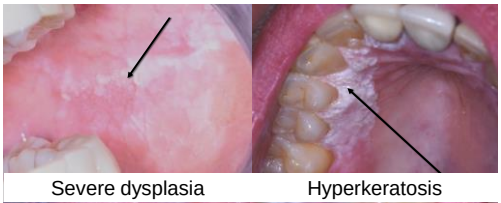
Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Leukoplakia - PVL

- PVL is difficult to treat because lesions nearly always recur; the only treatment is to repeatedly destroy tissue
- PVL is unusual because there is a 4:1 F:M predilection
- There is no known etiology (it is not associated with tobacco use)

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

© Photo(s): Dr. Ashley Clark, University of Kentucky College of Dentistry



Severe dysplasia

Hyperkeratosis

Leukoplakia

- The first step in the treatment of leukoplakia is arriving at a definitive diagnosis
- Therefore, biopsy is mandatory and should be taken from most severe looking areas of involvement
  - This is sometimes difficult to determine

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Leukoplakia

- When to refer?
  - Old thought: wait two weeks to see if the lesion clears up
  - New thought: if you think the lesion may be a potentially malignant disorder, biopsy or refer for biopsy immediately
- Where to refer?
  - I refer oral potentially malignant lesions to an oral surgeon or periodontist if I do not feel comfortable performing the biopsy myself
  - One can refer to an oral pathologist, but ensure that person does their own biopsies before referral (also insurance considerations here we will not get into)
- With few exceptions, oral pathology labs like mine will ship biopsy kits including formalin, paperwork, return mailing, etc. for free almost anywhere in the country

Lingen MW, Abt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. JADA. 2017;148(10):712-727.

Ashley Clark Exceptions®

Leukoplakia

- After the biopsy report comes back, you will have a diagnosis…now what?
- Hyperkeratosis/acanthosis: follow-up every 6 months and re-biopsy if the lesion changes
- Mild dysplasia: it depends on the patient and their habits, lesion size, and clinician preferences
  - **I recommend tissue destruction**
  - Surgical excision decreases the risk of malignant transformation by half
  - If the lesion is small and the patient smokes, it may also be appropriate to re-evaluate mild dysplasia in 3 months after habit cessation to see if it regresses on its own
- Moderate dysplasia or worse: complete destruction!

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

Treatment

- Long-term (20 year!) follow-up at least every 6 months is important because recurrences are frequent and additional leukoplakias or erythroplakias may develop
- The overall recurrence rate ranges from 10-35%
  - PVL has close to 100% recurrence rate
- Recurrences should be re-biopsied to establish diagnosis
- It is important to encourage the patient to discontinue risky behaviors such as smoking cigarettes and drinking alcohol

Reichart PA, Philipsen HP. Oral erythroplakia – A review. *Oral Oncology*. 2005;41:551-561.
Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 355-390.

SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma

- Patients who develop oral SCCa are typically older white men who have been aware of an alteration in mucosa for 6 months
  - The early growth phase of SCCa is painless, which may explain the delay in seeking care
- If the oral health care professional doesn't have a high degree of suspicion, it can delay treatment and diagnosis
- There is almost always a premalignant lesion (leukoplakia, erythroplakia) before the development of outright SCCa in the oral cavity proper

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 374-389.

Squamous cell carcinoma

- There is a varied clinical appearance, including
  - **Exophytic** (mass forming, fungating) or **endophytic** (invasive, burrowing, ulcerated)
  - **Leukoplakic**, **erythroplakic**, or **erythroleukoplakic**
- The exophytic lesions have an irregular surface which is often ulcerated, can range in color from white to red, and are usually indurated (feels hard)
- Endophytic lesions usually have a central ulceration with a rolled border and are irregularly shaped

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 374-389.

Squamous cell carcinoma

- The most common locations are:
  - 1. Lateral border of the tongue
  - 2. Ventral surface of the tongue
  - 3. Floor of mouth
  - 4. Gingiva – do not forget this one!

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 374-389.

