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Ankara Memorial Hastanesi
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İSTANBUL
Focal Management of Large Brain Metastases and Risk of Leptomeningeal Disease

Marcrom SR, Foreman PK, McDonald AM, Riley KO, Guthrie BL, Markert JM, Wiley CD, Bredel M, Fiveash JB

University of Alabama at Birmingham
Study Rationale & Objective

• Brain metastases are increasingly managed with postoperative cavity SRS with risk of leptomeningeal disease (LMD) recurrence

• Fractionated stereotactic radiotherapy (FSRT) is an effective means of more safely providing definitive treatment for large brain metastases as compared to single fraction SRS
Study Rationale & Objective

• The purpose of this study was to define the rate of LMD progression and local control in large brain metastases managed with either Surgery + SRS vs FSRT
Study Design

• Single institutional retrospective analysis

• All brain metastases patients, with lesions ≥ 3 cm, treated between 2004-2017, with some follow up and treatment by either:
  • Surgery + SRS
  • FSRT (25-30 Gy in 5 fractions)

• Endpoints
  • Local failure: new nodular enhancement within 5 mm to surgical cavity or > 25% increase in solid tumor diameter
  • Leptomeningeal disease: new meningeal enhancement > 5 mm from index lesion
Results

- 122 patients with 125 eligible metastases
- **Surgery + SRS:** 82 patients
- **FSRT:** 40 patients (43 tumors)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>122</td>
</tr>
<tr>
<td>Number of Tumors</td>
<td>125</td>
</tr>
<tr>
<td>Sex (Male : Female)</td>
<td>63 : 59</td>
</tr>
<tr>
<td>Median Age in Years (Range)</td>
<td>59 (26-83)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>NSCLC (%)</td>
<td>59 (47%)</td>
</tr>
<tr>
<td>Breast (%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Melanoma (%)</td>
<td>20 (16%)</td>
</tr>
<tr>
<td>GI (%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>Renal (%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Median KPS (Range)</td>
<td>80 (50-100)</td>
</tr>
<tr>
<td>Median GPA (FSRT)</td>
<td>1.5</td>
</tr>
<tr>
<td>Median GPA (Surg + SRS)</td>
<td>2.5</td>
</tr>
<tr>
<td>Median DS-GPA (FSRT)</td>
<td>2.0</td>
</tr>
<tr>
<td>Median DS-GPA (Surg + SRS)</td>
<td>3.0</td>
</tr>
<tr>
<td>Median Tumor Diameter (FSRT)</td>
<td>3.67 cm</td>
</tr>
<tr>
<td>Median Tumor Diameter (Surg + SRS)</td>
<td>4.23 cm</td>
</tr>
</tbody>
</table>

*p<0.001
p=0.001
Results

• Median follow up 7 months
• Increased LMD failure
  Surgery + SRS vs FSRT
  (12 mo 45% vs 19%,
  p=0.044)
Results

- No difference in LC between Surgery + SRS vs FSRT (12 mo 70% vs 69%, p=0.770)
Results

No difference in high grade toxicity or overall survival

\[
\text{p} = 0.229
\]

\[
\text{p} = 0.302
\]
Authors’ Conclusions

• Patients with large (>3 cm) brain metastases have an increased risk for leptomeningeal disease after surgery + SRS vs FSRT

• Because leptomeningeal disease after surgery + SRS is higher but achieves similar OS and toxicity vs FSRT

FSRT may be a preferred strategy for these patients
Comments

• **Strengths:**
  - Fairly strong number of uniformly treated patients
  - Explores consequences of current practices in light of evolving management away from WBRT

• **Limitations:**
  - Retrospective study, limited follow up (albeit great by historic standards)
  - LMD is still disease/CNS failure, arguably an inferior clinical outcome

• **Future direction:**
  - This provides representative data to support options in management of large brain metastases
  - Surgery + fractionated RT to tumor bed should be explored as another local therapy option
Implications of HER2 status on local control and adverse effects after SRS for breast cancer brain metastases

J Chan, Y Yu, SE Braunstein, JL Nakamura, SE Fogh, L Ma, PV Theodosopoulos, MW McDermott, PK Sneed
University of California, San Francisco
Study Objective

• Conflicting information exists on the significance of Her2 status and clinical outcomes for patients with metastatic breast cancer and brain metastases

• This study sought to evaluate the implications of HER2 status on freedom from progression (FFP) and risk of adverse radiation effects (ARE) among patients with brain metastases from breast cancer treated with SRS
Study Design

