Spine SBRT: A Clinician's Update On Techniques and Outcomes

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Disclosures

- I have no relevant financial or personal relationships/circumstances/conflicts of interest to disclose

Outline

- Spinal Metastases
- Spine Conventional EBRT
- Spine SBRT
  - Indications/Rationale
  - Technical Considerations
  - Principles of Target Delineation
  - Overview of Outcomes Data
  - Toxicity Avoidance
  - Patterns of Failure
  - Response Assessment
Spinal Metastases

- **Uncomplicated spine metastases**
  - Tumor contained within bone
  - Normal spinal alignment and no fracture
  - Pain that is not positional
  - 5% can progress to MESCC or fracture

- **Complicated spine metastases**
  - Mechanical instability
  - Bulky “Mass” type tumors
  - MESCC
    - Surgical candidates

Bilsky Epidural Spinal Cord Compression (ESCC) Grading Scale

Spinal Instability Neoplastic Score (SINS)
Conventional EBRT (cEBRT)

De-novo cEBRT

- Overall pain response rate ~60%, complete response ~23%
- Imaging-based LC range from 61-86%, but as low as 46% for mass-type tumors at 1 year


cEBRT Re-irradiation: SC.20 multi-center RCT
SC.20 Results

<table>
<thead>
<tr>
<th>Intention-to-treat analysis</th>
<th>Per-protocol analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Efficacy</td>
</tr>
<tr>
<td>80 Gy/10 fractions vs. 80 Gy/5 fractions</td>
<td>80 Gy/10 fractions vs. 80 Gy/5 fractions</td>
</tr>
<tr>
<td>Overall response (CR+PR)</td>
<td>80 Gy/10 fractions vs. 80 Gy/5 fractions</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>80 Gy/10 fractions vs. 80 Gy/5 fractions</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>80 Gy/10 fractions vs. 80 Gy/5 fractions</td>
</tr>
</tbody>
</table>

80 Gy/10 non-inferior to 80 Gy/5 and less toxic; however, findings not robust in per-protocol analysis, and tradeoffs between efficacy and toxicity must be considered.


Spine SBRT


Spine SBRT Indications

<table>
<thead>
<tr>
<th>Symptom</th>
<th>ECOG 0-2</th>
<th>ECOG ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardinal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Symptom compression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Radiculopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Scoliosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Paraplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Pseudocysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Metastases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic: Card compression or cauda equina syndrome.
Why Spine SBRT?

- Common doses used in spine SBRT vs. cEBRT

<table>
<thead>
<tr>
<th>Total Dose (Gy)</th>
<th>Dose/Fraction (Gy)</th>
<th>Fractions</th>
<th>Biological Equivalent (GyRBE)</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>24</td>
<td>1</td>
<td>84.4</td>
<td>SBRT</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
<td>2</td>
<td>51.0</td>
<td>SBRT</td>
</tr>
<tr>
<td>27</td>
<td>9</td>
<td>3</td>
<td>51.0</td>
<td>SBRT</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>1</td>
<td>50.4</td>
<td>SBRT</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>5</td>
<td>48.0</td>
<td>SBRT</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>5</td>
<td>46.2</td>
<td>SBRT</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>5</td>
<td>45.0</td>
<td>SBRT</td>
</tr>
</tbody>
</table>

- Represents 2-6x tumor BED as compared to palliative cEBRT

Technical Considerations

- How do you do it?
- And do it safely?

Technical Considerations at the University of Toronto

- Near rigid-body immobilization
  - Ex. BodyFIX
- Treatment Planning
  - CT Sim: 1mm slice thickness
  - MPR: volumetric T1/T2 axial for fusion
  - IMRT/VMAT
- Delivery
  - 4 mm MLC
  - IGRT
    - CBCT: pre/intra/post
    - Conformal threshold: 1 mm and 1 degree
  - Rotation Corrections
  - Hexapod robotic couch (6 dof of freedom)
Intra-fractional Motion

Reproducibility of patient positioning during treatment delivery within 1.2mm and 0.9° with 95% confidence
PRV 1.5mm; PTV 2mm

Principles of Target Volume Delineation

Epidural CTV Cranio-Caudal Extension

5mm CTV cranio-caudally beyond visible disease within the canal excluding spinal cord
Epidural Disease and Dose Distribution

Multi-Institutional De-Novo SBRT Outcomes

Kaplan Meier
12-month OS: 64.9%
12-month LC: 89.9%
Sunnybrook Experience: 24Gy/2

- LC @ 1 year: 90.3%
- LC @ 2 years: 82.4%

De-novo SBRT Pain Relief Outcomes

Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1-2 trial

Stereotactic body radiation therapy (SBRT) is increasingly used to manage spinal metastases, yet its role in effectively controlling local lesions of spinal metastases has not been well described. This study investigated the clinical benefit of SBRT for managing spinal metastases and reducing pain-related symptoms.

