


**Nebraska Dental**  
ASSOCIATION



**ORAL CANCER**

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Conflicts of interest & disclaimers

- Conflict of interest: None
- The opinions expressed in this presentation are those of the speaker and not 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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Course objectives

- Upon completion of this course, you will be able to:
  - Determine where oral cancer is most likely to occur
  - Discuss differences between human papillomavirus-driven oropharyngeal squamous cell carcinoma (SCCa) and conventional SCCa
  - Determine when and where to refer patients

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Oral cancer

- ~53K people in the United States will be diagnosed with oral or oropharyngeal cancer this year
  - ~10K patients will succumb to disease
- 2:1 M:F with an average age of 62
- Squamous cell carcinoma (SCCa) is the most common type of oral cancer by far (~85%)
  - The second most common are malignant salivary gland tumors (~6.5%)
  - The third most common are lymphomas (~4.5%)

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

<https://pubmed.ncbi.nlm.nih.gov/30483319/>

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Introduction

- 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
  - HPV-negative with unknown etiology (not tobacco/alcohol)
    - Even in patients under 30 who smoke or drink, the duration of exposure is insufficient to account for SCCa development
  - The literature states the risk for oral cancer increases after 21 years of smoking

Uwehlym CO, Lindtner K, Bell J, et al. An analysis of risk factors for oral cancer in young people: a case-control study. *Oral Oncol*. 2024;40:304-313.

Terry JF, 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*. 2012;47:146-152.

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## 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

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

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## Etiology

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

Neufil B, Gorman D, Allen C, et al. *Oral and Maxillofacial Pathology: Fourth Edition*. Elsevier Inc.; St. Louis, Missouri; Pg 305-308.

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## Etiology – human papillomavirus

- Common, highly transmissible virus with over 140 types
- 40 affect oral mucosa; 15 can lead to cancer

No risk	High risk
2 – verruca vulgaris	16
4 – verruca vulgaris	18
6 – condyloma	31
11 – condyloma	33
13 – Heck disease	45
32 – Heck disease	35, 51, 52, 56, 58, 59

Centers for Disease Control and Prevention (CDC). CDC Grand Rounds: Reducing the Burden of HPV-Associated Cancer and Disease. *MMWR Morbidity and Mortality Weekly Report*. 2014;63(04):69-72.  
Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers—United States, 2004-2008. *MMWR Morbidity and Mortality Weekly Report*. 2012; Apr 20;61:258-64.

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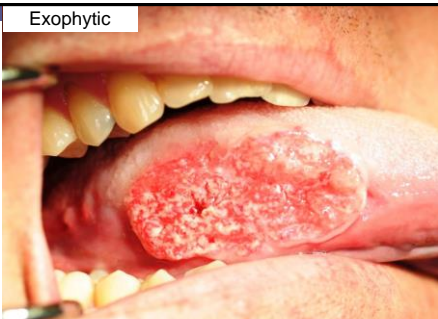
## Clinical features

- HPV-negative SCCa starts as a PMD
- Early lesions cause minimal pain, which may delay care
  - The average time the patient is aware of the lesion is 4-8 months
- The clinical presentation varies for the intraoral lesions; the lesion may be exophytic or endophytic, leukoplakic or erythroplakic, or a combination
- Lesions are typically indurated (feels hard)

Neufil B, Gorman D, Allen C, et al. *Oral and Maxillofacial Pathology: Fourth Edition*. Elsevier Inc.; St. Louis, Missouri; Pg 305-308.

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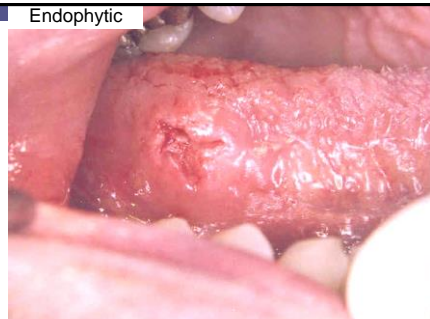
Exophytic



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

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Endophytic



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### Clinical features

- The most common sites are:
  - Posterior lateral tongue
  - Ventral tongue
  - Floor of mouth
  - Gingiva
- Other sites of involvement, in decreasing order:
  - Buccal mucosa
  - Labial mucosa
  - Hard palate

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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### Clinical features

- Gingival carcinomas are unique:
  - Mimic benign and reactive lesions!
  - Arise from keratinized mucosa
  - Least associated with tobacco smoking
  - More common in females
  - Can cause tooth mobility
    - May go unnoticed until the tooth is extracted and the lesion proliferates out of the socket, where it looks clinically similar to granulation tissue

Neville B, Damm D, Allen C, et al. Oral and Maxillofacial Pathology, Fourth Edition. Elsevier, Inc.; St. Louis, Missouri; Pg 355-390.  
Fitzpatrick SG, Neuman AN, Bhattacharyya I, Cohen DC. The Clinical and Histologic Presentation of Gingival Squamous Cell Carcinoma: A Study of 539 Cases. Oral Surg Oral Med Oral Pathol. 2012; 114(4):509-15.

