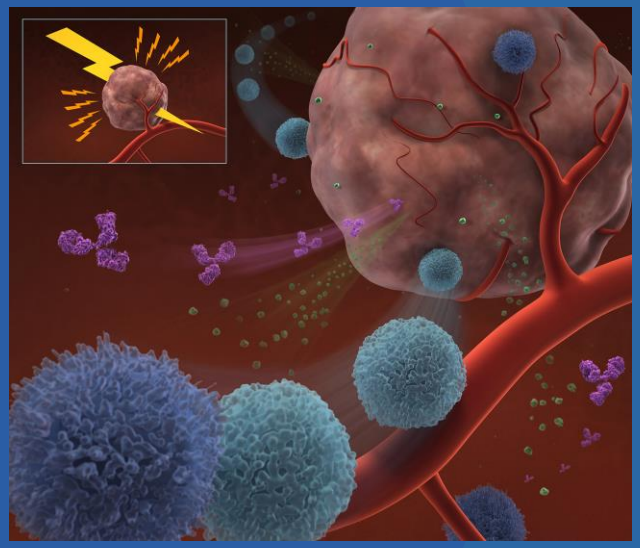
Spatially Fractionated, Flash and Microbeam Radiation Therapy



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This talk will focus to discuss published and unpublished data originated from my previous affiliation and from other laboratories

Novel modalities

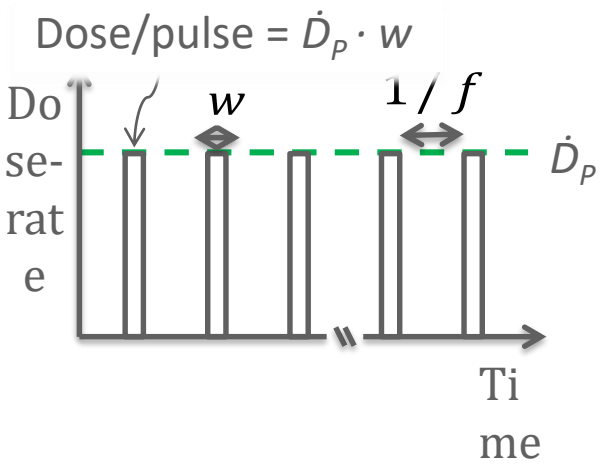
1. *FLASH radiotherapy*
2. *Microbeam radiotherapy*
3. *GRID radiotherapy*

FLASH RADIOTHERAPY

Flash radiotherapy

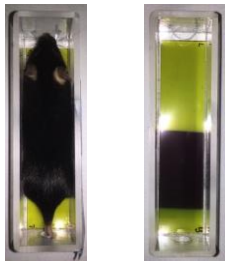
Jaccard *et al. Med. Phys. 2017*

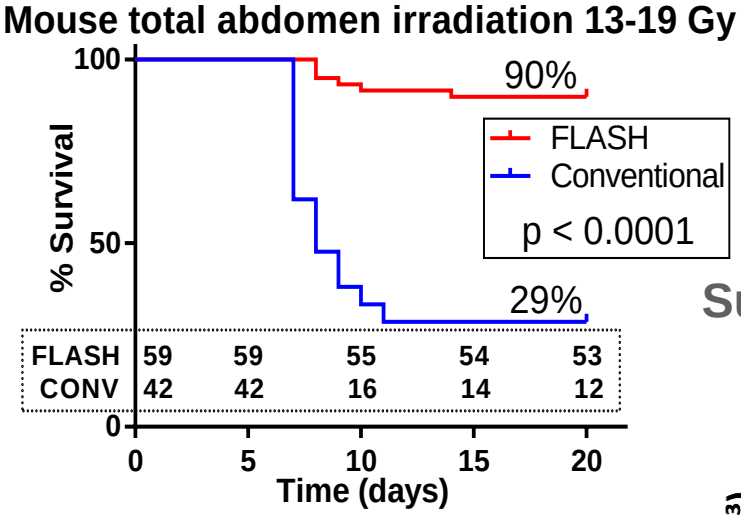
	Conventional RT	FLASH RT
Dose rate	≈10^{-1} Gy/s	30-10^{7} Gy/s
Dose/pulse	≈10^{-4} Gy	1–10^{1} Gy
Time for 10 Gy delivery	10^{2} s	10^{-6}–10^{-1} s



Why FLASH?

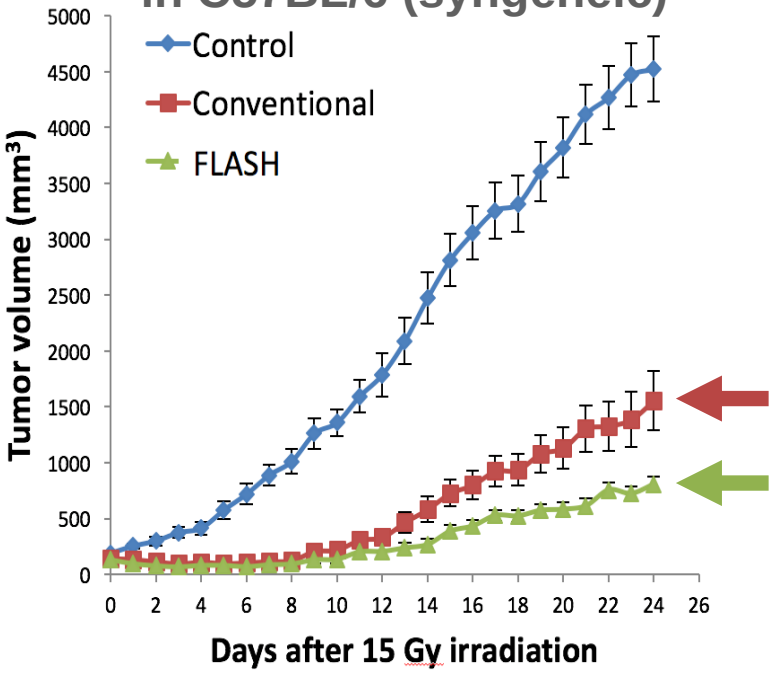
Unprecedented preclinical demonstration of *increased therapeutic index*





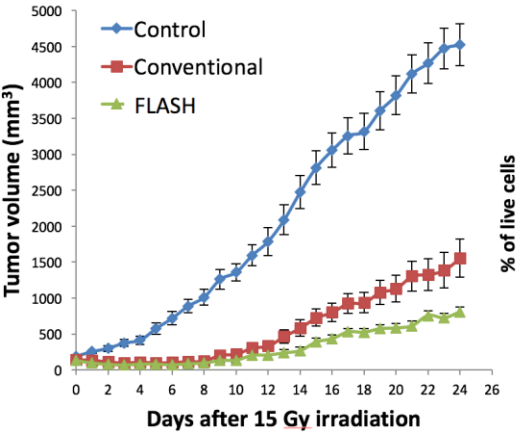
Loo *Am Rad Soc* 2017

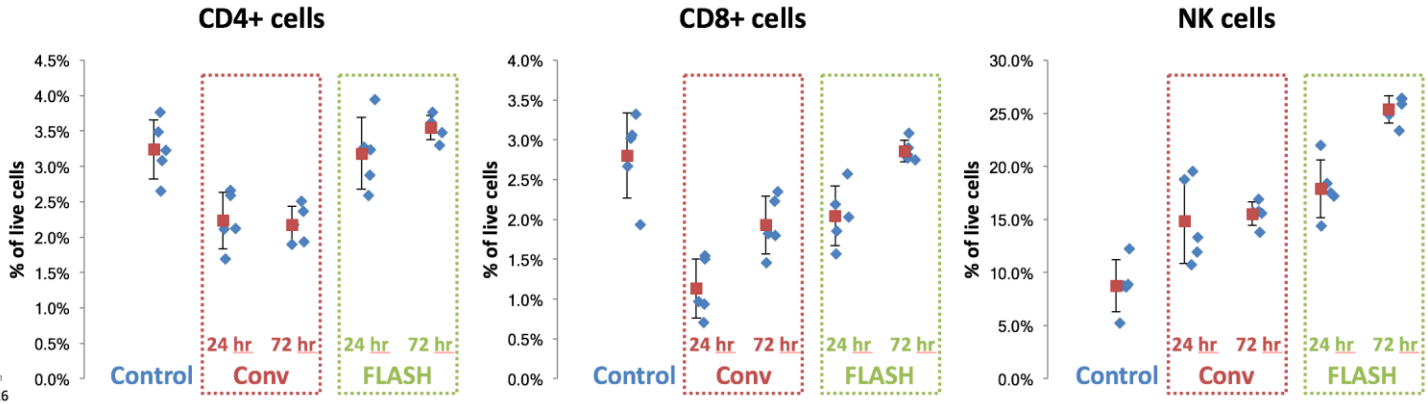
Subcutaneous Lewis lung carcinoma in C57BL/6 (syngeneic)

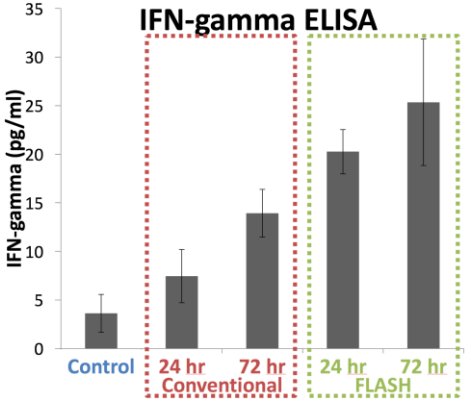


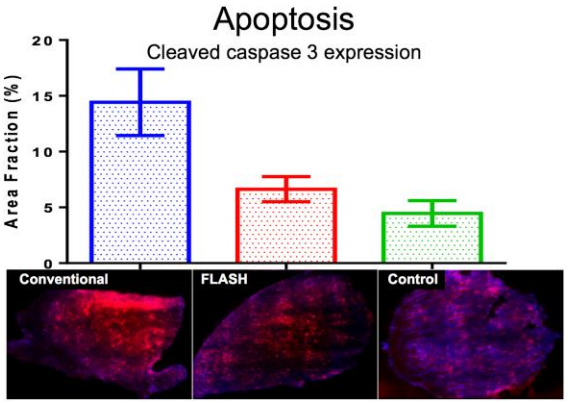
Chou, Lartey *Unpublished* 2017

FLASH: Improved tumor control









Subcutaneous Lewis lung carcinoma in C57BL/6 (syngeneic)

Chou, Lartey
Unpublished
2017


P Devauchelle


P De Fornel

- Good tolerance
  - Only mild acute reactions
  - Irreversible alopecia

- Promising results
  - PFS=84% at 1 year


27 Gy FLASH

Microbeam Radiotherapy

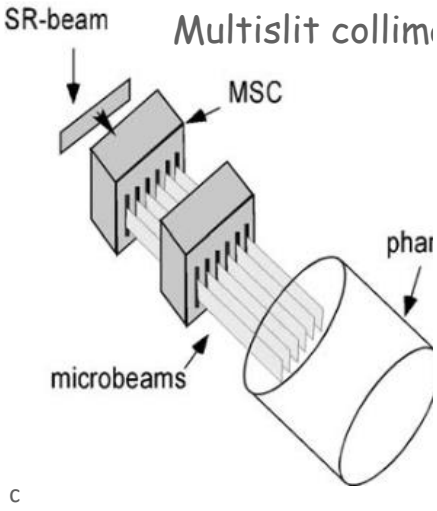
Microbeam Radiation Therapy (MRT)