Methods: 148 patients with mechanically stable, non-cord-compressing spinal metastases were given SBRT in a phase 1-2 study. Patients received a total dose of 24 Gy in three fractions.

De-novo SBRT Pain Relief Outcomes
Re-irradiation Example Case

- 72M metastatic early castrate resistant prostate ca with multi-level mets to C+T spine treated with conventional RT 20Gy/5 C4-T4

At initial cEBRT 12 months later

Re-irradiation Example Case

- Right arm paresthesia; Bilsky 1B; SINS 7
- ECOG 1

Prospective Re-irradiation SBRT Outcomes

Prospective Evaluation of Spinal Reirradiation by Using Stereotactic Body Radiation Therapy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neurological</th>
<th>Hematological</th>
<th>Gastrointestinal</th>
<th>Other Toxicity (except grade)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 1: Tumor progression for all cases is shown.
Re-irradiation Stereotactic Body Radiotherapy for Spinal Metastases: A Multi-Institutional Outcome Analysis

Ahmed H. Hashim, MD; Matthias Guckenberger, MD; Ron Kaseh, MD; Peter C. Granstein, MD; Frederik Blanquet, MD; Iryna B. Khilko, MD; John D. Fleckinger, MD; John H. Shin, MD; Daniel K. Fakler, MD; Bruna Worey, PhD; Anne On, MD; B.C.; John Chiu, PhD; MD; Daniel Leotouwaz, PhD; Jason Shreath, MD, PhD; and Aryan Sahgal, MD

Kaplan-Meier 12-Month OS: 64%
12-Month LC: 83%

Reirradiation Spine Stereotactic Body Radiation Therapy for Spinal Metastases: Systematic Review

International Stereotactic Radiosurgery Society practice guidelines

Shan Blyth, MD; Arjun Sahgal, MD; Masahiro Hayashi, MD; Marc Lenvit, MD; Liping Ma, PhD; Roberto Martinez, MD; Ian Pedrick, MD; Jean Regis, MD; Samuel Ryla, MD; Don Stomski, MD, PhD; and Antonio De Salles, MD, PhD

| Table 4: Spine SBRT Reirradiation systematic review treatment outcomes |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Author & Year   | Median FU in Ma | Max (range)     | FU Schedule    | Definition of Progression | Local Control | Overall Survival | Symptom Assessment | Pain Response |
| Simeone et al., 2006 | 7.1-8.14 | 8-14 | 4-6 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |
| Chen et al., 2011   | 6.0-6.16 | 6-8  | 1-2 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |
| Cram et al., 2012   | 6.0-6.16 | 6-8  | 1-2 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |
| McCready et al. 2013 | 6.0-6.16 | 6-8  | 1-2 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |
| Ahmed et al., 2013 | 6.0-6.16 | 6-8  | 1-2 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |
| Cheng et al., 2014 | 6.0-6.16 | 6-8  | 1-2 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |
| Tsurkum et al. 2015 | 6.0-6.16 | 6-8  | 1-2 T | Pain, neurologic | 9/10            | 9/10            | 9/10            | 9/10            |

FACT-G: Functional Assessment of Cancer Therapy-General; P.o. at follow-up: OR = 2.01;
Late Toxicities: VCF Post-SBRT

Baseline VCF 24Gy/1 Fracture Progression


Late Toxicities: VCF Post-SBRT

Cumulative incidence of fracture at 1 year: 12.35%

Predictors of VCF

<table>
<thead>
<tr>
<th>Factor</th>
<th>Urate (mg/dL)</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral body collapse</td>
<td>&lt; 181</td>
<td>0.001</td>
<td>1.000 to 1.000</td>
</tr>
<tr>
<td>Vertebral body collapse</td>
<td>≥ 181</td>
<td>0.001</td>
<td>1.000 to 1.000</td>
</tr>
<tr>
<td>Vertebral body collapse</td>
<td>&lt; 181</td>
<td>0.001</td>
<td>1.000 to 1.000</td>
</tr>
<tr>
<td>Vertebral body collapse</td>
<td>≥ 181</td>
<td>0.001</td>
<td>1.000 to 1.000</td>
</tr>
</tbody>
</table>

NOTE: For vertebral body collapse, the reference is no VCF and less than 50% vertebral body involvement; for classification, the reference is 0% to 10%. Values in brackets indicate the number of patients. Radiation dose was grouped as only one patient had a radiation dose of 60 Gy or greater. In cases where vertebral compression fractures were grouped as only one patient had a radiation dose of 60 Gy or greater, the reference for bone loss was grouped according to mixed and complete. In either case osteoporosis, a group of 625% to 12.5% of VCFs. To understand the pathologic anatomy, consult one of the three figures (A, B, or C).
Prophylactic Surgical Stabilization?

