Oropharyngeal Cancer and HPV: An Emerging Epidemic

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Today’s topics
- Presentation and profile of HPV+ oropharyngeal squamous cell cancers versus HPV- oral cancers
- Components of an external and internal head and neck examination
- Key features of patient education regarding oropharyngeal squamous cell carcinomas
- Strategies for supporting patients undergoing treatment for oropharyngeal cancer

Global Significance
- Head and Neck Cancers (including oropharyngeal)
  - 7th most prevalent cancer worldwide
  - Higher incidence in south-central Asia and India
  - 9th most common malignancy in the USA


What We Know
2019 Data ~ USA

- ~ 53,000 will be diagnosed with an oral cavity/head and neck/oropharyngeal cancer
- Estimated 10,860 will die from their disease annually
- As of 4/6/20 - 10,938 people have died from coronavirus

Current Disease Trends

- Overall incidence of oral cancers has decreased in recent years. However...
- Prevalence of oropharyngeal cancers in the USA alone has increased 225% from 1988-2004
- Since 2005, 3 out of 4 ~ 80% newly diagnosed oropharyngeal cancers are HPV+
- Incidence of HPV+ oropharyngeal cancers predicted to surpass cervical cancer by 2020


Current Disease Trends

- Incidence rate for OCSCC of tongue increasing
  - Anterior 2/3
  - Elevated in white men (5.1% annual increase 2008-12) and women (6.6% annual increase 1973-2012)
  - under age 50
  - Unknown specific causes


International Trends

- HPV - head and neck cancers (oral cavity cancers)
  - Decreased tobacco use in Canada/Australia = lower rates
  - Increased tobacco use in Eastern Europe/Asia = higher rates
  - Other factors - combinations of tobacco and alcohol, nutritional and socioeconomic status
- HPV + head and neck cancers (oropharyngeal)
  - Increases similar to the USA - developed countries


Head and Neck Squamous Cell Carcinomas

Oral Cavity SSC
- Lips
- Anterior 2/3 tongue
- Gingiva
- Buccal mucosa
- Floor of the mouth
- Hard palate
- Retromolar trigone

Oropharynx SSC
- Hard/soft palate junction
- Soft palate/uvula
- Circumvallate papillae of tongue
- Posterior 1/3 tongue
- Palatine and lingual tonsils
- Tonsillar pillars
- Pharyngeal walls
Disease Profiles

**HPV – Oral Cavity Cancer**
- Tobacco use
- Heavy consumption of alcoholic beverages
- Simultaneous alcohol / tobacco use
- Betel quid chewing
- Dietary factors
- Males, especially African American
- Peak: late adult (55-69 yrs)
- Stage: varies

**HPV+ Oropharyngeal Cancer**
- "College" educated
- Caucasian, male
- Non-smokers
- "Social" alcohol use
- "High risk" sexual behaviors
- Bimodal peaks: early (30-34 yrs) and late adult (60-64 yrs)
- Stage: early or advanced

The tobacco link...
- Tobacco use + HPV can = poorer prognosis
- Tobacco use = immunosuppression
- Increased retention of HPV in oropharynx
- Retrospective studies report 50 y/o individuals with HPV+ OPSCC report a history of tobacco use in early adult years

Oral cancer risk today???

What We Know
- HPV+ OPSCC behaves differently than HPV- OSCC
  - Epidemiology
  - Tumor biology
  - *Presentation*
  - Response to treatment
  - Prognosis
    - Estimated overall survival rates at 2 years
    - HPV+: ~95% versus HPV-: ~62%

Human Papillomavirus
- DNA viruses
  - Pieces of code – blueprint for cell division
  - Infect stratified epithelium of skin and mucus membranes
  - Over 200 types
Human Papillomavirus

- Low risk - HPV 1, 6, 11
  - Cutaneous warts
  - Spread through casual contact – breaks in the skin
  - Shared objects
  - Auto-inoculation - nail biting

Human Papillomavirus

- Oral mucosal warts – papillomas
  - Asymptomatic
  - Elevated pink or white papules
  - Buccal, gingival, labial mucosa, tongue, hard palate

