Overview

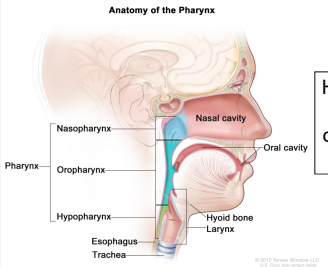
- Discuss features of oral cancer that affect survival.
- Discuss emerging information on HPV-related oropharyngeal cancer.
- Discuss soft tissue pathology.
- Diagnostic approaches for ulcers and vesiculo-erosive lesions.
- Discuss common unilocular and multilocular radiolucencies.

Oral Cancer: Features that Affect Survival

- Prevention
- Early Detection
- Staging and Treatment selection
- Recurrence and metastasis

- Future directions?

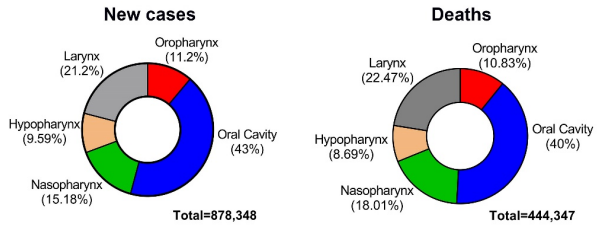
Head and Neck Cancer



Head and neck cancers usually arise from squamous cells that line the oral cavity, oropharynx, nasopharynx and hypopharynx.

Source: PDQ Screening and Prevention Editorial Board. Oral Cavity, Oropharyngeal, Hypopharyngeal, and Laryngeal Cancers Prevention (PDQ®): Health Professional Version. 2021 Oct 15. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65979/

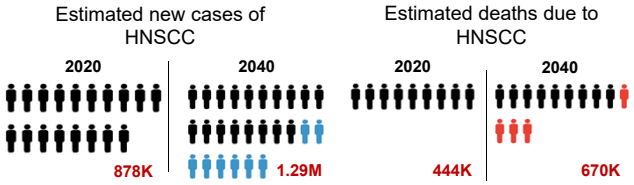
Head and Neck Cancer



GLOBOCAN, 2020

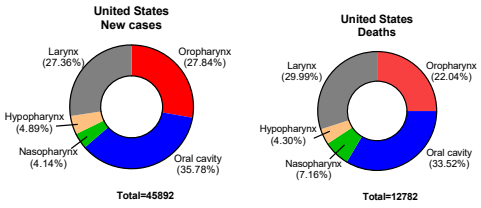
Lim and D'Silva, *Oncogene* 2024

Head and Neck Cancer



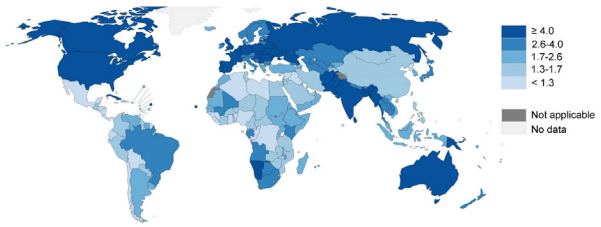
GLOBOCAN, 2020

Head and Neck Cancer in the USA



GLOBOCAN, 2020

Oral Cavity Cancer

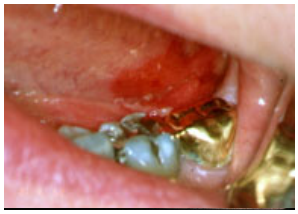


GLOBOCAN, 2020

Lim and D'Silva, *Oncogene* 2024

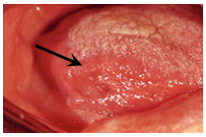
SCC – Clinical Features

- Exophytic (fungating, papillary, verruciform)
- Endophytic (invasive, ulcerated)
- Leukoplakia
- Erythroplakia



Oral cavity cancer - Risk factors

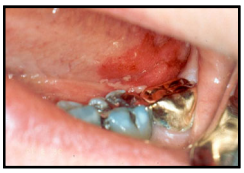
- Tobacco-
  - 80% of patients with oral cancer are smokers.
- Alcohol
  - Synergistic effect with tobacco.
- Risks are dose- and time-dependent.



Bouvard et al, International Agency for Research on Cancer, NEJM 2022

Oral Cavity Cancer

- Late detection.
- Debilitating treatment.
- Treatment selection.



Late detection! Why?

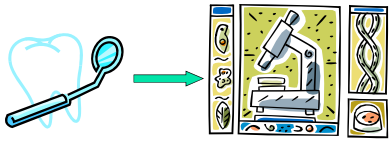
- Cancers may look innocuous; benign lesions may look aggressive.
- Access to dental care.
- Lack of public awareness.
- Some high risk areas are poorly visualized.
- Frequency of screening – only 13% of Americans report having an oral cancer exam in prior year (Horowitz, JADA 2001).

Requirements for screening tests

- Can be performed chair side.
- Objective.
- False negative and false positive results do not occur i.e. 100% specificity.
- If cancer is present, it will be detected. i.e. 100% sensitivity.
- Predictive of biologic behavior.

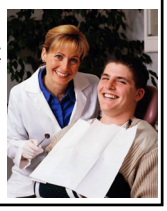
Oral Cavity Cancer: Detection methods

- Clinical exam
- Brush biopsy
- Toluidine blue
- Vizilite
- Velscope
- Biopsy

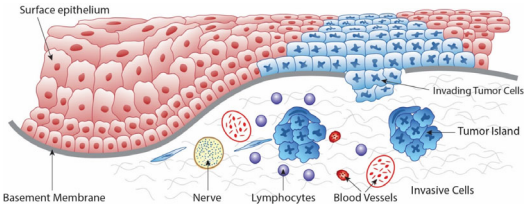


Clinical Exam - Indications

- Routine part of dental and medical check-ups.
  - Tell your patient what you are doing and why – practice builder.
  - History of alcohol or tobacco use?
  - Look for changes in CTSA: color, texture, swelling, abnormalities.
  - Clinically suspicious lesions – biopsy right away. Otherwise - follow-up. If more than 2 weeks duration → biopsy.
  - High risk sites – ventro-lateral tongue, lips, floor of mouth, soft palate.



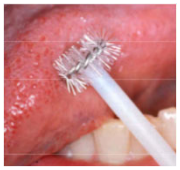
Histopathology

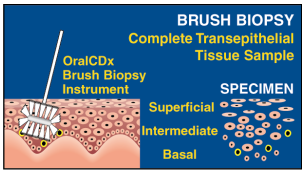


Adapted from: Inglehart et al, *Oral Oncology* 2014

Oral Cdx Brush Biopsy

- Description:
  - Variant of oral exfoliative cytology
  - Special barbed brush
  - Samples disaggregated cells from all layers of epithelium including basal cell layer.

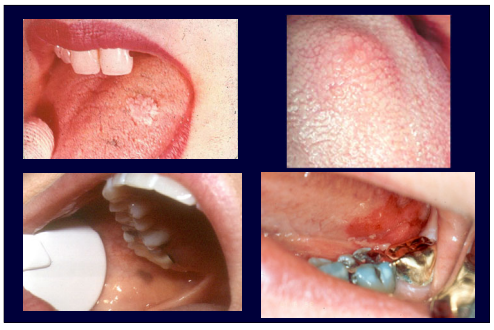




Oral Cdx Brush Biopsy: Indications

- Assessment of "minimally suspicious" white lesions in low risk sites that you would likely have "ignored in the past" !?
- <u>Not for submucosal, pigmented, suspected inflammatory or ulcerated lesions</u>
- Severely medically compromised patient who may be at risk for a conventional biopsy?
- Monitor suspicious areas in a patient with previous oral cancer?
- Non-compliant patient who may not return for follow-up.
- Patient with multiple lesions.