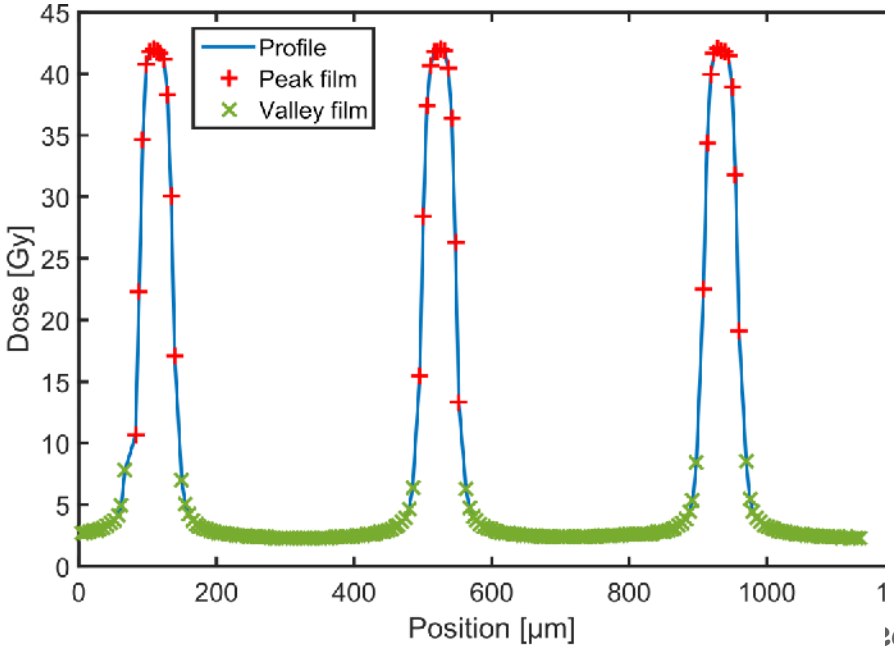
UNIVERSITÄT BERN

What we need to demonstrate prior clinical application!?

- Efficacy, i.e. satisfactory tumor control
- High normal tissue tolerance, i.e. tumor selectivity
- Mechanism of action

European Synchrotron Radiation Facility (ESRF, Grenoble)





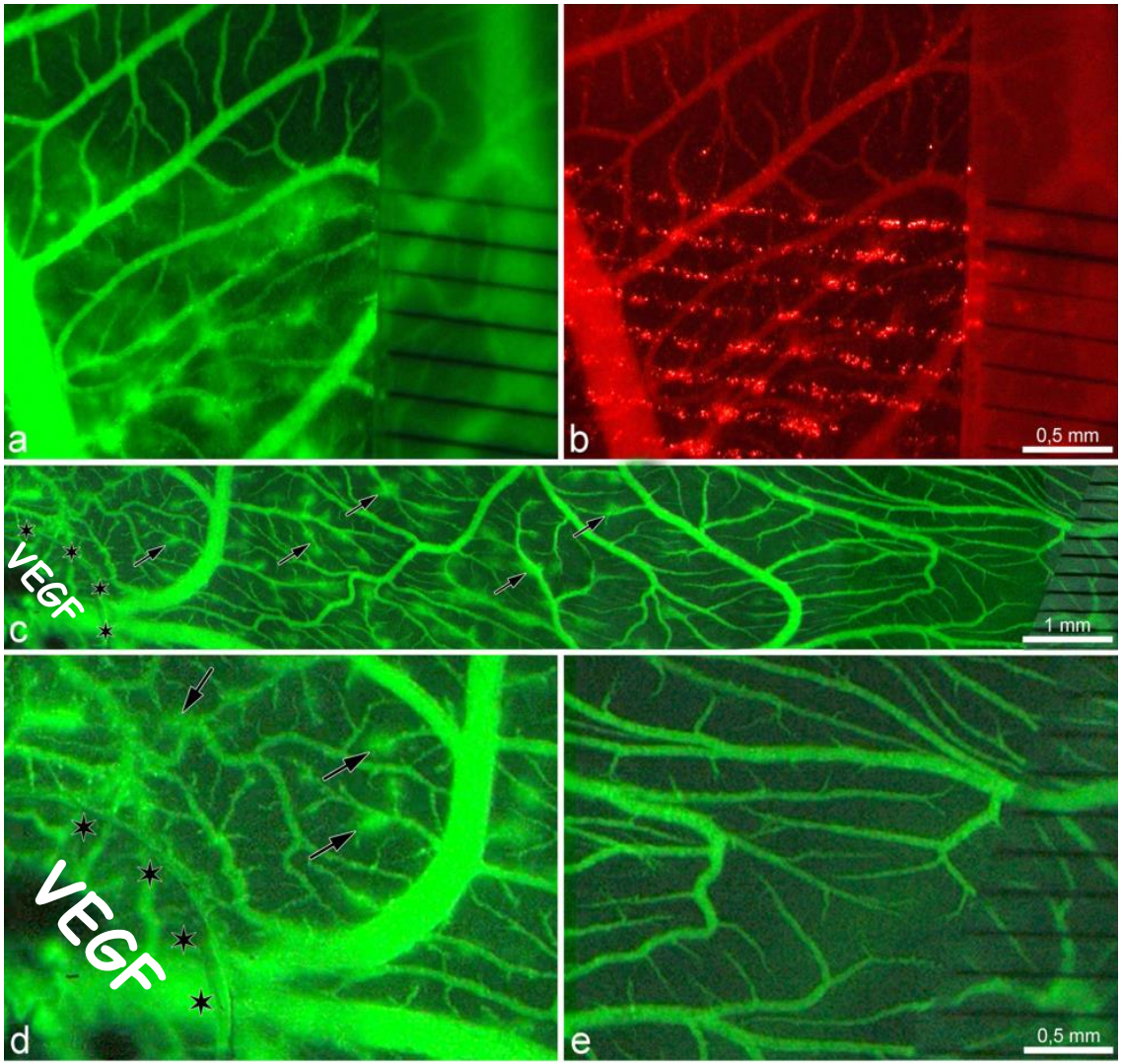
MRT = synchrotron generated X-rays with particular geometry

- Multiple
- Parallels
- Very thin: 25-100 μm
- 50-400 μm spaces
- Variable height

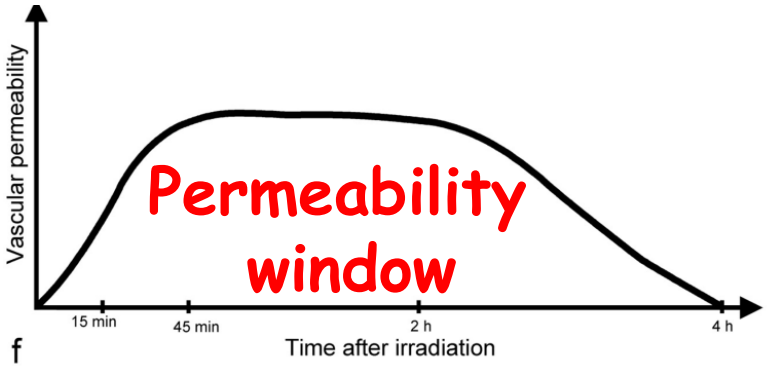
MRT allowing delivery **ec.**

Transient permeability window induced by low dose MRT

Patent: Microbeam Radiation Enhanced Drug Delivery



Green fluorescence: FITC- Dextran (30 nm) ; Red fluorescence: Rhodamine (100 nm)



1. Low dose of MRT (100Gy) well tolerated/industry MRT
2. Only one, single short shot (<1 sec) MRT
3. Transient 15min → 4h
4. More effective in immature vessels

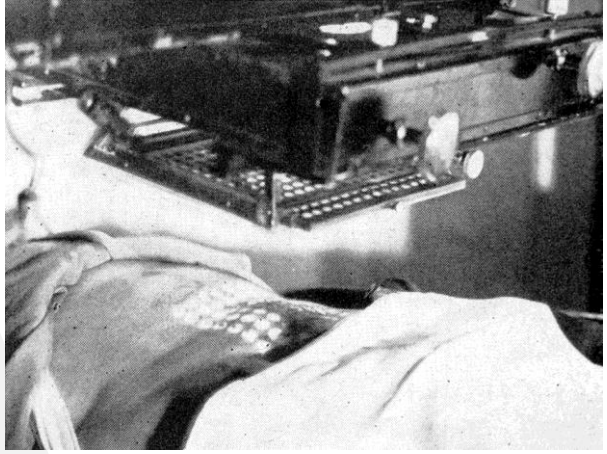
Tumor treatment

Sabatasso et al. unpublished

Spatially Fractionated Grid Radiotherapy

- **Kohler et al introduced SFRT in 1909, with the intention of treating deep-seated tumors and overcoming the skin toxicities associated with the poorly penetrating orthovoltage x-rays of the time.**

- **It was noted that smaller irradiated volume permitted higher dose tolerance, and through spatial fractionation, doses as high as 20 times the conventional doses could be tolerated by the skin.**



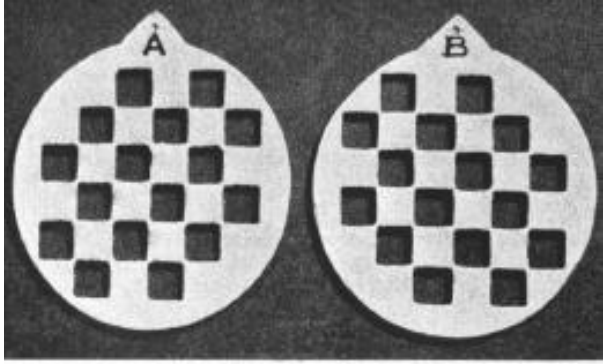
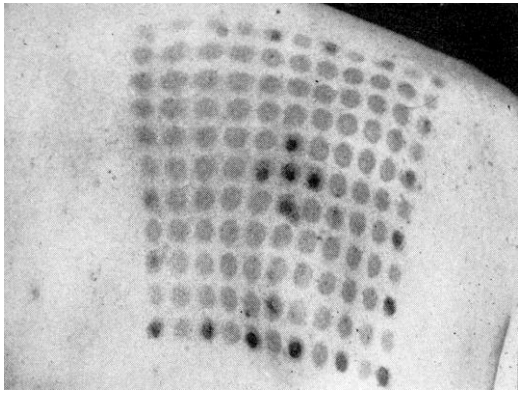


FIG. 21. Lead chess-board sieve for alternating therapy for superficial lesions. 7 cm. diam. area. 1 sq. cm. transparent and shielded squares.



