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## POTENTIALLY MALIGNANT DISORDERS – A FOCUS ON PREVENTION

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Ashley Clark, DDS, FACD, FICD, FAAOMP

Diplomate, American Board of Oral and Maxillofacial Pathology

Vice President, CAMP Laboratory

AshleyClarkDDS@gmail.com

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### Conflicts of interest & disclaimers

- Conflicts of interest: None
- The opinions expressed in this presentation are those of the speaker and not necessarily those of my lab.
- The opinions expressed in this course should not be construed as advice to care for specific patients.

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### Objectives

- Upon completion of this course, the participant should be able to:
  - Determine areas of the oral cavity that are high-risk for potentially malignant disorders
  - Recognize how potentially malignant conditions present in the oral cavity
  - Determine an appropriate treatment plan when potentially malignant conditions are discovered

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### Potentially malignant disorders

- The WHO adopted the phrase "potentially malignant disorders" to describe lesions with potential to progress to malignancy
- Terminology has changed; "pre-malignant" was formerly used
  - This term fell out of favor because it suggests these lesions eventually undergo malignant transformation, though some do not

Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;125:612-627.

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### Potentially malignant disorders

- Oral entities associated with an increased risk of squamous cell carcinoma are numerous and include:
  - Leukoplakia (and proliferative verrucous leukoplakia, or PVL)
  - Erythroplakia (and erythroleukoplakia)
  - Actinic cheilitis
  - Oral submucous fibrosis
  - Smokeless tobacco keratosis
  - Oral lichen planus
  - Dyskeratosis congenita
  - Fanconi anemia
  - Nicotine stomatitis in people who reverse smoke
  - Others!

Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018;125:612-627.

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### Potentially malignant disorders

- Clinically, most of these are red patches or red and white patches
  - 2.5% of Americans will have leukoplakia
- Therefore, we will focus on these entities

Mahanna HM, Kettay T, Smith L, et al. Treatment and Follow-up of Oral Dysplasia – A Systematic Review and Meta-Analysis. *Head & Neck.* 2009;31(12):1650-1659.

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## LEUKOPLAKIA

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## Leukoplakia

- 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, lichen planus, and etc. are not leukoplakias
- Lesions tend to change overtime; they don't always remain white
  - The more "red" they get, the greater the chance of malignant transformation
  - The red lesions are more difficult to detect (IMO!)
- A clinical term; leukoplakia is never a diagnosis
  - This means you will not receive a biopsy report from me with "leukoplakia" on the diagnosis line

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Tobacco pouch keratosis; not leukoplakia



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Frictional keratosis, not leukoplakia



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## Leukoplakia

- Leukoplakia comprises 85% of oral potentially malignant disorders, though not all progress to SCCa
- Dysplastic epithelium or squamous cell carcinoma (SCCa) is seen in 20% of biopsy samples of clinical leukoplakia
  - This means 80% are benign hyperkeratosis
- Malignant transformation potential is 5% to 50%, depending on clinical subtype
  - The overall malignant potential of leukoplakia is ~10%

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

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

Seeght PA, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:613-617.

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## 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
  - 70% of leukoplakias are found on the lip vermillion, buccal mucosa, and gingiva
  - 90% with dysplasia or carcinoma are found on the lip vermillion, lateral/ventral tongue, floor of mouth

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### Leukoplakia

- Thin leukoplakia represents the earliest lesions and 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

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Thin leukoplakia; hyperkeratosis



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Thin leukoplakia; mild dysplasia



© Photo(s): Dr. Kara Holt, Holt Family Dental, DeLand, Texas

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Thin leukoplakia; mild dysplasia




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



© Photo(s): Dr. Louis Halkias

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## 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

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## Thick leukoplakia; mild dysplasia

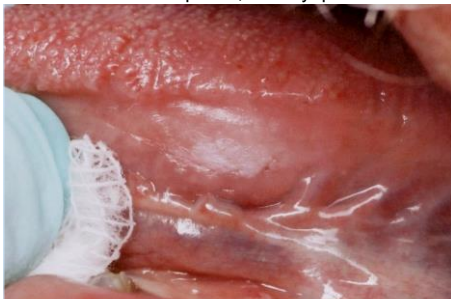


## Thin leukoplakia; hyperkeratosis

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## Thick leukoplakia; mild dysplasia



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## Thick leukoplakia; mild to focally moderate dysplasia



© Photo(s): Dr. David Nasselsker (top), Dr. Ashley Clark (bottom)

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## Thick leukoplakia; mild dysplasia with hyperkeratosis



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## 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

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Verruciform leukoplakia; severe dysplasia



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Verruciform leukoplakia; atypical epithelial proliferation



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## 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

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Erythroleukoplakia; moderate dysplasia



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Erythroleukoplakia – severe dysplasia



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Erythroleukoplakia – squamous cell carcinoma



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## 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

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## 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, etc.)

