Multiple brain metastases

• What is ‘multiple’ with respect to brain metastases?
  • 2+ (literal definition)?
  • >4 (definition for which relatively few studies exist for SRS alone)?
  • >10 (definition for which many would consider whole brain radiotherapy – WBRT – vs. SRS alone)?
Multiple brain metastases

• What is multiple with respect to brain metastases?

\[ 2+ \]

\[ 2-4 \]

\[ >4 \]

For SRS alone:
- Limited data
- Primarily retrospective and single arm prospective
- Plenty of retrospective data
- Recent Phase III data

Cancer factors

- Intracranial extent
- Extracranial ± or extent

Treatment

- WBRT
- SRS/fractionated SRS
- Resection

Patient factors

- Karnofsky Performance Scale

KPS

extracranial ± or extent

"Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation.

ASTRO Model Policy for SRS

Indications and Limitations of Coverage and/or Medical Necessity

Indications for Coverage:

7. Metastatic brain, independent of the number of lesions if other positive clinical indications exist, with stable systemic disease, Karnofsky Performance Status 40 or greater (and expected to return to 70 or greater with treatment), and otherwise reasonable survival expectations, OR ECOG Performance Status of 3 or less (or expected to return to 2 or less with treatment).

Updated in 2014
What are the data on SRS alone vs. SRS+WBRT for multiple metastases?

<table>
<thead>
<tr>
<th>Study 1st author</th>
<th>Patients</th>
<th>RCT arms</th>
<th>1-year local recurrence</th>
<th>1-year distant recurrence</th>
<th>Rate of salvage therapy</th>
<th>Rate of salvage WBRT</th>
<th>Median survival (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama (Japan)</td>
<td>2006</td>
<td>132 patients with 1-4 metastases, all ≤3 cm</td>
<td>SRS</td>
<td>28% (p&lt;0.001)</td>
<td>64%</td>
<td>16%</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBRT+SRS</td>
<td>11% (p=0.002)</td>
<td>41% (p&lt;0.001)</td>
<td>43%</td>
<td>16% (p&lt;0.001)</td>
<td>7.5 (p=0.42)</td>
</tr>
<tr>
<td>Chang (MDACC)</td>
<td>2009</td>
<td>58 patients with 1-3 brain metastases</td>
<td>SRS</td>
<td>23%</td>
<td>55% (p=0.003)</td>
<td>87%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBRT+SRS</td>
<td>0% (p=0.01)</td>
<td>27% (p=0.002)</td>
<td>55%</td>
<td>27%</td>
<td>5.7</td>
</tr>
<tr>
<td>Kocher (EORTC)</td>
<td>2011</td>
<td>359 patients with 1-3 brain metastases</td>
<td>SRS or resection</td>
<td>WBRT+SRS or WBRT+resect</td>
<td>~31% (p&lt;0.003)</td>
<td>~57% (p&lt;0.003)</td>
<td>~19% (p&lt;0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBRT+ SRS</td>
<td>~31%</td>
<td>~57%</td>
<td>~19%</td>
<td>~27%</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBRT+resect</td>
<td>~31%</td>
<td>~57%</td>
<td>~19%</td>
<td>~27%</td>
<td>10.7 (NS)</td>
</tr>
<tr>
<td>Brown (Alliance)</td>
<td>2016</td>
<td>213 patients with 1-3 metastases, all ≤3 cm</td>
<td>SRS</td>
<td>23% (p=0.003)</td>
<td>30%</td>
<td>8% (p&lt;0.001)</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WBRT+SRS</td>
<td>10% (p=0.003)</td>
<td>8% (p=0.001)</td>
<td>32%</td>
<td>8% (p&lt;0.001)</td>
<td>10.4</td>
</tr>
</tbody>
</table>

* p value of addition vs. omission or WBRT

48%, 57%, 81% and 52% of patients in these 4 studies (respectively) had only 1 metastasis.

Omission of WBRT in patients with 1-4 brain metastases:

- increases local tumor recurrence (~23-31% vs. 0-19% @ 1Y)
- increases distant brain recurrence (~30-64% vs. 8-41% @1Y)
- increases rate of salvage treatment (~32-87% vs. ~7-16%)
**Omission of WBRT in patients with 1-4 brain metastases**

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- increases rate of salvage treatment (~32-87% vs. ~7-16%)
- does NOT detriment overall survival

