Management of Oropharynx Cancer – Does HPV make a difference?

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Case
- The patient is a 45-year-old lawyer
- Healthy, no smoking, glass of wine on weekends
- No significant co-morbidities
- He presents to his physician with a painless right neck mass, but otherwise exhibits no additional symptoms
- After two courses of antibiotics without any improvement, his PCP refers him to otolaryngology

Case: Which statement is false regarding the relationship between HPV infection and head and neck cancer?

1. HPV 16 is the viral subtype in the majority of these tumors
2. HPV-positive tumors are associated with better survival rates compared to HPV negative tumors
3. Smoking status is not relevant in HPV positive patients
4. Associated with ↑ number of sexual partners and certain sexual practices
5. Tonsillar cancer has a higher association with prior HPV infection than oral tongue cancer
Case: How would you treat this patient?

1. Concurrent cisplatin chemoradiotherapy
2. Cetuximab weekly plus radiation (Bonner)
3. Low dose radiation given HPV status
4. Surgery followed by definitive radiation or chemoradiation
5. Induction chemotherapy followed by concurrent chemoradiation (TAX324)

Why change our thinking now?

- Incidence of oropharyngeal cancer (OPSCC) is increasing
  - Attributed to HPV
  - The incidence of cancers of the tonsil and base of tongue has ↑ by 5% per year
  - More common in young adults (~50 years age)

Current Trends and Concepts

- Non-surgical therapy of tumors of the tonsil and tongue base have been favored for 10-15 years
- Factors associated with this trend
  - Similar overall treatment results
  - Morbidity and Functional impairment associated with surgery
  - Chemo/Radio-sensitivity implied by trial results
  - Minimally invasive surgical options evolving and practiced only at few centers

RT vs. Surgery – similar survival

- Mendenhall WM (2000) – RT for Tonsil cancer
  - 5 YR Local control rates – T1 83%, T2 81%, T3 74%, and T4 60%
- Selek (2004) – RT for Early-stage OP cancer
  - 5 YR local, regional, locoregional, and disease specific survival rates were 85%, 93%, 81%, and 77%
Radiotherapy - Limitations

- Full course RT can be offered only once; the rate of second primary cancers of the head neck among patients with oral and OPSCC is 20% to 27%
- RT and CRT are also associated with significant short- and long-term adverse effects
- This is more relevant today --> a younger HPV-positive OPSCC survivor will tend to live longer, being more susceptible to either late adverse effects or need RT in the future for a second primary

What then is the role of surgery?

- Best opportunity to biologically stage disease so adjuvant therapy can be used in a judicious manner and dose -- ?pN stage / ?ECS status
- Advent of trans-oral approaches and improved surgical tools allow better access, exposure and consequently control on surgical margins.
  - Transoral laser oropharyngectomy for SCC tonsil
  - Transoral Robotic Surgery (TORS) for Base of Tongue Neoplasms
- Advent of selective neck dissection allows neck treatment without adding significant morbidity to surgical therapy

<table>
<thead>
<tr>
<th>eStage</th>
<th>pStage</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
<td>3</td>
</tr>
<tr>
<td>Stage I</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage II</td>
<td>9</td>
<td>5</td>
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<tr>
<td>Stage III</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>49</td>
</tr>
</tbody>
</table>

- Surgical staging altered clinical staging in 40% (20/49)
- Neck dissection changed nodal status in 23% (11/46) of patients
  - The incidence of occult nodal metastasis was 26% (7/27, cN0→pN+)
  - 21% were down staged (4/19, cN1→pN0)
- T staging changed in 26% (13/49) of patients
  - 2/18, cT1→pT2 and 11/31, cT2→pT1
- ECS was identified in 28% (5/18 neck dissections)

Rohan R. Walvekar, Ryan J. Li, William E. Gooding, Michael K. Gibson, Dwight Heron, Jonas T. Johnson, Robert L. Ferris. ROLE OF SURGERY IN LIMITED (stage I-III) CANCERS OF THE OROPHARYNX Laryngoscope, 2008 Dec;118(12):2129-34
**HPV+ OPSCC – A New Disease**

![Diagram showing HPV+ OPSCC](image)

**ECOG 2399: Study Design**

- **Induction chemotherapy**
  - Paclitaxel 175 mg/m²
  - Carboplatin AUC 6
  - q21 days
  - 2 cycles

