Novel Mechanisms of Response for Stereotactic Radiosurgery. Food for Thought for the Management of Chordomas

Yoshiya (Josh) Yamada MD FRCPC
Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center
NY NY USA
Disclosures

The Institute for Medical Education, Speakers Bureau

Varian Medical Systems, Consultant
## Stereotactic Radiosurgery Chordoma

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td><strong>FU</strong></td>
<td>24 months</td>
<td>6-51 months</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>65 years</td>
<td>36-80 years</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>13 male</td>
<td></td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>C = 7</td>
<td>T = 4</td>
</tr>
<tr>
<td></td>
<td>L = 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S = 10</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>2400cGy x 1</td>
<td>(1800-2400cGy)</td>
</tr>
<tr>
<td><strong>Tumor Volume</strong></td>
<td>81cc</td>
<td>(20-859cc)</td>
</tr>
</tbody>
</table>

### Local Control Graph

- **Chordoma 18-2400cGy x 1 Local Control**

  - Percent Local Control
  - Months

  ![Graph showing local control over time for chordoma patients treated with 18-2400 cGy.](image)
Treatment Complications

- **Neurologic**
  - Partial vocal cord paralysis
    - Prior RT to 4600cGy
  - Foot drop
    - Tumor invaded sciatic nerve
- **Fracture**
  - 1 Lumbar
  - 2 Sacral
Pathologic Outcomes. N = 6

<table>
<thead>
<tr>
<th>Patient</th>
<th>Level</th>
<th>Time from SRS (m)</th>
<th>Extent of necrosis</th>
<th>Follow-up (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L2</td>
<td>2</td>
<td>conventional chordoma</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>L3</td>
<td>4</td>
<td>&gt;90%</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>Sacrum</td>
<td>4</td>
<td>&gt;90%</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>Sacrum</td>
<td>5</td>
<td>50%</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>Sacrum</td>
<td>5</td>
<td>5%</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>Sacrum</td>
<td>8</td>
<td>&gt;90%</td>
<td>40</td>
</tr>
</tbody>
</table>
Deficiencies of the LQ Model for SBRT Response
Kirkpatrick et al. Sem Radiat Oncol 18, 2008

• Brain metastases are well controlled with 15-20Gy (25-35Gy calculated)

• Cancer stem cells may require a higher threshold dose of radiation to overcome inherent radioresistance (>13 Gy for intestinal stem cells)

  • LQ model doesn’t model threshold effects

• Classical radiobiology based upon in vitro rather than in vivo data

  • LQ model can’t account for other in vivo mechanisms of response at high doses
Endothelial Apoptosis: An In Vivo Effect for High Dose Radiosurgery

Single Dose Radiation (>8-10Gy)
- Endothelial Membrane Alterations
  - ASMase
  - SM
- Ceramide
- Endothelial Apoptosis
- Tumor Cell Damage
- Microvascular Dysfunction
- Tumor Cell Death
- Tumor Response

Fractionated Radiation (1.8-3Gy/fraction)
- Cell Death Signals
  - Hypoxia / Reperfusion / ROS
  - Hypoxic Tumor Cells
    - HIF-1 Translation
    - VEGF / bFGF
- Endothelial Apoptosis
- Tumor Cell Damage
- Microvascular Dysfunction
- Tumor Cell Death
- Tumor Response

Garcia-Barros, 2003
Moeller and Dewhirst, 2004
Anti-VEGF G6-31 Sensitizes MCA/129 Fibrosarcoma

Truman et al. PLoS One 2010
Modulating Response: VEGF and Endothelial Apoptosis

A

asmase^{++}

13.5Gy+ Isotype
13.5Gy+ DC101

Tumor volume (mm^3)

400
300
200
100
0

Days after tumor implantation

14 16 18 20 22 24 26

C

% Endothelial apoptosis

35
30
25
20
15
10
5
0

Control
DC101
13.5Gy+ Isotype
13.5Gy + DC101

ASMase^{++}
ASMase^{-/-}
Uptake curves of representative voxels from DCE-MRI of B16 melanoma irradiated in wild-type and asmase\(^{−/−}\) mice

The images show the uptake of Gd-DTPA in B16 melanoma tumors before and after irradiation with 20 Gy. The uptake curves are shown for both wild-type (asmase\(^{+/+}\)) and asmase\(^{−/−}\) mice. The graphs indicate a decrease in uptake after irradiation, suggesting changes in tumor metabolism.