• Retrospective single institutional experience

• All breast cancer brain metastases treated between 1998-2013 with Gamma Knife SRS, solid tumors (no cavities), have some imaging and clinical follow up data

• Primary endpoints: freedom from progression (FFP) and adverse radiation events (ARE)
Results

- 204 breast cancer patients
- 1314 brain metastases: 578 new, 736 recurrent
- 43% HER2 positive
- Within one month of SRS:
  - Trastuzumab (91%)
  - Lapatinib (12%)
- Median imaging follow up 9.0 months
Results

FFP inferior for Her2+ metastases

ARE equivalent by Her2+ status

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Results

HER2pos status associated with worse FFP for both ERpos and ERneg brain mets

ERpos

\[ p < 0.0001 \]

ERneg

\[ p = 0.048 \]
Results

Tumor size by quadratic mean diameter (QMD)

Example:

\[ QMD = \sqrt{\frac{1.7^2 + 1.5^2 + 1.6^2}{3}} = 1.6 \text{ cm} \]

Larger lesions treated with lower SRS dose

SRS dose correlates with ↑FFP and ↑ARE

Chan ASTRO 2017
Authors’ Conclusions

• Her2+ brain metastases in breast cancer have an inferior tumor control after SRS as compared to Her2- brain metastases
• Adverse radiation effects are low regardless of Her2 status
• More aggressive therapy should be considered for breast cancer patients with Her2+ brain metastases
Comments

• **Strengths:**
  - Nearly half of patients were Her2+ with large overall number of cases
  - Rigorous determination of tumor volume by QMD which is more valuable than single 2D measurement

• **Limitations:**
  - Retrospective study with biased dose selection
  - Findings are in contrast to other studies demonstrating superiority of Her2+ patient outcomes
  - Her2 and other molecular profile are not necessarily conserved in metastases

• **Future directions:**
  - These data are inconclusive, larger scale prospective studies with consideration of dynamic molecular status should be factored
Phase 1 study of spinal cord constraint relaxation with single session spine stereotactic radiosurgery in the primary management in patients with inoperable, previously unirradiated metastatic epidural spinal cord compression


University of Texas, MD Anderson Cancer Center
Background

- Primary spinal stereotactic radiosurgery (SSRS) achieve 1 year local control rates of ~90%
- Up to 60% of failures involve the epidural space or posterior vertebral body
  - Cord constraints limit adequate dose delivery to gross disease
- Spinal cord constraints vary from institution to institution while myelopathy rates are generally <1%
Background

• Strategies to improve local control in those with epidural disease
  • Vertebrectomy
  • Separation surgery
  • Laser interstitial thermotherapy

• Role of SSRS in patients with inoperable epidural disease unclear
Study Purpose

• To assess the safety of relaxing spinal cord dose constraint to improve therapeutic management of metastatic epidural spinal cord compression (MESCC)
Study Design

• Prospective phase I clinical trial
• MESCC, thoracic spine, no prior history of RT at site
• Inoperable: medical comorbidities, patient refusal, neurosurgical evaluation
• Single fraction SSRS delivered (18-24 Gy)
• Clinical/radiographic assessments every 3 months
Study Design

• Begin with cord Dmax dose of 10 Gy
• If no tumor progression (TP), no dose escalation
• If TP occurs, then escalate with 2 Gy increments
• If radiation myelopathy (RM) occurs and exceeds TP occurrences (and >1 RM event), then accrual stopped
• Hard study cord Dmax 16 Gy
# Patient Characteristics

<table>
<thead>
<tr>
<th>Histology</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>11</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Bowel</td>
<td>3</td>
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<tr>
<td>Breast</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Total</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (yr)</td>
<td>62.7</td>
</tr>
<tr>
<td>KPS, median</td>
<td>90</td>
</tr>
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</table>
Metastatic Epidural Spinal Cord Compression (MESCC) Scale

Grade 0: bone only
Grade 1a: epidural impingement
Grade 1b: thecal sac deformation
Grade 1c: thecal sac deformation with cord abutment
Grade 2: cord compression
Grade 3: cord compression with no CSF visible around the cord

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# Patient Characteristics

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<thead>
<tr>
<th>Characteristic</th>
<th>1A</th>
<th>2</th>
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<tbody>
<tr>
<td>ESCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1B</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>1C</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>BPI Worst Pain</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>BPI Mean Pain Interference</td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>MDASI Mean Pain Severity</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>MDASI Mean Interference</td>
<td></td>
<td>1.7</td>
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</table>