Human Papillomavirus

- High risk – oncogenic types
  - HPV 16 – 95% of cervical cancers and up to 90% of OPSCC
  - HPV 18 and 10 others – less common

Human Papillomavirus

- Most common sexually transmitted disease
  - CDC data 2019 – www.cdc.gov/cancer/ucs
  - Estimated 20 million currently infected with HPV in the USA
  - 6.2 million new infections annually
  - Infections lead to genital warts and cancer
  - ~18,000 new cases of head and neck CA annually
  - ~12,000 cervical cancer cases
  - Based on 2012-2016 surveillance data

Human Papillomavirus

- Most infections unnoticed and self-resolve!
  - HPV “evades” the immune system
  - Cell life cycle within the epithelium
  - No viremia
  - No inflammation
  - No apoptosis

*Clearance of the virus can take several years

HPV life cycle

- Infection initiated at basal epithelium
HPV and oncogenesis

- HPV oncoproteins
  - E5, E6, E7
- Interfere with cell functions controlling growth/cell division
- Ultimate disruption of tumor suppressor proteins p53, pRb
- Allow for tumor progression
- *Most HPV infections are cleared before genetic damage occurs*


Human Papillomavirus

- “De-regulated” viral gene expression = tumor genesis
  - Hypertrophy and dysplasia
  - Deficient DNA repair mechanism
  - High levels of genetic damage in infected cells
- Range of 10-20 years before carcinogenesis
- Unknown time of infection or who else might be infected!

Persistent HPV 16 infections

Males ♂
- Higher number of active infections to produce antibodies – up to 10 partners!
- Infection is cutaneous
- Infection lingers longer
- Immunosuppression
- Tobacco
- Alcohol use

Females ♀
- Develop antibodies after fewer partners
- Initial infection – vaginal mucosal
- Generally better immune systems
- Immune response may decrease with age

Presentation

HPV negative
- Tongue
- Floor of the mouth
- Buccal mucosa
- Gingiva
- Hard palate
- Lips

HPV positive
- Affinity for lymphoid tissue
- Lingual and palatine tonsils
- Base of tongue
- Posterior oropharynx
  - Waldeyer's Ring
- Visible sites in the oral cavity
- Larger lesion size
- Later metastases
- Neck mass, dysphagia
- Tumor location
- Lesion size
- Lymph node metastases
Head and Neck Examinations

- Overall evaluation of the asymptomatic individual
- Conventional visual and tactile examination
- Comprehensive health history
- Patient education opportunity
- Self-examination skills

Extraoral Examination

- Skin lesions
- Salivary gland neoplasms
- Thyroid abnormalities
- Lymphadenopathy

Dermatologic Assessments

- Skin lesions
  - Open lesions, red patches
  - shiny nodules
- Pigmented lesions
  - Asymmetry
  - Border
  - Color
  - Diameter
  - Evolving

Salivary Gland Assessments

- Parotid = 85% of salivary gland tumors
  - 25% malignancy rate
- Pleomorphic adenoma most common benign tumor
- Tx = surgical excision
- Malignancies
  - Surgery, radiation, chemotherapy
Minor salivary gland malignancies

Adenoid cystic carcinoma

- Slow growing
- Aggressive
- High recurrence rate
- Grows on neural pathways
- Common symptom = swelling, difficulty swallowing, pain
- Peak incidence 40 – 60 years

Lymphadenopathy

Infection related
- Soft
- Painful or tender
- Moveable
- Patient may be unaware of any infection

Possible malignancy
- Firm
- Fixed
- Asymptomatic

Thyroid palpatation

- Thyroid gland examination videos: Stanford 25
- https://stanfordmedicine25.stanford.edu/the25/thyroid.html

Stanford 25 ~
Clinical examination skills from a medical perspective
https://stanfordmedicine25.stanford.edu

Intraoral Examination

* Image credit: Cleveland Clinic
Intraoral Examination
- Internal features
  - Lips
  - Labial, buccal mucosa
  - Tongue
    - Dorsal and ventral surfaces
    - Lateral borders
    - Base and lingual tonsils
  - Floor of the mouth
    - Palpate salivary glands
    - Hard and soft palate
    - Uvula
    - Tonsils
    - Posterior pharyngeal wall

