National Cancer Institute

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

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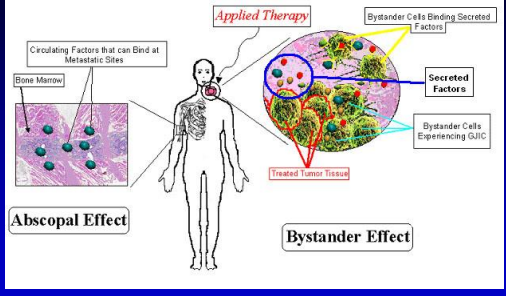
THE VIEWS AND OPINIONS PRESENTED HERE DOES NOT REFLECT THE OPINIONS OF NIH OR NCI. IT IS BASED ON EXPERIMENTS DONE IN MY PREVIOUS INSTITUTIONS.

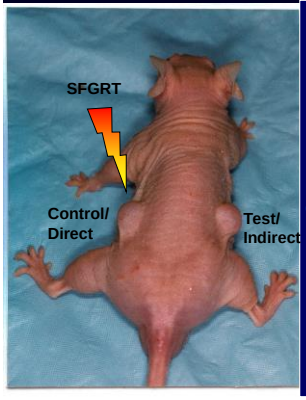
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Non-targeted Radiation Effects



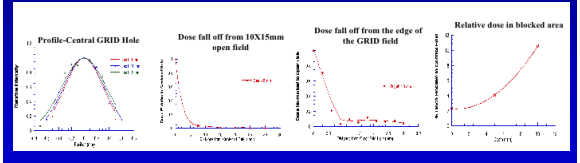
Peters ME, Shareef MM, Gupta S, Zagurovskaya-Sultanov M, Kadhim M, Mohiuddin M, Ahmed MM. Potential utilization of bystander/abscopal-mediated signal transduction events in the treatment of solid tumors. Current Signal Transduction Therapy. 2007 May;2(2):129-43.

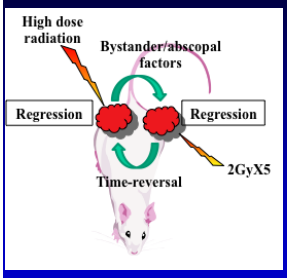
Radiation-induced systemic effect
Non-immunological



Direct and Indirect effects
Of SFGRT

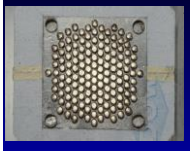
Animal Studies
GRID for animals

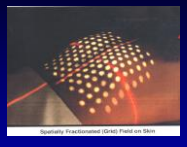


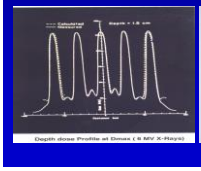


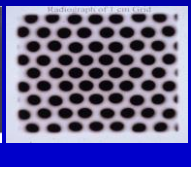
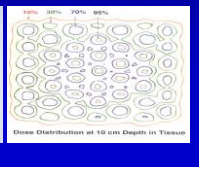
- The results demonstrate that high-dose SFGRT or conventional IR (CIR) exposure to LT induces the release of factors such as cytokines /ceramide causing distant effect such as regression of the un-irradiated RT.
- Further, exposure of RT to fractionated CIR resulted in enhanced effects on LT leading to time reversal effect.

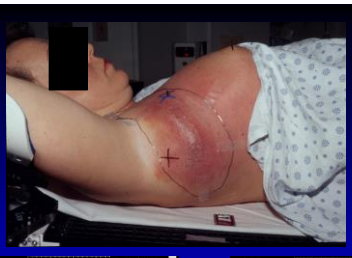
CLINICAL SFGRT



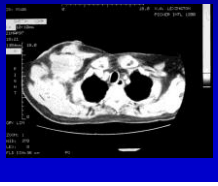
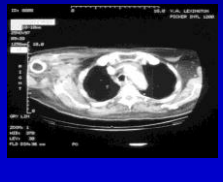




