The tolerance of the nervous system to SBRT: dogma, data and recommendations

Paul Medin, PhD

Disclosure

• Paul Medin teaches radiosurgery courses sponsored by BrainLAB
• Many animals (and humans) were harmed to make this presentation possible!
Dogma

- The spinal cord never forgets.
- Dose-volume constraints help us to prevent myelopathy in the spinal cord.
- The spinal cord exhibits regional sensitivity, e.g. cervical versus thoracic.
- Peripheral nerves tolerate greater dose than the spinal cord.

Where does spinal cord toxicity data come from?

- \( \approx 2\% \)
- \( \approx 80\% \)
- \( \approx 6\% \)
- \( \approx 6\% \)
- \( \approx 6\% \)
Toxicity in humans following de novo SBRT

- 9 cases in the literature

<table>
<thead>
<tr>
<th>First Author</th>
<th>Fraction</th>
<th>Median Cord Dose (Gy)</th>
<th>Latency (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daly</td>
<td>1</td>
<td>17.9</td>
<td>3</td>
</tr>
<tr>
<td>Gibbs</td>
<td>1</td>
<td>8.3</td>
<td>2</td>
</tr>
<tr>
<td>Gibbs</td>
<td>1</td>
<td>10.0</td>
<td>2</td>
</tr>
<tr>
<td>Ryu</td>
<td>1</td>
<td>14.6</td>
<td>15</td>
</tr>
<tr>
<td>Sahgal</td>
<td>1</td>
<td>12.7</td>
<td>12</td>
</tr>
<tr>
<td>Sahgal</td>
<td>1</td>
<td>13.6</td>
<td>3</td>
</tr>
<tr>
<td>Sahgal</td>
<td>1</td>
<td>13.6</td>
<td>6</td>
</tr>
<tr>
<td>Gibbs</td>
<td>2</td>
<td>75.3</td>
<td>9</td>
</tr>
<tr>
<td>Gibbs</td>
<td>3</td>
<td>28.6</td>
<td>9</td>
</tr>
</tbody>
</table>

Toxicity in humans following Retreatment with SBRT

- 6 cases in the literature

<table>
<thead>
<tr>
<th>First Author</th>
<th>Non Radiation Failure, Median Cord Dose (Gy)</th>
<th>Interval to Reflurrence (months)</th>
<th>Interval to Deficit (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibbs</td>
<td>40.22</td>
<td>10.3</td>
<td>21.2</td>
</tr>
<tr>
<td>Gibbs</td>
<td>35.2, 38</td>
<td>19.6</td>
<td>38</td>
</tr>
<tr>
<td>Gwak</td>
<td>17.8*</td>
<td>11.0</td>
<td>21.5</td>
</tr>
<tr>
<td>Sahgal</td>
<td>38.2, 33*</td>
<td>12.0</td>
<td>14.7</td>
</tr>
<tr>
<td>Sahgal</td>
<td>30, 10</td>
<td>1.5</td>
<td>14.7</td>
</tr>
</tbody>
</table>

*Doses estimated by Sahgal
**Doses reported to thecal sac

Animal Studies of Retreatment

- Retreatment with Single-fraction SBRT 1 year after 3 Gy times 10.

<table>
<thead>
<tr>
<th>Initial Dose</th>
<th>ED\textsubscript{50} (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
<td>20.0</td>
</tr>
<tr>
<td>3 Gy times 10</td>
<td>19.7</td>
</tr>
</tbody>
</table>

Both Dose-Response Curves are nearly identical!


