HPV in Oropharynx Cancers and Prophylactic Dental Care

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Disclosure

• We have no conflicts of interest to disclose.
Learning Objectives

- To describe HPV related Oropharynx cancers
- To identify the prevention of HPV in Oropharynx cancers
- To identify the anatomy of the oropharynx
- To identify the treatment modalities for HPV related Oropharynx cancers and their acute and late side effects
- To describe the importance of prophylactic dental care related to radiation treatment in Oropharynx cancers.
Anatomy
Waldeyer's Tonsillar Ring

• Tonsillar pillars surround palatine tonsil

• Ant: covers glossopalatine muscle

• Post: covers pharyngopalatine muscle

• Inferior part of TF: glossopalatine sulcus

Courtesy McGraw-Hill
What is HPV?

Human Papillomavirus

- HPV: is the most commonly sexually transmitted disease in the United States, that can infect the oropharynx (tonsils and back of throat), anus and genitals.

- There are many types of HPV. Some types cause cancer, warts, or have no effect.

- Oral HPV infection leads to HPV-OSCC (HPV-positive oropharyngeal squamous) cell cancer after many years.
Human Papillomavirus (HPV)

- DNA virus
- >100 different types
- Infects skin and mucosa
- Asymptomatic
- Benign growths – warts
- Oncogenic (cancer causing) types are mostly 16 and 18

Courtesy of NCI
Epidemiology

- This year, an estimated 48,330 adults (34,780 men and 13,550 women) in the United States will be diagnosed with oral or oropharyngeal cancer.
- Cancer of the oral cavity ranks as the eighth most common cancer among men.
- It is estimated that 9,570 deaths (6,910 men and 2,660 women) from these 2 diseases will occur this year.

Etiologies:

- Smoking
- Chewing tobacco
- Alcohol
- HPV infection (80% of cases)

Cancer.Net
<table>
<thead>
<tr>
<th></th>
<th>HPV negative</th>
<th>HPV positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Any</td>
<td>Tonsil</td>
</tr>
<tr>
<td>Age</td>
<td>Older</td>
<td>Younger</td>
</tr>
<tr>
<td>Gender</td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Alcohol</td>
<td>Oral sexual behavior</td>
</tr>
<tr>
<td></td>
<td>Tobacco</td>
<td></td>
</tr>
<tr>
<td>Incidence Rates</td>
<td>Decreasing</td>
<td>Increasing</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Poor</td>
<td>Good</td>
</tr>
</tbody>
</table>
### Table 2. Associations of Oropharyngeal Cancer with Sexual Behaviors.

<table>
<thead>
<tr>
<th>Sexual Behavior</th>
<th>Patients with Oropharyngeal Cancer (N=100)</th>
<th>Control Patients (N=200)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
<th>All Patients</th>
<th>HPV-16+ Patients‡</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime no. of vaginal-sex partners</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td>31 (31)</td>
<td>108 (54)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>6–25</td>
<td>41 (41)</td>
<td>63 (32)</td>
<td>2.7 (1.2–4.0)</td>
<td>2.7 (1.4–5.3)</td>
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<tr>
<td>≥26</td>
<td>28 (28)</td>
<td>29 (14)</td>
<td>3.1 (1.5–6.5)§</td>
<td>4.2 (1.8–9.4)¶</td>
<td></td>
</tr>
<tr>
<td>Lifetime no. of oral-sex partners</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12 (12)</td>
<td>38 (19)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>1–5</td>
<td>46 (46)</td>
<td>110 (55)</td>
<td>1.9 (0.8–4.5)</td>
<td>3.8 (1.0–14.0)</td>
<td></td>
</tr>
<tr>
<td>≥6</td>
<td>42 (42)</td>
<td>52 (26)</td>
<td>3.4 (1.3–8.8)†</td>
<td>8.6 (2.2–34.0)**</td>
<td></td>
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<tr>
<td>Anal sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>55 (55)</td>
<td>129 (64)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>45 (45)</td>
<td>71 (36)</td>
<td>1.3 (0.8–2.2)</td>
<td>1.6 (0.9–2.8)</td>
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<tr>
<td>Casual-sex partner††</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42 (42)</td>
<td>120 (60)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>58 (58)</td>
<td>80 (40)</td>
<td>1.7 (1.0–3.0)</td>
<td>2.4 (1.2–4.7)</td>
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<tr>
<td>Age at first intercourse</td>
<td></td>
<td></td>
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<tr>
<td>18 yr or older</td>
<td>30 (30)</td>
<td>87 (44)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>17 yr or younger</td>
<td>70 (70)</td>
<td>113 (56)</td>
<td>1.3 (0.7–2.3)</td>
<td>2.1 (1.1–3.6)</td>
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<tr>
<td>Condom use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Usually or always</td>
<td>28 (28)</td>
<td>90 (45)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Never or rarely</td>
<td>72 (72)</td>
<td>110 (55)</td>
<td>2.2 (1.2–3.8)</td>
<td>2.1 (1.3–4.0)</td>
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<tr>
<td>Sex with same-sex partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>92 (92)</td>
<td>186 (93)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Yes</td>
<td>8 (8)</td>
<td>14 (7)</td>
<td>1.0 (0.4–2.6)</td>
<td>1.1 (0.3–3.3)</td>
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<tr>
<td>Sexual partner with history of HPV-associated cancer¶¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>86 (86)</td>
<td>190 (95)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (3)</td>
<td>2 (1)</td>
<td>3.0 (0.5–20.5)</td>
<td>3.9 (0.6–25.8)</td>
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<tr>
<td>Unsure</td>
<td>11 (11)</td>
<td>8 (4)</td>
<td>2.3 (0.8–6.5)</td>
<td>2.8 (0.9–8.3)</td>
<td></td>
</tr>
</tbody>
</table>

