Non-Standard uses of Radiotherapy to Induce Immune Modulation: Low-dose Radiation Therapy and Partial Radiation Therapy

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DISCLAIMERS

THE VIEWS AND OPINIONS PRESENTED HERE DOES NOT REFLECT THE OPINIONS OR ENDORSEMENTS OF NIH OR NCI.

This talk will focus to discuss published and unpublished data originated from my previous affiliation and from other laboratories

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Non-standard of care Radiotherapy

- Low-Dose Fractionated Radiotherapy (LDFRT)
- Partial volume radiation

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"Shades of Gy" in immunobiology of Radiation Oncology

The dose of radiation per fraction and the number of fractions

Clinically relevant dose
(1.8 to 2.2 Gy)

Low-dose RT
(0.1 Gy to 1 Gy)

High-dose RT / ablation
(8 Gy and above)

Robust immune activation has been reported at opposite ends of the dose spectrum.

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LDFRT: Underlying molecular mechanisms

	Normal cells	Tumor cells
IRR (LDFRT (<0.5 Gy)	ATM activation and DNA repair programs induced	Bax upregulation with Bcl-2 down-regulation, pro-apoptotic proteins upregulated
IRR dose (>1 Gy)	ATM activation and DNA repair programs induced	ATM activation, pro-survival transcription factors (NFκB and NF-Y) upregulated, MEK-1 upregulated
LDFRT + chemotherapy	No data	Bax upregulation with Bcl-2 down-regulation, cytochrome-C release, several pro-apoptotic proteins are upregulated XIAP was downregulated, but upregulated in LDFRT-resistant cells
IRR dose + chemotherapy	No data	Bcl-2 and PDK1 protein increased, increase in NFκB and NF-Y activity XIAP is significantly upregulated

IRR, induced radiation resistance; IRRS, hyper radiation sensitivity; LDFRT, Low Dose Fractionated Radiation Therapy

Prasanna et al. New biology of hypo- and hyper-fractionated radiation therapy. Journal of Thoracic Disease, Vol 6, No 4 April 2014

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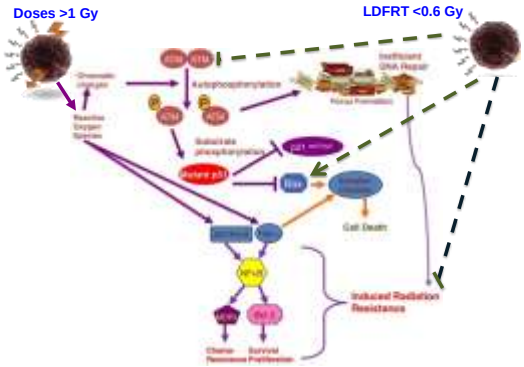
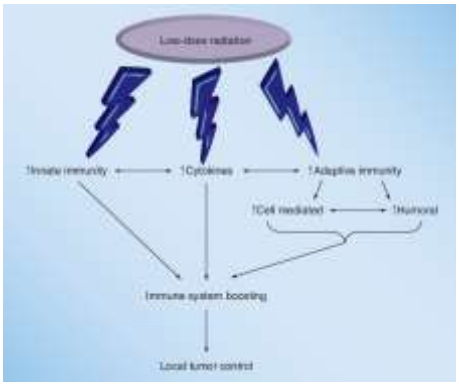
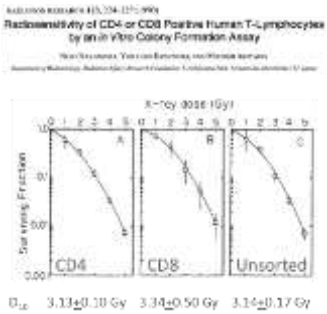
Reported molecular events in IRR and LDFRT.



Prasanna et al. New biology of hypo- and hyper-fractionated radiation therapy. Journal of Thoracic Disease, Vol 6, No 4 April 2014



Farooque A, Mathur R, Verma A, et al. Low-dose radiation therapy of cancer: role of immune enhancement. *Expert Rev Anticancer Ther.* 2011;11(5):791-802

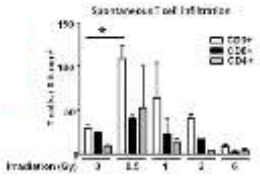


D_{10} 3.13±0.10 Gy 3.34±0.50 Gy 3.14±0.17 Gy

D_{10} for CD4 and CD8 is 3-3.5 Gy:

- Increased Th1 response that attract naïve T-cells and promote its differentiation and activation.