Signs and Symptoms Requiring Further Follow-up
- Tissue that is a different color than that of the surrounding tissue
  - Leukoplakia, erythroplakia, leuko/erythroplakia
- Non-healing ulcers
- Exophytic tissue
- Induration in movable tissue
- Asymmetry in the tonsillar or retro-molar trigone
- Indurated lymph nodes
  - *Neck mass
  - Abnormalities that do not resolve within 2-3 weeks

Documentation of Findings

Signs and Symptoms Requiring Further Follow-up
- **Verbal Inquiry Questions**
  - Changes or difficulty in swallowing
  - Unexplained oral numbness
  - Hoarseness or sore throat that does not resolve
  - Ipsilateral ear pain

  Abnormalities that do not resolve within 2-3 weeks

Most Common Symptoms of HPV+ OSCC

<table>
<thead>
<tr>
<th>Presenting Symptom</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral neck mass</td>
<td>57%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>33%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>16%</td>
</tr>
<tr>
<td>Visualized mass</td>
<td>13%</td>
</tr>
<tr>
<td>Globus sensation</td>
<td>10%</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>9%</td>
</tr>
<tr>
<td>Oralgia</td>
<td>7%</td>
</tr>
</tbody>
</table>
  
  *No detectable pre-cancerous phase*


Cancer “Screening” Tests
- Detection of early disease in asymptomatic individuals
  - Mammography, PSA tests, Pap smears, colonoscopy
- Positive screening results = persons at increased risk
- “Test performance” measurement
  - **Sensitivity** = chance that a person with cancer has a positive test
  - **Specificity** = chance a person without cancer has a negative test
Oral Cancer “Screening”

- Adjunctive screening tools and devices
- **Polling question!**
- How many of you are using a screening device or adjunct in your practices?

Screening Challenges HPV+ OSCC

- How to identify high risk individuals?
- No Pap smear equivalent!
- Location of the primary lesion???
- 50 y/o males
  - 3 – 5x more vulnerable than women
  - 8% active infections
  - 0.7% develop OPSCC

Adjunctive Screening Tools

- Cytologic tests – Brush biopsy
  - Test suspicious sites
  - Results in ~5 days

Adjunctive Screening Tools

- Vital staining ~ Toluidine blue dye
  - Used to detect mucosal abnormalities
  - May bind to tissues undergoing rapid cell division or DNA change
  - Abnormal tissue is stained

Adjunctive Screening Tools

- Autofluorescence ~ Velscope®
  - Rapidly dividing or DNA damaged mucosal tissue absorb and reflect light differently

Adjunctive Screening Tools

- Tissue reflectance and vital staining ~ Vizilite Plus with TBlue®
Adjunctive Screening Tools

- Salivary diagnostics – OralDNA
  - Saliva sample to test for the presence of HPV viral strains
  - Not approved by the FDA to reduce oral cancer morbidity/mortality

Clinical Practice Guidelines ~ Report of the ADA

- Expert panel of general dentists, hygienists, oral medicine specialists, ENTS, oncologists
  - Exclusion criteria: potential financial and intellectual conflicts of interest
- Scope of guideline: patients with no lesions, non-suspicious lesions, potentially malignant lesions and malignant lesions
- Target audience: DDD’s, MD’s, PA’s, DT’s, RDHs, RNs, NPs
- Update of the 2010 Guidelines

Clinical Practice Guidelines

- Systematic review of the research/literature
  - “triage tools” of cytologic testing, autofluorescence, tissue reflectance and vital staining, vital staining
- Guidelines assist clinicians and patients in decision making process
- Recommendations based on the strength of the “evidence” and patient/practitioner values

Clinical Practice Guidelines

- Good practice statement –
  - “Clinicians should obtain an updated medical, dental and social history and perform an intraoral and extraoral conventional visual and tactile examination (CVTE) in all adult patients”
- 6 Recommendations based on the potentially malignant disorder

Range of intraoral findings

- Image credits: Clinical Practice Guidelines, JADA; 2017
Clinical Practice Guidelines

- “In adult patients with clinically evident, potentially malignant, or seemingly malignant lesions, clinicians should perform a biopsy of the lesion immediately or refer the patient to a specialist. If the patient declines a biopsy or cannot be referred, cytologic adjuncts could act as a triage tool to offer additional information for clinical decision making.”