Oral CDx NOT indicated for:



Toluidine Blue

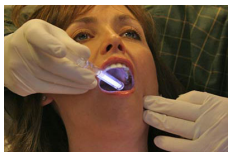
- Oratest™
- Screening test
  - Assess clinically suspicious lesions.
  - Help to map biopsy sites.
- Not a diagnostic test
  - Doesn't tell you what "lesion" is
- Not FDA approved for use by itself
- FDA approved in conjunction with Vizilite

Toluidine Blue: Indications

- Recommended (by manufacturer) for:
  - monitoring of suspicious lesions that have baseline histopathological evaluation.
  - screening in high risk individuals.
  - routine follow-up of patients with history of oral cancer.
  - determining optimal biopsy site for large, heterogeneous lesions.

Vizilite

- Screening test
  - "Whether Bx needed"
  - "Where to do Bx"
  - Detect lesions not seen under visible light?
- Not a diagnostic test
  - Doesn't tell you what it is.



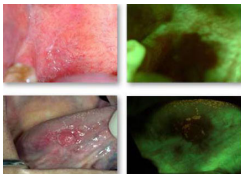
VELscope- Background

- Fluorescence visualization in oral cavity.
- Takes 1-2 min.
- Adjunct to clinical exam. Good baseline understanding of normal is essential.
- For surgeon to help identify margins (clinically).
- No rinses or stains.
- FDA approved.

Lingen et al, Oral Oncology, 2007 Critical evaluation of diagnostic aids for the detection of oral Cancer.

VELscope – Results

- Suspicious areas
  - Very dark.
  - High risk location
  - Unilateral presentation
  - Asymmetry, irregular shape.



Summary of screening tests

Test	Principle	Drawbacks
Routine clinical exam	Visual exam, palpation	Poor visualization of high risk areas.
Toluidine blue vital staining	Binds to nuclei with high DNA, RNA as in malignant cells.	High incidence of false positives; detects reactive, inflammatory lesions.
Autofluorescence	Autofluorescence upon exposure to lasers varies between normal and cancer tissue.	Detects pigmented, reactive, inflammatory lesions.

D'Silva and Ward, Alpha Omegan 2008

Summary of screening tests

Test	Principle	Drawbacks
Oral Brush Biopsy	Scrapes all 3 layers of oral epithelial cells, stained and cytology studied for atypical changes.	Reactive lesions may exhibit atypical cells.
Chemiluminescence	Dehydrates cells with acetic acid thereby highlighting cells with increased nuclear to cytoplasmic ratios (dysplastic, cancerous) as whitish.	Detection of reactive, inflammatory, and benign lesions.

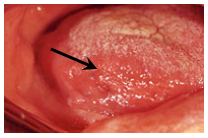
"Cytologic testing appears to be the most accurate adjunct among those included in this review. The main concerns are the high rate of false-positive results and serious issues of risk of bias and indirectness of the evidence. Clinicians should remain skeptical about the potential benefit of any adjunct in clinical practice."

Lingen et al, JADA, 2017 148 (11): 797-813.

Oral Cavity Cancer - Prevention

- Primary - cessation
  - Risk for oral cancer reduces after cessation.
  - Risk decreases with longer duration of abstinence.
    - Approached that of never smoker at ~20 years.
- Secondary - screening
  - Clinical oral exam

    "no better screening alternative"



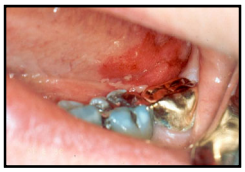
Bouvard et al, International Agency for Research on Cancer, NEJM 2022

Acknowledgements (Diagnostic Tests)

- NIDCR website
- https://www.nidcr.nih.gov/health-info/oral-cancer/more-info#causes
- Drs. Paul Edwards, Peter Polverini.
- Websites for Oral CDx, Vizilite, Velscope.
- Lingen et al, Oral Oncology, 2007. Critical evaluation of diagnostic aids for the detection of oral Cancer.
- Lingen et al, JADA, 2017. Adjuncts for the evaluation of potentially malignant disorders in the oral cavity

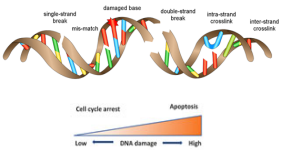
Oral Cavity Cancer

- Late detection.
- Debilitating treatment.
  - Surgery
  - Radiation
  - Chemotherapy
  - Immunotherapy



Treatment: Radiation

- Ionizing Radiation
  - Conventional
  - Intensity modulated radiation therapy (IMRT)



  - DNA damage
  - Single agent or multi-modal
  - Increase limited by toxicity

Treatment: Chemotherapy

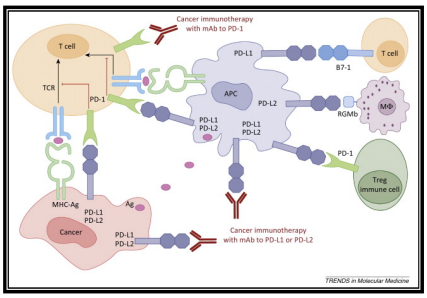
- Cisplatin: DNA damage
- Fluorouracil: anti-metabolite
- Paclitaxel (Taxol™): anti-mitotic

Creative commons

- Not single agent; adjunct or palliative
- Increase limited by toxicity

Treatment: Immunotherapy

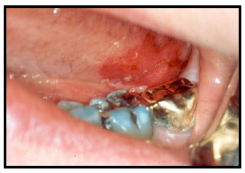
- Using the body's immune response to combat cancer.
- Pembrolizumab (anti-PDL1).
- Nivolumab (anti-PD1).



Ohaegbulam, 2015 Trends in Mol Med

Oral Cavity Cancer

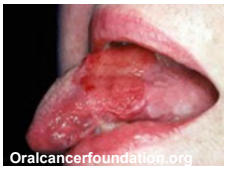
- Late detection.
- Debilitating treatment.



- Treatment selection.
  - Tumor stage
  - Lymph nodes
  - Depth of Invasion
  - Perineural invasion

Lymph Node Involvement

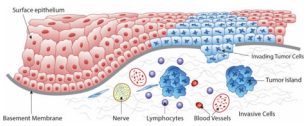
- AJCC 8th edition
- Extracapsular spread/ extranodal extension
  - Upstages pathologic N category
- Occult lymph node involvement



American Joint Committee on Cancer staging manual, 2018
Ettinger et al, Oral Maxillofac Surg Clin N Amer 2019.

Depth of Invasion

- DOI correlates with risk of lymph node metastasis.
- Incorporated into AJCC TNM 8th ed staging system.
- Horizontal line from basal layer in adjacent histologically normal epithelium; perpendicular line from this to depth.
- Every 5mm → increases T stage
  - <5 mm T1
  - 5-10 mm T2
  - >10 mm T3/T4



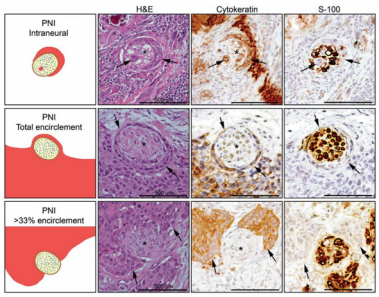
American Joint Committee on Cancer staging manual.
Ettinger et al, Oral Maxillofac Surg Clin N Amer 2019.

