Immunomodulatory Effects of Stereotactic Body Radiation Therapy

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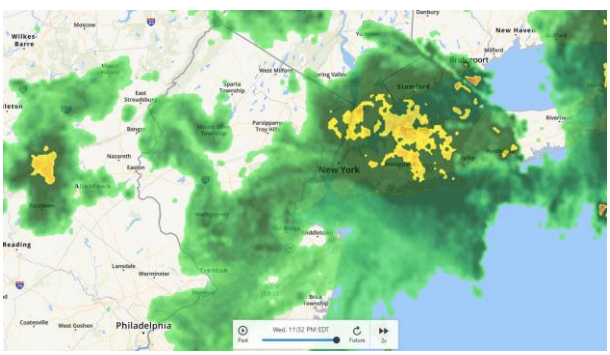
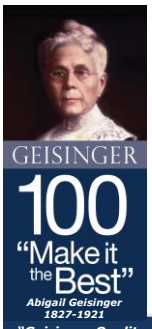
Memorial Sloan Kettering Cancer Center

Financial Relationships

No relevant financial relationship(s) exist

Memorial Sloan Kettering Cancer Center





I am not Dr. Marciscano! But I can at least try to show some implications of Immunomodulatory Effects in the models for SBRT

Jimm Grimm, PhD

AAPM 2019
San Antonio

"Geisinger Quality – Striving for Perfection"

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

FDA 510k Number K092928 Rx Only US Patents 9,019,307 & 9,192,782
www.DiversiLabs.com service@DiversiLabs.com
Soli Deo Gloria

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

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HyTEC Vision Paper

Immunomodulatory Effects of Stereotactic Body Radiation Therapy: Preclinical Insights and Clinical Opportunities

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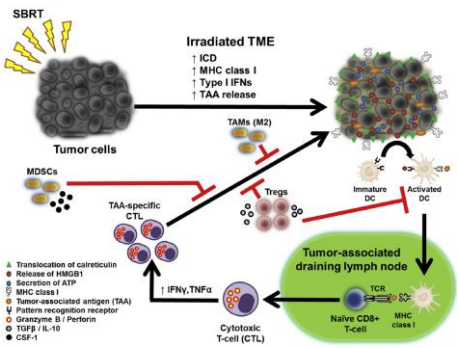
Can SBRT trigger the body's immune system?

(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

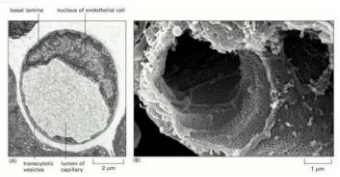


Figure 22-23 Capillaries

(A) Electron micrograph of a cross section of a small capillary in the pancreas. The wall is formed by a single endothelial cell surrounded by a basal lamina.

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

- **Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular Biology of the Cell.**
- **4th edition. New York: Garland Science; 2002**

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

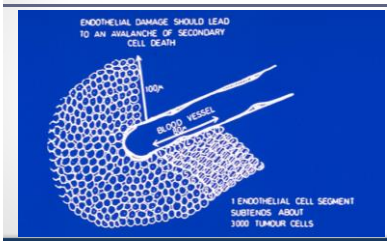
Image from SciencePhotoLibrary

Think Small

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

Image from SciencePhotoLibrary

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**

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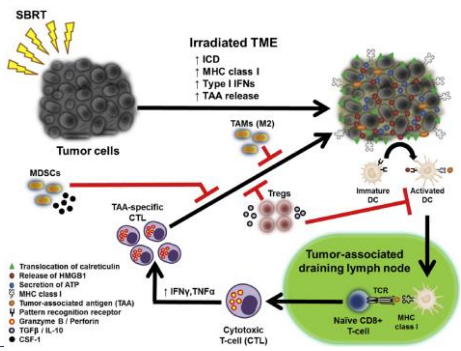
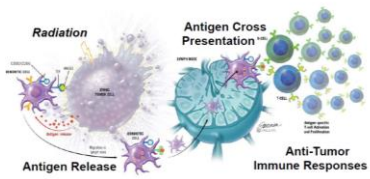
(SAMs question)



