The Role and Importance of HPV Infection in Head and Neck Cancer.

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Disclosure

• No disclosures or conflicts of interest
Objectives

• Review epidemiology of Human Papilloma Virus (HPV) infection

• Review the epidemiology of HPV-related head and neck cancer

• Discuss the impacts of HPV on treatment and prognosis

• Review treatment options, areas of exploration & prevention

Human Papilloma Virus Epidemiology

• Most common sexually transmitted virus/infection in the US.
  • 12,000/day ages 15 - 24 are infected
  • Correlate with # lifetime sexual partners
    • ≥ 26 number of lifetime vaginal-sex partners - (OR) 3.1
    • 6 or more lifetime oral-sex partners - (OR) 3.4

• >80% of Americans will have an HPV infection in their lifetimes

• 6.2 million new infections/year in the United States (CDC estimate)

• 26 million Americans/day active oral HPV infection.
  • Of those approximately 2600 are HPV16.

• The vast majority of individuals will clear the virus
HPV role in Oncogenicity

- HPV is a DNA oncovirus with 120 different HPV subtypes
  - Low-risk types - **HPV 6 and HPV 11**
    - papillomas and benign warts
  - High-risk oncogenic types **HPV 16 and HPV 18**

- 90% of cervical cancers & 70% of anogenital cancers,
- **20-72% of Oropharyngeal Squamous Cell Cancer (OPSCC)**
  - Most prevalent strain HPV 16 (9-15 other strains)
  - HPV oncoproteins E6 & E7
  - Target the p53 & pRB (retinoblastoma)
    - tumor suppressor pathways

HPV Mechanism of Action

- 9 confirmed oncologic strains

**HPV+ OPSCC**
- p53 degradation
- RB down-regulation
- p16 up-regulation.

**HPV- OPSCC (tobacco)**
- p53 mutations
- RB up-regulation
- p16 Down-regulation
Oropharyngeal Cancer Epidemiology

- Head and Neck Squamous Cell Cancer (HNSCC)
  - 6th leading cause of cancer mortality
  - 650,000/year & 300,000 deaths/year.

- Oral & Oropharyngeal SCC - 50,000 incident cases annually

- HPV positive oropharyngeal cancer - **18,000 cases/yr**
  - increasing by 3% per year
Mucosal Head and Neck Cancer Incidence

Oropharyngeal Cancer Incidence
HPV Effect on OPSCC Incidence

Dramatic Rise in HPV + Tonsil Cancer

- Male:Female - 3-4:1
- Non-smoking males / non drinker
- Younger age - 35 to 55
- Higher socioeconomic status and education
- Less frequent in non-Caucasians
- Lymphoid Primary - Tonsil or Base of Tongue (BOT)
HPV + OPSCC Demographics

- Male:Female - 3-4:1
  - Why less in females? - Theory by Gillison et al.
    - Earlier seroconversion vaginal mucosal contact
    - Earlier generation of antibodies
    - less partners
    - More likely to develop immune response
- Men
  - More contacts/partners required
  - less mucosal contact
  - repeat exposures before seroconversion

HPV–Associated Oropharyngeal Cancer Rates by Race, Ethnicity, and Sex, per Year, United States, 2011–2015

[Bar chart showing age-adjusted rates per 100,000 persons by race, ethnicity, and sex.]
### Clinical Presentation

#### Symptoms
- **Painless neck adenopathy**
- Uncommon
  - Throat Pain
  - Difficulty swallowing
  - Ear Pain

#### Findings
- Lymphoid Primary
  - tonsil/BOT
  - often subtle
  - Early neck disease
- Inconspicuous primaries
  - Role of PET/CT
  - Role of viral typing