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Animal Studies of Retreatment

- Retreatment with Single-fraction SBRT after SBRT dose scheme

<table>
<thead>
<tr>
<th>Initial Dose</th>
<th>Re-Tx 8 weeks</th>
<th>Re-Tx 28 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 Gy times 2</td>
<td>14.8 Gy (12.2-17.3)</td>
<td>16.2 Gy (15.8-16.7)</td>
</tr>
<tr>
<td>9 Gy times 3</td>
<td>9.8 Gy (8.4-11.2)</td>
<td>14.6 Gy (13.9-15.3)</td>
</tr>
<tr>
<td>10.25 Gy times 3</td>
<td>6.1 Gy (5.1-7.0)</td>
<td>12.2 Gy (11.6-12.8)</td>
</tr>
</tbody>
</table>

Animal Studies of Retreatment

- Retreatment with Single-fraction radiosurgery
- 1 year after Single-fraction radiosurgery

<table>
<thead>
<tr>
<th>Initial Dose</th>
<th>ED\textsubscript{50} (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
<td>20.5</td>
</tr>
<tr>
<td>10 Gy</td>
<td>19.5</td>
</tr>
</tbody>
</table>


Volume Effect: Length

Single-dose irradiation.
Endpoint: paralysis.
Bijl, et. al., IJROBP, 2002.

Rat ED\textsubscript{50}'s:
- 20 mm: ED\textsubscript{50} = 20.4 Gy
- 8 mm: ED\textsubscript{50} = 24.9 Gy (22-29)
- 4 mm: ED\textsubscript{50} = 53.7 Gy (49-62)
- 2 mm: ED\textsubscript{50} = 87.8 Gy

(Figures from Albert van der Kogel)
Volume Effect: Width

Grazing Proton Beam:
50% isodose at midline of spinal cord

The spinal cord tolerance dose for rats is significantly increased (30 Gy vs 20.4 Gy) if only 50% is irradiated in the lateral direction.

Grazing Distribution in a Pig

Non-uniform Distribution

Uniform Distribution

ED$_{50}$ = 20.0 Gy

ED$_{50}$ = 20.2 Gy

Figures from Albert van der Kogel
Dose-volume effect in humans?

TOxicity of the spinal cord to stereotactic radiosurgery: insights from eNHANCeD eNhancdeTomas

Michael E. Daly, M.D.1,2,3 Clara Y. H. Che, M.D., Ph.D.1,2,3 Brian C. Gibbs, M.D.1,2,3 John R. Adler, Jr., M.D.1,2,3 Steven D. Chang, M.D.1,2,3 Robert E. Livindien, M.D.1,2,3, and Scott G. Soliotes, M.D.1,2,3

17 patients
Median single-fraction max cord dose = 22.7 Gy (range 17.8-30.9 Gy)

Extremely small volumes and short lengths!
Median V10 = 454 mm³ (range 226-3543 mm³)

Patient with potential Grade 2 toxicity had lowest cord dose of the series (17.8 Gy)

Regional Sensitivity
Cervical vs Thoracic vs Lumbar

• Regional variation in radiosensitivity has been suggested in the human spinal cord literature but never established by objective analysis.
• **All regions have been studied in rats with similar results.
• RTOG 0631 protocol is consistent with animal data in that prescribed dose is not dependent on vertebral level.

Spinal Cord Dose Recommendations, de novo SBRT

- Ryu, et al. 2007
  - Partial-volume tolerance is at least 10 Gy to 10% of the spinal cord volume when the spinal cord volume is defined to extend 6 mm superior and inferior to the radiosurgery target.

  - Caution when considering radiosurgery plans that expose more than 1.0 cm³ of spinal cord to greater than 8 Gy dose equivalent.

- Sahgal, et al. 2010
  - Dose threshold of 10 Gy to the thecal sac

- Sahgal, et al. 2013
  - Risk of RM 5% or less for max thecal sac dose
    - 12.4 Gy in one fraction
    - 17.0 Gy in two fractions
    - 20.3 Gy in three fractions
    - 23.0 Gy in four fractions
    - 25.3 Gy in five fractions

RTOG 0631—dose constraint table

<table>
<thead>
<tr>
<th>Serial Tissue</th>
<th>Volume</th>
<th>Volume Max (Gy)</th>
<th>Endpoint (2 Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>&lt;0.035 cc</td>
<td>14 Gy</td>
<td>Mysitis</td>
</tr>
<tr>
<td></td>
<td>&lt;0.35 cc</td>
<td>15 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1.2 cc (SBRT only)</td>
<td>17 Gy (SBRT only)</td>
<td></td>
</tr>
</tbody>
</table>
Spinal Cord Dose Recommendations, Reirradiation