RT Exposure/Release of Tumor-Associated Antigens (TAAs)



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

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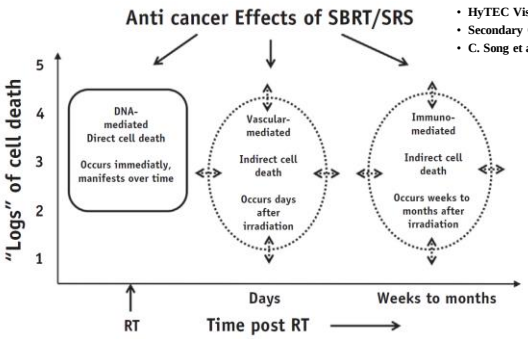
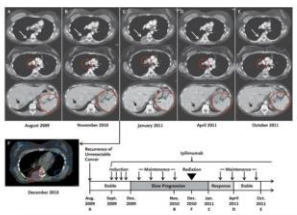
Sharabi AB et al. *Lancet Oncol* 2015



- **HyTEC Vision Paper:**
- **Secondary Cell Death**
- **C. Song et al.**

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 includes the potential for regression of metastatic cancer outside of the irradiated field (ab scopus) known as the **abscopal effect**, potentially mediated by CD8 T-cells recognizing neoantigens upregulated by radiation



Clinical Experience supports that the abscopal effect is real but EXCEPTIONALLY rare

- how to consistently elicit this phenomenon in currently unknown

The Abscopal Effect of Stereotactic Radiotherapy and Immunotherapy: Fool's Gold or El Dorado?

D. Xing [1], S. Siva [1], G.G. Hanna [1]

NEJM report of melanoma pt @ MSK on Ipilimumab (anti-CTLA4) with POD that underwent SBRT 28.5Gy in 3 Fx over 7 days to a paraspinal mass with 6MV photon coplanar 6-field IG-IMRT.

Near complete regression of disease after SBRT while continuing on Ipilimumab

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Postow M et al. *NEJM* 2012

If these are true, why still use LQ?

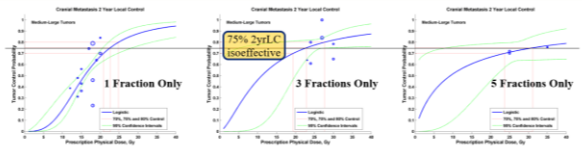
- Vascular Damage
- Immunomodulatory Effects
- Stem Cell Effects

- 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

Medium-to-Large Tumors, Physical Dose Fractionation Comparison: 2-Year Local Control

JOHNS HOPKINS MEDICINE RADIATION ONCOLOGY & MOLECULAR RADIATION SCIENCES



- Each dot is a stratified dose-fractionation-size group from the literature search
- Area of circle is proportional to number of patients in the study
- Logistic model, maximum-likelihood parameter fitting, profile likelihood 95% confidence intervals
- Physical dose in each fractionation, no biological effective dose (BED) model needed

HyTEC Cranial Metastases TCP

Medium-to-Large Tumors, Physical Dose Fractionation Comparison: 2-Year Local Control

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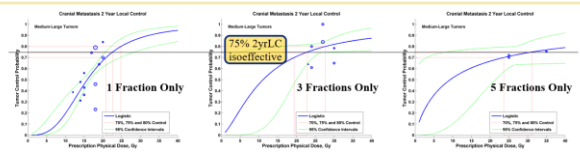

- For medium-to-large sized tumors, the dose required to achieve 75% local control at 2 years was 22.6Gy in 1 fraction, 22.9Gy in 3 fractions, or 31.1Gy in 5 fractions.
- The α/β required to equate 25.6Gy/1fx with 31.1Gy/5fx is much larger than 20 Gy (36 Gy), but that seems abnormally high, so in the following models, **a more conservative α/β=20 Gy was used**

HyTEC Cranial Metastases TCP

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