Perineural Invasion

- Important in multiple cancers.
- Adverse risk predictor.
- Challenge to eradicate → likelihood of metastasis.
- Poor survival
- Clinical Manifestations
  - Sensory disturbances, pain.
- Aggressive treatment.

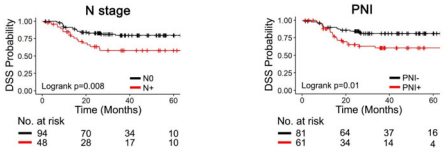
Schmitd et al, 2018
Chinn et al, 2013
Liebig et al, 2009

What is Perineural Invasion?



Liebig et al, 2009 'close proximity to nerve and involving at least 33% of its circumference or tumor within any three layers of the nerve sheath'.

PNI is an independent predictor of poor prognosis in SCC



Schmitd, Perez et al, *Clinical Cancer Research* 2022

Oral Cancer: Recurrence and Metastasis

- Greater depth of invasion
- Perineural invasion
- Moderately or poorly differentiated SCC
- Lymphovascular invasion

American Joint Committee on Cancer staging manual.
Subramaniam et al, Eur J Surg Oncol 2019.

Oral Cancer: Features that Affect Survival

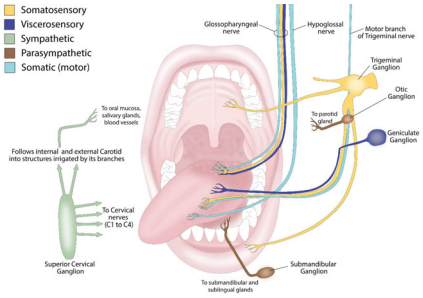
- Prevention
- Early Detection
- Staging and Treatment selection
- Recurrence and metastasis

- Future directions?

Oral Cancer Survival: Future directions

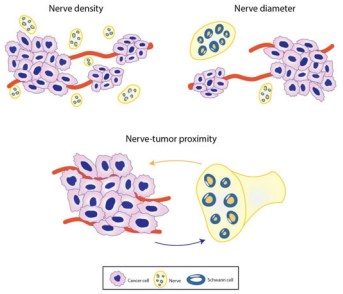
- Understanding biology
- ⇩
- Identify new biomarkers
- ⇩
- Facilitate treatment selection
- ⇩
- Improve survival.

Innervation Varies by Site in the Oral Cavity



D'Silva et al, *Advanced Biology* 2023

3Ds: Density, Diameter, and Distance Matter for Clinical Outcomes

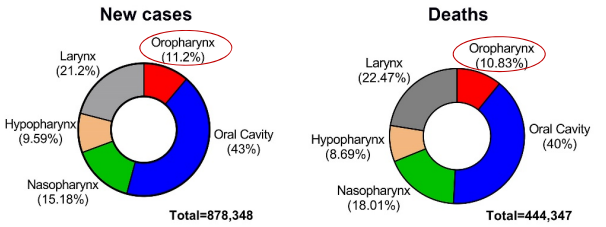


D'Silva et al, *Advanced Biology* 2023

Overview

- Discuss features of oral cancer that affect survival.
- Discuss emerging information on HPV-related oropharyngeal cancer.
- Discuss soft tissue pathology.
- Diagnostic approaches for ulcers and vesiculo-erosive lesions.
- Discuss common unilocular and multilocular radiolucencies.

Head and Neck Cancer



GLOBOCAN, 2020

Oropharyngeal Cancer

- Strongly associated with HPV16.
- Proportion of HPV-related OPSCC is rising.
  - HPV-negative, smoking-related OPSCC is falling.
  - 1980s: 16% HPV positive
  - 2000s: 73% were HPV positive.
- Incidence of HPV-positive OPSCC rising
  - From 1988- 2004: 28% increase

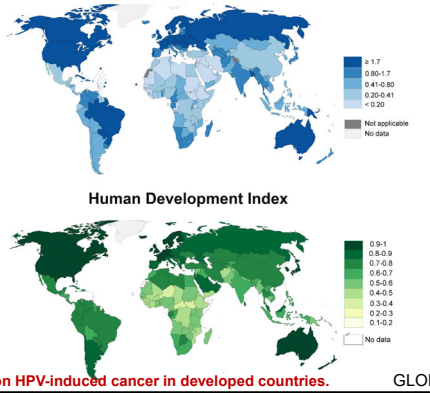
Fakhry and D'Souza, 2013 Oral Oncology

Oropharyngeal Cancer

- Global incidence escalated in high income, developed countries.
  - Due to rise in HPV infection.
- Overtaken cervical cancer to become most common HPV-associated cancer in USA, UK.

Chaturvedi et al, J Clin Oncol. 2022
Lorenzoni et al, Cancer Epid Biomarkers Preven. 2019
Mahal et al, Cancer Epid Biomarkers Preven. 2019
Faraji et al, Cancer. 2019
Jemal et al, JNCI. 2013
Lechner et al, Nat Rev Clin Oncol. 2022
Fakhry and D'Souza, Oral Oncology. 2013

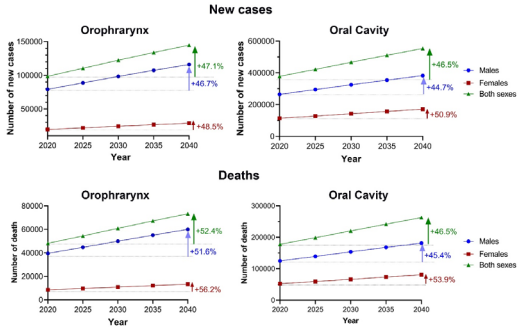
Oropharyngeal Cancer



Most common HPV-induced cancer in developed countries.

GLOBOCAN, 2020

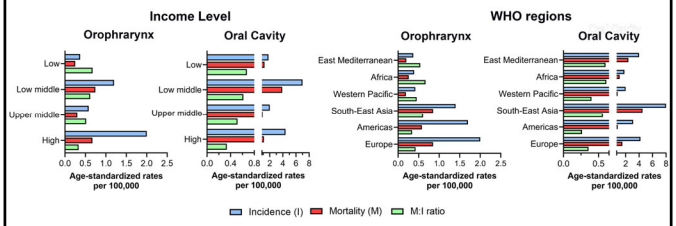
Oral Cavity and Oropharyngeal Cancer



Lim and D'Silva, *Oncogene* 2024

GLOBOCAN, 2020

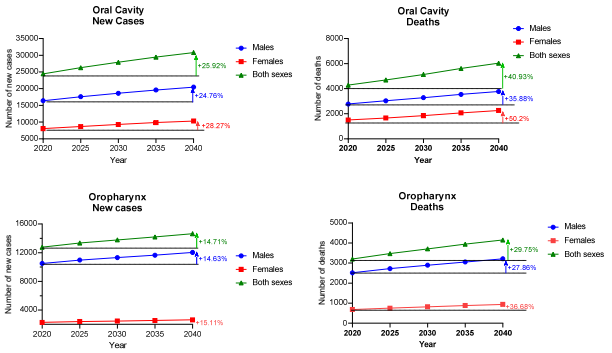
Oral Cavity and Oropharyngeal Cancer



Lim and D'Silva, *Oncogene* 2024

GLOBOCAN, 2020

Oral Cavity and Oropharyngeal Cancer - USA



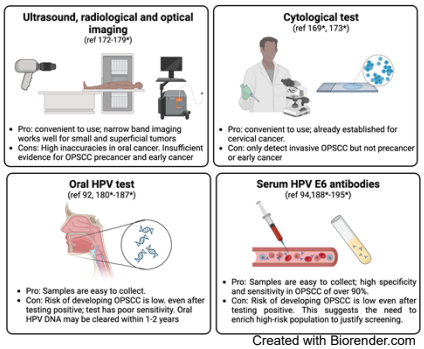
GLOBOCAN, 2020

Oropharyngeal Cancer- Clinical Features

- Linked to oral HPV infection.
- HPV+ OPSCC is distinct from classical tobacco-associated, HPV(-) OPSCC.
  - Demographics, clinical features, molecular profiles.
- HPV+ has better survival than HPV(-) OPSCC.
- Precancerous lesion not yet identified.

