Stereotactic Radiosurgery (SRS) for brain metastases - NO more WBRT please!

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Elekta: Honorarium for educational seminars

SRS vs. WBRT
Brain SRS

- High dose of “ablative” radiation delivered to a target localized in three-dimensions with an overall end-to-end precision in the order of 1-2 mm delivered over 1 to 5 fractions

- Technical principles
  - Localize the tumor in three dimensions
  - Invasive head frame provides the reference 3D co-ordinates
  - MRI for tumor delineation
  - Immobilize the head
  - Invasive stereotactic head frame now frameless solutions
  - Radiotherapy system such that accuracy of delivery is <2 mm
  - Dedicated Linac-based systems or Gamma Knife

SRS Technologies

Case

- 50 year old male with known melanoma
  - 6 years later seizure
  - CT/MRI 2 brain mets
  - Staging 2 lung metastases
  - Excellent performance status
    - KPS <70 MS 3 months
    - KPS and up to 3 metastases MS 13 months
    - BRAF V600 +ve
Case

- Management:
  • WBRT
  • SRS alone
  • WBRT+SRS boost
  • Surgery + WBRT
  • Surgery alone
  • Chemo/Targeted agent alone

- Most debate between SRS alone vs. WBRT+SRS
- Do we need the WBRT?

What do we know about the toxicities of WBRT?
Toxicity of WBRT vs. no WBRT: NSCLC PCI RCT

- Closed early due to accrual—Primary endpoint was OS
- 340 patients evaluated with Stage III NSCLC
  - 163 treated with WBRT vs. 177 Observed

- Hopkins verbal learning test (HVLT)
  - Validated and reliable assessment of memory

- Results:
  - OS/DFS not different
  - PCI recurrence rate of 8% vs. 18% in observation arm at 1 year
  - HVLT outcomes:

Table 4: Testing of Discrimination Scores From Baseline to Hopkins Verbal Learning Test During Follow-Up Using Reliable Change Index

<table>
<thead>
<tr>
<th>Time Point</th>
<th>HVLT</th>
<th>No Deletion</th>
<th>Deletion</th>
<th>No Deletion</th>
<th>Deletion</th>
<th>Adj P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>Recall</td>
<td>28</td>
<td>45</td>
<td>58</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Delayed recall</td>
<td>38</td>
<td>44</td>
<td>56</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>6 months</td>
<td>Recall</td>
<td>11</td>
<td>19</td>
<td>81</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Delayed recall</td>
<td>8</td>
<td>15</td>
<td>85</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>12 months</td>
<td>Recall</td>
<td>15</td>
<td>28</td>
<td>72</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Delayed recall</td>
<td>11</td>
<td>32</td>
<td>68</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

8% recurrence rate 18% recurrence rate
QOL: WBRT vs no WBRT

- QOL analysis (EORTC QLQ-C30) from the EORTC study randomizing following SRS or Surgery to WBRT vs. observation

- Patients receiving WBRT had significantly worst QOL scores overall
- Despite lower risk of brain relapse

Soffietti et al. JCO, 2013.

Memantine: Neuroprotective Drug

- RCT: Memantine for 6 months vs placebo (508 patients) in patients receiving WBRT
- Standardized neurocognitive testing with HVLT:
  - Significant benefits to memantine
    - Time to neurocognitive decline prolonged (p=0.01)
    - At 6 months probability of cognitive function failure 53.8% vs. 64.9% in placebo arm
    - Therefore one can conclude that WBRT adversely affects neurocognition!
Neurocognitive outcomes for SRS vs. WBRT + SRS

Multiple Brain Mets: SRS vs. WBRT + SRS

- Chang RCT:
  - 58 patients with 1-3BM:
    - SRS alone vs. SRS+ WBRT
    - Primary endpoint:
      - Neurocognitive changes
      - HVLT:
        - Total recall @ 4months
        - 5 point drop is a failure
  - 18% absolute difference in the 2 arms favoring SRS alone

Potential benefits of SRS alone

- Tolerate treatment better with less fatigue, appetite loss, less steroid dependence
- Chemotherapy delays were minimized
- Patients with SRS alone tolerated more chemo cycles
Summary

- If you irradiate a normal brain then you cause memory damage.
- It is the WBRT and not recurrent disease that impairs function.
- WBRT impacts QOL negatively.
- Strategies using drugs or hippocampal avoidance have been shown to lessen the damage induced by WBRT.
- Proof of principle that WBRT is toxic.
- SRS vs. WBRT plus SRS
  - SRS better strategy to preserve neurocognitive function.

