Conflict of interest disclosure

I have no conflict of interest to disclose.

Outline

Evolution from conventional RT to SRS to SBRT
Epidemiology, Rationale, Indications using SBRT for spinal metastases
Radiobiology of SBRT
MD Anderson clinical pathway for spinal metastases
Summary of Results from Literature
Case presentations
Summary and conclusion

IG-IMSRT Evolution

• Historically fractionated RT required large safety margins
  ~2cm around tumor for treatment uncertainties

• Associated with unacceptable toxicity at single dose levels
  needed for tumor response

• CT-treatment planning, and hi-precision targeting with
  stereotaxy has permitted safe delivery of single-dose
  RT to intracranial lesions (SRS) with very small to
  no margins
IG-IMSRT Evolution

• SRS for brain metastasis yields:
  1-, 2-yr FFP 50% for 15–18Gy
  and
  >80% for 22-24Gy
  (Vogelbaum, J Neurosurg 104:907-12, 2006)

• Current SBRT technology includes IG robotic techniques, MLC, inverse planning software to generate IMRT plans conforming to tumor with steep dose gradients needed near OARs such as spinal cord

Evolution of intracranial SRS to SBRT…

Intracranial SRS

Extracranial SBRT delivery systems
Background on Spinal Metastases

A common sequela of cancer, present in 30–70% of patients at postmortem examination, of which 14% will be symptomatic (pain, neurologic symptoms) at sometime during their illness.1

40% of skeletal metastases occur in the spine which is the most common osseous site of tumor spread.

Conventional radiation therapy widely used but is inherently limited by spinal cord tolerance.

1Perrin RG. Metastatic tumors of the axial spine. Curr Opin Oncol 1992;4:545-532
RATIONALE

• Many pts develop recurrent or progressive pain, tumor progression or neurologic deterioration despite conventional external beam irradiation, radiopharmaceuticals, surgery, or systemic therapy
• Patients are very interested in noninvasive treatment options for spinal metastases which are not amenable to or are refractory to conventional irradiation

GENERAL INDICATIONS

LIMITED DISEASE - Newly diagnosed solitary or oligo-spinal metastases
PRIMARY - “Radioresistant” subtypes
POST-OP - adjuvant or elective treatment
SALVAGE - surgical or RT recurrences

Spinal instability is a contraindication
Previously irradiated spinal cord, melanomas, Renal cell cancer, sarcomas etc.

Little or no therapeutic window exists for conventional irradiation.

SBRT dosimetrically widens the therapeutic window by lowering dose to the OAR.

Limitations in the linear-quadratic model for high doses

\[ \text{BED}_a = E_a/a = d + \left[ \frac{d^2}{(a/\beta)} \right] \quad \text{for} \quad d < D_T \]

and

\[ \text{BED}_a = D_T \left[ \frac{D_T^2/(a/\beta)}{d} \right] + \left| \frac{\gamma}{d} \right| (d - D_T) \quad \text{for} \quad d \geq D_T \]

Astrahan M, IJROBP 71:3:963,2008
Single Fraction Equivalent Dose (SFED) vs BED
For high dose ablative RT
Defined - as dose in a single fx that would have same biological effect as any large daily dose fractionation regimen


Spinal Cord Radiation Exposure

Henry Ford group proposes 10 Gy to 10% spinal cord as tolerance
White Matter Necrosis of Rat spinal cord

- Major cause of paralysis
- Occurs within 120 - 210 days after irradiation 20 Gy x 1
- Pathogenesis focused on either primary glial or vascular origin
- Characterized by demyelination, loss of axons, focal necrosis, liquefactive necrosis after ≥ 20 Gy x 1
- Vascular edema is usually associated with development of white matter necrosis

Bijl HP et al. Van Der Kogel AJ, IJROBP 52:205-11, 2002

Isoeffect Dose (ED50) according to irradiated length of rat cord

Bijl HP et al. Van Der Kogel AJ, IJROBP 52:205-11, 2002

High precision proton irradiation of rat spinal cord

Grazing Lateral Beams (constant depth dose profile)