Lydiatt et al, ASCO Educational Book. 2018
Mahal et al, Cancer Epid Biomarkers Preveny. 2019
Fakhry et al, JNCI. 2008
Ang et al, NEJM. 2010
Lawrence et al, Nature. 2015
Seiwert et al, Clin Can Res. 2015
Sartor et al, Epigenetics. 2011

Attempts to detect Oropharyngeal Precancer



Created with Biorender.com

Lim and D'Silva, *Oncogene* 2024

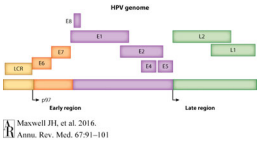
Oropharyngeal Cancer

- Men>> women
- White, younger male (50-59y), non-smokers, non-drinkers.
- Tonsils, base of tongue, soft palate, posterior pharyngeal wall.
- Most unknown primaries in HNC arise from HPV+ OPSCC.
- No recommended screening tests for HPV infection.

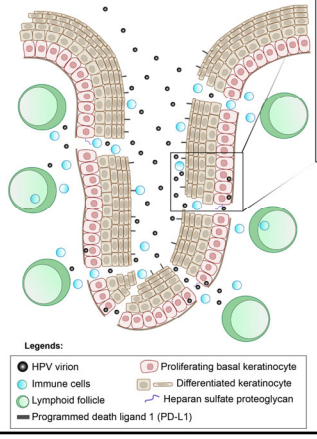
Fakhry and D'Souza, 2013 Oral Oncology.
Ettinger et al, 2019 Oral Maxillofac Surg Clin N Am.

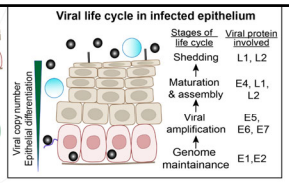
HPV16 infection

- >200 HPV types; 15 high-risk i.e. associated with cancer.
- HPV16 induces 80-90% of HPV+ OPSCC.
- Transmission via sexual contact.
- Most infections cleared in 2 years.
- Persistent high risk HPV may lead to OPSCC.
- Infection likely decades prior to clinical presentation.
- HPV oral DNA: detected up to 7 years before OPSCC diagnosis.



Lim, et al. Under review. 2023
Castellsague et al, JNCI. 2016
Ndiaye et al, The Lancet Oncol. 2014
Wierzbicka et al, Reviews in Med Virology. 2022
D'Souza et al, JNCI Cancer Spectrum. 2020
Agalliu et al, JAMA Oncol. 2016



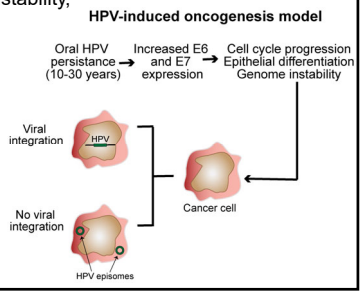


- HPV infection
- Infection of basal, mitotic cells.
  - Oropharynx: reticulated epithelium.
- Myeloid cells in crypt → permissive microenvironment, evade immunosurveillance.

Lim, et al. *Oncogene*, 2023

E6 and E7 oncoproteins

- HPV E6, E7 oncoproteins are key drivers.
- Target p53 and Rb, respectively.
- Affect: DNA repair, genomic instability, immune escape.
- Integration into host genome
  - 50-70% of OPSCC.
- Rest is episomal.



Lim, et al. *Oncogene*, 2023
Della Fera et al, *Viruses*. 2021
Koneva et al, *Mol Cancer Res*. 2018
Labarge et al, *Mol Cancer Res*. 2022

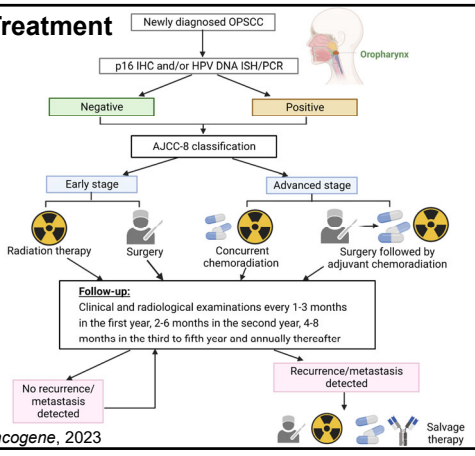
Oropharyngeal Cancer - diagnosis

- HPV detection now a clinical standard of care in oropharyngeal malignancy (*NCCN Guidelines).
- Confirmatory testing using in situ hybridization or PCR.
- Clinically, p16 positivity by IHC 95% concordance to HPV DNA positivity.
  - Discordance between these two → poorer outcomes.

*National Comprehensive Care Network

Fakhry et al, J Clin Oncol. 2018
Mehanna et al, The Lancet Oncol. 2023

OPSCC: Treatment



Lim, et al. *Oncogene*, 2023

OPSCC: Treatment response

- Better response to treatment and prognosis if HPV16+.
- ~25% progress within 2 years of standard treatment.

- No significant difference in overall survival between stages I and II or between II and III even after AJCC8.
  - other clinical variables may be relevant.

Fakhry and D'Souza, Oral Oncology 2013
Fakhry et al, JNCI 2008
Ang et al. NEJM 2010
Vijayvargiya et al, The Oncologist. 2022
Wuerdemann et al, Oncology Res and Treatment. 2017

Risk Phenotype

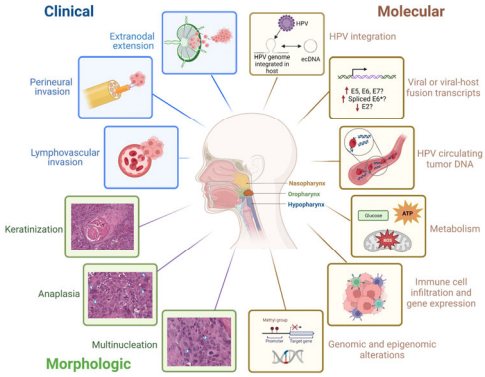
- HPV+ OPSCC, non smokers. Low risk
- HPV+OPSCC, smokers: Intermediate risk.
- HPV(-) OPSCC: High risk.

Creative commons

- Treatment de-intensification in unselected populations did not show non-inferiority.
- Suggests heterogeneity.
- Need to select low-risk patients for de-intensified treatment.

Ang et al. NEJM. 2010

Heterogenous Disease



Lim, et al. *Oncogene* 2023

HPV vaccine

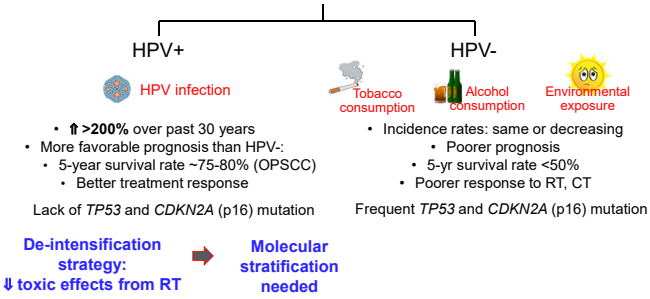
- Prevents getting new infections
- Will not clear existing infection
- Recommended age: 9-26 years.


