Localized Radiation Can Induce Systemic Anti-Cancer Immune and Non-Immune Responses and How We Might Utilize It

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THE VIEWS AND OPINIONS PRESENTED HERE DOES NOT REFLECT THE OPINIONS OF NIH OR NCI. IT IS BASED ON EXPERIMENTS DONE IN MY PREVIOUS INSTITUTIONS.

Non-targeted Radiation Effects

Radiation-induced systemic effect
Non-immunological

Direct and Indirect effects of SFORT

Animal Studies
GRID for animals
The results demonstrate that high-dose SFGRT or conventional IR (CIR) exposure to LT induces the release of factors such as cytokines/ceramide causing distant effect such as regression of the un-irradiated RT.

Further, exposure of RT to fractionated CIR resulted in enhanced effects on LT leading to time reversal effect.
Activation of SSMase is also detectable in serum from SFGRT-treated patients

SFRT increases the concentration of ceramide in serum
IMMUNOLOGICAL EVENTS

### Innate Immunity

**Components**
1. Physical and chemical barriers
2. Phagocytes
3. Inflammatory mediators
4. Natural killer cells
5. Plasma proteins (complement)

**Activity**
- Always present
- Broadly reactive

**Response and Potency**
- Immediate response, but has a limited and short duration.

**Specificity**
- Cannot recognize specific classes of pathogens (e.g., bacteria, viruses, fungi, parasites), but rather changes the environment to make it hostile to the pathogens.

**Course**
- Requires an immediate trigger, such as bacteria or viruses.

**Memory?**
- No - needs re-exposure to the same pathogen.

### Adaptive Immunity

**Components**
1. Humoral immunity (B cells, which make antibodies)
2. Cell-mediated immunity (T cells, which activate effector T cells and cytotoxic T cells)

**Activity**
- Can be acquired and are specific.

**Response and Potency**
- Slower response (over 1-2 weeks), but is more potent.

**Specificity**
- Recognizes highly specific antigens.

**Course**
- Requires a slower response, allowing time for activation of specific cells.

**Memory?**
- Yes - memory cells "remember" the specific pathogen and respond more quickly upon re-exposure.

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**A Schematic view of RT-induced immune modulations**
Radiation can
- Impact both innate and adaptive immunity
- Provide a source of robust tumor antigens
- Induce cytokines that can help to alter the profile and function of immune infiltrates
- Remodels the stromal and angiogenic compartments of the tumor microenvironment

More importantly
Surviving tumor cells after radiation therapy are more sensitive to immune-mediated killing

CHALLENGES

There are potential concerns that high-dose radiation to the whole tumor volume can eliminate tumor specific cytotoxic T cells.

Can irradiation of the partial tumor volume be equally effective as irradiating full tumor volume?

To answer this challenge, we investigated the tumor regression and immune modulation factors by comparing the effects of radiation to full tumor volume versus different partial volumes.
The Lewis lung carcinoma 1 (LLC1), a mouse cancer cell was used to develop syngenic tumors in C57BL/6 mice.

Single fraction, high-dose LRT significantly delayed growth of both local and distant tumors

- Mice treated with two lattice 10% vertices had reduced tumor growth both locally and distantly suggesting that 20% irradiated tumor volume has the potential to cause delay in the growth of the primary tumor (bystander event) and of the distant unirradiated tumor (systemic/abscopal effects).

- However, when 20% of the tumor volume was irradiated in a single vertex the effects on tumor growth were less than two 10% vertices group.

- On the contrary, the conventional open field IR to the whole tumor was more effective in the directly irradiated left tumor compared to the unirradiated right tumor.

- Interestingly, lattice single (50%) vertex did not have any significant effect on the growth of irradiated tumor but had systemic effect on distant unirradiated tumor.
Together, the tumor growth and the immune response data presented here suggest that high-dose LRT if delivered in a way that directly irradiates only about 20-50% of the tumor volume either alone or followed by open field radiation therapy could be an important strategy to exploit immune modulation for local as well as distant/metastatic tumor killing.

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Note: ↑ indicates upregulation over control and ↓ indicates downregulation over control. ND: not done, NC: no change.

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Conclusion
Lattice Radiation Treatment at BLK Cyberknife Center

Un-resectable Sarcoma
7 cGy x 3 Margin
18 Gy x 3 Maximum

Lattice Radiotherapy with RapidArc for Treatment of Gynecological Tumors

- The dose coverage of the ImTVs by the DCs was as originally planned, with the strategy that full coverage would not be required to elicit the responses desired.
- Since normal tissue constraints for the summed plans were attainable in all but one case, larger DCs with better ImTV coverage is possible.
- There were no grade 3 acute side effects seen and overall acute toxicity that was comparable to past experience with standard fractionation alone.
- The approach is feasible and well-tolerated acutely.


Chilling Question!!!!

Can we adopt “partial tumor radiation” in the clinic?

General consensus will be “NO”

BENEFITS

Partial high-dose irradiation promote intra-tumoral cytokine induction that can attract T-cell infiltration imparting a highly immunogenic tumor microenvironment.

- This concept of partial volume can be exploited in situations where whole tumor irradiation is not possible due to toxicity to critical surrounding normal tissue structures.
Chilling Question!!!!

If we adopt “partial tumor radiation” in the clinic, then how this can be utilized without compromising standard of care?

High-dose Partial radiation and standard of care

As an induction regimen

As a high-dose hypofractionation regimen

Days 1 5 9 13

Lattice Radiotherapy (8-12 Gy)

Chilling Question!!!!

Standard fractionation radiation has been reported to convert an inflamed tumor to non-inflamed tumor (Tolerogenic environment or immune tolerance).

Can space-time-fractionation (STF) be adopted to eliminate the occurrence of tolerogenic environment?
Animal Study
Slit-beam Block with kV-X

GI Toxicity Study
Open-beams block
Slit-beams block
310 cGy x 10
Open field
500 cGy/1x x 10
(5xPosition 1 + 5xPosition 2)
BED(α/β=5) = 50 Gy

UT STF Open
Space-Time Fractionated IMRT for Prostate Ca

Fractions 1,3,5... to Slice 1,3,5
Fractions 2,4,6... to Slice 2,4,6

Space-Time Fractionation (STF)
Anticipated advantages
1. Reduced toxicity
2. Same or improved tumor control
3. Dose escalation without increasing complication
4. Retreatment with reduced risk
5. Suitable for both low and high α/β
6. New BID scheme
7. Protecting immunogenicity
8. Can this be generalized for standard fractionation?

Take-home Thought Provoking Concept
New standard of care in radiotherapy

12-24 Gy
40-60 Gy

Preserving/boosting immunogenicity
Sustained systemic/abscopal effect
Broad window for adjuvant immunotherapy
Preserving reduced toxicity
Targeting tumor endothelium
Intra-tumoral bystander effect
Auto-Radiosensitization
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