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

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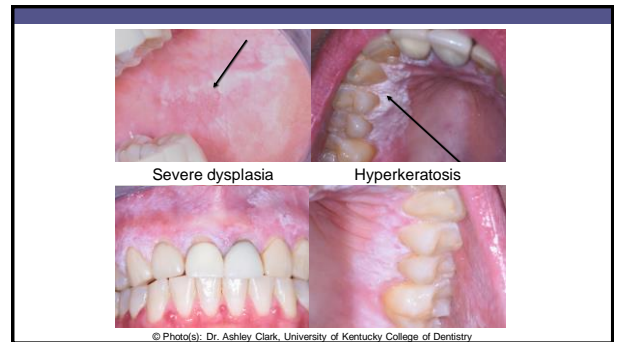
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## Leukoplakia

- 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

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## ERYTHROPLAKIA

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## Erythroplakia

- Defined as a red patch that cannot be diagnosed as any other condition
- Causes are unknown, but they are assumed to be the same as leukoplakia/SCCa
  - Tobacco and alcohol; high-risk HPV
- The good news: erythroplakia is not as common as leukoplakia (probably around 0.1% of Americans)
- The bad news: True erythroplakias are never completely benign and 90% show severe dysplasia or worse on biopsy
- Therefore, even though these lesions are not common, we MUST recognize them clinically

Reichart PA, Philipson 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; Pg 355-390.

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## Erythroplakia

- Erythroplakia predominantly occurs in asymptomatic middle-aged to older adults (the average age is 70) with no gender predilection
- Most common locations:
  - Floor of mouth
  - Soft palate
  - Ventral tongue
- Some studies suggest that the most common place for erythroplakia to occur in females is the gingiva
  - Ashley Clark Remark: these lesions can mimic many other forms of pathology so please do not ignore them!

Reichart PA, Philipson 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; Pg 355-390.

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## Erythroplakia

- The altered mucosa is usually a well-demarcated, less than 1.5 cm macule or plaque with a velvety texture
  - The mucosa may also have a granular surface
- The lesion is soft in the dysplastic phases and becomes indurated when it progresses to squamous cell carcinoma
- Lesions are red in color due to epithelial thinness and the lack of keratin
  - This lets underlying vasculature show

Reichart PA, Philipson 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; Pg 355-390.

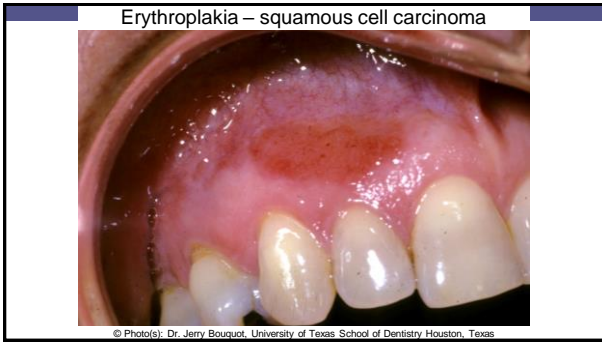
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## Erythroplakia

- Biopsy is mandatory for erythroplakia
- Treatment is guided by definitive diagnosis
- Recurrence and multifocal oral involvement is common; therefore, long-term follow up at least every 6 months is required
  - I typically recall patients every 3 months for at least the first year

