Oropharyngeal Cancer and HPV

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Disclosures

Consultant, Medtronic, Inc.
Consultant, Boulder Surgical
Medical Board, Castle Biosciences
The cancer burden

• American Cancer Society’s estimate oral cavity & oropharyngeal cancers in the United States 2019:
  • 53,000 cases
  • 10,860 deaths
  • About 70-75% of oropharynx cancer caused by HPV in US
  • 15,500 men and 3,500 women with HPV related oropharynx cancer
What’s the role of HPV

- Double stranded DNA virus
- Several hundred subtypes
- Unique to humans
- Type 16 and 18 are known carcinogens, but other less common ones (31,45) are also carcinogens
- Infects the basal epithelial cells
- Replicates with the host genome
US Cancers caused by HPV

- Burden of HPV oropharynx cancer is higher than the burden of cervical cancer in the US.
- We have no screening
- The incidence continues to rise
What do we do?

• We have a vaccine! (or three)
  • Gardisil- HPV 6, 11, 16, 18
  • Gardisil 9 HPV 6,11,16,18, 31,33,45,52,58
  • Cervarix- HPV 16,18

• Over 95% effective at preventing pre-cancers and cancers (cervical and vaginal) caused by HPV

• Not effective if patient already infected

• No proof yet, but preliminary research suggests it is effective against oropharynx cancer
Need to improve public awareness

- This is a cancer vaccine not just an STD vaccine!
  - AAP and CDC noted vaccine curves have flattened
- Vaccinate boys and girls
  - Higher incidence of this cancer in men
- According to the CDC, estimated 44,000 HPV related cancers in 2016
  - 25,000 in women (3,500 oropharynx)
  - 19,000 in men (15,500 oropharynx)
HPV Recommendations by CDC

• Girls AND boys receive three doses of vaccine at ages 11-12
• Can start as early as age 9, but should be done before age 13
• Also recommended for women until age 26, and men until age 21
• All health care providers should be advocates for HPV vaccination
• HPV vaccination is CANCER PREVENTION
• Vaccination now considered under some circumstances from age 26-45
How does this affect Head and Neck Cancer?

• Forced to reconsider some of our most routine “truths” in head and neck cancer
  • Patient demographics
  • Risk factors
  • Results of previous studies (race, gender, new drugs or surgeries, different demographics or countries)
  • Role of staging, nodes
  • Role of Extra-capsular spread (ECS)
Improved prognosis

• RTOG 0129 (2010)
  • Accelerated fraction RT and platinum compared to standard RT with platinum
  • Controlled for HPV
  • Survival (regardless of arm) was significantly different in HPV+ (82 vs. 57%)
Initial Symptoms in Patients With HPV-Positive and HPV-Negative Oropharyngeal Cancer

Wesley R. McIlwain, BS; Amit J. Sood, BA; Shaun A. Nguyen, MD, MA; Terry A. Day, MD

Table 3. Initial Chief Complaint: Based on Human Papillomavirus (HPV) Status

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Total Patients (n = 88)*</th>
<th>Positive (n = 71)</th>
<th>Negative (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck mass</td>
<td>39 (44)</td>
<td>36 (51)</td>
<td>3 (18)</td>
<td>.02</td>
</tr>
<tr>
<td>Sore throat</td>
<td>29 (33)</td>
<td>20 (28)</td>
<td>9 (53)</td>
<td>.09*</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>14 (16)</td>
<td>7 (10)</td>
<td>7 (41)</td>
<td>.005</td>
</tr>
<tr>
<td>Visualized mass</td>
<td>11 (13)</td>
<td>10 (14)</td>
<td>1 (6)</td>
<td>.60*</td>
</tr>
<tr>
<td>Globus sensation</td>
<td>9 (10)</td>
<td>7 (9)</td>
<td>2 (12)</td>
<td>.81*</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>8 (9)</td>
<td>4 (6)</td>
<td>4 (24)</td>
<td>.04</td>
</tr>
<tr>
<td>Otalgia</td>
<td>6 (7)</td>
<td>6 (8)</td>
<td>0</td>
<td>.48*</td>
</tr>
<tr>
<td>Pain (nonspecific)</td>
<td>6 (7)</td>
<td>4 (5)</td>
<td>2 (12)</td>
<td>.32*</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>2 (12)</td>
<td>.09*</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>2 (12)</td>
<td>.09*</td>
</tr>
<tr>
<td>Change in voice</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>1 (6)</td>
<td>.48*</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0</td>
<td>.99*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>.99*</td>
</tr>
</tbody>
</table>