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# Treatment

<table>
<thead>
<tr>
<th>Prescription Dose</th>
<th>18 Gy</th>
<th>17</th>
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<tr>
<td></td>
<td>24 Gy</td>
<td>15</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cord Dmax</th>
<th>10 Gy</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>12 Gy</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>14 Gy</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>16 Gy</td>
<td>8</td>
</tr>
</tbody>
</table>
### One Fraction

<table>
<thead>
<tr>
<th>Serial Tissue</th>
<th>Volume</th>
<th>Volume Max (Gy)</th>
<th>Max Point Dose (Gy)**</th>
<th>Endpoint (≥Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Pathway</td>
<td>&lt;0.2 cc</td>
<td>8 GY</td>
<td>10 GY</td>
<td>neuritis</td>
</tr>
<tr>
<td>Cochlea</td>
<td></td>
<td></td>
<td>9 GY</td>
<td>hearing loss</td>
</tr>
<tr>
<td>Brainstem (not medulla)</td>
<td>&lt;0.5 cc</td>
<td>10 GY</td>
<td>15 GY</td>
<td>cranial neuropathy</td>
</tr>
<tr>
<td>Spinal Cord and medulla</td>
<td>&lt;0.35 cc</td>
<td>10 GY</td>
<td>14 GY</td>
<td>myelitis</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2 cc</td>
<td>8 GY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)</td>
<td>&lt;10% of subvolume</td>
<td>10 GY</td>
<td>14 GY</td>
<td>myelitis</td>
</tr>
<tr>
<td>Cauda Equina</td>
<td>&lt;5 cc</td>
<td>14 GY</td>
<td>16 GY</td>
<td>neuritis</td>
</tr>
</tbody>
</table>

### Three Fractions

<table>
<thead>
<tr>
<th>Serial Tissue</th>
<th>Volume</th>
<th>Volume Max (Gy)</th>
<th>Max Point Dose (Gy)**</th>
<th>Endpoint (≥Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Pathway</td>
<td>&lt;0.2 cc</td>
<td>15.3 GY</td>
<td>17.4 GY</td>
<td>neuritis</td>
</tr>
<tr>
<td>Cochlea</td>
<td></td>
<td></td>
<td>14.4 GY</td>
<td>hearing loss</td>
</tr>
<tr>
<td>Brainstem (not medulla)</td>
<td>&lt;0.5 cc</td>
<td>15.9 GY</td>
<td>23.1 GY</td>
<td>cranial neuropathy</td>
</tr>
<tr>
<td>Spinal Cord and medulla</td>
<td>&lt;0.35 cc</td>
<td>15.9 GY</td>
<td>22.5 GY</td>
<td>myelitis</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2 cc</td>
<td>13 GY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Subvolume (5-6 mm above and below level treated per Ryu)</td>
<td>&lt;10% of subvolume</td>
<td>18 GY</td>
<td>22.5 GY</td>
<td>myelitis</td>
</tr>
<tr>
<td>Cauda Equina</td>
<td>&lt;5 cc</td>
<td>21.9 GY</td>
<td>25.5 GY</td>
<td>neuritis</td>
</tr>
</tbody>
</table>
Results

• 28/32 evaluable patients
• 1 yr local control: 80.5%
• Median clinical follow-up: 17.2 months
• No cases of radiation myelopathy
• Cord Dmax 16 Gy cohort
  • N=8
  • Median follow-up 15.4 months
  • No cases of radiation myelopathy
SSRS T11 – 24 Gy in 1 fx
Authors’ Conclusions

• Selective spinal cord dose escalation may be a reasonable strategy in inoperable patients with epidural disease undergoing SSRS

• Spinal cord Dmax of up to 16 Gy delivered to 0.01 cc in high risk patients risk patients appears safe
Comments

• **Strengths:**
  - High quality treatment performed at a center of excellence for spine SRS
  - Rigorous criteria in tumor definition and treatment guidelines

• **Limitations:**
  - Insufficient follow up to provide certainty of long-term safety
  - Does not factor potential added effect of systemic therapies

• **Future directions:**
  - Prospective investigation, longer follow up
  - Consider narrowing optimal tumor dose - 18 vs 24 Gy very discrepant with other associated concerns such as vertebral compression fracture
Imaging-based outcomes for 24 Gy in 2 daily fractions for patients with de novo spinal metastases treated with spine stereotactic body radiation therapy: An emerging standard

Chia-Lin Tseng, Mikki Campbell, Hany Soliman, Sten Myrehaug, Mark Ruschin, Young K. Lee, Eshetu Atenafu, Arjun Sahgal

