Oropharyngeal Squamous Cell Carcinoma: Surgery vs Radiation?

Daniel Clayburgh, MD PhD
Outline

• A brief history of oropharyngeal SCC treatment
• What is TORS?
• TORS oncologic outcomes
• TORS functional outcomes
• When is adjuvant therapy needed?
• Future directions
• TORS and the unknown primary
History of OPSCC treatment

Prior to the 1990’s, open surgery and adjuvant radiation were standard treatment for oropharyngeal SCC:

- Transoral radical tonsillectomy
- Mandibular swing
- Lateral pharyngotomy
- Transhyoid
Mandibular swing approach

Anatomic basis of tumor surgery
Wood, W, Staley, C, and Skandalakis, J
ed Springer, 2010
Many drawbacks

- Large, complex procedures
- Highly morbid – dysphagia, wound complications, jaw problems, etc
- Reconstructive options were more limited 25 years ago (microvascular reconstruction in its infancy)
1990s: Rise of chemoradiation

INDUCTION CHEMOTHERAPY PLUS RADIATION COMPARED WITH SURGERY PLUS RADIATION IN PATIENTS WITH ADVANCED LARYNGEAL CANCER

THE DEPARTMENT OF VETERANS AFFAIRS LARYNGEAL CANCER STUDY GROUP*


Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer

Arlene A. Forastiere, M.D., Helmuth Goepfert, M.D., Moshe Maor, M.D., Thomas F. Pajak, Ph.D., Randal Weber, M.D., William Morrison, M.D., Bonnie Glisson, M.D., Andy Trotti, M.D., John A. Ridge, M.D., Ph.D., Clifford Chao, M.D., Glen Peters, M.D., Ding-Jen Lee, M.D., Ph.D., Andrea Leaf, M.D., John Ensley, M.D., and Jay Cooper, M.D.

(N Engl J Med 2003;349:2091-8.)

Randomized Trial of Radiation Therapy Versus Concomitant Chemotherapy and Radiation Therapy for Advanced-Stage Oropharynx Carcinoma

Gilles Calais, Marc Alfonsi, Etienne Bardet, Christian Sire, Thierry Germain, Philippe Bergerot, Béatrix Rhein, Jacques Tortochaux, Patrick Oudinot, Philippe Bertrand

Journal of the National Cancer Institute, Vol. 91, No. 24, December 15, 1999
(Chemo)radiation for OPSCC

- Cure rates equivalent to prior surgical techniques
- Avoided sequelae of open surgery – organ preservation
- Surgery used primarily for recurrence/salvage
Long-term price of radiation

- Dysphagia/stricture
- Xerostomia
- Dental decay/osteoradionecrosis
- Risk of 2\textsuperscript{nd} malignancy

By the 2000’s, oropharyngeal cancer itself began to change
Head & Neck Cancer
Rising Incidence of Oropharyngeal Cancer

Chaturvedi AK. *J Clin Oncol* 2011
Human Papillomavirus (HPV)

- Sexually transmitted DNA virus
  - Replicates exclusively in keratinocytes
  - Infects basal cells in squamous epithelium via microtrauma to skin or mucosa
  - >100 types (high and low risk)

- Common
  - Prevalence: 3-5% adolescents, 5-10% adults
  - 80% acquire HPV during lifetime
  - 80% clear spontaneously
Human Papillomavirus (HPV)

- Associated with numerous cancers:
  - Cervical
  - Anal
  - Vaginal
  - Penile
  - Oropharynx

5.2% cancers worldwide
HPV and Cancer

Chan JK, Berek JS. JCO 2007
High-risk HPV Identified

Kreimer A et al. *Cancer Epidemiol Biomarkers Prev* 2005
HPV-associated Head & Neck Cancer
A Different Disease

- HPV+ OPSCC patients more likely to be:
  - White
  - married
  - college-educated
  - annual income > $50,000
- Not associated with tobacco or alcohol use
- STD; increased risk with increased # of lifetime sexual partners
<table>
<thead>
<tr>
<th>FACTOR</th>
<th>HPV+</th>
<th>HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sites</td>
<td>Tonsil, BOT</td>
<td>All</td>
</tr>
<tr>
<td>Gender</td>
<td>3:1 male</td>
<td>4:1 male</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>SES</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Risks</td>
<td>Sexual behavior</td>
<td>Tobacco</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol</td>
</tr>
</tbody>
</table>
HPV-associated Head & Neck Cancer
Improved survival

RTOG 0129: Phase III RCCT

Ang K et al. *NEJM* 2010
HPV-associated Head & Neck Cancer
Tobacco exposure still matters!

