ASTRO ANNUAL MEETING 2019

# News Briefing

## The Year in Radiation Oncology

Tuesday, September 17, 2019
1:30-2:15 p.m. CT

# News Briefing: The Year in Radiation Oncology

Moderator: Theodore L. DeWeese, MD, PhD, FASTRO, Chair of the ASTRO Board of Directors

Update on ORATOR: Radiotherapy vs. Trans-Oral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma

*David Palma, MD, PhD, London Health Sciences Centre*

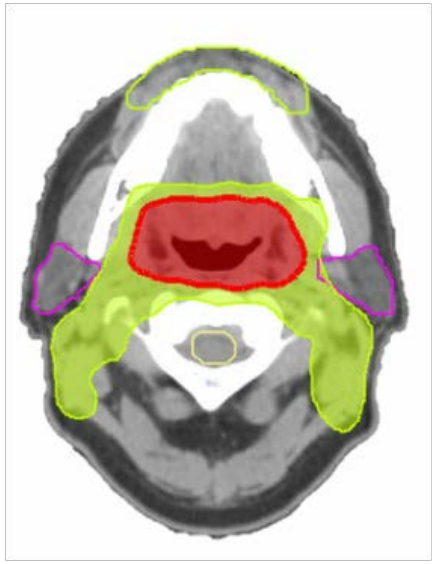
Update on NRG Oncology CC001: Hippocampal Avoidance during Whole-Brain Radiotherapy for Brain Metastases

*Vinai Gondi, MD, Northwestern Medicine*

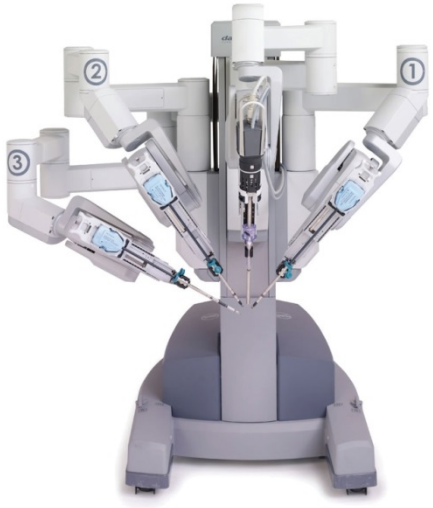
Preview of Cancer Breakthroughs: Takeaways from the Major Oncology Meetings of 2019

*Theodore L. DeWeese, MD, FASTRO, ASTRO Chair, Johns Hopkins Kimmel Cancer Center*

# 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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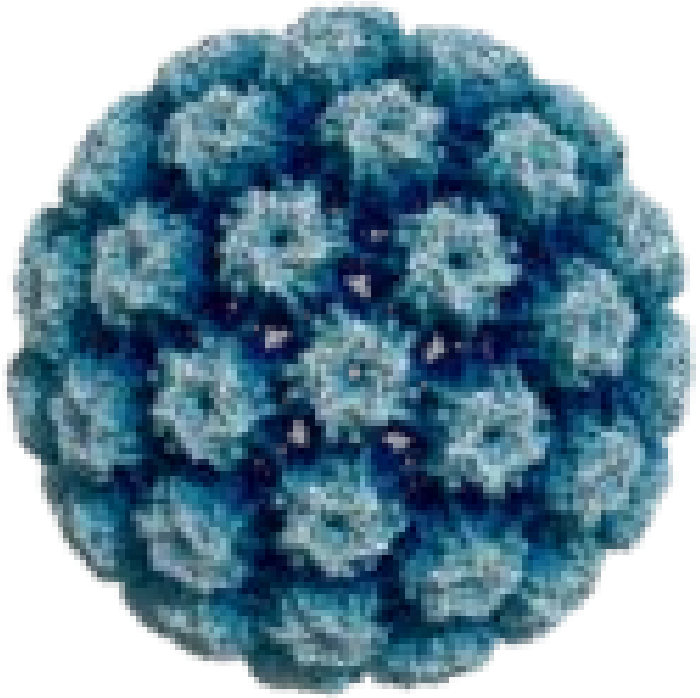
Canadian Cancer Society / Société canadienne du cancer

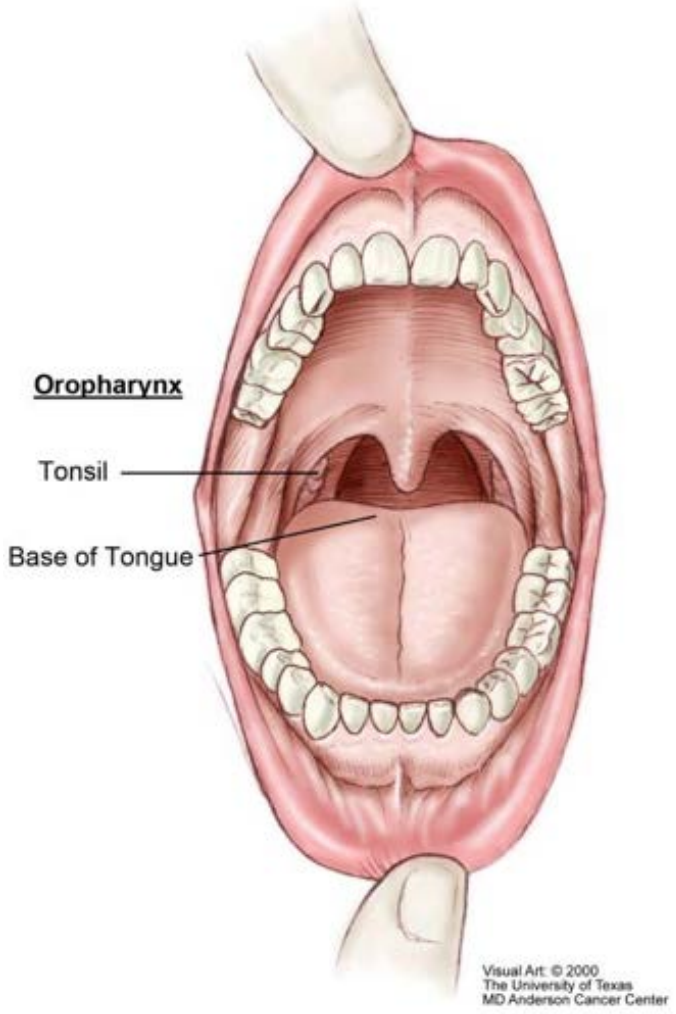
OICR Ontario Institute for Cancer Research

# 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

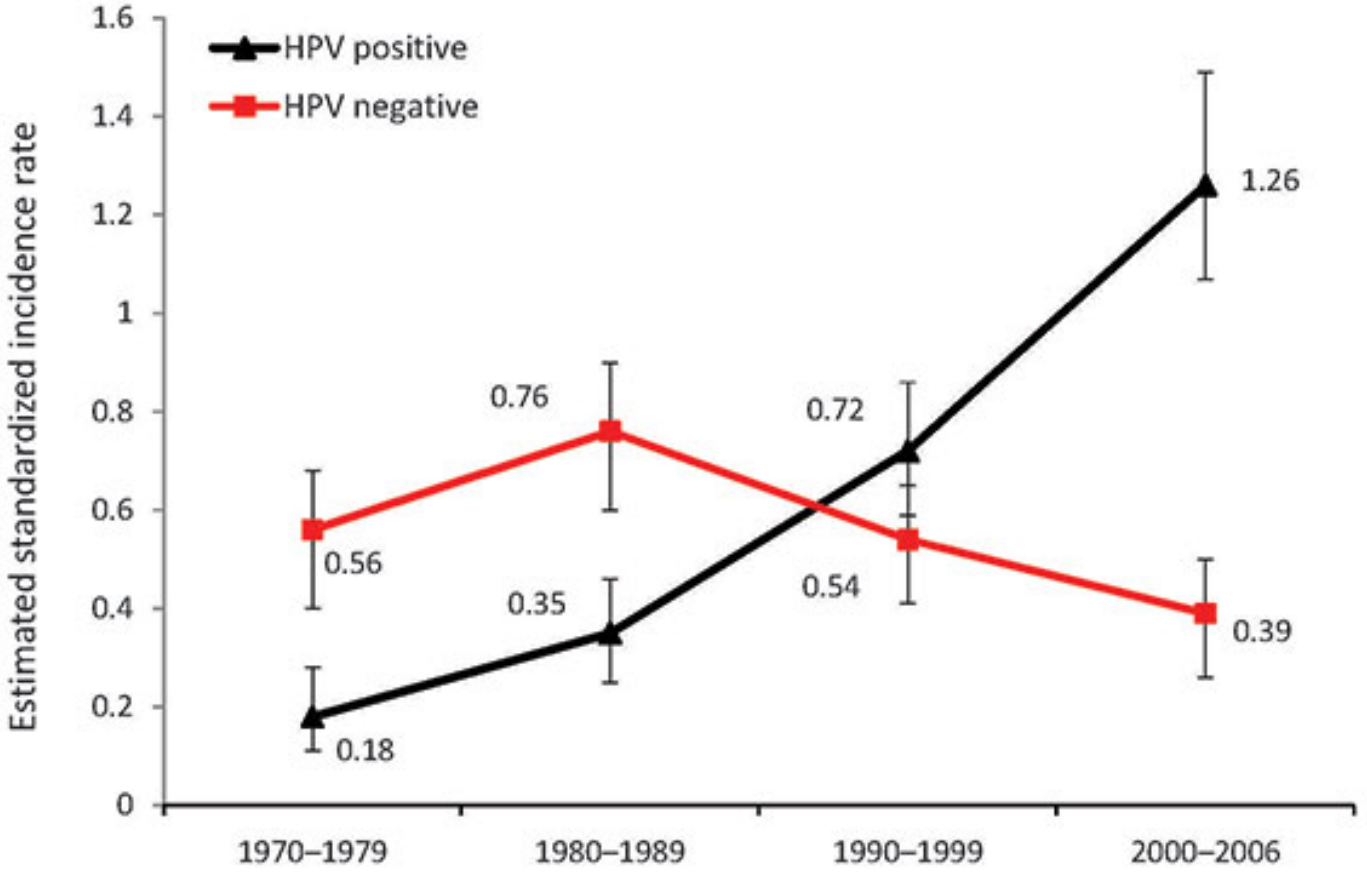
# The Oropharynx

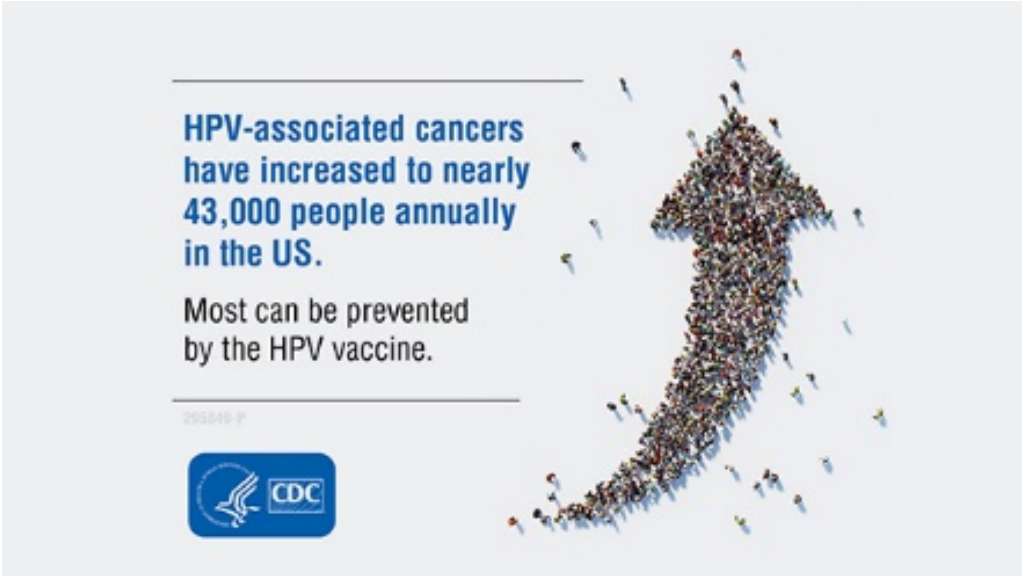



Risk factors for oropharyngeal HPV infection:

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

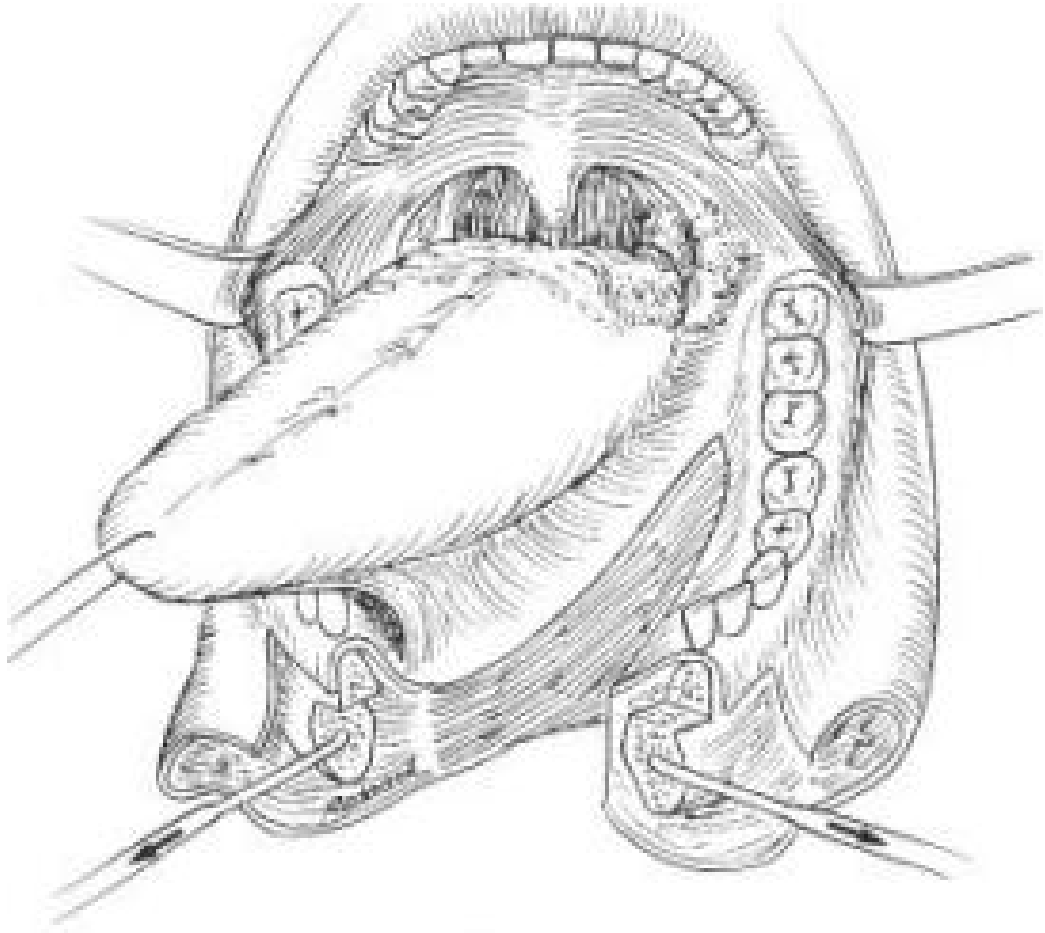
# CDC: HPV-related cancers increasing



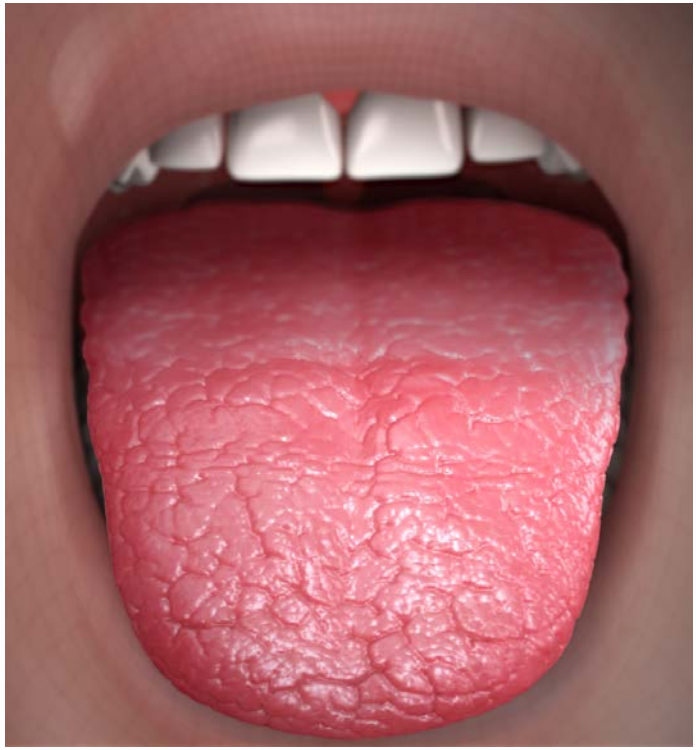

https://wwwnc.cdc.gov/eid/article/16/11/10-0452-f3

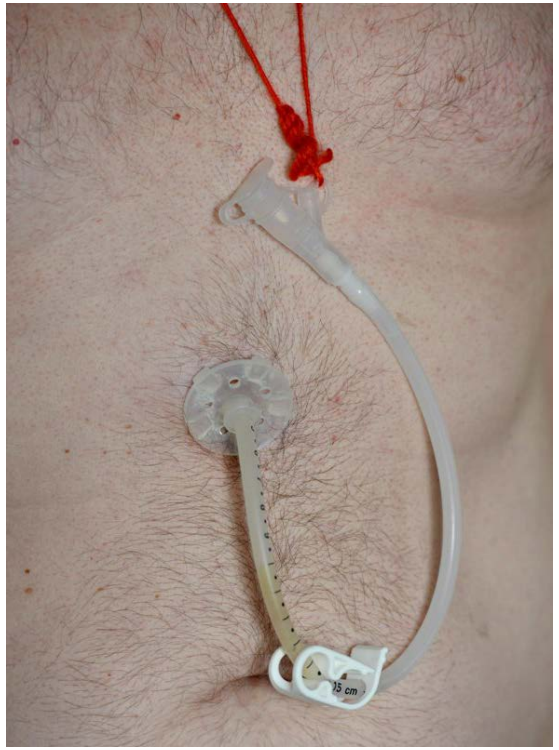
# Treatment: Older Surgical Techniques

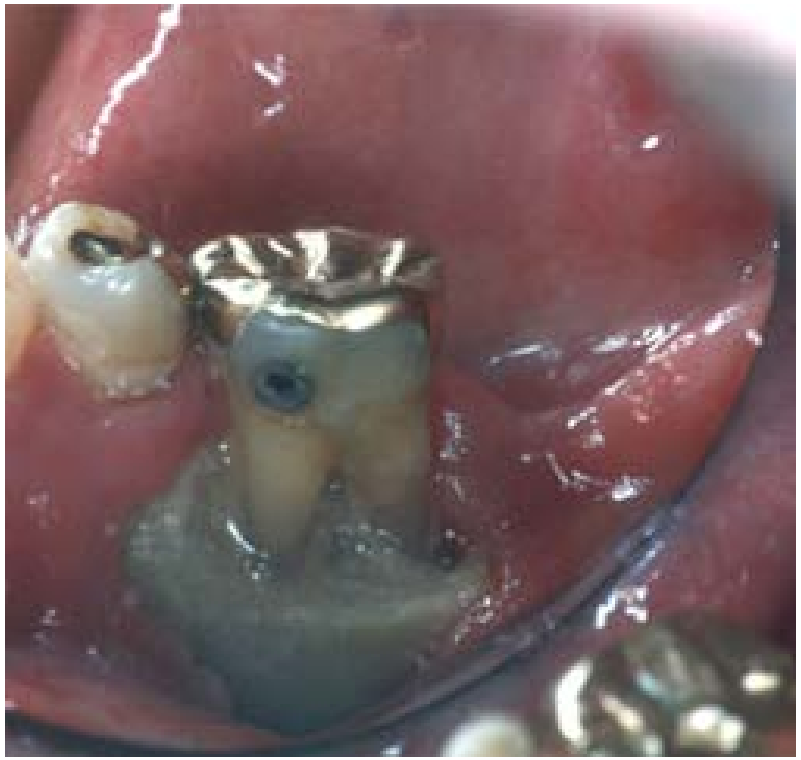


# Chemotherapy + Radiation

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



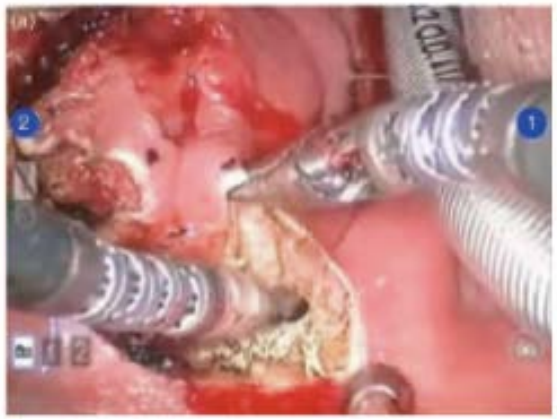


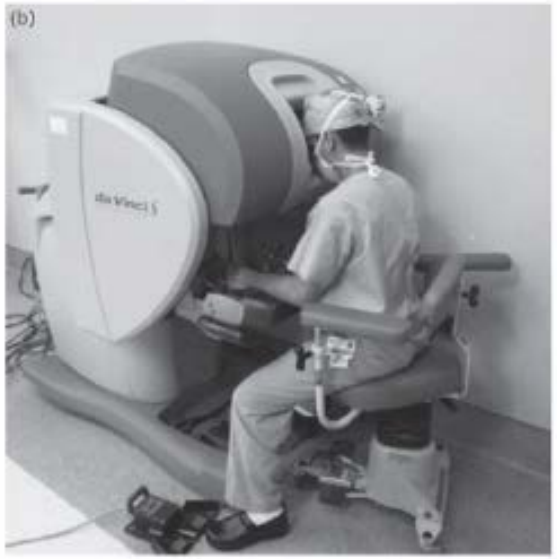


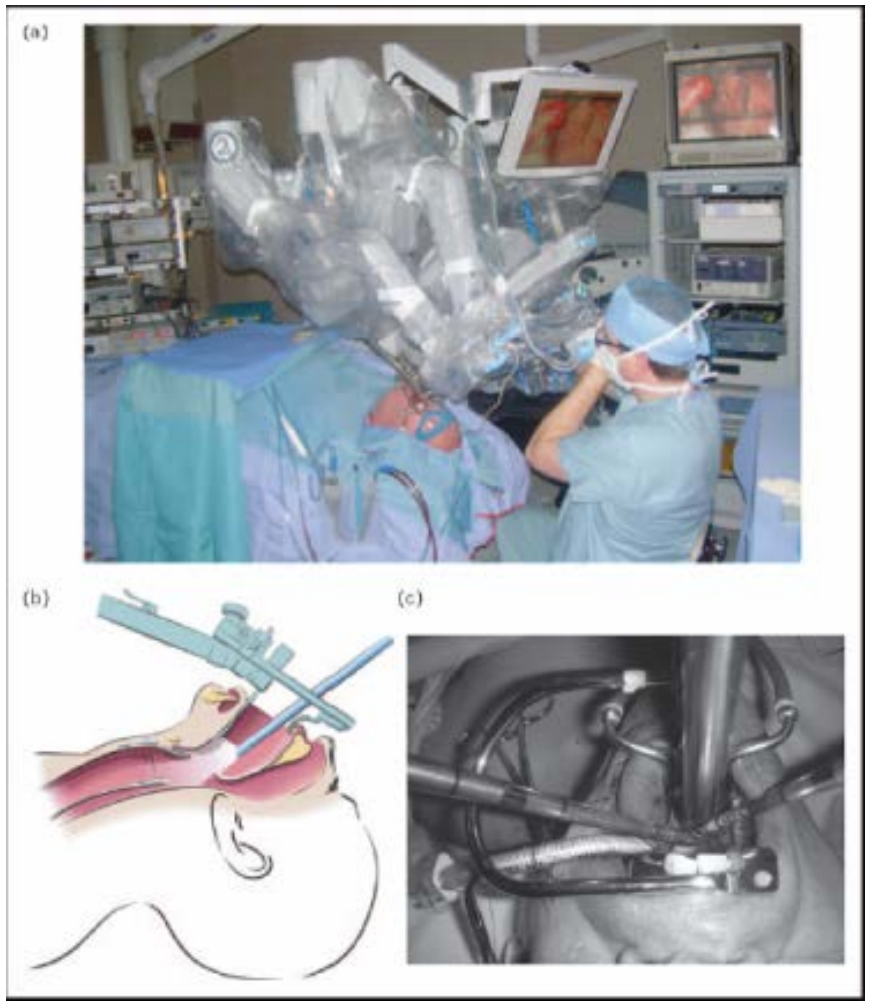
# A Patient's Perspective

- 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?"

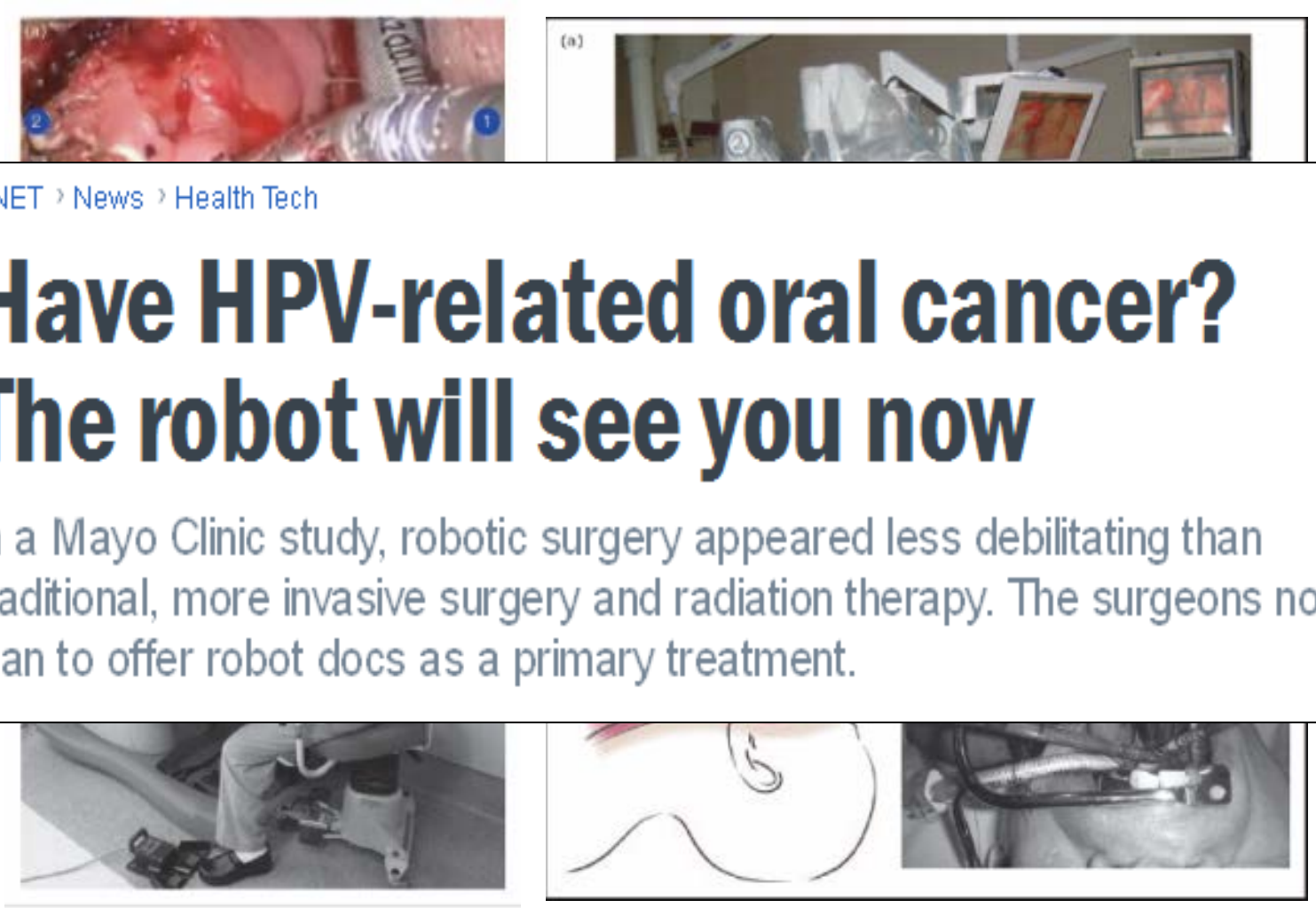
# Trans-Oral Robotic Surgery (TORS)





