Landmark Trials in Brain Metastasis

Dr Tanweer Shahid
Apollo Hospital, Kolkata
RTOG devised 3 prognostic groups using RPA based on 1200 patients treated on prospective clinical trials.
Purpose of GPA is to identify significant diagnosis-specific prognostic factors in an updated era (1985-2007) as compared with the RTOG RPA

Era of Graded Prognostic Assessment

Summary Report on the Graded Prognostic Assessment: An Accurate and Facile Diagnosis-Specific Tool to Estimate Survival for Patients With Brain Metastases

Paul W. Sperduto, Norbert Kased, David Roberge, Zhiyuan Xu, Ryan Shanley, Xianghua Luo, Penny K. Sneed.

CRITERIA
- Age
- KPS
- Number of brain metastasis
- Presence or absence of extracranial metastasis

SCORE
- Each criteria given a score of 0, 0.5, and 1

<table>
<thead>
<tr>
<th>GPA score†</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>≥80</td>
<td>50~59</td>
<td>&lt;50</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70~80</td>
<td>90~100</td>
</tr>
<tr>
<td>Number of lesions</td>
<td>&gt;3</td>
<td>2~3</td>
<td>1</td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>Present</td>
<td>-</td>
<td>None</td>
</tr>
</tbody>
</table>
Median survivals stratified by diagnosis and DS-GPA score for patients with newly diagnosed brain metastases.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overall median survival (mo)</th>
<th>Diagnosis-specific GPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GPA: 0-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median survival (mo)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>7.0</td>
<td>3.0</td>
</tr>
<tr>
<td>SCLC</td>
<td>4.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Renal cell</td>
<td>9.6</td>
<td>3.3</td>
</tr>
<tr>
<td>GI</td>
<td>5.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Breast</td>
<td>13.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Total</td>
<td>7.2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Gl, gastrointestinal; GPA, graded prognostic assessment; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.
LESSONs from HISTORY
When you find them SINGLE...

Single Metastases

WBRT with or w/o Surgery
1. Patchell RA, NEJM, 1990
2. Vecht CJ et al.
3. Mintz et al.

Surgery with or w/o WBRT
1. Patchell RA, JAMA 1998
EORTC Kocher et al, JCO, 2011
Christopher et al, Neuro Onco, 2010
SURGERY FOLLOWED BY WBRT
Vs
WBRT ALONE

SURGERY + WBRT is better than WBRT alone

- NEJM 1990
- ANNALS OF NEUROLOGY 1993
- CANCER 1996
SURGERY FOLLOWED BY WBRT Vs SURGERY ALONE

JAMA 1998

JCO 2011

NEURO ONCO 2010
Single Lesion

Surgery
- Lesion > 4cm
- Mass effect

SRS
- No mass effect
- Eloquent areas
- Lesion <4cm
- Unwilling for Sx
- Medically inoperable/unfit

Surgery Vs SRS
- No high quality RCT comparing Surgery Vs SRS in single mets.
- Most studies comparing Surgery Vs SRS report similar outcomes.
- They are Non-RCT & may be affected by selection bias (class IIIb).
After Surgical Resection for single mets...

What to give???

WBRT or SRS to surgical cavity...

- WBRT is the standard of care to improve intracranial control following resection.

- SRS to the surgical cavity: Used to reduce cognitive toxicity.

- High-level comparative data lacking.

- SRS on survival and cognitive outcomes compared with WBRT in patients with resected brain metastasis.
After resection of a brain metastasis, SRS should be considered one of the standards of care as a less toxic alternative to WBRT.
SURGERY FOLLOWED BY SRS Vs SURGERY ALONE

- SRS of the surgical cavity for 1, 2, or 3 metastases lowers local recurrence compared to observation.

- SRS after brain metastasis resection could be an alternative to WBRT.
What do we learn from these 2 trials? (Brown et al & Mahajan et al)

- Surgery alone is inadequate t/t.
- Surgery + WBRT is probably too much given the toxicities.
- SRS is a balance between preservation of neurocognition / QOL and improved intracranial tumor control.
- SRS is a reasonable postoperative t/t for resected brain metastases and a good trade-off between surgery alone and surgery + WBRT.

