HPV THE NEW SEX CANCER

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Oral Sex & Cancer

Media Hype vs. The Facts
HPV is now the leading cause of oral cancer.
Oral Cancer **KILLS** as many people as melanoma, and is now more common than leukemia.
HPV Infection and Cancer of the Oropharynx

Non-HPV = Yellow, HPV = blue
HPV = Human Papillomavirus

HPV is a very common virus; nearly 80 million people—about one in four—are currently infected in the United States.

Most HPV infections don't lead to cancer but certain types of HPV infection cause cancers. More than 100 varieties of human papillomavirus (HPV) exist.
**Human Papillomavirus (HPV) infection of epithelial cells.**

HPVs infect basal cells of squamous epithelia through sites of mechanical trauma. Infections with high-risk HPVs can lead to dysplasia and carcinoma in situ and to invasive squamous cell carcinoma. Progression is a rare and slow process and many lesions regress spontaneously.
How HPV causes cancer

Human papillomavirus (HPV) is a small deoxyribonucleic acid (DNA) virus of approximately 7900 base pairs.

Of the genes contained in the virus are viral oncogenes E6 and E7 which have transforming properties by their interaction with growth-regulating host cell proteins.

E6 interferes with the p53 protein that normally regulates growth, and E7 interferes with Rb protein which also normally regulates growth.

When Rb protein is knocked out, another regulatory protein (p16) is overexpressed (i.e. increased).
HPV and Oropharyngeal Cancer

Latency from infection:

Cervix (29 years) peak infection (20y) to cancer (49y)

HPV (10-30y) peak infection (25-30 and 55-60) and cancer 58y

HPV Vaccine impact expected by 2050
Using P16 or HPV

Either HPV status or p16 status can be used as a marker of HPV infection. In one multi-institutional trial Ten percent of those positive by p16 were negative for HPV, and 7 percent of those negative for p16 were positive for HPV.

However, studies using p16 (tumor suppressor protein) as a surrogate marker for HPV positivity appear to have demonstrated a similar impact on survival.

The p16 status, as assessed by immunohistochemistry, may provide additional information beyond HPV positivity. In a study comparing the effect of p16 expression and HPV DNA presence, cases that were HPV positive with high p16 expression had a better prognosis than those that were HPV positive but with low expression.
### New Cancer Cases in the US in 2016

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>11,700</td>
<td>4,400</td>
</tr>
<tr>
<td>Mouth</td>
<td>7,600</td>
<td>5,310</td>
</tr>
<tr>
<td>Pharynx</td>
<td>13,350</td>
<td>3,070</td>
</tr>
<tr>
<td>Oral (other)</td>
<td>2,130</td>
<td>770</td>
</tr>
</tbody>
</table>
Age: 10 y younger on one study median age 57 (versus 61 for HPV -)

Gender: 76% male

Smaller primary: T1/T2 64% (versus 44% for HPV -)

More Neck Nodes: N2/N3 in 69% (versus 51% for HPV -)

Less likely to have a second primary: 6% versus 13%
Most Common in White Men

HPV-Associated Oropharyngeal Cancer Rates by Race, Ethnicity, and Sex, United States, 2008–2012

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>1.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Black</td>
<td>1.5</td>
<td>6.9</td>
</tr>
<tr>
<td>AI/AN</td>
<td>0.9</td>
<td>4.4</td>
</tr>
<tr>
<td>A/PI</td>
<td>0.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>1.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.9</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Age-adjusted rate (cases per 100,000 persons)
Median Age for Women is 62

Rates of HPV-Associated Cancers and Median Age at Diagnosis Among Women in the United States, 2008-2012

Age-adjusted rate (cases per 100,000 women)

Age at diagnosis

<20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80

Cervix, Vagina, Vulva, Anus, Rectum, Oropharynx

Median age
Median Age for Men is 59

Rates of HPV-Associated Cancers and Median Age at Diagnosis Among Men in the United States, 2008-2012

- Oropharynx
- Penis
- Anus
- Rectum

Age-adjusted rate (cases per 100,000 men)

Age at diagnosis:
- <20
- 20-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70-79
- ≥80

Median age:
- 59
- 57
- 62

Centers for Disease Control and Prevention

CDC 24/7: Saving Lives, Protecting People™
Typical smoking related oropharynx cancer, presented with months of throat pain radiating into ear.
In HPV + cancers the primary may be small and hard to see.

Squamous Cell Carcinoma. This human papillomavirus-positive tumor presented as a diffuse erythroplakia of the left soft palate and tonsillar region.
<table>
<thead>
<tr>
<th>Signs and Symptoms of Oral Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth sore that doesn’t heal</td>
</tr>
<tr>
<td>Mouth sore that bleeds spontaneously</td>
</tr>
<tr>
<td>Velvety, white, red, or speckled patch in the mouth that is persistent</td>
</tr>
<tr>
<td>Hard, raised lesion (lump), crusts, eroded areas on the lips, gums or other areas inside the mouth</td>
</tr>
<tr>
<td>Unexplained bleeding in the mouth</td>
</tr>
<tr>
<td>Persistent pain in the mouth</td>
</tr>
<tr>
<td>Difficulty chewing, swallowing, speaking, or moving the tongue</td>
</tr>
</tbody>
</table>
## Oropharynx Symptoms Based on HPV Status

<table>
<thead>
<tr>
<th>HPV +</th>
<th>HPV -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck mass (51%)</td>
<td>Sore Throat (53%)</td>
</tr>
<tr>
<td>Sore Throat (28%)</td>
<td>Dysphagia (41%)</td>
</tr>
<tr>
<td>Dysphagia (10%)</td>
<td>Neck Mass (18%)</td>
</tr>
</tbody>
</table>
50 yo non-smoker, white male present with a lump in his left neck and the PET scan as noted.
The Oral Cancer Exam
FIGURE 3. A brief screen for oral cancer includes this eight-step examination of the inside of the mouth.
Squamous cell carcinoma under the tongue