# Trans-Oral Robotic Surgery (TORS)

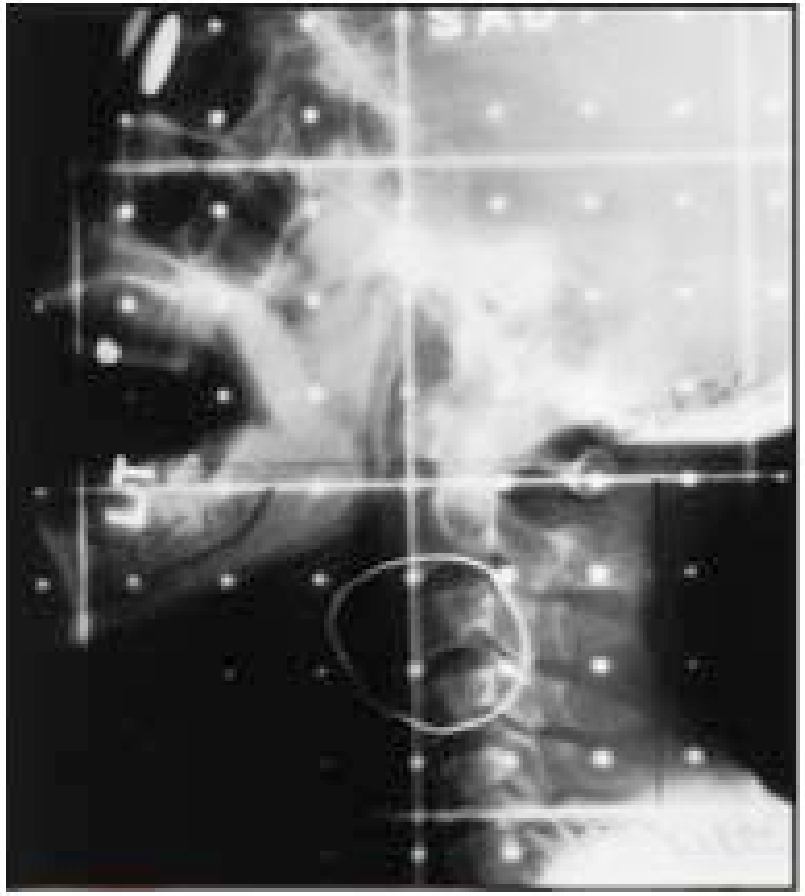


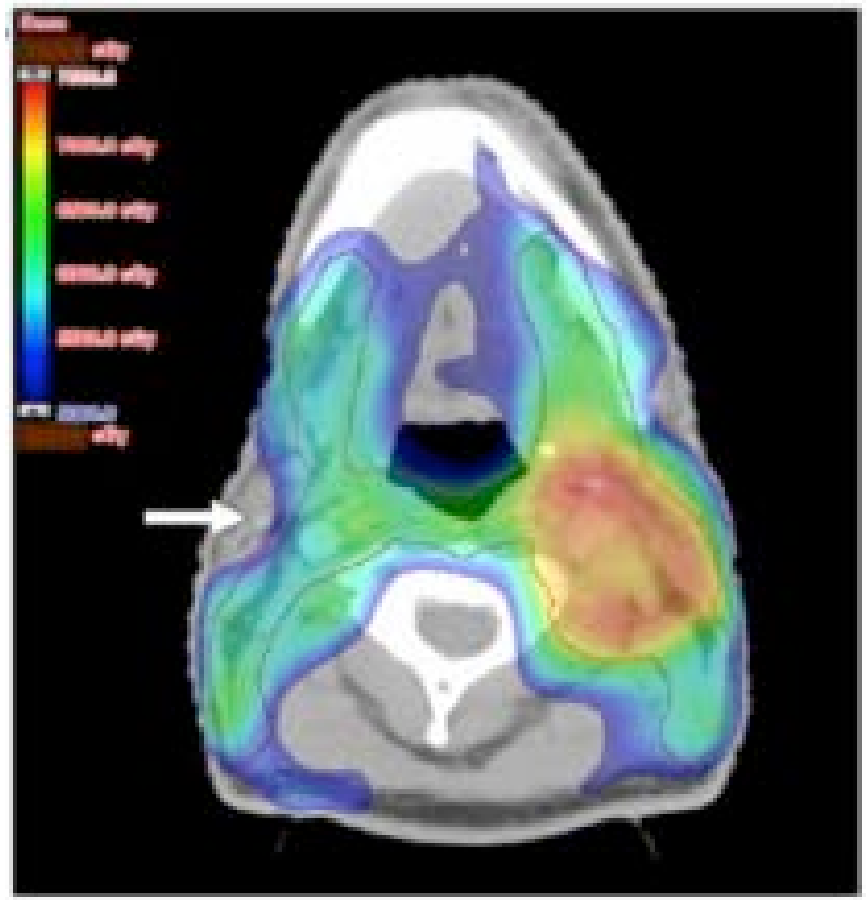
CNET › News › Health Tech

## 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%) | |

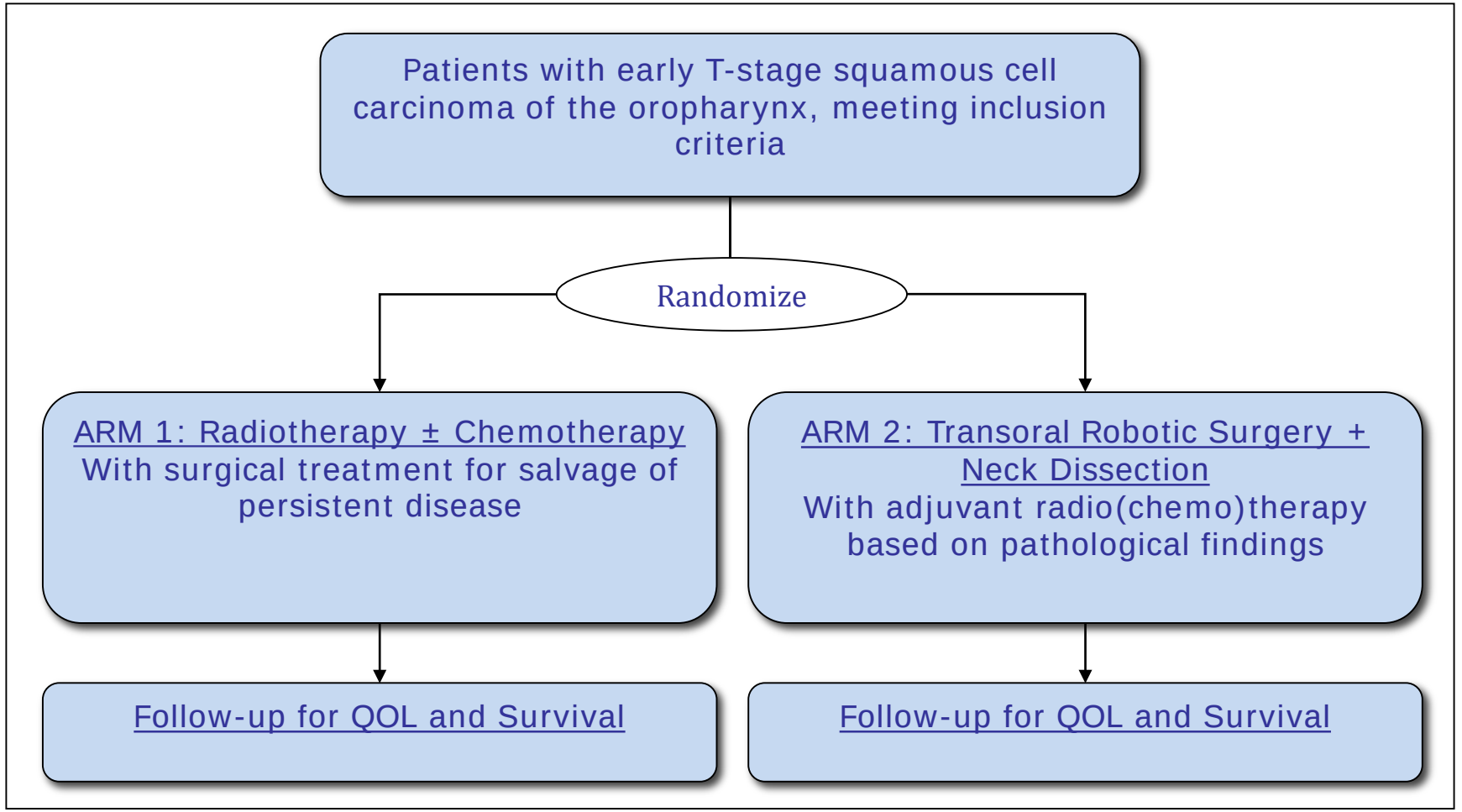
# Randomized Data Lacking

- 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

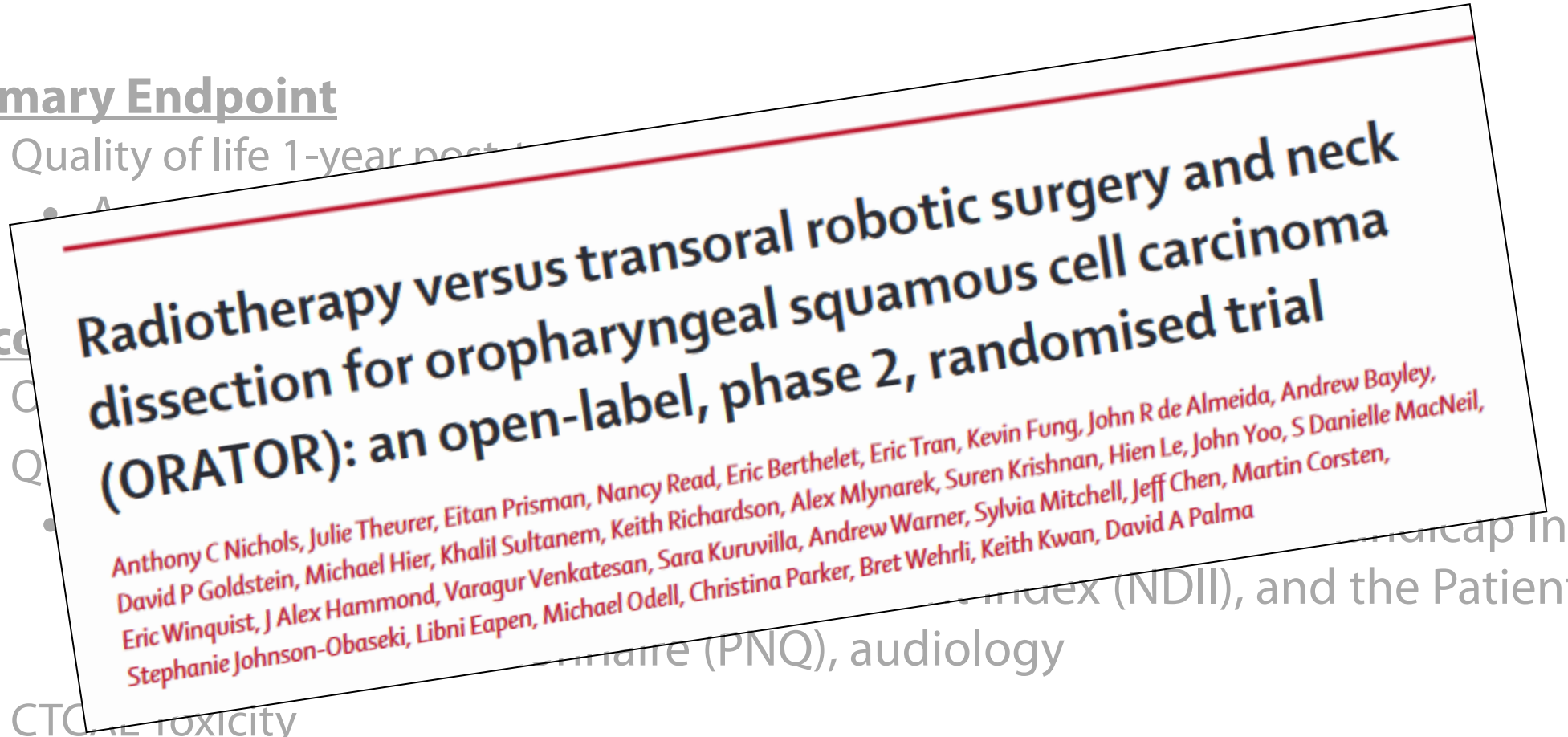
# Endpoints

**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

**Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial**

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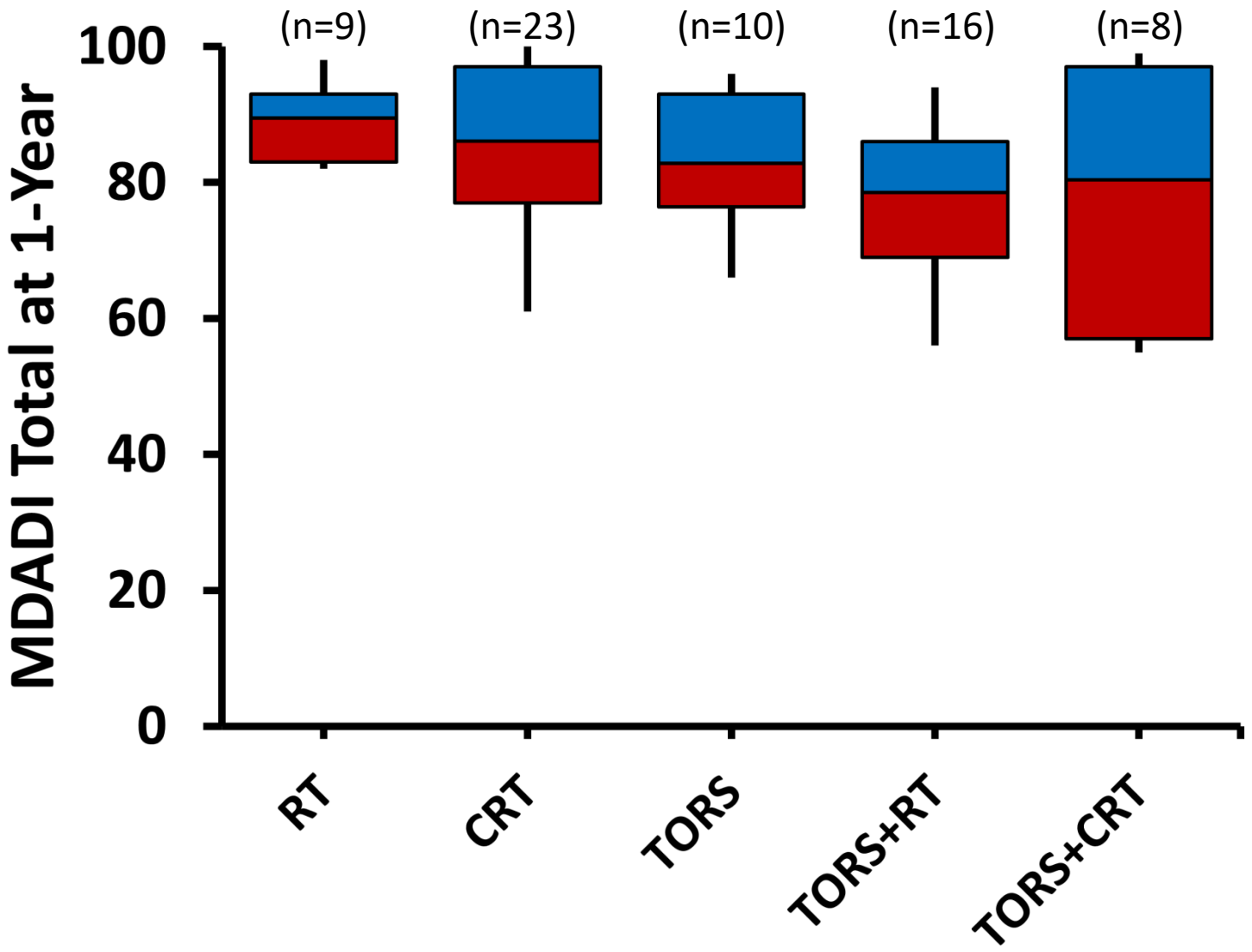
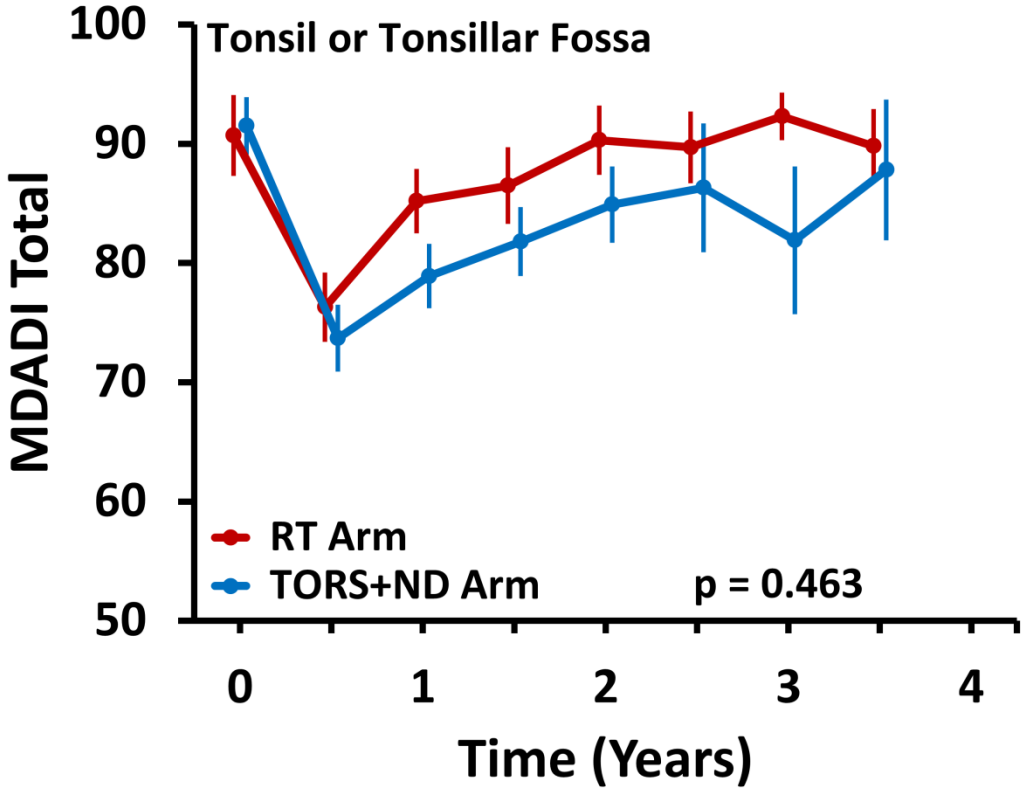
# Median MDADI Scores by Treatment Intensity

