Radiobiology:
Normal Tissue Effects of Therapy Affecting Clinical Outcome

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Disclosure

• **Employer:** University of Arkansas for Medical Sciences
• I have no conflicts of interest to disclose
Learning Objectives for Radiobiology Session

• Predict patterns of vascular and tumor cell damage in the context of fraction size and therapy approach

• Develop better understanding of determining optimal interval between fractions

• Increase awareness of when immunotherapy or other therapy may be optimally applied and abscopal/crosstalk effects between tumor and normal tissue
Outline

• Normal tissue responses to SRS/SBRT-like dose regimens
  • Pelvic, head and neck as examples

• Vascular and physiological response of normal vs tumor tissue
  • Indirect death mechanisms

• Immune system interaction with vasculature and considerations for improved optimized therapeutic ratios for SBRT application sites
Evolution of High Dose Ablative Radiation

- LDR
- HDR
- EBRT
- SBRT
Stromal cells important in response of normal tissue and tumor tissue to radiation.

1. Vascular response dictates many of the systemic effects of SBRT doses (inflammation, immune system access, indirect cell death)

2. Crosstalk between damaged cells and tissue/tumor regeneration an important factor
Figure 22.7. Isoeffect curves in which the total dose necessary for a certain effect in various tissues is plotted as a function of dose per fraction. Late effects are plotted with solid lines, acute effects with dashed lines. The data were selected to exclude an influence on the total dose of regeneration during the multifraction experiments. The main point of the data is that the isodoses for late effects increase more rapidly with a decrease in dose per fraction than is the case for acute effects. (From Withers HR: Cancer 55:2086, 1985, with permission.)
Figure 18.8. **Left:** Histology of normal testis. **Right:** Histology of testis 35 days after a dose of 9 Gy (900 rad) of γ-radiation. Some tubules are completely devoid of spermatogenic epithelium and some are not. (Sertoli’s cells persist in the tubules sterilized of spermatogenic cells.) Foci of spermatogenesis can be derived from single surviving stem cells. (Magnification ×200.) (From Withers HR, Hunter N, Barkley HT Jr, Reid BO: Radiation survival and regeneration characteristics of spermatogenic stem cells of mouse testis. Radiat Res 57:88–103, 1974, with permission.)
Prostate Tissue after SBRT

37.5 Gy / 5 fx then urinary retention 1 year later requiring TURP

10x - glandular atrophy with no evidence of residual cancer, fibrosis, or necrosis

40x – general hyperplasia and chronic inflammation, nuclear and cytoplasmic cellular changes

Late Toxicity for SBRT vs IMRT

- Retrospective data review from Medicare’s Chronic Condition Warehouse 2008-2011
- SBRT patients younger, fewer co-morbidities, less ADT, racial and socioeconomic differences
Chronic bladder changes include loss of submucosal vessels and fibrosis

Control

20 Gy RT

Blood vessels

Smooth muscle/Collagen

Thrombomodulin Expression

Head and Neck: Salivary gland as a measure of radiation effects on normal tissue vasculature in head and neck

Lombaert et al. Clin Can Research, 2008:

Fig. 4. Quantification of radiation-induced vascular damage. A, CD31 expression highlighted the presence of dilated blood vessels 90 d after IR, which are absent in normal glands (inset). B, quantification of the dilated blood vessel area (≥200 μm²) revealed a significant reduction in radiation-damaged blood vessels after G-CSF (IR + G-CSF) treatment compared with untreated irradiated (IR) glands. This effect was even more pronounced in the F/S/G group. Further visualization (C) and quantification (D) of capillaries (≤10 μm²) revealed a pronounced decrease in irradiated glands (IR). Glands from the G-CSF-treated (IR + G-CSF) and F/S/G-treated (IR + F/S/G) groups contained significantly more capillaries compared with untreated, irradiated ones. Bar, 50 μm. * P < 0.05.
Outline

• Normal tissue responses to SRS/SBRT-like dose regimens

• Vascular and physiological response and crosstalk of normal vs tumor tissue

• Immune cell interactions with tumor vasculature and considerations for improved optimized therapeutic ratios for SBRT application sites
Tumor is filled with normal tissue (stroma):

Photoacoustic mapping of ear vasculature and photofluorescent scanning of tumor mass co-opting the normal tissue
FSaII tumors: blue, perfusion (hoechst dye), green, hypoxia (pimonidazole, red, endothelium/vessels (anti-CD31) : 20x magnification

Control tumors  
n=2

24 h after 20 Gy  
N=4

48 h after 20 Gy  
N=4

Song, CW, Griffin RJ et al, Red Journal 2015
Indirect cell death from vascular damage in SBRT

Song CW, Griffin et al, IJROBP: 2015
Damaged, adhesive endothelium: conduit between tissue and immune/inflammatory system

Choi and Pober et al.  
Annu. Review Immunology 2004
**Therapy-induced apoptosis and tissue damage connected to tumor recurrence**

*Huang and Li et al, Nature Medicine 2011*

*Figure 1* Huang *et al.* show that cytotoxic oncology therapies induce caspase 3 activation, which, in turn, can generate competing effects on apoptotic cell death and stimulation of tumor growth. Thus, the balance between these two competing processes determines the final outcome for the tumor: shrinkage or recurrence. AA, arachidonic acid; iPLA$_2$, calcium independent phospholipase A$_2$. 