Appearance of lesion in incandescent light

Marker with tri...
Typical Imaging for HPV Oropharynx Cancer

CT = large cystic node metastases

PET = large neck mass with small primary in tonsil
CT Scan Typical HPV + Patient

Large, Lobulated neck mass of lymph nodes with no obvious primary source

Neck biopsy = squamous
PET Scan Typical HPV + Patient

Large lymph node metastases in the neck with no obvious primary source
PET-CT = hot, cystic neck node and small lesion in tonsil
Path = squamous cancer, HPV +
<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic Screening</th>
</tr>
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<tbody>
<tr>
<td>Patient Factors</td>
<td>Practitioner Factors</td>
</tr>
<tr>
<td>Seek out oral exam</td>
<td>Recognize Symptoms</td>
</tr>
<tr>
<td>Access to healthcare</td>
<td>Perform oral exams</td>
</tr>
<tr>
<td></td>
<td>Proficient at oral exam</td>
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</tbody>
</table>
Survival for Tonsil Cancer

Cumulative proportion surviving vs. time (months)

- HPV +
- HPV -
Overall Survival

- p16\textsuperscript{intK\textsubscript{4a}} pos: 62%
- p16\textsuperscript{intK\textsubscript{4a}} neg: 26%

Time Since Treatment (months)

Standard Stage System (AJCC 7th)

Oropharynx

T1  Tumor 2 cm or less in greatest dimension
T2  Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3  Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a Moderately advanced local disease
   Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b Very advanced local disease
   Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Standard Stage System (AJCC 7th)

Regional Lymph Nodes (N)

NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2  Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3  Metastasis in a lymph node more than 6 cm in greatest dimension
Superior Cure Rates if HPV +

5 Year Survival

HPV +
HPV -

Stage I, Stage II, Stage III, Stage IV

JCO March 10, 2015 836-845
5 Year Survival in 1907 patients with HPV+ oropharyngeal cancer

Stage I: 88%  II: 82%  III: 84%, and IVA: 81%, IVB: 60%

5-year overall survival did not differ among N0 (80%) N1–N2a (87%), and N2b (83%) subsets, but was significantly lower for those with N3 disease (59%)

So need to change the staging system (only deeply invasive T4b or huge nodes (N3 > 6cm) do poorly

Lancet Oncology Volume 17, No. 4, p440–451, April 2016
Oral Cancer Treatment

- Multidisciplinary Approach
  - Surgery – various subspecialties
- Radiation Therapy
- Oncology
  - Chemotherapy
    - Drugs
    - Vaccines
    - Biologic therapy
  - Chemoprevention
Cancer of the Oropharynx

Concurrent systemic therapy/RT\textsuperscript{f,h,k}

or

Induction chemotherapy\textsuperscript{h,l} (category 3) followed by RT\textsuperscript{f} or systemic therapy/RT\textsuperscript{f,h}

Any T, N2-3 →

or

Transoral or open resection\textsuperscript{g}

Primary and neck

N2a-b → Resection of primary, ipsilateral, or bilateral neck dissection\textsuperscript{g}

N3 → Resection of primary and bilateral neck dissection\textsuperscript{g}

Chemotherapy plus radiation (cisplatin or erbitux + 70Gy)
Cancer of the Oropharynx

Concurrent systemic therapy/RT\textsuperscript{f,h,k}

or

Induction chemotherapy\textsuperscript{h,l} (category 3) followed by RT\textsuperscript{f} or systemic therapy/RT\textsuperscript{f,h}

As of 2016 the NCCN guidelines do not recommend treating HPV + patients with less intense therapy
Quick Response to Radiation combined with chemotherapy, Tonsil cancer gone by 2 ½ weeks

Squamous Tonsil Cancer

2.5 weeks after chemoradiation
Short Term Side Effects of Radiation to the Throat and Neck

1. Skin irritation
2. Dry Mouth and changes in taste and possible problems with teeth
3. Sore throat and problems with swallowing and dehydration and possible need for a feeding tube
4. Pain management problems
5. Laryngitis
6. Fatigue
Long Term Side Effects of Radiation to the Throat and Neck

1. The dryness may be permanent, depending on the amount of saliva glands in the field

2. Teeth may be vulnerable to decay, and caution is need with future dental care to avoid jaw bone problems (osteonecrosis)

3. Problems with swallowing

4. Persistent hoarseness

5. Small risk of low thyroid

6. Carotid stenosis
Transoral Robotic Surgery (TORS)
Survival if HPV + based on smoking (PY = pack years) age and stage

Adjusted Survival (probability)

Time (years)

Group I (n = 283)
Group II (n = 143)
Group III (n = 120)
Group IVA (n = 27)

Prognostic group

T
N
M
Age

I
T1-3
N0-N2c
M0
Any
≤ 20

II
T1-3
N0-N2c
M0
Any
> 20

III
T4, Any N
Any T, N2c
M0
≤ 70
Any

IVA
T4, Any N
Any T, N3
M0
> 70
Any

IVB
Any T
Any N
M1
Any
Any

JCO March 10, 2015 836-845
De-Escalation Trials for HPV…Can we use less chemotherapy or lower dose radiation and get the same result with less toxicity?
Projected Numbers of New Cases in the Future

- Oropharynx
- Oral Cavity
- Larynx
- Other pharynx

Annual Number of Cases

Calendar Year

J Clin Oncol 29:4294-4301. © 2011
HPV vaccine is CANCER PREVENTION.
www.cdc.gov/vaccines/teens