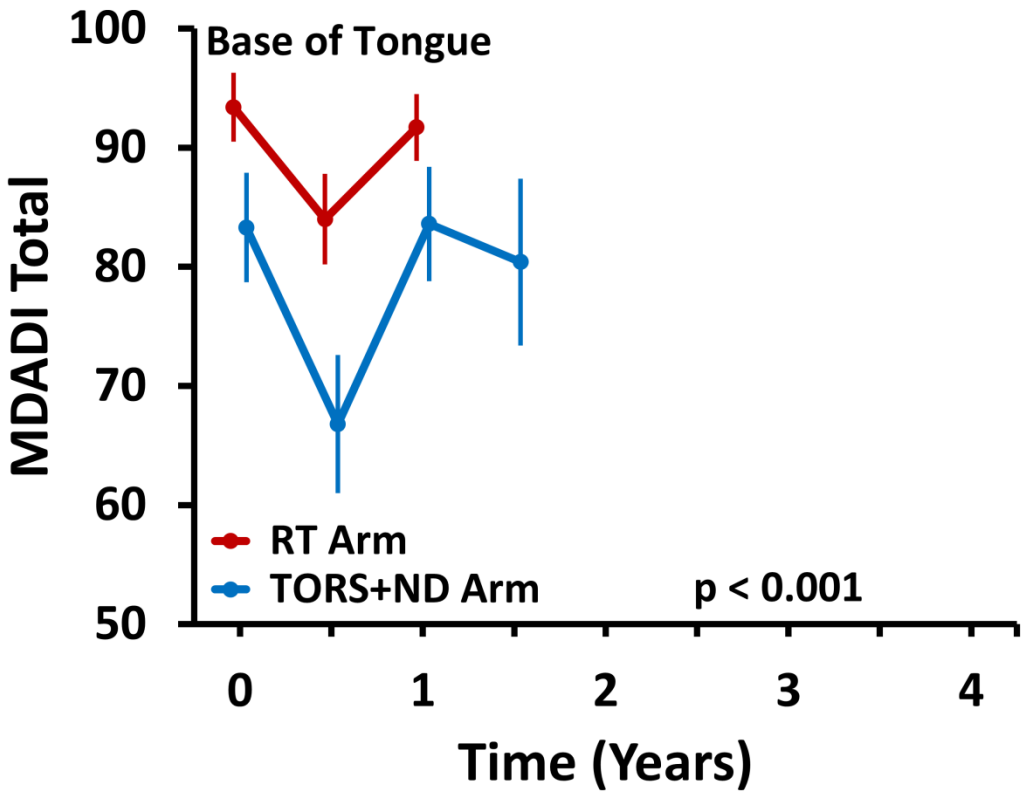


# MDADI Scores by Disease Site




Number of completed surveys

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

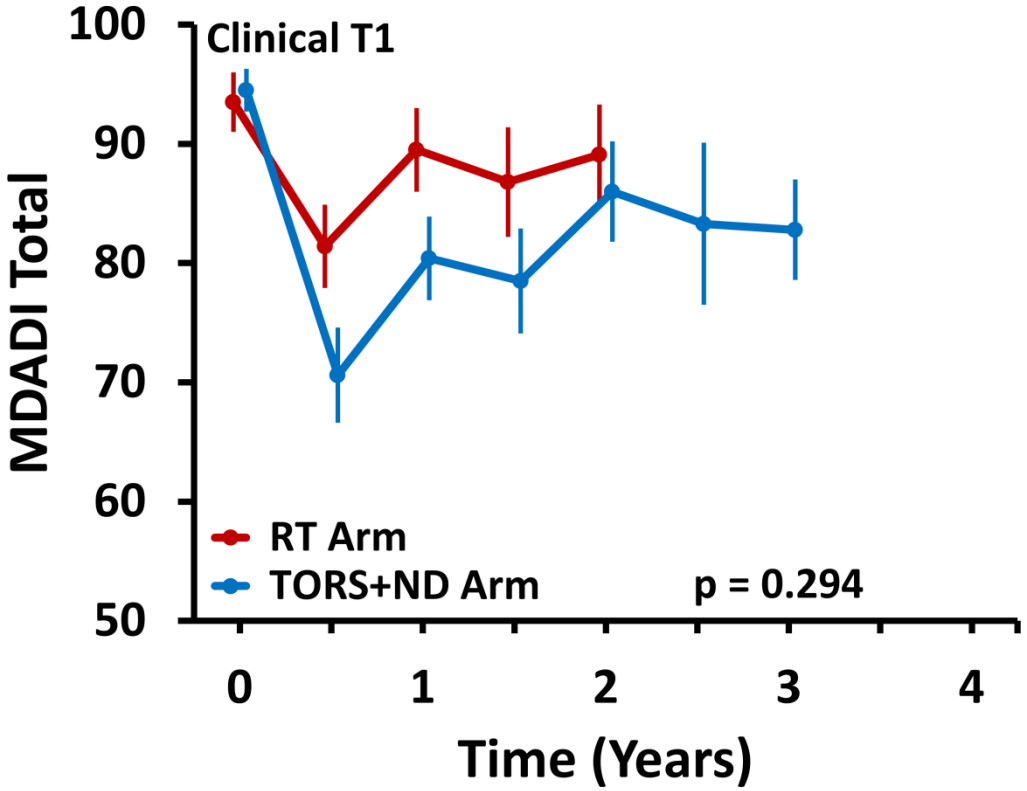



Number of completed surveys

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

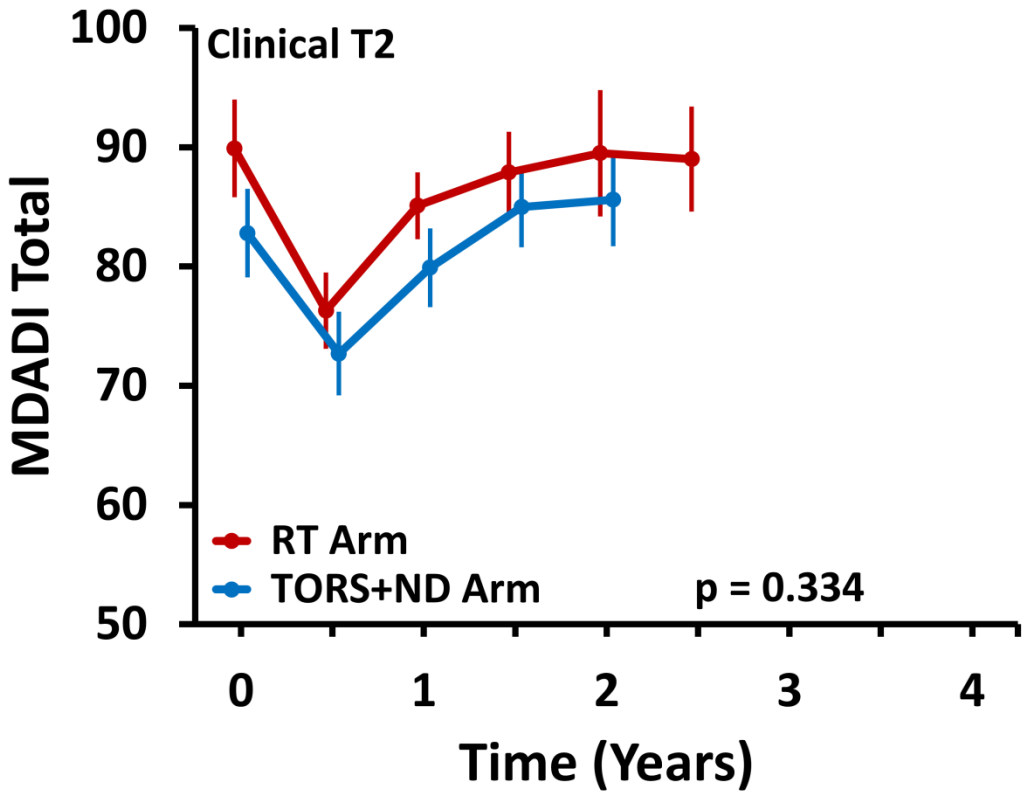
*Curves truncated when n<5

# MDADI Scores by T-Stage




Number of completed surveys

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

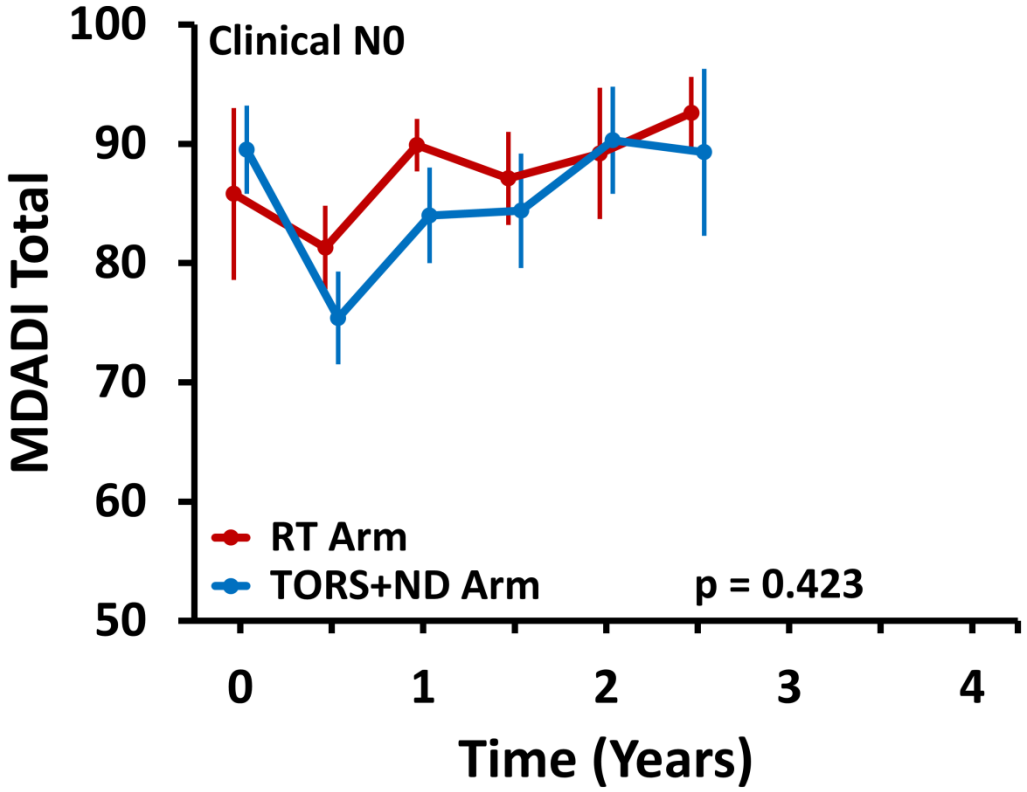



Number of completed surveys

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

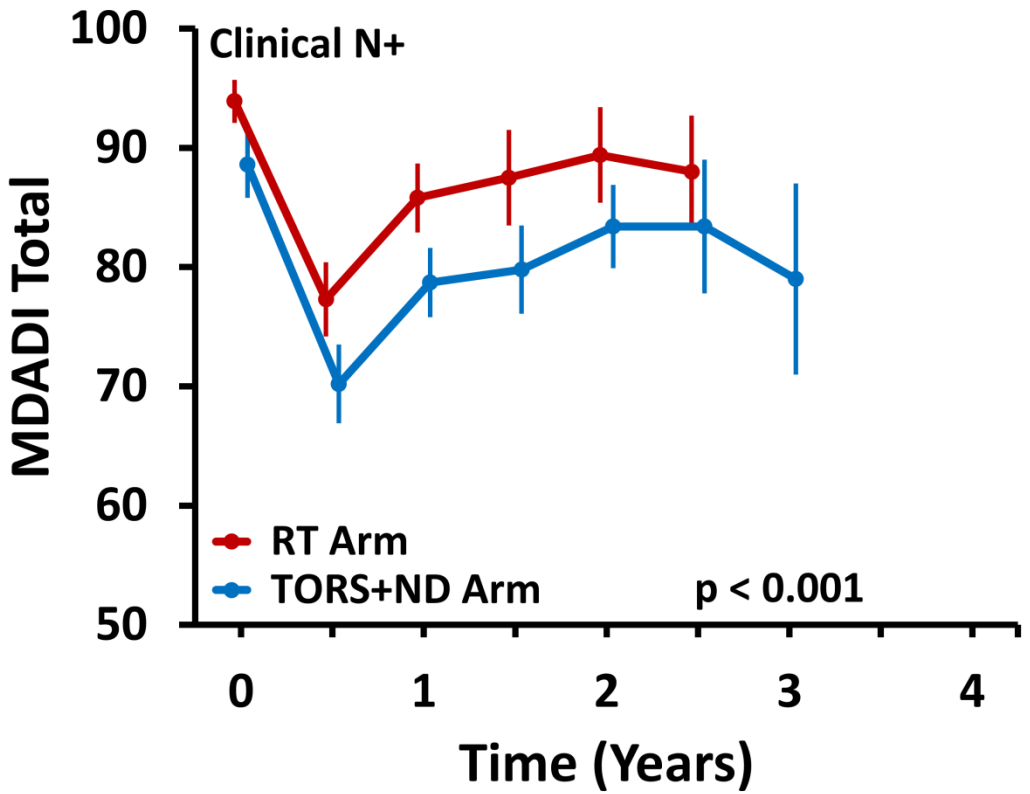
*Curves truncated when n<5

# 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

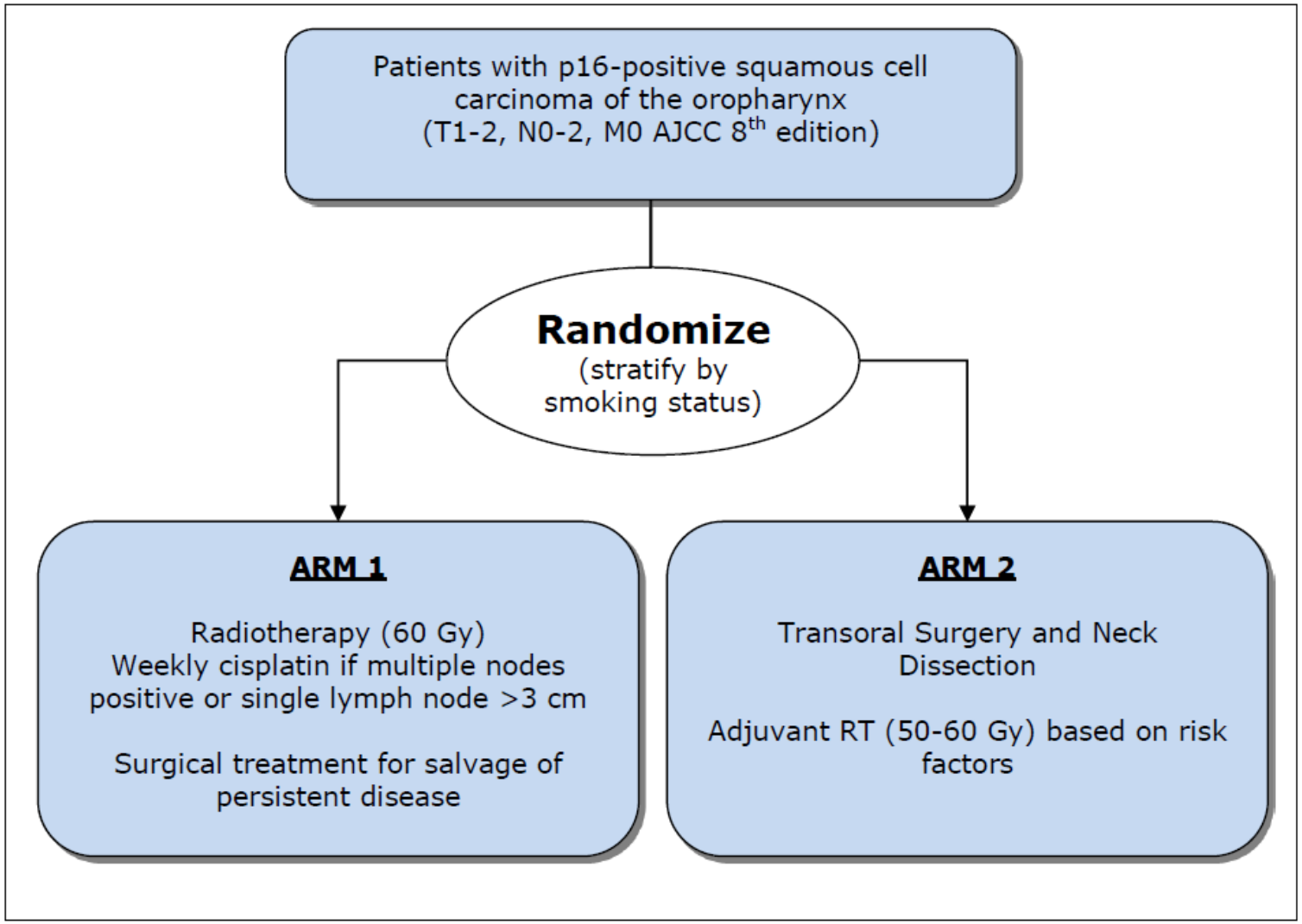
# Take Home Messages

- 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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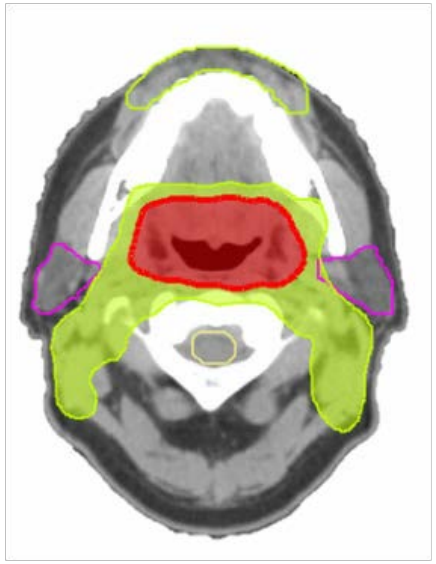
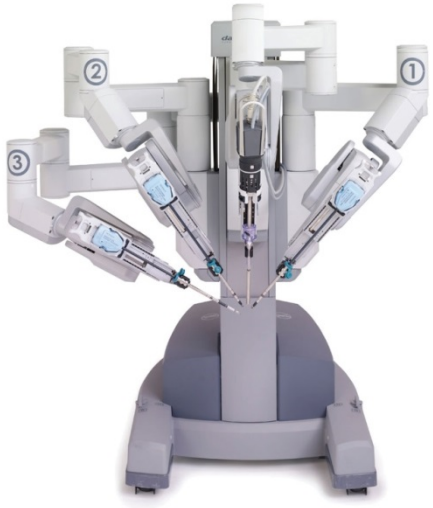


vs.

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ASTRO ANNUAL MEETING 2019

# Q & A

Use the "Question" tab in GoToWebinar to submit your questions.

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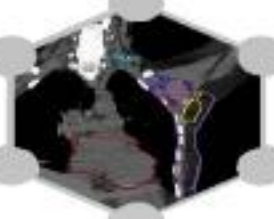


# Significant Preservation of Neurocognitive Function and Patient-Reported Symptoms with Hippocampal Avoidance during Whole-Brain Radiotherapy for Brain Metastases: Final Results of NRG Oncology CC001

**Vinai Gondi, MD*,** Stephanie Pugh, PhD, Paul D. Brown, MD*, Jeffrey S. Wefel, PhD, Wolfgang