Best way to spare the brain from radiation toxicity is not to treat normal brain at all and treat with SRS Alone!

Impact of tumor control/survival with WBRT?

RCT: SRS alone vs WBRT+SRS

- 3 RCT evaluating SRS vs. WBRT+SRS for patients presenting with 1-4 brain metastases.
**RCT 1-4 BM**

<table>
<thead>
<tr>
<th>RCT</th>
<th>% Single Brain Mets</th>
<th>Performance Status</th>
<th>Tumor Size</th>
<th>OS</th>
<th>Local Control</th>
<th>Distant Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayala et al.</td>
<td>60% vs. 68%</td>
<td>52%, 40% vs. 50%</td>
<td>Median 1.3 cm (0.5-3.5) cm vs. 1.4 cm</td>
<td>OS: 18.7 vs. 18.4 vs. 19.3</td>
<td>56% at 1 year</td>
<td></td>
</tr>
<tr>
<td>Chang et al.</td>
<td>50% vs. 54%</td>
<td>100%, KPS ≤ 70 (each arm)</td>
<td>OS: 16.6 vs. 19.5 months</td>
<td>OS: 17% at 1 year vs. 14% at 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koren et al.</td>
<td>80% vs. 56%</td>
<td>50% in each arm</td>
<td>OS: 2.7 cm (0.4-4.6) cm vs. 1.4 cm (0.4-3.4) cm</td>
<td>OS: 50% vs. 50% at 2 years vs. 52% vs. 57% NSD^2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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**Meta-Analysis**

Original Article

A Meta-Analysis Evaluating Stereotactic Radiosurgery, Whole-Brain Radiotherapy, or Both for Patients Presenting with a Limited Number of Brain Metastases

May Tsao, MD, Wei Xu, PhD, and Ayns Sahgal, MD^2


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**1-4 Brain Mets: Local Control**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log Hazard Ratio</th>
<th>SE</th>
<th>Hazard Ratio 95% CI</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayala 2006</td>
<td>1.575</td>
<td>0.45</td>
<td>1.05 [0.83, 1.32]</td>
<td>1.05 [0.83, 1.32]</td>
</tr>
<tr>
<td>Chang 2009</td>
<td>1.718</td>
<td>0.467</td>
<td>1.07 [0.87, 1.31]</td>
<td>1.07 [0.87, 1.31]</td>
</tr>
<tr>
<td>Kocher 2011</td>
<td>0.581</td>
<td>0.283</td>
<td>1.8 [1.0, 3.2]</td>
<td>1.8 [1.0, 3.2]</td>
</tr>
</tbody>
</table>

Total (95% CI): 100%, 2.61 [1.69, 4.06]

Heterogeneity: CHI^2 = 4.95, df = 2 (P = 0.09), P = 40%
Test for overall effect: Z = 4.28 (P = 0.0001)

**1-4 Brain Mets: Distant Brain Control**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE Weight</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama 2006</td>
<td>1.138</td>
<td>0.299</td>
<td>3.15</td>
<td>1.24, 7.91</td>
</tr>
<tr>
<td>Chang 2009</td>
<td>1.404</td>
<td>0.300</td>
<td>4.02</td>
<td>1.47, 11.32</td>
</tr>
<tr>
<td>Kocher 2011</td>
<td>0.48</td>
<td>0.210</td>
<td>1.63</td>
<td>1.01, 2.69</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2.10</td>
<td>1.00</td>
<td>2.08</td>
<td>1.00, 4.33</td>
</tr>
</tbody>
</table>

*Favours SRS alone*; *Favours WBRT and SRS*.


