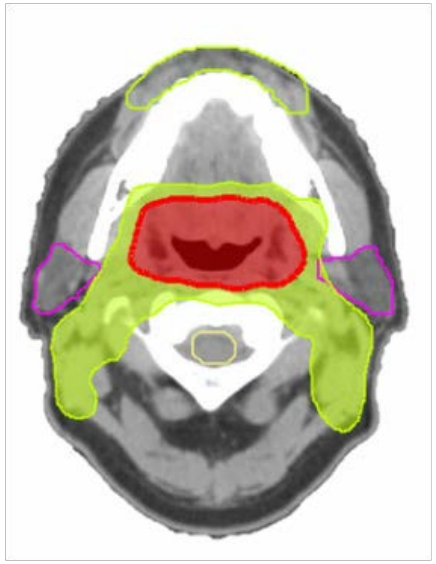
# A Randomized Trial of Radiotherapy vs. Trans-Oral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma (ORATOR)



vs.


D. Palma, J. Theurer, E. Prisman, N. Read, E. Berthelet, E. Tran, K. Fung, J. de Almeida, A. Bayley, D. Goldstein, M. Hier, K. Sultanem, K. Richardson, A. Mlynarek, S. Krishnan, H. Le, J. Yoo, S.D. MacNeil, E. Winquist, J. A. Hammond, V. Venkatesan, S. Kuruvilla, A. Warner, S. Mitchell, J. Chen, M. Corsten, S. Johnson-Obaseki, L. Eapen, M. Odell, C. Parker, B. Wehrli, K. Kwan, A. Nichols

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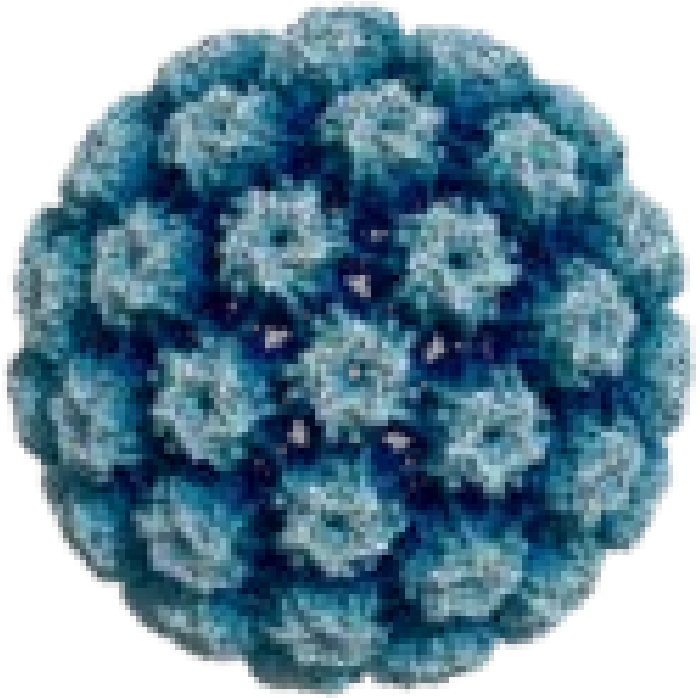
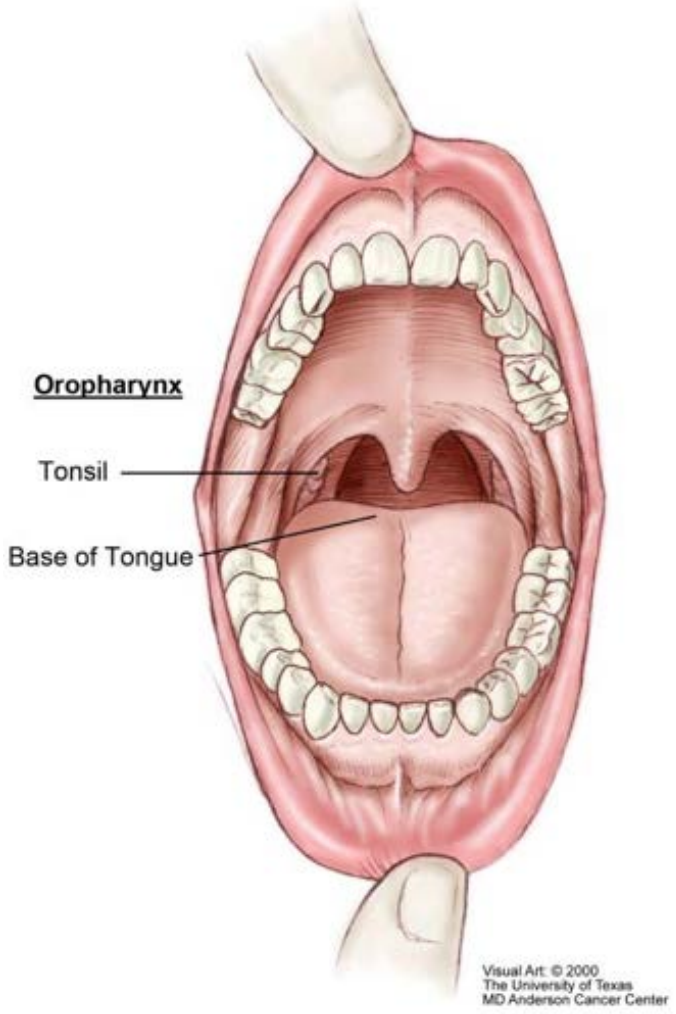
OICR Ontario Institute for Cancer Research

