HPV and Head and Neck Cancer:
What it means for you and your patients

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Epidemiology of Head and Neck Squamous Cell Carcinoma in the U.S.

- Incidence of HNSCC peaked in 1970s, declining since
- However, incidence of oropharynx SCC is rising
- Proportion of HNSCC arising in oropharynx
  - 18% in 1973
  - 31% in 2004
- 5-year survival rate for oropharynx SCC improving
  - 36.3% in 1974
  - 49.1% in 1997

Oropharynx squamous cell carcinoma

- Today: observing changing demographics of patients with oropharynx cancer
- Oropharynx carcinoma in North America
  - Rapid increase in incidence over past 30 years
  - Incidence has now surpassed cervical cancer
  - HPV identified as etiology in subset of oropharynx cancers
HPV and Head and Neck Cancer

- Human Papilloma Virus identified as causal agent in some head and neck cancers
  - A milestone development in head and neck oncology
  - Evidence of HPV infection in oropharynx cancers exceeds ~80% of new cases in most centers in North America
  - There are striking differences in the typical demographic profile and prognosis of HPV-positive vs. HPV-negative HNSCC

Human Papilloma Virus

- >100 different types, including high- and low-risk types
- HPV16 is most common high-risk type
  - 90% of HPV-related head and neck cancers
- HPV causes several human cancers
  - Cervical, vaginal, penile, anal, and head and neck

Natural history of oral HPV

- Exposure to HPV common, but most healthy individuals will clear the virus
  - Infects 75% of sexually active men and women
  - 90% of infected individuals clear virus within 2 years

Predilection of HPV for oropharynx

- Unique properties of reticulated squamous lymphoepithelium increase susceptibility to infection by HPV
- Long latency period between initial oral HPV infection and cancer development
  - 20 to 30 years, probably minimum of 15 years
- Less than 1% of oral HPV infections lead to oropharynx cancer
Pathogenesis of HPV-positive cancer

- Viral proteins E6 and E7
  - Bind to p53 and pRb, resulting in their inhibition
  - Role of pRb is to block cell cycle progression
  - E6 and E7 facilitate unchecked cellular replication and transformation

Pathogenesis of HPV-positive cancer

- Inhibition of pRb by HPV results in overexpression of p16, an upstream tumor suppressor protein
- Association of p16 overexpression with HPV infection is rationale for useful indirect clinical assay to identify HPV-associated tumor cells

Clinical testing for HPV-positive cancers

- No single test accepted as gold standard
- Direct detection of HPV DNA
  - PCR amplification of HPV-specific DNA primers
  - In situ hybridization using HPV-specific DNA probes in tissue

Clinical testing for HPV-positive cancers

- No single test accepted as gold standard
- Immunohistochemical detection of p16, a surrogate marker for HPV infection
  - p16 is overexpressed in keratinocytes infected with transcriptionally active high-risk HPV types
  - Simple assay that can be performed in most pathology labs
Clinical testing for HPV-positive oropharynx cancers

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<tr>
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<th>P16-Positive</th>
<th>P16-Negative</th>
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<tr>
<td>HPV-Positive</td>
<td>96%</td>
<td>4%</td>
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<tr>
<td>HPV-Negative</td>
<td>19%</td>
<td>81%</td>
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HPV-positive head and neck cancers

- Nearly always oropharynx: Tonsil or Base of tongue
- Usually poorly differentiated (basaloid)
- Higher N-stage, especially cystic metastases

HPV-positive head and neck cancers

- Frequently little or no tobacco exposure
- Younger age (40s – 60s)
- Men > Women
- Mostly White
- Higher socioeconomic status
  - More educated, higher income, more likely to be married

HPV-positive head and neck cancers

- Role of HPV in non-oropharynx HNSCC is likely small
  - Some nasopharynx, larynx, oral tongue cancers
  - Tumor location borders the oropharynx
HPV-positive head and neck cancers
- Risk factors for developing HPV+ HNSCC
  - Ever had oral sex
  - Increased number of lifetime genital or oral sex partners
  - Younger age of oral or vaginal sexual debut
  - Marijuana use

Heterogeneity of HPV-positive HNSCC
- Striking racial discrepancies in HPV-positive HNSCC in USA, with much lower incidence among Blacks, Asians, Hispanics
- Some research suggests there are differences in sexual behaviors among U.S. Whites, Blacks, Asians, and Hispanics
- Differences in oral sexual exposure may explain observed racial differences in HPV-positive HNSCC
  - Immunologic differences could also play a role

HPV-positive oropharynx cancers
- Have better prognosis than similar stage HPV-negative cancers
  - Improved survival / decreased recurrence
  - HPV-positive / never smokers do best
- Better response to radiation and chemotherapy

HPV-positive oropharynx cancers
- Not all HPV-positive oropharynx cancers do well
- Factors associated with poor prognosis for HPV-positive oropharynx cancer
  - >10 pack-year tobacco use
  - T4 primary tumors
  - Bulky nodal disease
HPV-positive oropharynx cancers

- Is de-intensification of treatment appropriate for HPV-positive tumors?
- Several trials in the U.S. studying treatment stratification by HPV status
  - ECOG1308—p16+ OPSCC patients receive Induction chemo followed by response-based dose of RT
  - ECOG 3311—p16+ OPSCC intermediate risk patients after TORS+ND randomized to receive 50 vs 60 Gy RT, no chemo
- At present, HPV tumor status which should only be consideration for patients enrolled in clinical trials

Questions patients with HPV-positive HNSCC will ask

- How did I get this cancer?
- If it’s caused by a virus, am I contagious?
- Should my spouse/partner be screened for cancer?
- Should I get the HPV vaccine? Should my spouse/partner?