Creative commons

- After 2045
  - Decrease in incidence of OPSCC in young, middle-aged (43-23% decrease).
  - Remains high in older individuals.

Fakhry and D'Souza, Oral Oncol. 2013
Zhang, Fakhry, D'Souza JAMA Oncol. 2021

Head and Neck Cancers



Götz, Bischof, Wolff, Kolk. Mol Clin Oncol. 2019;10:17
Chem. Res. Toxicol. 2014, 27, 4, 462–469
Chaturvedi, Engels, Pfeiffer, et al. J Clin Oncol 2011;29:4294

HPV+ vs HPV- HNSCC

	HPV+ cancer	HPV- cancer
Causes	Human papillomavirus infections	Carcinogens such as alcohol and tobacco
Demographics	Slightly younger, healthier lifestyle	Older with less healthy diet and smoking habits
Clinical Presentation	More aggressive- Poorly differentiated tumors with lymph node metastasis	Less aggressive than HPV+
Molecular profiles	• Lack of *TP53* and *CDKN2A* (p16) mutations • Overexpression of p16 • Unique TpC mutational signature due to enhanced APOEBC3 activity	Frequent loss-function mutations in *TP53* and *CDKN2A* (p16)
Incidence	↑ **~200%** over the past 20 years (especially oropharyngeal)	↓ over the past 2 years
Clinical outcomes	▪ 5-year survival rate **~60-90%** (for oropharyngeal) ▪ 5-year recurrence **10-15%** (for oropharyngeal) ▪ Better radiation therapy and chemotherapy response	▪ 5-year survival rate **~65%** ▪ 5-year recurrence **~50%** ▪ Poor response to treatment
Proposed treatment strategies	Treatment de-intensification (need for biomarker stratification)	Radiosensitizer or combined therapy

Oral Cancer: Financial burden


Creative commons

- 16,771 patients, 489 with HNC.
- Medical Expenditure Panel Survey database.
- Compared to other cancers:
  - More often members of a minority race/ethnicity.
  - Male, poor, less educated, lower health status.
  - Higher total medical expenses.
  - Higher out-of-pocket costs relative to income.
    - Highest in poor and publicly insured

Massa et al, JAMA Otolaryngology–Head & Neck Surgery. 2019

Overview

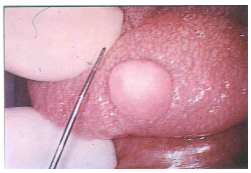
- Discuss features of oral cancer that affect survival.
- Discuss emerging information on HPV-related oropharyngeal cancer.
- Discuss soft tissue pathology.
- Diagnostic approaches for ulcers and vesiculo-erosive lesions.
- Discuss common unilocular and multilocular radiolucencies.

Exophytic Lesions

- Location?
- Sessile or pedunculated?
  - Sessile: base or attachment to normal mucosa is greatest diameter of the lesion.
  - Pedunculated: attachment to normal mucosa is smaller than greatest diameter of the lesion.
- Single or Multiple?
- Soft or hard on palpation?
- Pigmented or same color?

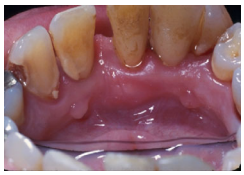
Localized enlargements of the tongue

- 1) Benign/ reactive/ developmental.
  - Squamous papilloma
  - Irritation fibroma
  - Granular cell tumor
  - Salivary gland tumors
  - Pyogenic granuloma
  - Mucocele
- 2) Malignant
  - Squamous cell carcinoma
  - Mucoepidermoid carcinoma



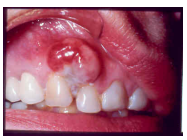
Multiple nodules

- Small, bilateral, smooth surfaced, papulonodular, pink.
- Gingival, lingual to teeth 22 and 27.
- Retrocuspid papilla
- Variant of normal



Metastatic disease to the oral cavity

- Uncommon site for mets → sign of widespread mets.
- 1st indication of malignancy: 18% - 25% cases
- Jaws >> soft tissues (2:1)
- Jaw symptoms → Pain, paresthesia, swelling
- Attached gingiva – most common soft tissue site; resembles a hyperplastic lesion.
- Diagnosis is challenging.

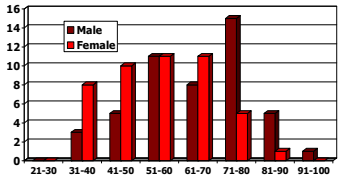


Hirshberg et al., Oral Oncol 2008.

Owosho et al, 2016 J Craniomaxilofac Surg

Metastatic disease to the jaws

- Equivalent gender distribution
- Earlier presentation in women.
- Breast – most common primary site
- Mandibular predilection
- Pain, paresthesia



D'Silva et al. JADA, 2006.

Flat Lesions

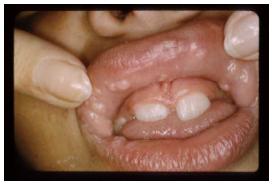
- Location?
- Macule or plaque?
- Single or Multiple?
- Pigmented or same color?

Focal gingival/ alveolar enlargements that are pigmented

- 1. Benign/ reactive/ developmental
  - a) Blood
  - b) Melanin
  - c) Superficial cyst
  - d) Foreign body reaction
- 2. Malignant
  - a) Blood
  - b) Melanin

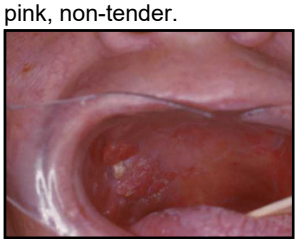
Multiple papillary lesions: Verruca vulgaris (wart)

- Children
- Skin, especially hands.
- Oral : vermillion, labial mucosa, anterior tongue.
- Papule, nodule → papillary or pebbly
- Pedunculated or sessile
- Usually white, <5 mm. Multiple lesions common.



Condyloma acuminatum (venereal wart)

– 20% of all sexually transmitted diseases.
– Occurs at site of sexual contact, trauma.
– Teenagers, young adults.
– Labial mucosa, soft palate, lingual frenum.
– Multiple, clustered, sessile, pink, non-tender.



Overview

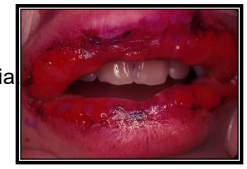
- Discuss features of oral cancer that affect survival.
- Discuss emerging information on HPV-related oropharyngeal cancer.
- Discuss soft tissue pathology.
- Diagnostic approaches for ulcers and vesiculo-erosive lesions.
- Discuss common unilocular and multilocular radiolucencies.

Ulcers: features to consider

- Persistent? If yes, →
  - Chronic trauma
  - Chronic infection, e.g. syphilis, TB
  - Neoplasia e.g. squamous cell carcinoma
  - Vesiculobulous disease e.g. pemphigoid
- Single or multiple?
  - Multiple, non persistent: aphthous ulcers.
  - Multiple, persistent: vesiculobullous disease, GI disease, immune defect.

Common causes of ulceration

- Traumatic: mechanical, chemical, thermal, electrical.
- Idiopathic: Aphthous stomatitis.
- Infectious: viral (herpes), bacterial, fungal
- Dermatologic diseases
- Drugs: e.g. cytotoxic, NSAIDs.
- Blood disorders: e.g. neutropenia
- Systemic disease: e.g. Crohn's.
- Neoplasia: e.g. OSCC



When is a biopsy indicated?

