Stereotactic Radiosurgery for Brain Metastasis: Changing Treatment Paradigms

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Overall Clinical Significance

- A major clinical challenge
- Very little in the way of major improvements
- Neurosurgeons must do our part in this battle

Epidemiology of Brain Metastases

- Annual U.S. incidence: 170,000 to 300,000
- Ratio Mets/Primary: 10:1
- All Cancer Patients: 15 - 30%
- Autopsy incidence: 10 - 30%
- Mean age: 60 years
- Median survival: ~ 6 months

Approaching a Patient with Brain Metastases

- Symptom management
- Staging of extracranial disease
- Chemotherapy
- Intracranial disease staging
  - 1 Lesion
    - Single evidence of systemic disease (primary)
    - Without evidence of systemic disease (solitary)
  - 2-3
  - All others
- KPS, RPA, GPA, dGPA status

Other known primary: 13%
Annual U.S. incidence: 170,000 to 300,000
Ratio Mets/Primary: 10:1
All Cancer Patients: 15 - 30%
Autopsy incidence: 10 - 30%
Mean age: 60 years
Median survival: ~ 6 months

Lung: 48%
Breast: 15%
Unknown primary: 10%
Melanoma: 9%
Colon: 5%

*Incidence increasing with better systemic Rx and improved survival

Chemotherapy

- Limited role of chemotherapy for:
  - Prevention of extracranial disease spread
  - Penetration of some agents through the blood brain barrier
  - May reduce intracranial disease progression

- Neurological decline as a result of chemotherapy can occur.
- Some agents are very expensive and require IV infusions

Chemotherapy with SRS

- No appreciable role for concurrent chemotherapy along with SRS and WBRT
- In RTOG 0320, the addition of Temodar or Erlotinib to WBRT and SRS may actually have been detrimental

Randomized Surgical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Rx</th>
<th>N</th>
<th>FR*</th>
<th>Median Survival (mo)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell</td>
<td>S+RT</td>
<td>15</td>
<td>65</td>
<td>12</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>15</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noordijk</td>
<td>S+RT</td>
<td>32</td>
<td>34</td>
<td>15</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>31</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mintz</td>
<td>S+RT</td>
<td>41</td>
<td>-</td>
<td>24</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>RT</td>
<td>43</td>
<td>-</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

*Functional Independence (KPS >70) in weeks

Surgery + RT Improves Survival in Selected Patients

Surgery for 2 to 4 Metastases

- **Study Design**
  - Retrospective review
  - 26 patients with completely resected multiple metastases
  - Comparison group: 26 pts with completely resected single metastasis
- **Survival was similar**
  - Median: 14 months
  - 1 year: 55% vs 50%
  - 2 years: 32% vs 30%
  - 5 years: 11% vs 16%
- **Potential selection bias; limited data**


**Surgical Resection of >1 Brain Met Remains Controversial**

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WBRT Outcomes

<table>
<thead>
<tr>
<th>Year of Study</th>
<th>N</th>
<th>Sy/Frac's</th>
<th>Med Surv. (mos)</th>
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<tbody>
<tr>
<td>1971-1973</td>
<td></td>
<td>227</td>
<td>40 / 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>233</td>
<td>40 / 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>217</td>
<td>30 / 15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>203</td>
<td>30 / 10</td>
</tr>
<tr>
<td>1973-1976</td>
<td></td>
<td>447</td>
<td>20 / 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>228</td>
<td>30 / 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>227</td>
<td>40 / 15</td>
</tr>
<tr>
<td>1976-1979</td>
<td></td>
<td>156</td>
<td>30 / 18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>153</td>
<td>50 / 20</td>
</tr>
</tbody>
</table>

Fractionation, schedule & dose do not impact survival
No significant difference between any schedule
There is no standard schedule

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WBRT and Graded Prognostic Assessment (GPA)

- Evaluated 1960 patients from 5 randomized RTOG studies

<table>
<thead>
<tr>
<th>Score</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.5-4</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1.5-2.5</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>KPS</th>
<th>Number of CNS metastases</th>
<th>Extracranial metastases</th>
<th>Present</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70</td>
<td>&gt;3</td>
<td>Present</td>
<td>-</td>
<td>None</td>
</tr>
<tr>
<td>&lt;70</td>
<td>&lt;3</td>
<td>None</td>
<td>-</td>
<td>None</td>
</tr>
</tbody>
</table>

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**Brain Metastases: What is Impact of WBRT?**
Brain Metastases:
What is Impact of WBRT after Extirpation?