Katie Vicari
Normal tissue damage also influenced by apoptotic pathway and dual roles of caspases leading to stem cell proliferation/regeneration

C-Y Li et al, Science Signaling, 2010
Additional recent additions to the story:

Senescence and targeting for improved normal tissue outcomes

Cellular senescence promotes adverse effects of chemotherapy and cancer relapse
*Cancer Discovery, Campisi, Zhou et al. Online Dec. 2016*

Inhibition of Bcl-2/xl with ABT-263 selectively kills senescent Type II pneumocytes and reverses persistent pulmonary fibrosis induced by ionizing radiation in mice
Jin Pan, Martin Hauer-Jensen, MD & PhD, Daohong Zhou, MD, Aimin Meng, MD et al.
*Accepted Feb 2017, Int J Radiat Onc Biol Phys*
Methods to overcome dose thresholds for SBRT and maintain therapeutic ratio

• Hypoxic tumor and vessels may comprise up to 20% of tumor, overall hypoxia even higher in many solid tumors.

• Destroying part or all of the hypoxic core with targeted agents or thermal therapy may complement SBRT and allow lower doses to be applied.

• New (old) use of conventional hyperthermia or other DNA damage inhibitors would allow SBRT to be applied to more tumor types, using lower radiation doses.
Outline

• Normal tissue responses to SRS/SBRT-like dose regimens

• Vascular and physiological response of normal vs tumor tissue

• Immune cell interactions with tumor vasculature/damage response and considerations for improved/optimized therapeutic ratios for delivering radiotherapy
Immune cell activation by radiation

- Ahmed Radiation Res, 2014

FIG. 1. Schematic representation of the envisioned mechanism of radiation-primed immunotherapy of advanced cancer.
Lattice irradiation promotes local and abscopal effects to greater extent than open field: increased tumor specific cytokines

Microbeam spatial fractionation suggests benefit of improved normal tissue response

Maximizing target dose while maintaining normal tissue integrity: interspersing MRT fields at ESRF
Microbeam spatial fractionation suggests benefits of improved normal tissue response.

Fig. 1. Horizontal section of the cerebellum of a piglet of 15 months after irradiation with a skin entrance dose of 300 Gy. Some cells and their nuclei directly in the path of microbeams were destroyed. There was no tissue destruction present, nor were there signs of hemorrhage. The paths of the microbeams appear in the section as thin, white horizontal parallel stripes, which are more easily visible in the insert. Beam width ~27 μm, spacing ~210 μm.
16 d after MRT; cerebellum

16 d after MRT; cerebellum, evidence of vascular bridging/repair
Typical MLC segments or block used for GRID

GRID Block for Linac
Manipulating the immune response/access to tumor antigens with radiotherapy: Spatial fractionation case report

Squamous cell carcinoma of unknown primary- decided to just treat the neck node (thinking it would not be controlled).

**GRID 2000 cGy 9/16/16**
10/24-11/18/16 250cGy x 19 (prescribed 20)

Followed with Pembrolizumab (PD1 inhibitor)

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Details</th>
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<tbody>
<tr>
<td>8/18/2016</td>
<td>Initial Diagnosis</td>
<td>Squamous cell carcinoma of head and neck; unknown primary; p16 negative.</td>
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<tr>
<td>9/12/2016</td>
<td>Chemotherapy</td>
<td>Docetaxel 75 mg/m2, Cisplatin 100 mg/m2, 5-FU 1000 mg/m2/d CIV 4 days</td>
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<tr>
<td>9/16/2016 - 11/18/2016</td>
<td>Radiation</td>
<td>RT to neck mass x 1 session. Planning up to 30 sessions - started 10/24/16</td>
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<tr>
<td>9/29/2016</td>
<td>Chemotherapy</td>
<td>Cetuximab - Anaphylactic reaction- intubated and admitted - discharged on 10/7/16</td>
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<tr>
<td>10/24/2016</td>
<td>Chemotherapy</td>
<td>Pembrolizumab 200 mg every 3 weeks</td>
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Different pneumonitis patterns related to anti-PD1 therapies.

Conclusions/Summary

• Vascular, immune activation key to local and systemic normal tissue effects of therapy.
• Sequence/Frequency of (hypo) fractions needs to be carefully considered for all goals in each patient.
• Thoughtful planning can be utilized to minimize volumes in high dose field to minimize toxicity.
• All SBRT is not the same: spatial fractionation?, immune cell engagement considerations
• Consider new approaches of lower doses to complement other treatments and logic
• “Practice changing” : Have to begin to think of radiotherapy as a local AND systemic treatment, affecting both target, surrounding tissue and other ‘normal’ systems by inflammatory/abscopal crosstalk.
• Keep the pulse on new approaches to control inflammation, sensitize stroma and issues surrounding incorporation of immunotherapy.
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