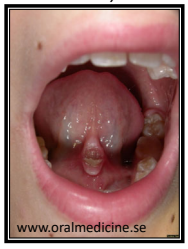
- Single, persistent ulcer >2-3weeks, no signs of healing.
- Ulcer with induration (firmness).
- Ulcer with concurrent skin lesions.
- Ulcer with concurrent lesions on other mucosae.
- Ulcer with systemic signs and symptoms but not herpetic.

Traumatic Ulcer

- Due to acute or chronic trauma.
- Surface ulcers, usually heal within days.
- Ulcerated region with covering fibrinopurulent membrane and surrounding eyrthema.

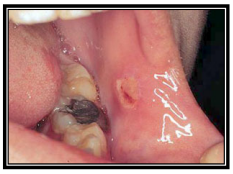
Traumatic Ulcer

- Clinical presentation usually suggests cause; e.g. adjacent to irritant.
- Tongue, lips, buccal mucosa (adjacent to teeth).
- Gingiva, palate, mucobuccal fold (toothbrush trauma?)



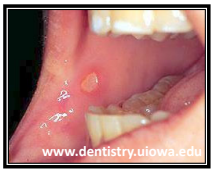
Traumatic Ulcer

- Treatment
  - Remove irritant.
  - Pain relief.
  - **Biopsy** if underlying cause is not identified or if ulcer persists after 10 d of removal of irritant.

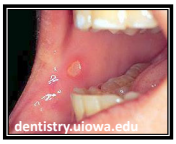


Aphthous stomatitis (canker sores)

- Recurrent aphthae - ~20% of the population.
- Etiology unclear.
  - Stress
  - Higher likelihood if parents also have RAS.
  - Aphthae-like ulcers occur in immunodeficient individuals.
  - Decreased mucosal barrier



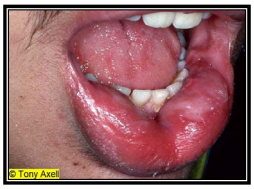
Minor Aphthous Ulcers



- Few recurrences, short duration; non keratinized mucosa.
- Starts as red macule and symptoms of burning, itching or stinging.
- Yellow-white membrane, surrounding erythema.
- 3-10 mm in diameter, heal without scarring.
- 7-14 days.
- 1-5 lesions per episode. Pain disproportionate to size of lesion.

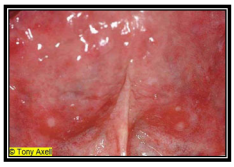
Major Aphthous Ulcers

- 1-3 cm in diameter, deeper lesions than minor.
- Longer duration; 2-6 weeks to heal.
- 1-10 lesions
- Labial mucosa, soft palate, tonsillar fauces.
- Onset after puberty. Recur for 20 years.
- Scar formation.



Herpetiform Aphthous Ulcers

- Resembles primary herpes.
- More lesions, greater recurrence frequency than major or minor.
- Usually non keratinized movable mucosa.
- Female >>> male; adults.
- 1-3 mm in diameter; up to 100 ulcers in single episode.
- Lesions may coalesce.
- Heal in 7-10 d, recurrences closely spaced.

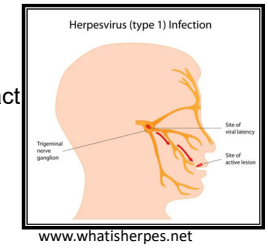


Aphthous stomatitis (canker sores)

- Treatment suggestions
  - Topical anesthetic for pain.
  - Topical corticosteroids.

HSV

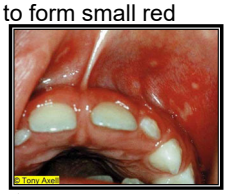
- DNA virus
- HSV1 → infections in the oral, facial and ocular areas.
- HSV2 → genital region.
- Clinical lesions from both types are identical.
- Antibodies against one cross-react with other.



www.whatisherpes.net

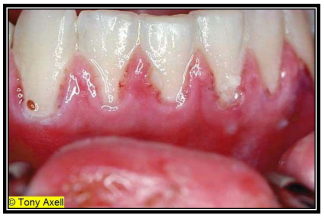
Acute herpetic gingivostomatitis (primary herpes)

- Young, asymptomatic, no significant morbidity.
- Virus goes to ganglia, remains latent.
- Several pinhead vesicles; collapse to form small red lesions.
- Enlarge, develop central ulceration with fibrin.
- Ulcers coalesce.
- Movable and attached mucosa.
- Gingiva: enlarged, painful, erythematous.



Acute herpetic gingivostomatitis

- Free gingival margin exhibits punched-out erosions.
- Labial lesions may extend to vermillion.
- Vesicles may occur in perioral skin.
- Primary infection in adults may exhibit pharyngotonsillitis.
- Mild cases resolve in 5-7 days.
- Severe case resolve in 2 weeks.



Recurrent herpes simplex infections

- At site of primary inoculation or in adjacent area of surface epithelium.
- Herpes labialis – most common recurrent herpetic lesion.
  - Also known as cold sore or fever blister.
- Herpetic whitlow – infection of thumbs or fingers, may be due to self-inoculation.

Herpes Labialis

- 15-45% of population have h/o herpes labialis.
- Prodromal symptoms:
  - 6-24 h before lesions
  - Pain, burning, itching, tingling, warmth, erythema.
- Clusters of fluid-filled vesicles.
- Rupture and crust in 2d.
- Heal in 7-10d.

Herpes simplex infections

- Often a clinical diagnosis.
- Otherwise viral isolation from fluid of intact vesicles. But, intraoral vesicles rupture early.

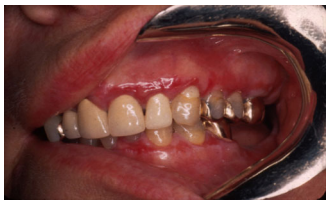
- Management suggestions
  - Antiviral medication during first 3 symptomatic days.
  - Avoid autoinoculation.

Vesiculoerosive Lesions

- Erosive lichen planus
- Mucous membrane pemphigoid,
- Pemphigus vulgaris

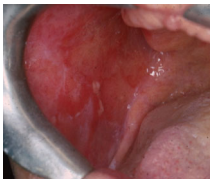
Erosive lichen planus

- Symptomatic.
- Atrophic erythematous areas with central ulceration.
- White striae at periphery.



Erosive lichen planus

- "Seen more frequently" than reticular LP because symptomatic.
- Peripheral radiating striae.
- Usually bilateral on buccal mucosa.
- If only gingiva → desquamative gingivitis.
- Red, atrophic areas with central ulceration.
- Severe → epithelial separation presenting as bullous LP.

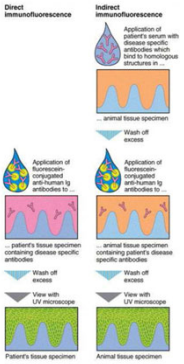


Lichen Planus

- Diagnosis
  - Reticular lichen planus
    - No symptoms →clinical diagnosis and no treatment, periodic follow-up.
  - Erosive LP or unilateral lesions → biopsy.
- Treatment (erosive LP)
  - Generalized lesions → steroid suspension/rinse
  - Localized lesions → topical steroids
  - Recalcitrant lesions: systemic steroids

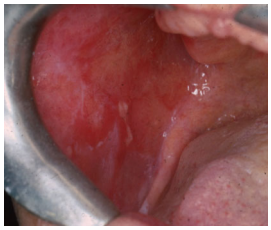
Direct and Indirect Immunofluorescence

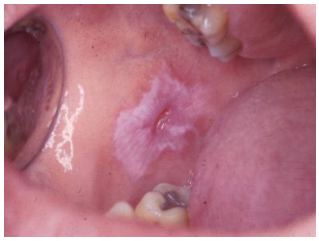
Split biopsy for light microscopy (formalin) and direct immunofluorescence (Michel's or Zeus solution).