# 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

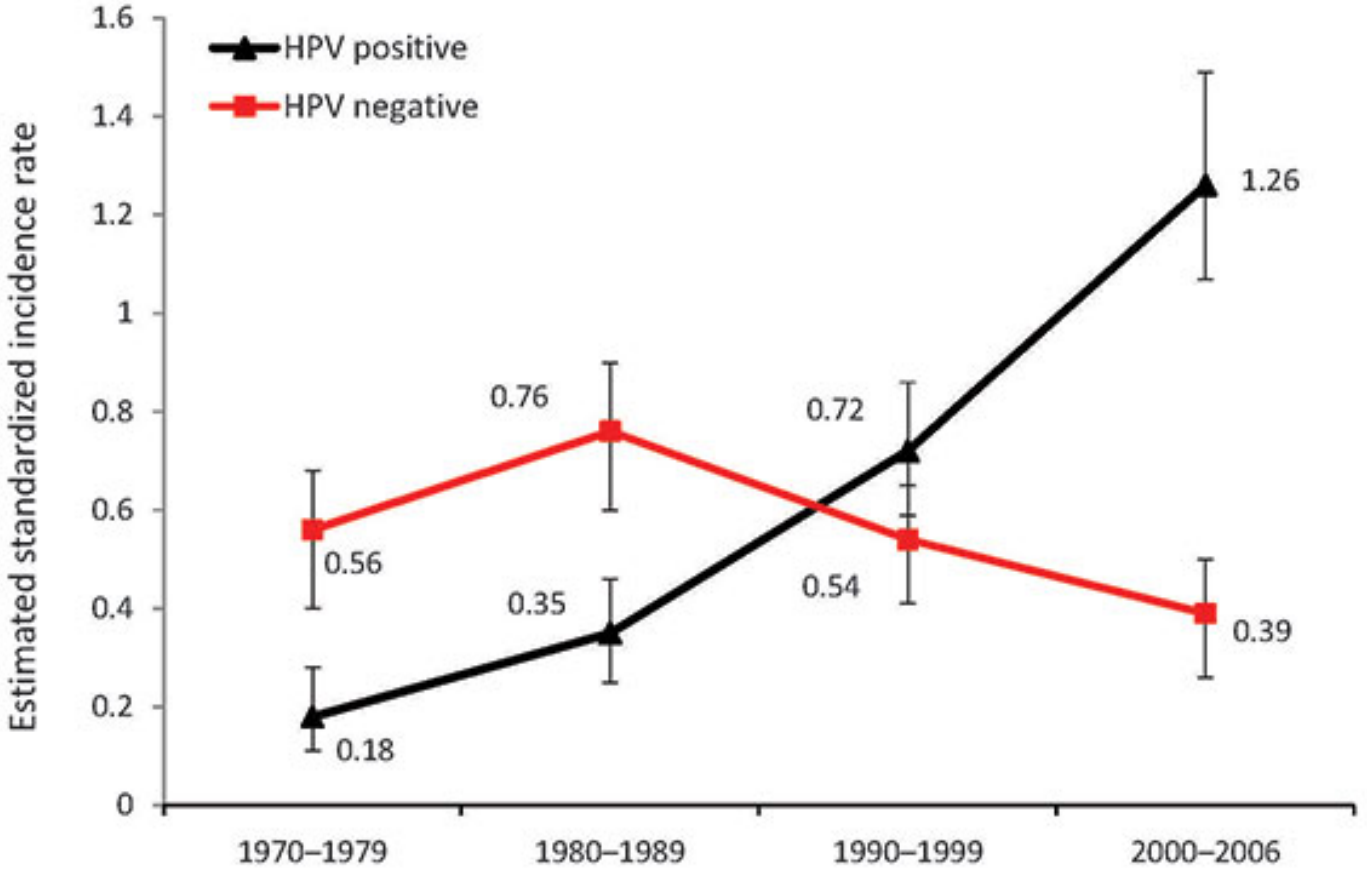
# The Oropharynx

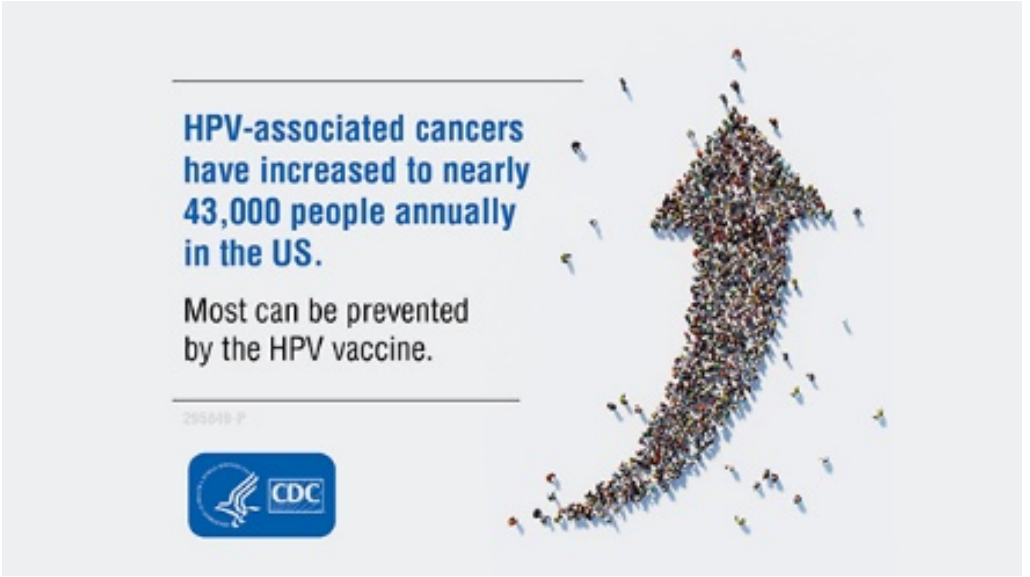



Risk factors for oropharyngeal HPV infection:

- Number of sexual (including oral sex) partners
- Number of open-mouthed kissing partners
- Older age
- Tobacco
- Marijuana