- **Concurrent chemoradiation**
  - RT 70 Gy / 35 fx / 7 weeks
  - Paclitaxel 30 mg/m²/week

**ECOG 2399: HPV Results**

<table>
<thead>
<tr>
<th></th>
<th>HPV-pos</th>
<th>HPV-neg</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>Larynx</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Total</td>
<td>38 (40%)</td>
<td>58 (60%)</td>
</tr>
</tbody>
</table>

* Determined by in situ hybridization for HPV serotype 16, 31, 33, 35

**ECOG 2399: Efficacy by HPV Status**

<table>
<thead>
<tr>
<th>Response</th>
<th>HPV-pos</th>
<th>HPV-neg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>82%</td>
<td>55%</td>
<td>.01</td>
</tr>
<tr>
<td>Protocol</td>
<td>84%</td>
<td>57%</td>
<td>.07</td>
</tr>
<tr>
<td>2-Year PFS</td>
<td>86%</td>
<td>53%</td>
<td>.02</td>
</tr>
<tr>
<td>2-Year OS</td>
<td>95%</td>
<td>62%</td>
<td>.005</td>
</tr>
</tbody>
</table>

- **Survival, OP cancers**
  - 2-Year PFS: 85% vs. 50%, p = .05
  - 2-Year OS: 94% vs. 58%, p = .004
**HPV Status and Survival in RTOG 0129**

- 433 (60%) Of 721 Had Oropharynx Primary
- 323 (75%) Of 433 Had HPV Determination
- 206 (64%) Of 323 Were HPV-positive
- 198 (96%) Of 206 Were HPV16-positive

<table>
<thead>
<tr>
<th></th>
<th>HPV-positive</th>
<th>HPV-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>P16-positive</td>
<td>192 (96%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>P16-negative</td>
<td>22 (19%)</td>
<td>94 (81%)</td>
</tr>
</tbody>
</table>

Kappa = 0.80; 95%CI 0.73-0.87
Ang and Gillison, NEJM, 2010

**HPV Status and Survival in RTOG 0129: Two-year Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV-Positive (%)</th>
<th>HPV-Negative (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>87.9</td>
<td>65.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progress-free Survival</td>
<td>71.8</td>
<td>50.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local-regional Failure</td>
<td>13.6</td>
<td>24.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Distant Metastases</td>
<td>9.7</td>
<td>12.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Second Primary Tumor</td>
<td>3.9</td>
<td>11.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Aerodigestive SPT</td>
<td>2.9</td>
<td>7.7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Gillison et al., ASCO 2009, #6003

**Long-term toxicity of Chemoradiation (CRT)**

Machtay et al. JCO 2008

- Long-term morbidity from CRT in three prospective clinical trials
- 99 / 230 (43%) with “severe” late toxicity

**Trials to address are this underway**

**ECOG 1308**

Induction followed by Reduced Dose (54Gy) IMRT/Cetuximab

**INDUCTION**

- (3 cycles)
  - Docetaxel 75mg/m² q21d
  - Cisplatin 75mg/m² q21d
  - Cetuximab 250mg/m² qwk

**CONCURRENT**

- IMRT 54Gy/30 fx
- IMRT 69.3Gy/35 fx
- Cetuximab 250mg/m² qwk

Accrual 90 (closed)

Cetuximab loading dose = 400mg/m² on Day 1 of cycle 1 with Induction

* CR indicates clinical CR and in patients with near CR will undergo biopsies of primary site to confirm pathological CR
Robotic Head & Neck Surgery

TORS MultiCenter Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N=177/192</th>
<th>Mayo N=36</th>
<th>Penn N=100</th>
<th>UAB N=41</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Margins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7/162 (4.3%)</td>
<td>1/35 (2.9%)</td>
<td>4/87 (4.6%)</td>
<td>2/40 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Estimated Blood Loss (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean SD</td>
<td>82.8 130.1</td>
<td>30.2 59.0</td>
<td>120.5 159.1</td>
<td>37.2 38.9</td>
<td></td>
</tr>
<tr>
<td>Long-Term Tracheostomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Rate</td>
<td>4/177 (2.3%)</td>
<td>0/36 (0)</td>
<td>2/100 (2.0%)</td>
<td>*2/41 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Swallowing without PEG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 (93%)</td>
<td>34 (97%)</td>
<td>81 (93%)</td>
<td>35 (88%)</td>
<td>–</td>
</tr>
</tbody>
</table>

Evolving Standard of Surgical Care in Oropharynx cancer

Transoral laser microsurgery and Robotic surgery are great for the primary tumor, but what about the neck?