D’Souza et al. NEJM 2007
# Prevalence HPV

## Table 3. Prevalence of HPV in HNSCCs by cancer site and geographic location

<table>
<thead>
<tr>
<th></th>
<th>No. studies</th>
<th>No. cases</th>
<th>Overall HPV prevalence (95% CI)</th>
<th>HPV16 prevalence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral cavity</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Europe</td>
<td>15</td>
<td>744</td>
<td>16.0 (13.4-18.8)</td>
<td>10.8 (8.6-13.2)</td>
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<tr>
<td>North America</td>
<td>8</td>
<td>577</td>
<td>16.1 (13.2-19.4)</td>
<td>10.1 (7.7-12.8)</td>
</tr>
<tr>
<td>Asia</td>
<td>13</td>
<td>1,133</td>
<td>33.0 (30.3-35.8)</td>
<td>22.3 (20.3-25.2)</td>
</tr>
<tr>
<td>Other*</td>
<td>2</td>
<td>188</td>
<td>18.1 (12.9-24.3)</td>
<td>14.9 (10.1-20.8)</td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>17</td>
<td>529</td>
<td>28.2 (24.4-32.2)</td>
<td>23.8 (20.2-27.7)</td>
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<tr>
<td>North America</td>
<td>7</td>
<td>285</td>
<td>47.0 (41.1-53.0)</td>
<td>42.1 (36.3-48.1)</td>
</tr>
<tr>
<td>Asia</td>
<td>4</td>
<td>54</td>
<td>46.3 (32.6-60.4)</td>
<td>35.2 (22.7-49.4)</td>
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<tr>
<td>Other*</td>
<td>2</td>
<td>101</td>
<td>36.6 (27.3-46.8)</td>
<td>33.7 (24.6-43.8)</td>
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<tr>
<td><strong>Larynx†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>19</td>
<td>799</td>
<td>21.3 (18.5-24.3)</td>
<td>13.8 (11.5-16.4)</td>
</tr>
<tr>
<td>North America</td>
<td>7</td>
<td>297</td>
<td>13.8 (10.1-18.3)</td>
<td>10.1 (7.0-14.1)</td>
</tr>
<tr>
<td>Asia</td>
<td>8</td>
<td>306</td>
<td>38.2 (32.8-43.9)</td>
<td>26.5 (21.6-31.8)</td>
</tr>
<tr>
<td>Other*</td>
<td>1</td>
<td>33</td>
<td>48.5 (30.8-66.5)</td>
<td>45.5 (28.1-63.6)</td>
</tr>
</tbody>
</table>

*Includes Central and South America, Australia, and Africa.
†Larynx includes cases of the hypopharynx.

Kreimer, 2005

D’Souza et al. NEJM 2007
BY 2020....

• The annual number of HPV-positive OPSCCs (approximately 8,700 patients) will surpass the annual number of cervical cancers (approximately 7,700 patients) with the majority occurring among men (approximately 7,400).

• By 2030, OPSCC will likely constitute a majority (47%) of all head and neck cancers.


Is There a Test for me to Find out if I Have Oral HPV?

• While there have been some commercial tests available in the dental community, the value of this testing is not clear
How can I lower My Risk of Giving or Getting oral HPV

- Condoms

- Dental Dams

When used consistently and correctly, will lower the chances of giving or getting oral HPV during oral sex.
The HPV vaccine **prevents** people from getting new HPV infections

The vaccine will **not** help you clear an infection you already have

The vaccine is recommended for people ages 5 to 26 years old

Modified from Fakhry C, D’Souza G. Discussing the diagnosis of HPV-OSCC: Common Questions and Answers, Oral Oncol (2013) Elsevier
Vaccines

GARDASIL/GARDASIL-9

• Protect against HPV types (HPV-16 and HPV-18, HPV-6, HPV-11)

• Gardasil-9 Protects against five other HPV strains responsible for 20% of cervical cancers (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58)

CERVARIX

• Protect against HPV types (HPV-16 and HPV-18)
HPV VACCINE SAFETY

- No deaths have been caused by the vaccine
- 0.05% have had “adverse events” primarily consisting of pain and swelling at the injection site or fainting
- Cervarix has been used much less in the US. 52 adverse events have been reported, most with “adverse events” as above.

The HPV Vaccine is Safe!!!

CDC.org
How does HPV cause cancer?