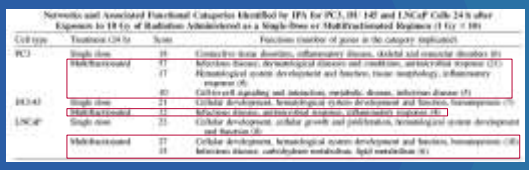
- Low dose chronic and acute irradiation stimulate enhanced immune function leading to in-situ vaccination, trafficking, infiltration and killing.



0.5 Gy is associated with greatest number of infiltrating T-cells with redirecting macrophage differentiation from a "tumor-promoting/immunosuppressive state" to one that enables CTLs to infiltrate tumors and kill cancer cells. Hence, homing of activated T-cell is increased in tumor milieu.

Klug *et al.* Cancer Cell 24, 589–602, November 11, 2013

1 Gy fractions can robustly activate immune gene program that can be conducive for trafficking and homing of T-cells that is similar to antimicrobial / inflammatory response.



Aryankalayil, M. J., Makinde, A. Y., Gameiro, S. R., Hodge, J. W., Rivera-Solis, P. P., Palayoor, S. T., Ahmed, M. M. and Coleman, C. N. Defining Molecular Signature of Pro-Immunogenic Radiotherapy Targets in Human Prostate Cancer Cells. Radiat. Res. 182, 139–148 (2014).

Is the use of low-dose fractionated radiation therapy tested in the clinic?

Reported clinical trials combining LDFRT with chemotherapy in solid tumors

Prasanna et al. New biology of hypo- and hyper-fractionated radiation therapy. Journal of Thoracic Disease, Vol 6, No 4 April 2014

Open clinical trials combining LDFRT with chemotherapy in solid tumors

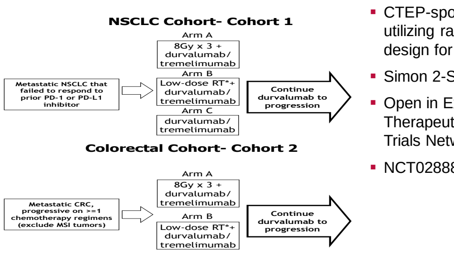
Clinical trial parameters	Phase II		
Site	Recurrent Anaplastic Astrocytoma and Glioblastoma Multiforme	Recurrent and Inoperable SCCHN	Recurrent Unresectable Locally Advanced SCCHN
Design	Temozolomide 150 to 200 mg per square meter for 5 days during each 28-day cycle; LDFRT 0.3 Gy of radiation therapy twice daily with the first six 28-day cycles of temozolomide	No description available	Erbitux 400 mg/m² as a loading dose one week prior to radiation and taxotere, and then at 250 mg/m² given weekly on Mondays. Taxotere 20 mg/m² IV once a week on Mondays on weeks 2 to 7. LDFRT 0.5 Gy per fraction BID at least 6 hours apart on Tuesday and Wednesday of weeks 2 to 7 for a total dose of 12 Gy
Duration	1 year	Not available	3.5 years
Recruitment	[illegible]	30	35
Clinicaltrials.gov identifier	[illegible]	[illegible]	[illegible]

Prasanna et al. New biology of hypo- and hyper-fractionated radiation therapy. Journal of Thoracic Disease, Vol 6, No 4 April 2014

EXPLOITING LOW-DOSE RADIATION IMMUNE MODULATION WITH CANCER IMMUNOTHERAPY

- **Augment dendritic cell maturation such as TLR or CD40 agonist or IFN-β to further intensify anti-tumor immunity effects.**
- **Kinetics of immune gene activation in tumor cells treated with 1 Gy multi-fraction demonstrates that the opportunistic widow (inflection point) to exploit the maximal immune function for adjuvant immunotherapy is around 6-10 Gy total dose.**
- **Cancer vaccines and adoptive T-cell therapy could boost radiation-induced in-situ vaccination.**
- **Furthermore, agonistic antibodies directed against co-stimulatory/co-inhibitory molecules on T cells can synergize an increase in T-cell function.**