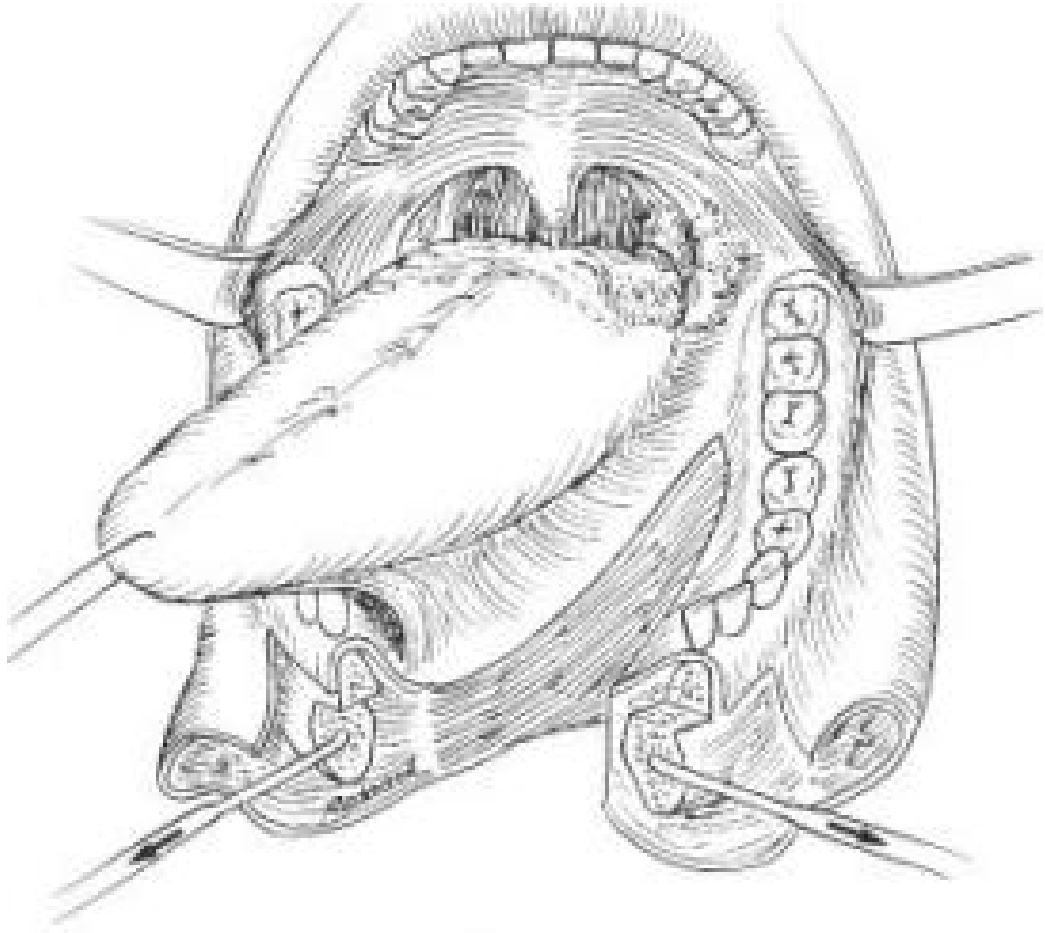
# CDC: HPV-related cancers increasing



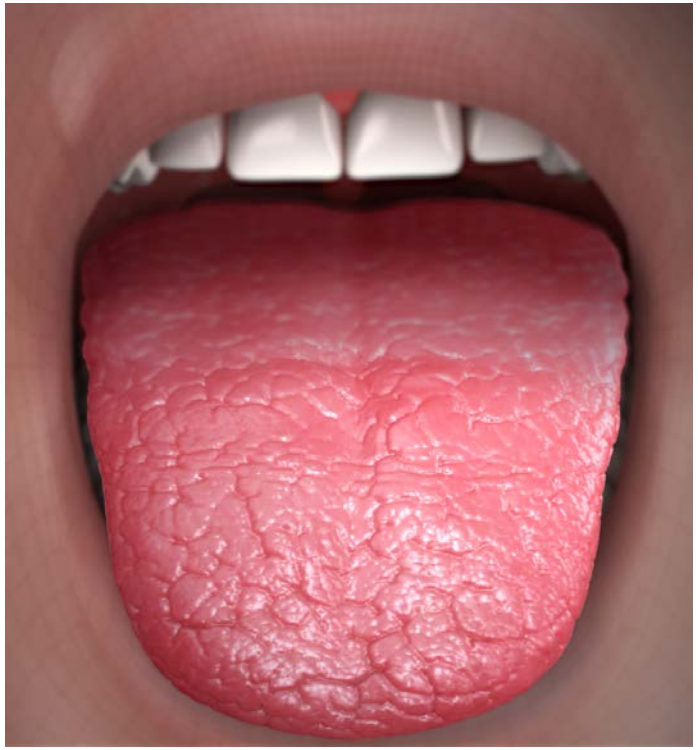

https://wwwnc.cdc.gov/eid/article/16/11/10-0452-f3

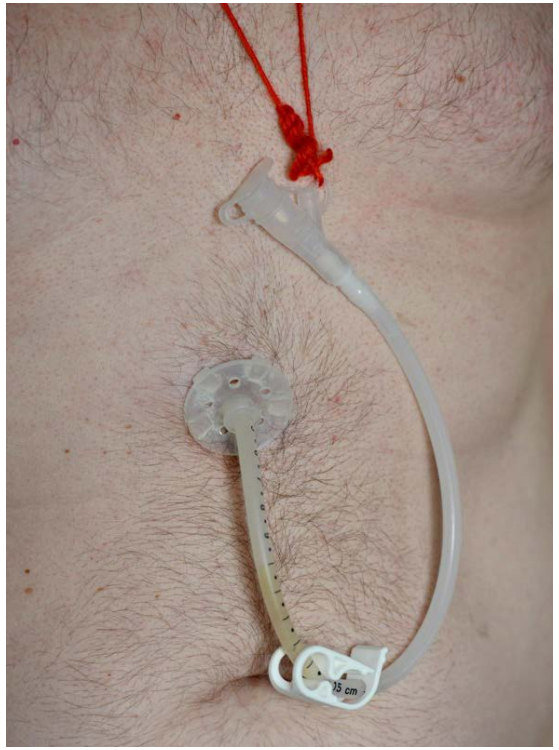
# Treatment: Older Surgical Techniques



# Chemotherapy + Radiation

- Standard treatment at most centres has been 7 weeks of radiation with high-dose chemotherapy

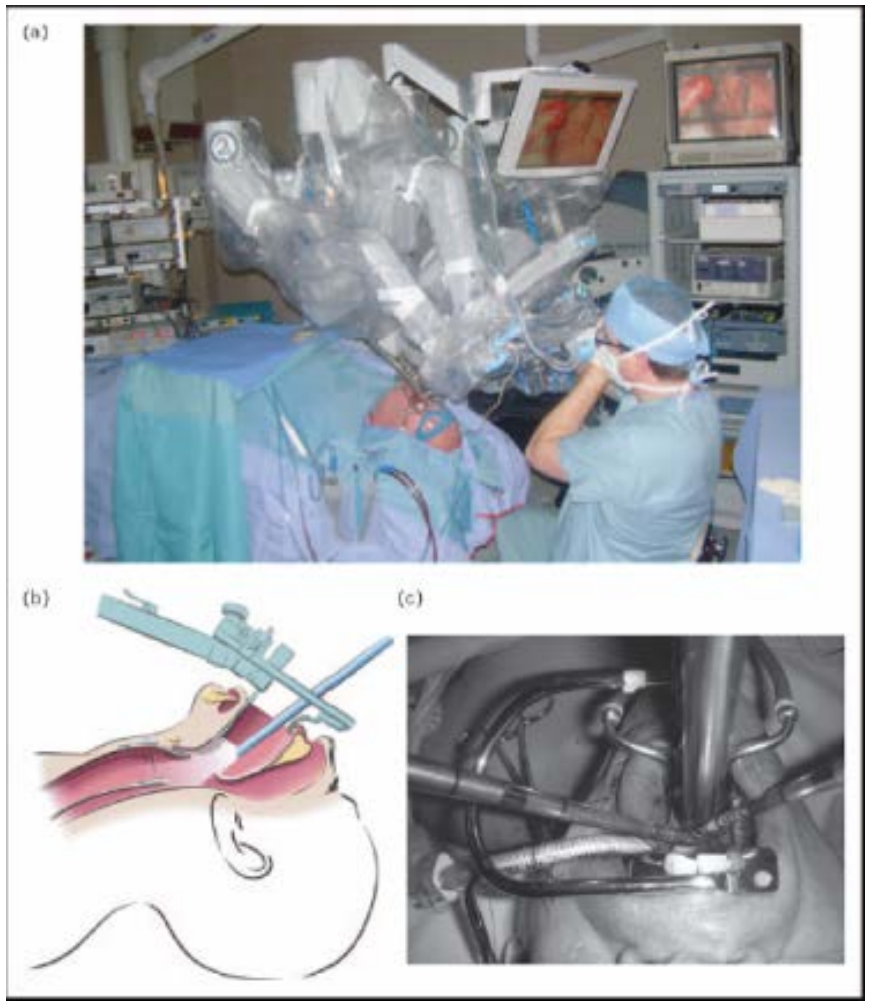




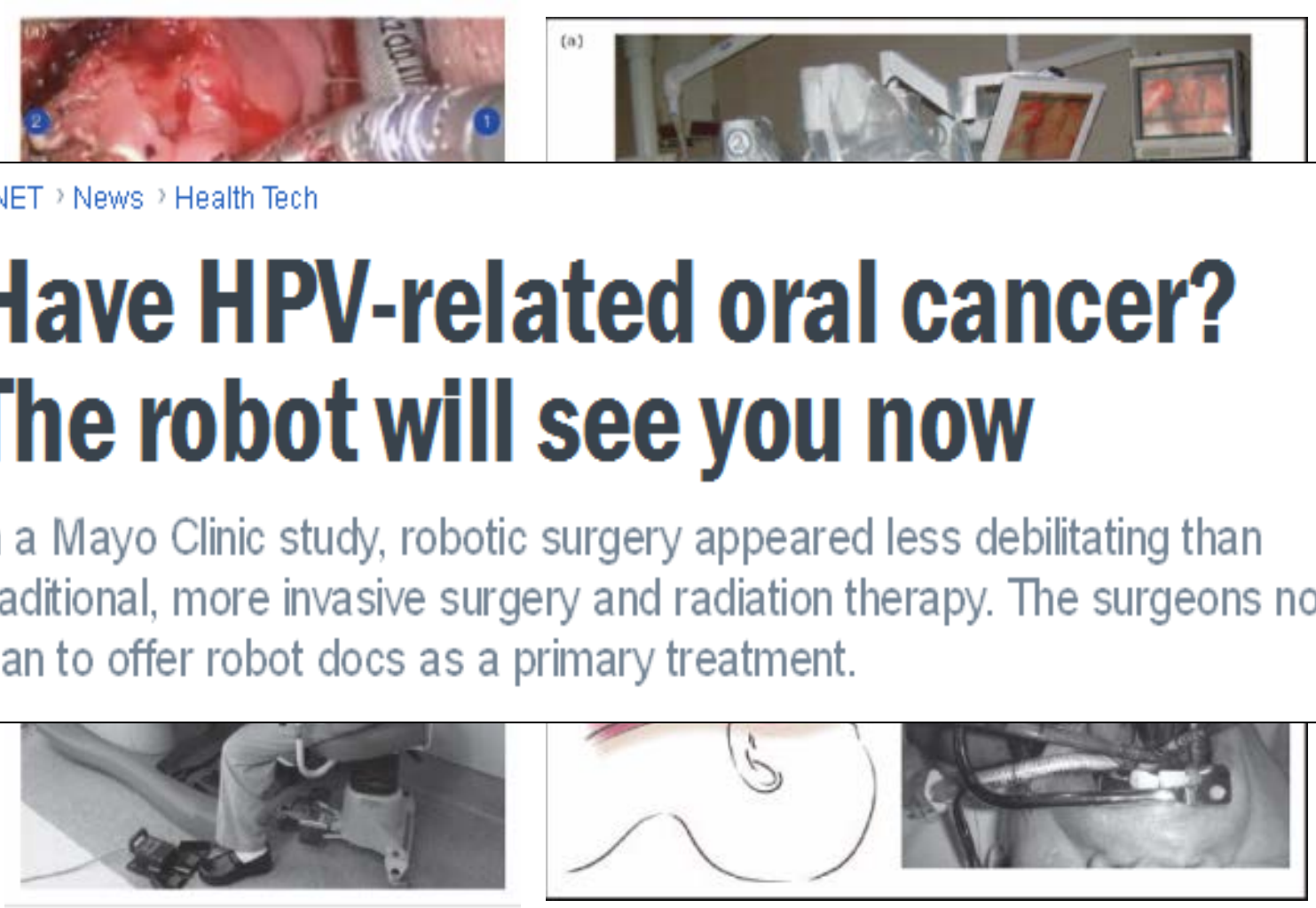
# A Patient's Perspective

- 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)