**4 RCTs of SRS alone vs. SRS+WBRT**

<table>
<thead>
<tr>
<th>Study (author)</th>
<th>SRS alone vs. + WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama (Japan) 2006</td>
<td>MMSE: average time until deterioration 7.6 vs. 16.5 months (p=0.05)</td>
</tr>
<tr>
<td>Aoyama (Japan) 2006</td>
<td>KPS: preserved at 1Y in 34% vs. 27% (p=0.33)</td>
</tr>
<tr>
<td>Aoyama (Japan) 2006</td>
<td>Neurologic function: preserved in 72 vs. 70% (p=0.99)</td>
</tr>
<tr>
<td>Chang (MDACC) 2009</td>
<td>HVLT–R: drop in total recall (64% vs. 20%) at 4 months (96% confidence in difference)</td>
</tr>
<tr>
<td>Chang (MDACC) 2009</td>
<td>Battery of other cognitive and QOL assessments performed as well</td>
</tr>
<tr>
<td>Kocher (EORTC) 2011</td>
<td>WHO–PS decline (to a score of &gt;2): 9.5 vs. 10 months (p=0.71)</td>
</tr>
<tr>
<td>Kocher (EORTC) 2011</td>
<td>QOL = multiple domains significantly worse with WBRT</td>
</tr>
<tr>
<td>Brown (Alliance) 2016</td>
<td>Cognitive function (battery of tests): deterioration at 3 months 91% vs. 63% (p=0.005)</td>
</tr>
<tr>
<td>Brown (Alliance) 2016</td>
<td>FACT–BR: worse at 3 months (p=0.03) with WBRT</td>
</tr>
<tr>
<td>Brown (Alliance) 2016</td>
<td>ADLs: similar</td>
</tr>
</tbody>
</table>

MMSE = mini mental status examination
KPS = Karnofsky Performance Scale
WHO PS = World Health Organization Performance Score
HVLT = Hopkins Verbal Learning Test (test of recall)
FACT = Functional Assessment of Cancer Therapy–Brain
WHS PS = World Health Organization Performance Score
ADL = Activities of Daily Living

**Omission of WBRT in patients with >4 brain metastases**

- increases local tumor recurrence (~23-31% vs. 0-19% @ 1Y)
- increases distant brain recurrence (~30-64% vs. 8-41% @1Y)
- increases rate of salvage treatment (~32-87% vs. ~7-16%)
- does NOT detriment overall survival
- less detriment in neurocognitive function

**SRS alone for >4 metastases?**
SRS alone for >4 metastases


- Systematic (PRISMA) literature search 1947 through 2015 for studies with ALL or SUBGROUP or patients having >4 metastases → 3,084 articles
- 10 articles (all but 1 were retrospective)
  - ALL patients had >4 metastases treated with SRS
  - 5-37 metastases (mean range from 6-17)
  - Total target volume 3.2-10.9 cc
- Additional 5 studies excluded for not reported distant brain control

SRS alone for >4 metastases

Prospective observational

- 1-year local recurrence: 6.5 - 58.3%
  - "heterogeneity in cohorts with respect to histology and definition of local tumor control"
  - "consistent with the literature overall"
- Distant brain recurrence: 22 - 90%
  - "heterogeneity in primary tumor type and definition of extracranial disease control status"
  - Prior WBRT in some patients
- Median survival: 3.4 - 13 months
  - Favorable factors: better RTOG RPA score, ↑KPS, favorable histology (i.e. breast), controlled extracranial tumor, ↓age
SRS alone for multiple metastases: JLGK0901 study

**Prospective observational study (2009-2012)**
- 1-10 metastases
- all <10 ml and <3 cm
- Cumulative volume ≤15 ml
- 1 metastasis (n=455)
- 2-4 metastases (n=531)
- 5-10 metastases (n=208) — included in Sahgal review


**1 vs. 2-4 vs. 5-10 metastases groups**
- OS: greater for 1 vs. 2-4 (median 13.9 vs. 10.8 M, p=0.0004)
- 2-4 similar to 5-10 (HR=0.97, p=0.78) — median 10.8 M for both
- Neurologic death similar across groups (p=0.27), and ≤10%,
- LC similar (p=0.78) across subgroups (10-16%)
- Distant brain metastases 48% for 1 metastasis
- Similar for 2-4 and 5-10 metastases (63 and 69%)
- Salvage WBRT used in ~10%
- Savage SRS used in 40% with serial brain MRI

With SRS alone for one or multiple brain metastases

- Survival outcomes: - better with 1 metastasis (vs. >1)
  - similar across patients with 2-10 metastases
  - worse with >10 metastases

- CNS distant control: worse >10 metastases
SRS alone for 1 or multiple metastases: lesion volume

<table>
<thead>
<tr>
<th>Study</th>
<th># patients</th>
<th># lesions</th>
<th>Outcomes analyzed by tumor volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatnagar (2006/2007)</td>
<td>205</td>
<td>4-18</td>
<td>OS: treatment volume was the most significant predictor (p&lt;0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RPA: best OS subgroup: total treatment volume &lt;7 cc and &lt;7 metastases</td>
</tr>
<tr>
<td>Serizawa (2012) Japan</td>
<td>2,246</td>
<td>1-10-+</td>
<td>Net tumor volume &gt;15 cc, worse (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS: neurologic survival (without neurologic death)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Qualitative survival (without impaired ADL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tumor volume → Tumor progression</td>
</tr>
<tr>
<td>Yamamoto (2013) Japan</td>
<td>2,353</td>
<td>1-89</td>
<td>OS: cumulative tumor volume of 118 cc (HR=1.6, p&lt;0.001 for all patients, and subgroups with 1-4 vs. 5+ mets)</td>
</tr>
<tr>
<td>JLGK0901 (2014) Japan</td>
<td>1,194</td>
<td>1-10</td>
<td>maximum tumor volume (10.6 vs. &lt;1.6 cm) cumulative tumor volume (10.9 vs. &lt;2.9 ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS: cumulative intracranial volume: HR of 1.015 per cc (p&lt;0.001)</td>
</tr>
</tbody>
</table>