CTEP 10021: Jonathan Schoenfeld & Arta Monjazeb

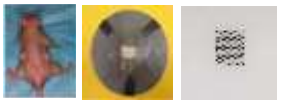


- CTEP-sponsored trial utilizing randomized design for NSCLC
- Simon 2-Stage for CRC
- Open in Experimental Therapeutics Clinical Trials Network
- NCT02888743

Partial Radiation Therapy

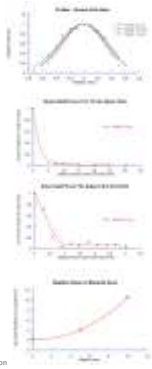
Spatially Fractionated High Dose Radiation Therapy
(Grid and Lattice)

In-vivo: NUDE MICE studies using A549 cells



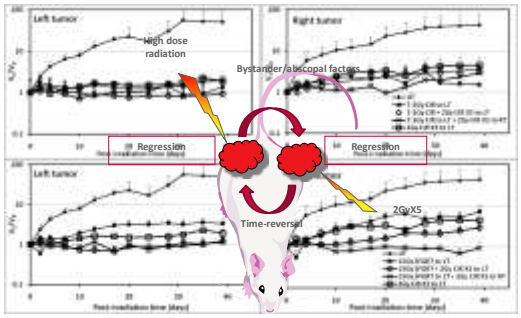
Low energy GRID

Film showing the GRID field



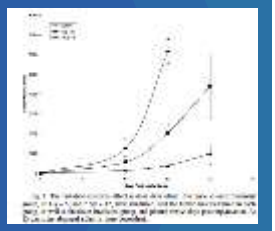
Gupta S, Zagurovskaya M, Wu X, et al. Spatially Fractionated Grid Highdose radiation-induced tumor regression in A549 lung adenocarcinoma xenografts: cytokines and ceramide regulators balance in abscopal phenomena. Sylvester Comprehensive Cancer Center, 2014:20.

Tumor growth curves



TARGET LOCATION AND TUMOR VOLUME

- Visceral metastasis irradiation results in more abscopal events than irradiation of osseous metastatsis.
- Even normal tissue can evoke abscopal response

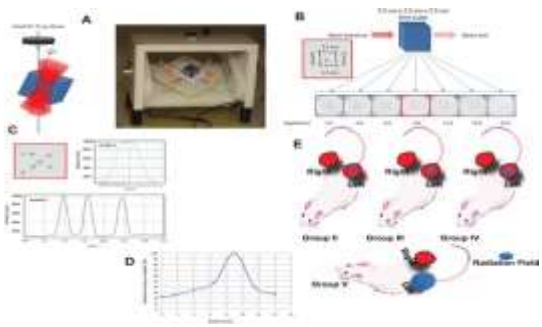


TARGET LOCATION AND TUMOR VOLUME

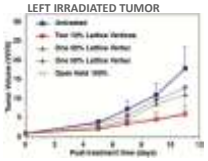
- Larger treatment field tend to expose circulating lymphocytes that can impact proliferating T-cells and T-cell priming in draining lymph nodes.
  - This is similar to protracted RT regimens that are lymphotoxic which may lead to T-cells clearance and lymphopenia.

To protect lymphocytes and T-cells and reduce lymphopenia, one can adopt strategies such as reducing the treatment field size, shortening beam-on treatment times, hypofractionation lattice radiotherapy.