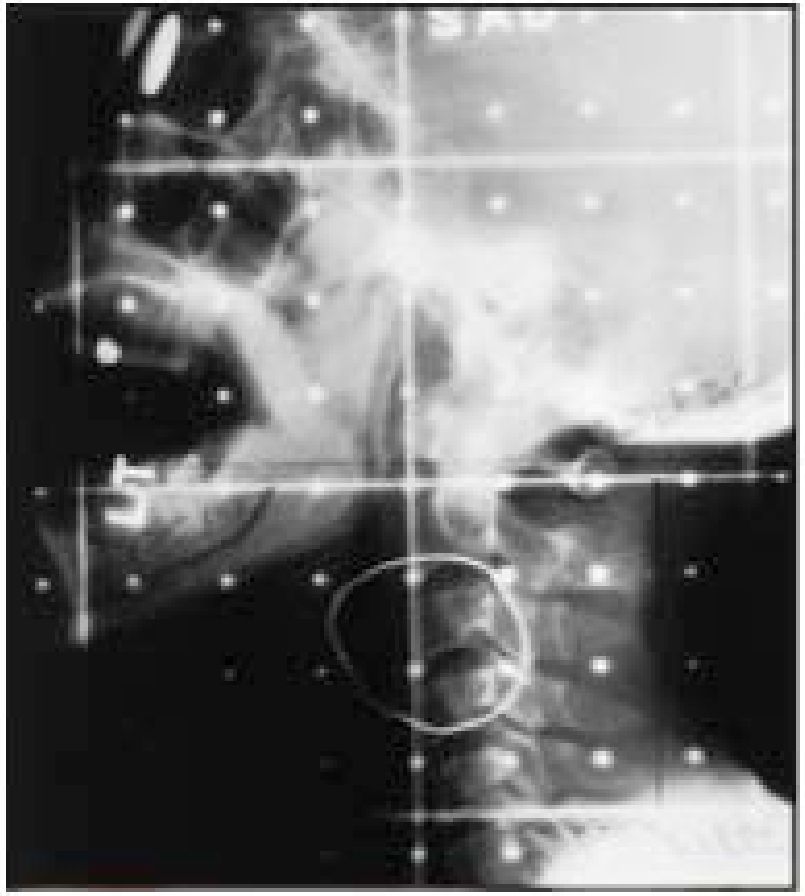


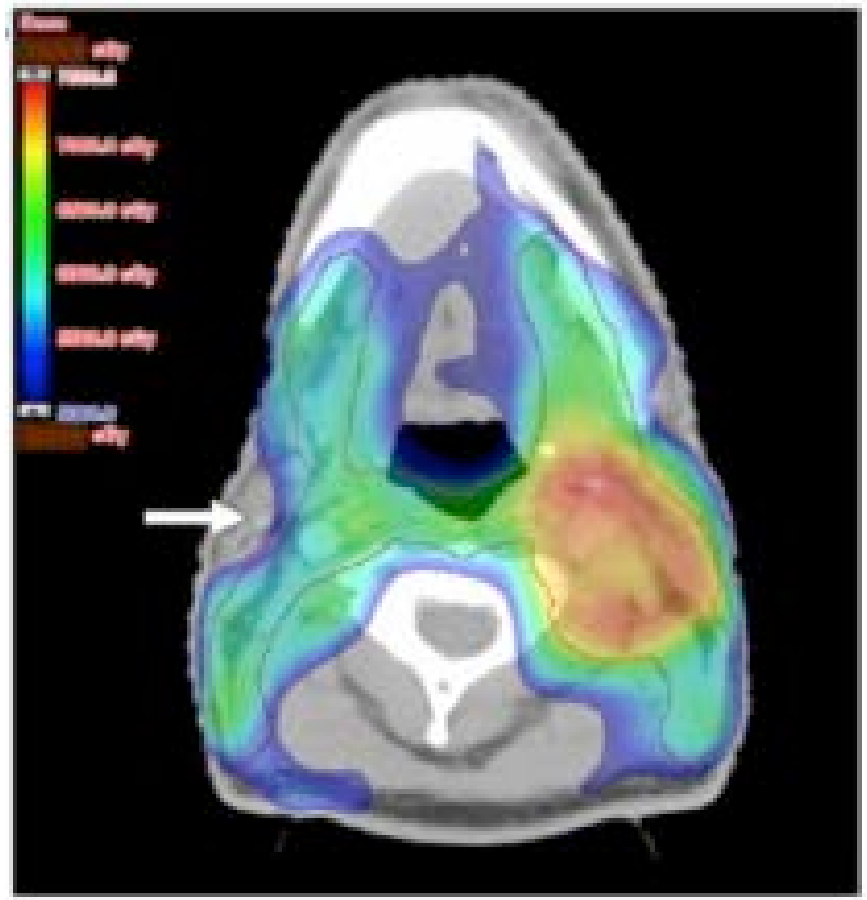
CNET › News › Health Tech

## 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





# Rise of Transoral Robotic Surgery (TORS) and Laser Microsurgery (TLM)

Cancer. 2016 May 15;122(10):1523-32. doi: 10.1002/cncr.29938. Epub 2016 Mar 11.

**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[1], Baxi SS[2], Morris LG[1], Ganly I[1], Patel SG[1], Cohen MA[1,3], Roman BR[1].

| Characteristic | Overall No. (Column %) | Primary Surgical Treatment (Versus Primary XRT) No. (Row % Compared With Primary XRT [Not Shown]) | P[a] |
|---|---|---|---|
| Year diagnosed | | | <.0001 |
| 2004 | 568 (6.5%) | 319 (56.2%) | |
| 2005 | 644 (7.3%) | 354 (55%) | |
| 2006 | 674 (7.7%) | 400 (59.3%) | |
| 2007 | 747 (8.5%) | 431 (57.7%) | |
| 2008 | 1052 (12%) | 674 (64.1%) | |
| 2009 | 1174 (13.4%) | 792 (67.5%) | |
| 2010 | 939 (10.7%) | 651 (69.3%) | |
| 2011 | 979 (11.2%) | 724 (74%) | |
| 2012 | 970 (11.1%) | 784 (80.8%) | |
| 2013 | 1021 (11.6%) | 838 (82.1%) | |