Screening Devices

- “The tantalizing implication that such technologies may improve detection of oral cancers and pre-cancers beyond conventional oral examination alone has yet to be rigorously confirmed.”
- Guidelines revised every 5 years
- “There is no standard or routine screening test for oral cancer” National Cancer Institute

Diagnosing Oral Pharyngeal Cancer

- Referral to an oral surgeon/ENT for evaluation/biopsy
- Scalpel biopsy = definitive diagnosis
- Oral pathologist for tissue evaluation
- Head and neck surgeon (ENT) for further evaluation/care

50 y/o female, RDH, no tobacco/alcohol hx
Asymptomatic lichenoid lesion, anterior 2/3 tongue, duration unknown, hx of “burning mouth syndrome” due to meds

Referral to oral surgeon, initial impression: “lichenoid reaction,” incision biopsy

Several days post biopsy
Dx: moderate dysplasia
Referral to ENT, full excision of lesion and margins

One week post op

3 to 4 weeks post op, lingering paresthesia lateral border and dorsal surface, 2 months post op

Treatment Planning

- Clinical staging
  - CT, MRI, PET scan, ultrasound
- Histologic grading
  - degree of differentiation
- HPV status
  - P16 marker in biopsy samples
- Treatment based on grading/staging

Treatment Planning

- T1 less than 2 cm
- T2 between 2-4cm
- T3 greater than 4 cm
- T4 invasive

CT-PET Scan: Base of Tongue OPSCC

- Image credit: Head and Neck Cancer Alliance, 2017
Treatment

- Early stage: surgery and or radiation therapy
  - "open" surgery versus TORS or laser

TORS at Johns Hopkins University

Treatment

- Locally advanced = multi-modal therapy
  - Surgery
  - Radiation
  - Chemotherapy and radiation

Prevention

- Education and self-care information – key!
  - Report any persistent oropharyngeal changes
    - Hoarseness
    - Swallowing
    - Unilateral swelling/hardness in lymph nodes
    - Unilateral ear pain
  - Stress need for medical follow-up care

Vaccinations

- Not effective for established infection/disease!
  - Gardasil® 9 – Merk
    - Protection against 9 HPV strains
    - Series of 2 or 3 injections over 6 months
    - 9-26 years *
    - Boys and girls
    - Most effective before HPV exposure

  * In 2008 FDA approved for use up to age 45

Health History Inquiry Questions

- Have you noticed any lumps or swelling in your neck?
- Have you experienced numbness around your face or jaw?
- Have you had any changes in your swallowing pattern?
- Have you experienced chronic hoarseness?
- Have you had any chronic ear pain?
- Have you been vaccinated for the human papilloma virus (HPV)?
- Would you like more information on the HPV vaccination?

Treatment Planning

- Clinical trials ongoing in “de-escalation” of treatment
  - American Joint Committee on Cancer 2017 guidelines
  - TORS
  - IMRT = focused radiation
  - Chemotherapy
  - Immunotherapy

Clinical trials registry
www.cancer.gov
HPV Vaccination Spots

- Who knew that I was going to be at risk for HPV? Did you??

HPV Vaccinations and Adults

- New HPV infections common in adolescence/young adulthood
- New sex partner = risk factor for new infection
- Long term-monogamous relationships unlikely to acquire new infection
- Most sexually active adults have been exposed to some but not all HPV strains
- No clinical antibody test can determine immunity or susceptibility to any given HPV type
- Vaccine efficacy highest among persons who have not been exposed

Implications of HPV Vaccinations

- First generation of vaccine in USA 2006
- CDC surveillance 2017
  - 68.6% girls/62.6% boys between 13-17 received first dose
- Australia provides vaccine for free
  - 92% reduction in genital warts