Bijl HP et al. IJROBP 61:543-551, 2005
White matter necrosis in left lateral column after grazing irradiation

Extensive white matter necrosis in Dorsal column

No lesions in gray Matter or lateral columns

Regional Differences in Radiosensitivity in Rat Spinal Cord

Bijl HP et al. IJROBP 61:543-551, 2005

Full width And Lateral beam

Dose-response Curves for Paralysis

Bijl HP et al. IJROBP 61:543-551, 2005

Central Beam

Bath/Shower Dose-response of Paralysis of Limbs to Unmodulated Protons in Rat Cervical Spinal Cord

Spinal cord tolerance of relatively small volumes (shower) strongly affected by low dose irradiation (bath)

Bijl HP et al. IJROBP 64:1204-10, 2006

Clinical Pathway for Stereotactic Body Radiotherapy program

Referral from neurosurgery
Medical oncology
Radiation oncology
Self referral

Multi-disciplinary Tumor board
• Referral assessment
• Discussion of complex cases
• Trimming complaints

Joint consultation
Pain, QOL assessment
Neurological exam, informed consent/roles
Protocol registration

SBRT simulation
1. immobilization
2. intrathecal contrast
3. CT acquisition

IMRT treatment planning
QA dosimetry
- Film
- Ion chamber

Treatment setup
CT acquisition
Image fusion, DRR, port film, delivery

Protocol follow-up q3 months
Pain, QOL, neuro exam, MRI

Spinal recurrence
Or new disease
Selected stereotactic spine radiation therapy series (FRACTIONATED)

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Pathology</th>
<th>Dose (Gy)</th>
<th>Pain relief</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura et al. 2003</td>
<td>18</td>
<td>Met</td>
<td>95.1</td>
<td>12.6</td>
<td>NA</td>
</tr>
<tr>
<td>Chang 2007</td>
<td>0.5</td>
<td>Met</td>
<td>80.4 to 20.4</td>
<td>90%</td>
<td>NA</td>
</tr>
<tr>
<td>Raiteri 2002</td>
<td>16</td>
<td>Primary</td>
<td>82.3 to 47.1</td>
<td>81%</td>
<td>NA</td>
</tr>
<tr>
<td>Yamada 2006</td>
<td>0.5</td>
<td>Met</td>
<td>&gt;100</td>
<td>80%</td>
<td>NA</td>
</tr>
<tr>
<td>Dodd 2006</td>
<td>0.3</td>
<td>Benign</td>
<td>60 to 112.6</td>
<td>80%</td>
<td>NA</td>
</tr>
<tr>
<td>M.D. Anderson 2005</td>
<td>4.7</td>
<td>Met</td>
<td>60 to 112.6</td>
<td>80%</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td></td>
<td>80%</td>
<td>80%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Selected stereotactic spine radiation therapy series (SINGLE SESSION)

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>Pathology</th>
<th>Dose (Gy)</th>
<th>Pain relief</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rus 2007</td>
<td>177</td>
<td>Met</td>
<td>8.1-8.6</td>
<td>80%</td>
<td>I radiation</td>
</tr>
<tr>
<td>Yamada 2006</td>
<td>103</td>
<td>Met</td>
<td>10-20</td>
<td>10-5</td>
<td>NA</td>
</tr>
<tr>
<td>Gerszten 2007</td>
<td>30</td>
<td>Met</td>
<td>10-20</td>
<td>10-5</td>
<td>NA</td>
</tr>
<tr>
<td>Dodd 2006</td>
<td>19</td>
<td>Benign</td>
<td>10-20</td>
<td>10-5</td>
<td>NA</td>
</tr>
<tr>
<td>Russell 2006</td>
<td>11</td>
<td>Benign</td>
<td>60-112.6</td>
<td>10-5</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>206</td>
<td></td>
<td>10-5</td>
<td>10-5</td>
<td>NA</td>
</tr>
</tbody>
</table>