Low risk:
HPV+, <10 pack-years
HPV+, >10 pack-years, N0-N2a

Medium risk:
HPV+, >10 pack-years, >N2b
HPV-, <10 pack-years, T1-3

High Risk:
HPV-, <10 pack-years, T4
HPV-, >10 pack-years

Risk of death from HNSCC increased 1% for each pack-year of smoking

Risk of death from HNSCC increased 1% for each pack-year of smoking
HPV-associated Head & Neck Cancer

Improved survival

- Implications for clinical trials
  - Need to stratify patients by HPV status

- Implications for patient care
  - Intensify therapy for HPV – patients?
  - Lessen therapy for HPV + patients?
Outline

• A brief history of oropharyngeal SCC treatment
• **What is TORS?**
• TORS oncologic outcomes
• TORS functional outcomes
• When is adjuvant therapy needed?
• Future directions
• TORS and the unknown primary
Development of TORS

- Robotic-assisted surgery 1st pioneered in 1980s – neurosurgery and urology
- Now utilized in a variety of surgical specialties
- 1st head and neck applications in early 2000’s
- TORS developed at U Penn – 1st case series published 2006
- FDA approved for oral cavity/oropharyngeal resections in 2009
TORS – Da Vinci surgical robot
TORS – Da Vinci surgical robot
TORS – Da Vinci surgical robot
TORS radical tonsillectomy
TORS – Medrobotics system
Increasing use of primary surgery for OPSCC

Liederbach et al Ann Surg Onc 2015 epub ahead of print
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• A brief history of oropharyngeal SCC treatment
• What is TORS?
  • TORS oncologic outcomes
  • TORS functional outcomes
• When is adjuvant therapy needed?
• Future directions
• TORS and the unknown primary
## Initial publications on TORS

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>HPV+ n (%)</th>
<th>Overall Survival</th>
<th>Disease-specific survival</th>
<th>Recurrence-free survival</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1y</td>
<td>1.5y</td>
<td>2y</td>
</tr>
<tr>
<td>Weinstein</td>
<td>47</td>
<td>n/a</td>
<td>96%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89</td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen</td>
<td>50</td>
<td>37 (74%)</td>
<td>96%</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Gendon</td>
<td>30</td>
<td>n/a</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore</td>
<td>66</td>
<td>44 (67%)</td>
<td></td>
<td></td>
<td>96%</td>
</tr>
</tbody>
</table>

Genden et al Laryngoscope. 2011;121(8):1668-1674
Meta-analysis of TORS outcomes for early stage OPSCC

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Event rate and 95% CI</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsen &amp; Moore</td>
<td>14/17</td>
<td>0.82</td>
<td>0.57</td>
<td>0.94</td>
<td></td>
<td>26.48</td>
</tr>
<tr>
<td>Mercante &amp; Rastico</td>
<td>10/10</td>
<td>0.95</td>
<td>0.55</td>
<td>1.00</td>
<td></td>
<td>5.12</td>
</tr>
<tr>
<td>Weinstein &amp; Quon</td>
<td>23/25</td>
<td>0.92</td>
<td>0.73</td>
<td>0.98</td>
<td></td>
<td>19.72</td>
</tr>
<tr>
<td>Sinclair &amp; McCulloch</td>
<td>42/42</td>
<td>0.99</td>
<td>0.84</td>
<td>1.00</td>
<td></td>
<td>5.30</td>
</tr>
<tr>
<td>Lawson &amp; Matar</td>
<td>6/7</td>
<td>0.86</td>
<td>0.42</td>
<td>0.98</td>
<td></td>
<td>9.19</td>
</tr>
<tr>
<td>Moore &amp; Olsen</td>
<td>30/33</td>
<td>0.91</td>
<td>0.75</td>
<td>0.97</td>
<td></td>
<td>29.23</td>
</tr>
<tr>
<td>Austre &amp; Yachine</td>
<td>6/6</td>
<td>0.93</td>
<td>0.42</td>
<td>1.00</td>
<td></td>
<td>4.98</td>
</tr>
</tbody>
</table>

Local control 96.2%, regional control 91%, distant control 100%
DSS: 90%, OS 95%

Kelly et al *Oral Oncology* 2014 50:696-703
Radiation vs transoral surgery

Meta-analysis:
- Primary treatment of T1-T2, N0, M0 OPSCC
- Either radiation or transoral surgery as treatment modality
- Included 2 yr, 3yr, or 5yr DSS
- Included at least 25 patients