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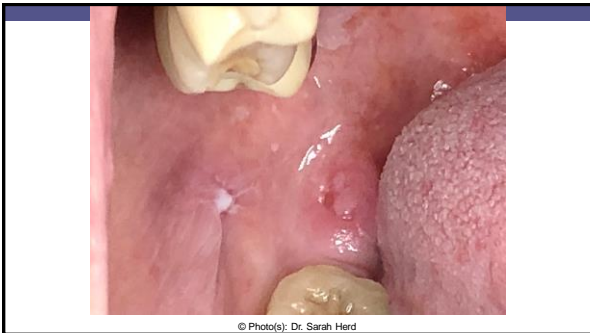
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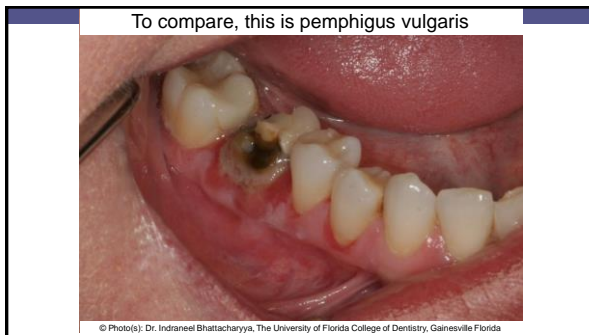
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### Clinical features

- Sites included in “oropharyngeal carcinoma” include:
  - Soft palate
  - Base of tongue
  - Tonsillar region (tonsil/fossa/pillars) – up to 80% of cases
  - Posterior pharyngeal wall
- Most of these SCCAs will test positively for HPV

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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### Clinical features

- SCCAs affecting the oropharyngeal area have the same basic look as those affecting the oral cavity if they get large enough
- They are more difficult to visualize and may go unnoticed
- ~80% have metastasized at the time of diagnosis
- Presenting symptoms include sore throat and pain or difficulty swallowing

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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### HPV-positive vs HPV-negative SCCa

<u>HPV-negative tumors</u>	<u>HPV-positive tumors</u>
<ul style="list-style-type: none"> <li>• 95% of patients have a history of long-term exposure to tobacco and alcohol</li> <li>• Almost always evidence of pre-malignancy (leukoplakia/erythroplakia)</li> </ul>	<ul style="list-style-type: none"> <li>• Develops independently of tobacco or alcohol exposure</li> <li>• No pre-malignant phase has been demonstrated</li> </ul>

Petrylla KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. Oral Oncol. 2014;16:380-386.

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### HPV-positive vs HPV-negative SCCa

- Incidence of HPV-negative oropharyngeal cancer decreased by 50% from 1988-2004, correlating with a decline in smoking
- HPV-positive oropharyngeal cancer increased 225% during the same period
- HPV-driven oropharyngeal cancer is more prevalent than cervical cancer

<https://www.cdc.gov/cancer/hpv/statistics/headneck.htm> <https://www.cdc.gov/cancer/hpv/statistics/cervical.htm>  
Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. J Clin Oncol. 2011;29(32):4264-4301.

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## HPV-positive SCCa

- HPV is the most common sexually transmitted disease
  - Point prevalence = **43-62%** in genital samples
  - ~**100%** of sexually active people will have HPV at some point
  - ~**98%** of those infections undergo spontaneous resolution in 2 years
- Changes in human sexual behavior are likely the driving force behind the HPV-positive oropharyngeal cancer epidemic

Centers for Disease Control. Ready-to-use STD Curriculum for Clinical Educators: Genital Human Papillomavirus (HPV) Module. 2013.

Petryak RB, Durrum KB, Savage DM. Epidemiology of HPV-associated oropharyngeal cancer. *Oral Oncol*. 2024;152:380-386.

