Treatment of Recurrent Brain Metastases

Background

- Brain metastases occur in 8.5-15% of cancer pts in population- vs. autopsy-based studies (Schouten 2002, Posner 1978).
- Cancer patients are living longer (5-yr survival 50% 1975-77, 54% 1984-86, 66% 1996-2004).
- There are more options for rx of brain mets and better imaging to dx & follow brain mets.

Incidence of New or Recur Brain Mets

<table>
<thead>
<tr>
<th>Initial treatment for brain mets</th>
<th>1st author, yr</th>
<th>n</th>
<th>Crude risk</th>
<th>1-yr prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS alone</td>
<td>Sneed, 1999</td>
<td>62</td>
<td>58%</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>Muacevic, 2008*</td>
<td>31</td>
<td>~26%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Aoyama, 2006*</td>
<td>67</td>
<td>60%</td>
<td>76%</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>Patchell, 1998*</td>
<td>46</td>
<td>70%</td>
<td>--</td>
</tr>
<tr>
<td>WBRT alone</td>
<td>Patchell, 1990*</td>
<td>23</td>
<td>57%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Andrews, 2004*</td>
<td>78/167</td>
<td>--</td>
<td>~34%</td>
</tr>
<tr>
<td>WBRT + SRS</td>
<td>Sneed, 1999</td>
<td>43</td>
<td>37%</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>Andrews, 2004*</td>
<td>75/164</td>
<td>--</td>
<td>~28%</td>
</tr>
<tr>
<td></td>
<td>Aoyama, 2006*</td>
<td>65</td>
<td>35%</td>
<td>47%</td>
</tr>
<tr>
<td>Surgery + WBRT</td>
<td>Patchell, 1990*</td>
<td>25</td>
<td>28%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Patchell, 1998*</td>
<td>49</td>
<td>18%</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Muacevic, 2008*</td>
<td>33</td>
<td>~18%</td>
<td>--</td>
</tr>
</tbody>
</table>

Dx of Tumor vs. Necrosis

- Necrosis
- Tumor
- Normal
**Treatment of Recurrent Brain Mets**

- Repeat WBRT
- Radiosurgery
- Surgery
- Surgery + Brachy / FSRS
- Chemotherapy / TKIs

**Repeat WBRT**

<table>
<thead>
<tr>
<th>Author, yr</th>
<th>n</th>
<th>Decreased Scheme</th>
<th>Decreased sx (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurup, 1980</td>
<td>56</td>
<td>20 Gy/10 fx</td>
<td>75%</td>
</tr>
<tr>
<td>Hazuka, 1988</td>
<td>44</td>
<td>6-36 Gy, 2-4 Gy/fx</td>
<td>27%</td>
</tr>
<tr>
<td>Cooper, 1990</td>
<td>52</td>
<td>~25 Gy/10 fx</td>
<td>42%</td>
</tr>
<tr>
<td>Wong, 1996</td>
<td>86</td>
<td>20 Gy/10 fx*</td>
<td>70%</td>
</tr>
<tr>
<td>Sadikov, 2007</td>
<td>72</td>
<td>20-25 Gy/10 fx or 15 Gy/5 fx or 20 Gy/8 fx</td>
<td>31%</td>
</tr>
</tbody>
</table>

*median dose

**Radiosurgery**

*Chao et al, 2008 (Cleveland Clinic)*

- Retrospective review of 111 patients treated with salvage SRS 1989-2004 for 243 recurrent brain mets after prior WBRT; median dose 23.6 Gy

- 24 RPA class 1 (< 65 yo, ø extracranial dz, KPS > 70); 80 RPA class 2; 7 RPA class 3 (KPS < 70)

- MST 9.9 months from SRS (6.8 vs. 12.3 mo for recurrence < vs. > 6 mo after WBRT; p = 0.006)

- At 1 year, LC 68% & distant brain ctrl 86%; 2 cases of radiation necrosis

**Radiosurgery**

*Caballero, Sneed et al, in preparation 2010 (UCSF)*

- Retrospective review of 310 patients treated with Gamma Knife SRS 1991-2007 for recurrent brain mets after prior WBRT

- Median age 56, KPS 80, 3 brain mets, 8.1 mo from WBRT to SRS; controlled 1° in 76%, extracranial mets in 60% of pts

- Median doses: 30 Gy/10 fx WBRT; 17 Gy SRS

- Survival measured from date of salvage SRS
### Radiosurgery

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MST (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>310</td>
<td>8.4</td>
</tr>
<tr>
<td>Breast</td>
<td>90</td>
<td>11.4</td>
</tr>
<tr>
<td>NSCLC</td>
<td>113</td>
<td>8.1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>42</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Caballero et al, 2010 (UCSF)

### Radiosurgery

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MST (mo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 65 yo</td>
<td>250</td>
<td>8.6</td>
<td>0.054</td>
</tr>
<tr>
<td>&gt; 65 yo</td>
<td>60</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>KPS &lt; 70</td>
<td>30</td>
<td>5.8</td>
<td>0.001</td>
</tr>
<tr>
<td>KPS &gt; 70</td>
<td>280</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>1° ctrl</td>
<td>236</td>
<td>9.1</td>
<td>0.001</td>
</tr>
<tr>
<td>1° not ctrl’d</td>
<td>74</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Extrcr mets</td>
<td>187</td>
<td>8.6</td>
<td>NS</td>
</tr>
<tr>
<td>ø extrcr mets</td>
<td>123</td>
<td>8.1</td>
<td></td>
</tr>
</tbody>
</table>