Table 4. Initial Presenting Symptoms vs Positive Human Papillomavirus Status: Spearman Rank Order Correlation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Correlation Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck mass</td>
<td>1.263</td>
<td>.01</td>
</tr>
<tr>
<td>Sore throat</td>
<td>-1.208</td>
<td>.05</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>-3.338</td>
<td>.001</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>-1.246</td>
<td>.02</td>
</tr>
<tr>
<td>Bleeding</td>
<td>-1.225</td>
<td>.03</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-1.225</td>
<td>.03</td>
</tr>
</tbody>
</table>

* Numbers do not all sum to 100% because patients often present with multiple symptoms.
* Non-significant P-values.
HPV and Management of OP Cancer

• Studies imply we should intensify treatment for HPV negative patients, and de-intensify for HPV positive (smoking?)

• NCCN currently has no recommendations for how to do this

• New staging system
  • Does not address treatment, only outcomes
  • “Stage using AJCC 8, treat using AJCC 7”
How Should We Treat These Cancers?
Minimally invasive surgery versus radiotherapy/chemoradiotherapy for small-volume primary oropharyngeal carcinoma


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary radiotherapy ± induction or concurrent chemotherapy</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Transoral, minimally invasive surgery ± adjuvant radiotherapy or adjuvant chemoradiotherapy</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Overall survival</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Locoregional control</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Gastrostomy rate (at 1 year)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Tracheostomy rate</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Swallowing function (MDADI):</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
<tr>
<td>Quality of life (EORTC QLQ-C30 and H&amp;N35)</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
<td>—</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MDADI: MD Anderson Dysphagia Inventory.
## Current Trials

### Table 1
Selection of treatment de-escalation trials for HPV-driven oropharyngeal cancer (details available at www.clinicaltrials.gov).

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Phase</th>
<th>Population</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substitution of cisplatin by cetuximab</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01302834&lt;sup&gt;a&lt;/sup&gt; RTOG 1016</td>
<td>III</td>
<td>N = 987 Stage III-IV</td>
<td>RT (70 Gy) with Cisplatin (100 mg/m² X 2) or weekly Cetuximab</td>
</tr>
<tr>
<td>NCT01874171&lt;sup&gt;a&lt;/sup&gt; De escalate HPV</td>
<td>III</td>
<td>N = 304 Stage III-IVA</td>
<td>RT (70 Gy) with Cisplatin (100 mg/m² X 3) or weekly Cetuximab</td>
</tr>
<tr>
<td>NCT01855451</td>
<td>III</td>
<td>N = 200 Stage III-IV</td>
<td>RT (70 Gy) with weekly Cetuximab or weekly Cisplatin (40 mg/m²)</td>
</tr>
<tr>
<td><strong>Induction chemotherapy followed by lower radiation dose in good responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01084083&lt;sup&gt;a&lt;/sup&gt; ECOG 1308&lt;sup&gt;[25]&lt;/sup&gt;</td>
<td>II</td>
<td>N = 80 Stage III-IV</td>
<td>Paclitaxel, cisplatin and cetuximab followed by low (54 Gy) or standard dose IMRT with cetuximab depending on the response to IC</td>
</tr>
<tr>
<td>NCT01706939 Quarterback trial</td>
<td>III</td>
<td>N = 365 Stage III-IV</td>
<td>3 Cycles TPF followed by low (56 Gy) or standard dose (70 Gy) IMRT with weekly cetuximab, carboplatin or carboplatin only, depending on the response to IC</td>
</tr>
<tr>
<td><strong>Induction chemotherapy followed by reduced (chemo)radiation dose and volume in good responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02259655&lt;sup&gt;a,b&lt;/sup&gt; OPTIMA trial</td>
<td>II</td>
<td>N = 62 Stage III-IV</td>
<td>Patients (pts) are classified as low-risk (&lt;T3, ≤N2B, ≤10 PYH) or high-risk (T4 or ≥N2C or &gt;10 pack/years) All pts receive 3 cycles of carboplatin and nab-paclitaxel and dose/volume adapted radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1) Low-risk pts with ≥50% response received low-dose radiotherapy alone to 50 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) Low-risk pts with 30–50% response OR high-risk pts with ≥50% response received low-dose chemotherapy to 45 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3) All other pts, i.e. poor responders, receive regular-dose CRT All pts also received de-escalated RT volumes limited to the first echelon of uninvolved nodes. CRT consisted of paclitaxel, 5-FU, hydroxyurea, and 1.5 Gy twice daily RT every other week. Primary site biopsy and neck dissection performed after de-escalated treatment for pathologic confirmation</td>
</tr>
<tr>
<td><strong>Radiation therapy alone (standard or reduced dose)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02254278 NRG HN002</td>
<td>II</td>
<td>N = 295 Stage III-IV</td>
<td>Reduced dose IMRT (60 Gy) with or without cisplatin (40 mg/m²)</td>
</tr>
<tr>
<td><strong>Upfront surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01898494 ECOG 3311</td>
<td>II</td>
<td>N = 377 Stage III-IVA</td>
<td>Transoral surgery followed by pathological risk stratification:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– low-risk patients do not have adjuvant therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– Intermediate-risk patients are randomized between 50 and 60 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– High-risk patients undergo RT (66 Gy) with weekly cisplatin (40 mg/m²)</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Accrual completed.

