



## Human papillomavirus and H&N Cancer

Umamaheswar Duvvuri MD, PhD  
Assistant Professor of Otolaryngology  
Director of Robotic Surgery  
Division of Head and Neck Surgery



University of Pittsburgh Medical Center

Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## Disclosure

- I have served as a proctor for Intuitive Surgical Inc
- I have received research support from Intuitive Surgical Inc



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## Learning Objectives

- Discuss the epidemiology and differential diagnosis of HPV in head & neck disease
- Recognize history and physical findings in HPV disease
- Describe prevention measures and management plan for HPV-related head & neck disorders



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## Outline

- Brief review of relevant anatomy
- Biology of HPV
- Risk factors for poor prognosis among HPV-positive patients
- Defining treatment paradigms based on risk stratification



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

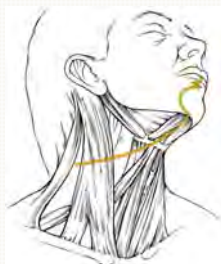
---

---

---

## Head and Neck Cancer

- About 50,000 new cases a year in NA
- HOWEVER, its one of the most common worldwide
  - Up to 560,000 cases worldwide
  - 300,000 deaths worldwide
- Derived from squamous mucosa
- Tobacco & alcohol



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

---

---

## SCCHN

- NORTH AMERICA / EUROPE**
- Cancers derived from the oropharynx are increasing in incidence
  - Associated with HPV exposure
  - Is this true worldwide?

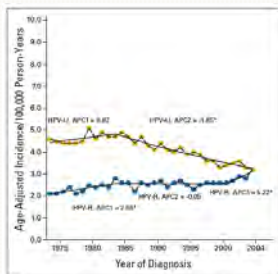


Fig 1. Age-adjusted incidence by calendar year of diagnosis for human papillomavirus (HPV)-related sites (including base of tongue, lingual tons, tonsil, oropharynx, and Waldeyer ring) and HPV-unrelated sites (including other and unspecified parts of oropharynx excluding base of tongue, tonsil, base of mouth, epiglottis, other parts of mouth). The annual percentage change (APC) in incidence is shown for HPV-related (HPV+) and HPV-unrelated (HPV-) oral squamous cell carcinomas. An asterisk for the APC value denotes statistical significance at  $P < .05$ .



Fourth Annual ENT for the PA-C

---

---

---

---

---

---

---

---

---

---



## Diagnosis

- Guided by the index of suspicion
- Physical exam including palpation of the oropharyngeal structures
- Look for the “bloody glove” sign
- Mirror exam and/or flexible laryngoscopy
- FNA biopsy of neck nodes can be very helpful



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## Staging

- Imaging is a valuable adjunct to the physical exam
  - CT with contrast
  - PET/CT to evaluate for metastases
  - MRI with contrast for (pre-)vertebral invasion
- Operative laryngoscopy allows definitive staging and sometimes treatment planning.
- Tissue diagnosis is essential, larger biopsies allow for molecular testing



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## HPV and carcinogenesis

- HPV is a known contributor to cervical dysplasia and carcinoma
- Dr. No-Hee Park: identified similarity between cervical/vaginal mucosa and OP mucosa
- Dr. Maura Gillison: described the association between HPV (**types 16/18**) and OP SCCa
- Most common histology is basaloid squamous carcinoma
  - In the context of HPV prone anatomic regions



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## Human Papillomavirus

- DNA virus
- 100 distinct sub-types
- Cutaneous & mucosal
- High-risk
  - Cervical cancer, OPC
  - Subtypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58
- Low-risk
  - Anogenital warts, laryngeal papillomatosis
  - Subtypes 6, 11