• HPV can cause normal cells in infected mucosa to turn abnormal

• It is unclear if having HPV alone is sufficient to cause oropharyngeal cancers, or if other factors (smoking or chewing tobacco) interact with HPV to cause those cancers.
Etiology - HPV
Presentation

- Sore throat
- Difficulty swallowing
- Earache (referred via CN9 to tympanic nerve of Jacobson)
- Painful swallowing
- Hot potato voice (with extrinsic tongue invasion-T4a)
- Hoarseness (with larynx invasion-T4a)
- Trismus (with invasion of masseter or pterygoid muscle-T4)
- Neck mass (up to 70% cLN+ on presentation)
- Enlarged LN
- Unexplained weight loss
Workup-NCCN

- H&P, including a complete H&N exam
- Mirror and fiberoptic exam as clinically indicated
- Biopsy
- **Tumor HPV testing suggested (p16)- surrogate marker that is more prognostic**
- Chest imaging
- CT and/or MRI with contrast of primary and neck
- Consider PET/CT for stage III-IV
- Dental evaluation, including panorex as indicated
- Nutrition, speech and swallow evaluation/therapy and audiogram as indicated
- EUA with endoscopy as indicated
- Pre-anesthesia studies
Why is a Pre Radiation Dental Evaluation Important?

Radiation affects the oral cavity:-

*Affects the salivary glands*- lubricates the mouth and balances the mouth’s acidity dryness in the mouth, called *xerostomia*

- Loss of lubrication to the teeth: causes dental decay and periodontal (gum) disease
- It also affect the bone: in osteoradionecrosis
The pre radiation dental evaluation may include:

- Custom topical fluoride trays
- Meticulous oral hygiene
- Long term maintenance includes three month visits to the dentist or periodontist for cleaning and checkups.
- This is a lifelong commitment that patients need to make for optimal oral health
Dental Factors

- Radiographs- panoramic
- Periodontal disease
- Caries (tooth decay)
- Root canals
- Impactions
- Large fillings, fractures
- Pain- teeth that are painful, have a history of pain sensitivity to percussion should be considered for extraction
Dental Prophylaxis

The ADA Council on Scientific Affairs encourages dentists to educate themselves and their patients about the relationships between HPV and oropharyngeal cancer, especially the growing prevalence of these cancers in younger non-smokers and non-drinkers.
Treatment
Simulation/mask making
TomoTherapy (TOMO)

Courtesy of Tomotherapy™
trueBEAM
# Radiation Side Effects

<table>
<thead>
<tr>
<th><strong>ACUTE</strong></th>
<th><strong>LATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Sore throat/mouth</td>
<td>Chronic swelling of Throat</td>
</tr>
<tr>
<td>Thick oral mucous</td>
<td>Poor wound healing after trauma, dental extraction, and difficulty swallowing</td>
</tr>
<tr>
<td>Loss of taste</td>
<td>Poor taste</td>
</tr>
<tr>
<td>Change in appetite</td>
<td>Trismus</td>
</tr>
<tr>
<td>Temporary loss of facial hair</td>
<td>Loss of thyroid function</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>Fibrosis</td>
</tr>
</tbody>
</table>
Cetuximab Rash

Causes acne-like rash

Goal is to reduce long-term toxicity
Late Side Effects

EDEMA (SWELLING)

FIBROSIS (DIFFUSE SCAR TISSUE)

Feeding Tube Dependence
Late Side Effect: Dry Mouth Syndromes

Dry mouth: speech, diet, taste, discomfort

Dental complications

Bone and soft tissue necrosis
How to improve QOL for HPV Survivors?
Research strategies to reduce toxicity

- Reduced radiation dose
- Reduced concurrent chemo dose
- Substitute biologic agent for chemo
- Use pre-radiation chemo (induction) to select best responders and then reduce radiation dose
- Clinical Trials
Future Technologies
Protons

- Dose Delivery uncertainty
- Access - still very few proton therapy machine
- $$$$$
- Phase II/III studies underway
Other Advances Possible in the future:

• HPV vaccines—not in the preventive setting but as therapies.

• Immunotherapy in head and neck cancer
Developing HPV Trials:
How can we reduce toxicity and maintain high chance for cure?

Challenges:
Safety monitoring to detect recurrences
Long term outcomes needed (>5 years)
National and International collaboration needed: smaller but more specific study populations
Long Term/Complex QOL studies are under-funded
Conclusions

- 70% to 80% of oropharyngeal SCCs are HPV related. This number is rapidly increasing.

- Men have a 3-fold higher rate of HPV infection and incidence of HPV cancer.

- 95% of HPV + oropharyngeal cancers are HPV-16 +

- The HPV vaccine is safe and effective. Both vaccines protect against the two HPV types 16 & 18 that cause most HPV oral cancers

- Dental work up is essential prior to starting radiation therapy.

- HPV infection is associated with better prognosis ~95%

- Advanced technologies in head and neck oncology lead to less acute side effects
Questions/Discussion
Thank You!

Jimmy Caudell  MD, PhD
Section Head and Associate Member
Section of Head & Neck/Cutaneous
Department of Radiation Oncology
Moffitt Cancer Center
References


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Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.