Centers for Disease Control and Prevention (CDC). Human papillomavirus-associated cancers - United States, 2004-2008. *MMWR Morbidity and Mortality Weekly Report*. 2012 Apr 20;61:258-61.

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## HPV-positive SCCa

- In 1950s, of approximately 6000 surveyed, fewer than 40% of women and 50% of men engaged in some form of oral sex
- As of 2010: 89% for women and 91% for men
- ~30% of single, sexually active people use condoms regularly (this drops to 3% during oral sex)

Kinsey AC, Pomeroy WB, Martin CE. *Sexual Behavior in the Human Male*. Philadelphia Pa: W. B. Saunders; 1948.

Kinsey AC, Pomeroy WB, Martin CE, et al. *Sexual Behavior in the Human Female*. Philadelphia Pa: W. B. Saunders; 1953.

Saichittar S, Chandra A, Liddell N, et al. Prevalence and Correlates of Heterosexual Anal and Oral Sex in Adolescents and Adults in the United States. *J Infect Dis*. 2007;196(12):1852-1859.

Herbenick D, Reisco M, Schick V, et al. Sexual Behavior in the United States: Results from a National Probability Sample of Men and Women Ages 14-94. *J Sex Med*. Special Issue: Findings from the National Survey of Sexual Health and Behavior (NSSHB) Center for Sexual Health Promotion, Indiana University. 2017;7:245-265.

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## HPV-positive SCCa

- HPV prevalence in oropharyngeal tumors was 16.3% from 1984-1989 and **72.7%** from 2000-2004
- HPV-positive patients are more likely to be younger, male, and white
- **The most commonly affected group are white males between the ages of 40-59**
  - Compared to HPV-negative, which tend to be diagnosed in older men (60s+)
  - No other group saw an increased incidence; however, this group saw an **annual 10% increase in incidence from 2000-2004**

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.

Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol*. 2008;26:613-9.

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## HPV-positive SCCa

- A 2011 article that accurately predicted HPV-positive oropharyngeal SCCa would outpace cervical cancer estimated oropharyngeal carcinomas would constitute approximately half of all head and neck cancers by 2030

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.

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## Oropharyngeal SCCa

- Currently: Around 19,700 people are diagnosed with HPV-driven oropharyngeal cancers each year, according to information published by the CDC

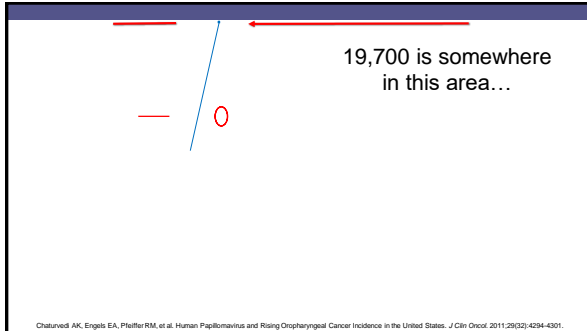
National Program of Cancer Registries SEER\*Stat Database: U.S. Cancer Statistics Incidence Analytic file 1998-2017. United States Department of Health and Human Services, Centers for Disease Control and Prevention. Released June 2020, based on the 2019 submission.

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Oropharyngeal  
(HPV-driven)  
carcinomas

Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.

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### Treatment

- SCCa of the lower lip are treated by surgical excision
  - Advanced cases may be treated by radiation + chemotherapy
- SCCa of the upper lip are rare; these patients may also undergo neck dissection
- Early lesions of intraoral, HPV-negative SCCa are treated with surgery
- Moderately advanced SCCAs are treated with surgery and possibly radiation therapy and chemotherapy
- Advanced lesions where surgical excision is not possible are treated with radiation and/or chemotherapy

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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### Treatment

- Other indications for post-surgical radiation  $\pm$  chemotherapy:
  - Close or positive margins on the resected tumor
  - High-grade histopathologic features
  - Extracapsular spread
  - Perineural or lymphovascular invasion

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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### Treatment

- Patients with intraoral SCCa almost always undergo radical, modified, or selective neck dissection
  - Radical neck dissection used to be preferred; it is removal of the lymphatics of the lateral triangle of the neck along with the internal jugular vein, submandibular gland, sternocleidomastoid muscle, and spinal accessory nerve
  - Modified = preserve the non-lymphatic structures
  - Selective = removal of only select cervical lymph node groups

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### Treatment

- For oropharyngeal squamous cell carcinoma:
  - Early-stage SCCa is treated by radiation therapy or surgery
  - Most cases are discovered at an advanced stage and require surgery, radiation therapy, and/or chemotherapy

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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### Prognosis

- HPV-positive cancers have an improved response to chemotherapy and radiotherapy
- 5-year survival rates:
  - HPV-positive: 75-80%
  - HPV-negative: 45-50%
- Overall, HPV-positive patients have a 69% reduction in risk of death compared with HPV-negative patients

Ang KK, Harris L, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *N Engl J Med*. 2010; 363:24-35.  
Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301.  
Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinoma in the United States. *J Clin Oncol*. 2008;26:612-9.

