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

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Disclosure

- No disclosures or conflicts of interest

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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

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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

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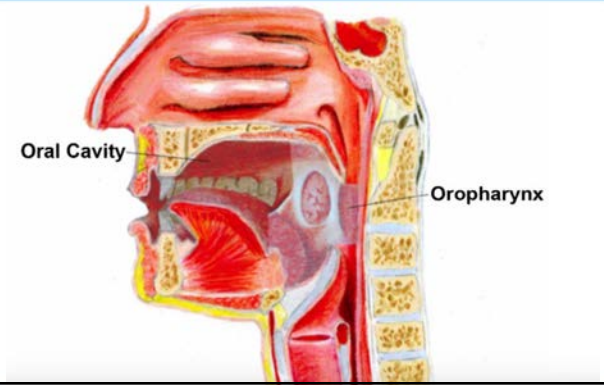

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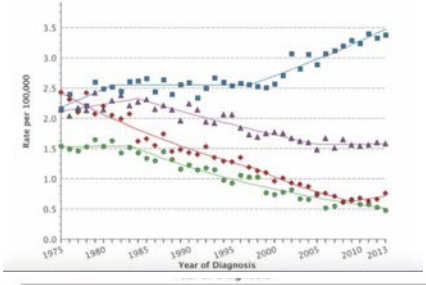
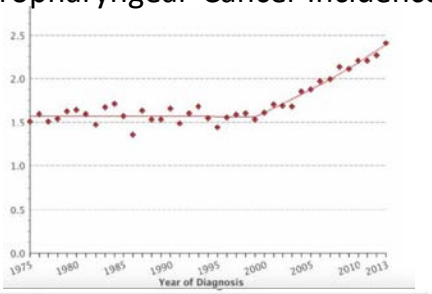
Mucosal Head and Neck Cancer Incidence



ALLIANCE A

Lip
Tongue
Floor of mouth
Gum & other mouth

Oropharyngeal Cancer Incidence



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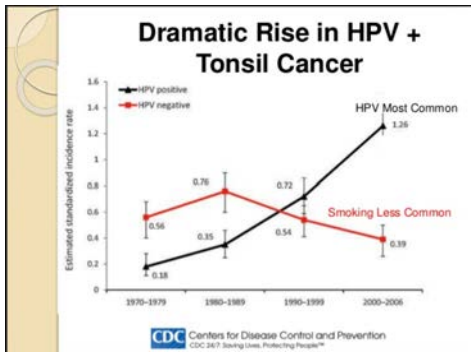
Oropharynx & Tonsil

HPV Effect on OPSCC Incidence



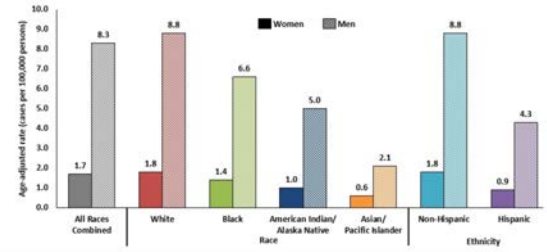
HPV + OPSCC Demographics

- 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



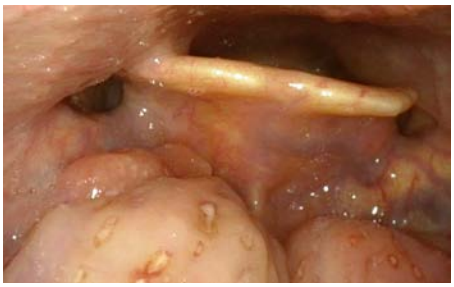
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

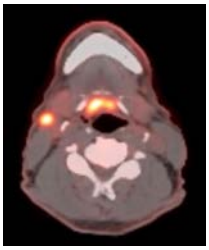
Clinical Presentation

Cancer Site	Oral Cavity	Oropharynx	
		HPV(-)	HPV(+)
Demographics[5]	• Smoker/drinker • Older • More African-Americans • Lower SES • Lower education	• Smoker/drinker • Older • More African-Americans • Lower SES • Lower education	• Nonsmoker • Male • Younger • Caucasian • Multiple partners • Higher SES • Higher education
Common Locations[6]	• Oral Tongue	• Pharyngeal wall • Soft Palate	• Tonsil • Base of tongue
Common Presentations[6]	• Soreness with red or white spots	• Sore throat • Dysphagia • Otalgia	• Painless neck mass