Sunnybrook Health Sciences Centre
University of Toronto
Background

• Spine stereotactic body radiotherapy (SBRT) is increasing employed but without consensus of fractionation scheme
  • Common practices: 18-24Gy/1, 24Gy/2, 24-30Gy/3, 30Gy/4, 30-40Gy/5
• Single fraction SRS (>20Gy per fraction) has been associated with high vertebral compression fracture (VCF) rates up to 39%

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Study Objective

• To report mature outcomes for spinal metastases with no prior radiation exposure treated with 24 Gy in 2 daily SBRT fractions
Study Design

• 279 de novo spinal metastases in 145 consecutive patients treated with 24 Gy in 2, SBRT

• Surveillance with a spine MRI at 2-4 month intervals
Results

Patient & Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 279 vertebral segments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>70 (25.1%)</td>
</tr>
<tr>
<td>Breast</td>
<td>68 (24.4%)</td>
</tr>
<tr>
<td>Lung</td>
<td>47 (16.8%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>43 (15.4%)</td>
</tr>
<tr>
<td>Others</td>
<td>51 (18.3%)</td>
</tr>
<tr>
<td><strong>Spine Location</strong></td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>32 (11.5%)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>150 (53.8%)</td>
</tr>
<tr>
<td>Lumbar</td>
<td>74 (26.5%)</td>
</tr>
<tr>
<td>Sacrum</td>
<td>23 (8.2%)</td>
</tr>
<tr>
<td><strong>Epidural Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84 (30.1%)</td>
</tr>
<tr>
<td>No</td>
<td>195 (69.9%)</td>
</tr>
<tr>
<td><strong>Paraspinal Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>106 (38.0%)</td>
</tr>
<tr>
<td>No</td>
<td>173 (62.0%)</td>
</tr>
<tr>
<td><strong>Median Follow-up</strong></td>
<td>15.1 months (range 0.1–71.6 months)</td>
</tr>
</tbody>
</table>
Results: Local Failure

Local failure at 1yr 9.7%, 2yr 17.6%

Higher grade of epidural compression associated with increased failure
Results: Overall Survival

Overall survival at 1yr 73%, 2yr 61%

Survival prognostic by histology

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Results: Toxicity

- 1-year cumulative incidence VCF: 8.5%
- 2-year cumulative incidence VCF: 13.8%
- No cases of radiation myelopathy/radiculopathy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Misalignment (SINS)</td>
<td>2.377</td>
<td>0.0121</td>
</tr>
<tr>
<td>Lytic Bone Lesion (SINS)</td>
<td>11.966</td>
<td>0.0143</td>
</tr>
<tr>
<td>Mixed (lytic/blastic) Bone Lesions (SINS)</td>
<td>11.341</td>
<td>0.0214</td>
</tr>
<tr>
<td>PTV D90</td>
<td>1.209</td>
<td>0.0085</td>
</tr>
</tbody>
</table>

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Authors’ Conclusions

• Spine SBRT delivered using the fractionation scheme of 24Gy in 2 daily fractions is safe and effective in achieving high tumor control rates in de novo spinal metastases

• Grade of epidural disease is a significant predictor of LC
  • Underscores the importance of patient selection and potential role of separation surgery to downgrade disease prior to SBRT

• Prognosis is associated with primary histology of malignancy

• Predictors of VCF: spinal misalignment, lytic/mixed disease, and PTV D90
Ongoing Study: Canadian SC.24

Patients with tumours (excluding seminoma, small cell lung cancer and metastases from hematologic malignancies - e.g. lymphoma, myeloma) who have MRI-documented spinal metastases, suitable for receiving radiation therapy, and fulfill the following criteria:

- Pain secondary to spinal metastases requiring treatment
- \( \leq 3 \) consecutive spinal segments involved by tumour to be included in the target volume

Primary Endpoint - Phase III

The primary objective of the phase III study is to assess complete pain response in the treatment area at 3 months post-radiation.

**ARM 1**
Standard Conventional Radiotherapy (CRT)**
20 Gy in 5 fractions

**ARM 2**
Stereotactic Body Radiotherapy (SBRT)**
24 Gy in 2 fractions

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Comments

• **Strengths:**
  • Better quality data than true retrospective study, these data were obtained from a prospectively collected database

• **Limitations:**
  • Not a true prospective study
  • No specification of cord constraint provided

• **Future Directions:**
  • SC.24: Phase 3 randomized trial of spine SBRT as 24 Gy/2 fx vs 20 Gy/5 fx (BUT these are inherently markedly different in intensity)
  • Additional prospective studies with longer follow up and exploration of other fractionation schemes
TEŞEKKÜRLER..