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

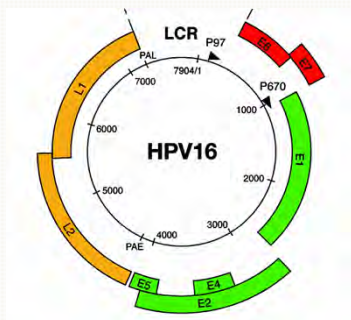
---

---

---

---

## HPV-16 Genome



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

## HPV-16 Genome

- Early region
  - E6: inactivates p53
  - E7: inactivates pRb
    - pRb inactivation induces over-expression of p16
- Late region
  - L1, L2: capsid proteins necessary for viral persistence
- Regulatory region
  - Replication/gene expression



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

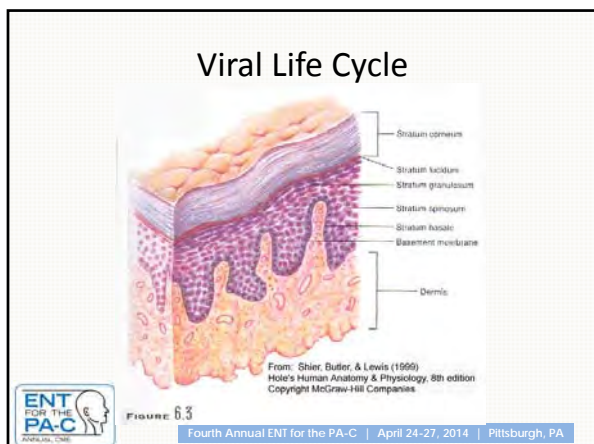
---

---

---

---

---




---

---

---

---

---

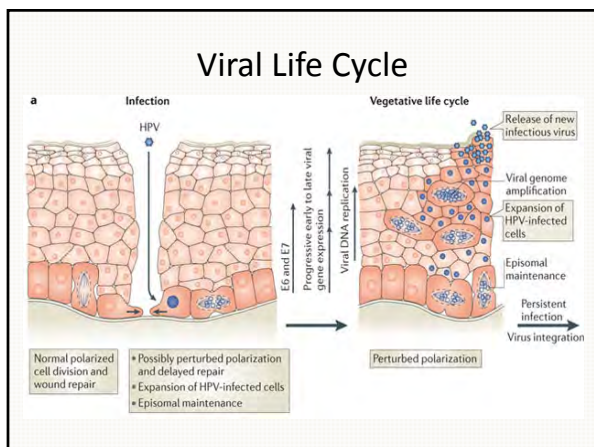
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

### Viral Life Cycle

- <1% prevalence of oral HPV infection
- 90% clear HPV infections
- Of those with persistent infections, a fraction progress to malignancy 10+ years later

**ENT FOR THE PA-C**  
ANIRLAK, ONE

D'Souza 2011; Kreimer 2013

Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

---

---

### Malignant Progression

Malignant progression

\* Invasion and metastasis  
\* Loss of polarity

- Integration into host DNA
- Loss of E2 causes deregulated expression of E6,E7
- Genetic instability (smoking, HIV, immunosuppression)

Bodily J 2011; Thorland EC 2003; Ferris RL 2005; Jeon 1995

---

---

---

---

---

---

---

---

---

---

---

---

### HPV and Head & Neck Cancer

- Chaturvedi et al JCO
  - Incidence of cancer in HPV related areas (OP) is rising
  - HPV + tumors tend to occur in middle-aged caucasian men
    - Non-smoker
    - Non-drinker
    - High number Sexual Partners

Fig 1. Age-adjusted incidence by calendar year of diagnosis for human papillomavirus (HPV)-related sites (including base of tongue, larynx, tonsil, tonsil, oropharynx, and nasopharynx) and HPV-unrelated sites (including soft palate and unspecified parts of tongue excluding base of tongue, pharynx, larynx, and nasopharynx). The HPV-related incidence shows a statistically significant increase (P < .001) compared with HPV-unrelated incidence (P < .001). The HPV-related incidence is significantly higher (P < .001) than the HPV-unrelated incidence. The APC value denotes statistical significance in P < .05.