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

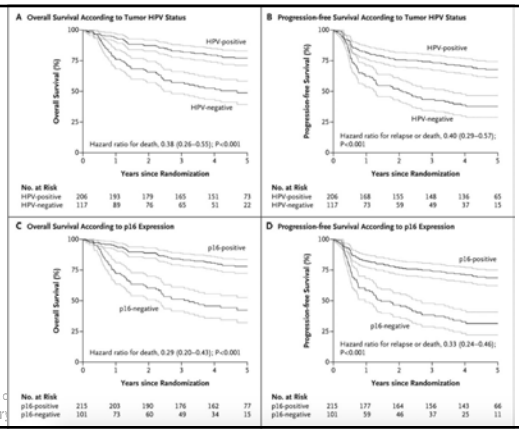




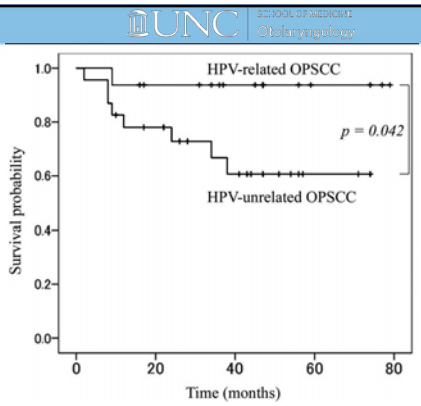
HPV Diagnostic Dilemma

- 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

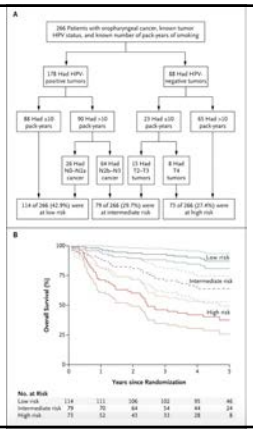


Ang et al NEJM 2010



Hasegawa et at. International Journal of Oncology 2014

Impact of Smoking
in
Era of HPV-driven OPSCC



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Ang et al NEJM 2010

HPV + OPSCC patients have improved outcomes

Degree of Risk	Characteristics	3-y OS Rate
Low	HPV+, smoking history of ≤10 pack years, and N0–N2a nodal history	93% (95% CI, 88.3–97.7)
Intermediate	HPV+, smoking history of >10 pack years, and N2b–N3 nodal disease; or	70.8% (95% CI, 60.7–80.8)
	HPV-, smoking history of ≤10 pack years, and N2b–N3 nodal disease or T2–T3 tumors	
High	HPV- and smoking history >10 pack years; or	46.2% (95% CI, 34.7–57.7)
	HPV-, smoking history ≤10 pack years, and T4 disease	

Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363 (1): 24–35, 2010.

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Revised Staging System based on HPV

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

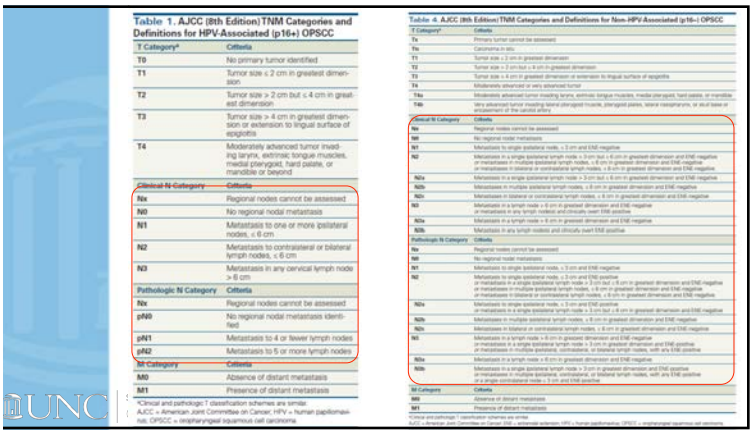

Table 1. AJCC (8th Edition) TNM Categories and Definitions for HPV-Associated (p16+) OPSCC