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

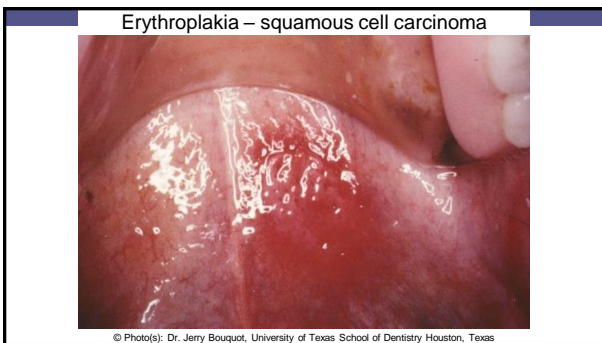
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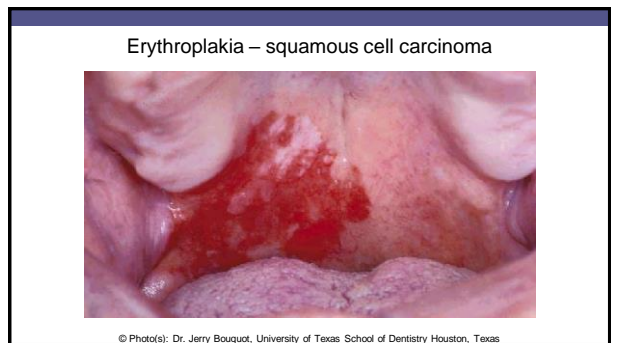
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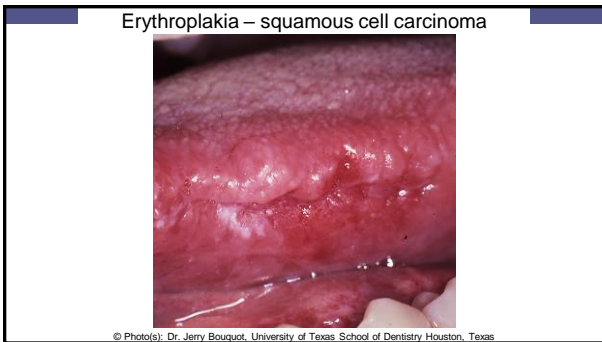
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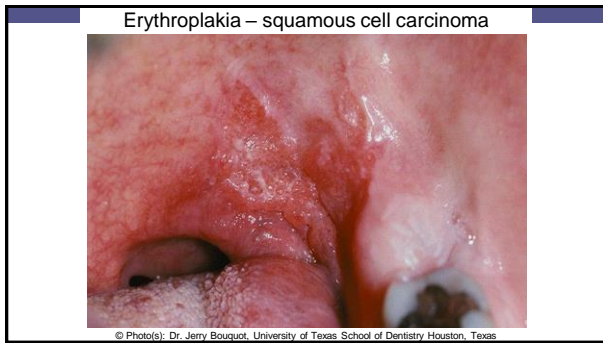


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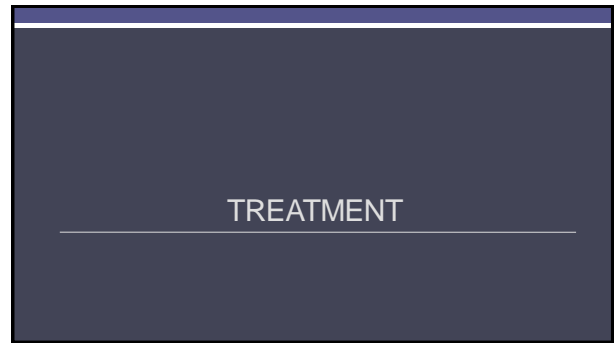


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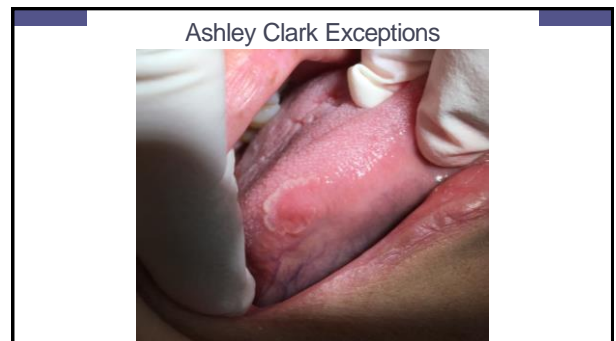
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Treatment

- 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 typically 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)
- With few exceptions, oral pathology labs 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.

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Treatment

- The biopsy will be evaluated by an oral pathologist
- What does your report mean?
- The differential diagnosis is:
  - Hyperkeratosis and/or acanthosis
  - Mild dysplasia
  - Moderate dysplasia
  - Severe dysplasia
  - Carcinoma-in-situ
  - Verrucous carcinoma
  - SCCa

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Treatment

- 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
  - recommend tissue destruction
- Leukoplakia with moderate epithelial dysplasia or worse warrants complete destruction of tissue

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology: Fourth edition. Elsevier, Inc.: St. Louis, Missouri. Pg 355-350.