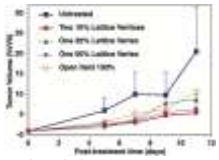
Rotational delivery device for high-dose LRT delivery in immune efficient mice



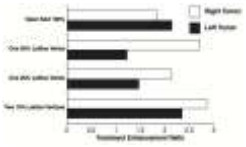
LEFT IRRADIATED TUMOR

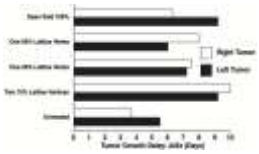


RIGHT UNTREATED TUMOR

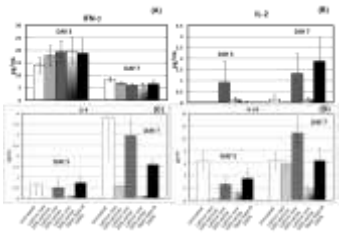


Mice treated with lattice two (10%) vertices led to reduced tumor growth both locally and distally





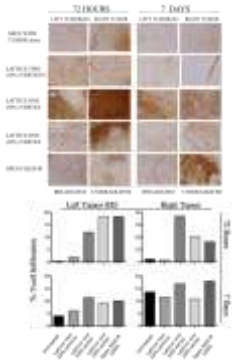
LRT and Immune modulation



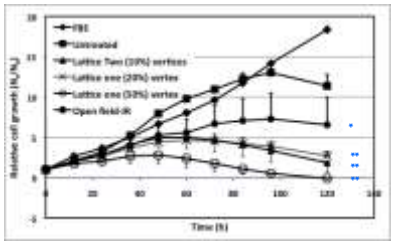
LRT showed a strong effect on the cytokines secretion involved in cellular responses (Th1 mediated).

There was a significant decrease of both IL-4 and IL-10 secretion in serum obtained from lattice one (50%) vertex at both time points. Treatment with lattice two (10%) vertices significantly reduced IL-4 and IL-10 secretion in serum though IL-10 levels returned to normal on day 7. **These results clearly demonstrate that LRT induces cellular mediated immune responses.**

- Lattice one (50%) vertex and lattice one (20%) vertex significantly enhanced CD3 infiltration in both irradiated and unirradiated tumors.
- Lattice one (50%) vertex treatment consistently enhanced CD3+ T cells infiltration compared to other LRT and open field IR treatments.
- Increased CD3+ tumor infiltrating lymphocytes correlates with reduced tumor growth by LRT.
- These results suggests cellular mediated immunity was responsible for the distal (abscopal) effect.

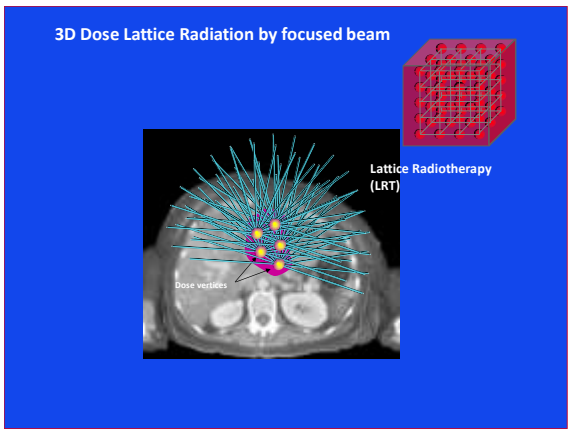


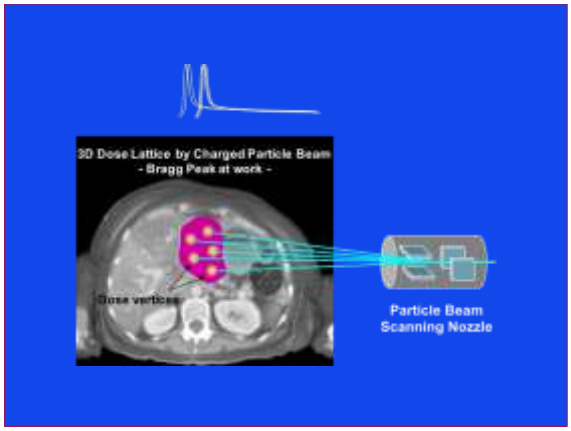
HUVEC growth was significantly reduced in response to all the LRT groups compared to cells that were grown in the serum obtained from either untreated or open field IR groups.