Squamous cell carcinoma

- Gingival & alveolar squamous cell carcinomas are unique
  - Usually painless
  - Can mimic benign lesions
  - Can mimic periodontal disease
  - Least association with tobacco use
  - More common in females

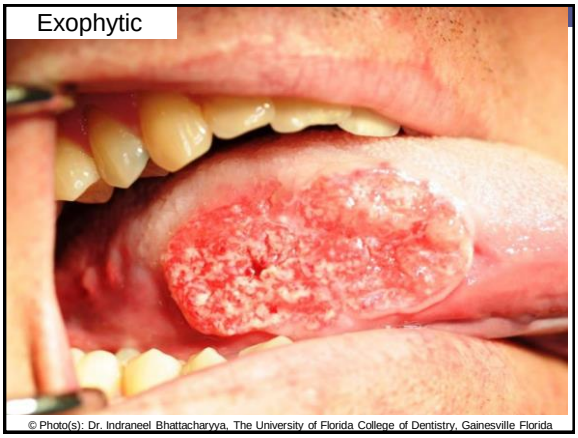
Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 374-389.
Fitzpatrick SG, Neuman AN, Bhattacharyya I, Cohen DC. The Clinical and Histologic Presentation of Gingival Squamous Cell Carcinoma: A Study of 519 Cases. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012; 114(4):509-15.

Squamous cell carcinoma

- Metastatic spread is largely via lymphatics; the dental professional will most commonly find metastatic spread by palpating the cervical lymph nodes
- Nodes will be enlarged, firm, painless, and possibly fixed
- The treatment plan is to recognize the lesion and refer to an oral surgeon for biopsy

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pp 374-389.

Exophytic

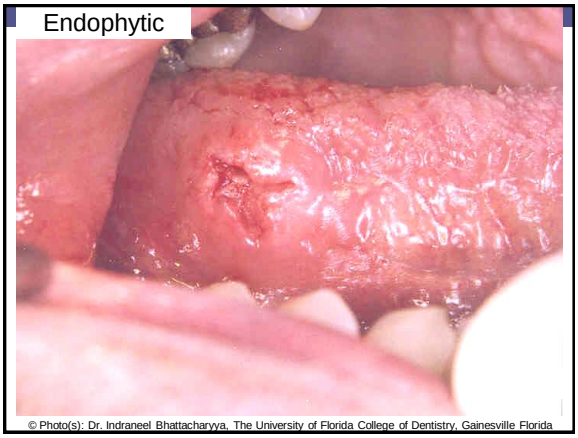


© Photo(s): Dr. Indraneel Bhattacharyya, The University of Florida College of Dentistry, Gainesville Florida

Exophytic

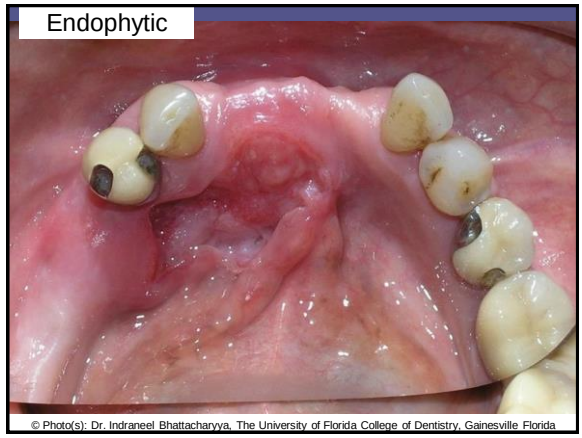
© Photo(s): Dr. Ashley Clark, University of Texas School of Dentistry Houston, Texas

Endophytic



© Photo(s): Dr. Indraneel Bhattacharyya, The University of Florida College of Dentistry, Gainesville Florida

Endophytic

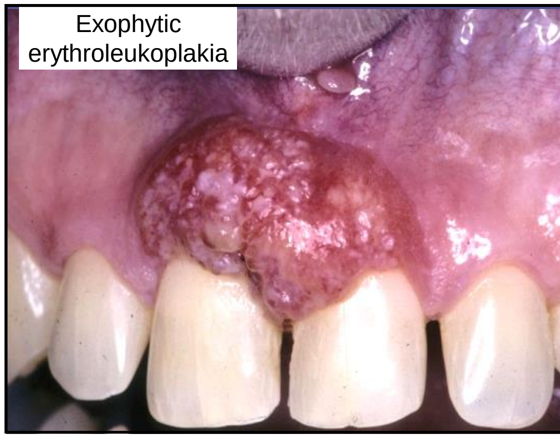


© Photo(s): Dr. Indraneel Bhattacharyya, The University of Florida College of Dentistry, Gainesville Florida