#### Demographics

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Oral Cavity</th>
<th>HPV(-)</th>
<th>HPV(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Smoker/drinker</td>
<td>Smoker/drinker</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td></td>
<td>Older</td>
<td>Older</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>More African-Americans</td>
<td>More African-Americans</td>
<td>Caucasian</td>
</tr>
<tr>
<td></td>
<td>Lower SES</td>
<td>Lower SES</td>
<td>Younger</td>
</tr>
<tr>
<td></td>
<td>Lower education</td>
<td>Lower education</td>
<td>Caucasian</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common Locations</th>
<th>Oral Tongue</th>
<th>Pharyngeal wall</th>
<th>Tonsil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Presentations</td>
<td>Soreness with red or white spots</td>
<td>Sore throat</td>
<td>Base of tongue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Otalgia</td>
<td></td>
</tr>
</tbody>
</table>
HPV Diagnostic Dilemma

- Young otherwise healthy adults - Not stereotypical HNSCC patient
  - Lower index of suspicion by patient and clinician
  - Delay in presentation/referral

- Typically will already have neck metastasis on initial presentation

- Social dynamics of link to STD (HPV)

- Solution - RAISE AWARENESS
HPV Driven Disease is Different

Ang et al NEJM 2010
Impact of Smoking in Era of HPV-driven OPSCC


Ang et al. NEJM 2010
HPV + OPSCC patients have improved outcomes

<table>
<thead>
<tr>
<th>Degree of Risk</th>
<th>Characteristics</th>
<th>3-y OS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>HPV+, smoking history of ≤10 pack years, and N0-N2a nodal history</td>
<td>63% (95% CI, 88.3–97.9)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>HPV+, smoking history of &gt;10 pack years, and N2b–N3 nodal disease; or HPV- smoking history of ≥10 pack years, and N2b–N3 nodal disease or T2–T3 tumors</td>
<td>70.8% (95% CI, 60.7–80.8)</td>
</tr>
<tr>
<td>High</td>
<td>HPV- and smoking history &gt;10 pack years; or HPV- smoking history ≤10 pack years, and T4 disease</td>
<td>46.2% (95% CI, 34.7–57.7)</td>
</tr>
</tbody>
</table>

Revised Staging System based on HPV

- AJCC 8th edition - down staging HPV+ OPSCCA
- N stage reduced
- Overall stage
- Treatment Changes - de-escalation

## Table 1. AJCC (8th Edition) TNM Categories and Definitions for HPV-Associated (p16+) OPSCC

<table>
<thead>
<tr>
<th>T Category</th>
<th>Criteria</th>
<th>N Category</th>
<th>M Category</th>
<th>Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumor identified</td>
<td>N0 or N1</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor size ≤ 2 cm in greatest dimension</td>
<td>N2</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor size &gt; 2 cm but ≤ 4 cm in greatest dimension</td>
<td>N0, N1, or N2</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor size &gt; 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
<td>N3</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced tumor invading larynx, extrinsic tongue muscles, medial pharynx, hard palate, or mandible or beyond</td>
<td>N0, N1, N2, or N3</td>
<td>M0</td>
<td>III</td>
</tr>
</tbody>
</table>

Clinical N Categories:
- N0: Regional nodes cannot be assessed
- N1: Regional nodes are not metastatic
- N2: Metastasis to one or more ipsilateral nodes, ≤ 6 cm
- N3: Metastasis to contralateral or bilateral lymph nodes, > 6 cm

Pathologic N Categories:
- Nx: Regional nodes cannot be assessed
- n0: No regional node metastases
- n1: Metastasis to single ipsilateral node, ≤ 3 cm and EN negative
- n2: Metastasis to single ipsilateral node > 3 cm but ≤ 6 cm in greatest dimension and EN negative
- n3: Metastasis to multiple ipsilateral nodes, > 6 cm in greatest dimension and EN negative
- nX: Metastasis to contralateral node(s) or bilateral node(s), ≤ 6 cm in greatest dimension
- nM: Metastasis to contralateral or bilateral lymph nodes, > 6 cm in greatest dimension

## Table 2. AJCC (8th Edition) Prognostic Stage Groups for HPV-Associated (p16+) OPSCC (Clinical)

<table>
<thead>
<tr>
<th>T Category</th>
<th>N Category</th>
<th>M Category</th>
<th>Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0, T1, or T2</td>
<td>N0 or N1</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T0, T1, or T2</td>
<td>N2</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3</td>
<td>N0, N1, or N2</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T0, T1, T2, T3, or T4</td>
<td>N3</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T4</td>
<td>N0, N1, N2, or N3</td>
<td>M0</td>
<td>III</td>
</tr>
</tbody>
</table>

Any T: Any T | N | M | Stage Group

AJCC = American Joint Committee on Cancer; HPV = human papillomavirus; OPSCC = oropharyngeal squamous cell carcinoma.