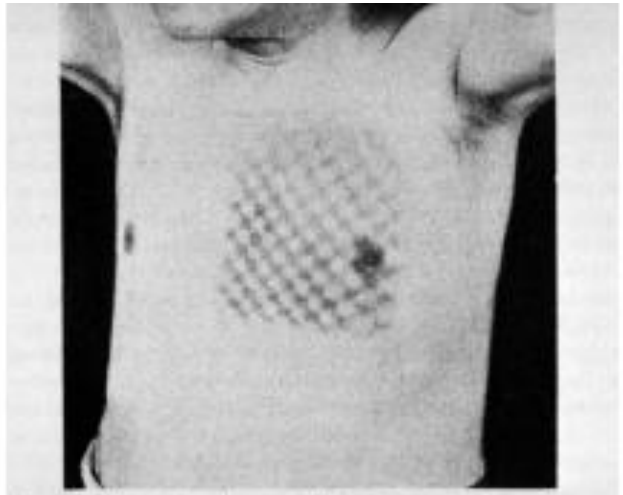
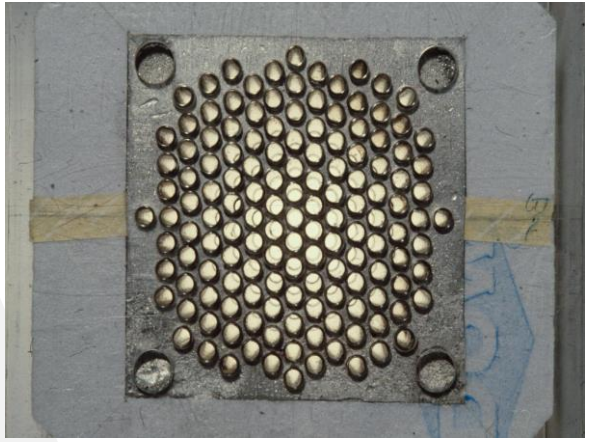
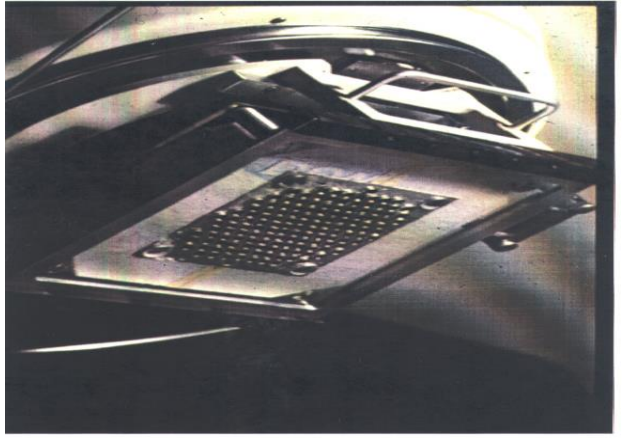


FIG. 23. Mosaic of erythema at end of sieve treatment for carcinoma of lung. 10,000 r were given in twenty-eight days (20 × 500 r) on anterior field and 5,000 r in nine days on posterior field.

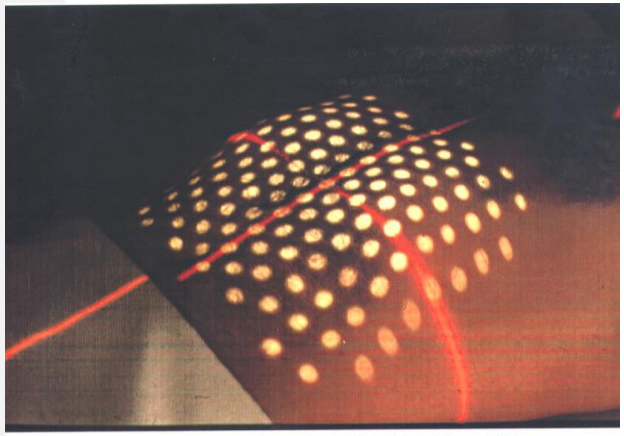
- However, SFRT was disregarded when deeply penetrating megavoltage linear accelerators rendered the primary objective of the method null.

- Interest in SFRT would not be renewed until 1990, when Mohiuddin et al demonstrated the feasibility of this technique with bulky and refractory tumors, historically considered to be resistant to standard fractionated radiation therapy.

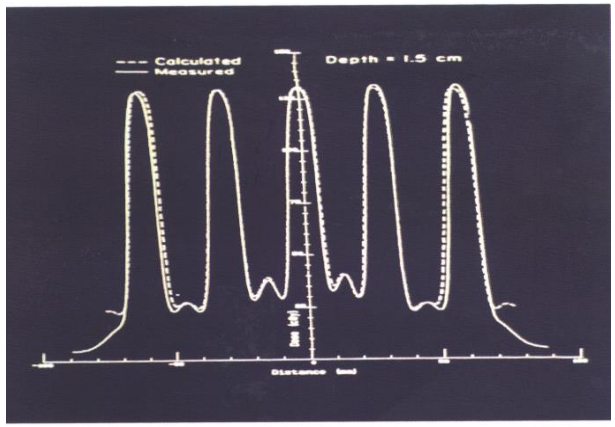




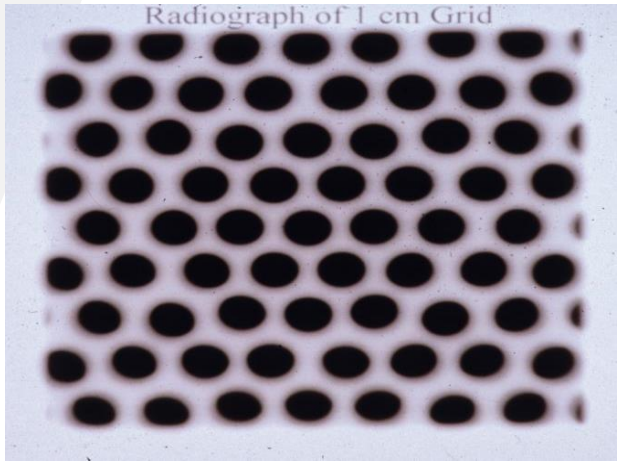
Treatment Grid (50:50) in Blocking Tray

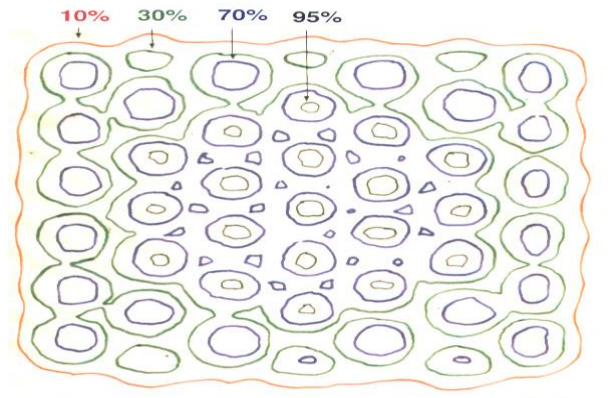


Spatially Fractionated (Grid) Field on Skin

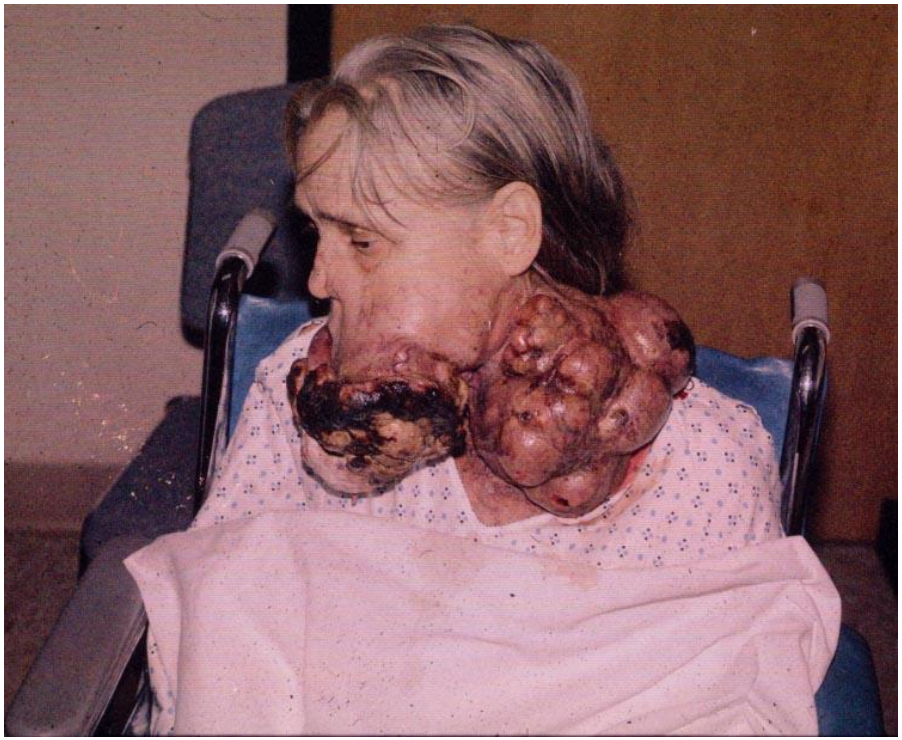


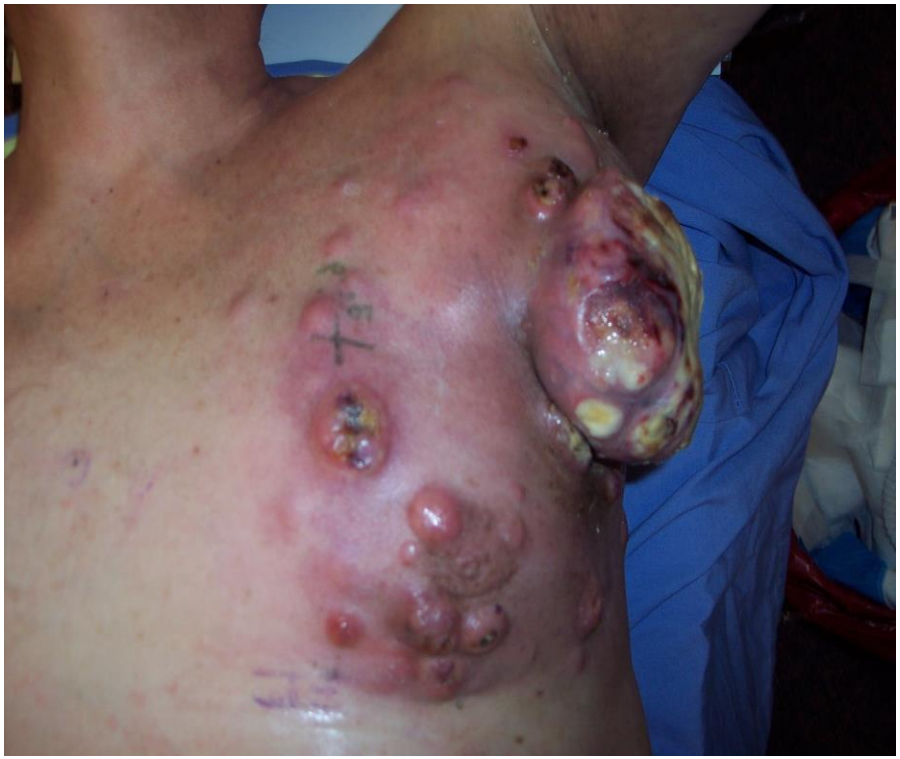
Depth dose Profile at Dmax (6 MV X-Rays)





Dose Distribution at 10 cm Depth in Tissue





Historically, use of high-dose radiation using GRID was either for palliation to alleviate pain or make amenable for surgery

Objectives

1. Pain Relief
2. Decrease size of mass
3. Control bleeding /ulceration

High Dose Spatially Fractionated (GRID) Radiation

Palliative Response to Treatment

Symptoms	CR	PR	NR	NE
Pain	20%	58%	17%	5%
		78%		
Mass	15%	54%	24%	7%
		69%		
Bleeding	50%	50%	----	--

High Dose Spatially Fractionated (GRID) Radiation

Response Rate By Histology

Histology	# Rx	CR	PR	NR	NE
Squamous	**117**	**24(21%)**	**68(58%)**	**8(8%)**	**4(7%)**
Adenocarcinoma	**135**	**20(15%)**	**83(61%)**	**10(7%)**	**22(17%)**
Melanoma	**20**	**7(35%)**	**9(45%)**	**3(15%)**	**1(5%)**
Sarcoma	**57**	**16(28%)**	**33(58%)**	**4(7%)**	**4(7%)**

