Treatment specificities of HPV-induced oropharyngeal cancer: the surgeon point of view
DISCLOSURE:

- PFIZER: TRIAL STEERING COMMITTEE
- MERCK: CONSULTANT
Epidemiology of oroparyngeal cancer

- Incidence of oropharyngeal cancer (OPC) in the US is 2.2/100,000 in 2009 (SEER 2013)
- Early stage OPC between 16.5% and 26% of all OPCs (Carvalho 2005)
Epidemiology: HPV and oropharyngeal cancer (US)

- Population level incidence /100,000 of HPV positive OPC increased from 0.8 (1988) to 2.6 (2004) corresponding to an increase of 225%
- Incidence of HPV negative OPC declined by 50%

Chaturvedi et al. JCO 2011
HPV positive oropharyngeal cancers have a better prognosis

Ang et al. New Engl J Med 2010
8\textsuperscript{th} AJCC clinical staging for HPV-positive OPC

<table>
<thead>
<tr>
<th>ICON-S stage classification</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N1</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N2</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>N3</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

*Figure 4: Proposed ICON-S stage tabulation grid for 8th edition TNM*

Note that distant metastatic disease (M1) is considered stage IV.

O'Sullivan Lancet Oncology 2016
Treatment options based on stage

AJCC 8\textsuperscript{th} edition

- **Stage 1:**
  - RT vs. Surgery vs. Surgery + RT/CRT vs. CRT

- **Stage 2:**
  - CRT vs. Surgery + CRT (rarely +RT)

- **Stage 3:**
  - CRT vs. Surgery + CRT
No computer use

2D planning

1950-1970

3D conformal

1970-1990

1990-2000

Present

IMRT

IMRT

IMRT

IMRT

1950-1970

1970-1990

1990-2000

Present

Courtesy of John Schreiner, Kingston Regional Cancer Centre, Ontario
RT-only for stage IV HPV-positive OPCs has low late toxicity and may not be inferior to CRT for tumor control.

Table 4

<table>
<thead>
<tr>
<th>Clinical characteristics of HPV+1 patients with stage IV disease: radiotherapy-alone vs. chemoradiotherapy.</th>
<th>RT-alone</th>
<th>CRT</th>
<th>p-Value</th>
<th>RT-alone &lt;10 pack-year</th>
<th>CRT &lt;10 pack-year</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>66</td>
<td>125</td>
<td>37</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>73 (70%)</td>
<td>96 (76%)</td>
<td>0.026</td>
<td>27 (73%)</td>
<td>50 (75%)</td>
<td>0</td>
</tr>
<tr>
<td>Age (&gt;70 years)</td>
<td>19 (29%)</td>
<td>7 (55)</td>
<td>0.001</td>
<td>8 (23%)</td>
<td>4 (65)</td>
<td>0</td>
</tr>
<tr>
<td>Smoking &gt;10 pack-years</td>
<td>45 (67%)</td>
<td>56 (86%)</td>
<td>0.020</td>
<td>5 (14%)</td>
<td>4 (65)</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol (&gt;10 pack-years)</td>
<td>5 (7%)</td>
<td>16 (24%)</td>
<td>0.034</td>
<td>5 (14%)</td>
<td>4 (65)</td>
<td>0</td>
</tr>
<tr>
<td>Tumor/lymph node base tumor</td>
<td>67 (100%)</td>
<td>119 (95%)</td>
<td>0.101</td>
<td>20 (56%)</td>
<td>64 (95%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Radiotherapy regime:
- 70 Gy/35Gy weeks: 8 (12%) 125 (100) 3 (8%) 67 (100)
- 70 Gy/35Gy weekends: 6 (9%) 0 4 (13%) 0
- 60 Gy/35Gy weekends: 35 (53%) 0 11 (32%) 0
- 64 Gy/35Gy weekends: 40 (62) 0 15 (43%) 0
- Others: 7 (10%) 0 4 (13%) 0

T stage (74)
- T1: 27 (41%) 20 (25%) 0.266 11 (30%) 10 (15)
- T2: 36 (55%) 64 (51) 0.056 11 (30%) 36 (54)

3-year OS (95% CI)
- T0: 66 (59-79) 86 (70-94) 0.005 86 (70-94) 88 (77-94)
- T1: 86 (70-88) 95 (88-99) 0.048 92 (82-100) 93 (86-99)
- T2: 98 (84-96) 95 (90-99) 0.101 93 (83-91) 93 (90-99)
- Others: 34 (24-48) 100 (100) 0.300 50 (24-71) 6 (9)

3-year late toxicity (95% CI)
- RT-alone: 14 (6-22) 100 (100) 0.300 50 (24-71) 6 (9)
- CRT: 67 58 28 7

O´Sullivan et al. Radiotherapy and Oncology 2012
Toxicity (%) at 1 year after IMRT for early stage OPSCC (RTOG grading) in RTOG 0022

MDADI and RT

**Figure 1.** Changes in MD Anderson Dysphagia Inventory (MDADI) score over time in 3 treatment cohorts. CRT, chemoradiotherapy.