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## Treatment

- Long-term 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%, though verruciform or granular leukoplakias recur 85% of the time
- Some studies show a recurrence rate of over 70% for erythroplakia
- 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

Reichert PA, Phillips HP. Oral erythroplakia - A review. *Oral Oncology*. 2005;41:555-561.  
Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology* Fourth edition. Elsevier, Inc. St. Louis, Missouri. Pp 355-390.

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## Treatment

- 12% of leukoplakias become SCCa, usually within 4 years
- Thin leukoplakia seldom becomes malignant without clinical change
- Thick leukoplakia transforms up to 7% of the time
- Verruciform leukoplakia transforms up to 15%
- Erythroleukoplakia transforms up to 50%
- Most cases of erythroplakia are already carcinoma in situ or SCCa
- PVL progresses in up to 100% of cases

Neville B, Damm D, Allen C, et al. *Oral and Maxillofacial Pathology*: Fourth edition. Elsevier, Inc.: St. Louis, Missouri; Pp 355-390.  
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.  
Speight PM, Khouram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;125:612-627.

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## Treatment

- Factors that decrease the risk for malignant transformation:
  - Surgical excision (decreases risk by half)

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.

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## Treatment

- Things to ponder: in a study of about 5,000 in California spanning 8 years:
  - Leukoplakia was associated with a 40.8-fold increased risk of oral cancer and a 5-year absolute risk of 3.3% (1 in 30 individuals progressing to cancer over 5 years)
  - Only a minority of oral cancers (<5%) were preceded by a documented clinical diagnosis of leukoplakia
    - We aren't doing a good job screening!
    - The American Dental Association recommends a visual and tactile examination of the oral mucosa on all dental visits
  - The authors concluded that, as previously mentioned, all leukoplakias require biopsy upon discovery

Chaturvedi AK, Malhotra N, Engels EA, et al. Oral Leukoplakia and Risk of Progression to Oral Cancer: A Population-Based Cohort Study. *JNCI Natl Cancer Inst*. 2010;102(10):728-734.

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## Potentially malignant disorders

- Takeaways:
  - Up to 1 in 200 patients have oral dysplasia
  - 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

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.

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## 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

Flore 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*. 2010; 283(24):3244-3254.

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## 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.

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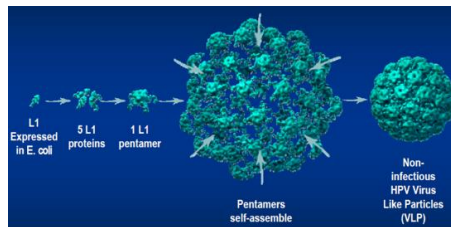
## How can we decrease risk?

- 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

Petrovsky E, Bouchimi J, 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):305-304.

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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-bioproducts.com/news-recombinant-hpv-11-vlp-68.htm>

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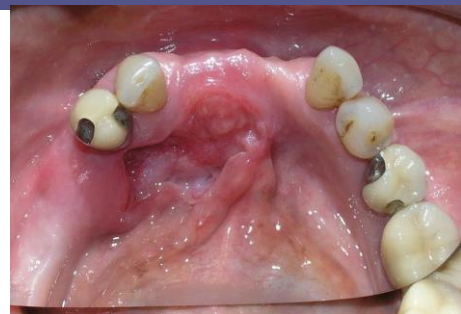
## HPV-positive SCCa

- A salivary diagnostic test became available for office use in Feb 2010
  - Rinse with sterile saline for 30 seconds
  - Expectorate into collection tube
  - PCR analysis & report generated by company
- Pros: Non-invasive and user-friendly
- Cons: ADA Center for EBD does not recommend, not FDA approved, most people who test positively for the virus will never have disease, unclear treatment plan if patient does not have a visible lesion

<https://www.oralcare.com/oral-lyp-testing.html>  
<https://www.doi.gov/10.1093/infdis/jiv008>  
Lingen MW, Alt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. JADA. 2019;148(10):712-727.