High Dose Spatially Fractionated (GRID) Radiation

Response Rate By External Beam Dose

Tx		CR	PR	NR	NE
0 Gy	95	14(15%)	55(57%)	8(9%)	18(19%)
		72%			
≤ 40 Gy	126	16(13%)	76(60%)	12(10%)	22(17%)
		73%			
≥ 40 Gy	136	46(34%)	77(57%)	6(4%)	7(5%)
		91%			

High Dose Spatially Fractionated (GRID) Radiation

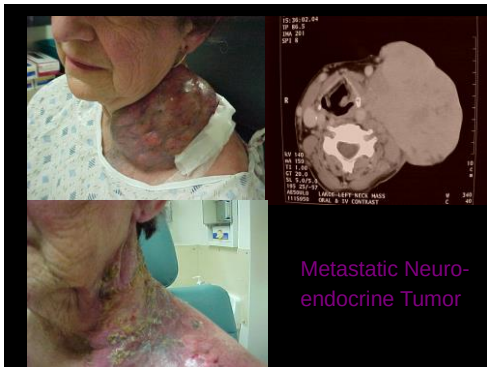
Survival:

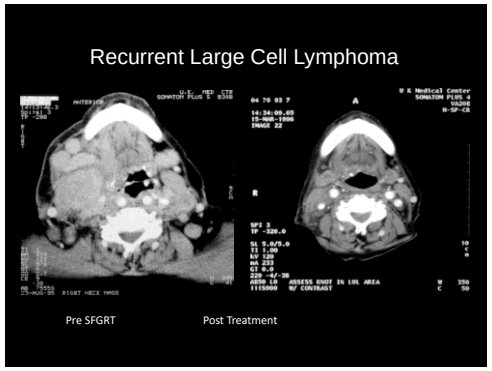
Range	**0 - 116 Months**
Median	**6 Months**
Alive 1 year	**99 patients**
Alive 5 years	**18 patients**

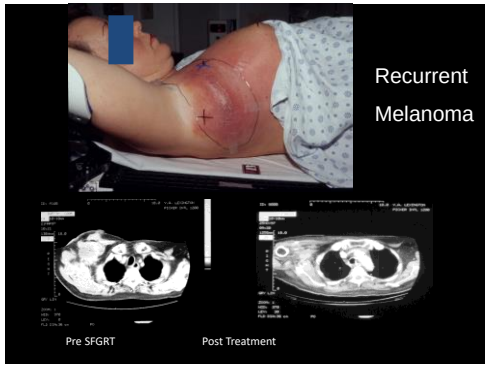
Summary of clinical studies
Using "GRID" as pre-boost (priming) for standard 2 Gy EBRT

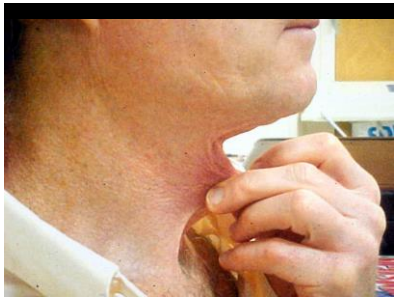
Authors	Treated Sites (n)	Follow-up, median (range) (mo)	Histology	GRID dose, median (range) (Gy)	Prior RT	GRID only	Control rates	Side effects
Mohiuddin et al, 1990[5]	22	NR (1-18)	Diverse	NR (10-15)	27%	36%	Response rate: 91%	1 acute skin erythema, 2 N&V, 2 diarrhea, 1 late SBO
Mohiuddin et al, 1996[7]	72	4 (0.5-28)	Diverse	NR (10-25)	24%	44%	Response rate: 91%	No grade 2 or higher acute toxicity
Mohiuddin et al, 1999[18]	87	7 (3-42)	Diverse	15 (10-20)	9%	20%	Response rate: 91%	1 grade 3 acute mucositis, 1 fatal carotid blowout
Kudrimoti et al, 2002[19]	20	NR	Melanoma	15 (12-20)	25%	25%	Response rate: 80%	No grade 3 or higher toxicities
Huhn et al, 2006[22]	27	10 (3-44)	SCC of H&N	15 (15-20)	0%	0%	(1) Neck control rate: 93%; (2) neck control rate 92%	(1) acute G 2-3 skin toxicity, 10 late G 2 soft tissue and muscle fibrosis; (2) 3 poor postoperative wound healing, 4 fibrosis limiting neck movement
Mohiuddin et al, 2009[20]	44	9 (2-44)	Soft tissue sarcoma	15 (12-20)	NR	9%	Response rate 76%	2 G 3 acute skin reactions
Penagaricano et al, 2010[23]	14	19.5 (2-38)	SCC of H&N	20	0%	0%	Local control rate: 79%	1 fatal carotid blowout, 11 acute G 2-3 skin reaction, 13 acute G 2-3 mucosal reaction, 4 late G 2-3 skin fibrosis
Neuner et al, 2012[13]	79	2 (0-51.6)	Diverse	15 (10-20)	NR	20%	Pain response rate, block: 95%, pain response rate, MLC: 74%, mass effect response rate, block: 84%, mass effect response rate, MLC: 79%	4 G 3-4 acute skin reactions with block versus 10 G 3-4 acute skin reactions with MLC
Mohiuddin et al, 2014[21]	14	14 (3-43)	Soft tissue sarcoma	18	0%	0%	Local control rate: 100%	1 G 3 acute skin, 2 delayed wound healing
Edwards et al, 2015[24]	53	mean 34 (1-239)	SCC of H&N	15	NR	0%	Local control rate: 81%	2 late toxicities requiring feeding tubes

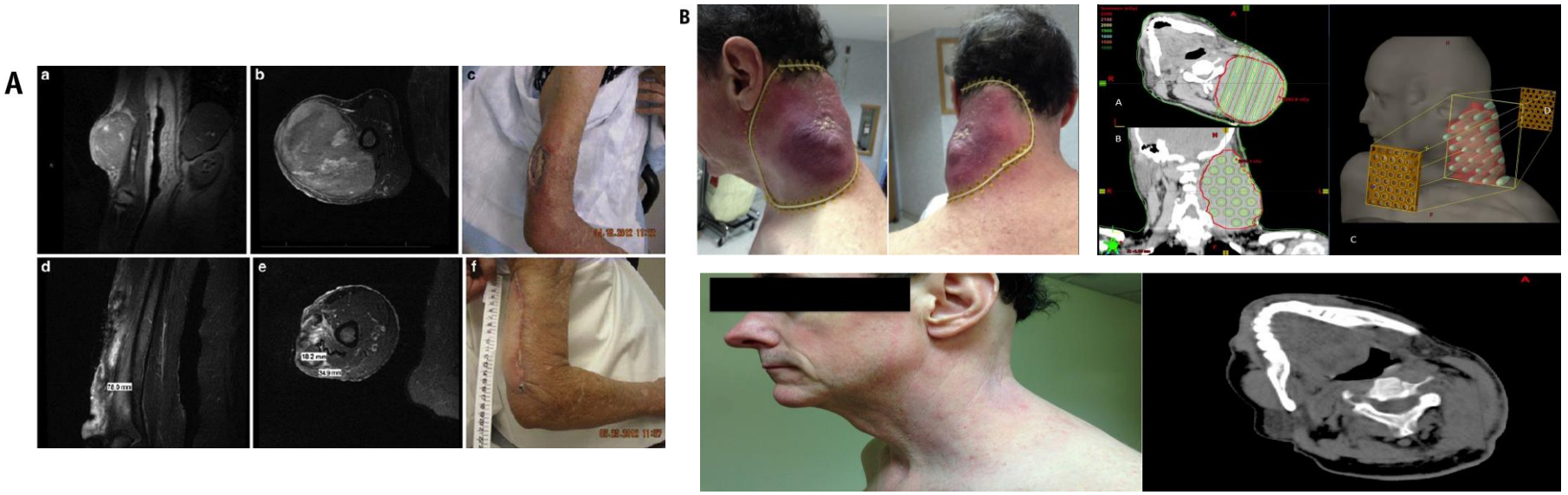
Abbreviations: G = grade; H&N = head and neck; MLC = multileaf collimator; N&V = nausea and vomiting; NR = not reported; RT = radiation therapy; SCC = squamous cell carcinoma.











(A) A rapidly progressing upper extremity spindle cell sarcoma despite conventional EBRT was treated with 18-Gy GRID boosted by 32-Gy EBRT. Tumor regression was 90%, including gross tumor involving the medial humerus that was shielded. (B) A patient with an uncontrolled 18-cm nodal melanoma mass, progressing after IL-2, ipilumimab, and pembrolizumab. The authors treated with 20-Gy SFRT followed by 50-Gy conventional EBRT and pembrolizumab with a complete and sustained response.

Grid clinical data interpretation

- **The results of available clinical data on GRID therapy are legitimate grounds for excitement:**
  - **The response rates appear to be higher than established historical precedent.**
- **However, there are also important limitations of the studies described. In most cases, interpretation of these studies is confounded by:**
  - **Lack of a control arm**
  - **Significant heterogeneity in the study population;**
  - **Uncontrolled or inconsistent combination with conventional EBRT**
  - **Unclear dose and delivery methods relative to target volumes and organ-at-risk (OARs).**

Key issues

- No dosimetry data as to what happens during a clinical treatment especially with multi-fractions or opposed fields if they are used.
- There is lack of standardization across centers.

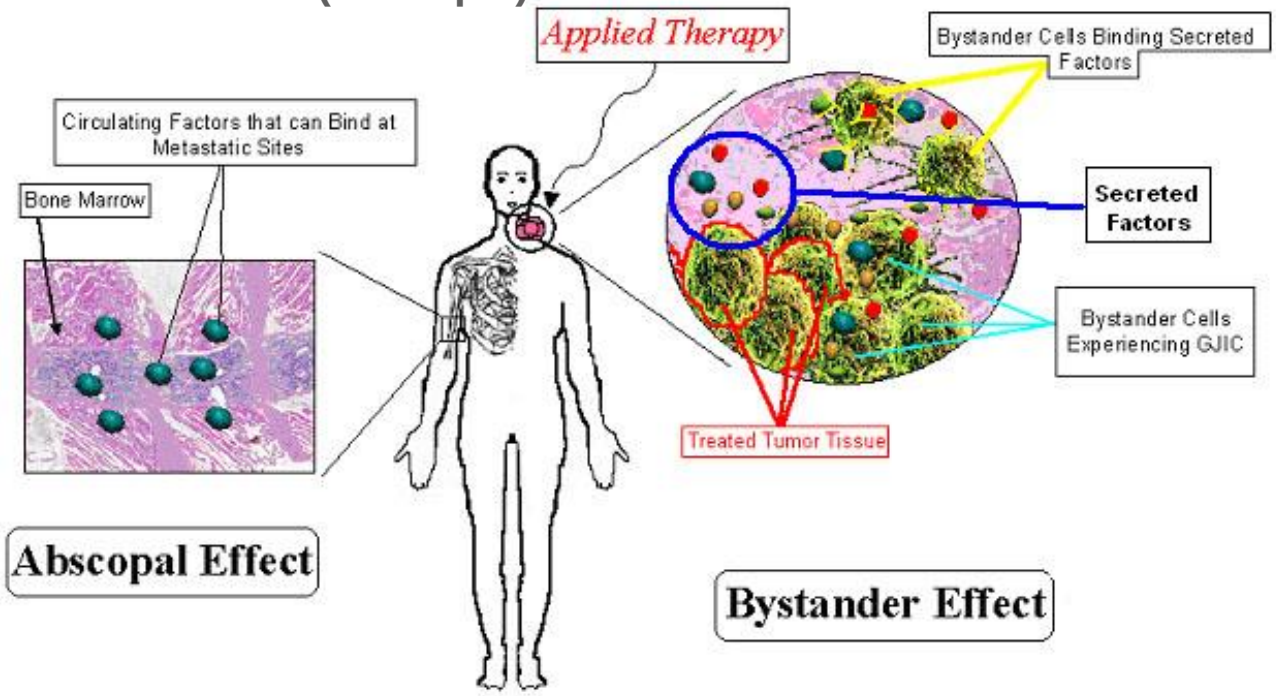
Hence, these gaps are a part interest for rigorous research.

