Human papillomavirus and H&N Cancer

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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
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

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

SCCHN

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

- Anterior inferior limit: circumvallate papillae
- Anterior superior limit: junction of hard and soft palate
- Lateral limit: lateral pharyngeal walls
- Posterior limit: posterior pharyngeal wall
- Inferior limit: vallecula and inferior base of tongue

Oropharynx is separated into:
1. Base of tongue
2. Soft palate
3. Tonsil pillars
4. Posterior pharyngeal wall

Waldeyer’s Ring is formed by:
- Lingual tonsils
- Palatine tonsils
- Inferior adenoid pad

Important in ‘unknown’ primary tumors

Presentation / Diagnosis

- Most common complaint
  - Painless neck mass (often cystic)
  - Adult neck masses are cancer till proven otherwise
- Sore throat
- Dysphagia
- Dysarthria
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

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

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
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

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

D’Souza 2011; Kreimer 2013
Malignant Progression

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


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

Optimal detection of HPV?

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

- 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
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

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

Ang et al. 2010
Tobacco Smoking and Increased Risk of Death and Progression for Patients With p16-Positive and p16-Negative Oropharyngeal Cancer

Martina L. Gillison, Qiang Zhang, Richard Jordan, Weihong Tian, William H. Westra, Andy Truss, Sharon Spencer, Jacek Potocki, Christine H. Chang, and E. Han Avr

HPV-related oropharyngeal malignancy; treatment responsiveness reflects different tumor biology

Licitra et al. JCO 2006

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
Nodal status correlates with T stage

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Higher nodal class associated with worse survival in HPV-positive patients
- N2b-N3 associated with worse OS

Nodal Class and Survival

- N2c
  - Benefit from chemotherapy in addition to radiation

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
Distant Mets and Survival

• Distant metastases
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Which HPV-positive patients develop distant metastases and why?

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

Treatment

• Surgery with adjuvant therapy
• Non-surgical

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)
Surgical Approaches to the Oropharynx

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

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!

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)

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?
Optimum Radiation Therapy

RTDG 90-03 trial
1073 pts with stage III-IV SCCHN randomized to 4 arms
Approximately 60% of patients in each arm had OP cancer
Oncologic control was main endpoint
Hyperfractionation and concomitant boost yielded superior results
Toxicity was also higher in these groups

Can we improve the toxicity & outcomes?

Chemo-Radiotherapy

INTENSITY-MODULATED RADIOTHERAPY IN THE TREATMENT OF OROPHARYNGEAL CANCER: CLINICAL OUTCOMES AND PATTERNS OF FAILURE
MEGAN E. DALY, M.D., QUYNH-THU LE, M.D., PETER G. MAXIM, PH.D., BILLY W. LOO, JR., M.D., PH.D., MICHAEL J. KAPLAN, M.D., NANCY J. FISCHBEIN, M.D., HARLAN PINTO, M.D., AND DANIEL T. CHANG, M.D.

Department of Radiation Oncology, Stanford University, Stanford, California

Chemoradiotherapy

- Calais et al. RCT
  - 222 pts
  - Stage III & IV oropharyngeal cancer
  - Randomized to XRT (70 Gy/7weeks) ± 5-FU & carboplatin
  - OS at 3 yrs: 51 vs 31%
    - Feeding tube rate 33 vs 13%
  - Local control rates also improved in the CRT group
  - Established that CRT is standard for advanced stage
What about surgery?

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

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??

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
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

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%

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
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

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

**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.

**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
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

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
PREVENTION OF DISEASE

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

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
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

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

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.
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

Thank You

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