Wilson et al. Otolaryngology—Head and Neck Surgery 2011
MDADI and IMRT

Fig. 1. MDADI total (composite) score following (chemo-)IMRT. Higher scores are better. The graph shows: quartiles with median (box), 1.5 × inter-quartile range (whiskers) and outliers (O). The table gives: the number of patients measured; the mean of the measurement; and the 95% CI. Rows 4 to 6 give paired differences, with p values as appropriate.

Roe et al. Oral Oncology 2014
Swallowing recovery for $T_{1,2} N_{1,2b}$ HPV-positive OPC after Chemo-IMRT

Goepfert et al 2016
Int J Radiat Oncol Biol Phys.
Trans-oral surgery (TOS) is a technique that reduces procedure-related morbidity.

**TLM**

**TORS**

- Microscope
- Robot
TLM: Techniques and instruments
Set-up
Resection of a BOT cancer with TORS (Si-System)
The Medrobotics system
The “Flex-system”
Experience with TORS in patients with OPCs

Figure 2. Overall Survival (OS) and Disease-Specific Survival (DSS) for Patients Treated With Transoral Robotic Surgery (TORS)

DSS and OS in patients with cancer treated with TORS (all sites, 396 patients)

Cumulative Survival

Elapsed Time Since Surgery, mo

No. at risk 396 187 39 1

Overall survival and DSS in all 396 study patients with head and neck cancer.

de Almeida, JAMA Otolaryngol Head Neck Surg; 2015
TORS-only has low early and late toxicity profiles

Sethia et al. Laryngoscope 2017

Choby et al. JAMA Otolaryngol Head Neck Surg. 2015
Functional outcome by MDADI after TORS+RT vs. CRT

Figure 1. Overall median M. D. Anderson Dysphagia Inventory (MDADI) scores in group 1 (transoral robotic surgery with adjuvant therapy) and group 2 (primary chemoradiotherapy).

More et al 2012 Head and Neck
Comparison of MDADI-evolution after TORS vs. RT vs. TORS+RT vs CRT

EORTC 1420
Comparison of MDADI-evolution after TORS vs. RT vs. TORS+RT vs CRT

RT (3D-conformal)

CRT (IMRT)

TORS +/- (C)RT

TORS+RT vs. CRT
Prospective observational cohort study: “TORS-CHUV”

- 29 pts. with T1,2 N0-2B OPCs included since 7/2012 (19 early stage, 10 advanced stage)
- 45% with history of HNSCC
- 45% HPV-positive
- Pts. excluded with signs of radiographic ECS
- Pts. had to undergo revision surgery for positive or closed margins (unless refused or adverse features requiring post-op RT)

Morisod et al. Head and Neck, 2017
Effect of RT as previous treatment on swallowing recovery after TORS for secondary primaries

**TABLE 3. Ordered probit model of variables having an impact on postoperative Functional Outcome Swallowing Scale score.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>SE</th>
<th>Z score</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.05</td>
<td>0.045</td>
<td>1.104</td>
<td>.270</td>
</tr>
<tr>
<td>Site</td>
<td>-1.766</td>
<td>0.871</td>
<td>-2.027</td>
<td>.043*</td>
</tr>
<tr>
<td>p16 status</td>
<td>1.227</td>
<td>0.889</td>
<td>1.38</td>
<td>.167</td>
</tr>
<tr>
<td>Past primary</td>
<td>0.269</td>
<td>1.232</td>
<td>0.21</td>
<td>.833</td>
</tr>
<tr>
<td>Past RT</td>
<td>7.711</td>
<td>2.33</td>
<td>3.309</td>
<td>.001*</td>
</tr>
<tr>
<td>pT stage</td>
<td>0.484</td>
<td>0.829</td>
<td>0.585</td>
<td>.559</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>5.947</td>
<td>2.021</td>
<td>2.943</td>
<td>.003*</td>
</tr>
<tr>
<td>Post-tx RT/CRT</td>
<td>2.585</td>
<td>1.318</td>
<td>1.961</td>
<td>.050*</td>
</tr>
<tr>
<td>Revision for margin</td>
<td>1.708</td>
<td>0.767</td>
<td>2.228</td>
<td>.026*</td>
</tr>
</tbody>
</table>

Abbreviations: RT, radiotherapy; bx, treatment; CRT, chemoradiotherapy.
*These figures indicate statistical significance.
Note: Site was distinguished into “tonsil,” “base of tongue,” “soft palate,” and “multiple sites” with “tonsil” having worse Functional Outcome Swallowing Scale score outcomes than base of tongue, soft palate, or multiple sites (coefficient 2.2 ± 1.1).