---

---

---

---

---

---

---

---

---

---

---

---

### Optimal detection of HPV?

VOLUME 27 | NUMBER 24 | DECEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Comparative Prognostic Value of HPV16 E6 mRNA Compared With In Situ Hybridization for Human Oropharyngeal Squamous Carcinoma

Wei Shi, Hayashi Kato, Ricardo Perez-Ordonez, Melissa Piantini, Shouhai Huang, Angela Han, Bruce O'Sullivan, John Waldron, Bernard Cummings, John Kim, John English, Estera A. Dawson, Patrick Gillies, Lillian Sic, Maria Gilliam, and Fei-Fei Liu

- What's more important E6 DNA, HPV ISH or p16?
  - 111 patients
  - E6 mRNA correlated with improved OS
  - P16 and HPV ISH correlated with DFS
  - Due to technical ease, HPV ISH and p16 are recommended

Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

---

---

---

---




THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

### Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

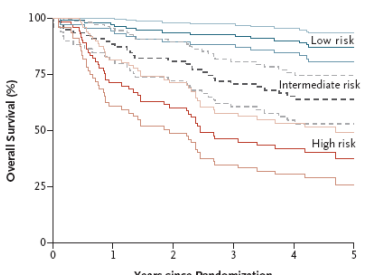
---

---

---

### Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

**B**



Overall Survival (%)


Years since Randomization

Low risk

Intermediate risk

High risk

Ang et al. 2010



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---


---

---

---

### Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

- Results:
  - HPV+ patients have better OS and PFS than HPV- patients
    - 3 yr OS 82% v 57%
  - Independent determinants of OS
    - 1. HPV status
    - 2. pack years ( $\leq 10$  v  $>10$ )
    - 3. nodal stage (N0-N2a v N2b-N3)



Ang et al. 2010

Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

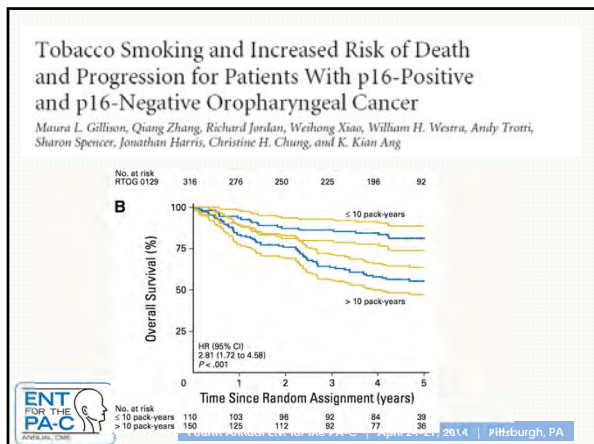
---

---

---

---






---

---

---

---

---

---

---

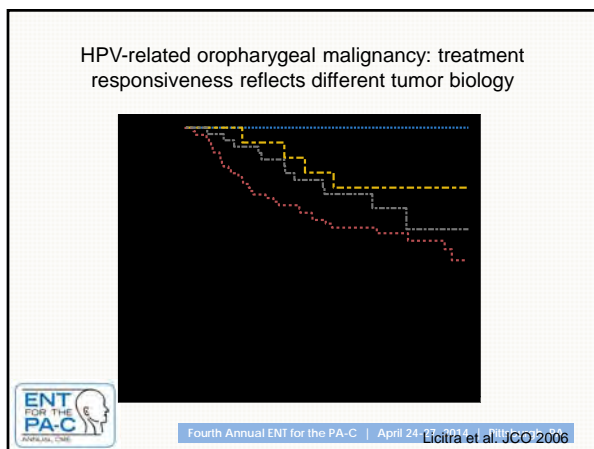
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

---

---

### Lymphatic drainage of the oropharynx

- Primary echelon
  - Internal jugular
  - Retropharyngeal
- Level V spread is rare
- Base of tongue & lateral walls
  - Level 2-3
- Posterior pharynx
  - Rouviere's node