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## How can we decrease risk?

- Smoking cessation and vaccination!
- 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 SZ 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*. 2016; 315(24):3044-3234.

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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 E, and Lancaster T. Pharmacological Treatments for Smoking Cessation. *JAMA*. 2014; 311(2):103-104.

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## Smoking cessation

- Nearly 30% experience nausea, trouble sleeping, or headache
- Patients with renal impairment need a medical consult
- Some patients have experienced adverse cardiovascular events
- Varenicline can interact with alcohol; patients should be encouraged to reduce or eliminate alcohol consumption
- Warning: some patients taking varenicline have "serious neuropsychiatric events" which include depression and suicide

<http://labeling.pfizer.com/ShowLabeling.aspx?id=557855.3>  
Jorsten DE, Hays T, Rigotti NA, et al. Efficacy of Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, vs Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomized Controlled Trial. *JAMA*. 2006; 296(11):156-63.

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## How can we decrease risk?

- Smoking cessation and vaccination!
- Vaccines:
  - Gardasil for women and men (original quadrivalent) - 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

Petrocchi E, Bochini JJ, Harris S, et al. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. *MMWR*. Morbidity and Mortality Weekly Report. 2015;64(13):360-364.

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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-bionics.com/news/innovations-how-it-works-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

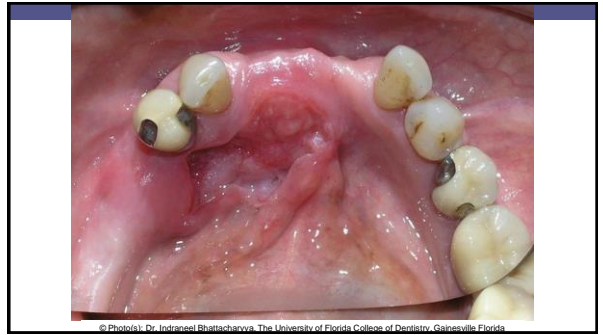
<https://www.orabio.com/oral-hpv-testing.html>  
<https://www.cdc.gov/eid/content/vol16/number04/16-0413.htm>  
Lingen MW, Alt E, Agrawal N, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity. *JADA*. 2017;148(10):712-727.