- N2/ECS are current determinants of adjuvant therapy – reassessment of prognostic value is ongoing in HPV/p16+ disease
**ECOG 3311 p16+ trial – Low Risk OPSCC:**

Personalized adjuvant therapy based on pathologic staging of surgically excised HPV+ oropharynx cancer

- **Assess Eligibility:** HPV (p16+) SQ oropharynx
- **Stage III-IV:** T1-2N1b (no T1N1)
- **Baseline Functional/QOL Assessment**

**LOW RISK:**

- T1-2N1b negative margins
- Transoral Resection (any approach) w/ neck dissection
- Observation

**INTERMEDIATE:**

- Clear margins < gross EGS or 2-3 metastatic LN
- Evaluate for 2-year PFS
- Local/Regional Recurrence, Functional Outcomes/QOL
- Radiation Therapy IMRT 50Gy/25 Fx

**HIGH RISK:**

- Positive Margins < Gross EGS or ≥4 metastatic LN
- Radiation Therapy IMRT 60 Gy/30 Fx +
  - CDDP 100 mg/m² q/weekly

**RANDOMIZED:**

- Low Risk: Observation
- Intermediate: Radiation Therapy IMRT 50Gy/25 Fx
- High Risk: Radiation Therapy IMRT 60 Gy/30 Fx +
  - CDDP 100 mg/m² q/weekly

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**The Virus Particle**

- The virus shell or coat has 2 proteins L1 and L2
- The virus shell consists of 72 pentamers each of 5 molecules of L1 that stud the surface of the particle
- L2 sits deep in the dimple in the centre of the rosette

- Virus neutralizing antibodies recognize conformational epitopes in L1
- Neutralizing antibodies to L2 are not made in natural infections

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**What is unique about HPV+/p16+ disease that inform trial design?**

- Survival good to outstanding (70-90%), so improvement in PFS unlikely -> equivalence design
- Functional/QOL measurements may assume status of primary endpoint
- Major benefit may be late (what is appropriate timeframe?), and may be difficult to measure (lack of validated instruments, i.e. fibrosis scale?)
- Younger patients may tolerate surgery, and conversely benefit more greatly from personalized treatment intensity

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**GARDASIL™ and Cervarix™:**

HPV-targeted Cancer Vaccines

- Quadrivalent HPV 6/11/16/18 L1 virus-like particle (VLP) vaccine
- VLPs are produced in *Saccharomyces cerevisiae*.
  - The L1 proteins self-assemble into VLPs.
  - Purified VLPs are adsorbed on aluminum-containing adjuvant.
  - The adjuvant is amorphous aluminum hydroxyphosphate sulfate (225 μg per dose).
- Each 0.5-mL dose contains HPV Types 6/11/16/18 (20/40/40/20 μg L1 protein, respectively).
“So Doctor, can the HPV vaccine prevent (probably) or treat (no) OPSCC?”

**Summary**

- Oropharyngeal cancer rising 5%/yr for 15-20 years
- HPV+ survival is very good, clouding interpretation of recent chemoradiation trial results
- Acute and long-term toxicity in a younger HPV+ group warrants re-evaluation of therapeutic approach – robotic surgery is feasible and safe (FDA approved)
- Surgical staging can permit personalized therapy
- Trials to demonstrate equivalent outcome with reduced radiation or chemotherapy are being designed – ECOG 3311 in development
- Therapeutic HPV vaccination is needed, after successful proof of principle for prevention vaccine
Multidisciplinary management of head and neck cancer patients

Collaboration for a Common Goal

OHNS
Jonas Johnson, MD
Eugene Myers, MD
Carl Snyderman, MD
David Eibling, MD
Alec Vaezi, MD, PhD
Seungwon Kim, MD
Uma Duvvuri, MD, PhD

Rand McNally Top 10 cities
1. Pittsburgh
2. San Francisco
3. Seattle
4. Portland
5. Philadelphia
6. Rochester, N.Y.
7. Washington, D.C.
8. San Jose-Sunnyvale, Calif.
9. Boston
10. Madison, Wis.

Vaccinate your kids

Radiation Oncology
Dwight Heron, MD
Greg Kubicek, MD

Medical Oncology
Michael Gibson, MD
James Ohr, MD