<table>
<thead>
<tr>
<th></th>
<th>Radiation</th>
<th>Surgery</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td># of studies</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td># of patients</td>
<td>729</td>
<td>276</td>
<td></td>
</tr>
<tr>
<td>5yr disease-specific survival</td>
<td>90.4%</td>
<td>89.6%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>5yr locoregional control</td>
<td>79.3%</td>
<td>86.7%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Salvage success</td>
<td>50.1%</td>
<td>93.6%</td>
<td>NR</td>
</tr>
<tr>
<td>5 yr overall survival</td>
<td>58.8%</td>
<td>78.1%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Morisod and Simon *Head & Neck* 2015 epub ahead of print
Outline

• A brief history of oropharyngeal SCC treatment
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• **TORS functional outcomes**
• When is adjuvant therapy needed?
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• TORS and the unknown primary
Functional consequences of OPSCC treatment

- Dysphagia
- Dysguesia
- Xerostomia
- Velopharyngeal insufficiency
- Chewing difficulty
- Speech problems
- Dental decay/ORN

Key factors:
- Advanced stage
- Base of tongue tumor
- Chemoradiation
Functional outcomes after XRT

Long-term G-tube dependence after radiation: 15-25%

Long-term G-tube dependence after chemoradiation: 18-51%

**most quoted data involves conventional XRT techniques**

<table>
<thead>
<tr>
<th>Variable</th>
<th>91-11</th>
<th>97-03</th>
<th>99-14</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding tube dependence &gt; 2 years post-radiation therapy</td>
<td>—*</td>
<td>29*</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>RTOG late toxicity criteria, grade 3+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngeal dysfunction</td>
<td>16</td>
<td>28</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>Laryngeal dysfunction</td>
<td>22</td>
<td>6</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Other (eg, infection, fistula)</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Any</td>
<td>38†</td>
<td>40†</td>
<td>21†</td>
<td>99†</td>
</tr>
<tr>
<td>No severe late toxicity event (controls)</td>
<td>50</td>
<td>62</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviation: RTOG, Radiation Therapy Oncology Group. *Feeding tube data were not collected at all in RTOG study 91-11. †Numbers do not always add up along columns, due to some patients having more than one toxicity event.

Machtay J Clin Oncol 2008; 26:3582-3589
## IMRT and functional outcomes

<table>
<thead>
<tr>
<th></th>
<th>CRT</th>
<th>IMRT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2yr &gt;grade 2 dysphagia</td>
<td>3.6%</td>
<td>10.5%</td>
<td>0.40</td>
</tr>
<tr>
<td>2 yr grade 1-2 xerostomia</td>
<td>26%</td>
<td>15%</td>
<td>0.15</td>
</tr>
<tr>
<td>3 month g tube dependence</td>
<td>51%</td>
<td>14%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 yr g tube dependence</td>
<td>0%</td>
<td>5%</td>
<td>0.55</td>
</tr>
<tr>
<td>2 yr grade 3 cervical esophageal stricture</td>
<td>0%</td>
<td>5.3%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

IMRT g tube dependence

McBride et al Head Neck 2014; 36:492-498
Setton et al Cancer 2015; 121:294-301
QOL measures after transoral surgery

Table 1. Functional outcomes of transoral surgical (TOS) approaches for oropharyngeal squamous cell carcinoma (OPSCC)

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>TNM</th>
<th>Adjuvant treatment</th>
<th>Functional outcomes at 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2015[21••]</td>
<td>TORS/TLM</td>
<td>T1-3/N1-2c</td>
<td>RT 100 %</td>
<td>UW-QOL for swallowing at 91.5/100</td>
</tr>
<tr>
<td>Leonhardt 2012[24]</td>
<td>TORS</td>
<td>T1-4/N0-2b</td>
<td>CRT 19 %/RT 60 %</td>
<td>PSS-HN back to baseline for eating, reduced for speech</td>
</tr>
<tr>
<td>More 2012[25]</td>
<td>TORS</td>
<td>T1-3/N0-2c</td>
<td>CRT 60 %/RT 20 %</td>
<td>MDADI back to baseline</td>
</tr>
<tr>
<td>Sinclair 2011[26]</td>
<td>TORS</td>
<td>T1-2/N0-2c</td>
<td>CRT 31 %/RT 45 %</td>
<td>MDADI from pre-tx 82 to post-tx 74</td>
</tr>
<tr>
<td>Genden 2011[22]</td>
<td>TORS</td>
<td>T1-2/N0-2c</td>
<td>CRT 60 %/RT 20 %</td>
<td>PSS-HN and FOIS back to baseline</td>
</tr>
<tr>
<td>Haughey 2011[13]</td>
<td>TLM</td>
<td>T1-4/N0-3</td>
<td>CRT 16 %/RT 58 %</td>
<td>FOSS back to 0–2 in 87 %</td>
</tr>
<tr>
<td>Grant 2006[23]</td>
<td>TLM</td>
<td>T1-4/N0-3</td>
<td>CRT 0 %/RT 47 %</td>
<td>FOSS back to baseline</td>
</tr>
</tbody>
</table>