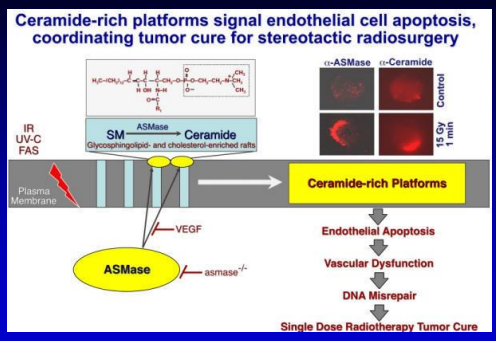





Recurrent Melanoma

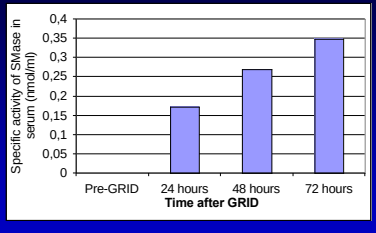



Of notable….

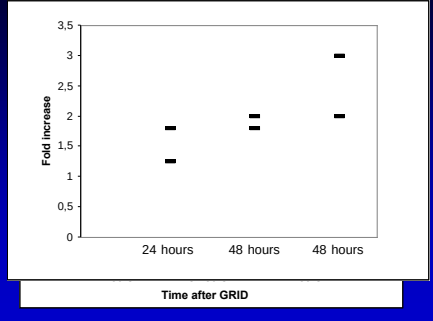


Kolesnick Group

Activation of SSMase is also detectable in serum from SFGRT -treated patients



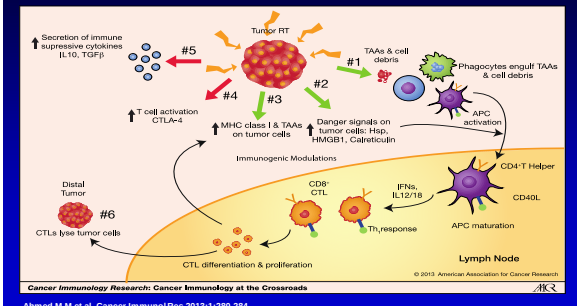
SFRT increases the concentration of ceramide in serum



IMMUNOLOGICAL EVENTS

	Innate immunity	Adaptive Immunity
Components	1. Physical and chemical barriers 2. Phagocytic leukocytes 3. Dendritic cells 4. Natural Killer cells 5. Plasma proteins (complement)	1. Humoral immunity (B cells, which mature into antibody secreting plasma cells) 2. Cell-mediated immunity (T cells, which mature into effector helper and cytotoxic T cells)
Activity	Always present	Normally silent
Response and potency	Immediate response, but has a limited and lower potency	Slower response (over 1-2 weeks, but is much more potent
Specificity	General: can recognize general classes of pathogens (i.e. bacteria, viruses, fungi, parasites) but cannot make fine distinctions	Recognizes highly specific antigens
Course	Attempts to immediately destroy the pathogen, and if it can't, it contains the infection until the more powerful adaptive immune system acts.	Slower to respond; effector cells are generally produced in 1 week and the entire response occurs over 1-2 weeks. However, this course can vary somewhat during different responses in an individual.
Memory?	No--reacts with equal potency upon repeated exposure to the same pathogen.	Yes--memory cells "remember" specific pathogens; upon re-exposure to a pathogen, these cells mount a much faster and more potent second response