With SRS alone for multiple brain metastases: lesion volume

- Survival outcomes: better with 1 metastasis (vs. >1)
- similar across patients with 2-10 metastases
- worse with >10 metastases
- worse with greater net GTV
- CNS distant control: worse >10 metastases

Future study for those with 4+ brain metastases

- Phase II studies of SRS alone
- Phase III studies of SRS alone vs. WBRT (±SRS)

With SRS alone for multiple brain metastases

- Survival outcomes: better with 1 metastasis (vs. >1)
- similar across patients with 2-10 metastases
- worse with >10 metastases
- worse with greater net GTV
- CNS distant control: worse >10 metastases

What is the role of SRS alone for 5-10 and for >10 brain metastases?
Phase II

<table>
<thead>
<tr>
<th>Study group</th>
<th>Study #</th>
<th># patients</th>
<th>Eligibility</th>
<th>Study arms</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT Southwestern (Phase II)</td>
<td>NCT01592968</td>
<td>45+</td>
<td>6+ metastases all &lt;4 cm</td>
<td>SRS</td>
<td>Cognition (HVLT-R)</td>
</tr>
<tr>
<td>MDACC</td>
<td>NCT01644591</td>
<td>49</td>
<td>4+ metastases from melanoma</td>
<td>SRS</td>
<td>Local control</td>
</tr>
<tr>
<td></td>
<td>NCT01592968</td>
<td>100</td>
<td>4-15 metastases all &lt;3.5 cm</td>
<td>WBRT - SRS</td>
<td>Local control</td>
</tr>
<tr>
<td></td>
<td>NCT03775330</td>
<td>125</td>
<td>5-20 metastases all &lt;2.5 cm</td>
<td>SRS</td>
<td>Cognition (HVLT-R)</td>
</tr>
</tbody>
</table>

Randomized

<table>
<thead>
<tr>
<th>Study group</th>
<th>Study #</th>
<th># patients</th>
<th>Eligibility</th>
<th>Study arms</th>
<th>Primary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC</td>
<td>NCT01592968</td>
<td>100</td>
<td>8-15 metastases all &lt;3 cm</td>
<td>SRS - WBRT</td>
<td>Local control</td>
</tr>
<tr>
<td>MDACC 12-16</td>
<td>NCT01717010</td>
<td>closed before accrual</td>
<td>8-15 metastases</td>
<td>SRS</td>
<td>Cognition</td>
</tr>
<tr>
<td>Netherlands</td>
<td>NCT02351001</td>
<td>260</td>
<td>8-10 metastases all &lt;3.5 cm</td>
<td>WBRT - SRS</td>
<td>QOL</td>
</tr>
<tr>
<td>Dutch Cancer Inst.</td>
<td>NCT01592968</td>
<td>196</td>
<td>5-20 metastases</td>
<td>WBRT (with or without hippocampal sparing) - SRS</td>
<td>QOL</td>
</tr>
<tr>
<td>Canadian Cancer/Trials Group/NRG</td>
<td>NCT03550391</td>
<td>206</td>
<td>5-20 metastases (allow up to 30)</td>
<td>SRS + WBRT - SRS</td>
<td>OS</td>
</tr>
<tr>
<td>Sunnybrook Health Sciences Centre</td>
<td>NCT01592968</td>
<td>125</td>
<td>5-20 metastases all &lt;2.5 cm</td>
<td>SRS + WBRT</td>
<td>Cognition (HVLT-R)</td>
</tr>
</tbody>
</table>

Future study for those with 4+ brain metastases

• Phase II studies of SRS alone
• Phase III studies of SRS alone vs. WBRT (±SRS)
• Phase II/III studies of systemic therapy
  • ALK-rearranged NSCLC
  • EGFR mutant NSCLC
  • BRAF-mutated melanoma
  • Solid cancers with high expression of PDL1

Take home points

• SRS alone for appropriately selected patients with:
  • 2-4 brain metastases: is an accepted standard based on level 1 evidence
  • >4 brain metastases: is emerging as an accepted standard
  • >10 brain metastases: is arguably investigational, though perhaps warranted in patients with low volume burden disease
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- Survival outcomes: - better with 1 metastasis (vs. >1)
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  - worse with greater net GTV
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- What is the role of SRS alone for 5-10 and for >10 brain metastases?