Radiobiology of SFRT

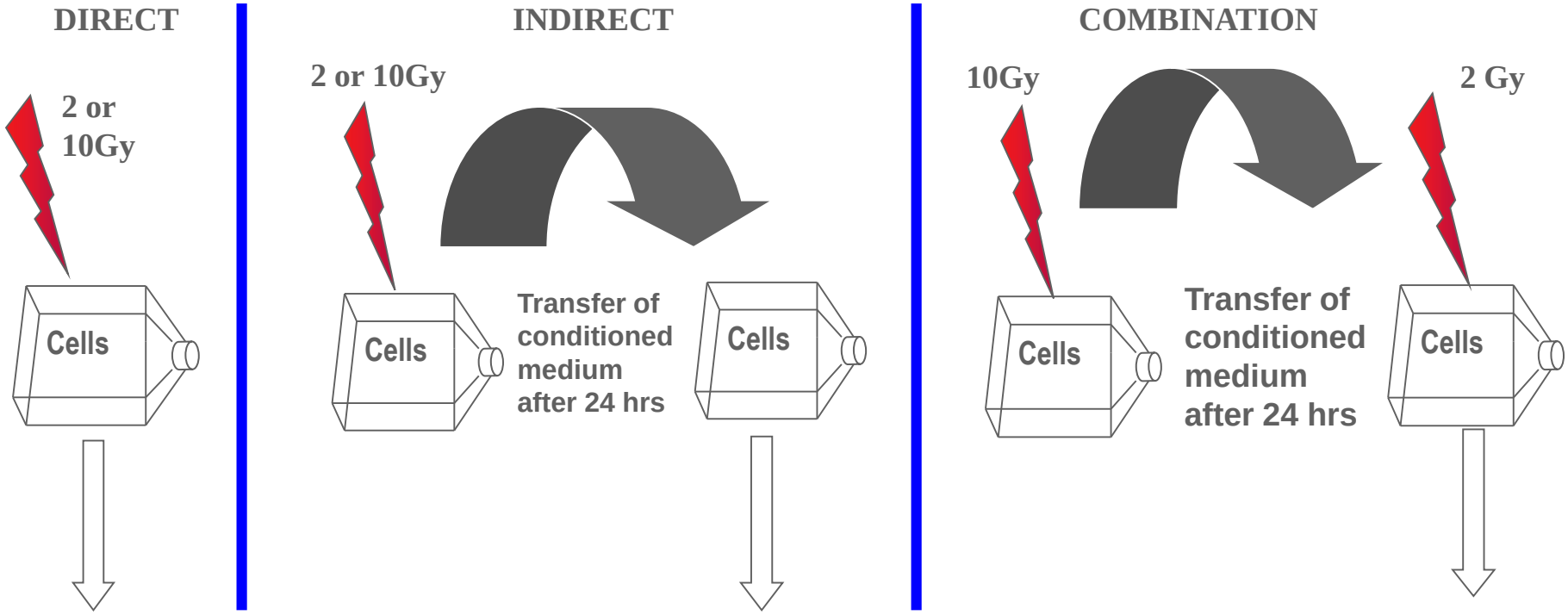
- Spatial fractionation minimizes the toxicity of high-dose radiation by limiting the volume of normal tissue receiving radiation (ie, the dose-volume effect). This allows nearby normal cells to migrate and mediate repair damaged areas.

- Although certain tumor volume is spared from direct physical radiation, SFRT remains clinically effective by leveraging nontarget effects and tumor microenvironment changes.

- The tumoricidal mechanisms putatively active in nonhomogeneous radiation fields involve signal-mediated effects in the neighborhood of the irradiated tumor (bystander) and in distant sites (abscopal).