Ulcerated erythroleukoplakia

© Photo(s): Dr. Ashley Clark, University of Kentucky College of Dentistry

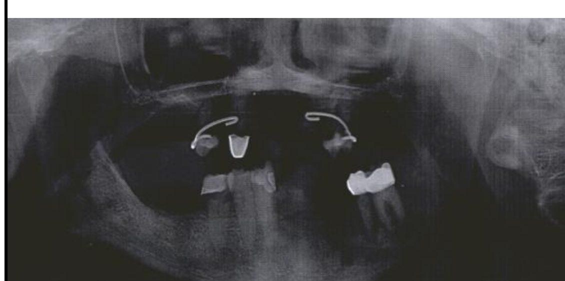
Exophytic erythroleukoplakia



© Photo(s): Dr. Ashley Clark, University of Texas School of Dentistry Houston, Texas

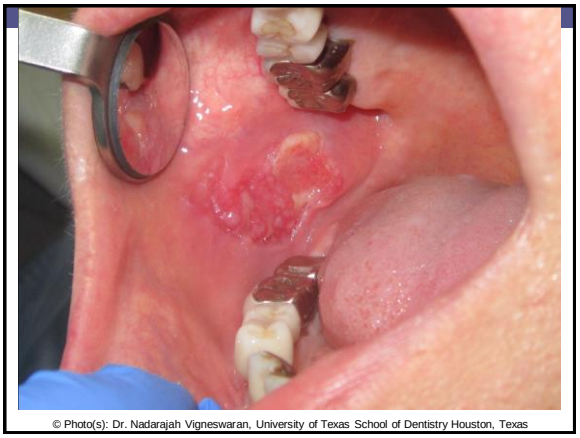
© Photo(s): Dr. Ashley Clark, University of Texas School of Dentistry Houston, Texas

© Photo(s): Dr. Ashley Clark, University of Texas School of Dentistry Houston, Texas



© Photo(s): Dr. Ashley Clark, University of Texas School of Dentistry Houston, Texas

© Photo(s): Dr. Indraneel Bhattacharyya, The University of Florida College of Dentistry, Gainesville Florida

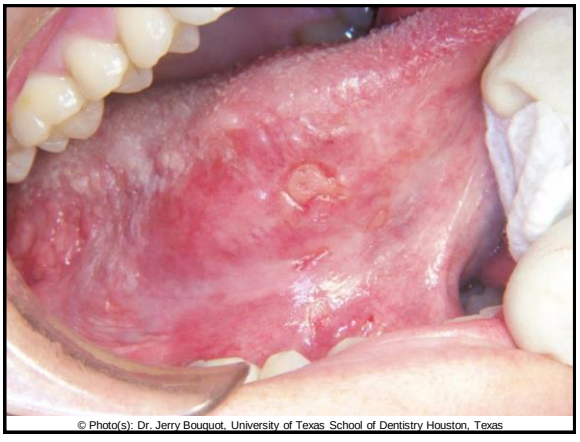


© Photo(s): Dr. Nadarajah Vigneswaran, University of Texas School of Dentistry Houston, Texas

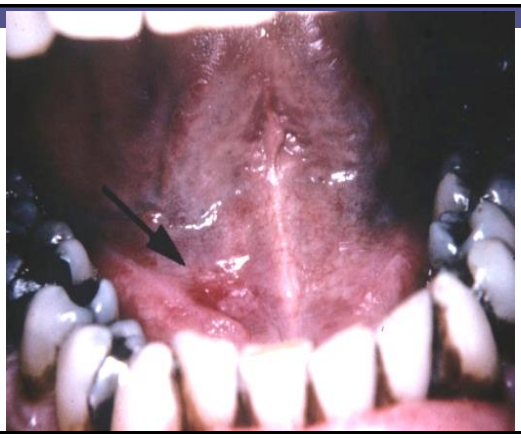
© Photo(s): Dr. Indraneel Bhattacharyya, The University of Florida College of Dentistry, Gainesville Florida