- The local control rates were lower than expected.
- Possible reasons:
  1. Low BED delivered, especially for larger cavities
  2. Surgical tract not included
  3. Radiation necrosis vs. progression
<table>
<thead>
<tr>
<th>Size of lesion</th>
<th>Maximum Tolerated Dose (MTD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2cm</td>
<td>24 Gy</td>
</tr>
<tr>
<td>2.1 – 3 cm</td>
<td>18 Gy</td>
</tr>
<tr>
<td>3.1 – 4 cm</td>
<td>15 Gy</td>
</tr>
</tbody>
</table>

- Radiation Necrosis (RN) is the dose limiting toxicity.
- V10 and V12 are the predictive factors for RN.
(SURGICAL CAVITY + 2 mm) VOLUME

<table>
<thead>
<tr>
<th>Volume</th>
<th>SRS Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.2 cc</td>
<td>20 Gy</td>
</tr>
<tr>
<td>4.2–7.9 cc</td>
<td>18 Gy</td>
</tr>
<tr>
<td>8.0–14.3 cc</td>
<td>17 Gy</td>
</tr>
<tr>
<td>14.4–19.9 cc</td>
<td>15 Gy</td>
</tr>
<tr>
<td>20.0–29.9 cc</td>
<td>14 Gy</td>
</tr>
<tr>
<td>≥30 cc</td>
<td>12 Gy</td>
</tr>
</tbody>
</table>

Volume of target (Surgical cavity + 1 mm) | SRS Dose
-----------------------------------------|---------
≤ 10 cc                                  | 16 Gy   |
10.1 – 15 cc                             | 14 Gy   |
> 15 cc                                  | 12 Gy   |

Organ                                      | Dose constraint
-------------------------------------------|----------------
Brainstem                                  | 1 cc < 12 Gy
Optic Nv & Tract                           | Max <9 Gy
Journey Continues...
Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

**WBRT + SRS**

- Better local control and performance status (i.e. functional autonomy, KPS) at 6 months
- Survival advantage only in patients with single metastasis (6.5 mo vs 4.9 mo).
Secondary Analysis of RTOG 9508, a Phase 3 Randomized Trial of Whole-Brain Radiation Therapy Versus WBRT Plus Stereotactic Radiosurgery in Patients With 1-3 Brain Metastases; Poststratified by the Graded Prognostic Assessment (GPA)

Prognostication is the key!!!
## Can we do away with WBRT for limited Brain metastasis?

<table>
<thead>
<tr>
<th>Study</th>
<th>LC at 1 yr (%)</th>
<th>OS (months)</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LC at 1 yr (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JROSG – 99-1</td>
<td>72.5</td>
<td>8.0</td>
<td>Better LC with SRS+WBRT</td>
</tr>
<tr>
<td>Aoyama et al (JAMA 2006)</td>
<td>88.7</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>(p =0.002)</td>
<td>(p=0.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDAC</td>
<td>67</td>
<td>15.2</td>
<td>No OS benefit with addition of WBRT</td>
</tr>
<tr>
<td>Chang et al (Lancet 2009)</td>
<td>100</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>(p =0.012)</td>
<td>(p=0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 22952-26001</td>
<td>69</td>
<td>10.7</td>
<td>Higher HRQOL in SRS alone arm</td>
</tr>
<tr>
<td>Kocher et al (JCO 2011)</td>
<td>81</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>(p =0.04)</td>
<td>(p=0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLIANCE – NCCTG – N0574</td>
<td>72.8</td>
<td>10.4</td>
<td>Decline in immediate &amp; delayed recall, verbal fluency, executive functioning in WBRT arm</td>
</tr>
<tr>
<td>Brown et al (JAMA 2016)</td>
<td>90.1</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(p=0.92)</td>
<td></td>
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</tbody>
</table>