A. Tome, PhD, Terri S. Armstrong, PhD, Deborah W. Bruner, PhD, Joseph A. Bovi, MD, Cliff G. Robinson, MD, Deepak Khuntia, MD, David R. Grosshans, MD, PhD, Andre A. Konski, MD, MBA, David Roberge, MD, Vijayananda Kundapur, MD, Kiran Devisetty, MD, Sunjay A. Shah, MD, Kenneth Y. Usuki, MD, Bethany M. Anderson, MD, Minesh P. Mehta, MD, Lisa A. Kachnic, MD

*Co-Principal Investigators contributed equally to this work.

Special Thanks to Snehal Deshmukh, MS of NRG Oncology Biostatistics.

# Disclosures for Dr. Gondi

- Partnership, Radiation Oncology Consultants, LLC; Honoraria, UpToDate; Honoraria/Travel expenses: Physicans' Education Resource

# Background

- Whole-brain radiotherapy is associated with cognitive toxicity
  - 1-4 brain metastases: N0574[1], N107C[2], MD Anderson trial[3]
  - Declining use of WBRT, rising use of radiosurgery

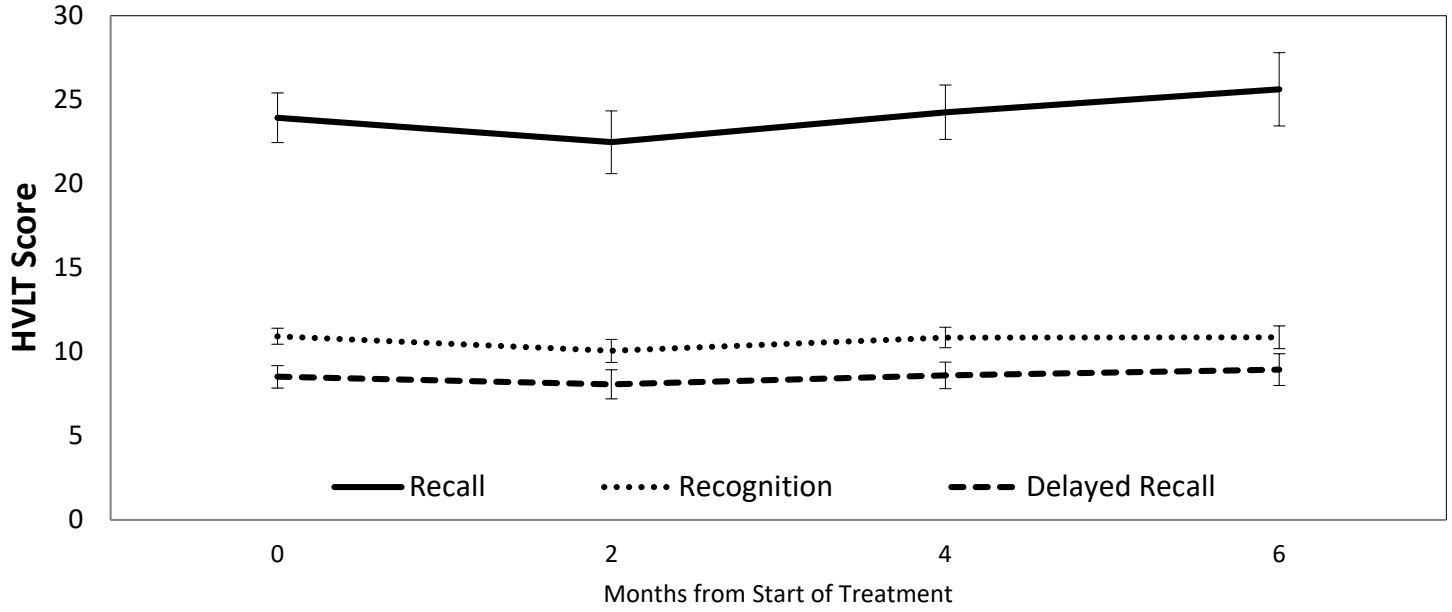
- Neuroregenerative stem cells within the hippocampal dentate gyrus are exquisitely radiosensitive and important to cognition
  - Preclinical/clinical evidence supports the hippocampal dentate gyrus as a memory-specific and radiosensitive structure-at-risk[4]

**Hypothesis: Hippocampal avoidance using IMRT prevents cognitive toxicity from WBRT**

[1]Brown et al. JAMA 2016
[2]Brown et al. Lancet Oncol 2017
[3]Chang et al. Lancet Oncol 2009
[4]Gondi et al. R&O 2010

# RTOG 0933

- Single-arm phase II trial of HA-WBRT (30 Gy in 10 fractions)
  - Credentialing and central review of hippocampal contouring and IMRT planning



