Immunomodulatory Effects of Stereotactic Body Radiation Therapy

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Financial Relationships

No relevant financial relationship(s) exist
Conflict of Interest

Dr. Grimm designed and holds intellectual property rights to the DVH Evaluator software tool (www.DiversiLabs.com) which is an FDA-cleared product in commercial use, and which has been used for this analysis.

Funding from Accuray, NovoCure

What about the SAMs Questions?

• At least I will be able to show you a picture explaining that immunogenic cell death potentially includes the following molecular events: translocation of calreticulin, release of high mobility group box 1 (HMGB1) from the nucleus, and extracellular passive secretion of adenosine triphosphate (ATP)

• And at least I will be able to explain that the abscopal effect is not just a bystander effect, and is not only observed in preclinical models, and does not happen only from immunotherapy
Can SBRT trigger the body’s immune system? (SAMs question)

Aorta and Major Vessel Dose Tolerance

- Aorta and Major Vessels are among the most radioresistant structures in the body
- For conventionally fractionated treatments we usually don’t even contour them
- Then how can vascular damage be true?
A Single Endothelial Cell

- The smallest capillaries consist of a single endothelial cell
- wrapped around to touch itself


Think Small

- If you want to understand
  - Vascular Damage
  - Immunomodulatory Effects

- You need to think small:
  - Like a single photon…
  - Like a single cell…

Think Small

- Think about a single blood cell
- squeezing through a capillary
- that consists of
- a single endothelial cell

Image from SciencePhotoLibrary
Think Small

- Think about radiation damage
- to the single endothelial cell
- causing leaky blood vessels

Little Things Are Big! - Yogi Berra

- A single endothelial cell can supply blood to about 3000 tumor cells
  - J. Denekamp, Acta Radiologica Oncol, 23, p217, 1984
  - C. Song, Rad Res, 177, p323, 2012

Can SBRT trigger the body’s immune system? (SAMs question)
**RT Exposure/Release of Tumor-Associated Antigens (TAA)s**

- SBRT promotes TAA release leading to antigen uptake/processing by DCs/APCs
- DCs then migrate to the DLN to cross-present TAA to naive T-cells

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**Anti-cancer Effects of SBRT/SRS**

<table>
<thead>
<tr>
<th>DNA-mediated Direct cell death</th>
<th>Immune-mediated (\rightarrow) Indirect cell death (occurs days after irradiation)</th>
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<td>Occurs immediately, manifests over time</td>
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**Immunomodulatory Effects of SBRT: Abscopal Effect**

Preclinical evidence has led to the intriguing hypothesis that local tumor irradiation can potentiate a systemic immune response – this is probably the potential for regression of metastatic cancer outside of the irradiated field (abscopal) shown as the **abscopal effect** potentially mediated by DCs. T-cells recognizing neoantigens upregulated by irradiation.

**Clinical Experience supports the abscopal effect**

- How to correctly identify this unique phenomenon in everyday practice?

- **Neo-adjuvant** treatment (pre-treatment) prior to SBRT +/- immunotherapy

- **Adjuvant** treatment following SBRT

- **Concomitant** treatment during SBRT

**Immunomodulatory Effects of SBRT: Abscopal Effect**

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If these are true, why still use LQ?

• Vascular Damage
• Immunomodulatory Effects
• Stem Cell Effects

• Why do we still use LQ?
  1) It’s the only model with 1000+ citations and data
  2) It still works reasonably well if you are careful
  3) We are still very interested in advanced models
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