TLM transoral laser microsurgery, TORS transoral robotic surgery, RT radiotherapy, CRT chemoradiotherapy, FOIS functional oral intake score, FOSS functional outcome swallowing scale, MDADI M.D. Anderson Dysphagia Inventory, PSS-HN performance status scale for head and neck cancer, UW-QOL University of Washington Quality of Life
# Initial TORS QOL data

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Tumor Site(s)</th>
<th>Temporary Tracheostomy</th>
<th>Tracheostomy dependence &gt;1 year</th>
<th>Oral diet only within 6 weeks</th>
<th>Gastrostomy tube</th>
<th>Permanent gastrostomy tube</th>
<th>Preoperative MDADI</th>
<th>1 month postoperative MDADI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boudreaux et al</td>
<td>36</td>
<td>OC, OP, larynx</td>
<td>3%</td>
<td>0%</td>
<td>79%</td>
<td>25%</td>
<td>17%</td>
<td>77</td>
<td>61</td>
</tr>
<tr>
<td>Gendon et al</td>
<td>18</td>
<td>OP + larynx</td>
<td>0%</td>
<td>0%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iseli et al</td>
<td>54</td>
<td>OC, OP, larynx</td>
<td>9%</td>
<td>0%</td>
<td>83%</td>
<td>17%</td>
<td>17%</td>
<td>75</td>
<td>65</td>
</tr>
<tr>
<td>Moore et al</td>
<td>45</td>
<td>OP</td>
<td>31%</td>
<td>0%</td>
<td>89%</td>
<td>18%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weinstein et al</td>
<td>47</td>
<td>OP (stage III+IV)</td>
<td>11%</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>White et al</td>
<td>89</td>
<td>OP + larynx</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gendon et al</td>
<td>30</td>
<td>OP + larynx</td>
<td>13%</td>
<td>0%</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Hurtuk et al</td>
<td>64</td>
<td>OP + larynx</td>
<td>n/a</td>
<td>n/a</td>
<td>100%</td>
<td>19%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moore et al</td>
<td>66</td>
<td>OP</td>
<td>26%</td>
<td>2%</td>
<td>97%</td>
<td>27%</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
QOL after TORS w/o adjuvant tx

Analysis of 34 patients receiving TORS alone

- 2 patients had temporary feeding tube placement

- no tracheostomies
Outline

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Utility of adjuvant RT in HNSCC

Radiotherapeutic Management of Surgical Recurrences and Postoperative Residuals in Tumors of the Head and Neck

GILBERT H. FLETCHER, M.D., and W. TH. EVERS, M.D.

ABSTRACT—One hundred and forty-seven cases of gross disease of the head and neck were irradiated between Jan. 1, 1963, and June 1, 1968. Nineteen patients were irradiated because the surgical specimen did not show an adequate margin. Only one patient was lost to follow-up. Tables give the relative importance of histologic type, anatomic site of primary lesion, and late recurrence, and also give the relation between prophylactic irradiation and gross recurrence and between failure above the clavicle and technique of treatment. Seven cases are reported in detail.

INDEX TERMS: Head, cancer • Larynx, cancer • Lips, cancer • Mouth, cancer • Neck, cancer • Paranasal Sinuses, cancer • Pharynx, cancer • Salivary Glands, cancer

Radiology 95: 186–188, April 1970

COMBINED RADIATION THERAPY AND SURGERY IN THE MANAGEMENT OF ADVANCED HEAD AND NECK CANCER: FINAL REPORT OF STUDY 73-03 OF THE RADIATION THERAPY ONCOLOGY GROUP

SIMON KRAMER, MD, RICHARD D. GELBER, PhD, JAMES B. SNOW, MD, VICTOR A. MARCIAL, MD, LOUIS D. LOWRY, MD, LAWRENCE W. DAVIS, MD, and RICHARD CHANDLER, MD