ENT FOR THE PA-C | APRIL 24, 2014 | PITTSBURGH, PA

---

---

---

---

---

---

---

---

---

---

---

---

### Nodal status correlates with T stage

Table 78-1 — PERCENTAGE INCIDENCE OF CERVICAL LYMPH NODE METASTASIS AS DETERMINED BY CLINICAL EXAMINATION

Location and Tumor Stage	Nodal Status		
	N <sub>0</sub>	N <sub>1</sub>	N <sub>2</sub>
<b>Oropharyngeal wall</b>			
T <sub>1</sub>	75	0	25
T <sub>2</sub>	70	10	20
T <sub>3</sub>	33	23	45
T <sub>4</sub>	24	24	52
<b>Soft palate</b>			
T <sub>1</sub>	92	0	8
T <sub>2</sub>	64	12	25
T <sub>3</sub>	35	26	39
T <sub>4</sub>	33	11	66
<b>Tonsillar fossa</b>			
T <sub>1</sub>	30	41	30
T <sub>2</sub>	33	14	64
T <sub>3</sub>	30	18	62
T <sub>4</sub>	11	13	77
<b>Base of tongue</b>			
T <sub>1</sub>	30	15	65
T <sub>2</sub>	29	15	67
T <sub>3</sub>	28	23	62
T <sub>4</sub>	16	9	76

From Lindberg R. Cancer 29:1446, 1972. by permission of the American Cancer Society.

---

---

---

---

---

---

---

---

---


---

---

---

### Nodal Class and Survival

- Higher nodal class associated with worse survival in HPV-positive patients
  - N2b-N3 associated with worse OS
- N2c
  - Benefit from chemotherapy in addition to radiation



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

---


---

---

---

### Distant Mets and Survival

- Distant metastases
  - Cause of death among HPV-positive patients
  - Account for 45% of deaths in OPC



Spector 2012; Ang 2010;  
Daly ME 2010; O'Sullivan 2012

Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

---

---


---

---

### Distant Mets and Survival

- Distant metastases
  - Cause of death among HPV-positive patients
  - Account for 45% of deaths in OPC

➔ Which HPV-positive patients develop distant metastases and why?



Spector 2012; Ang 2010;  
Daly ME 2010; O'Sullivan 2012

Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---


---

---

---

### Treatment

- Surgery with adjuvant therapy
- Non-surgical



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---


---

---

---

### Surgical approaches

- General principle is to take wide resection margins (tumors have propensity for submucosal spread) followed by thin patients margins (which if positive necessitate further resection and adjuvant radiation)



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Surgical Approaches to the Oropharynx

- Transoral
- Transpharyngeal
  - Transhyoid
  - Lateral pharyngotomy
- Transmandibular
  - Mandibulotomy
  - Mandibulectomy
    - Composite resection



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

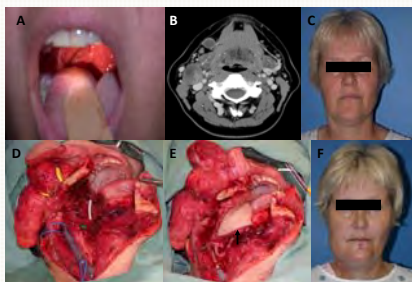
---

---

---

---

---



The application of a mandibulotomy approach to resect a tonsillar cancer. This was performed through a lip-splitting approach with resection of the right mandible. The defect was reconstructed with a radial forearm flap (arrowhead).

---

---

---

---

---

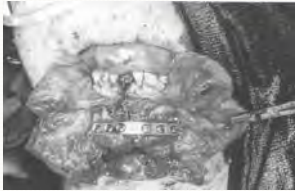
---

---


---

### The morbidity of surgery

- Need for
  - Tracheostomy
  - Gastrostomy
  - ICU stay
  - Prolonged rehabilitation /convalescence
- Lead to a transition to non-surgical management



**Many need  
XRT/CXRT anyway!**



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---


---

---

---

### Non-surgical therapy

- Alternative to surgery, since adjuvant therapy is frequently used
- Definitive therapy
  - Radiation Therapy
    - 60- 70 Gy
    - Often used for early stage tumors (stage I-II)
  - Combined chemotherapy with irradiation
    - Often used for locally advanced cases (Stage II-IV)



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---


---

---

---

### Radiotherapy alone

- Garden et al. MD Anderson experience
  - 175 pts
  - Stage I & II
  - ~50% treated with concomitant boost
  - OS at 5 yrs: 85%
    - 88% (stage I) vs 72% (stage II)
  - 29% (51 pts) developed a second primary
    - *How do we salvage these patients?*



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

---

---



### What about surgery?

- What are the indications for surgery?
  - Salvage
- Is surgery a viable definitive treatment option?



