THE EVOLVING TREATMENT OF SCCA OF THE OROPHARYNX

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Otolaryngology
Disclosures

- I have nothing to disclose.
Changing Role of Surgery

Chen Ay et al. Larygoscope. 2007; 117:16-21
RCT’S: A SHIFT TOWARDS ORGAN-PRESERVING NON-SURGICAL TREATMENT

• Veterans Affairs Laryngeal Cancer Study Group
  – Arm 1: Induction chemotherapy
    • Responders: proceed to XRT
    • Non-responders: proceed with surgery + post-op XRT
  – Arm 2: Surgery + post-op XRT
  – No difference in 5-yr overall survival

RCT’S CONTINUED…

• EORTC Head and Neck Cancer Cooperative Group
  – Similar to VA trial design: Stage III/IV pyriform sinus CA
  – Long-term survival rates were similar in the laryngectomy and induction chemotherapy groups


• Intergroup 91-11
  – Similar to VA trial, except showed that chemotherapy given CONCURRENTLY with XRT provided better local control than induction chemotx followed by XRT


• EORTC #22931 and RTOG #9501
  – In the post-operative management of patients with advanced head and neck cancer with high-risk features, adjuvant chemotherapy-enhanced radiation therapy (CERT) was shown to be more efficacious than radiotherapy alone in terms of locoregional control and disease-free survival.

SCCA OF THE OROPHARYNX
SURGERY, RADIATION OR BOTH

• Parsons et al
  – Review of 51 studies
  – 6400 patients (tonsil SCCA and tongue base)
    • Surgery with or without RT
    • RT with or without necks dissection

• Results: Base of Tongue
  – Local control → 79% vs 76% (P=0.087)
  – Local-regional control → 60% vs 69% (P=0.009)
  – 5 year survival → 49% vs 52%
  – 5 yr cause specific survival → 62% and 63% (P=0.4)
SCCA OF THE OROPHARYNX
SURGERY, RADIATION, OR BOTH

• Results: Tonsil
  – Local control \(\rightarrow\) 70\% vs 68\% (\(P=0.2\))
  – Local-Regional Control \(\rightarrow\) 65\% vs 69\% (\(P=0.1\))
  – 5 year survival \(\rightarrow\) 47\% vs 43\% (\(P=0.2\))
  – 5 year cause specific survival \(\rightarrow\) 57\% vs 59\% (\(p=0.3\))

• Complications
  – Base of Tongue
    • Severe \(\rightarrow\) 32\% vs 3.8\% (\(P<0.001\))
    • Fatal complication \(\rightarrow\) 3.5\% vs .4\% (\(P<0.001\))
  – Tonsillar region
    • Severe \(\rightarrow\) 23\% vs 6\% (\(P<0.001\))
    • Fatal complication (\(P<0.001\))
• Furthermore, available data on the functional consequences of treatment suggest the superiority of RT +/- ND. The authors conclude that RT +/- ND is preferable for the majority of patients with SCC of the oropharynx. *Cancer 2002;94:2967–80.*
Long-term Toxicity of Radiation

Machtay et al. JCO 2008

Long-term morbidity from RT, chemoRT in three prospective clinical trials

99 / 230 (43%) pts: “severe” late toxicity

<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></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.
CHANGING TRENDS IN HNSCC

Graph A: Pounds of tobacco per adult vs. Years (1880 to 1909)
Graph B: Rate/100,000 vs. Years (1975 to 2010)
HPV PREVALENCE

• Gillison et al 2012
  – Prevalence of infection pts aged 14-69 → 6.9%
    • HPV type 16 infection was 1.0%
  – Bimodal age distribution
    • Peak prevalence age 30-34 yrs (7.3%) and 60-64 yrs (11.4%)
  – Men higher prevalence than women for oral HPV infection
    • 10.1% vs 3.6%
  – Infection less common among those without a hx of sexual contact vs. those with a hx of sexual contact
    • 0.9% vs 7.5%
  – Prevalence increases with greater number of sexual partners and with cigarette smoking
  – The incidence of HPV+ OPSCCA is currently 2.6 per 100,000.
Phenotypically Favorable

- Perfect set up for TOS
  - Smaller primary tumors
  - Accessible
  - Better prognosis
    - Live longer
    - Avoid CRT in younger patients

**Table 1. Comparison of HPV-Negative and HPV-Positive Head and Neck Cancers**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HPV-Negative</th>
<th>HPV-Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>All sites</td>
<td>Tonsil, BOT</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Tobacco/alcohol</td>
<td>Sexual behavior</td>
</tr>
<tr>
<td>Cofactors</td>
<td>Poor oral hygiene</td>
<td>Marijuana use</td>
</tr>
<tr>
<td>Age</td>
<td>Older cohorts</td>
<td>Younger cohorts</td>
</tr>
<tr>
<td>Sex</td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td>Incidence</td>
<td>Decreasing</td>
<td>Increasing</td>
</tr>
<tr>
<td>Stage</td>
<td>Variable</td>
<td>Early T stage, advanced N stage</td>
</tr>
<tr>
<td>Histology</td>
<td>Keratinized</td>
<td>Basaloid/poorly differentiated</td>
</tr>
<tr>
<td>p53</td>
<td>Mutated</td>
<td>Wild type</td>
</tr>
<tr>
<td>p16</td>
<td>Decreased expression</td>
<td>Increased expression</td>
</tr>
</tbody>
</table>

BOT = base of tongue; HPV = human papillomavirus.