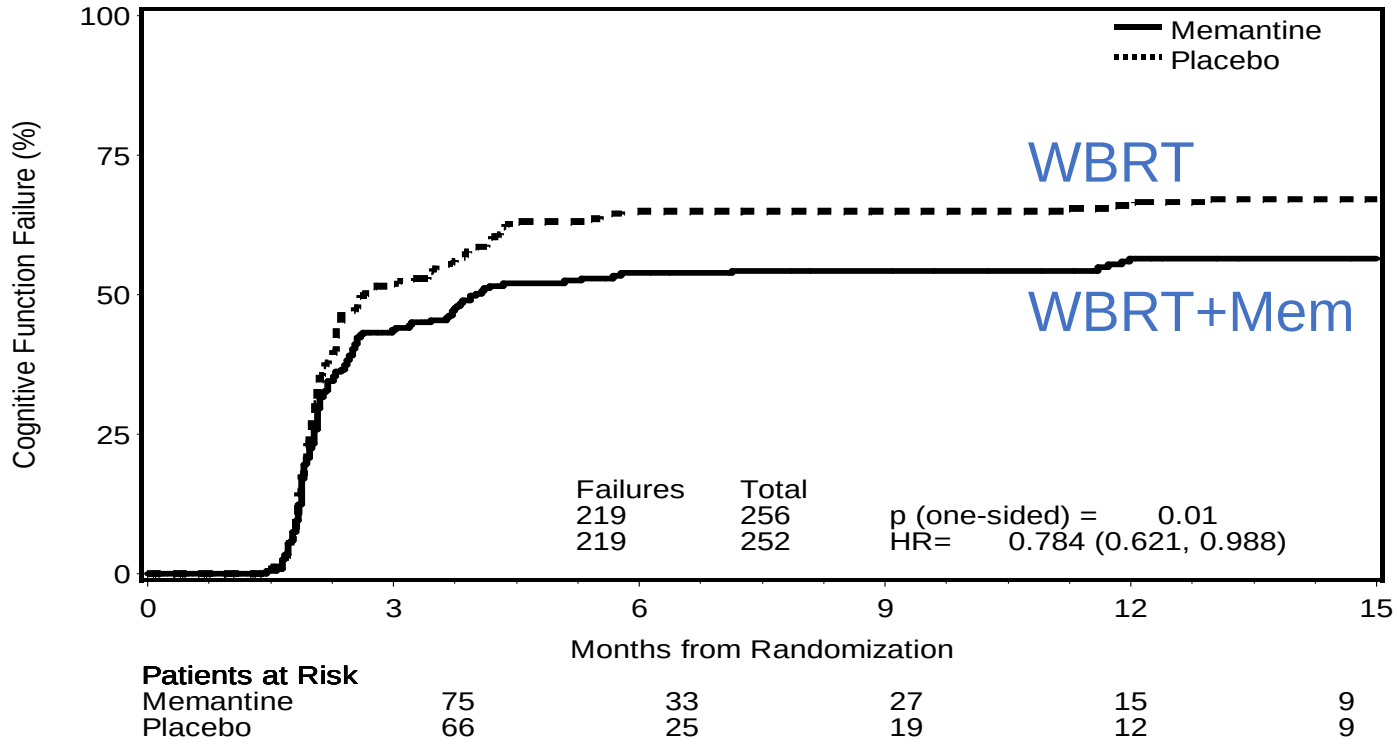

- **Mean decline in HVLT-Delayed Recall from baseline to 4 months:7.0% (95% CI: -4.7-18.7%)**
- Significantly less compared to historical control: 30% (*p*=0.0003)

**Need phase III data for level I evidence**

Gondi et al. JCO 2014

# RTOG 0614

- Phase III trial of WBRT with or without memantine

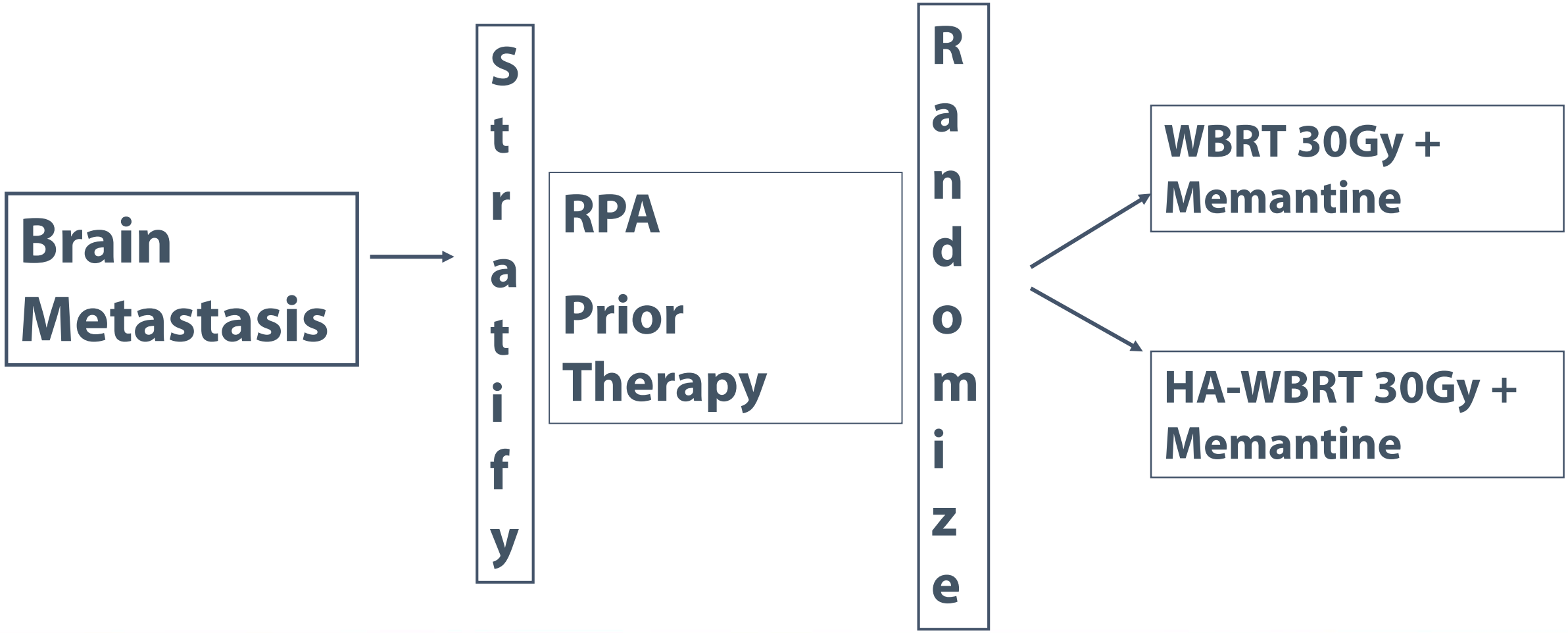



**Memantine during WBRT considered standard of care**

Brown et al. Neuro-Oncol 2013

# NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing



# Trial Design

- Primary endpoint: Time to cognitive failure
  - Cognitive battery: Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association, Trail Making Test
  - Cognitive failure: reliable change index defined decline on one or more tests
  - Cumulative incidence to estimate time to cognitive failure
    - Death without cognitive failure treated as competing risk
  - Secondary endpoints: patient-reported symptom burden (MDASI-BT), toxicity, progression-free and overall survival
- Probability of cognitive failure
  - Overall HR = 0.65
  - 382 analyzable patients for 90% power and two-sided $\alpha$=0.05
  - Sample size increased by 25% for possible non-compliance

**Target Accrual: 510 patients**

# Baseline Characteristics

518 randomized patients

| Baseline | WBRT+Mem n=257 | HA-WBRT+Mem n=261 | *p* value |
|---|---|---|---|
| Age | Median 61 | Median 62 | 0.66 |
| RPA class | Class I: 14.8%<br>Class II: 85.2% | Class I: 12.6%<br>Class II: 87.4% | 0.48 |
| Neurologic symptoms | None: 46.3%<br>Minor: 33.5% | None: 43.3%<br>Minor: 35.2% | 0.83 |
| Primary tumor | Lung 58.8%<br>Breast 17.5% | Lung 59.8%<br>Breast 19.5% | 0.81 |
| KPS | 70: 20.6% 80: 29.2%<br>90-100: 50.2% | 70: 18.4% 80: 31.0%<br>90-100: 50.6% | 0.38 |

**No differences in baseline patient characteristics, including cognitive function and patient-reported symptom burden**

# Toxicity

| Toxicity | WBRT+Mem n=257 | HA-WBRT+Mem n=261 | *p* value |
|---|---|---|---|
| Any relation | Grade 3: 89 (38.4%)<br>Grade 4: 20 (8.6%)<br>Grade 5: 35 (15.1%)<br>**Grade 3+: 144 (62.1%)** | Grade 3: 70 (31.4%)<br>Grade 4: 25 (11.2%)<br>Grade 5: 36 (16.1%)<br>**Grade 3+: 131 (58.7%)** | 0.47 |
| Treatment-related toxicity | Grade 3: 36 (15.5%)<br>Grade 4: 7 (3.0%)<br>Grade 5: 3 (1.3%)<br>**Grade 3+: 46 (19.8%)** | Grade 3: 36 (16.1%)<br>Grade 4: 4 (1.8%)<br>Grade 5: 3 (1.3%)<br>**Grade 3+: 43 (19.3%)** | 0.88 |

Treatment-related grade 5 toxicities:

WBRT+mem: Neoplasms benign, malignant and unspecified (n=3)

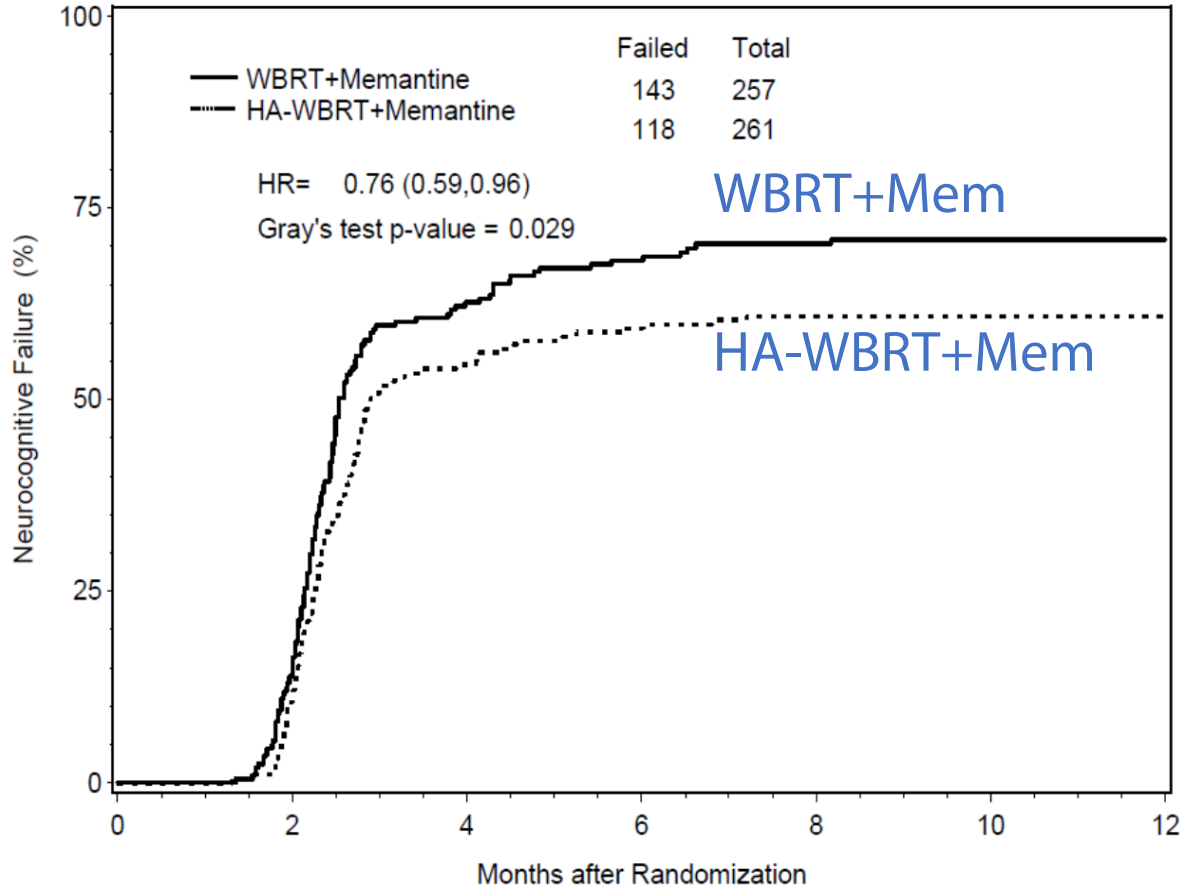
HA-WBRT+mem: Gen d/o's and administration site conditions (n=2, possible)

Somnolence (n=1, possible, 64d after tx start)

**No differences in any or treatment-related toxicity**

# Primary Endpoint

- Hippocampal avoidance <u>prevents cognitive function failure</u>
  - Hazard ratio = 0.756 $p$=0.029
  - Separation of the curves starting at 3 months and maintained through the follow-up period




**Patients at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| WBRT+Memantine | 257 | 133 | 34 | 19 | 11 | 9 | 5 |
| HA-WBRT+Memantine | 261 | 124 | 40 | 27 | 22 | 21 | 14 |

Median follow-up for alive patients: **12.1 months**

# Primary Endpoint

- Hippocampal avoidance <u>prevents cognitive function failure</u>
  - 26% relative risk reduction
- Multivariate analysis: Treatment arm and age
- No interaction between treatment arm and age
  - Effect of treatment remains significant independent of age

| Variable | HR | 95% CI | *p* value |
|---|---|---|---|
| **Treatment arm (HA-WBRT+Mem vs. WBRT+Mem[RL])** | **0.74** | **0.58-0.94** | **0.016** |
| **Age (≤61 vs. >61[RL])** | **0.61** | **0.47-0.80** | **0.0003** |
| RPA Class* (I vs. II[RL]) | 1.36 | 0.98-1.87 | 0.063 |
| Prior radiosurgery* (No vs. Yes[RL]) | 0.82 | 0.62-1.08 | 0.158 |
| Prior surgery* (No vs. Yes[RL]) | 1.10 | 0.84-1.44 | 0.504 |

*Stratification factor
[RL]: Reference level

Median follow-up for alive patients: **12.1 months**

# Cognition Domains at 4 Months

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)

**Deterioration at 4 months:**

| Cognitive Domain | WBRT +Mem n=109 | HA-WBRT +Mem n=93 | *p* |
|---|---|---|---|
| HVLT-R Total Recall | 35.5% | 29.0% | 0.33 |
| HVLT-R Delayed Recall | 33.0% | 24.7% | 0.19 |
| HVLT-R Recognition | 24.8% | 14.0% | 0.055 |
| Trail Making Test Part A | 24.8% | 20.4% | 0.46 |
| **Trail Making Test Part B** | **40.4%** | **23.3%** | **0.012** |
| Controlled Oral Word Association | 12.1% | 10.5% | 0.73 |