## Table 5. AJCC (8th Edition) Prognostic Stage Groups for Non-HPV-Associated (p16-) OPSCC

<table>
<thead>
<tr>
<th>T Category</th>
<th>N Category</th>
<th>M Category</th>
<th>Stage Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1s</td>
<td>N0</td>
<td>M0</td>
<td>0</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T4a</td>
<td>N0, N1</td>
<td>M0</td>
<td>IVA</td>
</tr>
<tr>
<td>T1, T2, T3, T4a</td>
<td>N2</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
<td>IVB</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IVC</td>
</tr>
</tbody>
</table>

Any T = Any T; N = N; M = M; Stage Group = Stage Group.
Treatment Implications

• HPV driven disease is different - better prognosis

• Paramount to identify HPV status

• Impacts prognosis
  • Patient counseling and expectations
  • Treatment decisions

Ancillary Testing

• Imaging
  • PET/CT accepted standard of cancer for patient with unknown primary HPV + OPSCC
    • Primary lesions harder to see
    • Finding primary impacts treatment & outcomes
      • Impact of laterality on treatment

• Molecular Typing
  • HPV testing critical to diagnosis, prognosis & treatment
College of American Pathologists now recommend HPV testing in all oropharyngeal cancers

Human Papillomavirus Testing in Head and Neck Carcinomas

Guideline From the College of American Pathologists

James S. Lewis Jr, MD; Beth Beadle, MD, PhD; Justin A. Bishop, MD; Rebecca D. Chenock, MD; Carol Colasacco, MHS, SCT(AACCP); Christina Lacchetti, MPHSc; Joel Todd Moncarz, MD, PhD; James W. Rocco, MD, PhD; Mary R. Schwartz, MD; Raja R. Seethala, MD; Nicole E. Thomas, MPH, CT(AACCP); William H. Westra, MD; William C. Fagin, MD, PhD

• Context—Human papillomavirus (HPV) is a major cause of oropharyngeal squamous cell carcinomas, and HPV (and/or surrogate marker p16) status has emerged as a prognostic marker that significantly impacts clinical management. There is no current consensus on when to test oropharyngeal squamous cell carcinomas for HPV/p16 or on which tests to choose.

  Objective—To develop evidence-based recommendations for the testing, application, interpretation, and reporting of HPV and surrogate marker tests in head and neck carcinomas.

  Design—The College of American Pathologists convened a panel of experts in head and neck and molecular pathology, as well as surgical, medical, and radiation oncology, to develop recommendations. A systematic review of the literature was conducted to address 6 key questions. Final recommendations were derived from strength of evidence, open comment period feedback, and expert panel consensus.

Results.—The major recommendations include (1) testing newly diagnosed oropharyngeal squamous cell carcinoma patients for high-risk HPV, either from the primary tumor or from cervical nodal metastases, using p16 immunohistochemistry with a 70% nuclear and cytoplasmic staining cutoff, and (2) not routinely testing non–squamous oropharyngeal carcinomas or nonoropharyngeal carcinomas for HPV. Pathologists are to report tumors as HPV positive or p16 positive. Guidelines are provided for testing cytologic samples and handling of locoregional and distant recurrence specimens.

  Conclusions. Based on the systematic review and on expert panel consensus, high-risk HPV testing is recommended for all new oropharyngeal squamous cell carcinoma patients, but not routinely recommended for other head and neck carcinomas.

(Arch Pathol Lab Med. doi: 10.5858/arpc.2017-0286-CP)

Guidelines issues in late 2017

p16 accepted as a common method of identifying HPV+ disease

But p16+ tumors overall do well, but not a perfect marker

Adapted from Lewis et al. American Journal of Surgical Pathology, 2010.