Lewis et al. Oncology, 2015.
HPV+ OPSCC

Clinical Presentation
- Earlier T-stage
- Advanced N-Stage
- Cystic appearing nodes
  - Indication for tonsillectomy and base of tongue biopsies in unknown primary

Histology
- Non-Keratinizing
- Poorly differentiated
Histology HPV+ vs HPV- SCCA
Risk Stratification – Two Different Cancers?

Ang et al. N Engl J Med. 2010
HPV+ vs HPV- Overall survival

Horne et al, 2016
Head and Neck Cancer in 2016

- HPV+ OPSCC
  - Excellent survival
  - What is the next step to improve treatment?
    - Speech and swallow – reducing long term complications

- Transoral endoscopic-assisted surgery: preserving function and healing by 1) minimizing size of resection and 2) nerve preservation
  - Transoral laser microresection (TLM)
  - Transoral robotic-assisted surgery (TORS)
Surgery – Adoption of a New Treatment

• Can it be done safely?

• Is it oncologically sound?

• How does it compare functionally to the current standard?
History of Transoral Surgery

- TOS first described in 1951
- Practiced selectively at some institutions in 1980s-90s
- TLM developed in 1990s in Germany

Transoral endoscopic-assisted surgery: Steiner revolution

- Endoscopic microresection of laryngeal tumors achieved equivalent local control to open surgical approaches
- Superior functional outcome

Table 5. Mean Performance Status Scale Scores (Percentage) by T Stage of 20 Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>T2 (n = 6)</th>
<th>T3 and T4 (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalcy of diet</td>
<td>92</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>Understandability of speech</td>
<td>88</td>
<td>92</td>
<td>86</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier estimate of local control.
da Vinci Robotic Surgery


- Three dimensional visualization
- Tremor filtration
- Wristed instrumentation
FK retractor
Potential Patient Benefits

- In comparison to other surgical approaches
- Avoidance of disfiguring mandibulotomy
- Avoidance of tracheostomy
- Quicker return to normal speech and swallowing
- Significantly less pain
- Less Blood loss
- Less risk of wound infection
- Shorter hospital stay
- Shorter recovery time
- Minimal scarring
Specific Contraindications to TORS

- Mandibular invasion
- Tongue base involvement requiring resection of > 50% of the tongue base
- Pharyngeal wall involvement necessitating resection of > 50% of the posterior pharyngeal wall
- Radiologic confirmation of carotid artery involvement
- Fixation of tumor to prevertebral fascia
- Involvement of the pterygoids
TORS applications

- Oropharynx and skull base
  - Tonsil
  - Tongue base
  - Palate
  - Pharyngeal wall
  - Parapharyngeal Space

- Larynx and hypopharynx
  - Supraglottis
  - Glottis
  - Pyriform sinus
  - Pharyngeal wall
TORS Radical Tonsillectomy

Table 4. Early Postoperative Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Patients, No. (%) (N=27)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucosal bleeding</td>
<td>1 (4)</td>
<td>Resolved following cauterization in operating room</td>
</tr>
<tr>
<td>Tracheotomy for exacerbation of sleep apnea</td>
<td>1 (4)</td>
<td>Tracheotomy tube removed on postoperative day 32</td>
</tr>
<tr>
<td>Moderate trismus</td>
<td>2 (7)</td>
<td>Persisted beyond the 30-day postoperative period but did not significantly interfere with deglutition</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (4)</td>
<td>Resolved with outpatient transoral scar resection</td>
</tr>
<tr>
<td>Nonsurgical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium tremens</td>
<td>1 (4)</td>
<td>Fully recovered</td>
</tr>
</tbody>
</table>
Operative Findings

- **Operative time**
  - Weinstein et al → 1hr43mins (range, 26 mins-3 hrs 53mins)
  - Moore et al → 71.3 minute

<table>
<thead>
<tr>
<th>Cases</th>
<th>Setup</th>
<th>Tumor Removal</th>
<th>Total OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 10</td>
<td>68.6 (64–59)</td>
<td>71.8 (45–320)</td>
<td>312.7 (106–737)</td>
</tr>
<tr>
<td>Subsequent 35</td>
<td>22.3 (14–28)</td>
<td>71.3 (6–309)</td>
<td>216 (45–350)</td>
</tr>
</tbody>
</table>

TORS = transoral robotic surgery; OR = operating room.