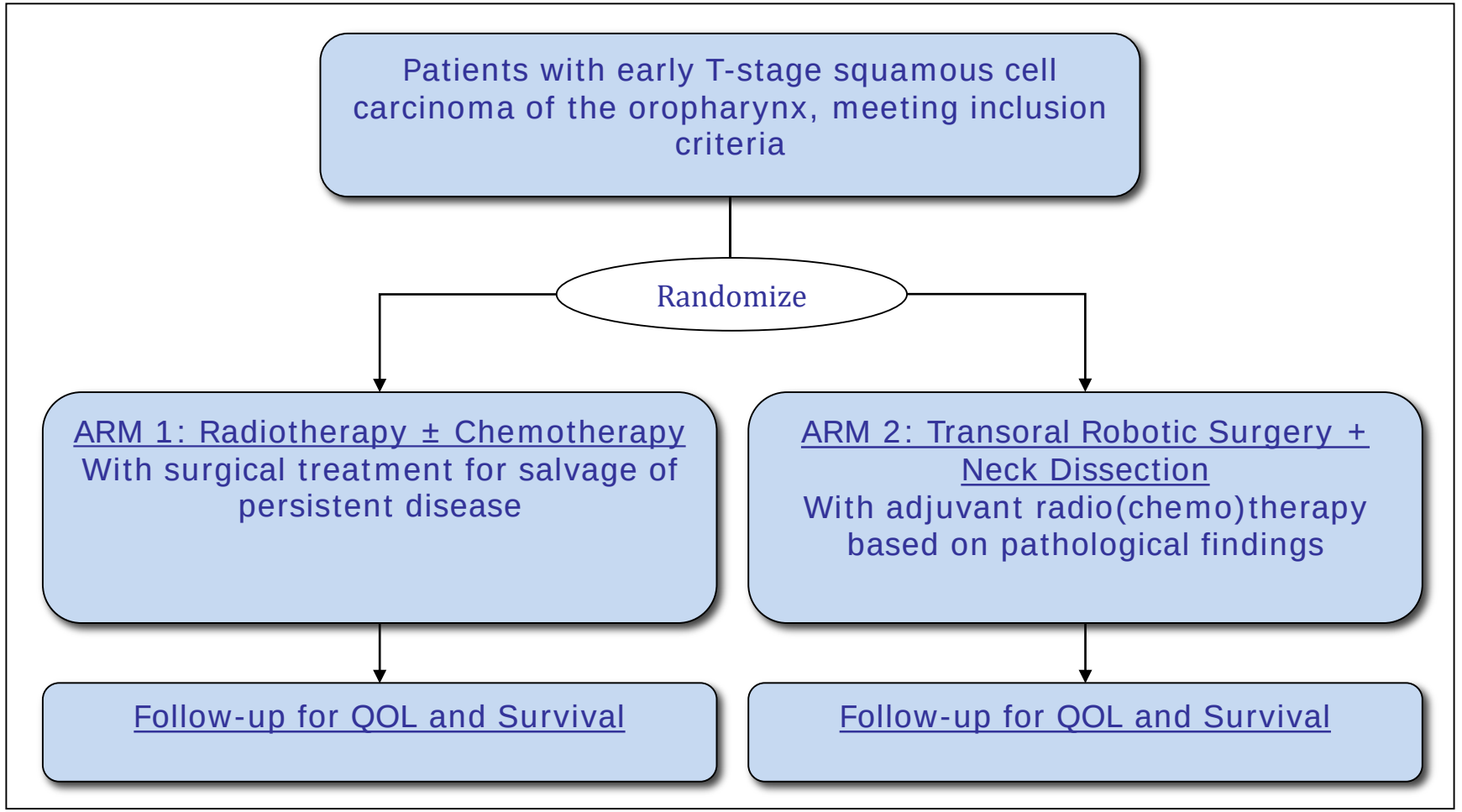
# Randomized Data Lacking

- 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

# ORATOR Schema



# 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

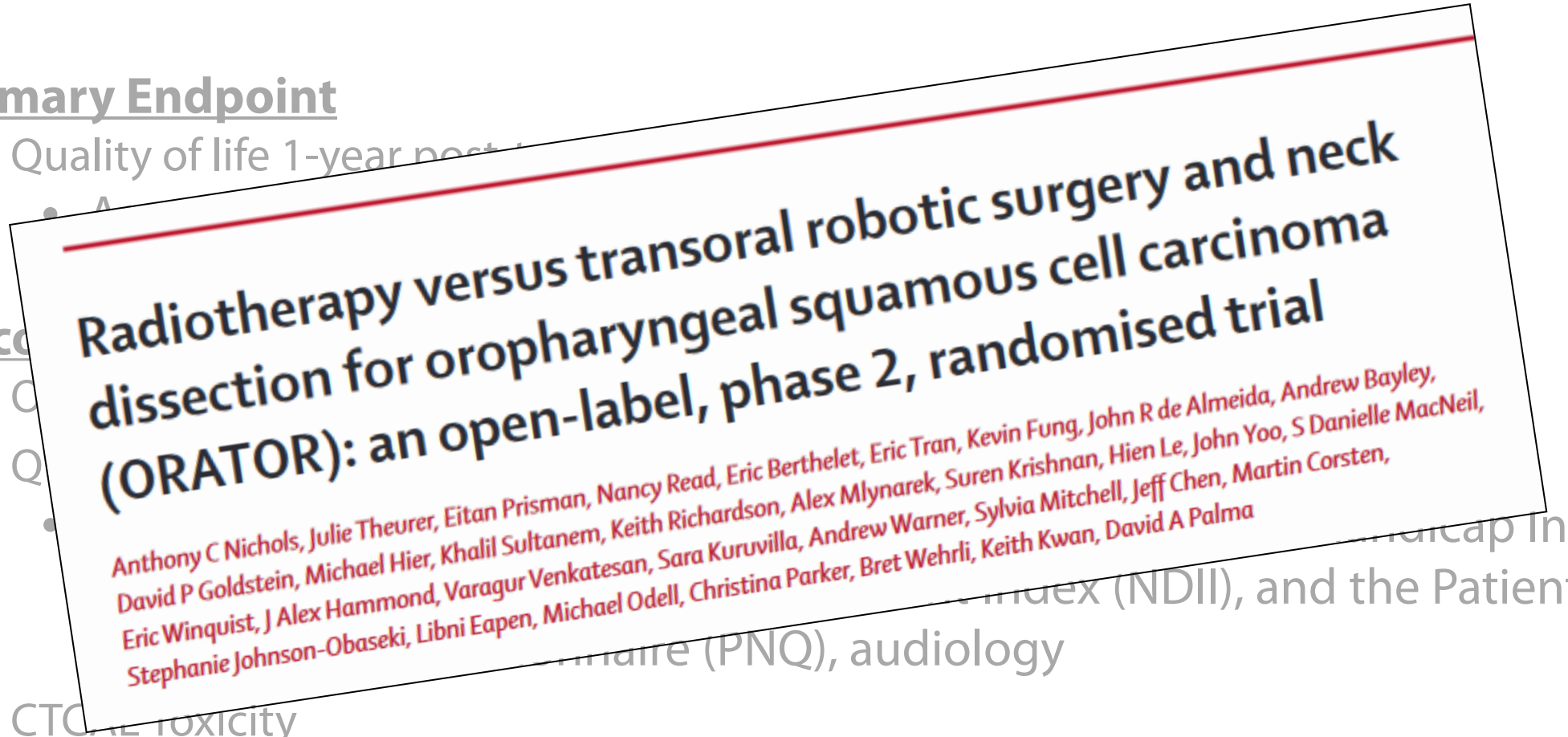
# Endpoints

**Primary Endpoint**

- Quality of life 1-year post-
  - A

**Secondary Endpoints**

- C
- Q
  - [illegible] Handicap Index (NDII), and the Patient [illegible]naire (PNQ), audiology
- CTCAE Toxicity
- Feeding tube rate at 1-year


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 Theurer, 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 Mlynarek, Suren Krishnan, Hien Le, John Yoo, S Danielle MacNeil, Eric Winquist, J Alex Hammond, Varagur Venkatesan, Sara Kuruvilla, Andrew Warner, Sylvia Mitchell, Jeff Chen, Martin Corsten, Stephanie Johnson-Obaseki, Libni Eapen, Michael Odell, Christina Parker, Bret Wehrli, Keith Kwan, David A Palma

# Today's Presentation

**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

My swallowing ability limits my day-to-day activities.

| Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree |
|---|---|---|---|---|

E2. I am embarrassed by my eating habits.

| Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree |
|---|---|---|---|---|

F1. People have difficulty cooking for me.

| Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree |
|---|---|---|---|---|

P2. Swallowing is more difficult at the end of the day.

| Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree |
|---|---|---|---|---|

E7. I do not feel self-conscious when I eat.

| Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree |
|---|---|---|---|---|

# 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

# Baseline Characteristics

Between 2012 and 2017, 68 patients were randomized at 6 centres in Canada and Australia

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

# Baseline Characteristics

| Characteristic | All Patients (n=68) | RT Arm (n=34) | TORS +ND Arm (n=34) |
|---|---|---|---|
| **Tonsil** | 50 (74) | 26 (76) | 24 (71) |
| **Base of Tongue** | 18 (26) | 8 (24) | 10 (29) |
| **Clinical T Stage – n(%)** | | | |
| **T1** | 30 (44) | 13 (38) | 17 (50) |
| **T2** | 38 (56) | 21 (62) | 17 (50) |
| **Clinical N Stage – n(%)** | | | |
| **N0** | 21 (31) | 12 (35) | 9 (26) |
| **N1** | 12 (18) | 5 (15) | 7 (21) |
| **N2** | 35 (51) | 17 (50) | 18 (53) |

# MDADI Scores

| Variable | 1-Year – mean ± SD | | |
|---|---|---|---|
| | RT Arm | TORS Arm | P-value |
| Total (Primary Endpoint) | 86.9 ± 11.4 | 80.1 ± 13.0 | **0.04** |