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CLINICAL IMAGES

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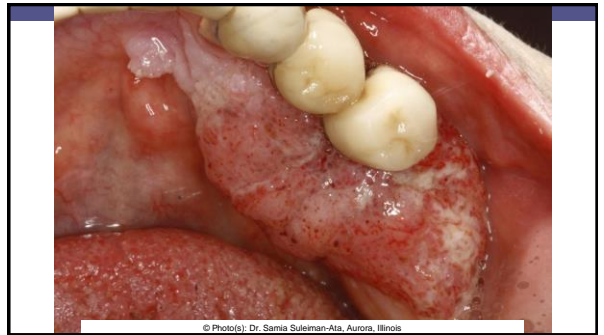
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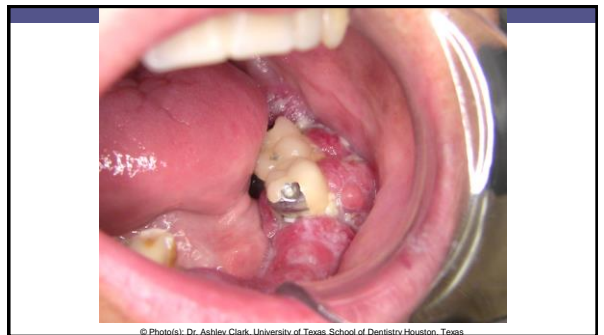
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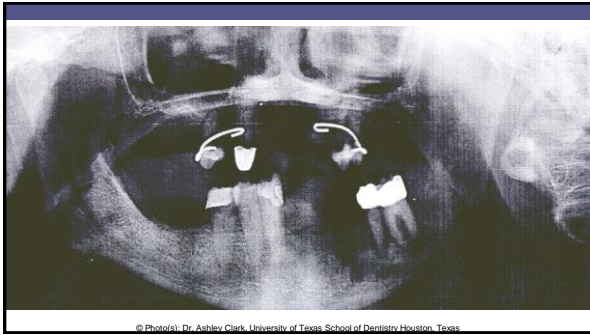
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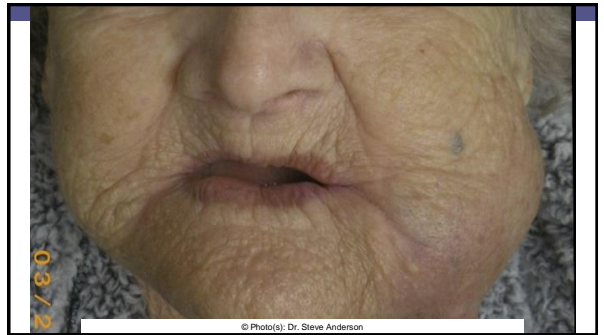
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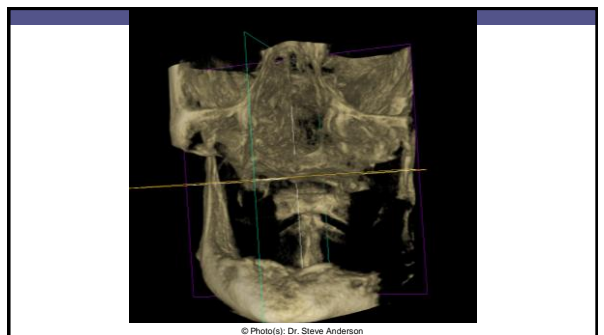
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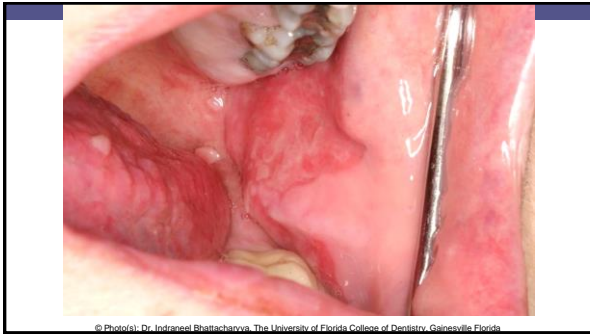
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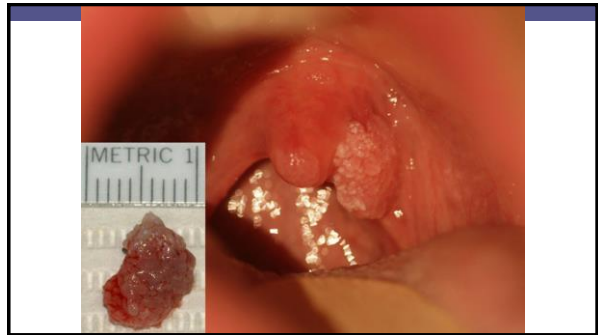
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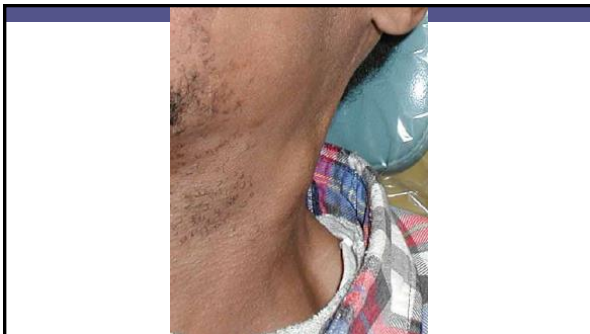




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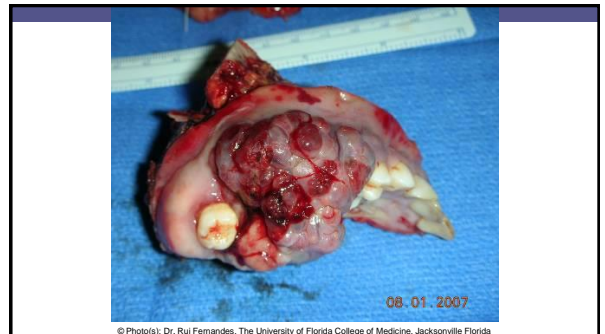
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CONCLUSIONS &  
QUESTIONS

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