A Randomized Trial of Radiotherapy vs. Trans-Oral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma (ORATOR)

Human Papillomavirus

• HPV is the most common sexually transmitted infection

• At least 80% of adults who have been sexually active have been exposed
  • Since infections can be transient, some experts believe the true exposure rate is near 100%

• HPV causes cancers of the cervix, vagina, penis, anus, vulva, and oropharynx
The Oropharynx

Risk factors for oropharyngeal HPV infection:
- Number of sexual (including oral sex) partners
- Number of open-mouthed kissing partners
- Older age
- Tobacco
- Marijuana
CDC: HPV-related cancers increasing

HPV-associated cancers have increased to nearly 43,000 people annually in the US.
Most can be prevented by the HPV vaccine.

https://wwwnc.cdc.gov/eid/article/16/11/10-0452-f3
Treatment: Older Surgical Techniques
Chemotherapy + Radiation

- Standard treatment at most centres has been 7 weeks of radiation with high-dose chemotherapy
A Patient’s Perspective

• Nearly all of our interaction with the world is done through our face
• Our neck and mouth are critical for self-image
  • “I can’t eat with others”
  • “I can’t go to restaurants”
  • “Meals take me hours to eat”
  • “I tube feed myself for 8 hours at night”
  • “I need to carry a water bottle at all times”
  • “My mouth is too dry to do my job in sales”
  • “I have ongoing pain”
  • “Am I the same person?”
Trans-Oral Robotic Surgery (TORS)
Trans-Oral Robotic Surgery (TORS)

Have HPV-related oral cancer? The robot will see you now

In a Mayo Clinic study, robotic surgery appeared less debilitating than traditional, more invasive surgery and radiation therapy. The surgeons now plan to offer robot docs as a primary treatment.
Radiation Has Also Improved
Increase in primary surgical treatment of T1 and T2 oropharyngeal squamous cell carcinoma and rates of adverse pathologic features: National Cancer Data Base.

Cracchiolo JR, Baxi SS, Morris LG, Ganly I, Patel SG, Cohen MA, Roman BR.

<table>
<thead>
<tr>
<th>Year diagnosed</th>
<th>No. (Column %)</th>
<th>No. (Row % Compared With Primary XRT [Not Shown])</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>568 (6.5%)</td>
<td>319 (56.2%)</td>
</tr>
<tr>
<td>2005</td>
<td>644 (7.3%)</td>
<td>354 (55%)</td>
</tr>
<tr>
<td>2006</td>
<td>674 (7.7%)</td>
<td>400 (59.3%)</td>
</tr>
<tr>
<td>2007</td>
<td>747 (8.5%)</td>
<td>431 (57.7%)</td>
</tr>
<tr>
<td>2008</td>
<td>1052 (12%)</td>
<td>674 (64.1%)</td>
</tr>
<tr>
<td>2009</td>
<td>1174 (13.4%)</td>
<td>792 (67.5%)</td>
</tr>
<tr>
<td>2010</td>
<td>939 (10.7%)</td>
<td>651 (69.3%)</td>
</tr>
<tr>
<td>2011</td>
<td>979 (11.2%)</td>
<td>724 (74%)</td>
</tr>
<tr>
<td>2012</td>
<td>970 (11.1%)</td>
<td>784 (80.8%)</td>
</tr>
<tr>
<td>2013</td>
<td>1021 (11.6%)</td>
<td>838 (82.1%)</td>
</tr>
</tbody>
</table>
Randomized Data Lacking

• Prior to ORATOR, no randomized trials compared primary surgery to primary radiation for oropharyngeal cancer

Purpose

• To compare swallowing quality of life (QOL) at 1-year for patients undergoing a primary radiotherapy approach versus a primary TORS approach
Patients with early T-stage squamous cell carcinoma of the oropharynx, meeting inclusion criteria

Randomize

ARM 1: Radiotherapy ± Chemotherapy
With surgical treatment for salvage of persistent disease