# 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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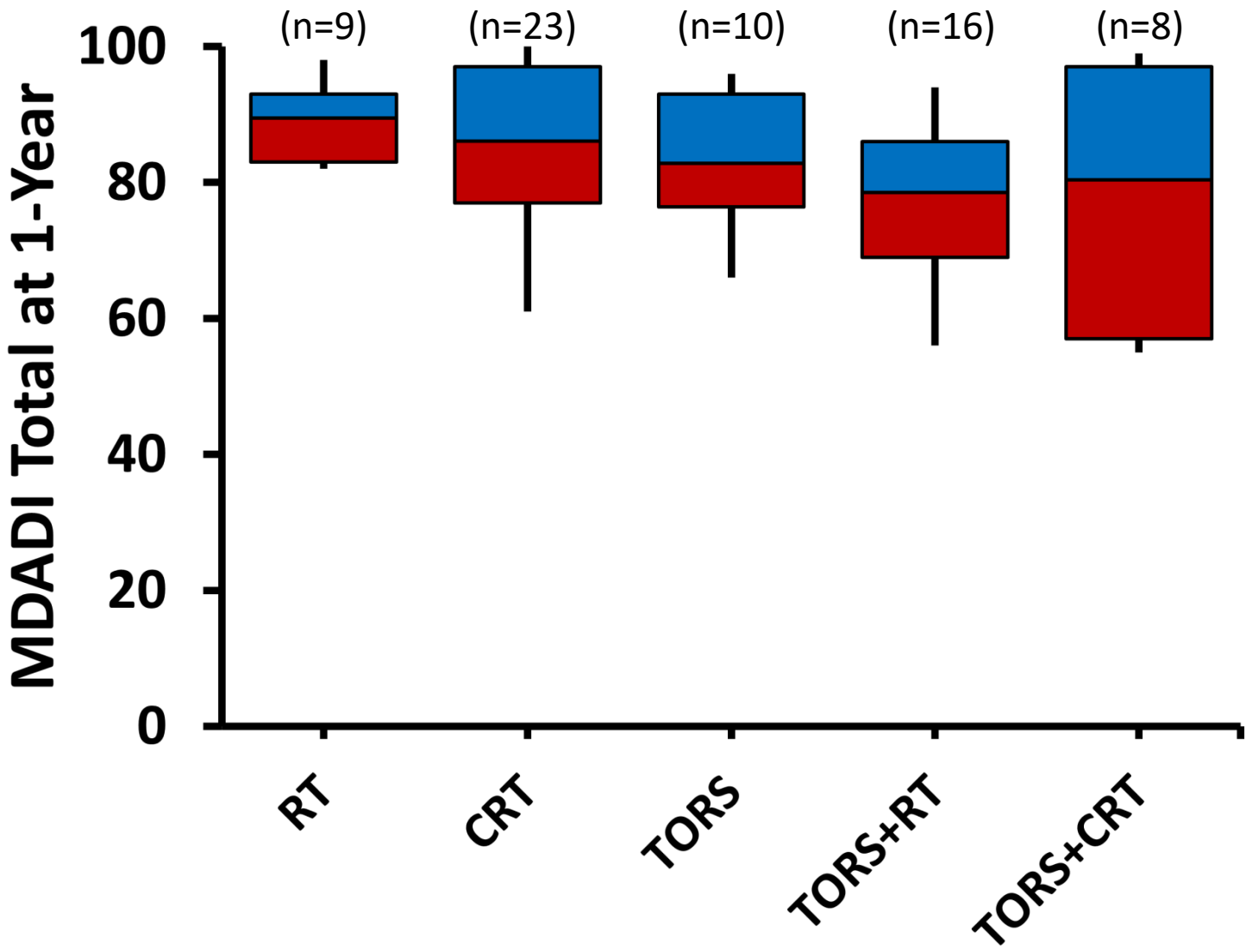
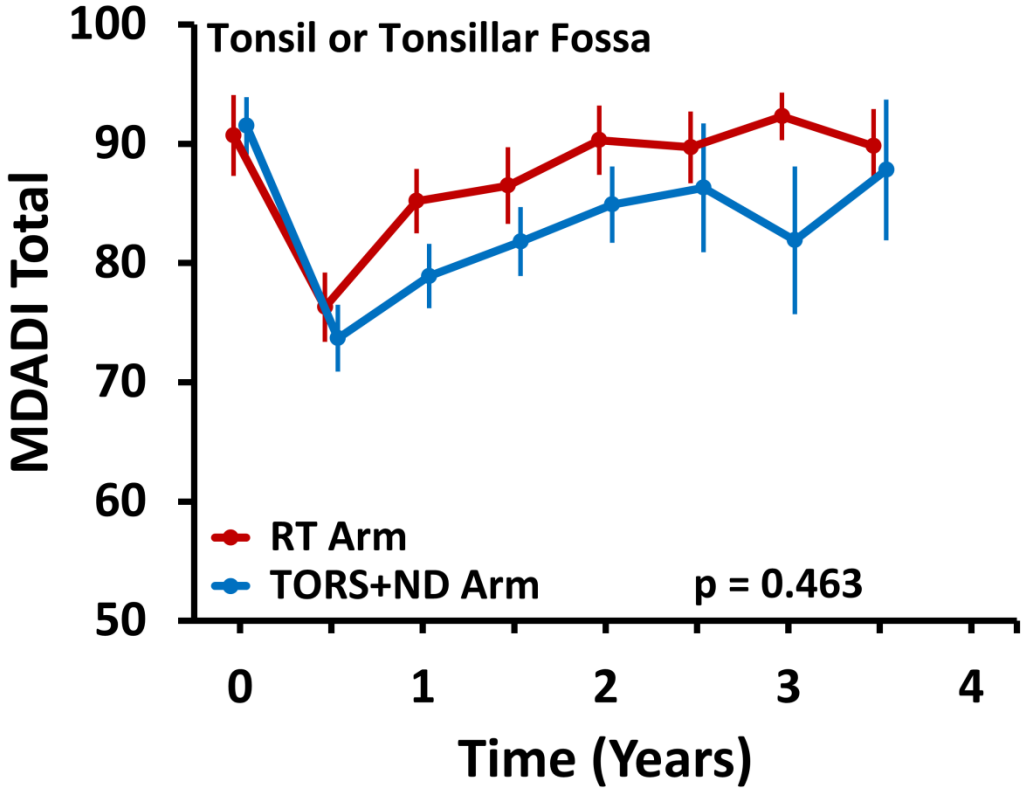
# Median MDADI Scores by Treatment Intensity

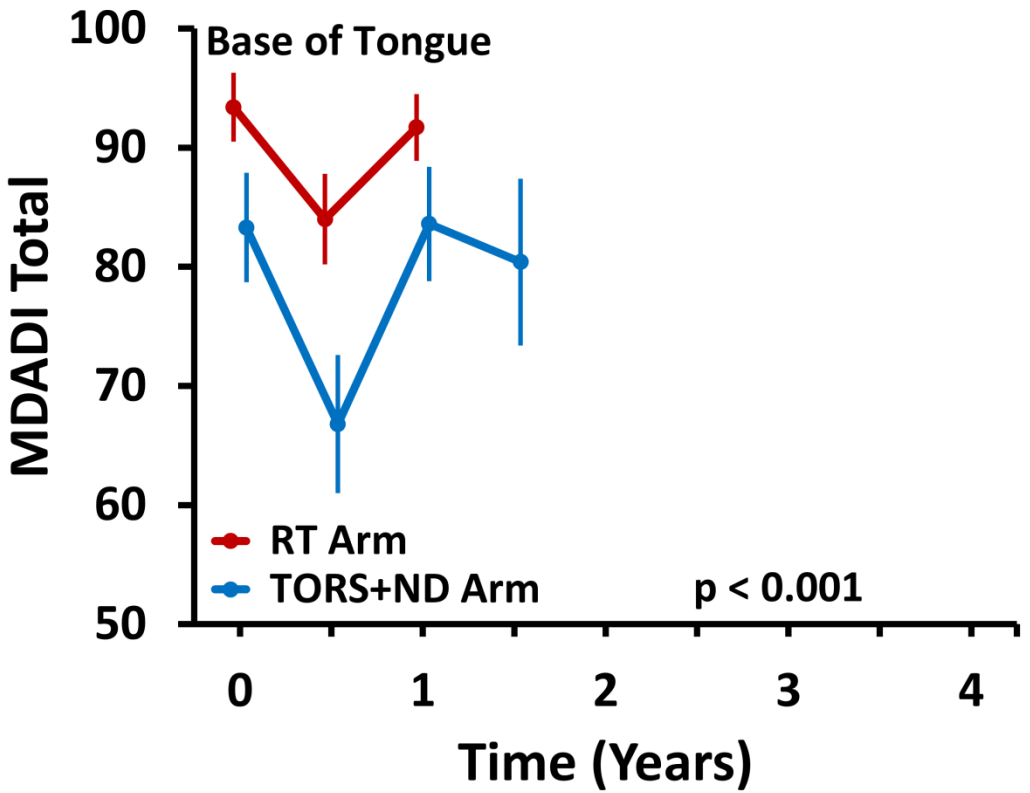


# MDADI Scores by Disease Site




Number of completed surveys

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| RT | 24 | 21 | 20 | 16 | 12 | 9 | 7 | 6 |
| TORS+ND | 21 | 23 | 22 | 14 | 14 | 9 | 7 | 6 |