Santoro, Stoopler, Werth, Dent Clin North America 2013

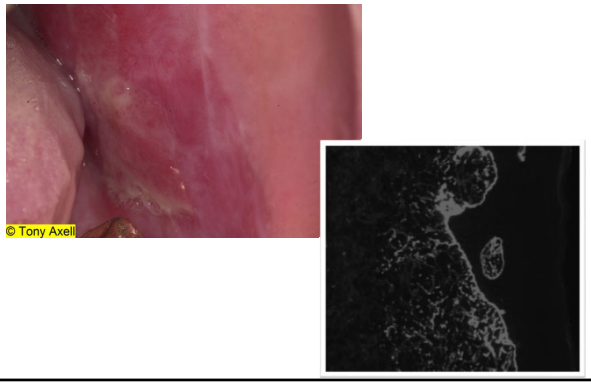
Lichen Planus





Plaque-like lesion with central ulcer and radiating striae.

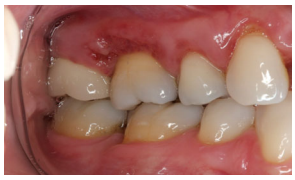
Lichenoid Drug reaction



Localized lichenoid lesions

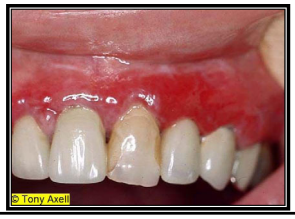
- Medication may yield similar clinical appearance.
- Adjacent to crown or large restoration.

Localized “desquamative gingivitis”: Foreign material related?



Mucous Membrane Pemphigoid (cicatricial pemphigoid, benign MMP)

- Blistering, autoimmune disease.
- Autoantibodies against basement membrane.
- Twice as common as pemphigus vulgaris.
- Clinically similar to pemphigus vulgaris.
- Eye lesions scar; oral lesions – very rarely.

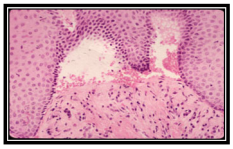


Mucous Membrane Pemphigoid

- 50-60 y; female predilection (2:1).
- Most patients have oral lesions.
- Other sites: conjunctival, nasal, esophageal, laryngeal, vaginal, skin.
- Vesicles or bullae.
- Usually diffuse but may be limited to gingiva.

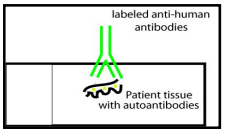
MMP: Diagnosis

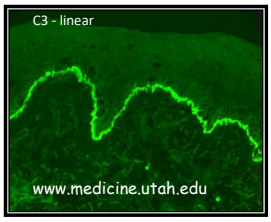
Split between surface epithelium and connective tissue.

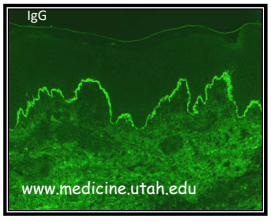


Mucous Membrane Pemphigoid: DIF

- Direct immunofluorescence
  – Usually IgG and C3 positive.







MMP: Complications

Eye lesions → scarring

- Symblepharons are adhesions between the bulbar and palpebral conjunctivae.
- Entropion → eyelids turning inwards
- Openings to the lacrimal glands close due to scarring → loss of tears.
- Cornea keratinizes → blindness

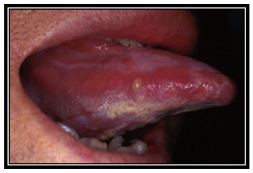
Mucous Membrane Pemphigoid

- Establish diagnosis.

- Ocular lesions, in ~25% of patients with oral lesions.
- Refer to ophthalmologist (regardless of ocular symptoms).
- Larynx; danger is airway obstruction.
- Personalized treatment – topical or systemic steroids.
- Good oral hygiene
- Dapsone – alternative systemic therapy.

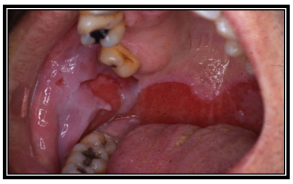
Pemphigus Vulgaris

- Rare; 1-5 cases diagnosed per million people.
- May be fatal.
- Oral lesions often first sign of disease.
- Blistering due to antibodies against desmogleins 3 & 1.
- Split is within epithelium →blister.



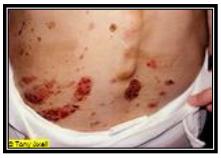
Pemphigus Vulgaris

- Adults; average age 50y
- Nearly all patients with intraoral lesions.
- Superficial ulcers and erosions on the oral mucosa.
- Palate, labial & buccal mucosa, ventral tongue, gingiva.
- Ocular lesions uncommon, scarring unusual.



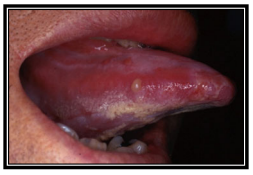
Pemphigus Vulgaris

- >50% oral lesions before skin lesions.
- Firm lateral pressure may induce bulla → termed positive Nikolsky's sign.
- Biopsy peri-lesional tissue



Pemphigus Vulgaris

- Diagnose early → disease control better.
- Systemic corticosteroids and other immunosuppressive drugs.
- Should be managed by a physician with expertise in immunosuppressive therapy.



Overview

- Discuss features of oral cancer that affect survival.
- Discuss emerging information on HPV-related oropharyngeal cancer.
- Discuss soft tissue pathology.
- Diagnostic approaches for ulcers and vesiculo-erosive lesions.
- Discuss common unilocular and multilocular radiolucencies.

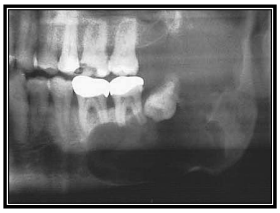
- **Odontogenic Cysts**
  - Developmental
    - Dentigerous
    - Odontogenic keratocyst (keratocystic odontogenic tumor)
    - Lateral periodontal cyst
  - Inflammatory
    - Periapical Cyst
- **Non odontogenic cyst**
  - Nasopalatine cyst (Incisive Canal Cyst)
- **Odontogenic Tumors**
  - Odontoma
  - Ameloblastoma

Pericoronal radiolucencies

- Hyperplastic dental Follicle (<5 mm in thickness)
- Dentigerous cyst (>5 mm in thickness)
- Odontogenic keratocyst
- Adenomatoid odontogenic tumor (anterior jaw)
- Ameloblastic fibroma (younger patients)
- Ameloblastoma (particularly unicystic)

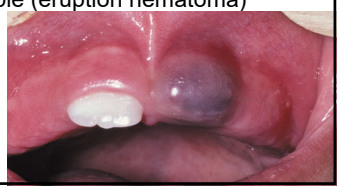
Dentigerous (Follicular) Cyst

- Most common developmental odontogenic cyst – 20% of jaw cysts.
- Unilocular RL around crown of unerupted tooth.
- Well defined, sclerotic border.
- Central, Lateral, Circumferential cysts.
- May displace tooth.
- Root resorption of adjacent teeth.