Very High Brain Relapse After Surgery if WBRT Is Omitted

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>No RT</th>
<th>WBRT</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any brain</td>
<td>70%</td>
<td>18%</td>
<td>~4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Original</td>
<td>46%</td>
<td>10%</td>
<td>3.6</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Complete resection without WBRT leads to 70% actuarial relapse. This is a relative risk increase of 4.


EORTC 22952-26001
No Radiotherapy vs. Whole Brain Radiotherapy for 1 to 3 Brain Metastases from solid tumour after initial surgical resection or radiosurgery

Primary Endpoint was functional survival (WHO PS ≤ 2)

HR = 0.96 (95% CI: 0.76–1.23)
P = 0.709, stratified by S vs RS

Median: 10.6 (95% CI: 8.3-11.7)
Median: 9.5 (95% CI: 7.6-11.6)
Study Conclusions

- 359 patients randomized: 179 no RT / 180 WBRT
- Few ineligible patients (1.7%)

- WBRT added to WBRT,
  - No significant difference for functional survival with PS<70 (p=0.1)
  - No significant difference for overall survival
  - Longer PFS with WBRT + SRS (p=0.4, stratified by 0 vs. RS)
  - Significant reduction of intracranial progression by WBRT (p=0.0001), both for previous or new sites

RTOG-9508 Results

<table>
<thead>
<tr>
<th>Survival Analysis</th>
<th>WBRT + SRS (months)</th>
<th>WBRT (months)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.5</td>
<td>5.7</td>
<td>0.13</td>
</tr>
<tr>
<td>1 brain met</td>
<td>6.5</td>
<td>4.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Selected subsets benefit from radiosurgery.


RTOG-9508: Outcomes

<table>
<thead>
<tr>
<th>Trait</th>
<th>WBRT</th>
<th>WBRT + SRS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stable / improved @ 3 m</td>
<td>33%</td>
<td>50%</td>
<td>.02</td>
</tr>
<tr>
<td>- Stable / improved @ 6 m</td>
<td>27%</td>
<td>43%</td>
<td>.03</td>
</tr>
<tr>
<td>Edema decreased @ 3 m</td>
<td>62%</td>
<td>73%</td>
<td>.04</td>
</tr>
<tr>
<td>Tumor response @ 3 m</td>
<td>47%</td>
<td>70%</td>
<td>.0017</td>
</tr>
<tr>
<td>Local control @ 1 yr</td>
<td>71%</td>
<td>82%</td>
<td>.01</td>
</tr>
<tr>
<td>CNS death</td>
<td>31%</td>
<td>28%</td>
<td>ns</td>
</tr>
<tr>
<td>Grade 3/4 late toxicity</td>
<td>&lt;2%</td>
<td>&lt;3%</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Significantly lower steroid dependence on RS arm

Rate of Regional Failure after RS Alone (1-4 mets): JROSG-9901

<table>
<thead>
<tr>
<th>SRS</th>
<th>SRS+RT</th>
<th>P-value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>67</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Survival (months)</td>
<td>8.0</td>
<td>7.5</td>
<td>.42</td>
</tr>
<tr>
<td>LC (%)</td>
<td>73</td>
<td>89</td>
<td>.002</td>
</tr>
<tr>
<td>DBF (%)</td>
<td>64</td>
<td>42</td>
<td>.003</td>
</tr>
</tbody>
</table>

Note: Local control (LC) and distant brain failure (DBF) at 12 months

The combination of RS and WBRT offers better overall intracranial control.
There was no difference in survival between the two treatment groups.