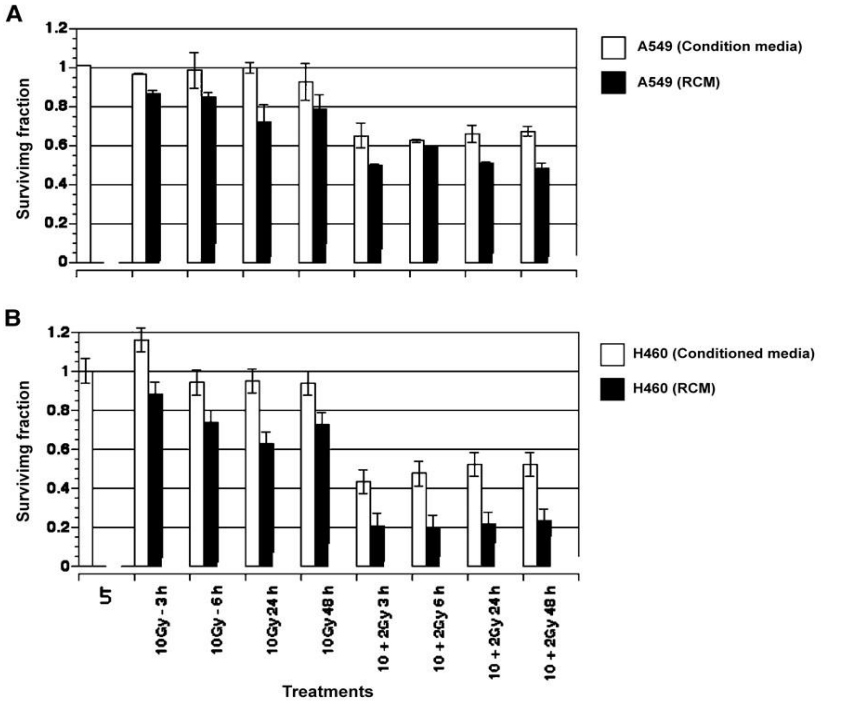


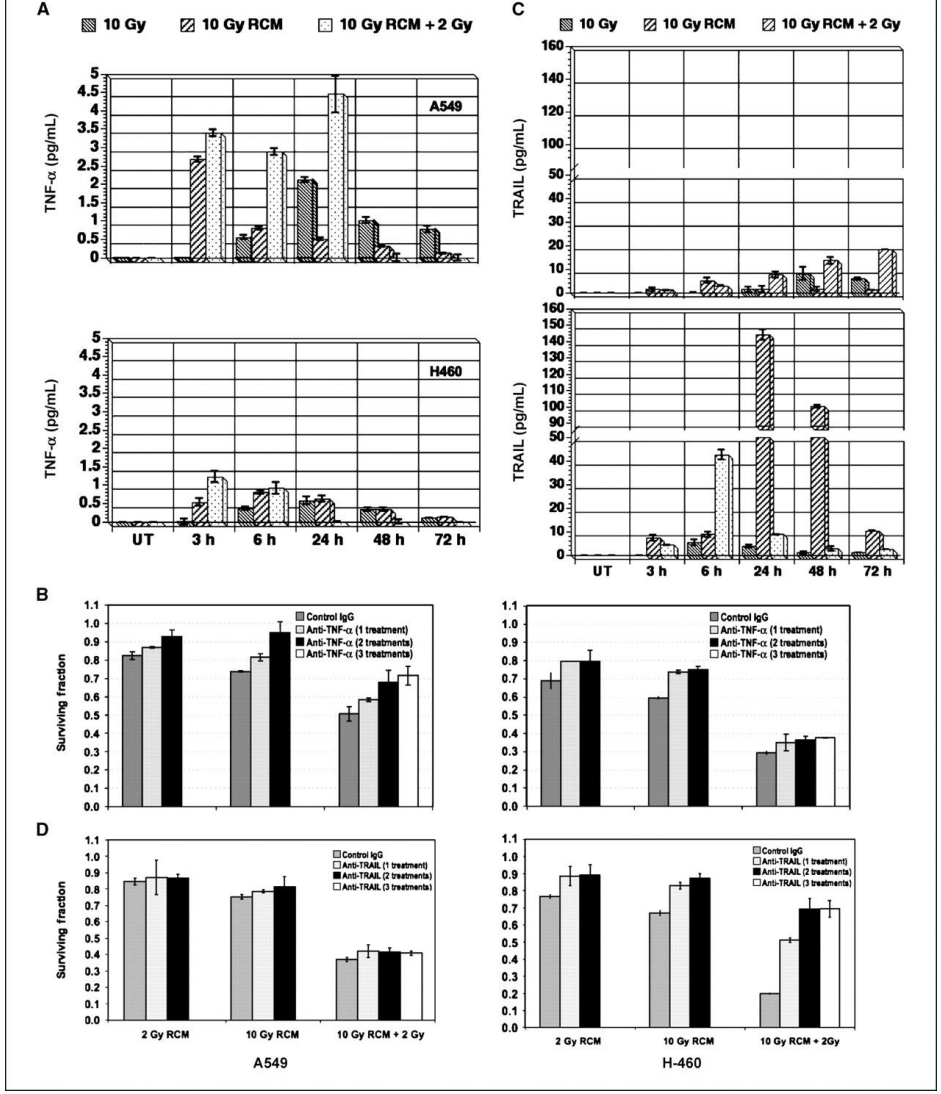
RADIOBIOLOGY OF SFRT
DIFFERENTIAL BYSTANDER SENSITIVIES AND ROLE OF CYTOKINES



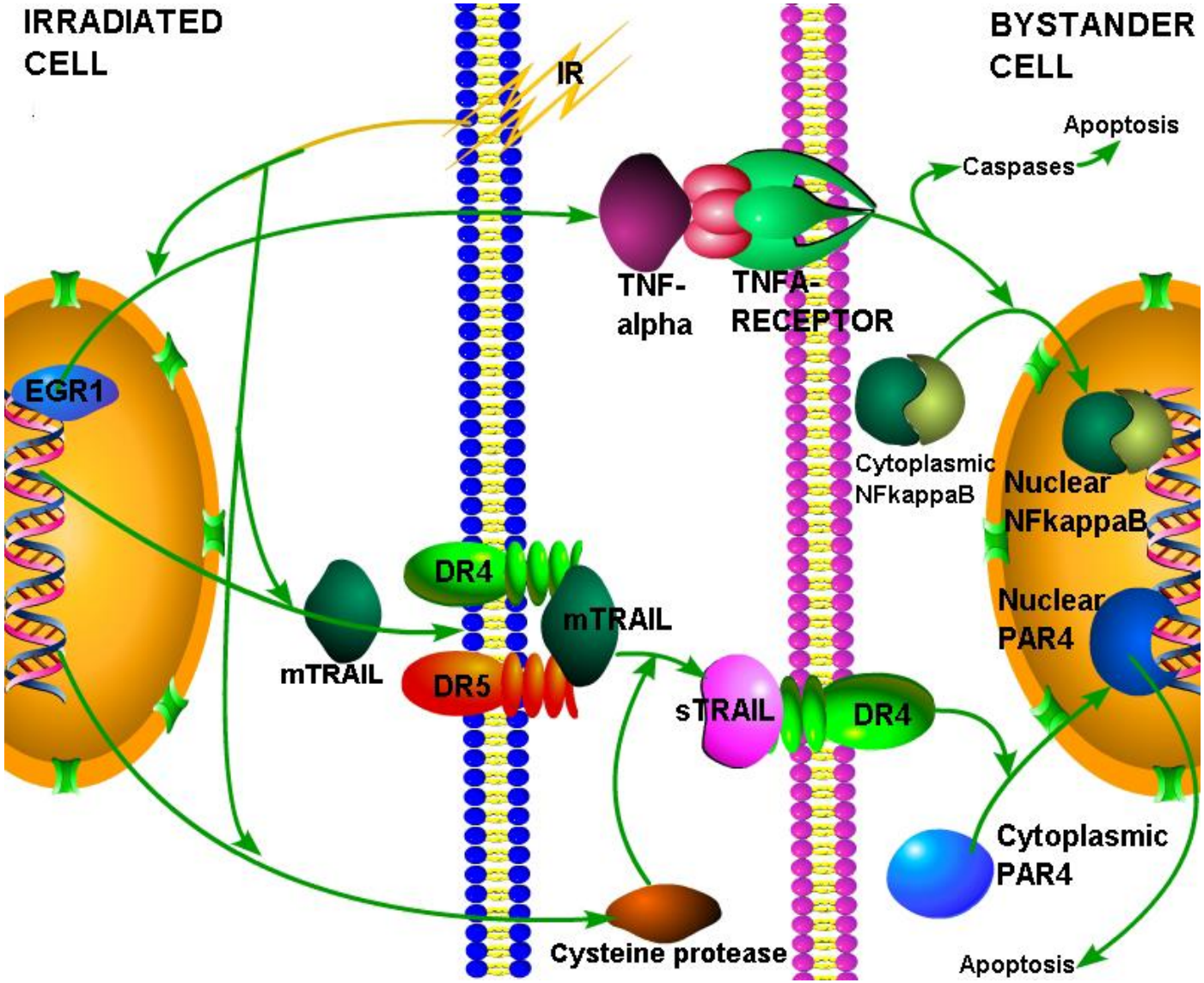
COLONY FORMING ASSAY/ WESTERN BLOT ANALYSIS EMSA/ ELISA/ TUNEL

DIFFERENTIAL BYSTANDER SENSITIVIES AND ROLE OF CYTOKINES



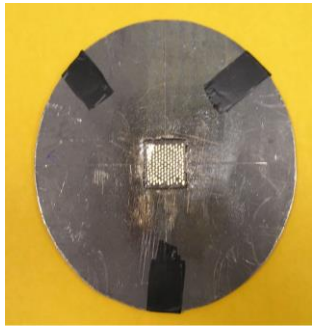


PROPOSED MECHANISM OF RADIATION-INDUCED BYSTANDER SIGNALING



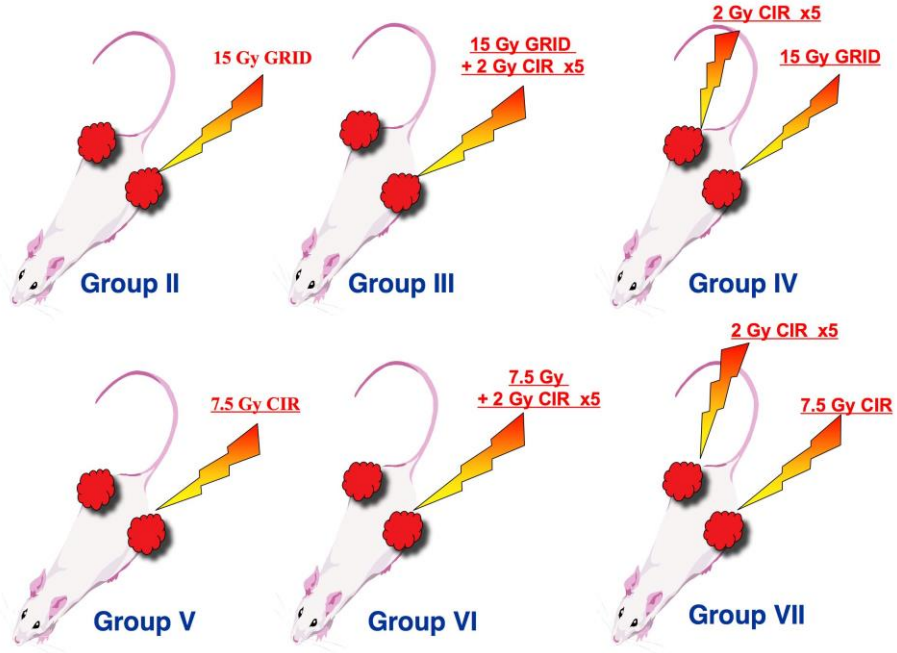
Shareef, M.M., Cui, N., Burikhanov, R., Gupta, S., Satishkumar, S., Shajahan, S., Mohiuddin, M., Rangnekar, V.M., and Ahmed, M.M. (2007). Role of tumor necrosis factor-alpha and TRAIL in high-dose radiation-induced bystander signaling in lung adenocarcinoma. Cancer Res *67, 11811-11820.*

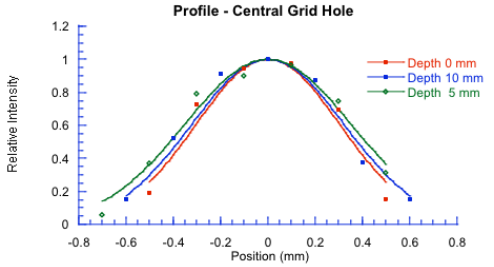
In-vivo: NUDE MICE studies using A549 cells