Vaccinations

- Polling question!
  - How comfortable would you be in discussing the HPV vaccine with a patient?
    - Completely comfortable
    - Fairly comfortable
    - Not comfortable at all

Supportive Care
Supportive Care

- Dental examination **before** cancer therapy begins
  - Complete any necessary dental treatment recommended
- Dental hygiene care prior to and during therapy
  - Schedule consultations at the end of the day
  - Provide patients with a variety of oral products/resources
- **Ongoing consultation** with oral healthcare providers as needed during treatment

Oral Care During Cancer Therapy

- Importance of regular mouth care
  - Ultra-soft tooth brush
  - Brush or rinse after eating
  - Use pH neutral mouth rinses
  - Interdental cleaning when able

Functional Disabilities During Cancer Therapy

- 100% OSCC patients
  - Impaired ability to eat, swallow and speak
  - Taste alterations
  - Loss of taste buds
  - Severely compromised nutrition
  - Increased caries and infection risks
- Compromised quality of life
  - Low self esteem, social isolation

Oral Mucositis

- Clinical manifestations
  - Soft palate, ventral tongue, floor of mouth and buccal mucosa
  - Erythema and burning sensation
  - Elevated white patches
  - Epithelial sloughing and ulceration

Oral Mucositis

Image credits: American Academy of Oral Medicine

Pathogenesis of Oral Mucositis
Radiation Induced Oral Mucositis

- Function of cumulative tissue dose
- Begins at ~ 15 Gy to 20 Gy
- Ulcerative mucositis at 30 Gy
- Affects all tissues in radiation field
- Prodromal signs: erythema, burning
- Exacerbated by existing oral infection/poor oral hygiene

Mucositis Management

- Initial and ongoing oral assessments
- Patient self report and professional examination
- Preventative/therapeutic oral care regimen
- Regular, systematic oral hygiene care
- Brushing, flossing, bland rinses, oral moisturizers
- Interdisciplinary approach to oral care
  - Nurse, MD, DDS, RDH, dietitian, pharmacist
- Multinational Association of Supportive Care in Cancer International Society of Oral Oncology, Mucositis Study Group 2013

Oral Care During Cancer Therapy

- Sore Mouth, Sore Throat
  - Rinse often with baking soda and salt water
  - Follow with plain warm water
  - Prescription pain medication
  - Topical lidocaine
  - Oral or patch medication
  - Cytoprotective gels

Oral Care During Cancer Therapy

- Xerostomia
  - Individualized approach
  - Over the counter rinses and sprays
  - Sugar free lozenges
    - Xylimelts™
  - Xylitol gum when able
  - Saliva substitutes
  - Room humidifiers for sleep

Trismus

- Reaches peak 3 to 6 months post treatment
- Daily stretching exercises are critical
  - Open and close the mouth as far as possible
  - Stretching devices
- Apply warm, moist heat

Osteonecrosis of the Jaw

- Can occur spontaneously during or post treatment
- Single or multiple lesions
- Requires medical intervention/observation
- Hyperbaric oxygen treatment – aid healing

Image credits: American Academy of Oral Medicine
Xerostomia Induced Radiation Caries
- Lifelong caries risk
- Xerostomia during and following treatment
- Swallowing difficulties
- Frequent dental evaluations
  - Ongoing supplemental fluoride therapy

Case Study
- JA – 59 y/o male presented with right cervical neck mass to ENT.
- Dx of HPV+ OSSC
- Tx: Radiation therapy
- Tx complications: severe mucositis, feeding tube
- Post tx complications: Radiation induced osteonecrosis at inferior border of the mandible, treated with surgical debridement, hyperbaric oxygen
Treating Head and Neck Cancers
- National Cancer Institute Designated Centers
  - 70 centers in 36 states
  - University medical centers
  - Free standing cancer centers

Collaboration in Health Care
- Interdisciplinary approach to cancer prevention and control
  - Better coordination of care
  - Increased patient understanding
  - Improved health outcomes
- RDH ideally positioned – trust, rapport, respect

Thank you!
References and resources are in the handout–

Questions???
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Stanford Health Library
www.healthlibrary.stanford.edu