**What kills earlier??**
1 – 4 Brain metastasis: Meta Analysis
SRS with WBRT Vs SRS ALONE

Clinical Investigation
Phase 3 Trials of Stereotactic Radiosurgery
With or Without Whole-Brain Radiation Therapy
for 1 to 4 Brain Metastases: Individual Patient
Data Meta-Analysis
Arjun Sahgal, MD,* Hidefumi Aoyama, MD, PhD,† Martin Kocher, MD,‡
Binod Neupane, PhD,§ Sandra Collette, PhD,‖ Masao Tago, MD,¶
Prakesh Shah, MD,* Joseph Beyene, PhD,§ and Eric L. Chang, MD** † ‡

< 50 years age:
• Survival advantage for SRS alone
• Distant brain relapse rates not affected by SRS alone

> 50 years age:
• No difference in survival
• Distant Brain failure: Risk decreased in WBRT
The Startup Journey Continues
Use of SRS: (3 Groups)
- With 1,
- 2 to 4 or
- 5 to 10 brain metastases.

Result:
- Similar OS
- Similar t/t related toxicity between groups with 2 to 4 & 5 to 10 mets.

Cumulative volume of metastases, rather than the number is important.
- SRS is suitable alternative for patients up to 10 brain metastases.
SRS for > 4 brain mets: An upcoming strategy

Conclusion:

• MMSE score maintenance comparable.

• Post-SRS complication comparable.

• SRS alone for patients with 5 to 10 mets. Vs 2 to 4 mets. is doable.
Why FSRS?

- **Toxicity**
  - Single session SRS dose is limited by tumor size
  - Fractionation allows for repair/recovery of radiation effects in the normal tissue
  - Use stereotactic techniques to spare dose to normal tissue
  - Reirradiation
- **Tumor control**
  - Able to give a higher cumulative dose to larger tumors/target volumes
- **Image guided frameless RT utilizing radiosurgical margins to minimize toxicity and maximize tumor control**
## FSRS – WHEN ? WHY ?

<table>
<thead>
<tr>
<th></th>
<th>Single #</th>
<th>Multi #</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr Local control</td>
<td>77 %</td>
<td>91 %</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Recurrence</td>
<td>25</td>
<td>11</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Radionecrosis</td>
<td>20 %</td>
<td>8 %</td>
<td>P = 0.004</td>
</tr>
<tr>
<td>1 yr Radionecrosis</td>
<td>18 %</td>
<td>9 %</td>
<td>P = 0.01</td>
</tr>
</tbody>
</table>

### CONCLUSIONS:
- Multifraction SRS: Effective t/t modality for large brain metastases.
- Better local control & reduced risk of radiation-induced radionecrosis. (Compared with Single Fraction-SRS).
**DOSE FOR FSRS**

- **BED** should be more than $\geq 48$ Gy
  - 30Gy in 5 fractions.
  - 27Gy in 3 fractions.
WBRT: What”s the indication???

**EANO**

- WBRT or best supportive care should be considered for patients with:
  - Short life expectancy
  - Low KPS score.
  - Progressive systemic disease.

- When employing initial WBRT, a monitoring of cognitive functions with specific batteries is recommended

**ASTRO**

- Poor life expectancy (less than 3 months).

- Use of WBRT may or may not significantly improve symptoms from brain metastases.

- Comfort measures only, or short course (20 Gy in 5 daily fractions) WBRT, is reasonable option.
WBRT + optimal supportive care vs Optimal Supportive care alone

Add life to your days, not days to your life
Does WBRT work in all???
Can WBRT be avoided in some patients???

Benefit of WBRT in RPA 3 patients is questionable...
• Standard fractionation: (30 Gy in 10 fractions or 20 Gy in 5 fractions).

• No differences in OS or symptom control with 30 Gy in 10 daily fractions or 20 Gy in 5 daily fractions.

• Others: 37.5 Gy in 15 daily fractions and 40 Gy in 20 daily (or twice daily) fractions.
Don’t routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.