Eruption Cyst (eruption hematoma)

- Soft tissue counterpart of the dentigerous cyst
- Clinical Features
  - Translucent swelling in soft tissue.
  - <10 years
  - 1st permanent molars, maxillary incisors.
  - Bleeding → blue to purple (eruption hematoma)
- Identical histology to dentigerous cyst
- Treatment
  - allow tooth to erupt; cyst will resolve.

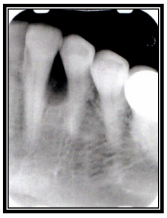


Unilocular radiolucency

- Residual periapical cyst
- Radicular cyst
- Dentigerous cyst (lateral)
- Odontogenic keratocyst
- Lateral periodontal cyst

Odontogenic Keratocyst (OKC)

- Small lesions are asymptomatic
- Pain, swelling, drainage may occur in large lesions.
- Antero-posterior growth; no bone expansion.
- Well-defined corticated, radiolucency.
- About 20% are multilocular (soap bubble).
- Unerupted tooth in 25 – 40% of cases.
- Root resorption is rare.



Odontogenic keratocyst

- Solitary or multiple
- Multiple → Nevoid Basal Cell Carcinoma Sdx
- Keratocystic odontogenic tumor (WHO 2005) ← neoplastic behavior, genetic profile.

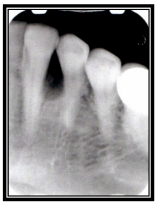
Support for neoplasm

- Most OKCs have chromosomal abnormalities → neoplastic identity.
- Biologic behavior (local destruction, recurrence).
- PTCH germline mutation in NBCCS.
- PTCH is a tumor suppressor (chr 9q22.3)
- Mutation in sporadic cancers.
- Mutation also in sporadic basal cell ca, non-syndromic OKC, orthokeratinized odontogenic cyst*.

*Diniz et al, J Oral Pathol Med, 2011

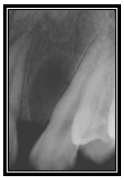
Lateral radicular radiolucencies

- Lateral radicular cyst (inflammatory cyst)
- Lateral periodontal cyst
  - Premolar region
  - Botryoid odontogenic cyst - multilocular variant.
- Odontogenic keratocyst
  - Unilocular or multilocular



Lateral Periodontal Cyst

- Remnants of dental lamina



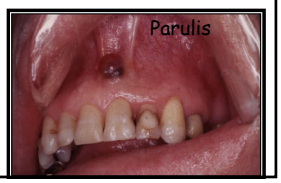
- Associated with vital, asymptomatic tooth.
- Mandibular premolar/ canine/ lateral incisor region– 80%.
- 5th – 7th decades.
- Well-circumscribed, unilocular radiolucency on lateral root surface.
- Polycystic – botryoid. Gross and microscopic = grape-like clusters.

Periapical radiolucencies

- Periapical granuloma (non vital tooth)
- Periapical cyst (non vital tooth)
- Periapical scar (endodontically treated tooth)
- Periapical cemental dysplasia (mandibular anterior teeth)

Periapical Cyst

- Most common odontogenic cyst >50%.
- Epithelium at apex is stimulated by inflammation.
- Source of epithelium – rests of Malassez, crevicular epithelium, sinus lining.
- Source of inflammation: pulpal necrosis or periodontal disease.

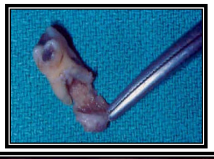


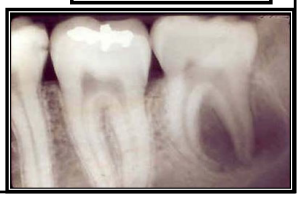
Periapical cyst

- Asymptomatic unless activated.
- Lateral radicular cyst.

Periapical Granuloma – similar, no lining epithelium.

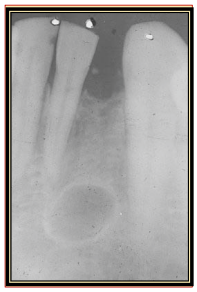
Periapical scar - may occur if cortical plate destroyed.





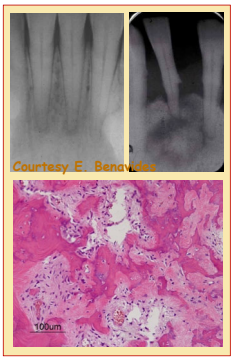
Residual periapical/ radicular cyst

- Residual periapical cyst that did not resolve following tooth extraction.
- Edentulous space that was previously dentulous
- Radiographic appearance
  - Unilocular, corticated/ non-corticated RL
- Diagnosis
  - Biopsy, plus history of extraction



Periapical Cemento-osseous Dysplasia

- Lower anterior incisors, vital teeth.
- Usually multiple lesions.
- Female predilection, African-Americans.
- 30-50 years
- Early lesions are radiolucent
- Late lesions may be mixed or radiopaque with a radiolucent rim.



Periapical radiolucency in anterior maxilla

- Nasopalatine duct cyst
- Periapical cyst
- Periapical granuloma

Nasopalatine duct cyst

- Most common non-odontogenic cyst – 1%.
- Remnants of nasopalatine duct.

- Swelling, drainage, pain in anterior palate.
- Pear or heart-shaped RL due to nasal spine.
- 1 – 2.5 cm.
- If diameter of radiolucency is <6 mm = incisive foramen.
- Root resorption rare.

Radiopacity with well demarcated borders

- Compound odontoma (tooth-like structures, anterior jaw, radiolucent rim)
- Complex odontoma (amorphous mass, posterior jaw, radiolucent rim)
- Torus or exostosis (bony surface mass)
- Condensing osteitis (apex of non vital tooth)
- Retained root tip

Odontomas

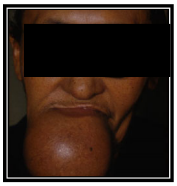
- Most common odontogenic tumor
- Compound → multiple tooth-like structures.
- Complex → irregular mass of dentin and enamel.

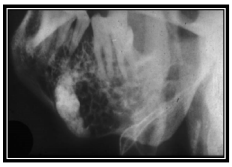
Multilocular radiolucencies

- Odontogenic keratocyst
- Ameloblastoma (posterior mandible, impacted tooth)
- Central giant cell granuloma (anterior mandible)
- Botryoid (Lateral periodontal) odontogenic cyst
- Odontogenic myxoma (delicate trabeculation)
- Calcifying epithelial odontogenic tumor (Pindborg tumor) (impacted tooth)

Ameloblastoma

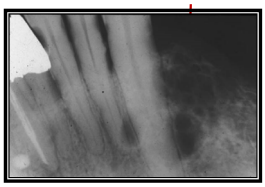
- 3rd -7th decades of life.
- Often asymptomatic.
- Painless swelling.
- Untreated, it continues to grow.
- Usually multilocular radiolucency
  - Soap bubble – large loculations
  - Honeycomb – small loculations
- Buccal and lingual cortical expansion



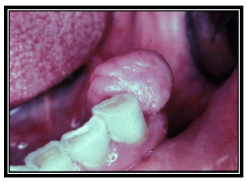


Intraosseous and soft tissue

Ameloblastoma



Peripheral Ameloblastoma



References

- Oral and Maxillofacial Pathology (3rd ed) Neville, Damm, Allen and Bouquot. Saunders Publishers, 2009.
- Gomes et al. Oral Oncol. 2009;45(12):1011-4. Review of the molecular pathogenesis of the odontogenic keratocyst.
- Caro, Low, Clin Can Res, 2010;16(13):3335-9. The role of the hedgehog signaling pathway in the development of basal cell carcinoma and opportunities for treatment.