Caballero et al, 2010 (UCSF)

### Radiosurgery

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>MST (mo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total target volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2.6 cc</td>
<td>77</td>
<td>11.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.62-5.7 cc</td>
<td>77</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>5.8-11.8 cc</td>
<td>78</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>11.81-54.4 cc</td>
<td>78</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>

Interval from WBRT to SRS

| <5 mo   | 77  | 7.3  | 0.011 |
| 5-8.0 mo| 77  | 7.0  |       |
| 8.1-14.2 mo| 78 | 9.1  |       |
| 14.3-86.0 mo| 78 | 11.8 |       |

Caballero et al, 2010 (UCSF)
Surgery

Advantages
- Tissue diagnosis
- Rapid relief of mass effect
- Rapid sx ↓ & steroid taper
- ↑ probability of local control

Disadvantages
- Small risks of surgical M&M
- Small risk of leptomeningeal dissemination
- Many patients/lesions aren’t candidates
- Signif. risk of recurrence w/o adjuvant radiation

Surgery for Tumor vs. Necr
50 yo F, breast 1°, 16 Gy; reop path = tumor + astrogliosis

53 yo M, melanoma 1°, 17 Gy; 1 yr post-op; necr

17 Gy post-op
1 yr
p reop; necr

Survival time (months)
0.00 0.25 0.50 0.75 1.00

Probability

Caballero et al, 2010 (UCSF)
How often is surgery needed after SRS?

Williams BJ, ... Sawaya RE, et al: J Neurosurg 2009

- 76 of 316 lesions (24%) in 273 pts ↑d after SRS; 45 resected; 32 (71%) tumor; 13 (29%) necrosis

How successful is salvage surgery p SRS?

Kano et al, J Neurosurg 2009 (U Pittsburgh)

- 58 pts had resection of brain met after prior SRS
- Median vol 7.7 cc at time of SRS; 15.5 cc at time of surgery
- Local control 71%@6 mo, 62%@1 yr, 43%@2 yr
- Mortality 1.7%; morbidity 6.9%
- Median survival after resection 7.7 mo
- Better outcome if LF > 3 mo after SRS

Surgery + Brachytherapy

59 yo F; lung adenoCA; solitary brain met

15 Gy, 23.5 cc
1 yr
Post-op CT

4.5 yr after brachy
A&W 6 yr after SRS + surg x 2
Surgery + Brachytherapy

Huang et al, 2006 (UCSF)
- Retrospective review of 40 pts rx’d with surgery + permanent brachy (w/o WBRT) 1997-2003
- 19 newly dx’d; 21 recurrent
- Median dose at 5 mm depth 400 Gy to 16.3 cc

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MST (mo)</th>
<th>1-yr Local FFP</th>
<th>1-yr Brain FFP</th>
<th>Sx necr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly dx’d</td>
<td>19</td>
<td>12.0</td>
<td>92%</td>
<td>43%</td>
<td>26%</td>
</tr>
<tr>
<td>Recurrent</td>
<td>21</td>
<td>7.3</td>
<td>86%</td>
<td>29%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Surgery + Single-Fx SRS

Kim et al, 2006 (Wake Forest)
- Retrospective review of 79 patients treated with surgery + post-op Gamma Knife SRS 1999-2005 for recurrent brain mets after prior WBRT
- Median age 53, SRS dose 18 Gy
- Median survival time 17 months from SRS
- Local control 95%
- Carcinomatous meningitis 5%
- Sx radionecrosis requiring reop 4%

Surgery + Fractionated SRS

62 yo M with esophageal 1°, HA, expr aphasia; confusion; no systemic disease

CK plan: 30 Gy/5 fxs to cavity + 2 mm margin

Chemotherapy

Blood brain barrier: fact or fiction?
- BBB is disrupted at sites of CE-ing lesions but probably intact at sites of micromets
- Cytochrome P450-inducing antiepileptics incr metabolism of many chemo agents (paclitaxel, CPT11, TKIs, etc.). Avoid such antiepileptics with chemorx.
- Numerous trials show efficacy of chemo for brain mets, with RRs as expected for extracranial mets or 1°.
- Anti-tumor activity is more important than CNS distrub.
- TMZ alone gave 6% PR, 44% SD x 4 mo, MST 6.6 mo among 41 pts with recur brain mets (Abrey et al, 2001)
59 yo F; lung adenoCA; WBRT 30 Gy in 10 fx 7 mo earlier

2 months after starting single-agent Tarceva (erlotinib)
(7 months later had GK to 7 new /residual brain mets)
Case reports: von Pawel et al, 2008; Popat et al, 2007

Choice of Salvage Therapy

Considerations
- Pt condition
- Pt prognosis
- Symptoms
- Response to steroids
- Prior therapy
- Number
- Size / total vol
- Location
- Primary site

18 Gy 6 mo

Summary
It is becoming more common to detect & rx recurrent brain mets
- Repeat WBRT (MST 1.8-4.0 mo)
- Radiosurgery (MST 8.4-9.0 mo)
- Surgery (Good for dx & rapid ↓ sx)
- Surgery + Brachy / SRS (↑ LC)
- Chemotherapy / TKIs
- Supportive Care