- **Positioning Time**
  - Weinstein et al → 9 min (range, 2-22 minutes)

- **Blood Loss**
  - Weinstein et al → 189 mls (range 0-500 mls)
  - Moore et al → 12.6 mL (range, 0-50 mL)

- **Surgical margins**
  - Weinstein et al → 25/27 patients (93%) negative
PEG Dependence

• Postoperative Swallowing
  – Weinstein et al:
    • 26/27 (96%) pts w/out gastrostomy
  – Moore et al:
    • 0/45 pts with gastrostomy
    • 48.9% with temporary DHT palces
    • Avg duration 12.5 days (range, 2-41 days)
  – Ozer et al:
    • 11/56 Gtube placement during RT
    • 0 pts with long term PEG dependence

  – Genden et al
    • 0 cases of long term PEG dependence

  – Literature reports 5-10% of CRT patients PEG dependent > 2 years after treatment
Trach Dependence

- **Tracheostomy Dependence**
  - Weinstein et al: 1/27 pts trach dependent
  - Moore et al: 0/45 pts trach dependent
    - 13.1% had temporary tracheostomy tube placement
  - Ozer et al: 0/56 pts trach dependent

- **Hospital stay**
  - Moore et al: 3.8 days
## Functional Results of TLMS and TORS

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Method</th>
<th>Patients N (% HPV+)</th>
<th>T3/T4 (%)</th>
<th>Stage 3,4 (%)</th>
<th>Normalcy of diet (%)</th>
<th>PEG tube at 1 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner et al (6)</td>
<td>TLMS, BOT</td>
<td>48 (?)</td>
<td>73%</td>
<td>94%</td>
<td>85%</td>
<td>6%</td>
</tr>
<tr>
<td>Haughey et al (9)</td>
<td>TLMS, OP</td>
<td>204 (74-90%)</td>
<td>34%</td>
<td>100%</td>
<td>87%</td>
<td>19%</td>
</tr>
<tr>
<td>Grant et al (10)</td>
<td>TLMS, OP</td>
<td>69 (?)</td>
<td>20%</td>
<td>64%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Moore et al (17)</td>
<td>TORS, OP</td>
<td>66 (89%)</td>
<td>18%</td>
<td>88%</td>
<td>97%</td>
<td>3%</td>
</tr>
<tr>
<td>White et al (16)</td>
<td>TORS</td>
<td>89 (?)</td>
<td>20%</td>
<td>73%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Weinstein et al (23)</td>
<td>TORS, OP</td>
<td>47 (74%)</td>
<td>22%</td>
<td>86%</td>
<td>97%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

*Abbreviations: BOT = base of tongue; OP = oropharyngeal; TLMS = transoral laser microsurgery; TORS = transoral robotic surgery.*

Hinni et al, 2012
WHICH MODALITY IS BETTER? ORGAN PRESERVATION?

- Survival

Worden et al. JCO 2008

Fakhry et al. JNCI 2008
WHICH MODALITY IS BETTER? SURGERY?

Cohen et al, 2011

Haughey et al, 2012
# HPV+ LITERATURE REVIEW

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>T3-4%</th>
<th>HPV+</th>
<th>OS for HPV+</th>
<th>Surv</th>
<th>Rec-LR</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worden</td>
<td>96</td>
<td>57</td>
<td>40</td>
<td>-</td>
<td>86%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ang</td>
<td>323</td>
<td>69</td>
<td>64</td>
<td>82</td>
<td>73.7%</td>
<td>13%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Posner</td>
<td>111</td>
<td>65</td>
<td>50</td>
<td>87</td>
<td>81%</td>
<td>13%</td>
<td>5%</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haughey</td>
<td>204</td>
<td>34</td>
<td>90</td>
<td>92</td>
<td>88%</td>
<td>6.8%</td>
<td>6%</td>
</tr>
<tr>
<td>Cohen</td>
<td>50</td>
<td>22</td>
<td>74</td>
<td>81</td>
<td>89.5%</td>
<td>0</td>
<td>5.4%</td>
</tr>
<tr>
<td>Moore</td>
<td>66</td>
<td>18</td>
<td>89</td>
<td></td>
<td>97.8%</td>
<td>5%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
Quality-of-Life Outcomes in Transoral Robotic Surgery

Agnes M. Hurtuk, MD\textsuperscript{1,2}, Anna Marcinow, MD\textsuperscript{1,2}, Amit Agrawal, MD\textsuperscript{1,2}, Matthew Old, MD\textsuperscript{1,2}, Theodoros N. Teknos, MD\textsuperscript{1,2}, and Enver Ozer, MD\textsuperscript{1,2}

![Chart showing HNC QOL Scores for different domains: Speech, Eating, Aesthetics, Social Disruption, and Overall QOL. Comparison between EI-Deiry and Funk et al. CRT, EI-Deiry and Funk et al. SRT, and Current study.]
Conclusions for TOS

– Can Trans Oral Surgery be performed safely?

