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)

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\(^1\), Baxi SS\(^2\), Morris LG\(^1\), Ganly I\(^1\), Patel SG\(^1\), Cohen MA\(^1,3\), Roman BR\(^1\).

<table>
<thead>
<tr>
<th>Year diagnosed</th>
<th>No. (Column %)</th>
<th>No. (Row % Compared With Primary XRT [Not Shown])</th>
<th>(P^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>568 (6.5%)</td>
<td>319 (56.2%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2005</td>
<td>644 (7.3%)</td>
<td>354 (55%)</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>674 (7.7%)</td>
<td>400 (59.3%)</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>747 (8.5%)</td>
<td>431 (57.7%)</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>1052 (12%)</td>
<td>674 (64.1%)</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>1174 (13.4%)</td>
<td>792 (67.5%)</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>939 (10.7%)</td>
<td>651 (69.3%)</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>979 (11.2%)</td>
<td>724 (74%)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>970 (11.1%)</td>
<td>784 (80.8%)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>1021 (11.6%)</td>
<td>838 (82.1%)</td>
<td></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
Endpoints

Primary Endpoint
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Secondary Endpoints
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• 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

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 Thuer, Eitan Prisman, Nancy Read, Eric Berthelet, Eric Tran, Kevin Fung, John R de Almeida, Andrew Bayley, David P Goldstein, Michael Hier, Khalid Sultanem, Keith Richardson, Alex Myrnam, Suren Krishna, Hien Le, John Yao, S Danielle MacNeil, Eric Winquist, J Alex Hammond, Varagor Venkatesan, Sara Korvella, Andrew Warner, Sylvia Mitchell, Jeff Chen, Martin Corsten, Stephanie Johnson-Obasoki, Libvi Fappen, Michael Odell, Christina Parker, Bret Wehrli, Keith Kwon, 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.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

E2. I am embarrassed by my eating habits.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

F1. People have difficulty cooking for me.

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>No Opinion</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
</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
Baseline Characteristics

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 – median (interquartile range)</strong></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>
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</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients</th>
<th>RT Arm</th>
<th>TORS +ND Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=68)</td>
<td>(n=34)</td>
<td>(n=34)</td>
</tr>
<tr>
<td>Tonsil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base of Tongue</td>
<td>50 (74)</td>
<td>26 (76)</td>
<td>24 (71)</td>
</tr>
<tr>
<td></td>
<td>18 (26)</td>
<td>8 (24)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>Clinical T Stage – n(%)</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>Clinical N Stage – n(%)</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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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 Theuree, Eitan Pisman, Nancy Reed, Eric Berthelet, Eric Tran, Kevin Fung, John R de Almeida, Andrew Bayley, David P Goldstein, Michael Hée, Khalfi Sussanam, Keith Richardson, Alex Mynderse, Soren Kirkman, Hien Le, John Poo, S Danielle MacNeil, Eric Wingatt, J Alex Hamilton, Vanessa van Breda, Sara Rumville, Andrew Warner, Sylvia Mitchell, Jeff Chen, Martin Carstens, Stephanie Johnson-Obeokpe, Libni Eppen, Michael Odell, Christina Parker, Brett Wehrli, Keith Kwan, Daniel A Palma

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2019 AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING
Median MDADI Scores by Treatment Intensity

- RT (n=9)
- CRT (n=23)
- TORS (n=10)
- TORS+RT (n=16)
- TORS+CRT (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
- $p < 0.001$

*Curves truncated when n<5*

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

- **Base of Tongue**
  - RT: 8, 8, 7
  - TORS+ND: 10, 10, 8, 7

*2019 American Society for Radiation Oncology (ASTRO) Annual Meeting*
MDADI Scores by T-Stage

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

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

Use the “Question” tab in GoToWebinar to submit your questions.
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: Physicians’ Education Resource
• Whole-brain radiotherapy is associated with cognitive toxicity
  • 1-4 brain metastases: N0574\textsuperscript{1}, N107C\textsuperscript{2}, MD Anderson trial\textsuperscript{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\textsuperscript{4}

Hypothesis: Hippocampal avoidance using IMRT prevents cognitive toxicity from WBRT