Follow-up for QOL and Survival

ARM 2: Transoral Robotic Surgery + Neck Dissection
With adjuvant radio(chemo)therapy based on pathological findings

Follow-up for QOL and Survival
Main Inclusion Criteria

- Squamous cell carcinoma of the oropharynx
- Tumor stage: T1 or T2, with likely negative resection margins
- Nodal stage: N0, N1, or N2
  - < 4 cm, no ECS on pre-randomization imaging
Arm 1 - Radiation

- T1-2 N0: Radiation Alone (70 Gy)
- T1-2 N1-2: Chemoradiation (high dose cisplatin preferred)
Arm 2 – Primary Surgery

• TORS of primary site with neck dissection

Adjuvant Therapy

• **Radiation:** close resection margins (<2 mm), positive lymph nodes, lymphovascular invasion, pT3-4 disease
• **Chemoradiation:** extranodal extension, positive margins
Endpoints

**Primary Endpoint**
- Quality of life 1-year post-treatment
  - Assessed with the MD Anderson Dysphagia Inventory (MDADI)

**Secondary Endpoints**
- Overall and progression-free survival
- Quality of life at other time points
  - MDADI, the EORTC QLQ-C30 and H&N35 scales, the Voice Handicap Index (VHI-10), the Neck Dissection Impairment Index (NDII), and the Patient Neurotoxicity Questionnaire (PNQ), audiology
- CTCAE Toxicity
- Feeding tube rate at 1-year
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Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial

Anthony C Nichols, Julie Thuerer, Eitan Prisman, Nancy Read, Eric Berthelet, Eric Tran, Kevin Fung, John R de Almeida, Andrew Bayley, David P Goldstein, Michael Hier, Khalil Sultanem, Keith Richardson, Alex Myhre, Suren Krishna, Hien Le, John Yao, S Danielle MacNeil, Eric Winquist, J Alex Hammond, Varagor Venkatesan, Sara Kanavilla, Andrew Warner, Sylvia Mitchell, Jeff Chen, Martin Corsten, Stephanie Johnson-Olusoji, Libby Egan, Michael Odeh, Christina Parker, Bret Wehrli, Keith Kwon, David A Palma
Primary Endpoint (MDADI) Comparisons in Specific Subsets

• MDADI scores based on treatment intensity
• Site of primary tumor (tonsil vs. BOT)
• T1 vs. T2
• N0 vs. N+
## The MDADI: Important Outcomes for Patients

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>My swallowing ability limits my day-to-day activities.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E2. I am embarrassed by my eating habits.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1. People have difficulty cooking for me.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2. Swallowing is more difficult at the end of the day.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sample Size and Analyses

- The primary endpoint was a definitive QOL comparison using total MDADI scores at 1-year.

- A 10-point difference was pre-specified as a clinically meaningful change (CMC).

- In order to detect a 10-point improvement in QOL in the TORS arm (Arm 2), a total of **68 patients** were required (34 in each arm).