– Is TOS oncologically sound?
  • TOS is equivalent to organ preservation protocols in the treatment of OPSCCA

– How does TOS compare functionally?
  • TOS demonstrates functional outcomes as good as non-surgical therapy
• Question?
  – What prognostic factors are important in treatment of HPV+ disease
  – How can those factors be used to modify treatment in the future?
Are typical High Risk features important in surgically treated HPV+ OPSCCA?

- RTOG 9501 and EORTC 22931
  - High-risk features = improved survival with cisplatin-based CRT
    - High-risk path
    - Positive margins
    - ECE
    - 2 or more nodes
    - Level 4/5 nodes
    - Perineural/vascular invasion
  - Combined analysis → positive margins and ECE

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

- **T Stage**

![Graph showing disease-free survival stratified by pathological T (pT) stage](image1)

**Fig. 4.** Disease-free survival stratified by pathological T (pT) stage (log-rank value, $P = .007$).

![Graph showing disease-specific survival stratified by pathological T (pT) stage](image2)

**Fig. 6.** Disease-specific survival stratified by pathological T (pT) stage (log-rank value, $P = .045$).
Extracapsular Spread and Adjuvant Therapy in Human Papillomavirus-Related, p16-Positive Oropharyngeal Carcinoma

Parul Sinha, MBBS, MS; James S. Lewis, Jr., MD; Jay F. Piccirillo, MD; Dorina Kallogjeri, MD, MPH; and Bruce H. Haughey, MBChB
PROGNOSTIC FACTORS

• Margin Status
  – Positive margins associated with reduced DFS
  – Close margins (<5mm) on primary specimen with additional negative frozen sections is sufficient
    • Without additional negative pathologic prognosticators radiation to the primary site may not be needed

• Prognostic Impact of Adjuvant Therapy
  – Chemotherapy did not demonstrate survival or recurrence advantage in comparison to those receiving RT alone
Prigonostic factors

- Presence of Angioinvasion
  - Prognostic for DSS
  - Greater rates of recurrence and death due to disease
  - Increased likelihood of distant metastases
Number of Nodes More Important than ECE

- Wash U
  - 220 patients with HPV+OPC
  - Surgical resection (TLM or TORS)

Fig. 2. Distribution of recurrences by the metastatic node number in oropharyngeal squamous cell carcinoma patients with pN+ disease.

Sinha, Haughey et al. Oral Oncol 2015
Number of nodes and DSS

- LN <5
  - No benefit from adjuvant therapy in regards to DSS
- +LN >/= 5
  - CRT and RT equal

Sinha, Haughey et al. Oral Oncol 2015
Table 2

Univariable Cox proportional hazard regression analysis for disease-specific survival and disease-free survival.