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Comparison of surgery versus CRT

- Soo KC et al Br J Cancer 2005
- 119 patients
- Stage III (20%), stage IVa (75%), Stage IVb (5%)
- Surgery & XRT (60Gy) vs (CDDP/5FU, 2 cycles) and XRT (66Gy)
- Oncologic outcomes same in both groups
  - Advanced patients
  - Sub-optimal adjuvant therapy??



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Future trends in oropharyngeal cancer

- Can we improve function?
  - Reduce morbidity
  - Maintain oncologic outcomes?
- The major demographic for HPV associated tumors is the middle aged Caucasian male



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---



### Transoral approaches

- Transoral oropharyngectomy
  - Lacourreye et al
    - 191 pts
    - Mostly T1/T2
    - 5 yr LC rate 82%, OS: 56%
  - Excellent functional results
    - No tracheotomy
    - No permanent feeding tubes



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Outcomes of MIS

- Moore et al (Mayo): 102 pts tonsillar SCC, 5 yr DFS 94%
- Henstrom et al (Mayo): 20 BOT pts, 2 yr DFS 94%
- Rich et al (Wash U): 84 ORX, 5 yr DFS 92%



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Robotic surgery

- Evolved from videoscopic surgery
- Two main concepts
  - 3-D visualization
  - ‘Wristed’ technology
    - Improved access
- Has 2 components
  - Robotic console
  - Patient-side device
    - Camera and 3 arms



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Why TORS?



- Weinstein et al.
  - 27 pts with tonsil cancer
  - Mostly T1 & T2 (75%)
  - Few T3
  - Staged neck dissection
- All pts had negative resection margins
- 11% (3/27) major complication
  - Unplanned operation
  - "Good" functional results

---

---

---

---

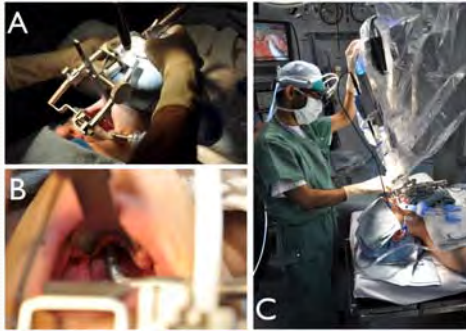
---

---

---

---

### TORS



---

---

---

---

---

---

---

---

### Robotic arm manipulation



---

---

---

---

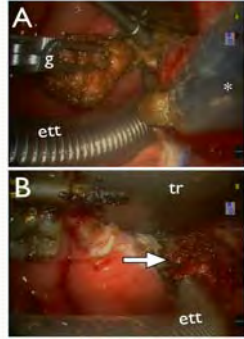
---

---

---

---

- Dissection performed with 8mm Prograsp and cautery
- Incision into area of lingual tonsil in midline
- From circumvallate papillae to vallecula
- Resection tailored to tumor



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Robotic base of tongue surgery



---

---

---

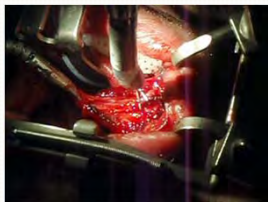
---

---

---

---

---



---

---

---

---

---

---

---

---

### Outcomes with TORS

- Limited data
- Preliminary studies from Upenn showed feasibility
- Recent studies from Europe and Korea have small numbers
- No / limited oncologic followup



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Outcomes

- Richmon et al Laryngoscope 2013
- Survey of national database comparing open to TORS
- 116 pts had TORS
- Lower rate of Gastrostomy 0% vs 19%
- Also lower rates of tracheotomy, LOS and cost.