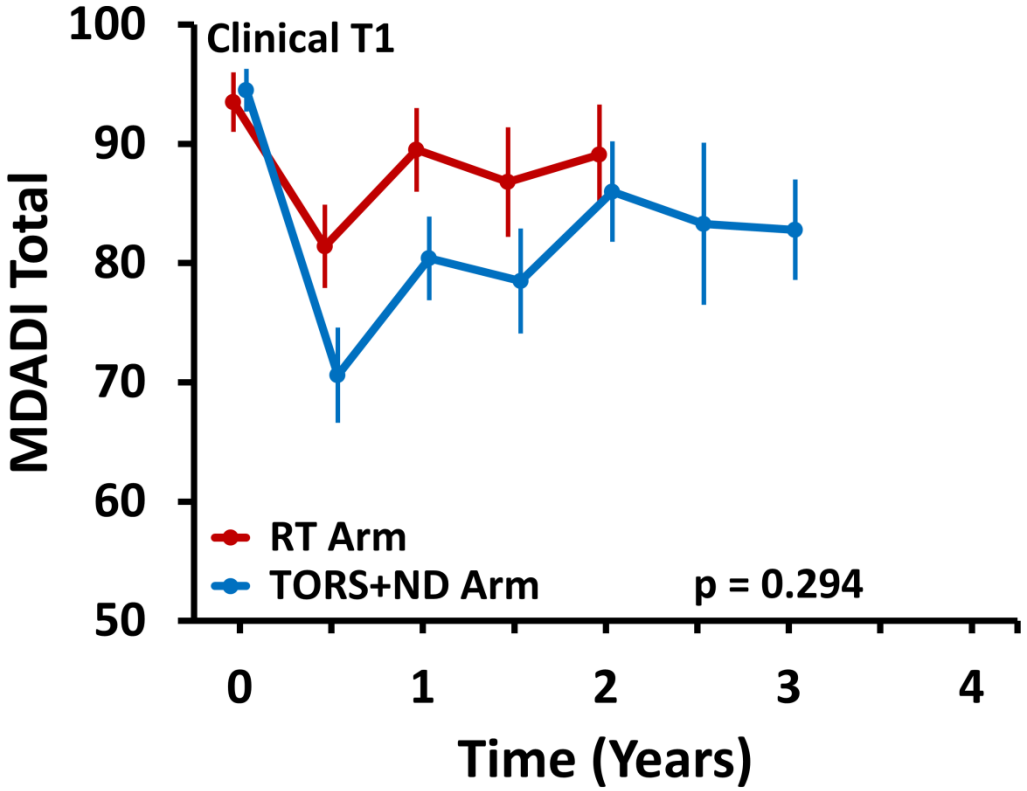



Number of completed surveys

| | | | | |
|---|---|---|---|---|
| RT | 8 | 8 | 7 | |
| TORS+ND | 10 | 10 | 8 | 7 |

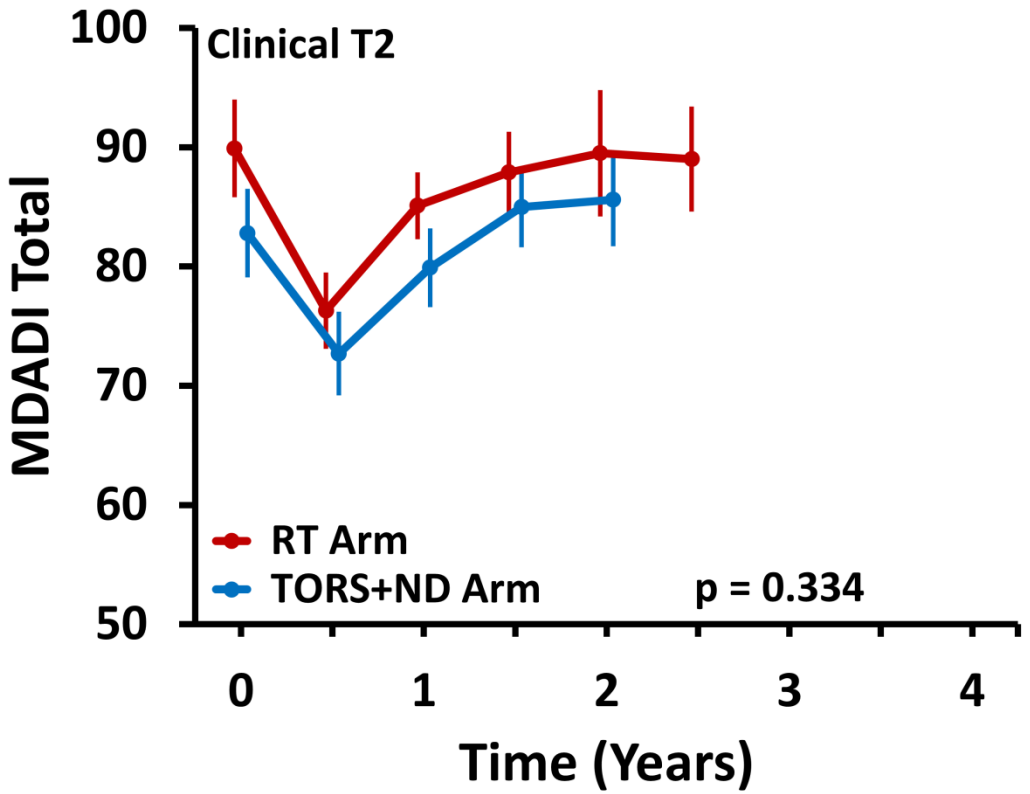
*Curves truncated when n<5

# MDADI Scores by T-Stage




Number of completed surveys

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| RT | 13 | 12 | 11 | 10 | 8 | | |
| TORS+ND | 16 | 17 | 14 | 12 | 9 | 7 | 5 |