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI) Disease-specific survival</th>
<th>p Value</th>
<th>HR (95% CI) Disease-free survival</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (0.99–1.11)</td>
<td>0.06</td>
<td>1.07 (1.03–1.11)</td>
<td>0.003</td>
</tr>
<tr>
<td>Sex (Female vs. male)</td>
<td>0.49 (0.36–3.75)</td>
<td>0.32</td>
<td>1.24 (0.48–3.23)</td>
<td>0.66</td>
</tr>
<tr>
<td>Site (BOT vs. tonsil)</td>
<td>1.05 (0.37–3.01)</td>
<td>0.92</td>
<td>1.03 (0.52–2.07)</td>
<td>0.93</td>
</tr>
<tr>
<td>Smoker (Ever vs. never)</td>
<td>2.09 (0.66–6.69)</td>
<td>0.21</td>
<td>2.27 (1.05–4.91)</td>
<td>0.037</td>
</tr>
<tr>
<td>Smoking (&gt;10 vs. ≤10)</td>
<td>0.79 (0.17–3.7)</td>
<td>0.76</td>
<td>0.66 (0.23–1.76)</td>
<td>0.41</td>
</tr>
<tr>
<td>Comorbidity (ACE-27 2–3 vs. 0–1)</td>
<td>0.99 (0.22–4.47)</td>
<td>0.99</td>
<td>0.91 (0.32–2.61)</td>
<td>0.87</td>
</tr>
<tr>
<td>T-classification (T3–T4 vs. T1–T2)</td>
<td>4.9 (0.168–14.28)</td>
<td><strong>0.003</strong></td>
<td>4.48 (2.22–9.03)</td>
<td><strong>&lt;0.0001</strong></td>
</tr>
<tr>
<td>N-classification (N2c–N3 vs. N0–N2b)</td>
<td>1.59 (0.44–5.76)</td>
<td>0.48</td>
<td>1.66 (0.71–3.85)</td>
<td>0.24</td>
</tr>
<tr>
<td>Nodal disease (Present vs. absent)</td>
<td>23.3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.44</td>
<td>0.71 (0.25–2.01)</td>
<td>0.52</td>
</tr>
<tr>
<td>Margin (Positive vs. negative)</td>
<td>4.82 (1.51–15.39)</td>
<td><strong>0.008</strong></td>
<td>2.69 (1.04–6.95)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>ECS (Present vs. absent)</td>
<td>0.88 (0.24–3.16)</td>
<td>0.85</td>
<td>1.27 (0.49–3.3)</td>
<td>0.62</td>
</tr>
<tr>
<td>Node number (≥3 vs. 0–2)</td>
<td>4.34 (1.36–13.87)</td>
<td><strong>0.013</strong></td>
<td>3.10 (1.51–6.36)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Node number (≥4 vs. 0–3)</td>
<td>3.61 (1.26–10.35)</td>
<td><strong>0.017</strong></td>
<td>2.62 (1.29–5.31)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Node number (≥5 vs. 0–4)</td>
<td>4.62 (1.58–13.48)</td>
<td><strong>0.005</strong></td>
<td>3.45 (1.65–7.19)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>PNI (Present vs. absent)</td>
<td>2.28 (0.63–8.21)</td>
<td>0.21</td>
<td>2.14 (0.88–5.21)</td>
<td>0.09</td>
</tr>
<tr>
<td>LVI (Present vs. absent)</td>
<td>4.15 (1.44–11.99)</td>
<td><strong>0.008</strong></td>
<td>2.8 (1.34–5.62)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Adjuvant therapy (Any vs. none)</td>
<td>0.74 (0.21–2.6)</td>
<td>0.65</td>
<td>0.44 (0.20–0.94)</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>(Chemoradiotherapy vs. radiotherapy)</td>
<td>0.61 (0.39–4.66)</td>
<td>0.52</td>
<td>1.38 (0.58–3.30)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

BOT = Base of tongue, ACE = Adult comorbidity evaluation, ECS = Extracapsular spread, PNI = Perineural invasion, LVI = Lymphovascular invasion.

Bold values indicate significant p values.

<sup>3</sup> Very high 95% CIs.
De-intensification is the Future
De-escalation … Many Ways to “Skin a Sheep”

- Improved survival irrespective treatment modality
- Radiation
  - Dose
  - Volume
  - Use
- CRT
  - Selective use
- Surgery
  - TOS

Table 2. Notable Ongoing De-escalation Trials in HPV-OPSCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Outcomes</th>
<th>HPV Testing</th>
<th>Invasion Criteria</th>
<th>Treatment</th>
<th>Primary Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 1598 (United States)</td>
<td>2 yr OS</td>
<td>HPV PCR</td>
<td>Stage I/II/III/IV oropharyngeal SCC</td>
<td>Low-dose IMRT (60 Gy × 30 fractions) vs standard-dose IMRT (60 Gy × 30 fractions)</td>
<td>2015</td>
</tr>
<tr>
<td>RTOG 1210 (Australia)</td>
<td>2 yr OS</td>
<td>p16 MC</td>
<td>Stage I/II/III oropharyngeal SCC</td>
<td>IMRT 60 Gy (30 fractions) + cetuximab vs IMRT 60 Gy (30 fractions) (control)</td>
<td>2016</td>
</tr>
</tbody>
</table>
| TROG 12.01 (Australia) | 2 yr OS | p16 MC | Stage I/II/III oropharyngeal SCC | IMRT 60 Gy (30 fractions) + cetuximab vs IMRT 60 Gy (30 fractions) (control) | 2020
| De-ESCALATE (United Kingdom) | 3 yr OS | p16 MC | Stage I/II/III oropharyngeal SCC | Standard-dose IMRT (60 Gy × 30 fractions) vs standard-dose IMRT (60 Gy × 30 fractions) + cetuximab | 2017 |
| ECOG 1609 (United States) | 2 yr OS | p16 MC | Stage I/II/III oropharyngeal SCC | Standard-dose IMRT (60 Gy × 30 fractions) vs standard-dose IMRT (60 Gy × 30 fractions) + cetuximab | 2018 |
| SIRS (New York, New York, United States) | 2 yr OS | p16 MC | Stage I/II/III oropharyngeal SCC | Standard-dose IMRT (60 Gy × 30 fractions) vs standard-dose IMRT (60 Gy × 30 fractions) + cetuximab | 2019 |
| ADEPT (Europe, United States) | 2 yr OS | p16 MC | Stage I/II/III oropharyngeal SCC | Standard-dose IMRT (60 Gy × 30 fractions) vs standard-dose IMRT (60 Gy × 30 fractions) + cetuximab | 2020 |
| CRADAR (Europe, United States) | 2 yr OS | p16 MC | Stage I/II/III oropharyngeal SCC | Standard-dose IMRT (60 Gy × 30 fractions) vs standard-dose IMRT (60 Gy × 30 fractions) + cetuximab | 2021 |