Median follow-up for alive patients: **12.1 months**

# Cognition Domains at 6 Months

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)

**Deterioration at 6 months:**

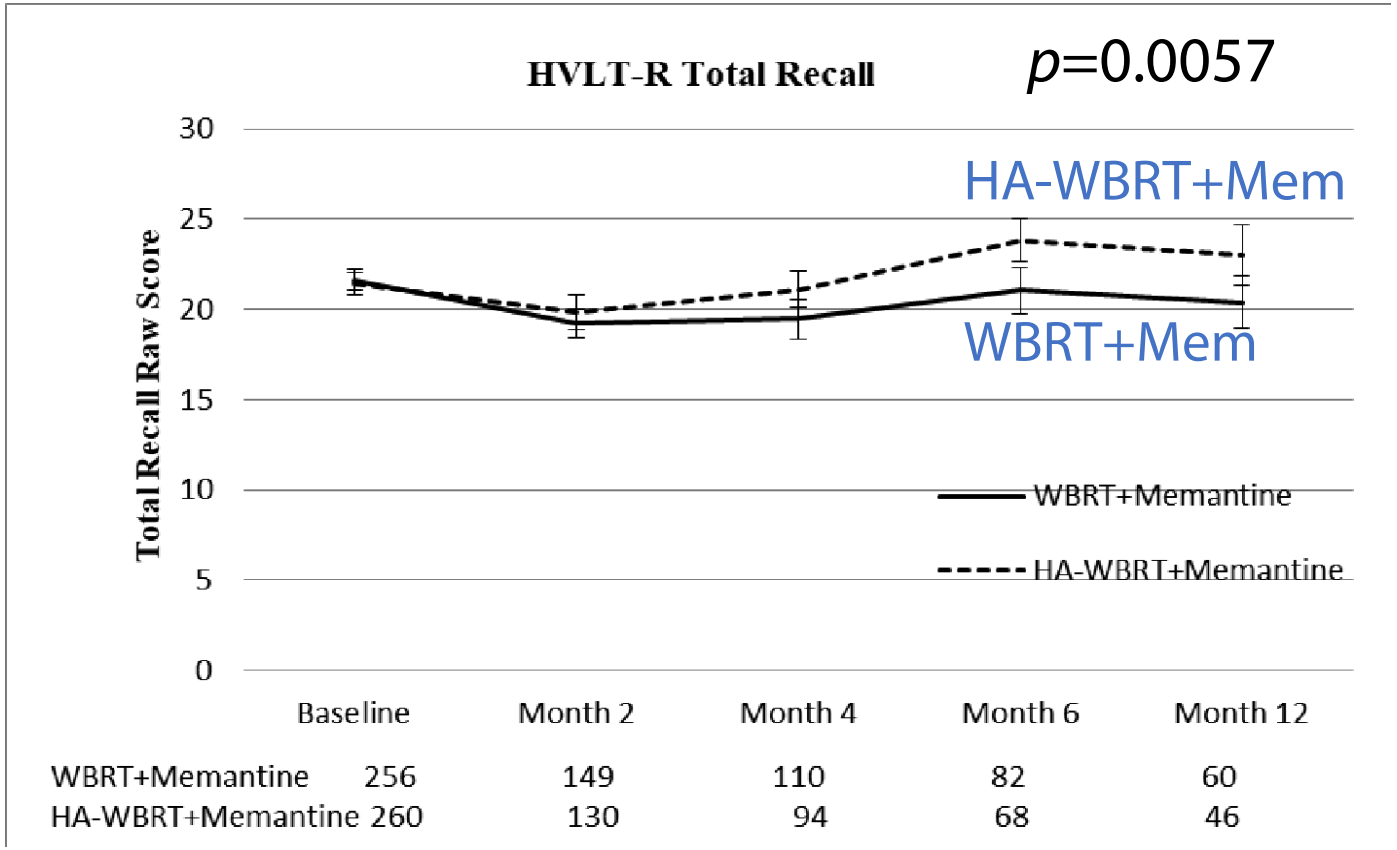
| Cognitive Domain | WBRT +Mem n=77 | HA-WBRT +Mem n=61 | *p* |
|---|---|---|---|
| HVLT-R Total Recall | 26.8% | 14.7% | 0.07 |
| HVLT-R Delayed Recall | 30.0% | 20.6% | 0.19 |
| **HVLT-R Recognition** | **36.3%** | **17.6%** | **0.011** |
| Trail Making Test Part A | 28.0% | 17.6% | 0.13 |
| Trail Making Test Part B | 35.9% | 23.9% | 0.12 |
| Controlled Oral Word Association | 6.2% | 11.8% | 0.23 |

Median follow-up for alive patients: **12.1 months**

# Cognition Domains Over Time

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)
- Hippocampal avoidance preserves all learning and memory domains over time
  - HVLT-R total recall, delayed recall and recognition

**Mixed effects models using multiple imputation:**




Higher score indicates better performance

Median follow-up for alive patients: **12.1 months**

# Cognition Domains Over Time

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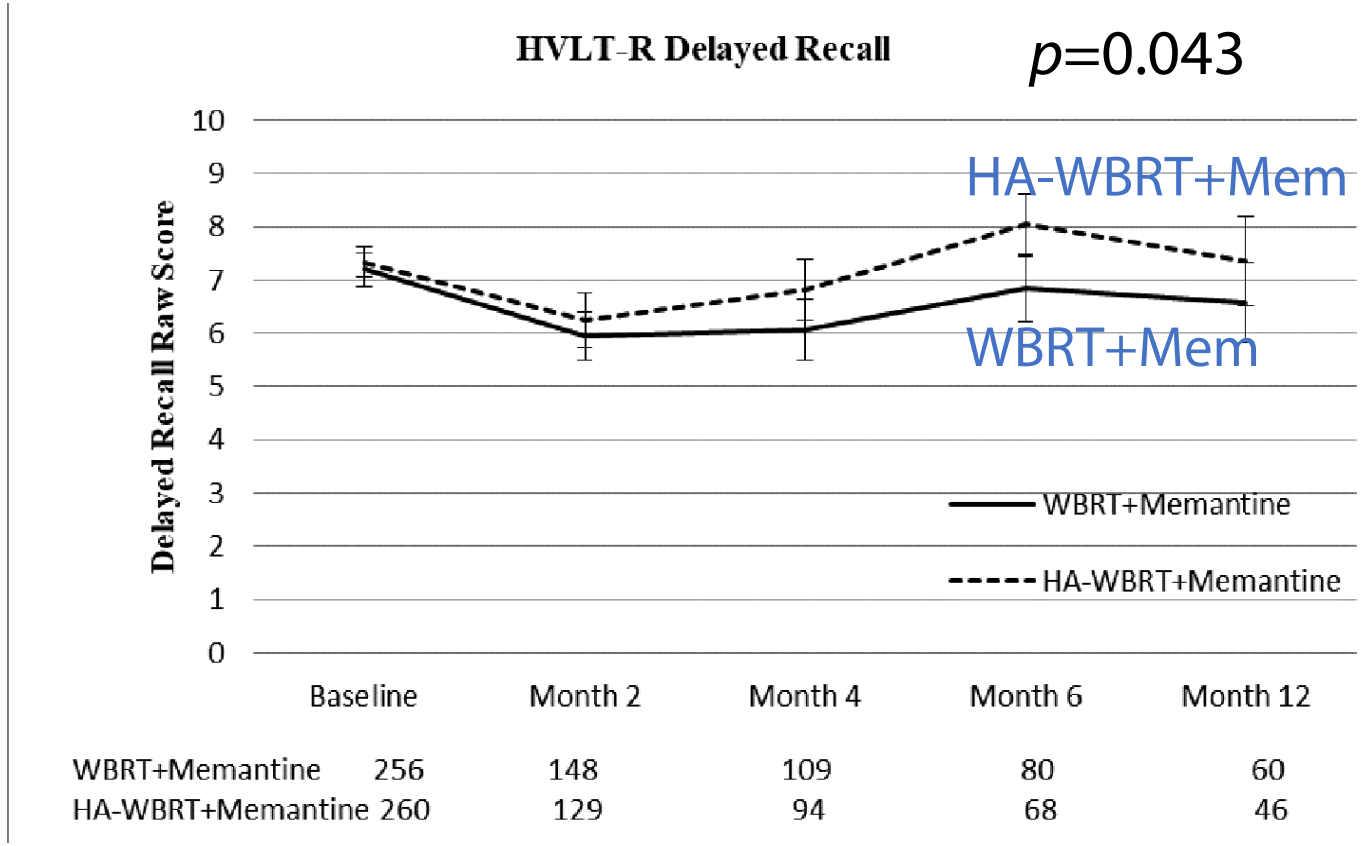


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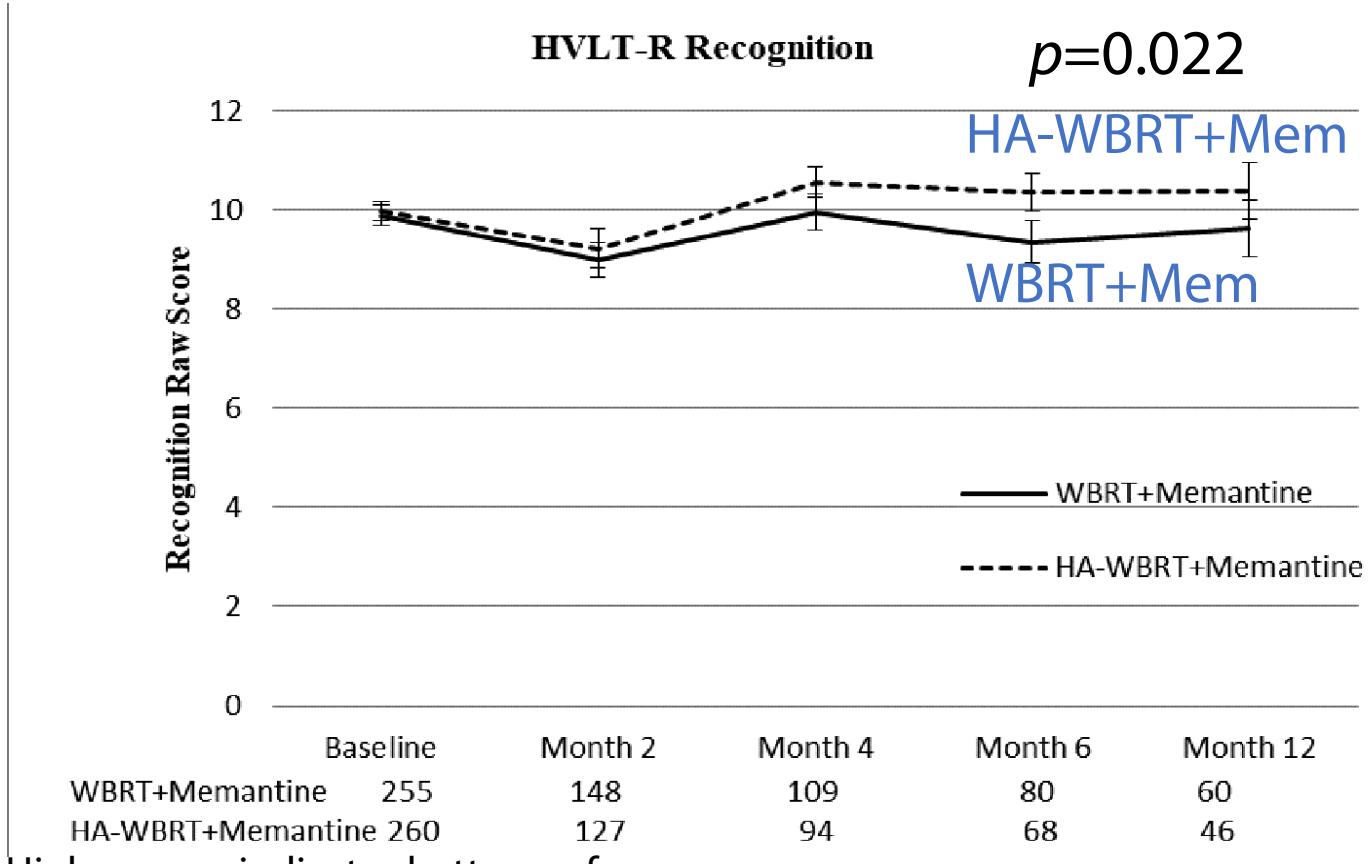



Higher score indicates better performance

Median follow-up for alive patients: **12.1 months**

# Patient-Reported Symptom Burden

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities

**Change from Baseline to 6 months:**

| Variable | Estimate | p value | Estimate | p value |
|---|---|---|---|---|
| | Complete Data | | Imputed Data | |
| Symptom | -0.26 | 0.083 | **-1.37** | **<0.001*** |
| **Interference** | **-5.07** | **0.003*** | **-1.93** | **0.0016*** |
| Cognitive factor | -0.05 | 0.77 | -0.17 | 0.35 |
| Neurologic factor | 0.213 | 0.32 | -0.13 | 0.56 |