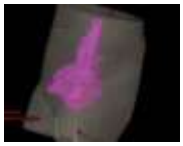
SUMMARY

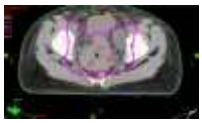
- In-vitro radiation-induced bystander crosstalk is regulated by cytokine mediated signal transduction mechanism.
- SFGRT caused both local and distal (abscopal) tumor regression in nude mice, as opposed to open field. This was associated with TNF and ceramide signaling.
- Time-reversal phenomenon was observed when abscopal exposed tumor was irradiated with 2 Gy fractions. This was absent in open field.
- LRT regressed both local and distant tumor growth, as opposed to open field.
- LRT induced cytokines responsible for cellular mediated immune response with increased CD3 infiltration in tumor and reduced angiogenic growth, as opposed to delayed immune modulation response in open field exposure.
- Distal effects were more pronounced in SFGRT/LRT treatment in both human and mouse cell lines irrespective of immune status.

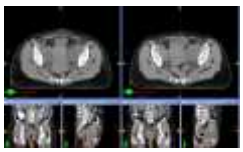




Lattice Radiotherapy with RapidArc for Treatment of Gynecological Tumors







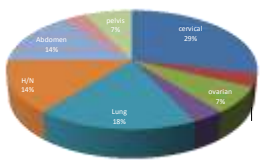
Amendola B E, Perez N, Amendola M a., Wu, X., Ahmed, M.M., et al. (2010-09-27 14:30:56 UTC) Lattice Radiotherapy with RapidArc for Treatment of Gynecological Tumors: Dosimetric and Early Clinical Evaluations. Cureus 2(9): e15. doi:10.7759/cureus.15

Clinical Experience

Innovative Cancer Institute, Miami

2009 - 2016

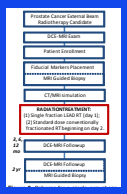
Patients treated with LRT



cervical	8
endometrial	1
ovarian	2
vaginal	1
Lung	5
H/N	4
Abdomen	4
chest	1
pelvis	2
extremity	1
total	29

This shows that LRT is tolerable for various disease sites

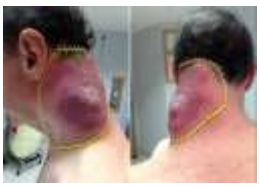
LATTICE EXTREME ABLATIVE DOSE (LEAD) TRIAL
NCI SUPPORTED TRIAL



- 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.

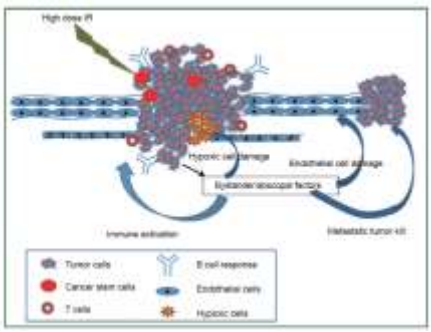
Prostate Cancer Phase 1 Lattice Extreme Ablative Dose (LEAD) Trial: Feasibility and Acute Toxicity. Pollack, A. et al. International Journal of Radiation Oncology • Biology • Physics , Volume 90 , Issue 1 , S455

High-Dose Radiation as a Dramatic, Immunological Primer in Locally Advanced Melanoma



2015 Mohiuddin et al. Cureus 7(12): e417. DOI 10.7759/cureus.417

Wild-biology exists in high-dose partial radiotherapy: Both immune and non-immune bystander / events are elicited

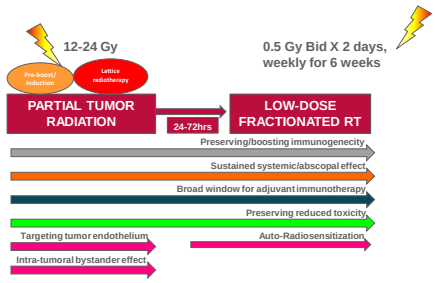


THERE IS LOT OF SKEPTICISM IN SUCH PARTIAL VOLUME RADIOTHERAPY APPROACHES: Potential limitations

- More than one fraction and even opposed fields will likely blur out the grid/LRT effect.
- Physicists in the audience may worry about QA of lattice.
- Need more randomized trials (IRB can have hard time to approve)

To address the above challenges, we have initiated a work group and planning to have a workshop with The Radiosurgery Society in August 2018.

Exploitation of partial and low-dose RT in clinic



Thanks