Patient Positioning Accuracy and Safety Data

M.D. ANDERSON PHASE I AND II DATA

RESULTS – Patient Characteristics

<table>
<thead>
<tr>
<th>Dates enrolled</th>
<th>Nov 2002 – Mar 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients n</td>
<td>63</td>
</tr>
<tr>
<td>Male</td>
<td>38 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (40%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Median 59, Range 21-82</td>
</tr>
<tr>
<td>Histology</td>
<td>Renal cell 25 (39.7%)</td>
</tr>
<tr>
<td></td>
<td>Breast 8 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>Sarcoma 6 (12.7%)</td>
</tr>
<tr>
<td></td>
<td>Lung 7 (11.7%)</td>
</tr>
<tr>
<td></td>
<td>Melanoma 2 (3.2%)</td>
</tr>
<tr>
<td></td>
<td>Colon 1 (1.6%)</td>
</tr>
<tr>
<td></td>
<td>Uterine Primary 2 (3.2%)</td>
</tr>
<tr>
<td></td>
<td>Other 9 (14.3%)</td>
</tr>
<tr>
<td>KPS score</td>
<td>60 4 (6.3%), 70 17 (27%), 80 17 (27%), 90 25 (39.7%)</td>
</tr>
</tbody>
</table>

RESULTS – Tumor Characteristics

| Tumor volume (cc) | median 37.4, range 1.6 – 357.9 |
| Spinal Metastases (n) | One 51, Two 12 |
| Lesion Location | Spinal 61, Paraspinal 13 |
| Level | cervical 5 (6.7%), thoracic 43 (57%), lumbar 26 (34.7%), sacral 1 (1.3%) |

RESULTS – Follow-up of Tumor and Vital Status

| Vital Status | alive 26 (41%), dead 37 (59%) |
| Tumor status | Stable 57 (77%), Progressed 17 (23%) |
| Follow-up | Median 21.3 mos, Range 0.5 – 49.6 mos |

TABLE 1

<p>| Spinal procedures performed in patients prior to study enrollment |</p>
<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Patients/1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>partial resection</td>
<td>1</td>
</tr>
<tr>
<td>laminectomy</td>
<td>1</td>
</tr>
<tr>
<td>laminectomy, facetectomy, stabilization</td>
<td>1</td>
</tr>
<tr>
<td>vertebrectomy, stabilization</td>
<td>5</td>
</tr>
<tr>
<td>vertebrectomy</td>
<td>3</td>
</tr>
<tr>
<td>spinal decompression</td>
<td>1</td>
</tr>
<tr>
<td>laminectomy, stabilization</td>
<td>1</td>
</tr>
<tr>
<td>vertebrectomy, laminectomy, facetectomy, stabilization</td>
<td>7</td>
</tr>
<tr>
<td>laminectomy, laminectomy, facetectomy, stabilization</td>
<td>7</td>
</tr>
<tr>
<td>retroperitoneal &amp; psoas muscle resection</td>
<td>1</td>
</tr>
<tr>
<td>laminectomy, facetectomy</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>29 (49%)</td>
</tr>
</tbody>
</table>

PAIN AND SYMPTOM CONTROL

Narcotic use decreased from 60% (baseline), 44% (3mos), 36% (6mos)

MDASI showed reduction in pain (p<0.001), sleep disturbance (p<0.01)
with no added impairment of daily function, while fatigue severity unchanged.

TABLE 2
Categorization of spinal SBRT according to indication

<table>
<thead>
<tr>
<th>SBRT Indication</th>
<th>No. of Patients (%)</th>
<th>Mean Interval From Prior Op to SBRT (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>postop SBRT</td>
<td>8 (12.7)</td>
<td>1.3 (0.6-3.67)</td>
</tr>
<tr>
<td>gross residual disease</td>
<td>7 (11.1)</td>
<td>1.3 (0.1-3.1)</td>
</tr>
<tr>
<td>salvage SBRT after RT failure</td>
<td>10 (15.6)</td>
<td>16 (6.9-39.5)</td>
</tr>
<tr>
<td>definitive SBRT</td>
<td>35 (56.3)</td>
<td>NA</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>65</td>
</tr>
</tbody>
</table>

* NA = not applicable; RT = radiotherapy.
† Values represent months.