T Category*	Criteria
T0	No primary tumor identified
T1	Tumor size ≤ 2 cm in greatest dimension
T2	Tumor size > 2 cm but ≤ 4 cm in greatest dimension
T3	Tumor size > 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced tumor invading larynx, extrinsic tongue muscles, medial pterygoid, hard palate, or mandible or beyond
Clinical N Category	**Criteria**
Nx	Regional nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis to one or more ipsilateral nodes, ≤ 6 cm
N2	Metastasis to contralateral or bilateral lymph nodes, ≤ 6 cm
N3	Metastasis in any cervical lymph node > 6 cm
Pathologic N Category	**Criteria**
Nx	Regional nodes cannot be assessed
pN0	No regional nodal metastasis identified
pN1	Metastasis to 4 or fewer lymph nodes
pN2	Metastasis to 5 or more lymph nodes
M Category	**Criteria**
M0	Absence of distant metastasis
M1	Presence of distant metastasis

*Clinical and pathologic T classification schemes are similar.
AJCC = American Joint Committee on Cancer; HPV = human papillomavirus; OPSCC = oropharyngeal squamous cell carcinoma.

Table 4. AJCC (8th Edition) TNM Categories and Definitions for Non-HPV-Associated (p16–) OPSCC

T Category*	Criteria
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor size ≤ 2 cm in greatest dimension
T2	Tumor size > 2 cm but ≤ 4 cm in greatest dimension
T3	Tumor size > 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced tumor
T4a	Moderately advanced tumor invading larynx, extrinsic tongue muscles, medial pterygoid, hard palate, or mandible
T4b	Very advanced tumor invading lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encasement of the carotid artery
Clinical N Category	**Criteria**
Nx	Regional nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis to single ipsilateral node, ≤ 3 cm and ENE-negative
N2	Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm in greatest dimension and ENE-negative or metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative or metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm in greatest dimension and ENE-negative
N2b	Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative
N2c	Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE-negative or metastasis in any lymph node(s) and clinically overt ENE-positive
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any lymph node(s) and clinically overt ENE-positive
Pathologic N Category	**Criteria**
Nx	Regional nodes cannot be assessed
N0	No regional node metastasis
N1	Metastasis to single ipsilateral node, ≤ 3 cm and ENE-negative
N2	Metastasis to single ipsilateral node, ≤ 3 cm and ENE-positive or metastasis in a single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension and ENE-negative or metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative or metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative
N2a	Metastasis to single ipsilateral node, ≤ 3 cm and ENE-positive or metastasis in a single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension and ENE-negative
N2b	Metastases in multiple ipsilateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative
N2c	Metastases in bilateral or contralateral lymph nodes, ≤ 6 cm in greatest dimension and ENE-negative
N3	Metastasis in a lymph node > 6 cm in greatest dimension and ENE-negative or metastasis in a single ipsilateral lymph node > 3 cm in greatest dimension and ENE-positive or metastases in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive
N3a	Metastasis in a lymph node > 6 cm in greatest dimension and ENE-negative
N3b	Metastases in a single ipsilateral lymph node > 3 cm in greatest dimension and ENE-positive or metastases in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE-positive or a single contralateral node > 3 cm and ENE-positive
M Category	**Criteria**
M0	Absence of distant metastasis
M1	Presence of distant metastasis

*Clinical and pathologic T classification schemes are similar.
AJCC = American Joint Committee on Cancer; ENE = extranodal extension; HPV = human papillomavirus; OPSCC = oropharyngeal squamous cell carcinoma.