- SINS Stable/Potentially Unstable
- SINS Unstable
  - Score >12

- Surgical Consult
  - Yes
  - No

Risk Factors:
- Baseline VCF
- Significant lytic tumor burden
- Spinal vertebrae involvement
- Significant spinal deformity
- Mechanical pain
- Bilateral pedicle and lamina involvement
- High-grade epidural disease (Bilsky 2 or 3)

- Any risk factor then surgical consultation
- No risk factor

Yes to surgery:
- Post-Op SBRT if suitable
- Surgery not indicated

No:
- SBRT or SBRT ≤20 Gy/1 fraction if suitable

Surgery not indicated:
- Post-Op SBRT if suitable

Radiation Myelopathy: MR-based Delineation of the Spinal Cord
Spinal Cord Motion?

Methods and Materials: We analyzed CNT motion in 65 patients with spinal metastases (11 cervical, 39 thoracic, and 24 lumbar segments) in the supine position using dynamic axial and sagittal magnetic resonance imaging (MRI; 3T Verio, Siemens) over a 137-second interval. Motion was segregated according to physiologic

Median oscillatory motion 0.16-0.44mm
Median bulk displacements 0.51-0.66mm

Evidence-Based: De-novo SBRT Cord Dose Limits

Evidence-Based: Re-irradiation SBRT Cord Dose Limits
Separation Surgery

- Limited approach where only the epidural component of the tumor is decompressed and stabilization is achieved to facilitate postoperative radiation
- Allows high dose SBRT to be delivered while maintaining dose constraints to the spinal cord

U of Toronto Experience

Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy

- LC @ 1 year: 84%
- OS @ 1 year: 64%

U of Toronto Post-op SBRT Experience

- Preoperative epidural grade
  - 0: 41.5%
  - 1a: 12.7%
  - 1b: 25.0%
  - 2: 15.8%
  - 3a: 6.3%
  - 3b: 4.9%

- Postoperative epidural grade
  - 0: 60.7%
  - 1a: 20.0%
  - 1b: 11.2%
  - 2: 6.7%
  - 3: 2.0%
MDACC Experience

- 66 patients (69 tumors)
- Fractionation: 16-24Gy/1, 27Gy/3, 30Gy/5

MDACC Post-op SBRT Experience

- LC @ 1 year: 85%
- OS @ 1 year: 74%

Dosimetric Benefits of Surgical Decompression

- 3.7 – 7.7 GY (25.8 – 31.2%) over 6 mm resected margins
- 0.62 – 1.28 GY (4.3 – 5.2%) per mm
Radiation Myelopathy Summary

- Radiation myelopathy is a rare event even in the re-irradiation scenario.

- Evidence based guidelines to guide safe practice applicable to thecal sac or cord + 1.5 mm PRV which represent the safest practice.

Patterns of Failure Post-SBRT

C2 met treated with 24Gy/2

Cord prv: 17Gy

Salvage SBRT delivered with 30Gy/5

Cord prv: 15.5Gy

Re-irradiation SBRT After Initial SBRT

Clinical Investigation

Salvage Stereotactic Body Radiotherapy (SBRT) Following In-Field Failure of Initial SBRT for Spinal Metastases

Isabelle Thibault, MD,* Mikki Campbell, MRT(1),* Chia-Lin Tseng, MD,† Eshetu G. Atenafu, MSc, Daniel Letourneau, PhD, Eugene Yu, MD, B.C. John Cho, MD,† Young K. Lee, PhD,* Michael G. Fehlings, MD, PhD, and Arjun Sahgal, MD.†
Re-irradiation SBRT After Initial SBRT

### Table 1 - Patterns, tumor, and treatment characteristics for the 166 spinal segments treated with a second salvage SBRT course