HEAD & NECK SURGERY 10:19–30, 1987

Use of adjuvant radiotherapy for advanced stage/high risk disease has been standard practice for decades.
Adjuvant chemoradiation in HNSCC

DEFINING RISK LEVELS IN LOCALLY ADVANCED HEAD AND NECK CANCERS: A COMPARATIVE ANALYSIS OF CONCURRENT POSTOPERATIVE RADIATION PLUS CHEMOTHERAPY TRIALS OF THE EORTC (#22931) AND RTOG (#9501)

Jacques Bernier, MD, PhD,1 Jay S. Cooper, MD,2 T. F. Pajak, PhD,3 M. van Glabbeke, Ir,4 J. Bourhis, MD, PhD,5 Arlene Forastiere, MD,6 Esat Mahmut Ozsahin, MD, PhD,7 John R. Jacobs, MD,8 J. Jassem, MD,9 Kie-Kian Ang, MD,10 J. L. Lefebvre, MD11

Overall Survival
Patients with positive margin and/or ECE

Bernier et al Head Neck 2005; 27:843-850

<table>
<thead>
<tr>
<th>Year</th>
<th># at Risk</th>
<th>EORTC</th>
<th>RTOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>122</td>
<td>130</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>111</td>
<td>116</td>
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<tr>
<td>2</td>
<td>59</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( P = 0.019 \) for EORTC 22931 vs. RTOG 9501
Current Guidelines

Cancer of the Oropharynx

Base of tongue/tonsil/posterior pharyngeal wall/soft palate

CLINICAL STAGING

T3-4a, N0-1

TREATMENT OF PRIMARY AND NECK

Concurrent systemic therapy/RT, cisplatin (category 1) preferred

or

Surgery for primary and neck

Adverse features

or

Induction chemotherapy (category 3) followed by RT or chemo/RT

ADJUVANT TREATMENT

Complete clinical response

Residual disease

Salvage surgery

RT

Follow-up (See FOLL-A)

Recurrence or Persistent Disease (See ADV-2)

No adverse features

Extracapsular spread and/or positive margin

Chemo/RT (category 1)

Other risk features

RT or Consider chemo/RT

Complete clinical response

Residual disease

Salvage surgery

Multimodality clinical trials

See Principles of Radiation Therapy (ORPH-A).

See Principles of Surgery (SURG-A).

See Principles of Systemic Therapy (CHEM-A).

Adverse features: extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular embolism (See Discussion).

See Discussion on induction chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HPV+ OPSCC prognostic features

Analysis of 5-year DSS in 170 OPSCC patients (98 HPV+, 72 HPV-)

<table>
<thead>
<tr>
<th>Adverse Feature</th>
<th>P value: HPV-</th>
<th>P value: HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT3-4</td>
<td>&lt;0.001</td>
<td>0.112</td>
</tr>
<tr>
<td>pN2-3</td>
<td>0.002</td>
<td>0.474</td>
</tr>
<tr>
<td>2 or more +LN</td>
<td>0.005</td>
<td>0.499</td>
</tr>
<tr>
<td>ECS+</td>
<td>0.030</td>
<td>0.628</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>0.003</td>
<td>0.476</td>
</tr>
</tbody>
</table>

Is ECS important in HPV+ OPSCC?

Maxwell et al Cancer 2013; 119:3302-8
Is ECS important in HPV+ OPSCC?

Gopalakrishna et al, 2015 Ann Surg Onc epub ahead of print
Chemotherapy may not be useful in older patients

Meta-analysis of 93 RCT’s with >17,000 subjects

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>LRT + CT</th>
<th>LRT</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>Absolute difference at 5 years ± sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 50</td>
<td>803/1296</td>
<td>860/1288</td>
<td>-107.6</td>
<td>386.9</td>
<td></td>
<td>9.8 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>51-60</td>
<td>1069/1645</td>
<td>1198/1661</td>
<td>-136.4</td>
<td>539.7</td>
<td></td>
<td>7.8 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>61-70</td>
<td>972/1368</td>
<td>988/1330</td>
<td>-56.2</td>
<td>457.8</td>
<td></td>
<td>3.0 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>71 or over</td>
<td>273/356</td>
<td>260/336</td>
<td>-3.5</td>
<td>114.7</td>
<td></td>
<td>-0.7 ± 3.9</td>
<td></td>
</tr>
</tbody>
</table>

p_inter = 0.02
p_trend = 0.003

Pignon et al Radiother and Oncol 2009; 92:4-14
Current thinking on adjuvant therapy for HPV+ OPSCC

