Stereotactic Radiosurgery Versus Whole-brain Radiation Therapy For Patients With 4-15 Brain Metastases: A Phase III Randomized Controlled Trial

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Background

• Up to 30% of cancer patients develop brain metastases
  • Rising incidence due to prolonged survival and better imaging surveillance
  • Historically poor overall survival (~1-4 months)
    • Main treatment modalities: radiation and surgery
    • Whole brain radiation (WBRT) associated with significant cognitive side effects

• In patients with 1-3 (or 4) brain metastases
  • Two Phase III randomized trials established stereotactic radiosurgery (SRS) as the standard care, replacing WBRT, due to better preservation of patients’ cognitive function, without compromising overall survival (Chang EL, Lancet Onc 2009; Brown PD, JAMA 2016)

• Purpose of the current study
  • To investigate if SRS could replace WBRT in patients with 4-15 brain metastases in a phase III randomized trial
Trial Design (Schema)

**Key Eligibility Criteria:**

- Adult patient with 4-15 untreated brain mets confirmed by neuroradiology (up to 20 lesions allowed at the time of treatment)
- All lesions amenable to SRS treatment
- KPS >/=70
- No LMD (radiographic or cytological)
- No prior WBRT
- Prior SRS to 1-3 brain mets with > 6 weeks intervals allowed
- Excluded prior surgical resection of brain mets
- Excluded histology: melanoma, small cell carcinoma, lymphoma/leukemia, or germ cell histology
- Systemic therapy allowed at the discretion of treating oncologist

**Stratification factors:**

- **Histology** (breast vs. other)
- **Age** (18-59 vs. 60 and over)
- **Number of lesions** (4-7 vs. 8-15)
- **KPS** (70-80 vs. 90-100)
- **Extra-cranial disease status** (progressive disease prior to enrollment vs. no progression)
- **Baseline HVLT** (< = 17 vs. >/=28)
- **Radiotherapy** (Prior SRS vs. no prior SRS)

**Neurocognitive function tests:**

- **Memory:** HVLT_R_TR, HVLT_R_DR, HVLT_R Recognition
- **Executive function:** COWA, and Trail Making test Part B (TMTB)
- **Attention Span:** WAIS-III Digit Span
- **Psychomotor Speed:** WAIS-III Digit Symbol, Trail Making test Part A (TMTA)
- **Motor dexterity:** Grooved Pegboard

**Primary Endpoints**

- Memory function at 4 mo (HVLT_R_TR)
- Local control at 4 mo
Memory Function at 4 Months
-- Primary Endpoint

- HVLT_R_TR: change of Z-score from baseline
- At 4 months
  - SRS: Increased by 0.21 (SD 1.15) (n=18)
  - WBRT: Decreased by 0.74 (SD 1.31) (n=13)
  - \( p = 0.041 \)
- At 1 month and 6 months
  - Clinically meaningful and statistically significant benefit with SRS was also observed at 1 month \( (p = 0.033) \) and 6 months \( (p = 0.012) \)
Composite score

- Mean Z-score from HVLT_R_TR, HVLT_R_DR, and HVLT_R Rec, COWA, TMTA, and TMTB
- Change from baseline

Better cognitive composite scores in SRS arm

- Statistically significant at months 1, 4 and 6

<table>
<thead>
<tr>
<th>Follow up Time Point</th>
<th>SRS</th>
<th>WBRT</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>1-mo (median [IQR])</td>
<td>-0.12 [-0.38, 0.47]</td>
<td>-0.71 [-1.26, -0.28]</td>
<td>0.024</td>
</tr>
<tr>
<td>4-mo (median [IQR])</td>
<td>0.28 [-0.03, 0.60]</td>
<td>-0.57 [-0.88, -0.17]</td>
<td>0.004</td>
</tr>
<tr>
<td>6-mo (median [IQR])</td>
<td>0.31 [-0.23, 0.70]</td>
<td>-0.16 [-0.84, -0.01]</td>
<td>0.027</td>
</tr>
<tr>
<td>9-mo (median [IQR])</td>
<td>0.64 [-0.16, 1.00]</td>
<td>-0.08 [-0.32, -0.01]</td>
<td>0.153</td>
</tr>
<tr>
<td>12-mo (median [IQR])</td>
<td>0.25 [-0.09, 1.03]</td>
<td>-0.12 [-0.14, 0.27]</td>
<td>0.823</td>
</tr>
</tbody>
</table>
Overall Survival

- **Overall survival by intention-to-treat**
  - 69 out of 72 pts evaluable for OS
    - 35 for SRS and 34 for WBRT
    - Estimate median OS

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events (death)</th>
<th>Median (month)</th>
<th>95% CI (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS</td>
<td>35*</td>
<td>30</td>
<td>7.8</td>
<td>6.1 – 14.6</td>
</tr>
<tr>
<td>WBRT</td>
<td>34**</td>
<td>26</td>
<td>8.9</td>
<td>6.4 – 26.4</td>
</tr>
</tbody>
</table>

*Include 6 patients who had more than 20 lesions at time of SRS planning and received WBRT off protocol
**Include 4 patients received SRS and 2 patients received HA-WBRT off protocol

Estimating Overall Survival Curves with the Kaplan-Meier Method by intention-to-treat: $P = 0.59$
Other Results

- Local Control at 4 mo
  - 95% (SRS) vs 87% (WBRT), p-value 0.79

- Distant brain control
  - 60% (SRS) vs 80% (WBRT), p-value 0.37

- **Time to systemic therapy**
  - 1.7 weeks (SRS) vs 4.1 weeks (WBRT), **p-value 0.001**

- Toxicities
  - ≥ Grade 3 toxicities 8% (SRS) vs 15% (WBRT)
  - Radiation necrosis: 17% at patient level and 4% at lesion level
Summary

Despite early termination of the trial due to NRG CC001 and use of memantine in 2/3 WBRT patients, in patients with 4-15 brain mets:

• SRS was associated with reduced risk of neurocognitive deterioration compared to WBRT, as demonstrated by a constellation of neurocognitive tests, individually or by composite scores
  • The differences between the two arms were large and clinically meaningful
• No difference in overall survival rates
• SRS was associated with shorter time to systemic therapy
Conclusion

The results from this phase III randomized trial strongly supports the use of SRS in patients with 4-15 brain metastases to better preserve cognitive function and to minimize interruption of systemic therapy, without compromising overall survival.