What are the side effects of WBRT?

Risk of Dementia with Postop WBRT for Brain Metastases

  - 5/47 (11%) patients treated with WBRT developed severe dementia
  - Dementia was associated with high dose per fraction
- A recent Cochrane review of different fractionation schemes for WBRT showed no difference in survival, neurological control, or symptomatic improvement between WBRT and other schemes (Tsao et al., 2006)

Neurocognitive Function after Radiosurgery

- Studied neurocognition in patients with other SRS or SRS & WBRT
- Used HVLT-R which included Total Recall, Delayed recall, Delayed Recognition
- Randomized trial of 98 patients that were either RPA class I or II
- Patients with SRS & WBRT (52% probability risk) were at greater risk of significant decline in learning and memory function by 4 months than the SRS alone group (24% risk)
- Interestingly, in that same issue of Lancet Oncology for leukemia

Source: Chang et al., Lancet Oncology, 2009
**MMSE in Brain Met Patients**

- Rates of deterioration in MMSE correlated more with progression of intracranial disease.

Aoyama et al., IJROBP (2007)

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**Some Commonsense Indications for SRS**

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**Lesions in Eloquent Locations**

Pre-GKS tumor volume=3.4 cc

12 months post-GKS volume=2.2 cc

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**Radioreistant Metastasis**

Pt with metastatic melanoma:
- KPS=100;
- At SRS (above left) and 7 months post Gamma surgery (below right)

Little role for WBRT in melanoma
And renal cell CA.
Radiosurgery to a Tumor Resection Cavity

- Following a gross total resection of a brain metastasis, recurrence occurs 47% of time.
- WBRT reduces the chance of recurrence.
- Radiosurgery with a 2 mm margin around — Also reduces recurrence
  — May avoid sequelae of WBRT
  — Hold WBRT until really needed

How well can we predict survival?

- 150 Brain mets patients (median survival 10.3 months; 95%CI 6.4 to 14)
- 14 experienced clinicians asked to predict survival

SRS for Multiple Metastases

- Neither neurosurgeons nor radiation oncologists could pick pt’s with ≥14 months survival
- 7 out of 14 had predictions that were in error by ≥18 months

- How many are too many?
- WBRT?
- Patient Expectations?
- Q of L > life expectancy>> Intracranial Disease Control
SRS for 1-10 brain metastases without WBRT

- Ongoing, multicenter trial in Japan (JLGX0901)
- Powered to show overall survival and neurological survival are equivalent for SRS alone for various brain metast cohorts
- Thus, SRS alone may be an effective (or even preferred) treatment for RPA class II patients

UVA Study of Patients with 5 to 15 Metastases

- 96 patients
  - 18.9% RPA class I
  - 81.1% RPA class II
- 704 brain metastases
- Median survival=4.73 months
  - (range 0.4 to 41.8)

Tumor control

Actuarial 6mo= 92.4%
Actuarial 12mo=84.8%
Actuarial 24mo=74.9%

Overall Survival

- RPA class I vs. RPA class II
  (p=0.038)
- No difference based upon number of tumors or total PTV
### Traditional Algorithm

#### Brain Metastasis

**Algorithm 2**

- ≤ 3 cm
  - S + SRS
- > 3 cm
  - SRS

**Algorithm 3**

- Multiple ≤ 4
  - KPS > 70
    - Minimal systemic disease or Candidate Systemic Therapy
    - S largest + SRS
  - Poor KPS
    - Massive Disease
    - Marginal Systemic Therapy
    - WBRT ± SRS

- Patient choice: QOL vs local control discussion
- Neurologic symptoms

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### Comparisons of published literature