DPS = disease-free survival, ECOG = Eastern Cooperative Oncology Group, ECS = endocervical squamous, HPV = human papillomavirus, HPV-OPSCC = HPV-associated oropharyngeal squamous cell carcinoma, IMRT = intensity-modulated radiation therapy, CRT = chemoradiation, TOS = transoral robotic surgery, TOS = transoral robotic surgery vs IMRT, IMRT = intensity-modulated radiation therapy, PCI = provisional chemotherapy, TOS = transoral robotic surgery vs IMRT, IMRT = intensity-modulated radiation therapy, PCI = provisional chemotherapy, TOS = transoral robotic surgery vs IMRT, IMRT = intensity-modulated radiation therapy, PCI = provisional chemotherapy, TOS = transoral robotic surgery vs IMRT, IMRT = intensity-modulated radiation therapy, PCI = provisional chemotherapy.
Single Modality Treatment

- 30 patients TORS + ND only
  - No HPV data
  - Majority T1/T2
  - 1/3 Node positive
  - Follow up >18 months
    - Local control → 97%
    - Locoregional control → 90%
    - Distant disease → 0%

Surgery as a Single Modality

- Limited to early stage tumors (T1-2, N0-1)
- Decreased morbidity
- Radiation for treatment of recurrence
Phase II Randomized Trial of Transoral Surgical Resection Followed by Low-Dose or Standard-Dose IMRT in Resectable p16+ Locally Advanced Oropharynx Cancer

Study Schema

Step 1:
- Arm S: Transoral resection with neck dissections

Step 2:
- Low Risk
- Intermediate Risk
- Unknown Risk
- High Risk

Long-Term Follow-Up
- Arm A: (7 wk) Observation
- Arm B: (5-7 wk) Radiotherapy IMRT 50 Gy/25 Fx
- Arm C: (5-7 wk) Radiotherapy IMRT 60 Gy/30 Fx
- Arm D: (5-7 wk) Radiotherapy IMRT 66 Gy/33 Fx + Cisplatin 40 mg/m² weekly

Total accrual goal = 515 patients.

- Resectable oropharynx carcinoma, p16+ by IHC, PS 0-1.
- Surrogate credentialing required, neck levels dissected, and nodal yield (> nodes/neck).
- Stratify by current/former smoking history (≤ 10 vs > 10 pk-yr).
- Low risk: T1-T2, N0-N1 and clear (≥ 3 mm) margins, and no extracapsular extension (ECE) or perineural invasion (PNI) and lymphovascular invasion (LVI).
- Intermediate risk: 1 or more "close" (< 3 mm) margin(s), or "minimal" (≤ 1 mm) ECE, or N2a (1 or more lymph nodes > 3 cm in diameter), or any diameter ≤ 6 cm), or with PNI or LVI.
- Unknown risk: N2C or N3 disease on final pathologic analysis.
- High risk: 1 or more positive margin(s) with any T stage, or "extensive" (> 1 mm) ECE, or ≥ 5 metastatic lymph nodes (regardless of primary tumor margin status).
- If ≥ 2 events are observed among first 10 patients registered on arm A within 1 year, currently enrolled and subsequently enrolled low-risk patients who have not progressed will receive IMRT 50 Gy.
- Intensity modulated radiotherapy (IMRT) given. Standard ECOG credentialing through QARC required.
Is HPV+ OPSCC staged correctly?
OS for HPV + OPSCCA based on stage per AJCC staging system (7th edition)
Out with the Old in with the New

Figure 1. Proposed human papillomavirus risk-adapted restaging structure.\textsuperscript{13}
What about the Treatment Failure?

Figure 6. Overall survival of patients diagnosed with metastatic disease at presentation and stratified by HPV positivity. HPV indicates human papillomavirus.
Immunotherapy for HNSCC

- HNSCC associated with immune suppressive state
  - Altered lymphocyte homeostasis
    - CD4+, CD3+, CD8+
  - PD-1 or PD-L1 routinely expressed in HNSCC
    - Prevents T-cell activation and allows tumor escape
Immuneonotherapy for Head and Neck SCCA – Pembrolizumab (Keytruda)

Seiwert et al
Pembrolizumab

- Approved Aug 5, 2016 by FDA
  - For treatment of patients with recurrent or metastatic HNSCC
  - With disease progression on or after platinum containing therapy
    - Pembrolizumab 10 mg/kg every 2 weeks
  - 174 pts
    - Objective response rate → 16%
    - Range of duration of response 2.4 months-27.7 months
    - 28 responding patients
      » 23 (82%) had responses of longer than 6 months
Base of tongue tumor: T2N0 vs. N1
Base of tongue tumor
Base of tongue tumor
Base of tongue tumor

• Pathology report: 2.2 cm moderately differentiated invasive carcinoma. Negative margins
• Staged neck dissection: 0/22 positive lymph nodes
• Pathologic Stage II: no adjuvant treatment recommended
Base of tongue tumor: postoperative healing – 3 months
Questions?