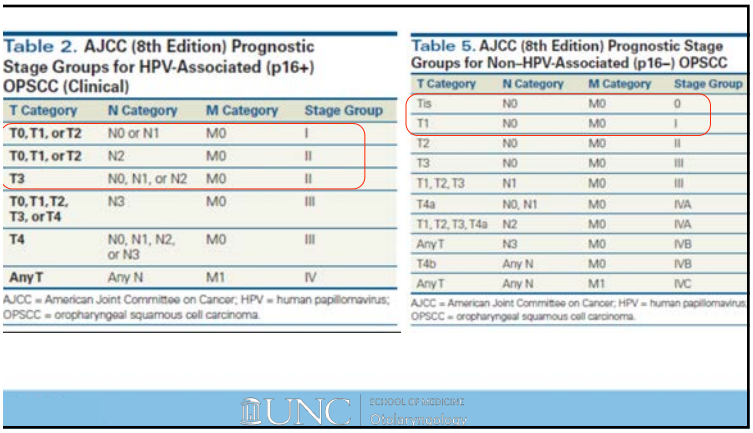

Table 2. AJCC (8th Edition) Prognostic Stage Groups for HPV-Associated (p16+) OPSCC (Clinical)

T Category	N Category	M Category	Stage Group
T0, T1, or T2	N0 or N1	M0	I
T0, T1, or T2	N2	M0	II
T3	N0, N1, or N2	M0	II
T0, T1, T2, T3, or T4	N3	M0	III
T4	N0, N1, N2, or N3	M0	III
Any T	Any N	M1	IV

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T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

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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. Chernock, MD; Carol Colasacco, MLIS, SCT(ASCP); Christina Lacchetti, MHSc; Joel Todd Moncur, MD, PhD; James W. Rocco, MD, PhD; Mary R. Schwartz, MD; Raja R. Seethala, MD; Nicole E. Thomas, MPH, CT(ASCP)[CM]; William H. Westra, MD; William C. Faquin, 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.

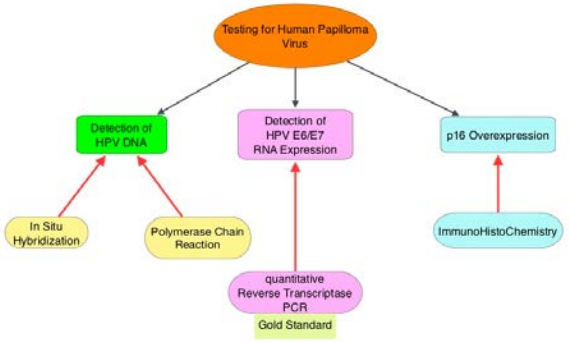
Conclusions.—Based on the systematic review and on expert panel consensus, high-risk HPV testing is recommended for all new oropharyngeal squamous cell carcinoma patients, but not routinely recommended for other head and neck carcinomas.

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

Guidelines issues in late 2017

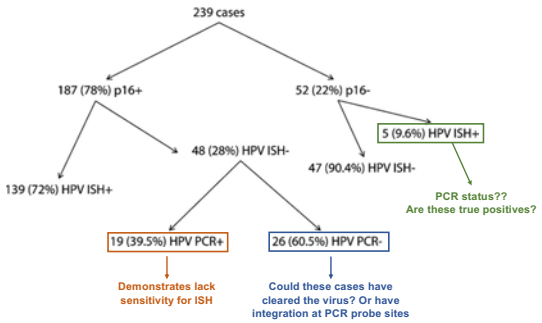
- **Pathologists still do not have a strong consensus on whether HPV or p16 positivity is the best method for reporting OPSCC tumor status**
- **Data suggest p16 has better outcome data than HPV DNA testing.**

p16 accepted as a common method of identifying HPV+ disease



Chung CH, Zhang Q, Kong CS, et al. J Clin Oncol 2014; 32:3930-3938

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

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T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