ECOG 3311 risk stratification

Low risk: T1-2, N0-1 >3mm margins no adverse features

Intermediate risk:
• Close (<3mm) margins
• Microscopic (<1mm) ECS
• 2-4 +LN metastases
• PNI/ALI

High risk:
• Positive margins
• Gross ECS
• >4 +LN metastases

Observation

Radiation

Chemotherapy+ Radiation
Outline

• A brief history of oropharyngeal SCC treatment
• What is TORS?
• TORS oncologic outcomes
• TORS functional outcomes
• When is adjuvant therapy needed?
• Future directions
• TORS and the unknown primary
Two lines of thinking in current OPSCC treatment

Treatment de-intensification in low-risk HPV+ OPSCC

Treatment intensification in high-risk HPV- OPSCC
Patient Population:
Oropharyngeal squamous cell carcinoma

REGISTER

Positive for p16

STRATIFY: RT planning: unilateral vs. bilateral

RANDOMIZE

ARM 1: 60 Gy in 6 weeks + Cisplatin weekly for 6 weeks

ARM 2: 60 Gy in 5 weeks using 6 fractions per week
ECOG 33-11

Accrual: 377

1. Resectable oropharynx carcinoma, p16+ by IHC, PS 0-1
2. Credentialing of surgeon required as part of site participation, neck levels dissected and nodal yield (> nodes/neck)
3. Radiotherapy will be given with an intensity modulated radiotherapy (IMRT) technique. Standard ECOG credentialing through QARC will be required.
4. Stratify by current/former smoking history (≤ 10 pk-yr vs. > 10 pk-yr)
5. Low Risk: T1-T2, NO-N1 AND clear (> 3mm) margins, AND no ECE or PNI/LVI.
6. High Risk: Any of the following features: one or more positive margin(s) with any T stage, OR "Extensive" (> 1mm) ECE, OR > 5 metastatic lymph nodes (regardless of primary tumor margin status).
7. Intermediate Risk: Any of the following features: one or more "close" (< 3mm) margin(s), OR "Minimal" (1 mm) ECE, OR 2-4 metastatic lymph nodes [N1-N2b neck disease (regardless of primary tumor margin status)], OR with perineural invasion or lymphovascular invasion.
8. If ≤ 2 events are observed among the first ten patients registered on Arm A within one year, currently enrolled and subsequently enrolled low risk patients who have not progressed will be treated with IMRT 50 Gy
9. Unknown Risk. Patients found to have N2C or N3 disease on final pathologic analysis.
Randomized Phase II Trial of Transoral Endoscopic Head and Neck Surgery followed by Risk-Based IMRT and Weekly Cisplatin versus IMRT and Weekly Cisplatin for HPV Negative Oropharynx Cancer

**RTOG 1221**

**Arm 1: eHNS* + Neck Dissection** (Experimental Arm)

“Risk-based” post-operative Adjuvant Therapy, +/- IMRT (60 Gy) +/- Weekly cisplatin for high-risk patients with ≥5 metastatic nodes, extracapsular extension, or positive surgical margins on final surgical pathology

**Arm 2: Chemoradiotherapy** (Control Arm)

IMRT (70 Gy) + Weekly cisplatin

* eHNS = TLM or TORS

Study terminated 2/11/15 due to poor accrual
Outline

• A brief history of oropharyngeal SCC treatment
• What is TORS?
• TORS oncologic outcomes
• TORS functional outcomes
• When is adjuvant therapy needed?
• Future directions
• TORS and the unknown primary
Overview

• What is CUP? Why is finding the primary important?
• Algorithm for the use of IHC to identify tumor type
• Utility of PET in CUP
• Panendoscopy and tonsillectomy
• TORS and base of tongue biopsy
• Algorithm for workup of CUP
Epidemiology of CUP

- Carcinoma of unknown primary (CUP): histological diagnosis of metastatic disease without identification of the primary tumor
- 1.5% to 9% of all head and neck malignancies with 50-75% of these being SCC
- Subsequent manifestation of the primary site occurs in 20 to 30% of cases
- Typical patient: male, 55 to 65 years old, history of tobacco and/or alcohol use
  - This pattern is expected to change with an increase HPV associated oropharyngeal cancer
Historical Workup