Slide courtesy of Z Fuks MD
High Dose IGRT and Vascular Response

• Vascular collapse an important aspect of high dose RT response

• Significant endothelial apoptosis (ceramide repressed by VEGF inhibition) –within minutes of RT!
  • Radioresistant phenotypes become radiosensitive with VEGF suppression—ceramide activation
  • *Dose de-escalation for IGRT+ VEGF inhibitors?*

• DCE MRI changes: Evidence for the vascular effect?
Results

- On average $V_p$ decreased by 64% after 1 hour
- On average $K_{trans}$ decreased by 34% after 1 hour
- Average follow up of 23 months - No local progression

<table>
<thead>
<tr>
<th>Region</th>
<th>% Change from Baseline</th>
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</thead>
<tbody>
<tr>
<td>T5</td>
<td></td>
</tr>
<tr>
<td>$V_p$</td>
<td>-81%</td>
</tr>
<tr>
<td>$K_{trans}$</td>
<td>-15%</td>
</tr>
<tr>
<td>T10</td>
<td></td>
</tr>
<tr>
<td>$V_p$</td>
<td>-31%</td>
</tr>
<tr>
<td>$K_{trans}$</td>
<td>-52%</td>
</tr>
<tr>
<td>L2</td>
<td></td>
</tr>
<tr>
<td>$V_p$</td>
<td>-60%</td>
</tr>
<tr>
<td>$K_{trans}$</td>
<td>-29%</td>
</tr>
<tr>
<td>L3</td>
<td></td>
</tr>
<tr>
<td>$V_p$</td>
<td>-84%</td>
</tr>
<tr>
<td>$K_{trans}$</td>
<td>-60%</td>
</tr>
<tr>
<td>L4</td>
<td></td>
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<tr>
<td>$V_p$</td>
<td>-63%</td>
</tr>
<tr>
<td>$K_{trans}$</td>
<td>-16%</td>
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</table>
DCE: A Window into the Tumor

Prior to RT  

2400cGy×1  

Day 10  

Day 50
Plasma Volume and Recurrence
Changes in Plasma Volume and Local Recurrence

% change in parameter value (pre to post treatment)

Local Recurrence

V_p, K_trans, AUC, Peak
Results

• Recent similar study looked at 19 spinal metastases with perfusion imaging performed 10-187 days after treatment.

• The 17 successfully treated lesions showed a similar drop in Vp (average of 65%), the two unsuccessfully treated lesions showed significant increased Vp.

• Suggests that we can have similar results with perfusion imaging only one hour after treatment
Role of DCE MRI

• High dose radiation may have a significant impact upon small vessel changes in tumors

• Plasma significant differences in plasma volume in tumors destined to recur vs. those that do not

• Preliminary results suggest that DCE findings can predict for tumor recurrence before standard MRI findings

• Currently analyzing data in chordoma patients

• DCE MRI is a non invasive method of assessing response to high dose RT
High Dose Radiotherapy: Multi Compartment Targets
High Dose RT and Immunologic Response with Ipilimumab

Abscopal effect of CTLA 4 (T cell) stabilizer

Phenomenon noted with Hypofractionation

Increased immunogenicity with high dose RT
Mucosal Melanoma

• 65 yo M with mucosal melanoma of the right maxilla.

• Maxillectomy, orbital extent / flap reconstruction

• Multiorgan metastases

• Chemo (cis/decarbazine/vinblastine, 6/2011)

• Post op bed: Hypofractionated radiation (9/2011, 36Gy/3 fractions) with Ipilimumab
Abscopal Effect

• Systemic response on PET imaging

  • Near complete resolution of all multiple peritoneal, hepatic, splenic, osseus, LN lesions

• No evidence of maxillary recurrence
Multiple Osseus and Visceral Metastases

Near Complete Systemic Response

9/23/2011

3/29/2012
IL 2 and Melanoma and RCC + SBRT


- IL 2 CR + PR = 6% and 10% for melanoma
- IL 2 CR + PR = 8% and 7% for RCC
- Median time of response 40 months and 54 months
  - 70% of melanoma CR are without recurrence at 15 years
  - 70% of RCC CR are disease free at 10 years
- SBRT: 20Gy x 1-3
- IL 2 (600,000 IU/kg every 8 hours x 14 doses) start Monday after RT, repeated 16 days later
- 100% CR of irradiated lesions
Fig. 1. Waterfall plot of best tumor response by RECIST criteria of all target lesions not treated with SBRT. Each bar represents the response of an individual patient. A dashed line is placed at 30% to indicate the minimum regression of tumor to qualify for a PR by RECIST criteria of target lesions.
IL 2 and High Dose SBRT: T Cell Effects
T cell deficient (nude mice) significantly less response to 25Gy\times1 compared to the wild type

Reduced response to 20Gy\times1 if the wild type CD8+ T cells are depleted
SBRT/SABR and Tumor Immunology

Threshold Effect for High Dose Radiosurgery

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- SM
- ASMase
- VEGF
- bFGF
- Ceramide
- Endothelial Apoptosis

Tumor Cell Damage
- Microvascular Dysfunction
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Immune Response

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Garcia-Barros, 2003
Moeller and Dewhirst, 2004
High Dose Radiotherapy: Multi Compartment Targets

Tumor Stromal Cell Compartment

Tumor Stem Cell Compartment

Increased Immune Response?
Summary

• SBRT/high dose radiation is an evolving paradigm with excellent tumor control (better than expected)
  • The dose of radiation delivered is important to maximize the therapeutic ratio
• New biology: Beyond traditional radiobiology
  • Endothelial/vascular effects
  • Immune response
  • Others???
Chordoma Radiosurgery Summary

- Preliminary data is favorable
- High dose radiosurgery response likely radiobiologically different to conventional fractionation
- Multi institutional study
  - Neoadjuvant single fraction SRS followed by surgery
    - Endpoints
      - Pathologic assessment
      - Vascular response
      - Toxicity