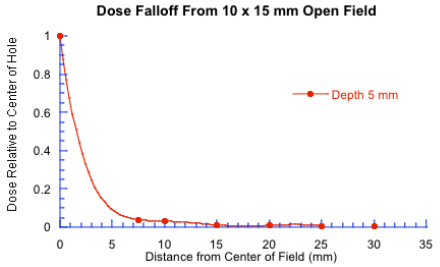


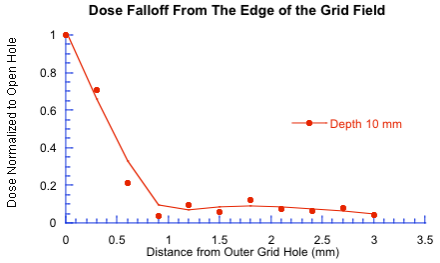
Low energy GRID

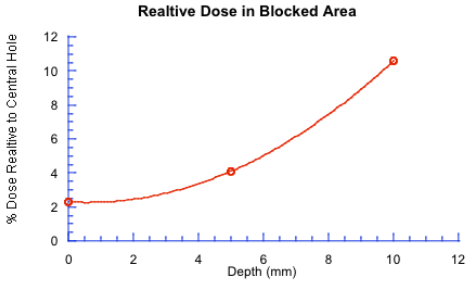
Film showing the GRID field





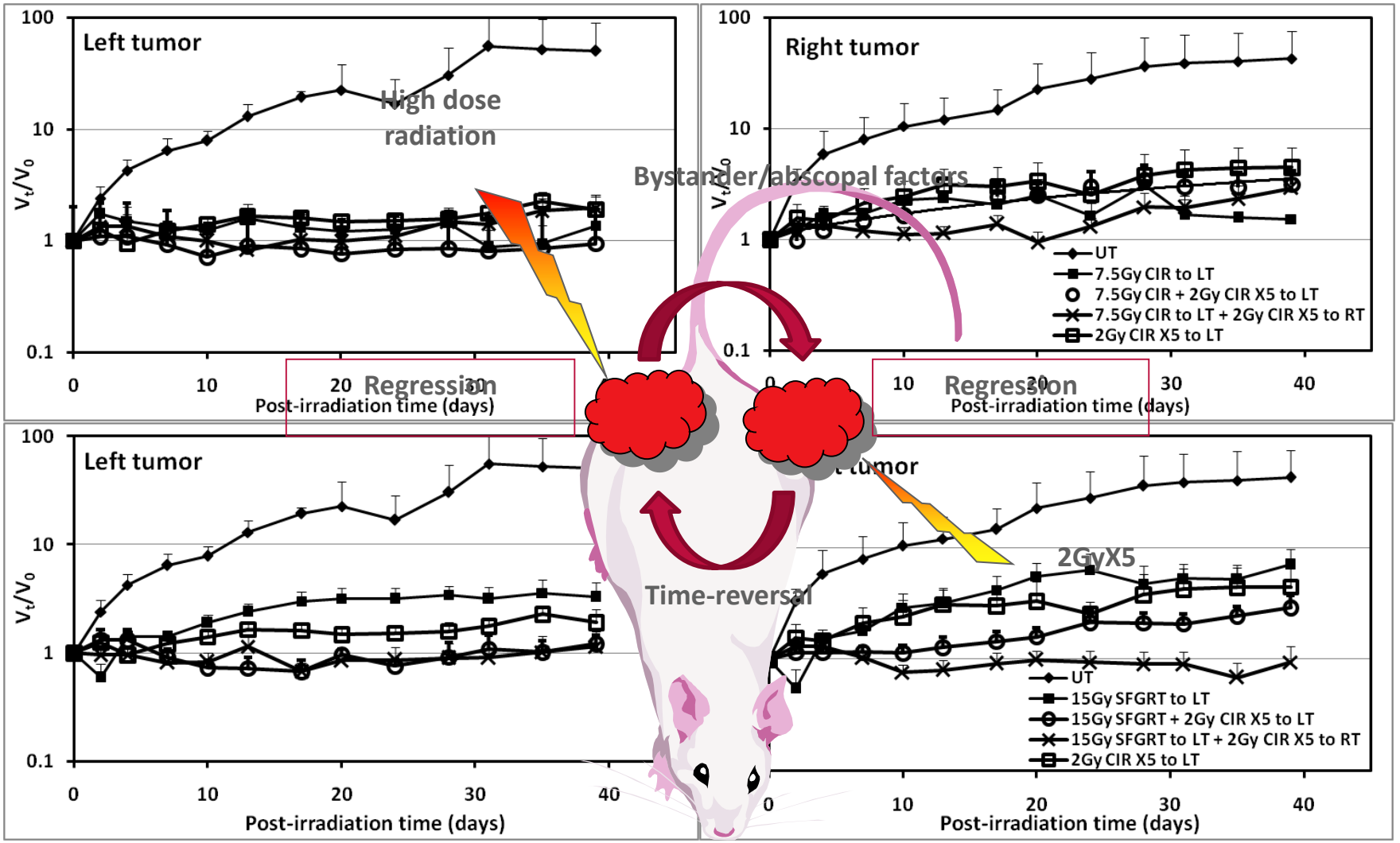


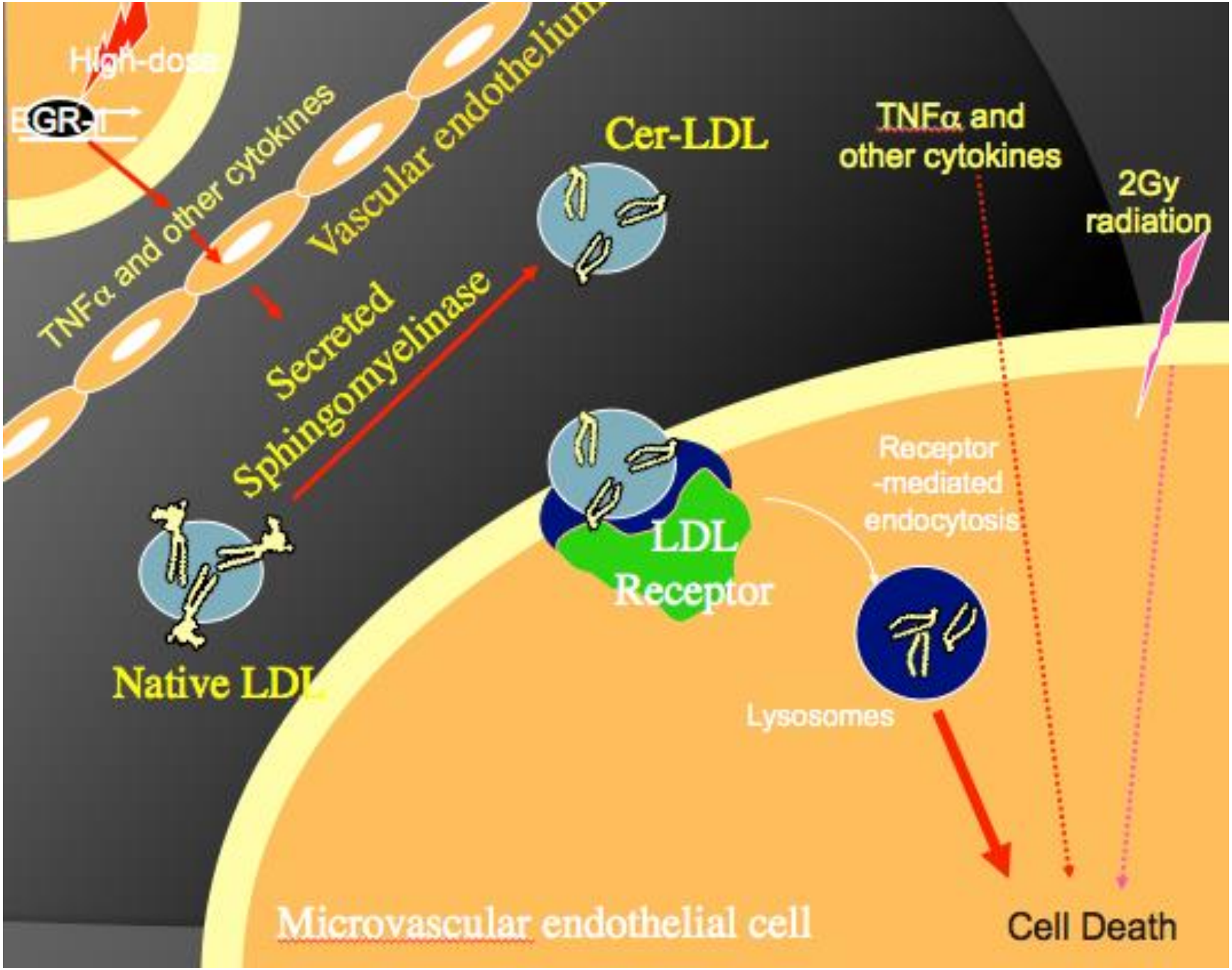




Gupta S, Zagurovskaya M, Wu X, et al. Spatially Fractionated Grid Highdose radiation-induced tumor regression in A549 lung adenocarcinoma xenografts: cytokines and ceramide regulators balance in abscopal phenomena. Sylvester Comprehensive Cancer Center, 2014:20.

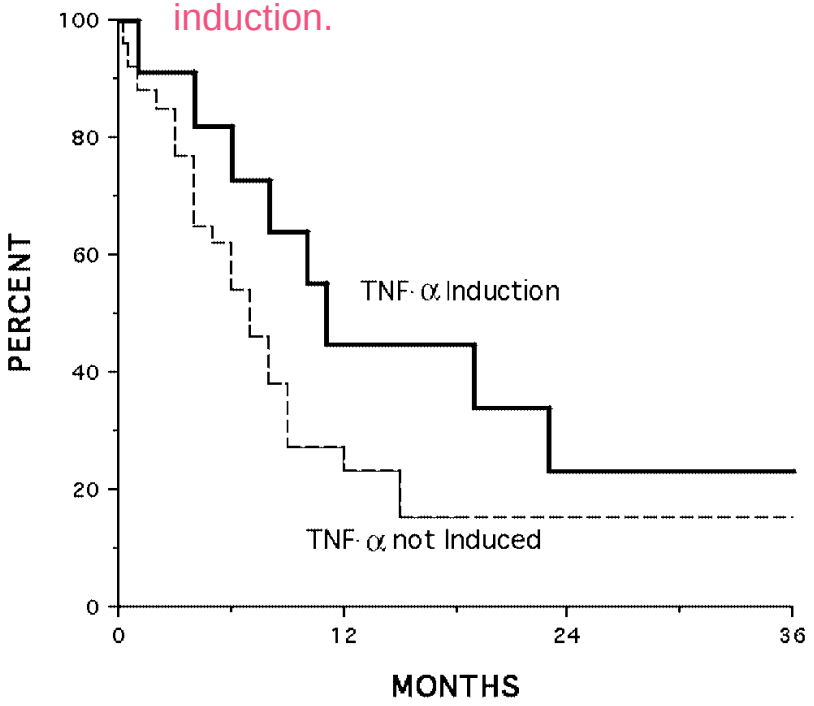
Tumor growth curves



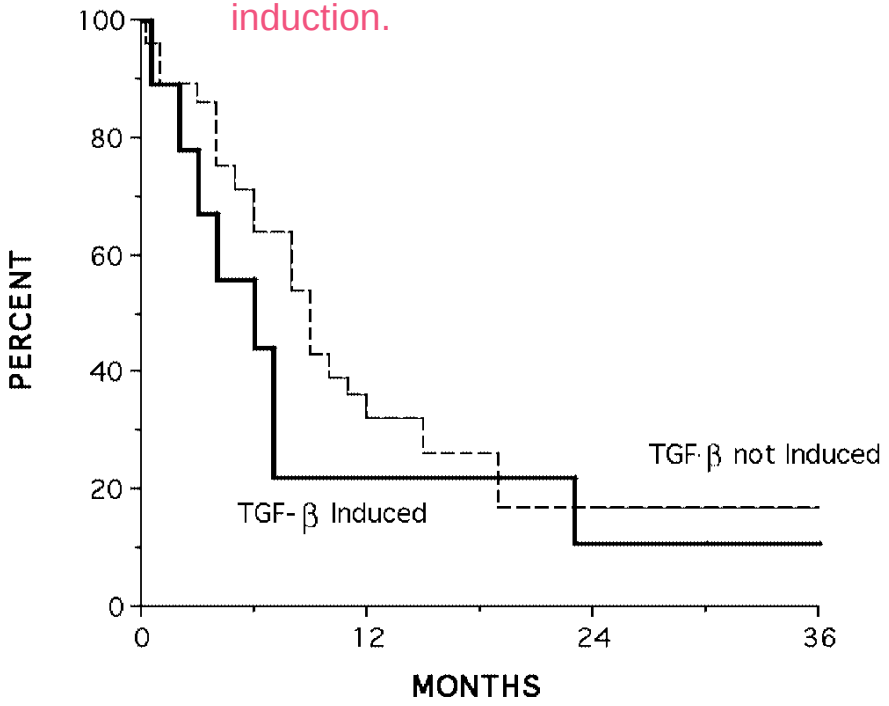

High-dose
EGR-1
TNFα and other cytokines
Vascular endothelium
Cer-LDL
TNFα and other cytokines
2Gy radiation
Secreted Sphingomyelinase
Receptor -mediated endocytosis
LDL Receptor
Native LDL
Lysosomes
Microvascular endothelial cell
Cell Death

High Dose Spatially Fractionated (GRID) Radiation in Patients with bulky tumors

High dose spatially fractionated radiation survival of patients by TNF-α induction.



High dose spatially fractionated radiation survival of patients by TGF-β induction.



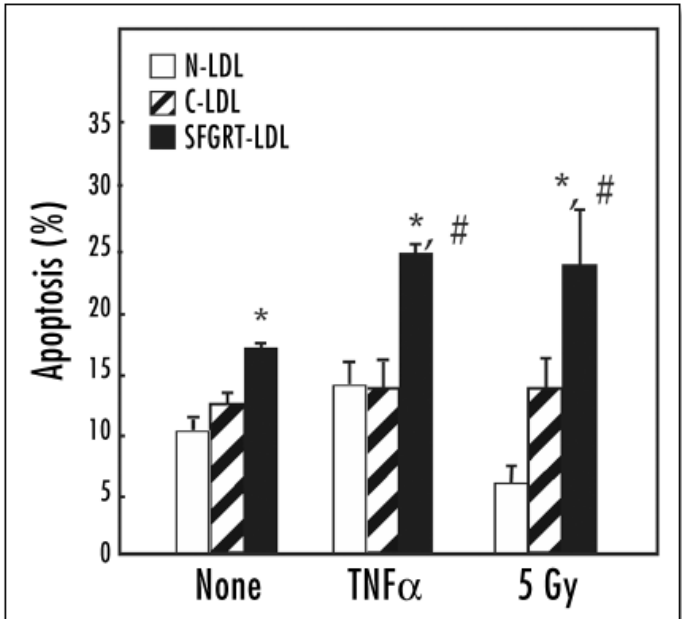
Technology in Cancer Research & Treatment, Volume 1, Number 2, April 2002

ASMase and Ceramide activity in serum of SFGRT treated patients cause induction of apoptosis in HUVECs

Table 2 **S-SMase activity and ceramide mass in serum patients at before and 72 h after Grid radiation (15 Gy)**

Patient ID	S-SMase activity (pmol/ml/hour)			Ceramide (nmol/ml)			
	PreGrid	72 h	Change (fold)	PreGrid	72 h	Change (fold)	Response
16	21.4 ± 0.1	858.1 ± 0.1*	40.8	5.9 ± 0.1	9.1 ± 0.2*	1.54	CR
55	940.3 ± 0.1	935.5 ± 0.1	0.99	11.3 ± 0.6	18.5 ± 1.1*	1.64	CR
57	141.3 ± 0.1	55.2 ± 14.4	0.39	11.9 ± 1.0	18.2 ± 2.1*	1.53	CR
70	45.0 ± 0.1	107.1 ± 0.1*	2.40	n.d.	n.d.	n.d.	CR
13	<12.1	117.1 ± 12.2*	9.7	17.1 ± 2.9	18.2 ± 2.1	1.06	PR
29	790.3 ± 0.1	895.9 ± 0.1*	1.13	6.5 ± 0.6	11.6 ± 0.4*	1.78	PR
32	904.6 ± 0.1	972.6 ± 0.1*	1.07	11.0 ± 1.2	25.1 ± 1.6*	2.14	PR
45	119.1 ± 0.8	52.1 ± 60.5	0.43	11.7 ± 1.3	6.1 ± 0.4	0.52	PR
44	82.8 ± 22.9	57.1 ± 25.4	0.69	10.8 ± 0.9	9.6 ± 1.4	0.88	NR
63	57.0 ± 20.2	34.9 ± 5.8	0.61	8.5 ± 1.4	10.4 ± 1.9	1.22	NR
71	125.7 ± 0.1	72.0 ± 1.8	0.33	n.d.	n.d.	n.d.	NR