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median # lesions</th>
<th>Median OS</th>
<th>Median PTV</th>
<th>RPA Class</th>
<th>Statistically Significant Prognostic Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>U of Virginia</td>
<td>96</td>
<td>7 (5-15)</td>
<td>4.7 mo</td>
<td>6.12 cm</td>
<td>I = 18.9%</td>
<td>II = 81.1% III = 0% RPA class</td>
</tr>
<tr>
<td>U of Pittsburgh</td>
<td>61</td>
<td>mean: 13.2</td>
<td>4 mo</td>
<td>4.86 cm</td>
<td>I = 13.1%</td>
<td>II = 75.4% III = 11.5% KPS &lt; 90 vs KPS ≥ 90 Prior to concurrent WBRT</td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>64</td>
<td>6 (5-10)</td>
<td>7.5 mo</td>
<td>4.91 cm</td>
<td>I = 27%</td>
<td>II = 63% III = 11% KPS ≤ 70 vs KPS ≥ 80 Prior vs concurrent WBRT</td>
</tr>
<tr>
<td>U of Pittsburgh</td>
<td>205</td>
<td>5 (4-18)</td>
<td></td>
<td>6.8 cm</td>
<td>I = 10%</td>
<td>II = 75% III = 15% Planned treatment volume, age, RPA class, marginal dose</td>
</tr>
<tr>
<td>Ajou U, Suwon, Korea</td>
<td>36</td>
<td>mean: 7 (4-10)</td>
<td>9.1 mo</td>
<td>1.2 cm</td>
<td>I = 8.3%</td>
<td>II = 88.9% III = 2.8% Uncontrolled primary tumor, KPS &gt; 70 vs KPS &lt; 70</td>
</tr>
<tr>
<td>Sungkyunkwan U, Seoul, Korea</td>
<td>26</td>
<td>mean: 16.6 (10-37)</td>
<td>34 weeks = ~7.3 mo</td>
<td>10.9 cm</td>
<td>I = 11.5%</td>
<td>II = 88.5% III = 0% Uncontrolled primary tumor, KPS ≥ 80, short duration from diagnosis to metastases, &gt;2 cycles chemotherapy post GKS</td>
</tr>
</tbody>
</table>

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### Algorithm 2

- **Solitary**
  - ≤ 3 cm
    - S + SRS
  - > 3 cm
    - SRS
  - WBRT + SRS

- *Surgical Ease (Age/other disease/location)*
- *Patient Choice*
- *Neurologic symptoms*
Algorithm 4

- Patient choice: QOL vs local control
- How many > 4? (Yamamoto-2013)

Multiple > 4

WBRT + SRS

SRS alone

Algorithm 5

- Multiple > 4
- Multiple ≥ 3cm

S + SRS ± WBRT

WBRT ± SRS

Algorithm 6

- Multiple ≤ 4
- all ≤ 3 cm

SRS

Patient choice: Local control discussion

Evidence Based Studies

Parachutes use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C Smith, JFP Poll
BMJ 2003;327:1459–61
Conclusions

1. Radiosurgery yields a favorable risk to benefit profile for patients with single or multiple brain metastases without significant mass effect.

   Radiosurgery is particularly useful for patients:
   a. with 1-4 brain met at presentation
   b. new brain mets after WBRT
   c. treatment of symptomatic met prior to WBRT
   d. radiation resistant mets (e.g. renal cell CA and melanoma)
   e. Metastasis in the brainstem and other areas difficult to access surgically

2. Multi-center clinical trials are currently attempting to better define the role of SRS in the treatment armamentarium.
   1. SRS +/- WBRT
   2. SRS +/- Resection
   3. SRS alone
   4. Neuro-cognitive effects of SRS
   5. >5 brain metastases

Conclusions (continued)

3. WBRT has a significant role but:
   a. at what time and in which pt’s should it be employed?
   b. at what neurocognitive cost?

4. Large metastases with marked intracranial pressure should be extirpated by surgery.

5. Increasing role for:
   • Chemotherapy
   • Hormonal / Receptor Status of cancer subtype testing