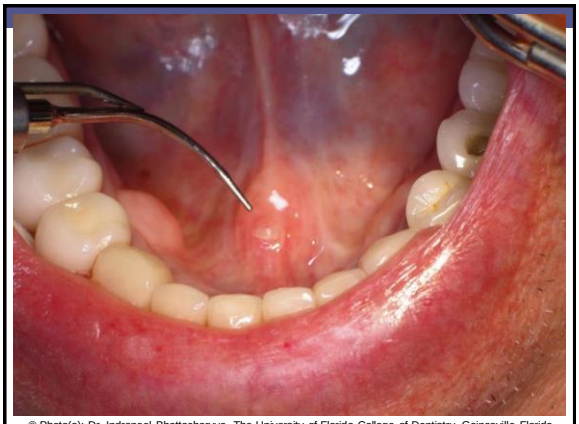
© Photo(s): Dr. Nadarajah Vigneswaran, University of Texas School of Dentistry Houston, Texas

© Photo(s): Dr. Indraneel Bhattacharyya, The University of Florida College of Dentistry, Gainesville Florida



© Photo(s): Dr. Jerry Bouquot, University of Texas School of Dentistry Houston, Texas





How can we decrease risk?

- Smoking cessation and vaccination!
- The role of the dentist in tobacco cessation:
  - 1. Screen every patient for use
  - 2. Document tobacco status
  - 3. Advise users to quit
    - Cessation medication, counseling, assistance, follow-up, referral
- The 5 As:
  - 1. Ask about tobacco use
  - 2. Advise to quit
  - 3. Assess willingness to quit
  - 4. Assist in quitting
  - 5. Arrange follow-up

Fiore MC, Bailey WC, Cohen SJ et al (The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives). A Clinical Practice Guideline for Treating Tobacco Use and Dependence: A US Public Health Service Report. *JAMA*. 2000. 283(24):3244-3254.

Smoking cessation

- Possible pharmacological cessation tools:
  - Nicotine replacement therapy (NRT) – works for 17.6%
  - Bupropion (Wellbutrin® or Zyban®) – works for 19.1%
  - Varenicline (Chantix®) – works for 27.6%
  - **Varenicline with NRT works for 31.5%**
  - Placebo worked for 10.6%

Cahill K, Stevens S, and Lancaster T. Pharmacological Treatments for Smoking Cessation. *JAMA*. 2014. 311(2):193-194.

How can we decrease risk?

- Smoking cessation and vaccination!
- Three vaccines are (or have been) available for the prevention of high-risk HPV
  - Gardasil for women and men (quadrivalent originally) - 2006
  - Gardasil-9 for women and men (9-valent; **recommended**) - 2014
  - Cervarix for women (bivalent) – 2009
- To be used before patient is sexually active; recommended age is to start the 2 or 3 shot series between ages 11-12

Petrosky E, Bocchini Jr JA, Hariri S, et al. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2015;64(11);300-304.

Virus Like Particles (VLPs) are artificial nanostructures that resemble a virus
They do not contain genetic material
They cannot cause HPV infection

https://www.creative-diagnostics.com/news-recombinant-hpv-l1-vlp-68.htm

Takeaways

- Up to 1 in 200 patients have oral dysplasia
- Screen every patient, every time
- Dysplasia carries a significant risk for malignant transformation
  - This risk increases for severe dysplasia or worse
- Surgical excision decreases the risk of malignant transformation but does not eliminate it
  - Therefore, long-term follow-up is required; the literature suggests a minimum of 20 years
- Limited data is available for HPV-associated oral intraepithelial neoplasia; it has been reported to have about a 20% malignant transformation rate

Woo S-B, Cashman EC, and Lerman MA. Human papillomavirus-associated oral intraepithelial neoplasia. *Modern Pathology*. 2013;26:1288–1297.

Mehanna HM, Rattay T, Smith J, et al. Treatment and Follow-Up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck*. 2009;31(12):1600-1609.

QUESTIONS?

Ashley.Clark.DDS@uky.edu