- History and physical examination with FFL
- FNA of lymph nodes with appropriate staining
- Cross sectional imaging
  - Detects tumor in 9.3 to 20% with neg exam
- PET scan
  - Detection rate: 24.5%, sens: 88, spec 75%
  - FP in OP / salivary glands, 5mm min size
- Laryngoscopy with directed biopsies and tonsillectomy
Historical Sites of Found Primaries in CUP after Completion of Workup

• Cianchetti 2009
  – Retrospective review of 236 patients
  – Occult primary found in 53%
  – Tonsillectomy resulted in finding primary in 15%
Rationale for Finding the Primary: Unknown Primary Treatment Fields
Rationale for Finding the Primary: Definitive Treatment Fields
Rationale for Finding the Primary: Post TORS Treatment Fields
Survival Benefit to Finding the Primary

- McQuone et al 1998
  - Retrospective review
  - 37 patients with CUP
  - 9 primaries found with routine tonsillectomy
  - Improved OS and DFS in found primary group
Survival Benefit in the Era of HPV

- Davis et al 2014
  - Matched cohort study of 44 patients
  - Taken to OR for DL & tonsillectomy/TORS
  - HPV nodal status associated with rate of finding primary
  - Finding primary associated with improved OS & DFS

<table>
<thead>
<tr>
<th>HPV status</th>
<th>Identified (n = 22)</th>
<th>Unidentified (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Positive</td>
<td>21</td>
<td>95.5</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Overview

• What is CUP? Why is finding the primary important?
• Algorithm for the use of IHC to identify tumor type
• Utility of PET in CUP
• Panendoscopy and tonsillectomy
• TORS and base of tongue biopsy
• Algorithm for workup of CUP
Immunohistochemistry in CUP

FNA of neck mass - carcinoma

p63 → HNSCC

- p16

Melanoma
Lymphoma
Thyroid
Others

- Cytokeratin

+ mucicarmine → Adenoid cystic?

+ Adenocarcinoma NOS
Overview

- What is CUP? Why is finding the primary important?
- Algorithm for the use of IHC to identify tumor type
- **Utility of PET in CUP**
- Panendoscopy and tonsillectomy
- TORS and base of tongue biopsy
- Algorithm for workup of CUP
Utility of PET/CT

Multiple studies have examined the role of PET and PET/CT
- primary detection rates range from 14-44%
- meta-analysis limited by different inclusion criteria, scanner changes, other issues

What is the true clinical utility?

Rudmik et al performed PET/CT prior to panendoscopy
- the surgeon performing panendoscopy was blinded to PET results, biopsied based on examination and CT imaging
- the PET/CT results were then revealed in the OR, and additional biopsies were taken as directed by imaging

<table>
<thead>
<tr>
<th>Biopsy result</th>
<th>Traditional</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Positive</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Study was stopped at interim analysis due to significance of results

Overview

- What is CUP? Why is finding the primary important?
- Algorithm for the use of IHC to identify tumor type
- Utility of PET in CUP
- Panendoscopy and tonsillectomy
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Panendoscopy and tonsillectomy: How should the tonsil be managed?

A highly suspicious tonsillar lesion should be biopsied, rather than tonsillectomy
- simple tonsillectomy is not an oncologic resection
- later radical tonsillectomy for treatment is easier if the tonsil is not fully removed

In the absence of an obvious lesion, tonsillectomy is better than random deep biopsies
- 29.5% detection rate vs 3.2% for biopsies

Bilateral tonsillectomy should be considered
- some studies show contralateral involvement in 23-30% of patients
- others show rates of 1-2%
- may make post-treatment surveillance easier

Overview

• What is CUP? Why is finding the primary important?
• Algorithm for the use of IHC to identify tumor type
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• Panendoscopy and tonsillectomy
• TORS and base of tongue biopsy
• Algorithm for workup of CUP
TORS BOT resection for detection of unknown primary

• Does it improve detection rates?

• Does detection allow for reduction in chemoradiation dose?

• What are the risks?

• Is it cost-effective?
### Does adding BOT resection increase primary detection rate?