  - SBRT at least 5 months after conventional radiotherapy
  - Reirradiation thecal sac point max dose nBED = 20-25 Gy
  - Total point max nBED < 70 Gy
  - SBRT thecal sac point max dose nBED < 50% of total nBED

Conclusions: Spinal Cord Tolerance

- Spinal cord tolerance data from animals is abundant and consistent.
- Spinal cord tolerance data from humans is sparse and inconsistent.
- The field appears to have arrived at 14 Gy as an acceptable maximum spinal cord dose. By animal standards, 14 Gy is conservative and appears be safe for humans.
- I believe the tolerance of young, healthy humans is similar to animal tolerance but acknowledge that humans have many variables not present in animal studies, (advanced age, comorbidities, other therapies, etc).
Where have we caused spinal cord toxicity?

≈ 25

≈ 37

≈ 15

≈ 126

What is the source of SBRT peripheral nerve tolerance data?

The dog data is actually from the intraoperative radiotherapy setting.

Clinical Neuropathy from Spine SBRT

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Cases</th>
<th>Neuropathy</th>
<th>Rx Dose (Gy)</th>
<th>Fx</th>
<th>Latency to Deficit (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>Stubblefield</td>
<td>14</td>
<td>Pain and weakness Grade 1=14% Grade 2=64% Grade 3=21%</td>
<td>18-24 Gy</td>
<td>1</td>
<td>4-32 (median=10)</td>
</tr>
</tbody>
</table>

*No relationship between dose and injury detected

Clinical Neuropathy from lung SBRT

<table>
<thead>
<tr>
<th>Year</th>
<th>First Author</th>
<th>Cases</th>
<th>Neurophy</th>
<th>Dose(s)</th>
<th>Fractions</th>
<th>Latency to Deficit (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Chung, JY</td>
<td>3</td>
<td>Grade 2-3 Brachialplesopathy</td>
<td>&gt;35Gy</td>
<td>4</td>
<td>Not stated</td>
</tr>
<tr>
<td>2013</td>
<td>Prendergast, BM</td>
<td>1</td>
<td>Grade 2-3 Brachialplesopathy</td>
<td>Not Stated</td>
<td>Not Stated</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>2009</td>
<td>Kwon, T</td>
<td>1</td>
<td>Thromb Numbness, (Brachial Plesus)</td>
<td>47 Gy (mean), 62.5 Gy (max)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2006</td>
<td>Fernandez, JA</td>
<td>7</td>
<td>Grade 2-4 Brachialplesopathy</td>
<td>18-82 Gy (max), 30 Gy (mod)</td>
<td>3-4</td>
<td>7 median (6-23)</td>
</tr>
</tbody>
</table>

Constraints for single-fraction SBRT

<table>
<thead>
<tr>
<th></th>
<th>Volume (%)</th>
<th>Volume Max (Gy)</th>
<th>Max Point Dose (Gy)</th>
<th>Endpoint (Grade 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>&lt;0.15</td>
<td>14</td>
<td>14</td>
<td>Myelitis</td>
</tr>
<tr>
<td></td>
<td>&lt;1.2</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>&lt;3</td>
<td>14</td>
<td>14</td>
<td>Neuropathy</td>
</tr>
<tr>
<td></td>
<td>&gt;14.4</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Single-Fraction dose constraints, RTOG-0915 (Stage 1, RECIST).
SBRT Animal data

A = normal
B = normal
C = paralysis
D = paralysis


Spinal nerve dose-response (15mm segment)

Preliminary Results!
Conclusions: Peripheral Nerves

- Peripheral nerve tolerance is still poorly understood.
- Animal and human data is very limited.
- A study is in progress to evaluate spinal nerve tolerance using pigs.
- Human guidelines for sacral and brachial plexus indicate that these peripheral nerves have a greater tolerance than the spinal cord.
- Emerging data from a pig study suggests that spinal nerve tolerance is the same as the spinal cord tolerance.