When cancer invades your life, you want a miracle.
## Surgical Margins

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sites (all stages, unless otherwise indicated)</th>
<th>Patients</th>
<th>Margin definition</th>
<th>Locoregional recurrence (inadequate versus adequate margins)</th>
<th>Survival (inadequate versus adequate margins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al[^4]</td>
<td>1987</td>
<td>Oral, oropharyngeal, laryngeal, hypopharyngeal</td>
<td>270</td>
<td>5 mm</td>
<td>55% vs 17%</td>
<td>7% vs 39% 5-year disease-free survival</td>
</tr>
<tr>
<td>Loree and Strong[^5]</td>
<td>1990</td>
<td>Oral</td>
<td>303</td>
<td>5 mm</td>
<td>30% vs 18%</td>
<td>52% vs 60% 5-year OS</td>
</tr>
<tr>
<td>El-Husseiny et al[^7]</td>
<td>2000</td>
<td>Tongue</td>
<td>66</td>
<td>5 mm</td>
<td>0% vs 63% DFS</td>
<td>21% vs 72%</td>
</tr>
<tr>
<td>de Visscher et al[^14]</td>
<td>2002</td>
<td>Lip</td>
<td>72</td>
<td>3 mm</td>
<td>8 patients had inadequate margins. LR developed in 1 of these 8 patients, plus 1 patient with adequate margins.</td>
<td></td>
</tr>
<tr>
<td>Sutton et al[^15]</td>
<td>2003</td>
<td>Oral</td>
<td>200</td>
<td>5 mm</td>
<td>55% positive vs 33% close vs 12% negative</td>
<td>0% positive vs 26% close vs 54% negative alive and disease-free</td>
</tr>
<tr>
<td>McMahon et al[^13]</td>
<td>2003</td>
<td>Oral and oropharyngeal</td>
<td>332</td>
<td>10 mm</td>
<td>Margin status associated with LR and DSS on univariate analysis but not multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>Amaral et al[^8]</td>
<td>2004</td>
<td>Oral, Stage I/II</td>
<td>188</td>
<td>5 mm</td>
<td>6.6% vs 7.9% (adequate versus close, positive margins excluded)</td>
<td>66% vs 73% DFS</td>
</tr>
<tr>
<td>Weijers et al[^9]</td>
<td>2004</td>
<td>Oral</td>
<td>68</td>
<td>5 mm</td>
<td>&quot;Positive margins did not influence survival&quot;</td>
<td></td>
</tr>
<tr>
<td>Brandwein-Gensler et al[^12]</td>
<td>2005</td>
<td>Oral and oropharyngeal</td>
<td>168</td>
<td>5 mm</td>
<td>23% vs 13% (adequate versus close margins, positive margins excluded)</td>
<td></td>
</tr>
<tr>
<td>Garzino-Demo et al[^10]</td>
<td>2006</td>
<td>Oral</td>
<td>245</td>
<td>5 mm</td>
<td>This group examined the impact of different resection margin cut-off values for resection margins (≤ 3 mm to ≤ 11 mm, in 1 mm intervals) by hazard ratio and 95% confidence intervals. On multivariate analysis, resection margins of ≤ 7 mm were significantly associated with decreased local disease control.</td>
<td>48% vs 65% 5-year OS</td>
</tr>
<tr>
<td>Liao et al[^10]</td>
<td>2008</td>
<td>Oral</td>
<td>827</td>
<td>5 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Prognostic Factors and Survival Unique to Surgically Treated p16+ Oropharyngeal Cancer

Bruce H. Haughey, MBChB, FRACS, FACS; Parul Sinha, MBBS, MS

![Image of survival curves]

**Fig. 2.** Disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) for the study cohort (N = 171).
SMOKING STATUS

• Nonsurgically treated patients
  – Smokers with HPV positive OPSCC cancers reported
    • Poorer survival both overall and disease specific
    • Greater risk of recurrence
    • Distant metastases

Surgically treated patients
  – Smokers had worse OS than never smokers
  – On multivariate analysis neither current smoking history alone or tobacco exposure (>10 and >20 pack years) demonstrated an increased hazard of poorer DSS
  – Would expect smokers to have worse OS given poorer general health

Haughey et al, 2012
FUTURE DIRECTIONS FOR HPV + OPSCCA

• Is there a role for further de-escalation of therapy in P16 positive oropharynx tumors?