**FIGURE 3. Distribution in percent of Functional Outcome Swallowing Scale scores before treatment (tx) and >12 months after finishing treatment or in case of <12 months follow-up at last follow-up. Blue: Prior treatment; Red: After treatment. [Color figure can be viewed at wileyonlinelibrary.com]**

Moridsod et al. Head and Neck 2017
In terms of adjuvant treatment...

<table>
<thead>
<tr>
<th></th>
<th>With re-resection and ECS-selection</th>
<th>Without re-resection and ECS-selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early stage OPCs (19 pts.)</td>
<td>RT 2 pts. CRT 0 pts</td>
<td>RT 7 pts. CRT 3 pts.</td>
</tr>
<tr>
<td>Advanced stage OPCs (10 pts.)</td>
<td>CRT 1 pt. RT 6 pts.</td>
<td>CRT 5 pts. RT 5 pts.</td>
</tr>
</tbody>
</table>
Prospective observational cohort study: “TORS-CHUV”

Morisod et al. Head and Neck, 2017
## Smoking in the HPV-positive OPC-population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Study Patients</th>
<th>Patients with Oropharyngeal Cancer and Known Tumor HPV Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard-Fractionation Radiotherapy and Cisplatin (N = 361)</td>
<td>Accelerated-Fractionation Radiotherapy and Cisplatin (N = 340)</td>
</tr>
<tr>
<td></td>
<td>HPV-Positive (N = 206)</td>
<td>HPV-Negative (N = 117)</td>
</tr>
<tr>
<td>Nodal stage — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>67 (18.6)</td>
<td>69 (19.2)</td>
</tr>
<tr>
<td>N1</td>
<td>54 (15.0)</td>
<td>53 (14.7)</td>
</tr>
<tr>
<td>N2a</td>
<td>28 (7.8)</td>
<td>32 (8.9)</td>
</tr>
<tr>
<td>N2b</td>
<td>94 (26.0)</td>
<td>95 (26.4)</td>
</tr>
<tr>
<td>N2c</td>
<td>89 (24.7)</td>
<td>84 (23.3)</td>
</tr>
<tr>
<td>N3</td>
<td>29 (8.0)</td>
<td>27 (7.5)</td>
</tr>
<tr>
<td>AjCC stage — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>77 (21.3)</td>
<td>81 (22.5)</td>
</tr>
<tr>
<td>IV</td>
<td>284 (78.7)</td>
<td>279 (77.5)</td>
</tr>
<tr>
<td>Tobacco exposure — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>44 (12.2)</td>
<td>69 (19.2)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>191 (52.9)</td>
<td>183 (50.8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>83 (23.0)</td>
<td>68 (18.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>43 (11.9)</td>
<td>40 (11.1)</td>
</tr>
<tr>
<td>Tobacco-smoking history — no. of pack-years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>Range</td>
<td>0–137.5</td>
<td>0–152.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 1. Patient and tumor characteristics according to human papillomavirus status.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Tobacco cigarettes/day</td>
</tr>
<tr>
<td>0–19</td>
</tr>
<tr>
<td>≥20</td>
</tr>
<tr>
<td>Primary site</td>
</tr>
<tr>
<td>Tonsil</td>
</tr>
<tr>
<td>Base of tongue</td>
</tr>
<tr>
<td>Soft palate</td>
</tr>
<tr>
<td>Pharyngeal wall</td>
</tr>
<tr>
<td>Disease stage</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>T classification</td>
</tr>
<tr>
<td>T1–2</td>
</tr>
<tr>
<td>T3–4</td>
</tr>
<tr>
<td>N classification</td>
</tr>
<tr>
<td>N0–1</td>
</tr>
<tr>
<td>N2–3</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Radiation dose</td>
</tr>
<tr>
<td>&lt;70 Gy</td>
</tr>
<tr>
<td>≥70 Gy</td>
</tr>
</tbody>
</table>

Abbreviation: HPV, human papillomavirus.

Ang et al. N Eng J Med 2010  
Cerezo L. et al. Head and Neck 2013
Projected incidence of secondary primaries in SCCOP-pts.

Figure 2. This chart illustrates a Kaplan-Meier analysis of the proportion of patients with squamous cell carcinoma of the oropharynx who had a secondary primary malignancy (SPM) segregated by human papillomavirus (HPV) phenotype (age <60 years, men, non-Hispanic white, never-smoker/former smoker, tonsil/base of tongue cancer site, and stage T1-T2/N1-N3 disease; N = 285) versus all others (N = 785; log-rank test of equality of survival curves; P < .001).

Gan et al. Cancer 2013
Impact of RT on treatment of secondary primaries, i.e. in the larynx

- SCPL with CH(E)P contraindicated in pts. with chronic pulmonary disease

Weinstein, Laccoureye, Brasnu, Laccoureye: Organ preservation surgery for laryngeal cancer; 2000
LFS-DSS at 5 years in pts. with T1a laryngeal cancer treated either with TLM or RT

Low et al. Laryngoscope 2017
Thank you for your attention
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