A Schematic view of RT-induced immune modulations



Ahmed M M et al. Cancer Immunol Res 2013;1:280-284

Immune modulators

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

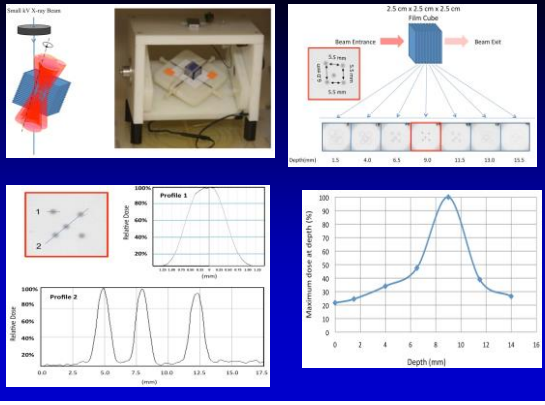
CHALLENGES

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

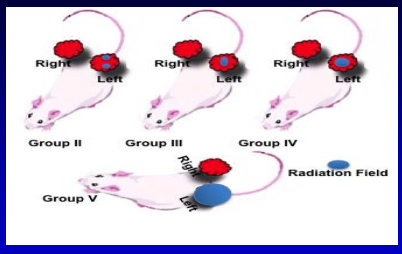
Can irradiation of the partial tumor volume be equally effective as irradiating full tumor volume?

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.

Mouse Irradiation

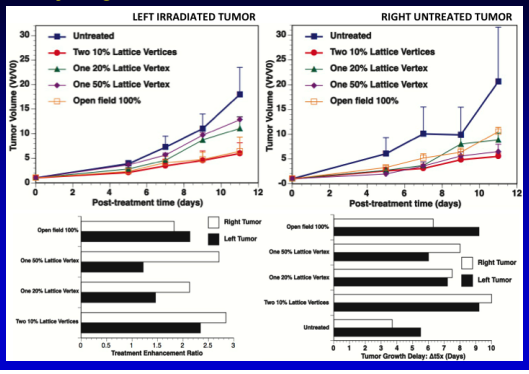


MOUSE MODEL AND SCHEMES



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



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.

LATTICE RADIOTHERAPY AND IMMUNE MODULATION

Secretion or Levels of Several Factors after LRT or Open-Field Irradiation Compared to Untreated Controls in the Serum Obtained at Days 3 or 7 after Irradiation

	LRT						Open field	
	Two 10% vertices		One 20% vertex		One 50% vertex		100%	
Factors	Day 3	Day 7	Day 3	Day 7	Day 3	Day 7	Day 3	Day 7
IFN-γ	↑	NC	↑	NC	↑	NC	↑	NC
IL-2	NC	NC	NC	NC	↑	↑↑	NC	↑↑
IL-4	↓	↓↓	NC	↓	↓	↓↓	NC	↑
IL-10	↓↓	NC	↓	↑	↓↓	↓↓	↓	NC
KC	↓	NC	↓	↓	↓	↓↓	↓	↓↓
ASMase	ND	↑↑	ND	↑	ND	↑↑	ND	↑
TNF-α	↑↑	↑	↑↑	↑	↑↑	↓	↑↑	↑

Notes. ↑ Indicates upregulation over controls and ↓ indicates downregulation over controls. ND = not done; NC = no change.

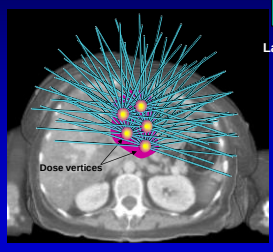
Kanagavelu, S., Gupta, S., Wu, X., Philip, S., Wattenberg, M. W., Hodge, J. W., Couto, M. D., Chung, K. D. and Ahmed, M. M. In Vivo Effects of Lattice Radiation Therapy on Local and Distant Lung Cancer: Potential Role of Immunomodulation. Radiat. Res. 182, 149–162 (2014).

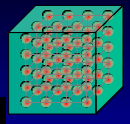
Conclusion

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.

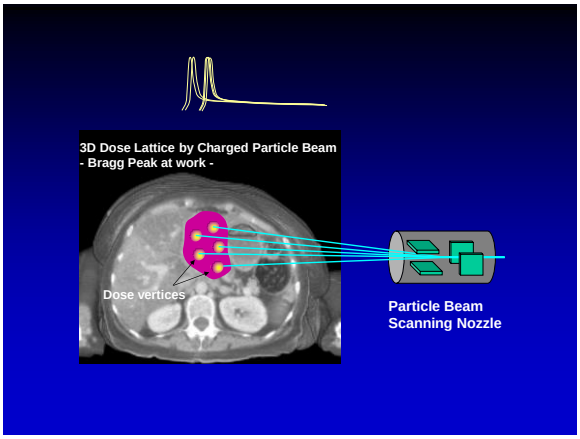
CLINICAL UTILITY OF LATTICE RADIOTHERAPY