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### De-escalation

- If HPV positive patients have improved outcomes
  - Can we de-escalate treatment to reduce morbidity?
  - Need to maintain oncologic outcomes
- WE NEED CLINICAL TRIALS



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---


---

---

---

**ECOG 3311**  
**TORS followed by Low-dose or Standard-dose IMRT in p16+ Locally Advanced OPC**

- **Objective:**
  - To evaluate the 2-yr PFS in HPV+ OPC patients treated with low-dose adjuvant RT
  - Secondary end points: Toxicity, swallowing, QOL, OS



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---


---

---

---

**ECOG 3311 Trial Design**

- **Methods:**
  - Phase II trial of intermediate risk HPV+ (P16+) OPC patients randomized to either low-dose (50 Gy) or standard-dose RT (60 Gy)
  - p16+, cT1-2N0-N2b OPC
  - Credentialing of surgeon



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

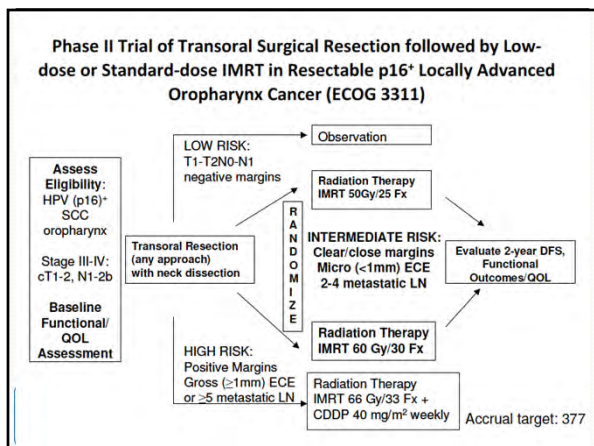
---

---

---

---

---




---

---

---

---


---

---

---

---

**PREVENTION OF DISEASE**



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---


---

---

---

**AN OUNCE OF PREVENTION...**

- Recombinant HPV vaccine 6, 11, 16, 18
- Targets the high-risk subtypes
- Was developed to help prevent
  - Penile cancer, vulvar, anal, H&N disease (16 & 18)
  - Genital Warts (6 & 11)
- Does not treat the infection



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---


---

---

---

**HPV infection**

- HPV infection is quite common
- The risk of HPV infection is increasing in sexually active women
- HPV rates rise quickly in the teen's to 20's
- Decreased rate in older adults



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Current recommendations

- Vaccination for girls before sexual debut
- Vaccination can also be administered to boys
- Uptake has been low < 30%
  - Numerous factors
- Nonetheless, vaccination will only have a measurable effect on tumor incidence after several years / decades



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Conclusions

- Oropharyngeal cancer is on the rise
  - Expected to exceed cervical cancer by 2020
- Causes include HPV infection
  - Any adult with a neck mass should be considered to have cancer
- In general HPV-associated tumors have a good prognosis!
  - Treatment options include
    - Chemoradiation
    - Robotic surgery



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Conclusions

- Not all HPV-positive patients have good clinical outcomes
- Risk factors for failure in HPV-positive patients:
  - tobacco use, N2c-N3, T4 tumors
- Genetic markers of poor prognosis will allow for further stratification of HPV-positive patients, directing de-intensification strategies for some low to intermediate risk patients.



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---



### Future directions

- The management of this cancer is evolving
- The initial results with robotic surgery is encouraging
- Prospective trials will be useful in defining the role of TORS



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---

### Thank You

Jonas T. Johnson  
Robert L. Ferris  
Seungwon (Steve) Kim  
Kara Davis  
Ken Byrd  
Vikas Mehta



Fourth Annual ENT for the PA-C | April 24-27, 2014 | Pittsburgh, PA

---

---

---

---

---

---

---

---