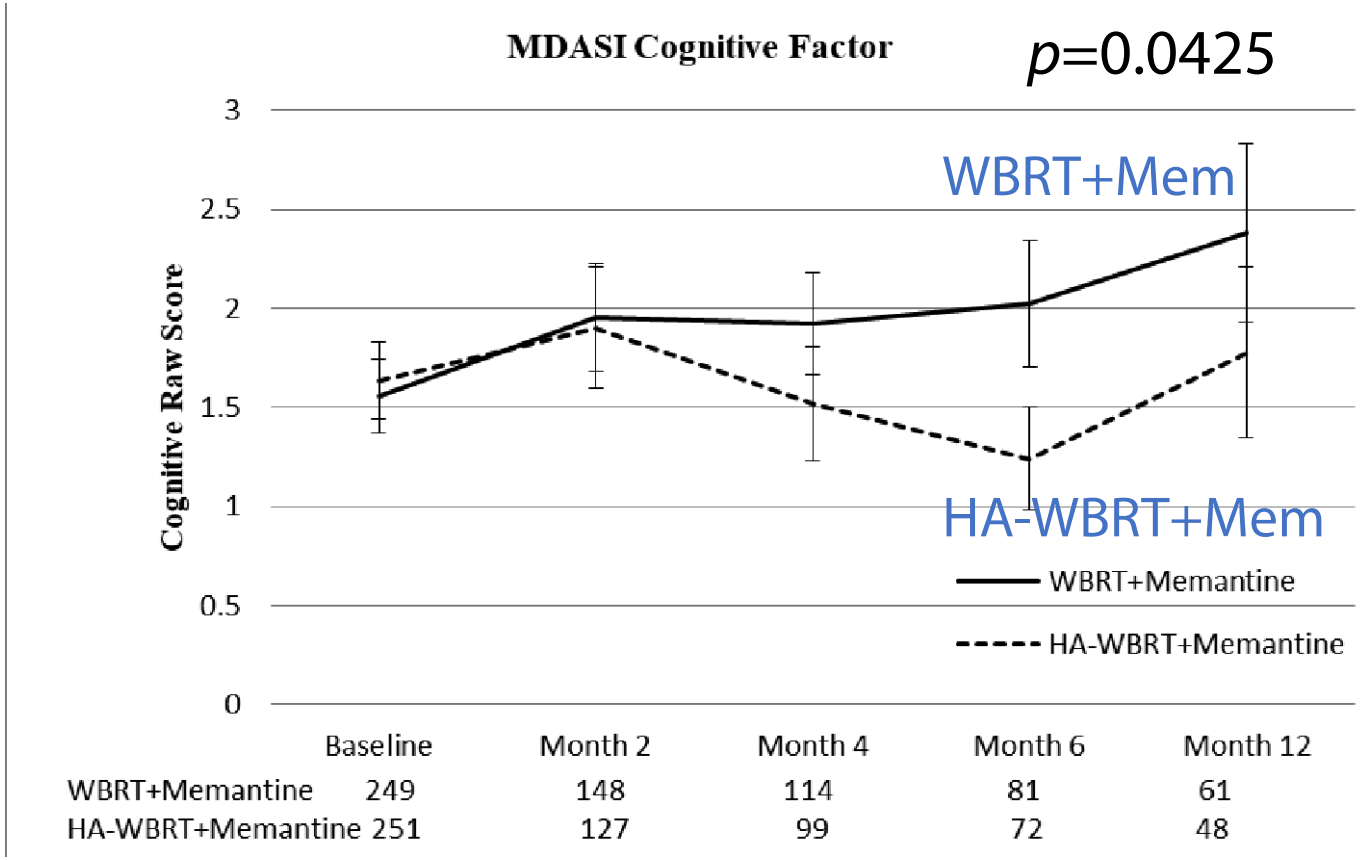
*Significant using Hochburg's multiplicity adjustment

Median follow-up for alive patients: **12.1 months**

# Patient-Reported Outcomes

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities
- Hippocampal avoidance preserves patient-reported cognitive factor over time:
  - Hippocampal avoidance associated with less problems remembering things at 6 months ($p$=0.016)

**Mixed effects models using multiple imputation:**




Higher score indicates more symptoms

Median follow-up for alive patients: **12.1 months**

# Survival

| Toxicity | WBRT+Mem n=257 | HA-WBRT+Mem n=261 | *p* value |
|---|---|---|---|
| Intracranial Progression-Free Survival | Median: 5.3 months<br>95% CI: 4.7-6.0 | Median: 5.0 months<br>95% CI: 4.4-6.2 | **0.076** |
| | HR = 1.20 95% CI: 0.98-1.47 | | |
| Overall Survival | Median: 7.6 months<br>95% CI: 5.8-10.1 | Median: 6.3 months<br>95% CI: 4.0-7.7 | **0.242** |
| | HR = 1.14 95% CI: 0.91-1.43 | | |

**No significant differences in intracranial PFS or overall survival**

**HA region relapses:**

**HA-WBRT+Mem 11 WBRT+Mem 17**

Median follow-up for alive patients: **12.1 months**

# Conclusions

- Hippocampal avoidance during WBRT plus memantine preserves cognitive function and patient-reported symptoms in brain metastasis patients
  - Improvements in patient-reported cognition over time and 6-month change in neurologic symptom burden, interference of neurologic symptoms with daily activities, and problems remembering things
  - Benefits in executive functioning at 4 mos, recognition at 4 and 6 mos, and all domains of learning and memory over time
  - Similar toxicity, intracranial PFS and overall survival outcomes

**For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.**

# Conclusions

National Comprehensive Cancer Network®

**NCCN Guidelines Version 1.2019**
**Central Nervous System Cancers**

NCCN Guidelines Index
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Discussion

**PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD**

**Brain Metastases**

- WBRT: Doses vary between 20 and 40 Gy delivered in 5–20 fractions.
  - The standard regimens include 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.
  - Nevertheless, 20 Gy in 5 fractions is a good option for patients with poor predicted prognosis.[19]
  - For patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.[20]
  - For patients with a better prognosis (4 months or greater), consider hippocampal-sparing WBRT.[21-22]

**For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.**

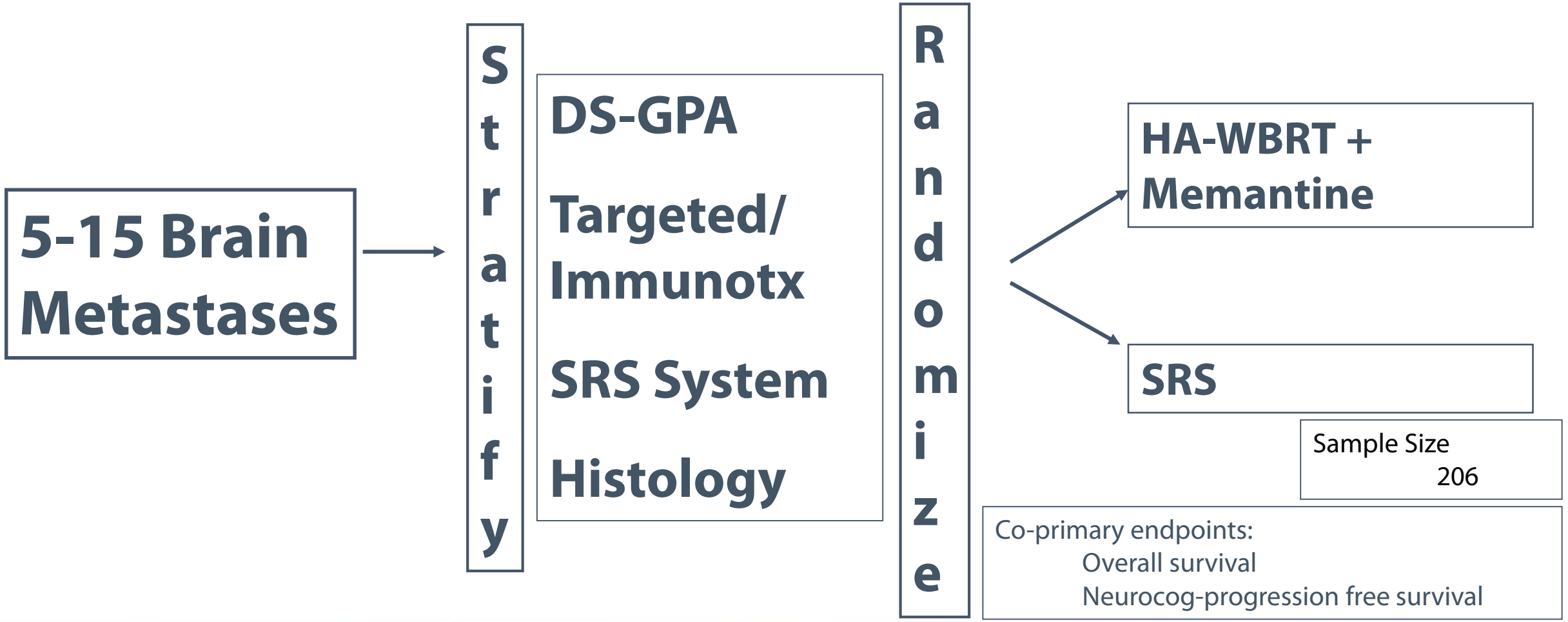
# Conclusions

- Contributes to debate over SRS vs. WBRT for brain metastases
  - RTOG 0614: HR=0.78 with addition of memantine to WBRT
  - NRG CC001: HR=0.74 with addition of HA to WBRT+memantine
  - Combined HR with memantine+HA = 0.78 x 0.74 = 0.58

**Comparable to phase III trials favoring SRS in lieu of WBRT**

# CCTG CE.7: Phase III Trial Stereotactic Radiosurgery versus Hippocampal Avoidant WBRT+memantine for 5-15 Brain Metastases

Basic Eligibility: 5-15 brain mets; largest met <2.5cm; total brain met vol ≤30cc



# Conclusions

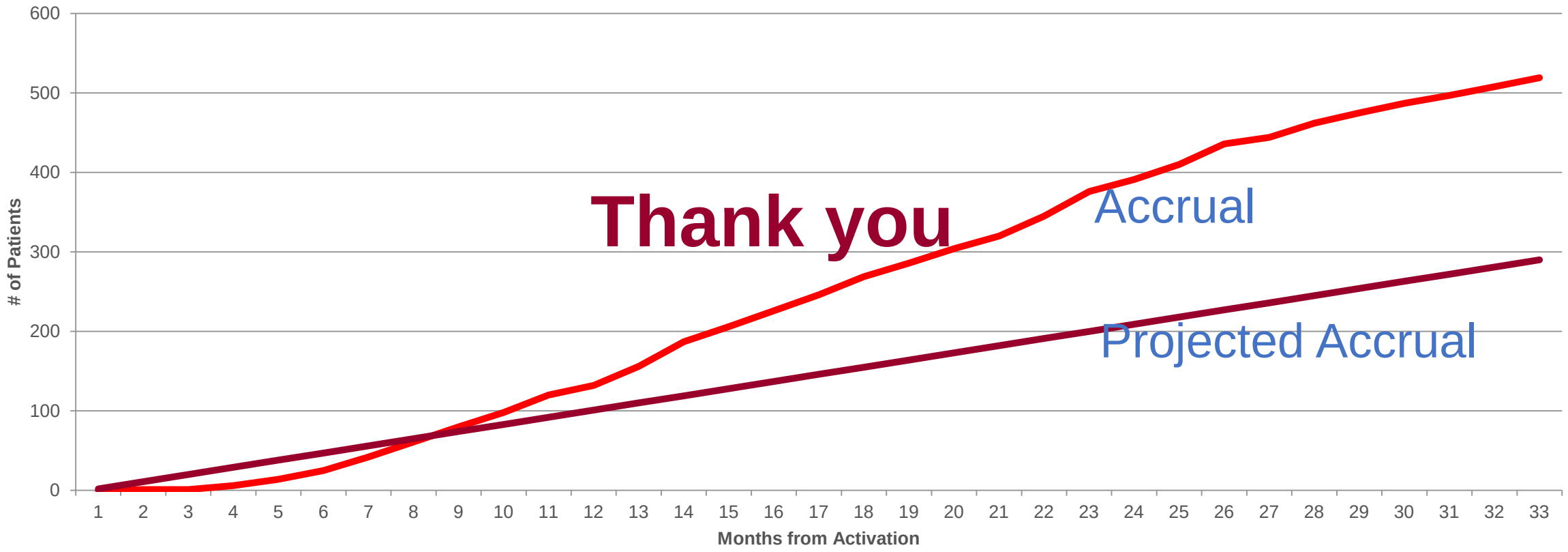
- Contributes to debate over SRS vs. WBRT for brain metastases
  - RTOG 0614: HR=0.78 with addition of memantine to WBRT
  - NRG CC001: HR=0.74 with addition of HA to WBRT+memantine
  - Combined HR with memantine+HA = 0.78 x 0.74 = 0.58

**Comparable to phase III trials favoring SRS in lieu of WBRT**

- Evidence strongly supports hippocampal radiosensitivity
  - Radiosensitivity of regenerative stem cell niche in the hippocampal dentate gyrus is central to cognitive effects of brain irradiation
  - Builds upon decades of preclinical/clinical research on the pathophysiology of hippocampal radiosenstivity

**Supports the hippocampus as a cognition-specific organ at risk for all forms of brain irradiation**

# NRG CC001 Accrual




Accrual 16 pts/month  Completed 2 years earlier than projected

Community's interest in developing safer approaches to deliver WBRT

ASTRO ANNUAL MEETING 2019

# Q & A

Use the "Question" tab in GoToWebinar to submit your questions.

ASTRO ANNUAL MEETING 2019

# Cancer Breakthroughs - Takeaways from the Major Oncology Meetings of 2019

*A preview of Wednesday's presentations*

Theodore L. DeWeese, MD, FASTRO

*Chair, ASTRO Board of Directors*

*Vice Dean for Clinical Affairs, Sidney Kimmel Professor and Director of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins University School of Medicine*

# Cancer Breakthroughs

## Takeaways from 2019's Major Oncology Meetings

- Wednesday, 9:15-11:00 a.m., General Session room (W375)

- Scientific reviews of research highlights from major oncology associations
  - ASCO: American Society of Clinical Oncology
  - AACR: American Association for Cancer Research
  - AAPM: The American Association of Physicists in Medicine
  - RRS (RADRES): Radiation Research Society

# Research Highlights from ASCO

Phase III MONALEESA-7 trial of premenopausal patients with HR+/HER2- advanced breast cancer (ABC) treated with endocrine therapy ? ribociclib: Overall survival (OS) results

Phase 3 international trial of adjuvant whole brain radiotherapy (WBRT) or observation following local treatment of 1-3 melanoma brain metastases (MBMs)

**To be presented by Lori Pierce, MD, ASCO President-elect**

# Research Highlights from AACR

A dose escalation trial of the wee1 inhibitor AZD1775, in combination with gemcitabine and radiation for patients with locally advanced pancreatic cancer

Identifying molecular determinants of response to apalutamide in patients with nonmetastatic castration-resistant prostate cancer in the SPARTAN study

**To be presented by Robert Den, MD**

# Research Highlights from AAPM

Multiparametric breast MRI radiomics in distinguishing between benign and malignant breast lesions

First human imaging studies with the EXPLORER total-body PET scanner

**To be presented by Kristy Brock, PhD**

# Research Highlights from RRS

Flash-radiation therapy (ultra-high dose rate) protects normal tissue without compromising tumor control: Mechanisms and clinical perspectives

Dissecting mechanisms of response and resistance to radiation and immunotherapy

**To be presented by David Kirsch, MD, PhD, FASTRO**

ASTRO ANNUAL MEETING 2019

# Q & A

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