\textsuperscript{1}Brown et al. JAMA 2016
\textsuperscript{2}Brown et al. Lancet Oncol 2017
\textsuperscript{3}Chang et al. Lancet Oncol 2009
\textsuperscript{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
• 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

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

No differences in baseline patient characteristics, including cognitive function and patient-reported symptom burden.
### Toxicity

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

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 prevents cognitive function failure
  - Hazard ratio = 0.756  \( p = 0.029 \)
  - Separation of the curves starting at 3 months and maintained through the follow-up period

Median follow-up for alive patients: 12.1 months
### Primary Endpoint

- Hippocampal avoidance prevents cognitive function failure
  - 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

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

*Stratification factor

[RL]: Reference level

Median follow-up for alive patients: **12.1 months**
Hippocampal avoidance reduces deterioration of 
- 4 months: Executive function (Trail Making Test B)

### Deterioration at 4 months:

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>WBRT +Mem n=109</th>
<th>HA-WBRT +Mem n=93</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R Total Recall</td>
<td>35.5%</td>
<td>29.0%</td>
<td>0.33</td>
</tr>
<tr>
<td>HVLT-R Delayed Recall</td>
<td>33.0%</td>
<td>24.7%</td>
<td>0.19</td>
</tr>
<tr>
<td>HVLT-R Recognition</td>
<td>24.8%</td>
<td>14.0%</td>
<td>0.055</td>
</tr>
<tr>
<td>Trail Making Test Part A</td>
<td>24.8%</td>
<td>20.4%</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Trail Making Test Part B</strong></td>
<td><strong>40.4%</strong></td>
<td><strong>23.3%</strong></td>
<td><strong>0.012</strong></td>
</tr>
<tr>
<td>Controlled Oral Word Association</td>
<td>12.1%</td>
<td>10.5%</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Median follow-up for alive patients: **12.1 months**
Hippocampal avoidance reduces deterioration of
- 4 months: Executive function (Trail Making Test B)
- 6 months: Learning and memory (HVLT-R Recognition)

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

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:

<table>
<thead>
<tr>
<th></th>
<th>HA-WBRT+Mem</th>
<th>WBRT+Mem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>256</td>
<td>149</td>
</tr>
<tr>
<td>Month 4</td>
<td>260</td>
<td>130</td>
</tr>
<tr>
<td>Month 6</td>
<td>260</td>
<td>94</td>
</tr>
<tr>
<td>Month 12</td>
<td>260</td>
<td>68</td>
</tr>
</tbody>
</table>

Higher score indicates better performance

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

Median follow-up for alive patients: **12.1 months**
Cognition Domains Over Time

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  - 6 months: Learning and memory (HVLT-R Recognition)

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  - 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**
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:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate Complete Data</th>
<th>p value Complete Data</th>
<th>Estimate Imputed Data</th>
<th>p value Imputed Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td>-0.26</td>
<td>0.083</td>
<td>-1.37</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Interference</td>
<td>-5.07</td>
<td>0.003*</td>
<td>-1.93</td>
<td>0.0016*</td>
</tr>
<tr>
<td>Cognitive factor</td>
<td>-0.05</td>
<td>0.77</td>
<td>-0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>Neurologic factor</td>
<td>0.213</td>
<td>0.32</td>
<td>-0.13</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*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:

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

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>WBRT+Mem n=257</th>
<th>HA-WBRT+Mem n=261</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial Progression-Free Survival</td>
<td>Median: 5.3 months 95% CI: 4.7-6.0</td>
<td>Median: 5.0 months 95% CI: 4.4-6.2</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td>HR = 1.20 95% CI: 0.98-1.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>Median: 7.6 months 95% CI: 5.8-10.1</td>
<td>Median: 6.3 months 95% CI: 4.0-7.7</td>
<td>0.242</td>
</tr>
<tr>
<td></td>
<td>HR = 1.14 95% CI: 0.91-1.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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 radiosensitivity

  **Supports the hippocampus as a cognition-specific organ at risk for all forms of brain irradiation**
Accrual 16 pts/month  
Completed 2 years earlier than projected  
Community’s interest in developing safer approaches to deliver WBRT

Thank you
Q & A

Use the “Question” tab in GoToWebinar to submit your questions.
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
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
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
Q & A

Use the “Question” tab in GoToWebinar to submit your questions.
More information and press materials:

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