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

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*Co-Principal Investigators contributed equally to this work.
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Disclosures for Dr. Gondi

• Partnership, Radiation Oncology Consultants, LLC; Honoraria, UpToDate; Honoraria/Travel expenses: Physicians’ Education Resource
Background

• 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
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 \( \geq \) 70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing

Brain Metastasis → Stratify

- RPA
- Prior Therapy

Randomize

- WBRT 30Gy + Memantine
- HA-WBRT 30Gy + Memantine
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 α=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 symptoms</td>
<td>None: 46.3%</td>
<td>None: 43.3%</td>
<td>0.83</td>
</tr>
<tr>
<td></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>Grade 3: 89 (38.4%)</td>
<td>Grade 3: 70 (31.4%)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Grade 4: 20 (8.6%)</td>
<td>Grade 4: 25 (11.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 5: 35 (15.1%)</td>
<td>Grade 5: 36 (16.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Grade 3+: 144 (62.1%)</strong></td>
<td><strong>Grade 3+: 131 (58.7%)</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment-related toxicity</td>
<td>Grade 3: 36 (15.5%)</td>
<td>Grade 3: 36 (16.1%)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Grade 4: 7 (3.0%)</td>
<td>Grade 4: 4 (1.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 5: 3 (1.3%)</td>
<td>Grade 5: 3 (1.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Grade 3+: 46 (19.8%)</strong></td>
<td><strong>Grade 3+: 43 (19.3%)</strong></td>
<td></td>
</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

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</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)

Cognition Domains at 4 Months

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>Trail Making Test Part B</td>
<td>40.4%</td>
<td>23.3%</td>
<td>0.012</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)

### Deterioration at 6 months:

<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><strong>HVLT-R Recognition</strong></td>
<td><strong>36.3%</strong></td>
<td><strong>17.6%</strong></td>
<td><strong>0.011</strong></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:

Higher score indicates better performance

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

2019 AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) ANNUAL MEETING
Hippocampal avoidance reduces deterioration of
- 4 months: Executive function (Trail Making Test B)
- 6 months: Learning and memory (HVLT-R Recognition)

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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:

- $p=0.022$

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>p value</th>
<th>Estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete Data</td>
<td></td>
<td>Imputed Data</td>
<td></td>
</tr>
<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:**

![Graph showing cognitive raw score over time]

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

Co-primary endpoints:
- Overall survival
- Neurocog-progression free survival

Sample Size: 206
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**
NRG CC001 Accrual

Accrual 16 pts/month
Completed 2 years earlier than projected
Community’s interest in developing safer approaches to deliver WBRT

Thank you