• Do patients need treatment to 60-66 Gy in post-surgical settings?

• Is chemotherapy necessary in post-operative treatment of HPV + OPSCCA?
OBJECTIVES

• Describe the epidemiology and demographics of HPV+ SCCA
• Prevalence
• Clinical Presentation
• History
• Outcomes
  – Surgical
  – Non-Surgical
• Prognostic factors in surgically treated HPV+ OPSCC
Margins

- No universal definition of inadequate margins
- No RCTs comparing margins
- Improvement in LR and survival in later studies
  - Better assessment?
  - Tumor shrinkage?
    - 20-25%
  - Better adjuvant therapy?
  - HPV factor?
- “Close Margins” now generally accepted for OPC
“Surgical Intensification” in HPV-Negative, For Comparison

RTOG 1221: Phase II Schema

<table>
<thead>
<tr>
<th>Stratify</th>
<th>T Stage</th>
<th>Randomize</th>
</tr>
</thead>
<tbody>
<tr>
<td>N stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zubrod Status</td>
<td>1. 0</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Eligible
- Oropharyngeal SCC: Tonsil, BOT, GPC
- Stage III-IV: T1-2, N1-2b
- p16 NEGATIVE (IHC)

*eHNS = TLM or TORS
**Italicized text will be added at next protocol amendment (in progress)
HPV AND HNSCC

• 2000 - Gillison et al
  – Assayed HNSCC tumor specimens from 253 pts
    • HPV detected in 25% of cases
    • HPV16 detected in 90% of HPV positive tumors
    • HPV + oropharyngeal tumors less likely to have TP53 mutations

• 2009 – Klussman et al
  – Compared 28 HPV+ tumors to 32 HPV unrelated tumors
    • HPV- tumors
      – Increased chromosomal alterations
      – Fewer 16q losses
    » Greater 16q loss associated with better overall survival and disease free survival
DEMOGRAPHICS

- **HPV+ OPSCCA**
  - Caucasian
  - Middle aged (40-60)
  - High SES
  - M:F = 3:1
  - Sexual

- **HPV- OPSCCA**
  - Older age (60)
  - Low SES
  - M:F = 3:2
  - Tobacco/ Alcohol
Table 1  Oncologic results of TLMS and TORS

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Method</th>
<th>Patients, N (% HPV+)</th>
<th>T3/T4 (%)</th>
<th>Stage 3,4 (%)</th>
<th>Postop RT/CRT (%)</th>
<th>LC</th>
<th>OC</th>
<th>OS</th>
<th>DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiner et al (6)</td>
<td>TLMS, BOT</td>
<td>48 (?)</td>
<td>73%</td>
<td>94%</td>
<td>23 (48%)</td>
<td>85%</td>
<td>73%</td>
<td>52%</td>
<td>73%</td>
</tr>
<tr>
<td>Haughey et al (9)</td>
<td>TLMS, OP</td>
<td>204 (74-90%)</td>
<td>34%</td>
<td>100%</td>
<td>74%</td>
<td>93%</td>
<td>87%</td>
<td>78%</td>
<td>84%</td>
</tr>
<tr>
<td>Grant et al (10)</td>
<td>TLMS, OP</td>
<td>69 (?)</td>
<td>20%</td>
<td>64%</td>
<td>0%</td>
<td>94%</td>
<td>82%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Moore et al (17)</td>
<td>TORS, OP</td>
<td>66 (89%)</td>
<td>18%</td>
<td>88%</td>
<td>83%</td>
<td>97%</td>
<td>94%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>White et al (16)</td>
<td>TORS</td>
<td>89 (?)</td>
<td>20%</td>
<td>73%</td>
<td>63%</td>
<td>97%</td>
<td>91%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Weinstein et al (23)</td>
<td>TORS, OP</td>
<td>47 (74%)</td>
<td>23%</td>
<td>100%</td>
<td>89%</td>
<td>98%</td>
<td>85%</td>
<td>85%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Abbreviations: CRT = chemoradiation therapy; DSS = disease-specific survival; LC = local control; OC = overall control; OP = oropharyngeal; OS = overall survival; RT = radiation therapy; TLMS = transoral laser microsurgery; TORS = transoral robotic surgery.

The advanced T stage and overall stage and the percentage of the patient series that was HPV+ is shown (if reported).
Extracapsular Spread and Adjuvant Therapy in Human Papillomavirus-Related, p16-Positive Oropharyngeal Carcinoma

Parul Sinha, MBBS, MS; James S. Lewis, Jr., MD; Jay F. Piccirillo, MD; Dorina Kalogjeri, MD, MPH; and Bruce H. Haughey, MBChB

Disease-free Survival (%) vs Time (months)

STM report
- Present
- Absent-censored
- Present-censored

Adjuvant therapy
- RT
- ChemoRT
- RT-censored
- ChemoRT-censored