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Status of Initial SBRT</th>
<th>salvage second SBRT dose</th>
<th>salvage second SBRT volume</th>
<th>BED (EQD2)</th>
<th>1-yr imaging-based LC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor site</td>
<td>15 (27.5%)</td>
<td>21 (32.5%)</td>
<td>10 (16.2%)</td>
<td>15.5 (25.6%)</td>
<td>47.8</td>
</tr>
<tr>
<td>Thoracic</td>
<td>15 (27.5%)</td>
<td>21 (32.5%)</td>
<td>10 (16.2%)</td>
<td>15.5 (25.6%)</td>
<td>47.8</td>
</tr>
<tr>
<td>Lumbar</td>
<td>3 (5.4%)</td>
<td>3 (5.4%)</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
<td>5.3</td>
</tr>
<tr>
<td>Pelvic</td>
<td>10 (16.2%)</td>
<td>10 (16.2%)</td>
<td>5 (8.1%)</td>
<td>5 (8.1%)</td>
<td>7.5</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>12 (20.9%)</td>
<td>12 (20.9%)</td>
<td>6 (10.1%)</td>
<td>6 (10.1%)</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Patterns of Failure Post-SBRT Take Home

- **Epidural progression** is the most common pattern of failure
  - Relative under-dosing of the epidural space
  - Bad tumor biology
  - Geographic miss

- **Reirradiation spine SBRT**, most often with 30 Gy in 4 fractions, for spinal metastases that failed initial SBRT is a feasible and efficacious salvage treatment option
Challenges of Response Assessment


Pseudo-progression After Spine SBRT

- Tumor Growth confined to 80% IDL
- Increased GTV/VB_T2 intensity ratio

Consensus Response Assessment Post-SBRT

<table>
<thead>
<tr>
<th>Response</th>
<th>Imaging-based local tumour response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI preferred</td>
<td></td>
</tr>
<tr>
<td>Images should be interpreted by a radiation oncologist and radiologist</td>
<td></td>
</tr>
<tr>
<td>Local control may be defined as the absence of progression within the treated area on serial imaging (e.g. then contrast MRI scans 6-8 weeks apart)</td>
<td></td>
</tr>
<tr>
<td>Local progression may be defined as</td>
<td></td>
</tr>
<tr>
<td>Gross intratumoral increase in tumour volume or linear dimensions</td>
<td></td>
</tr>
<tr>
<td>Any new or progressive feature within the outlined target</td>
<td></td>
</tr>
<tr>
<td>Neurological deterioration attributable to pre-existing spinal disease with normal or increased spinal disease dimensions on MRI</td>
<td></td>
</tr>
<tr>
<td>Pseudoprogression and necrosis should be considered, with repeat imaging and biopsy to confirm whether it is due to</td>
<td></td>
</tr>
<tr>
<td>RECIST criteria are not optimum to monitor response in spinal metastases treated with SBRT, and consensus criteria for imaging-based tumour response are needed</td>
<td></td>
</tr>
<tr>
<td>Pain response</td>
<td></td>
</tr>
<tr>
<td>MRI preferred, with assessment based on worst pain score</td>
<td></td>
</tr>
<tr>
<td>CRPS should be adapted on standard guidelines for pain response</td>
<td></td>
</tr>
<tr>
<td>Pain response should be assessed at 3 months after SBRT</td>
<td></td>
</tr>
</tbody>
</table>

Imaging Follow-Up Frequency

- Spine MRI every ≥3 months after SBRT for the first 12-18 months, and every 3-6 months thereafter
Ongoing Studies

RADIATION THERAPY ONCOLOGY GROUP
RT0631
PHASE III STUDY OF IMAGE-GUIDED RADIOSURGERY/SBRT FOR LOCALIZED SPINE METASTASIS

- Randomizing patients with up to 3 separate sites of spinal metastases to 8 Gy in 1 fraction of cEBRT vs. SBRT to a dose of 16-18 Gy/1

- Primary objective:
  - Pain response rates as measured by the 11-point Numerical Rating Pain Scale (NRPS) at 3 months

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Canadian SC.24 Schema

Patients with tumors (excluding soft tissue, 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
- ≥3 consecutive spinal segments involved by tumor 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.
Conclusions

- Spine SBRT is an emerging field with great promise for patient care
  - Uniquely suited for selected patients as it allows dose escalation to the tumor while attaining rapid dose falloff to minimize spinal cord doses
  - Good LC and pain response rates in reported series
- Much work has been done in technique and consistent contouring approach defined
- Imaging-based (MRI) outcomes and follow-up now standard: SPINO
- Serious toxicities rare although caution must be exercised with respect to cord dose limits and management of VCF risk
- Higher level of evidence limited
  - Randomized trials ongoing to help define practice