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**1-4 Brain Mets: Overall Survival**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE Weight</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama 2006</td>
<td>0.315</td>
<td>0.193</td>
<td>2.72</td>
<td>1.04, 7.10</td>
</tr>
<tr>
<td>Chang 2009</td>
<td>-0.643</td>
<td>0.311</td>
<td>1.90</td>
<td>0.82, 4.42</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00, 0.00</td>
</tr>
</tbody>
</table>

*Favours SRS alone*; *Favours WBRT and SRS*.


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**SRS vs. WBRT + SRS for 1 to 4 Brain Metastases Individual Patient Data (IPD) Meta-Analysis**

Arjun Sahgal1,2, Hidefumi Aoyama M.D. Ph.D.3, Martin Kocher M.D.4, Binod Neupane Ph.D.5, Sandra Collette Ph.D.6, Masao Tago M.D.7, Prakesh Shah M.D.8, Joseph Beyene Ph.D.9, Eric Chang M.D.10,11

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4University of Cologne, Cologne, Germany
5McMaster University, Hamilton, Canada
6European Organisation for Research and Treatment of Cancer - Headquarters (EORTC HQ), Belgium
7Teikyo University, Minomaki Hospital, Kanagawa, Japan
8Mount Sinai Hospital, University of Toronto, Canada
9University of Southern California, Los Angeles, California, USA
10MD Anderson Cancer Center, Houston, Texas, USA
Methods

- IPD meta-analysis of the 3 RCTs (raw patient data obtained) to determine the effect of treatment (SRS vs. WBRT+SRS) on OS, DBC and LC
  - Adjusted *a priori* for co-variates:
    - Age, RPA and number of brain metastases (1 vs ≥2)
  - Restricted inclusion to those with RPA 1 or 2 and KPS ≥70
    - Final cohort: 364 of 389 patients
    - Median follow-up 9.2 months
      - SRS alone 10.1 months, WBRT+SRS 8.6 months

Results: Baseline characteristics

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total N=389 patients</th>
<th>SRS alone cohort N=192</th>
<th>WBRT+SRS cohort N=197</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS/WBRT + SRS</td>
<td>184(47%)</td>
<td>102(53%)</td>
<td>82(43%)</td>
<td>—</td>
</tr>
<tr>
<td>Female/Male</td>
<td>120(31.0%)</td>
<td>63(32.7%)</td>
<td>57(29.0%)</td>
<td>0.3923</td>
</tr>
<tr>
<td>Median Age (yr)</td>
<td>42</td>
<td>62</td>
<td>63</td>
<td>0.3221</td>
</tr>
<tr>
<td>Age ≤50</td>
<td>119(30%)</td>
<td>57(30.6%)</td>
<td>62(31.7%)</td>
<td>0.5778</td>
</tr>
<tr>
<td>RPA (1 vs 2)</td>
<td>210(53.5%)</td>
<td>111(57.8%)</td>
<td>99(50.3%)</td>
<td>0.0999</td>
</tr>
<tr>
<td>KPS ≥70</td>
<td>364(100%)</td>
<td>192(100%)</td>
<td>172(100%)</td>
<td>—</td>
</tr>
<tr>
<td>Tumor ≥2.4 cm</td>
<td>213/176(90.4%)</td>
<td>118/78(64.5%)</td>
<td>95/98(49.5%)</td>
<td>0.9999</td>
</tr>
<tr>
<td>Extranodal Mets</td>
<td>302(77.5%)</td>
<td>160(82.7%)</td>
<td>142(72.5%)</td>
<td>0.2689</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>114(29.1%)</td>
<td>63(32.7%)</td>
<td>51(26.1%)</td>
<td>0.9495</td>
</tr>
<tr>
<td>Breast</td>
<td>17(4.4%)</td>
<td>12(6.1%)</td>
<td>5(2.6%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Kidney</td>
<td>3(0.8%)</td>
<td>2(1.0%)</td>
<td>1(0.5%)</td>
<td>0.9601</td>
</tr>
<tr>
<td>Others</td>
<td>83(21.3%)</td>
<td>44(23.0%)</td>
<td>39(20.0%)</td>
<td>0.9502</td>
</tr>
<tr>
<td>Local Failure</td>
<td>22(5.6%)</td>
<td>11(5.7%)</td>
<td>11(5.6%)</td>
<td>0.9994</td>
</tr>
<tr>
<td>Distant Brain Failure</td>
<td>156(40.4%)</td>
<td>96(50.0%)</td>
<td>60(30.9%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Death by study completion</td>
<td>314(80%)</td>
<td>157(82.4%)</td>
<td>157(80.8%)</td>
<td>0.5638</td>
</tr>
</tbody>
</table>