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th># of patients</th>
<th>BOT resection modality</th>
<th>Hit rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta et al (2013)</td>
<td>Pittsburgh</td>
<td>10</td>
<td>TORS</td>
<td>90%</td>
</tr>
<tr>
<td>Patel et al (2013)</td>
<td>Univ of Washington, MD Anderson, UAB, Univ of Texas-Houston, Johns Hopkins, OHSU</td>
<td>47</td>
<td>TORS</td>
<td>72.3%</td>
</tr>
<tr>
<td>Durmus et al (2014)</td>
<td>Ohio State</td>
<td>22</td>
<td>TORS</td>
<td>77.3%</td>
</tr>
<tr>
<td>Graboyes et al (2014)</td>
<td>Washington Univ.</td>
<td>65 (all p16+)</td>
<td>TORS/TLM</td>
<td>89%</td>
</tr>
</tbody>
</table>

**Historical detection rate: 17-53%**
Does detection allow for reduced chemoradiation treatment?

True randomized trial data for this do not exist

Virtually all studies performed neck dissection in conjunction with TORS - clears gross disease and allows for postop RT doses - provides complete pathologic staging data to guide adjuvant therapy

**Durmus et al (Ohio State)**
- 100% of patients received postop RT
- 59% were able to avoid chemotherapy

**Graboyes et al (Washington Univ)**
- 25% Surgery alone
- 27% Adjuvant RT
- 48% Adjuvant chemo-RT

When indicated, post-resection RT doses are typically lower than definitive treatment doses (60 Gy vs 70Gy)
What are the risks?

Bleeding is the most feared complication of TORS. Overall rate 3.1%-7.5%

<table>
<thead>
<tr>
<th>Study</th>
<th>Institution</th>
<th># of patients</th>
<th>Complications</th>
<th>Trach/PEG (during adjuvant therapy unless specified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehta et al (2013)</td>
<td>Pittsburgh</td>
<td>10</td>
<td>none</td>
<td>0 trach, 1 PEG</td>
</tr>
<tr>
<td>Patel et al (2013)</td>
<td>Univ of Washington, MD Anderson, UAB, Univ of Texas-Houston, Johns Hopkins, OHSU</td>
<td>47</td>
<td>Hemorrhage (4) Tongue swelling (1)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Durmus et al (2014)</td>
<td>Ohio State</td>
<td>22</td>
<td>NR</td>
<td>none</td>
</tr>
<tr>
<td>Graboyes et al (2014)</td>
<td>Washington Univ.</td>
<td>65 (all p16+)</td>
<td>Hemorrhage (6) Shoulder weakness (5)</td>
<td>8% trach, 28% PEG</td>
</tr>
</tbody>
</table>

What are the costs?

Radiation average medicare payment schedules (2012):
3D CRT: $11335.88
IMRT: $20,606.02

Chemo cost (whole cost of drug, does not include admin, supportive care, etc):
3 cycles of cisplatin = $372
8 cycles of cetuximab = $36,000


Table 6. Incremental Cost-Effectiveness Ratio for Each Treatment Strategy.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Hospital Costs, $</th>
<th>Physician Costs, $</th>
<th>Total Costs, $</th>
<th>Effectiveness</th>
<th>Incremental Cost, $</th>
<th>Incremental Effectiveness, %</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUA/tonsillectomy</td>
<td>832</td>
<td>528</td>
<td>1360</td>
<td>0.3</td>
<td>0</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>Sequential EUA/TORS</td>
<td>5318</td>
<td>954</td>
<td>6272</td>
<td>0.87</td>
<td>4913</td>
<td>0.57</td>
<td>8619</td>
</tr>
<tr>
<td>Simultaneous EUA/TORS</td>
<td>6037</td>
<td>986</td>
<td>7023</td>
<td>1</td>
<td>751</td>
<td>0.13</td>
<td>5774</td>
</tr>
</tbody>
</table>

Abbreviations: EUA, examination under anesthesia with tonsillectomy; ICER, incremental cost-effectiveness ratio; TORS, transoral robotic surgery.
TORR BOT resection for detection of unknown primary

• Does it improve detection rates?
  Yes – increases hit rate to 80-90% (possibly higher in HPV+)

• Does detection allow for reduction in chemoradiation dose?
  Possibly – clear margins – postop dose; possible dose reduction (pending ECOG 3311 results)

• What are the risks?
  Hemorrhage, local tissue damage/injury

• Is it cost-effective?
  Probably – further analysis including chemo/RT costs needed
Technique in Pancake Biopsy

Video courtesy of Uma Duvvuri, MD PhD
Overview

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- Algorithm for workup of CUP
Proposed Current Workup Scheme

Clinical history/physical examination

↓

FFL

CT/MRI with contrast

↓

PET-CT

+ -

FNA of neck mass (with IHC if possible)

Panendoscopy

+ -

Biopsy of obvious lesion(s)

Tonsillectomy (unilateral vs bilateral)

↓

TORS base of tongue resection