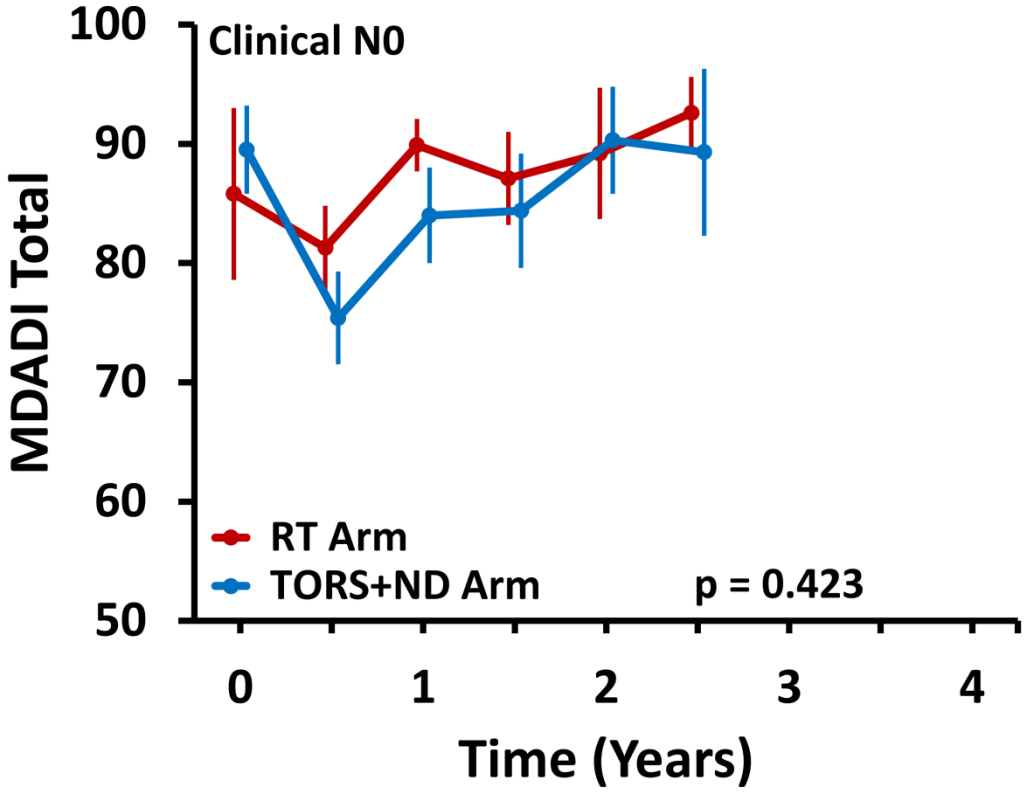



Number of completed surveys

| | | | | | | |
|---|---|---|---|---|---|---|
| RT | 19 | 17 | 16 | 10 | 6 | 6 |
| TORS+ND | 15 | 16 | 16 | 9 | 8 | |

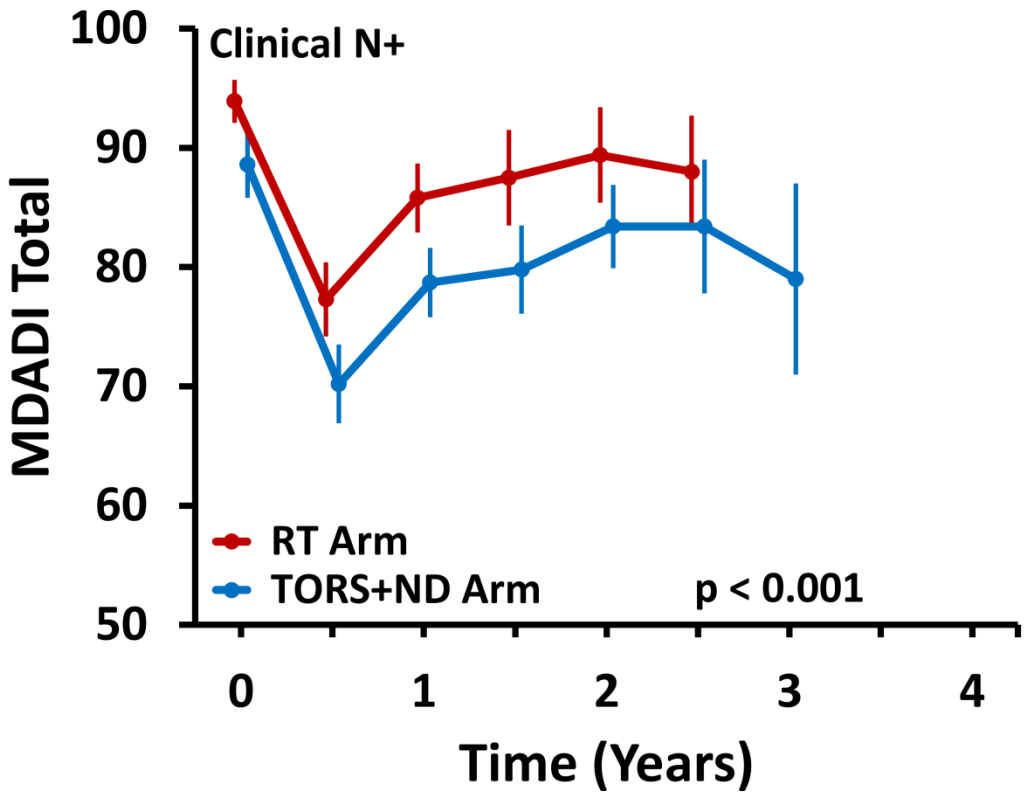
*Curves truncated when n<5

# MDADI Scores by N-Stage




Number of completed surveys

| | | | | | | |
|---|---|---|---|---|---|---|
| RT | 10 | 8 | 7 | 8 | 6 | 5 |
| TORS+ND | 8 | 9 | 8 | 7 | 6 | 6 |




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

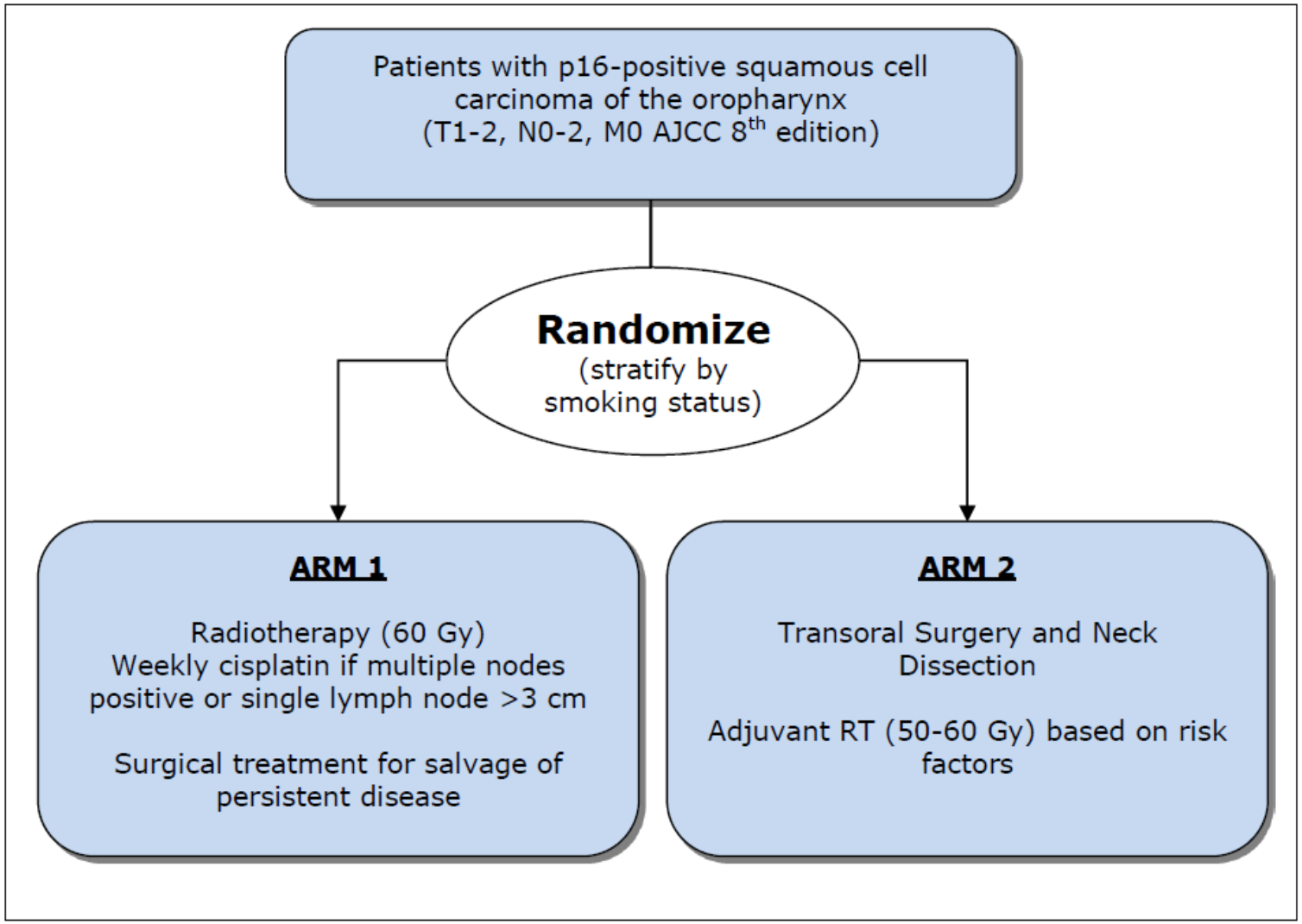
# Take Home Messages

- 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



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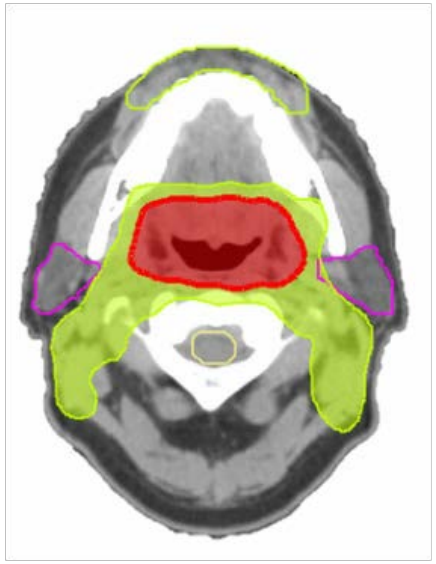

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