SBRT (I): Clinical and Radiobiological Considerations, part 2

Educational Objectives

1. Review and understand the major issues related to the use of SBRT for tumors in the spine or paraspinous region, including key clinical observations
   - Covered by Dr. Chang

2. Review and understand the common clinically observed normal tissue responses to SBRT and the inferences to be drawn regarding the practical radiobiology of high dose per fraction therapy

3. Explore and highlight the major issues related to clinical application of SBRT for tumors in the lung and liver, including key clinical observations

Segue from Dr. Chang: MSKCC spinal SBRT outcomes

Clinical observation

SBRT as focal anti-angiogenic?

Is there a clinical dose-response?

Should we abandon the LQ model?

What do other clinical observations imply?

Any normal tissue lessons?

SBRT for NSCLC outcomes summary

Practical radiobiological correlate

MSKCC spinal SBRT experience

- 93 patients, 103 lesions
- No spinal cord compression
- Single fraction 18-24 Gy
- CTV usually vertebral body
- PTV = CTV + 2 mm
- Spinal cord max 12-14 Gy
- Better control at higher dose (24 Gy) than lower (above)

Metastatic colorectal ca example

Note apparent devascularization

MSKCC argument why SBRT works well:
Radiation as potent, focused anti-angiogenic agent

• Fibrosarcoma and melanoma models
• Growth delay after RT influenced by apoptotic capacity
• Dose-dependence of percent apoptosis in endothelial cells

Garcia-Barros et al, Science, 2003

SBRT dose-response observation:
McCannon R et al, in press, IJROBP 2008

• 141 pts, 246 lesions
• 3 yr local control 89% for highest dose cohort

But think about it…

• Median dose in middle cohort was 42 Gy in 3 fractions
• LQ-based BED\(_{10}\)Gy
  • \(42(1+14/10)\) = 100.8 Gy\(_{10}\)
  • equivalent to approx 84 Gy in 2 Gy fractions
• …and we still only got 60% local control? — disappointing

The problem of modeling SBRT doses using LQ formalism—deviation at high dose

Park et al, IJROBP 70(3): 847-852, 2008
UTSW Proposed solution: The “Universal Survival Curve”

- Essentially a step function
  - Below the transition dose, DT, the LQ model is used
  - Above DT, the multi-target model is used
- Backed by some experimental evidence


Derived from the USC: Single fraction equivalent dose (SFED)

“BED” reserved for conventionally fractionated RT modeling here

$$\text{SFED} = \begin{cases} \alpha \cdot D \cdot \left(1 + \frac{d_1}{\alpha D} \right) + D_0, & \text{if } d=D_0 \\ D - (n-1) \cdot D_0, & \text{if } d>D_0 \end{cases}$$

“Toward a Unified Survival Curve”

- I like the USC and SFED and applaud Park and colleagues, but maybe there is still room for improvement
- First, the high-dose region of the curve approaches a straight line on a log-linear graph:

$$x \rightarrow \infty, \quad S_{x+\delta} = S_x e^{-K_{\text{omega}} \cdot \delta}$$
"Unified Survival Curve", continued

- A “shoulder” caused by dose-related increase in the exponent may be easily incorporated:

\[ S = e^{-K_{\text{growth}} \cdot \alpha \cdot (1 - e^{-K_{\text{growth}} 260/260 Q_{R}})} \]

- But let’s not forget low-dose hypersensitivity, which involves a decaying exponent:

\[ S = e^{-K_{\text{growth}} \cdot \alpha \cdot (1 - e^{-K_{\text{growth}} 260/260 Q_{R}})} \]

And then put it all together, adding in some hypersensitivity data points to the Park data and re-fit the total curve:

At least concordant with the “Universal Survival Curve”: SBRT regimens converted to 2 Gy/fx replacement using that formula.
Liver SBRT trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of lesions</th>
<th>Fractionation</th>
<th>Median FU</th>
<th>Actuarial Local Control</th>
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</thead>
<tbody>
<tr>
<td>Herfarth et al.</td>
<td>55</td>
<td>1 x 14-26 Gy</td>
<td>6 mo</td>
<td>18mo 67%</td>
</tr>
<tr>
<td>Hoyer et al.</td>
<td>141*</td>
<td>3 x 15 Gy</td>
<td>4.3 yrs</td>
<td>2yr 79%</td>
</tr>
<tr>
<td>Milano et al.</td>
<td>293**</td>
<td>10 x 5 Gy</td>
<td>41 mo***</td>
<td>2yr 67%</td>
</tr>
<tr>
<td>Mendez Romero et al.</td>
<td>45</td>
<td>3 x 12.5 Gy#</td>
<td>13 mo</td>
<td>2yr 82%</td>
</tr>
<tr>
<td>U of Colorado (unpublished)</td>
<td>49</td>
<td>3 x 20 Gy</td>
<td>18 mo</td>
<td>2yr 92%</td>
</tr>
</tbody>
</table>

* Total number of CRC metastases; All liver metastases
** Total number of lesions treated; 45% of patients had hepatic metastases treated
*** Surviving patients
# Different fractionation (3 x 10Gy or 5 x 5Gy) used for patients with HCC or lesions < 4 cm

SBRT for liver mets

\[
y = 0.0098x + 0.4083
\]

\[
R^2 = 0.7177
\]

SBRT normal tissue effects in liver and lung

Strategies for setting normal liver dose constraints

- NTCP-based
  - Eg. PMH experience
    - I defer to Dr. Dawson on this one!