Hazard Ratios for SRS alone and Overall Survival

Overall survival significantly increased with SRS alone in patients ages 35-50 relative to their age matched cohort treated with WBRT + SRS
• Distant brain failure was no greater with SRS alone for age ≤ 50 relative to their age matched cohort treated with WBRT + SRS

• Age was not a treatment effect modifier and overall reduced risk of local failure

### Summary of Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aggregate meta-analysis*</th>
<th>IPD Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>No survival benefit for WBRT+SRS</td>
<td>SRS alone favored for age ≤ 50</td>
</tr>
<tr>
<td>Local control</td>
<td>WBRT+SRS favored</td>
<td>WBRT+SRS favored</td>
</tr>
<tr>
<td>Distant brain control</td>
<td>WBRT+SRS favored</td>
<td>WBRT+SRS favored but not in patients age ≤ 50</td>
</tr>
</tbody>
</table>

• Conclude: OS results support SRS alone and not WBRT + SRS for patients age ≤ 50
Hypothesis

- Recent RCT’s have confirmed the detrimental effects of WBRT on both neurocognition and quality of life (Chang et al., Sun et al., Soffietti et al.);
  - OS favoring SRS alone in younger patients (age ≤50) may be explained by the lack of benefit of WBRT with respect to distant brain control while exposing them to the toxicities of worse memory function and harming QOL which compromised survival.


Case

5 years later: SRS alone
Multiple Metastases: SRS alone for more than 4 mets

Multiple Metastases: Why now?

- Dogma of >4 metastases had to be treated WBRT
- Thought risk of new mets developing 100%
- Data emerging showing similar rates of new metastases as compared to patients with 1 to 4 mets (MRI era)
- Technical advances allowing several metastases treated with SRS alone in a single session are now available and practical
- Early on in this experience: data emerging (retrospective)
- Randomized trials for 5 or more mets ongoing

34 Mets including a brainstem lesion and a cavity all treated SRS one session: No WBRT
Drug Therapy Alone for Melanoma Brain Metastases

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial
Lo et al. 2011, JRON

<table>
<thead>
<tr>
<th>12 WEEKS POST</th>
<th>Cohort A (n=53)</th>
<th>Cohort B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mW HO</td>
<td>dEx</td>
</tr>
<tr>
<td>CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>8 (16%)</td>
<td>8 (38%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (10%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>PD</td>
<td>38 (72%)</td>
<td>38 (72%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Asymptomatic no dexamethasone  Symptomatic on dexamethasone

Interpretation: Ipilimumab has activity in some patients with advanced melanoma and brain metastases, particularly when metastases are small and asymptomatic. The drug has no unexpected toxic effects in this population.

Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial

<table>
<thead>
<tr>
<th>BRAF mutant</th>
<th>Cohort A</th>
<th>Cohort B</th>
</tr>
</thead>
<tbody>
<tr>
<td>V600Glu/Val</td>
<td>0 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td>V600Glu/Val</td>
<td>0 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td>V600Lys/Val</td>
<td>0 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td>V600Lys/Val</td>
<td>0 patients</td>
<td>0 patients</td>
</tr>
</tbody>
</table>

Table 3: Details of response
Logical NEXT Step:

SRS alone
plus
Dabrafenib
Combined with
Tramitinib

Conclusions

- Patients with brain metastases are living longer
- SRS alone will be the standard of care for all patients as we learn more and more that WBRT is toxic to memory and QOL
- New targeted melanoma agents can penetrate the BBB
  - Duration of response questionable
  - Treat gross disease with SRS and use the drug to enhance both the SRS effect and control micro-metastatic brain metastases to reduce the distant brain relapse