Brain Metastases: Changing the Paradigm

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SRS is the choice, but:

• Do we need WBRT?
• How many mets can we treat?
• What could be the prescribed dose?
• Does size matter?
• Salvage therapy after SRS?
• Targeted therapies-immunotherapy and SRS?
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• Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases
  • Aoyama et al. JAMA, 2006

• Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial
  • Chang et al. Lancet, 2009

• Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Result of the EORTC 22952-26001 Study
  • Kocher et al. JCO, 2011

• Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial
  • Brown et al. JAMA, 2016
SRS alone vs WBRT + SRS

• WBRT does not improve overall survival
• WBRT improves local and distant control
• WBRT is associated with worse neurocognition
ASTRO releases second list of five radiation oncology treatments to question, as part of national Choosing Wisely® campaign

September 15, 2014
ASTRO releases second list of five radiation oncology treatments to question, as part of national Choosing Wisely® campaign

Encourages more detailed conversations between physicians and patients

- Don’t routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

Randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors. The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened, self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small cell lung cancer. Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the
SRS is the choice, but:

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• Salvage therapy after SRS?
• Targeted therapies-immunotherapy and SRS?
• Yamamoto et al.
• Prospective observational study
• 23 centers
• 1-10 mets
• 1194 patients
• Grup A : 1 met
• Grup B : 2-4 mets
• Grup C : 5-10 mets

Yamamoto et al., Lancet Oncology, 2014
Figure 1

<table>
<thead>
<tr>
<th>Group</th>
<th>MST (95% CI)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (1 tumour)</td>
<td>13.9 (12.0–15.6)</td>
<td>0.774 (0.676–0.887)</td>
<td>0.0002</td>
</tr>
<tr>
<td>B (2–4 tumours)</td>
<td>10.8 (9.5–12.3)</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>C (5–10 tumours)</td>
<td>11.1 (9.2–13.1)</td>
<td>0.999 (0.844–1.184)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Overall survival vs. time after stereotactic radiosurgery (months)

No. at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>1 tumour</th>
<th>2-4 tumour</th>
<th>5-10 tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>455</td>
<td>249</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>73</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>24</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
• 1194 patients
• 1 tumor; 455 patients, median OS 13.9 months
• 2-5 tumors; 531 patients, median OS 10.8 months
• 5-10 tumors; 208 patients, median OS 10.8 months
• 9(%2), 13(%2), 6(%3) patients grade 3-4 side effect

Yamamoto et al., Lancet Oncology, 2014
Not number but volume?
## Multivariate Analysis for overall survival

<table>
<thead>
<tr>
<th></th>
<th>Volume</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatnagar, IJROBP 2006</td>
<td>p=0.002</td>
<td>p=0.3</td>
</tr>
<tr>
<td>Likhacheva, IJROBP 2012</td>
<td>p&lt;0.1</td>
<td>p=0.2</td>
</tr>
<tr>
<td>Choi, IJROBP 2012</td>
<td>p=0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Baschnagel, JNS 2013</td>
<td>p=0.003</td>
<td>p=0.1</td>
</tr>
<tr>
<td>Shultz, IJROBP 2015</td>
<td>p&lt;0.01</td>
<td>p=0.1</td>
</tr>
</tbody>
</table>
Yamamoto study

• Largest tumor volume was <10 cm³, diameter <3cm
• Total tumor ≤15 cm³

Yamamoto et al., Lancet Oncology, 2014
SRS is the choice, but:

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SRS Dose (RTOG 90-05)

• Phase I dose escalation study

• To determine the maximum tolerated dose of single fraction SRS in patients previously irradiated primary brain tumors and brain mets.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild neurologic symptoms; no medication required</td>
</tr>
<tr>
<td>2</td>
<td>Moderate neurologic symptoms; outpatient medication required (e.g., steroids)</td>
</tr>
<tr>
<td>3</td>
<td>Severe neurologic symptoms; outpatient or inpatient medication required</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening neurologic symptoms (e.g., uncontrolled seizures, paralysis, or coma); includes clinically or radiographically suspected radionecrosis and histologically proven radionecrosis at the time of an operation</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