3D Dose Lattice by focused beam





Lattice Radiotherapy

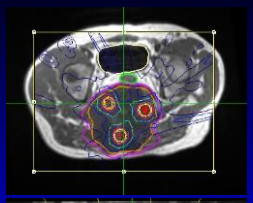


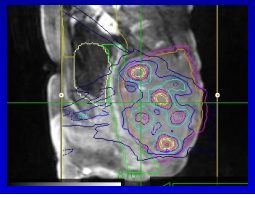
Lattice Radiation Treatment at BLK Cyberknife Center

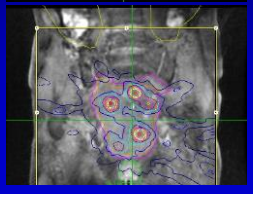
Un-resectable Sarcoma

7 cGy x 3 Margin

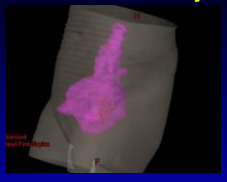
18 Gy x 3 Maximum

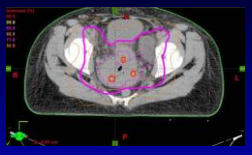


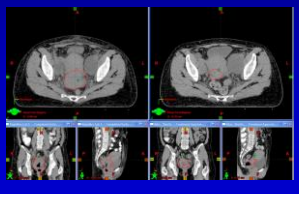




Lattice Radiotherapy with RapidArc for Treatment of Gynecological Tumors

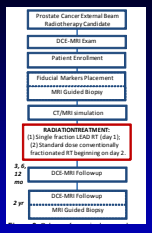


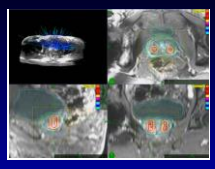




Amendola B E, Perez N, Amendola M a., Wu, X., Ahmed, M.M., et al. (2010-09-27 14:30:56 UTC) Lattice Radiotherapy with RapidArc for Treatment of Gynecological Tumors: Dosimetric and Early Clinical Evaluations. Cureus 2(9): e15. doi:10.7759/cureus.15

LATTICE EXTREME ABLATIVE DOSE (LEAD) TRIAL





- 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.

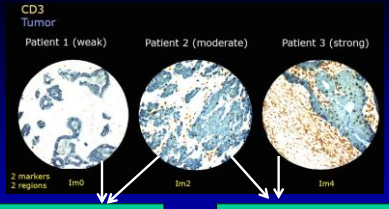
Prostate Cancer Phase 1 Lattice Extreme Ablative Dose (LEAD) Trial: Feasibility and Acute Toxicity. Pollack, A. et al. International Journal of Radiation Oncology • Biology • Physics , Volume 90 , Issue 1 , S455

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.

Partial irradiation of tumor will still have these infiltrating cells (CD3+/CD4+/CD8+) in the unirradiated areas that can promote stronger immunogenic cell death than the open field irradiation.

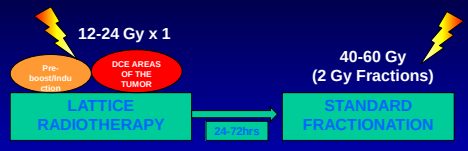
- This concept of partial volume can be exploited in situations where whole tumor irradiation is not possible due to toxicity to critical surrounding normal tissue structures.