<sup>b</sup> Very preliminary data [52] (1 year median follow-up) were presented during ASCO 2017 showing promising rates of response to induction chemotherapy and high rates of pathological response after dose reduced radiotherapy. Severe mucositis and PEG tube dependency at 3 months post RT were correlated with RT dose (p < .03 and <.001 respectively). Longer follow-up needed to consider survival results.
HPV Stratification Studies: Non-Surgical

- **ECOG 1308**
  - HPV + patients
  - Induction chemo with deintensification of RT for cCR
  - For cCR (70% of patients) 2 yr PFS and OS of 96% and 96% in patients <T4,<N2C,<10 Pack years smoking

- **Quarterback**
  - TPF, then randomize to standard or deintensified RT with carboplatin
  - Just published: 23 patients, similar 3 yr PFS/OS (87.5% vs 83.3%). 50% of failures in high risk HPV variants.
  - Conclusion: rdCRT after IC may be appropriate. HPV variant testing and smoking relevant

- **RTOG 1016**
  - HPV + patients
  - Platinum based CRT vs RT with cetuximab
  - Results favor platinum

- **De-Escalate HPV**
  - Similar to 1016
  - Results favor platinum
HPV Stratification Studies: Surgical

- **ECOG 3311**
  - HPV + patients
  - Randomized Phase II Trial
  - Transoral surgery then randomize intermediate group to standard vs de-intensified RT
- **Completed enrollment**
HPV Stratification Studies: Surgical

• ADEPT
  • Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral (ADEPT)
  • Patients can randomize or choose
  • Does ECE matter in HPV+ HNSCCa?
  • Completed Enrollment
HPV Stratification Studies: Randomized

- ORATOR- Randomize primary TORS with primary CRT
- Non-US trial
- 68 patients
- Primary endpoint- QOL at 1 year
Results

• Swallowing related scores were better in RT arm at 1 year (not a clinically meaningful difference)
• Toxicity patterns were different
• Patients should be informed of both options

Caveats
• After a bleeding death, all surgical patients were recommended for a tracheostomy.
• Wider than average margins
• 6 centers, unclear level of expertise/volume
Outcomes

- Survival
- Adverse Events
- Swallowing/QOL
Decision-making

- There is no Level 1 evidence*
- Multi-D tumor board including surgeon
- Determine unresectability
- HPV and smoking are relevant
- T1-2, N0-N3, surgery or RT
- T3-4, primary RT ***
Counseling patients

- 85-90% of humans will be infected with the HPV virus
- Most people clear it within 1-2 years of infection
- Virus, like many viruses, can remain dormant and then resurface
- Vaccinate your kids/grandkids/relatives
Conclusion

- HPV testing should be considered a reflex test
  - All head and neck SCCa
  - All head and neck unknown primary
  - Subtype testing should be considered
- Counsel patients
- Counsel dental community, doctors and media
- Refer to Multidisciplinary Center
- Participate in clinical trials
Bibliography

• Cochrane Database Syst Rev. 2016 Dec 11;12:
• Mönner Y, Simon C. Curr Treat Options Oncol. 2015 Sep;6(6):42.
Thanks