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## CLINICAL IMAGES



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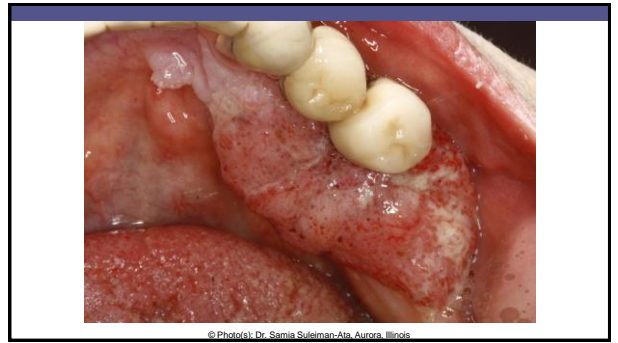
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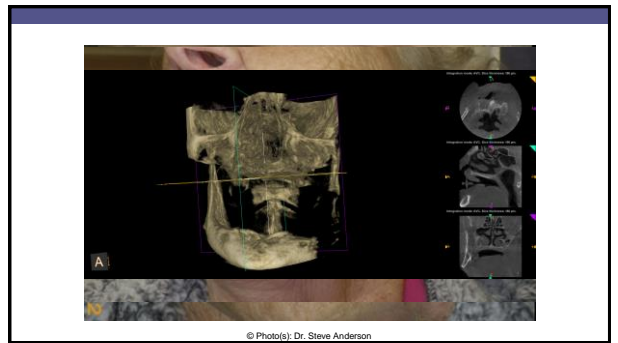
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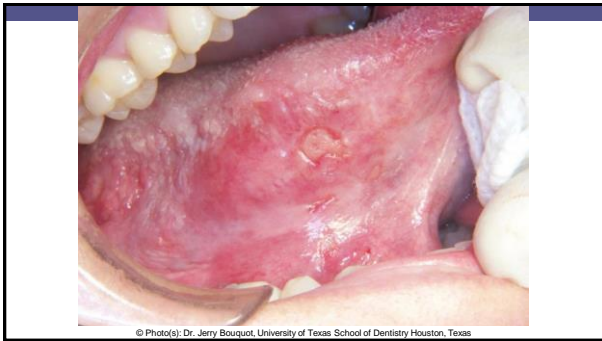
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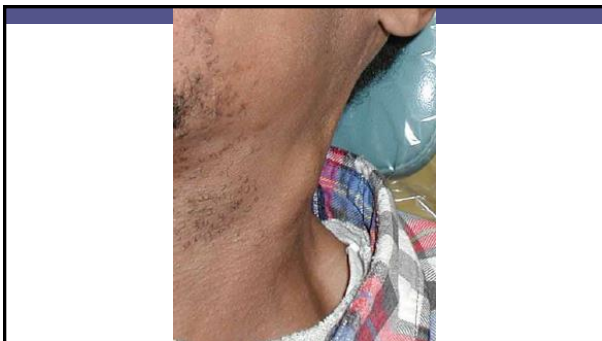
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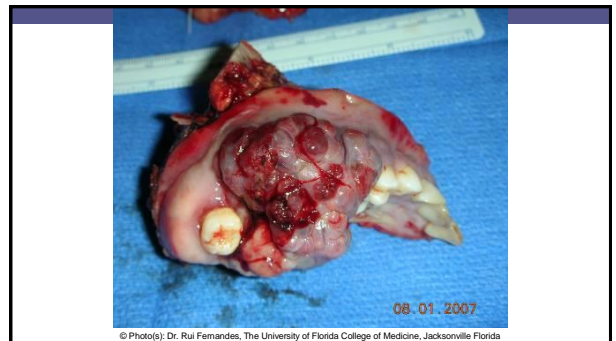
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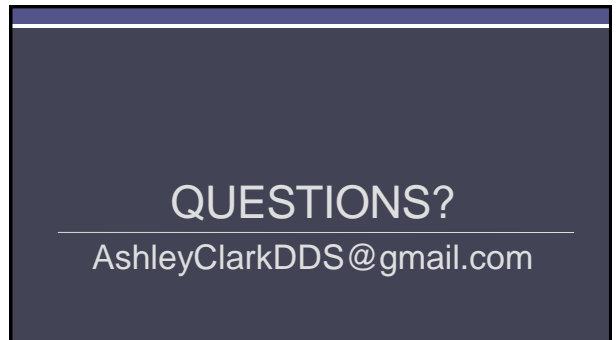
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