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



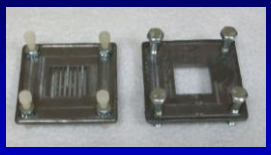
As a high-dose hypofractionation regimen

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

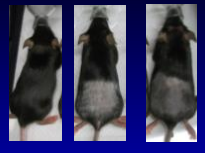
Slit-beams block

310 cGy x 10
Open field

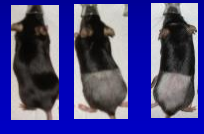
500 cGy/fx x 10
(5xPosition 1 + 5xPosition 2)

BED(α/β=5) = 50 Gy

5 Gy x 5 3.1 Gy x 10

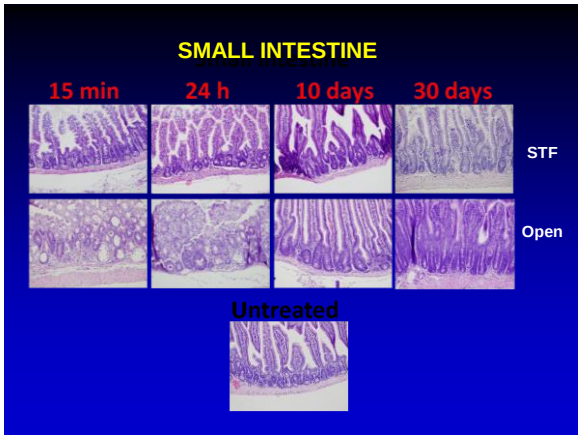


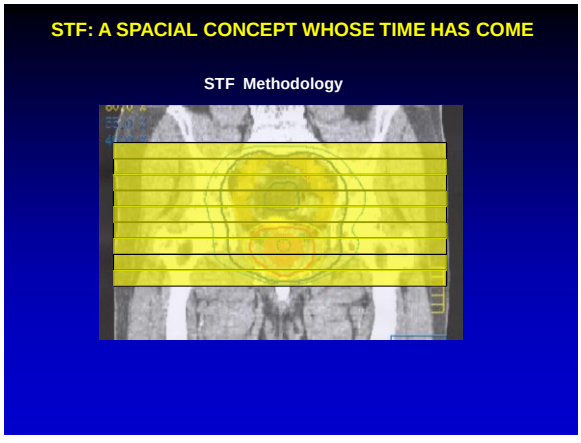
1 Month

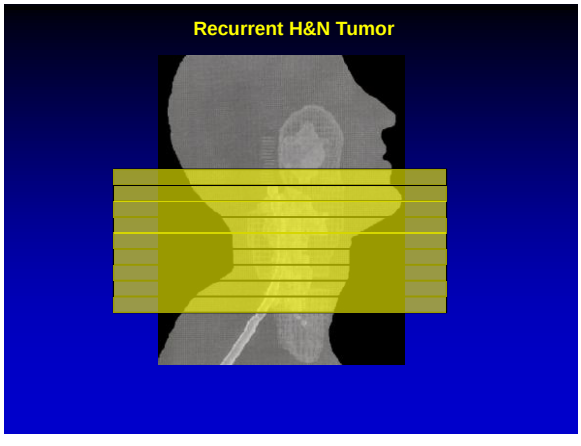


2 Months

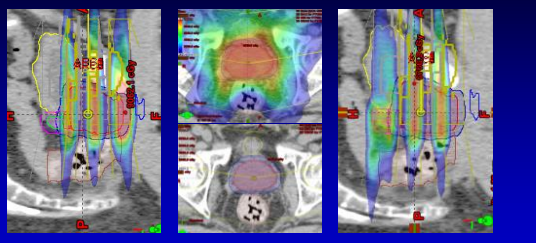
UT STF Open


SMALL INTESTINE
15 min
24 h
10 days
30 days
STF
Open
Untreated


STF: A SPACIAL CONCEPT WHOSE TIME HAS COME
STF Methodology


Recurrent H&N Tumor

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

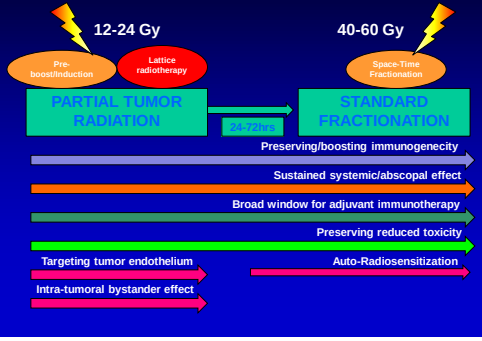
SPACE-TIME FRACTIONATION (STF)

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

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