Prognosis with HPV+ OPSCC

- Why do HPV positive HNSCC patients have a better prognosis?
- 1) Harbour fewer or different genetic alterations.
- 2) Higher radiosensitivity - intact apoptotic response to radiation
- 3) Absence of field cancerization.
- 4) Role of Immunologic response to viral specific tumor antigens
- 5) Younger age, good performance status, fewer comorbidities
Treatment options for HPV OPSCC

• Surgery with adjuvant therapy

• Radiation +/- chemotherapy

• Clinical Trial
  • Immunotherapy
  • De-escalation (radiation dose, chemotherapy, etc)

Treatment choice morbidity based

• Excellent Survival Outcomes HPV OPSCC

• Focus on morbidity reduction

• What are the morbidity
  • How do we identify and measure?
  • How do we compare?
  • What is the timeline?
Early Stage HPV+ OPSCC

• What does this mean?
  • AJCC 8th ed Stage 1/2 includes N2 & T3 disease
  • Nodal status staged differently

• Tendency for monotherapy
  • Surgery alone / Radiation alone
  • How to adjust to new staging system
Surgery for OPSCC

• Area of Interest and controversy
• Transoral Surgery
  • Transoral Robotic (TORS), Transoral Laser (TLM)
  • Maximize primary tumor resection
  • Preservation of skeletal anatomy
    • Improved speech and swallowing outcomes
    • Reduced feeding tube and tracheostomy rate
  • Potential to de-escalate dose and extent of radiation
    • Avoidance of radiation complications
Radiation for OPSCC

• Morbidity Reduction
• Intensity Modulated Radiation Therapy (IMRT)
  • Reduce radiation scatter
  • Preserve Salivation - unclear
  • Reduce Grade 3/4 toxicity
  • Improved QOL
    • speech/swallow
    • lower g-tube rates
Role of chemotherapy / Immunotherapy

• Area of active controversy and investigation
• Eliminate chemotherapy - Not needed
  • Chemotherapy increases toxicity of radiation
  • Necessity for a disease with high survival?

• Induction chemo/immunotherapy
  • Role of immune system activation to immunogenic cancer

UNC a leader in HPV OPSCC Clinical Trials

• De-escalation chemoradiation trial, Chera et al 2018.
  • Lower the dose of radiation from 70 to 60 Gy
  • 3-year local control, regional control, cause-specific survival, distant metastasis-free survival, and overall survival rates were 100%, 100%, 100%, 100%, and 95%, respectively.

• Induction Chemo/immunotherapy Transoral Surgery Trial, Weiss et al 2018
  • Risk adaptive Adjuvant Therapy
  • 3-year local control, regional control, distant metastasis-free survival and overall survival were 100%, 100%, 100%, and 100%
  • 75% of patients avoided adjuvant radiation
National Trials

- Surgery
  - TORS with reduced XRT (2-3 weeks vs 6 weeks)
  - Induction immunotherapy +/- stereotactic XRT and surgery
- Radiation
  - Immunotherapy/Radiation trials
  - De-escalation trials

Quality of Life debate

- Which is less morbid
  - Lower dose Radiation with avoidance of surgery
  - Transoral surgery +/- chemo/immunotherapy without XRT
- Short term / Long term
- How/what do you measure?
  - What metric do you use?    Is there reporting bias?
- No head to head trial
- Not enough long term data
What is the best option

• Truth - We don’t know

• Not enough longterm data to know the impact of choices of treatment on a younger population

• Naive to think we have it figured out yet

• Better detection, Better prevention, Safely reducing morbidity

Future Directions

• Continued Trial investigation and population surveillance

• Better Detection

• Vaccinations

• Tumor Vaccines?
How p16 works in the background of HPV infection


HPV related cancer detection

- Pap Smear equivalent for OPSCC?
- No current viable screening test for HPV positive OPSCC
- There are oral HPV infection tests on the dental market
  - they can detect oral HPV infection, but no indicator cancer progression.
  - only about 1% of individuals that develop a high risk type oral HPV infection ever cascade into cancer,
  - most often occurs decades after infection
- The utility of the screening tests are highly in question when it comes to providing meaningful and actionable information.
Cancer Classification Question