- Critical volume model
  - At least 700 cc normal liver received < 15 Gy cumulative
Sample case:
54 Gy cohort
(18 Gy × 3 fxns)

- s/p initial cisplatin and 70 Gy, salvage dissection and brachytherapy for neck recurrence, and later weekly gemcitabine and cisplatin for biopsy-proven liver met
  - Transient minor response

- 6 mos later, Phase I SBRT study enrollment

Case study:
pre-op SBRT for liver metastasis

- Pre-op chemorT for rectal cancer
- SBRT for solitary liver met
- At time of APR, resection of treated liver and new, previously unknown other liver met

Typical post-SBRT normal liver image a few mos after SBRT
Hepatocyte/endothelial damage, central v occlusion = "red cell lakes"

Also common: transient normal liver volume reduction

And another example

**The Human Liver After Radiation Injury**

**Summary**

Therapeutic irradiation of the adult human liver with doses of 3,000 to 5,000 rads was followed by hepatocellular and hepatocellular, non-neoplastic foci, some resembling the lesions of cirrhosis. This was associated with progressive dilatation of small branches of the hepatic venule. The process is interpreted as a variety of non-vascular damage in which collagen tissue appears progressively within vascular channels without preventing dilatation. Possible mechanisms are discussed. In patients who survived more than 12 months there was evidence of remodelling of an effective hepatitis cirrhosis, with regression of the hepatic structures toward normal. Relatively little scarring of the liver developed, even after 10 years.

Olsen et al., in press, IJROBP

Reed GB and Cox AJ. The Human Liver after Radiation Injury. Am J Pathol 1966; 48:597-611
Liver V30 and Mean dose versus percent volume change

Example case:
T1N0 medically inoperable lung cancer

- 62-year-old male, h/o emphysema, on 3-5 L/min supplemental O2
  - 70 pack-yr smoker
- CT in 2003 revealed LUL lesion (T1)
  - Repeat CT 3 mos later showed enlargement of the left upper lobe nodule, up to 1.5 x 2 cm
- Biopsy: adenocarcinoma
- FEV1 0.9 L (28% of predicted)

Treatment: 60 Gy/3 fractions

Characteristic radiographic findings

- Baseline
- 4 mos, CR
- 8 mos, subtle fibrosis
- 12 mos, mature fibrosis
- 18 mos, NED
Caveats interpreting the proximal airway observations

- Note that location could have had an effect on dose calculation with possibly higher doses given to central tumors as a result of the lack of heterogeneity correction?

- Overlooked (?) is the fact that tumor volume was also a significant predictor of toxicity (p = 0.017)
  - GTV > 10 cc had 8-fold higher risk of high-grade toxicity

- The grade 5 toxicities assigned by the data monitoring as possibly related to SBRT are as follows:
  - Four cases of pneumonia
    - Note that pts with medically inoperable NSCLC are susceptible to this event, regardless
  - One patient died from a pericardial effusion
  - One death occurred in a patient who had proven local recurrence and subsequently had massive bleeding—scored as treatment-related toxicity instead of local recurrence!!!
Spectrum of potential indications for SBRT

- Intensified treatment to a primary cancer
  - Stage I lung cancer
  - Best studied to date
  - Primary HCC
  - Pancreas cancer
  - Prostate cancer
  - Favorable due to low alpha/beta ratio
- Treatment of selected spinal/paraspinal lesions
- Palliation for challenging sites of recurrence
  - Retroperitoneal
  - Previously irradiated volumes
- Adjunct systemic cytoreductive therapy
  - "Radical" treatment for isolated liver, lung, and other mets

Prospective Trials of SBRT for Stage I NSCLC*

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>SBRT dose and fractionation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indiana University</td>
<td>4</td>
<td>7</td>
<td>24-66 Gy/3 fractions</td>
</tr>
<tr>
<td>Indiana University</td>
<td>7</td>
<td>60-66 Gy/3 fractions</td>
<td>2 yr local control 95%</td>
</tr>
<tr>
<td>Aarhus University</td>
<td>6</td>
<td>Original fractions</td>
<td>2 yr local control 85%</td>
</tr>
<tr>
<td>Kyoto University</td>
<td>4</td>
<td>50 Gy/4 fractions</td>
<td>1 yr local control 85%</td>
</tr>
<tr>
<td>University of Marburg</td>
<td>3</td>
<td>30 Gy/3 fractions</td>
<td>1 yr local control 80%</td>
</tr>
<tr>
<td>Technical University, Munich</td>
<td>5</td>
<td>37.5 Gy/5 fractions</td>
<td>1 yr local control 87%</td>
</tr>
<tr>
<td>Radiation Therapy Oncology Group (RTOG) 0236</td>
<td>9</td>
<td>60 Gy/3-5 fractions</td>
<td>1 yr local control 98%</td>
</tr>
</tbody>
</table>

*probably an incomplete list*

Overall Survival after SBRT for early stage NSCLC vs conventional

Thanks for your attention!