Counseling patients with HPV-positive oropharynx cancers

- Sensitivity to potential social stigma if perceived as STD
- Despite viral etiology, cases of both patient and partner having HPV-positive HNSCC are unusual
- HPV vaccine not indicated

HPV vaccines and oropharynx cancer

- Two HPV vaccines approved in the U.S. for prevention of cervical cancer
  - Most effective prior to exposure of virus
  - Recommended for girls and boys, age 11-26; prior to onset of sexual activity
- Do these vaccines prevent oropharynx cancer?
  - Unknown, if direct effect
  - Indirectly, through “herd” effect
HPV-positive Oropharynx Cancer: Clinical Implications

Work up of unknown primary

- Many HPV-positive HNSCC present initially with neck metastasis, unknown primary
- Many, if not most, patients presenting as unknown primary have HPV-positive oropharynx cancer
- Unknown primary work-up
  - FNA cytology for p16
  - When p16 is positive → Focus evaluation on oropharynx for primary site, especially thorough assessment of base of tongue

Work up of unknown primary

- 56 year old man never-smoker presents with right upper neck mass
- Outside FNA—Lymphocytes and benign epithelium, most likely represents a lymphoepithelial lesion or chronic sialadenitis

Work up of unknown primary

- 56 year old man never-smoker presents with right upper neck mass
- Outside FNA—Lymphocytes and benign epithelium, most likely represents a lymphoepithelial lesion or chronic sialadenitis
- Clinical Exam: mobile, 3 cm right level II neck mass; OC/OP/NP/Lx unremarkable
Work up of unknown primary

- 56 year old man never-smoker presents with right upper neck mass
- Repeat FNA biopsy—metastatic squamous cell carcinoma with basaloid features; strongly p16 positive

MRI—
- 2 enlarged adjacent lymph nodes in right level II, each measuring up to 1.7 cm
- Subtle asymmetric prominence of the right tongue base. Otherwise, normal appearance of the aerodigestive tract mucosa.

PET/CT—
- Right level II lymph node conglomerate with corresponding hypermetabolic activity. No evidence of a primary neoplasm is seen within the head, neck, chest, abdomen, or pelvis.

To OR for Panendoscopy
Work up of unknown primary

- To OR for Panendoscopy
  - Unremarkable oral cavity, oropharynx, larynx, hypopharynx; normal esophagoscopy and bronchoscopy
- Next step?

Work up of unknown primary

- Use of TORS
    - 13/18 (72.2%) patients without PE or imaging suggestive of primary site, had primary tumor identified after TORS

Work up of unknown primary

- TORS lingual tonsillectomy
- Path: 1.1 cm invasive SCC with basaloid features, 1.5 mm thickness
HPV-positive Oropharynx Cancer: Clinical Implications

• Role of triple endoscopy for p16+ HNSCC?
  – Negligible incidence of synchronous primary tumors

HPV-positive Oropharynx Cancer: Clinical Implications

• Management of N+ neck, p16+ → interpretation of post-chemoradiation treatment imaging
  – Utility of p16 status

HPV-positive Oropharynx Cancer: Clinical Implications

• p16 status may predict need for post-RT neck dissection (Shonka et al, 2009)
  – p16-neg oropharynx tumors significantly more likely to have viable tumor in subsequent ND specimens than p16+ tumors (50% vs 18%, p=.02)
  – 3 of 8 p16-neg tumors had residual neck disease despite complete response on imaging

HPV-positive Oropharynx Cancer: Clinical Implications

• p16 status may predict need for post-RT neck dissection (Shonka et al, 2009)
  – No p16-pos tumors who had complete response on imaging had any pathologic residual metastatic lymph nodes
  – p16-pos tumors with residual neck disease were associated with incomplete response on imaging
  – Suggests that p16-pos tumors with complete response to radiation on post-treatment imaging do not need neck dissection
HPV-positive Oropharynx Cancer: Clinical Implications

- p16 status may predict recurrence (Zhang et al, 2011)
  - Initial post-treatment PET/CT negative and tumor is p16 + \( \rightarrow \) 0/6 recurrences at 2 years
  - Initial post-treatment PET/CT negative and tumor is p16 - \( \rightarrow \) 3/8 recurrences at 2 years

SUMMARY

- The incidence of oropharynx cancer is rising and HPV is the cause of the vast majority of new cases
- Oral HPV is primarily transmitted through oral sex
- Very few oral HPV infections result in cancer, and only after a long latency period (> 15 years)

SUMMARY

- Most HPV-positive HNSCC have better prognosis and show better response to treatment
- HPV status has important clinical implications for the work-up and follow-up surveillance of HNSCC
- Optimal treatment for HPV-positive HNSCC balancing efficacy and toxicity remains to be determined