TABLE 3
Neurological status based on the McCarron neurological function system

<table>
<thead>
<tr>
<th>Neurological Function Grade 9</th>
<th>No. of Patients (%)</th>
<th>Baseline</th>
<th>Last Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54 (94.7)</td>
<td>47 (82.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (5.3)</td>
<td>8 (14.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>2 (3.5)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

* Neurological function definitions: Grade 1, normal to mild focal deficit; Grade 2, moderate deficit, significant motor or sensory loss, but able to function independently; Grade 3, moderate-to-severe deficit, requires assistance to ambulate; and Grade 4, severe deficit, unable to function independently or ambulate.
† Of 63 study patients, 57 had baseline and follow-up neurological function data available.


Fig. 2. Graph demonstrating the actuarial tumor progression-free survival (dashed line) and survival (solid line) in treated patients.
Neurotoxicity evaluation

Grade 1
- headache (1)
- numbness (1)*
- tingling (4)*
- numbness and tingling (1)*
(all reversible)

Grade 2-4
none

Grade 3-4 toxicity

Grade 3
- Nausea (1)
- Fatigue (1)
- Non-cardiac chest pain (1)
- Pain, severe tongue edema, trismus (1)

Grade 4
None

Reported Toxicity in Literature

<table>
<thead>
<tr>
<th>Acute Transient*</th>
<th>Sub-Acute</th>
<th>Permanent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Radiation</td>
<td>Myelopathy (8 cases)</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>Pain Flare (transient worsening of tumor related pain)</td>
<td>Vertebral Compression Fracture</td>
</tr>
<tr>
<td>Darrka</td>
<td></td>
<td>Tracheo-oesophageal fistula</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trismus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CLINICAL CASES

Fractionated SBRT
Case 1: 46 M previously irradiated (40 Gy in 16 fx) Lung cancer T12 metastasis progressed (biopsy proven)  
July 2004 → July 2005

Case 2: 52 M solitary renal cell carcinoma metastasis centered on cervical vertebrae 2
Case 3: 20 F plasmacytoma causing back pain, failed conventional RT and surgery
- Extradural extension causing cord compression at T10
- Needle bx revealed plasmacytoma
- 45 Gy in 25 fractions to T9-11
- 3 mos later, recurred below: Epidural dz T11-12.
  RT was not an option at the time
- Laminectomy, facetectomy, resection tumor
- 4 mo later recurred above: Rt T7-8 neuroforamen
- Received SBRt to epidural disease
- Attending college and remains disease-free 4 years later
Summary and conclusions

- Literature and phase I/II data support the safety and effectiveness of stereotactic body radiosurgery for the spine.
- POF data suggest routinely treating the pedicles and posterior elements using a wide bony margin posterior to the diseased vertebrae.
- Prospective trials are needed to determine the true spinal cord tolerance and to compare efficacy of SBRS against conventional RT.

All the following are indications for performing stereotactic body radiosurgery for spinal metastases EXCEPT:

- 25% 1. Solitary or oligometastatic disease
- 25% 2. Failure of prior XRT or surgery
- 25% 3. Spinal instability
- 25% 4. Gross residual disease after surgery

Based on pooled published data on spinal metastases, SBRT is associated with a crude local control rate of:

- 25% 1. 65-70%
- 25% 2. 70-75%
- 25% 3. 75-80%
- 25% 4. 80% or higher

The following statements regarding spinal cord tolerance to single session stereotactic body radiosurgery (SBRS) are true EXCEPT:

- 25% 1. Human spinal cord tolerance unknown
- 25% 2. <12 Gy has been reported as safe
- 25% 3. 10 Gy to 10% of the spinal cord volume
- 25% 4. Rat spinal cord tolerance can be directly applied to humans