### Pros & Cons

**Adjuvant WBRT + SRS:**
- No OS benefit (Especially in pt. with Good PS)
- Diminished cognitive function

**SRS alone:**
- Importance of Surveillance
- More risk of Distant brain failure
- Better QoL without OS compromise
Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tome, Chip Caine, Ben Corn, Andrew Kanner, Howard Rowley, et al.

**Objectives**
- Cognitive Decline assessed by HVLT-R DR (Hopkins Verbal Learning Test–Revised, Delayed recall)
- QOL assessment

**Test Arm**
- Brain mets 5 mm away from Hippocampus
- Primary Solid tumors except SCLC/GCT
- RTOG RPA class I or II

**Historical Control**
- Matched eligibility criteria
- Control arm of the PCI-P-120-9801 phase III trial

**Results**
- HA-WBRT associated with significant memory preservation
- Mean relative decline in HVLT-R DR from baseline to 4 months: 7% for HA vs 30% for standard, p= .001
- Cognitive decline greater with ↑age, ↑D100% of Hippocampus, previous neurological symptoms
- QOL preserved with HA-WBRT
- Risk of developing brain mets in the HA region → low

**Conclusion**
- HA-WBRT can be safely delivered for brain mets
- Hippocampal neural stem-cell niche is central to RT-induced memory decline

**Preservation of Memory With Conformal Avoidance of Hippocampal Neural Stem-Cell Compartment During WBRT for Brain Mets - RTOG 0933**

- Hippocampal neural stem-cell injury during WBRT → may play a role in memory decline.
- IMRT to avoid hippocampus → may yield clinically significant neurocognitive benefit.
Hippocampal avoidance (HA) - WBRT, to preserve cognition.

Baseline evaluation
- MRI Brain, Cognitive tests, QoL, Symptom burden

WBRT: 30 Gy / 10 #

HA-WBRT + Mem (N-261)

WBRT + Mem (N-257)

R

Risk of cognitive failure => significantly lower
↓ deterioration in
  • executive function at 4 m
  • Learning and memory at 6 m

1° End Point:
Time to Cognitive Function Failure,

2° End Points:
OS, Intracranial PFS, Toxicity, & Patient-Reported Symptom Burden

Evaluated @ 2 m, 4 m, 6 m and 12 m
Med F.U. 7.9 m (for alive pts)

No significant difference in
- OS, intracranial PFS, or toxicity.
@ 6 m: Pt reported symptom burden ↓

CONCLUSION:
HA-WBRT + Memantine
- better preserves cognitive function and patient-reported symptoms,
- with no difference in intracranial PFS and OS
⇒ Should be considered a Standard of Care for pts with
  ✓ good PS &
  ✓ no mets in the HA region
Let’s Summarise
Take Home Message:

- Prognostication is the key.
- (Age, KPS, Extracranial control, Primary ds…) – Choose wisely.

Number of lesion:

- Single:
  - Without mass effect: SRS alone no compromise in OS
  - With Mass effect: Sx -> SRS +/- WBRT; if not resectable SRS +/- WBRT
  - FSRS is another option if volume is big.
Take Home Message:

- Oligo / Limited: 1 – 3 or 1 – 4 or 5 – 10...

- Multiple:
  - WBRT + SRS boost
  - WBRT Hippocampal sparing
  - WBRT alone

- Volume of Metastatic lesion(s).

- SRS Dose: Lesser the volume – Higher the dose
Take Home Message:

SRS alone:
- Better Neurocognitive function / Better QOL
- Risk of distant brain failure is high
- Increased requirement of surveillance and salvage t/t

FSRS: For Larger Volume disease to prevent RN

WBRT: Poor KPS and poorly controlled disease,

Future direction:
- WBRT hippocampal sparing with SIB vs SRS alone
- WBRT with Memantine (To preserve neurocognition)
Acknowledgement:
- Dr Mukti Mukherjee
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- Dr Jibak Bhattacharya
- Dr Riddhijyoti Talukdar
- Dr Asesh Samanta
- Dr Chandrasekhar