  (Two-sided, independent-sample t-test with an alpha level of 0.05 and power of 90%, and assumed dropout rate of 10%)
Results
Between 2012 and 2017, 68 patients were randomized at 6 centres in Canada and Australia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=68)</th>
<th>RT Arm (n=34)</th>
<th>TORS+ ND Arm (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> – median (interquartile range)</td>
<td>58.5 (52.9, 65.2)</td>
<td>60.0 (53.2, 65.2)</td>
<td>58.1 (52.6, 64.5)</td>
</tr>
<tr>
<td><strong>p16 Status</strong></td>
<td>60/68</td>
<td>30/34</td>
<td>30/34</td>
</tr>
<tr>
<td><strong>Gender – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59 (87)</td>
<td>31 (91)</td>
<td>28 (82)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (13)</td>
<td>3 (9)</td>
<td>6 (18)</td>
</tr>
<tr>
<td><strong>Smoking History – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>17 (25)</td>
<td>8 (24)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>Previous (&gt; 1 year since quit)</td>
<td>32 (47)</td>
<td>20 (59)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Non-Smoker</td>
<td>19 (28)</td>
<td>6 (18)</td>
<td>13 (38)</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=68)</th>
<th>RT Arm (n=34)</th>
<th>TORS +ND Arm (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsil</td>
<td>50 (74)</td>
<td>26 (76)</td>
<td>24 (71)</td>
</tr>
<tr>
<td>Base of Tongue</td>
<td>18 (26)</td>
<td>8 (24)</td>
<td>10 (29)</td>
</tr>
<tr>
<td><strong>Clinical T Stage – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>30 (44)</td>
<td>13 (38)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>T2</td>
<td>38 (56)</td>
<td>21 (62)</td>
<td>17 (50)</td>
</tr>
<tr>
<td><strong>Clinical N Stage – n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>21 (31)</td>
<td>12 (35)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>N1</td>
<td>12 (18)</td>
<td>5 (15)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>N2</td>
<td>35 (51)</td>
<td>17 (50)</td>
<td>18 (53)</td>
</tr>
</tbody>
</table>
## MDADI Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>1-Year – mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT Arm</td>
<td>TORS Arm</td>
</tr>
<tr>
<td>Total (Primary Endpoint)</td>
<td>86.9 ± 11.4</td>
<td>80.1 ± 13.0</td>
</tr>
</tbody>
</table>
Overall Summary of Secondary Endpoints

**Favor RT**
- Swallowing
  - MDADI
  - FOIS
- Less pain and pain medication use
- No bleeding
- Less Trismus
- Trend towards less shoulder impairment

**Favor Surgery**
- Less Tinnitus and Hearing Loss
- Less neutropenia
- Less constipation

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Median MDADI Scores by Treatment Intensity

(n=9) (n=23) (n=10) (n=16) (n=8)
MDADI Scores by Disease Site

**Tonsil or Tonsillar Fossa**

- RT Arm
- TORS+ND Arm
- **p = 0.463**

**Base of Tongue**

- RT Arm
- TORS+ND Arm
- **p < 0.001**

Number of completed surveys:
- RT: 24, 21, 20, 16, 12, 9, 7, 6
- TORS+ND: 21, 23, 22, 14, 14, 9, 7, 6

*Curves truncated when n<5*
MDADI Scores by T-Stage

**Clinical T1**

- RT Arm
- TORS+ND Arm
- \( p = 0.294 \)

**Clinical T2**

- RT Arm
- TORS+ND Arm
- \( p = 0.334 \)

*Curves truncated when \( n < 5 \)
MDADI Scores by N-Stage

Clinical N0

MDADI Total

Time (Years)

RT Arm
TORS+ND Arm

p = 0.423

Number of completed surveys
RT 10 8 7 8 6 5
TORS+ND 8 9 8 7 6 6

Clinical N+

MDADI Total

Time (Years)

RT Arm
TORS+ND Arm

p < 0.001

Number of completed surveys
RT 22 21 20 12 8 5
TORS+ND 23 24 22 14 11 5 5

*Curves truncated when n<5
Discussion
Take Home Messages

• Previous assertions that TORS is superior to RT appear incorrect
  • In subset analyses today, we were unable to identify a group where TORS is superior

• Our evidence suggests that the widespread adoption of TORS in the U.S. was been premature

• The pros and cons of BOTH modalities need to be discussed with all patients with OPSCC.
Upcoming Data: De-Escalation

ORATOR2

Current Accrual
34/140

Patients with p16-positive squamous cell carcinoma of the oropharynx (T1-2, N0-2, M0 AJCC 8th edition)

Randomize (stratify by smoking status)

**ARM 1**
- Radiotherapy (60 Gy)
- Weekly cisplatin if multiple nodes positive or single lymph node >3 cm
- Surgical treatment for salvage of persistent disease

**ARM 2**
- Transoral Surgery and Neck Dissection
- Adjuvant RT (50-60 Gy) based on risk factors

2019 AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING
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