### Results

**Table 5. Incidence of Grade 3, 4, and 5 CNS toxicity by tumor size and treatment arm**

<table>
<thead>
<tr>
<th>Tumor size*</th>
<th>Arm</th>
<th>Dose</th>
<th>No. of patients</th>
<th>% of Patients With Toxicity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>≤ 20 mm</td>
<td>1</td>
<td>18 Gy</td>
<td>12</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21 Gy</td>
<td>18</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>24 Gy</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>21–30 mm</td>
<td>2</td>
<td>15 Gy</td>
<td>15</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>18 Gy</td>
<td>15</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>21 Gy</td>
<td>13</td>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>24 Gy</td>
<td>12</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>31–40 mm</td>
<td>3</td>
<td>12 Gy</td>
<td>21</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>15 Gy</td>
<td>22</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>18 Gy</td>
<td>18</td>
<td>17</td>
<td>33</td>
</tr>
</tbody>
</table>

* Maximum tumor diameter.

---

<table>
<thead>
<tr>
<th>Lesion diameter</th>
<th>Maximum Tolerance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20 mm</td>
<td>24 Gy</td>
</tr>
<tr>
<td>21-30 mm</td>
<td>18 Gy</td>
</tr>
<tr>
<td>31-40 mm</td>
<td>15 Gy</td>
</tr>
</tbody>
</table>

Yamamoto study

• 22 Gy <4 cm³ and 20 Gy to others

Yamamoto et al., Lancet Oncology, 2014

<table>
<thead>
<tr>
<th>Planning Treatment Volume</th>
<th>RTOG 90-05</th>
<th>Number of Metastases</th>
<th>Radioresistant / Prior WBRT</th>
<th>Radioresistant / No Prior WBRT</th>
<th>Radiosensitive / Prior WBRT</th>
<th>Radiosensitive / No Prior WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4.5 cc</td>
<td>24 Gy</td>
<td>5-10</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4</td>
<td>22 Gy</td>
<td>22 Gy</td>
<td>22 Gy</td>
<td>22 Gy</td>
</tr>
<tr>
<td>4.6-7.0 cc</td>
<td>18 Gy</td>
<td>5-10</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>18 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td>7.1-8.5 cc</td>
<td>18 Gy</td>
<td>5-10</td>
<td>18 Gy</td>
<td>20 Gy</td>
<td>18 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>20 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td>8.6-11.0 cc</td>
<td>18 Gy</td>
<td>5-10</td>
<td>18 Gy</td>
<td>18 Gy</td>
<td>18 Gy</td>
<td>18 Gy</td>
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<tr>
<td></td>
<td></td>
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<td>20 Gy</td>
<td>18 Gy</td>
<td>18 Gy</td>
<td>20 Gy</td>
</tr>
<tr>
<td>11.1-14.0 cc</td>
<td>18 Gy</td>
<td>5-10</td>
<td>16 Gy</td>
<td>18 Gy</td>
<td>16 Gy</td>
<td>18 Gy</td>
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<tr>
<td>14.1-22.0 cc</td>
<td>15 Gy</td>
<td>5-10</td>
<td>16 Gy</td>
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<td>16 Gy</td>
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<tr>
<td>22.1-34.0 cc</td>
<td>15 Gy</td>
<td>5-10</td>
<td>16 Gy</td>
<td>16 Gy</td>
<td>15 Gy</td>
<td>16 Gy</td>
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We still need to define the best prescription doses according to:

• Tumor volume
• Histopathology
• Extracranial disease status
• Medical treatment
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You can not increase the total dose

- 2 cm  \( 4.8 \, \text{cm}^3 \)
- 2.5 cm  \( 9.2 \, \text{cm}^3 \)
- 3 cm  \( 15.6 \, \text{cm}^3 \)
- 3.5 cm  \( 24.2 \, \text{cm}^3 \)