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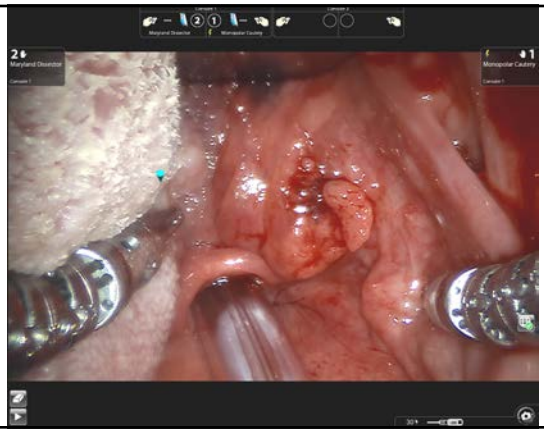
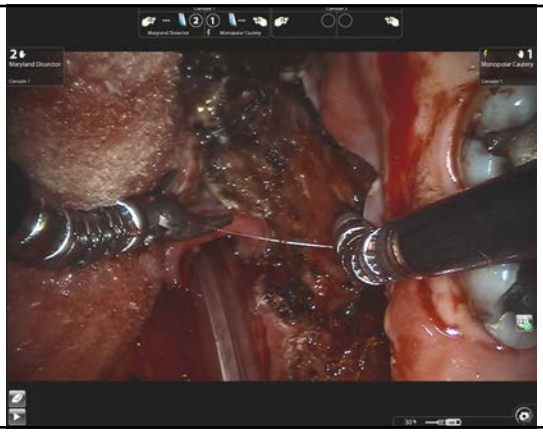
Surgery for OPSCC

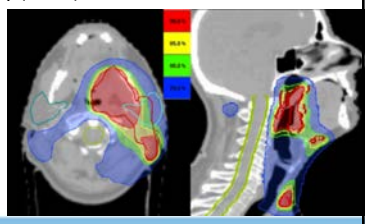
- Area of Interest and controversy
- Transoral Surgery
  - Transoral Robotic (TORS), Transoral Laser (TLM)
  - Maximize primary tumor resection
  - Preservation of skeletal anatomy
    - Improved speech and swallowing outcomes
    - Reduced feeding tube and tracheostomy rate
  - Potential to de-escalate 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?
  - Recovery time? Dry mouth? Diet changes? Recurrence? Overall QOL
  - What metric do you use ? Is there reporting bias?
- No head to head trial
- Not enough long term data

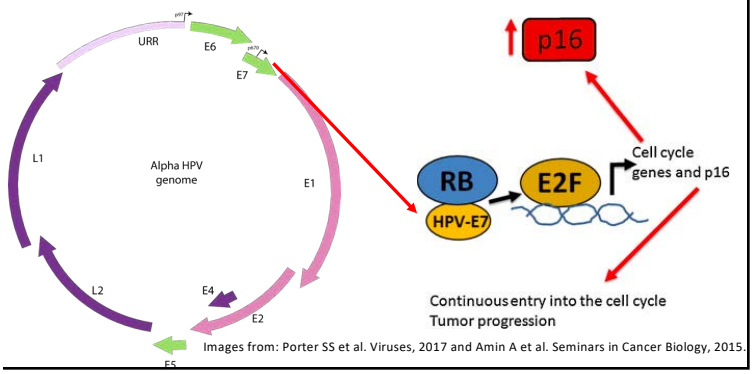
What is the best option

- 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



Images from: Porter SS et al. Viruses, 2017 and Amin A et al. Seminars in Cancer Biology, 2015.

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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 in 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

Research

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation | FROM THE AMERICAN HEAD AND NECK SOCIETY

RNA Oncoimmune Phenotyping of HPV-Positive p16-Positive Oropharyngeal Squamous Cell Carcinomas by Nodal Status

Wesley H. Stepp, PhD; Douglas Farquhar, MD; Siddharth Sheth, MD; Angela Mazul, PhD; Mohammed Mamdani, MD, PhD; Trevor G. Hackman, MD; D. Neil Hayes, MD; Jose P. Zevallos, MD

- **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

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Role of Patient Counseling for HPV

- Multidisciplinary Management Critical
- Clinical Equipoise with treatment discussion
- Patient Priorities and QOL
- Survivorship

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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.

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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