- p16 a reasonable marker, but not perfect
- Not all HPV/p16 disease created equal
- Can we stratify patients beyond p16 into prognostic groups?
  - Who needs radiation vs surgery
  - Who will have higher side effects with therapy
  - Account for patient specific factors

Role of DNA and RNA in HPV disease

- Plasma cell free deoxyribonucleic acid (cfDNA) has emerged as a powerful tool for cancer surveillance, with tumor-specific genotypes acting as a biomarker upon release of cellular DNA upon apoptosis, necrosis or active secretion in exosomes (Gulley 2010).
- Unlike tumor tissue biopsy, cfDNA in blood can be sampled conveniently at multiple time points (Heitzer 2015, Tsujiura 2014), potentially adding value to current tools for monitoring tumor status (Schwarzenbach 2011, Economopoulou 2017).
- Current patent pending RNA testing underway at UNC
Demographics: 21 cases total
- 15 N+, 6 N0
- Most patients were >50 years old
- Most were male
- Similar numbers of smokers vs non-smokers
- No significant differences between any of the categorical variables

Role of Patient Counseling for HPV
- Multidisciplinary Management Critical
- Clinical Equipoise with treatment discussion
- Patient Priorities and QOL
- Survivorship
Role of Patient/Family Counseling for HPV

- Sexual partners who have been together for a while tend to share all types of sexual infections.
- HPV viral infections also are commonly shared.
- This means that the partner of someone who tests positive for HPV likely has HPV already, even though they may have no signs or symptoms.
- Like most Americans, their immune system will customarily clear it in under 2 years.

Patient Counseling - continued

- If you test positive for HPV:
  - No way to know when you were infected with HPV
  - May be decades before cancer develops
  - Testing positive for an HPV infection does negate monogamy
  - May have long periods of viral inactivity or dormancy
    - Decades
    - Negative test for HPV
Screening and Detection

- Best screen for HPV related oral & oropharyngeal cancer
  - visual and tactile exam
  - oral history taking to ask about signs and symptoms
  - Most of the symptoms of a developing HPV positive infection are discovered by asking questions not using a test, a light or other device to do so.

Prevention

- US population of over 300 million people, the incidence rate of oral cancers from it are still relatively rare mathematically

- Oral & oropharyngeal cancers (50,000 in 2017)
  - the rapid increase in them is certainly alarming.
  - Steep upward trend line since the early 1970’s.

- With proper use of the **HPV vaccination** in our youth, we should see progress against this trend in future generations.
HPV Vaccine

- Millions of young girls have been safely vaccinated
- Original clinical trials were done only on cervical cancers
  - FDA restricts the manufacturers from expanding indications
- Herd immunity needed to resolve HPV OPSCC

Vaccination Update OPSCC

- National Advisory Committee on Immunization Practices recommends routine HPV vaccination for girls and boys ages 11 and 12, as well as individuals ages 13 to 26 if they haven’t received the vaccine already.
- Gardasil vaccine approved in boys and men, ages 9 through 26 years old.
  - For adults the age range has been extended from 27 to 45 years old.
- The value of vaccination at a later stage of life might be higher in those who have had a limited number of sexual partners in their lifetime than others.
- These vaccines are most effective if given to children before they become sexually active.
Testing and Vaccines

- Pap Smear - cervical cancer
- Anal Swabs - anal cancer
- No test for oropharyngeal cancer

- Two vaccines known as Gardasil and Cervarix protect against the strains of HPV that cause cervical cancers (HPV16 and 18), Gardasil also protects against other versions that cause genital warts (HPV6 and 11).
- A new version of the Gardasil vaccine protects against 9 versions of HPV.

Ultimate Future Goal

- Patient-specific personalized treatment
  - genomic-test driven treatment
  - personalized tumor vaccines

- Disease Elimination with Herd Population Vaccination
  - Decades in the making