Fractionation

- 27-30 Gy in 3 fx
- 31-35 Gy in 5 fx
- Effective and tolerable

Murai et al. Fractionated Stereotactic Radiotherapy using Cyberknife for the Treatment of Large Brain Metastases: A Dose Escalation Study. Clinical Oncology, 2014
Single vs multifraction SRS: Meta-analysis of 24 trials

• In the treatment of large brain metastases with radiosurgery
• MF-SRS may offer a relative reduction of radionecrosis
• MF-SRS maintains or improves relative rates of 1-year LC compared to SF-SRS

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• A simple grading system is developed
• Brain metastasis velocity (BMV), which is specifically applicable to salvage treatment of newly arising tumors after SRS alone
• The BMV score is the cumulative number of new BMs developing after the first SRS divided by the time (in years) since the initial SRS

• Japanese retrospective cohort study
  • 833 patients who underwent second SRS
  • 250 third SRS
  • 88 fourth SRS
• Analyzed patients by brain metastasis velocity (BMV) = cumulative # of brain mets developed/time since initial SRS

Yamamoto M et al. Validity of a Recently Proposed Prognostic Grading Index, Brain Metastasis Velocity, for Patients With Brain Metastasis Undergoing Multiple Radiosurgical Procedures. IJROBP 2019
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Checkpoint inhibitors for asymptomatic melanoma brain metastasis

- Checkmate 204, phase II multicenter single arm study
- Nonirradiated brain metastasis (tumor diameter, 0.5 to 3 cm)
- No neurologic symptoms
- Nearly 75% had 1-2 lesions
- Nivolumab plus ipilimumab for up to four doses
- Followed by nivolumab until progression or unacceptable toxic effects
- The rate of intracranial clinical benefit was 57%
  - complete response was 26%,
  - partial response was 30%
  - stable disease for at least 6 months was 2%.

Tawbi et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. NEJM, 2018
Checkpoint inhibitors for symptomatic melanoma brain metastasis

• Outcomes are inferior with checkpoint inhibitors alone
• Intracranial response rate was 16.7%
• Timing of radiation is still unanswered

Tawbi et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. NEJM, 2018
NSCLC Brain Metastases and Checkpoint inhibitors

- Yale phase 2 study – pembrolizumab
- Asymptomatic untreated brain mets > 2cm
- Response rate (CR + PR) among 18 patients - 33%
- There might be a role for systemic immunotherapy in patients with asymptomatic untreated or progressive brain metastases

Checkpoint inhibitors + SRS

- Large retrospective series suggest superior outcomes with concurrent SRS and immune checkpoint inhibitors vs delayed radiation
- Lehrer Meta-analysis
- 534 patients, 1570 lesions (mostly melanoma)
  - 1-year OS (64.6% vs 51.6%, p<0.001) and
  - regional brain control (38.1% vs 12.3%, p=0.049),
  - Trend in LC (89.2% vs 67.8%, p=0.09)

Sequencing with SRS

• Optimal sequencing to minimize toxicity: unanswered question
Targeted agents for brain metastases

• Lung adenocarcinoma
  • EGFR mutant
  • ALK positive

• Melanoma
  • BRAF mutated
• 3rd generation TKI, Osimertinib is more effective for asymptomatic brain metastases than cytotoxic chemotherapy and 1st generation EGFR TKI’s
• 2nd and 3rd generation ALK/ROS1 inhibitors yield promising CNS control superior to 1st generation
EGFR-TKI therapy and SRS sequencing

• Retrospective study
• 31 pts received SRS
• 176 pts., 61 % upfront TKI, 39 % upfront local therapies
• Upfront LT group showed significantly better OS compared with TKI group
  • 35 vs 23 months

• Pooled multi-institutional retrospective series suggest **upfront SRS** in TKI-naïve patients is **associated with improved OS** vs delaying radiation until progression

• Developing brain metastases on TKI is associated with worse OS
• SRS in brain metastases
  • Mostly first choice
  • WBRT and surgery could be used in selected cases
  • Dose selection is important
  • Could be used in large, multiple and radioresistant metastases
  • New systemic agents are promising

• Brain metastasis is not a single disease
Brain Metastases: Changing the Paradigm

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