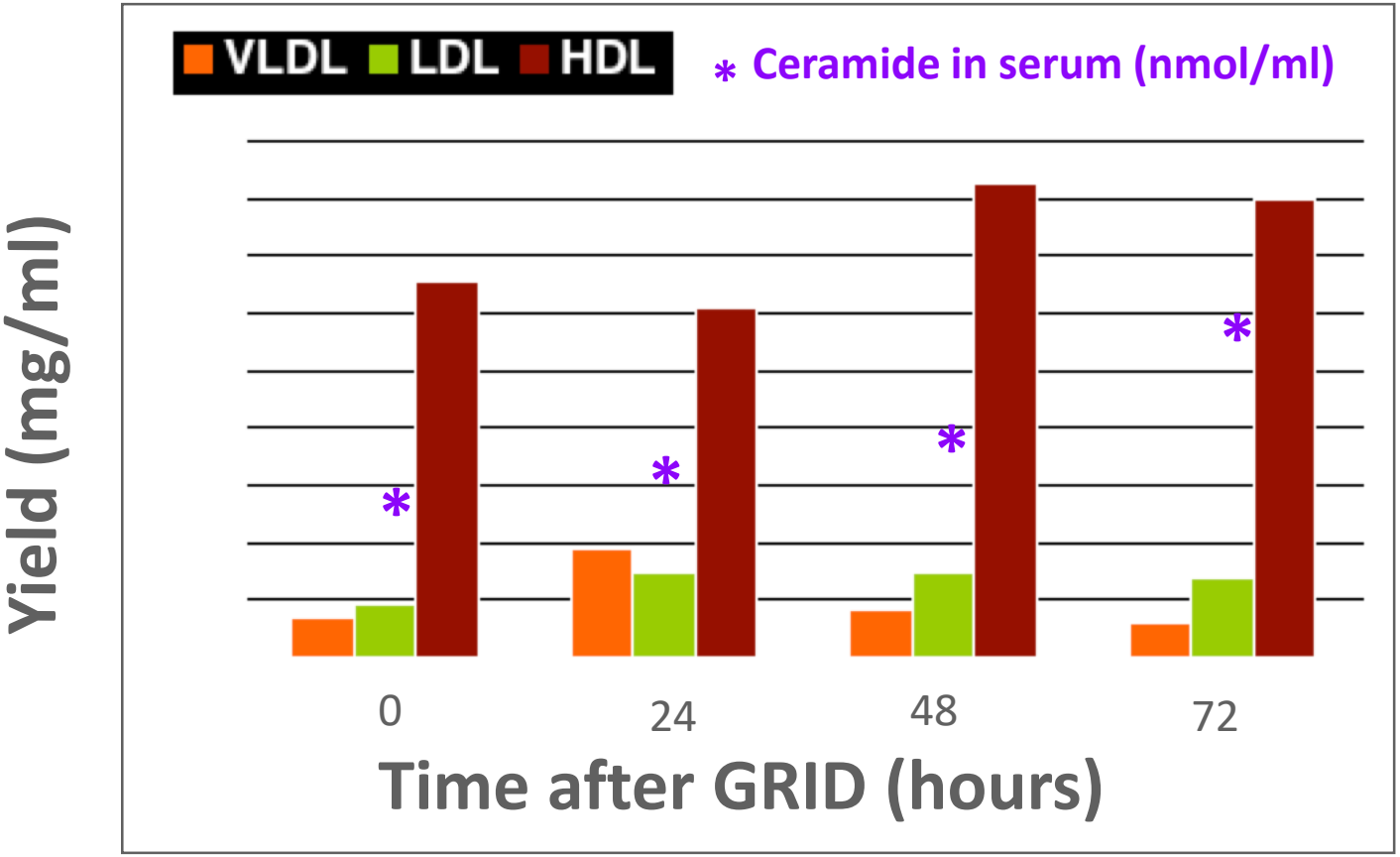
Blood samples were collected 1hour prior and at 72 hours after irradiation with 15 Gy delivered through grid. SMase activity and ceramide content was measured in serum. S-SMase activity was monitored using LDL-enriched NBD-SM as a substrate and HPLC-based method for quantitation of the generated NBD-Ceramide. The mass of endogenous ceramide was quantified by TLC/HPLC as described in the Materials and Methods section. CR, complete response; PR, partial response, NR, no response; nd, not determined. Data are average ± SD (n = 3 replicates per serum sample). *indicates SFGRT induced S-SMase/Ceramide.



LDL isolated from SFGRT patients induces apoptosis in HMEC-1 cells. LDL were separately isolated from the freshly collected serum samples of two patients before (C-LDL) and at 72 h after SFGRT (SFGRT-LDL). LDL from healthy volunteer (N-LDL) was used also as a control. HME-1 cells were treated with the different LDL preparations (150 µg/ml) for 16 hours in low-serum medium (0.2%). Cells were also treated with TNFa (25 ng/ml, added simultaneously) or irradiated with 5Gy (5–10 min after LDL addition). Results are representative for lipoproteins isolated from two patients.

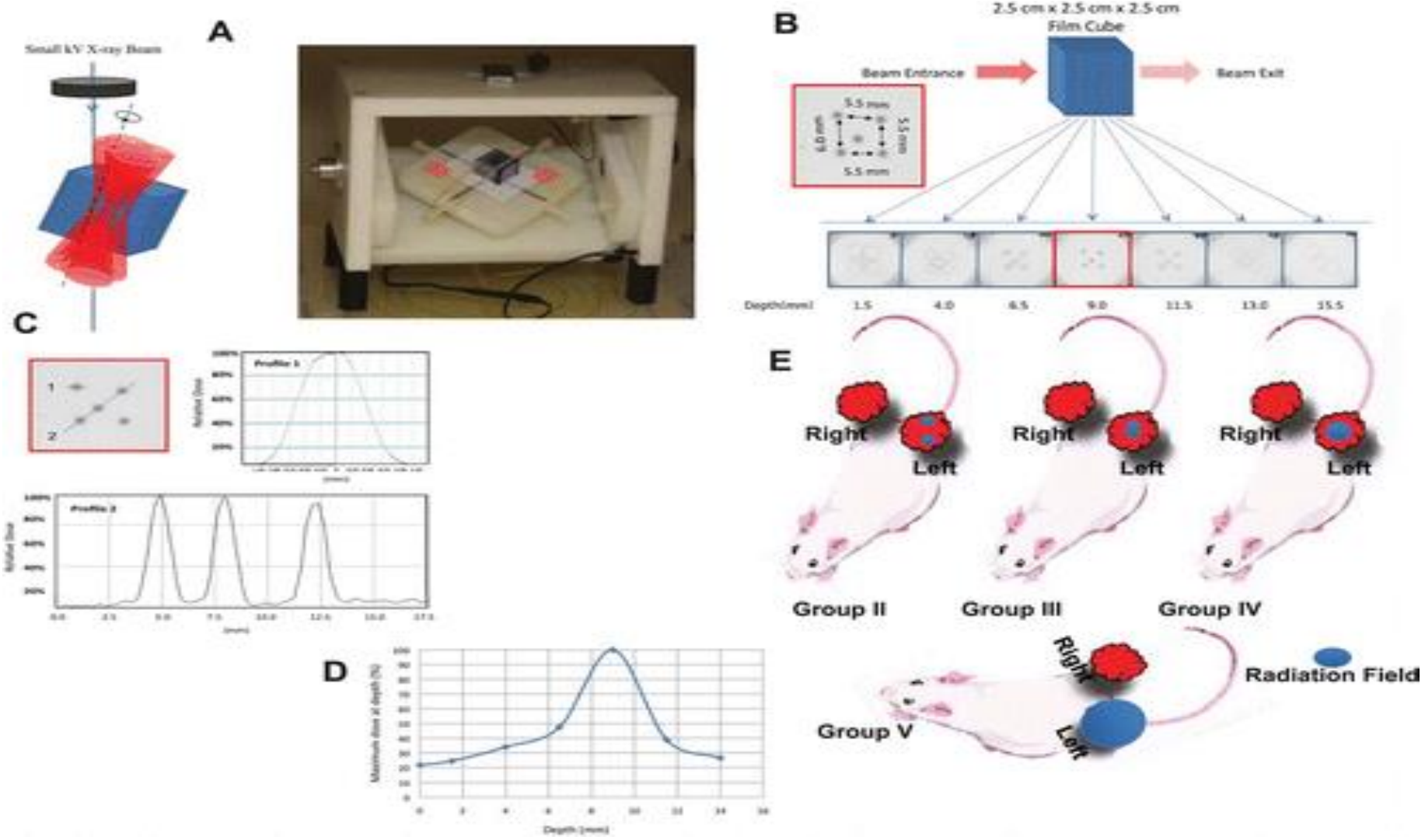
Cancer Biol Ther. 2005 Sep;4(9):979-86.

SFGRT-induced increases in serum ceramide are not due to changes in lipoprotein profile

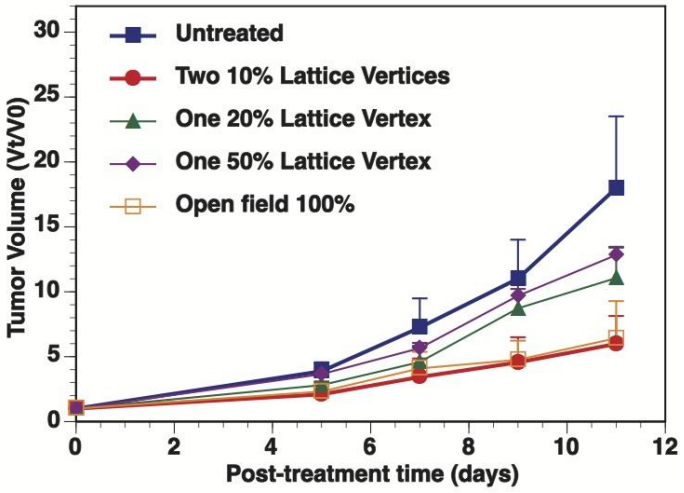


Spatially Fractionated Lattice Radiotherapy

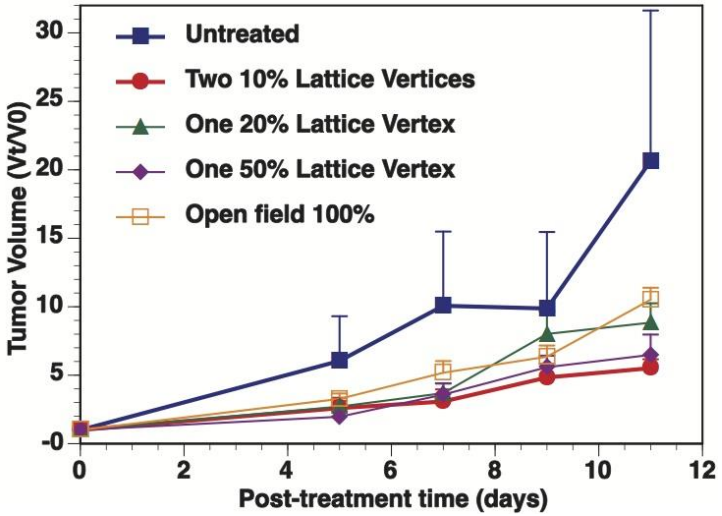
Rotational delivery device for high-dose LRT delivery in immune efficient mice



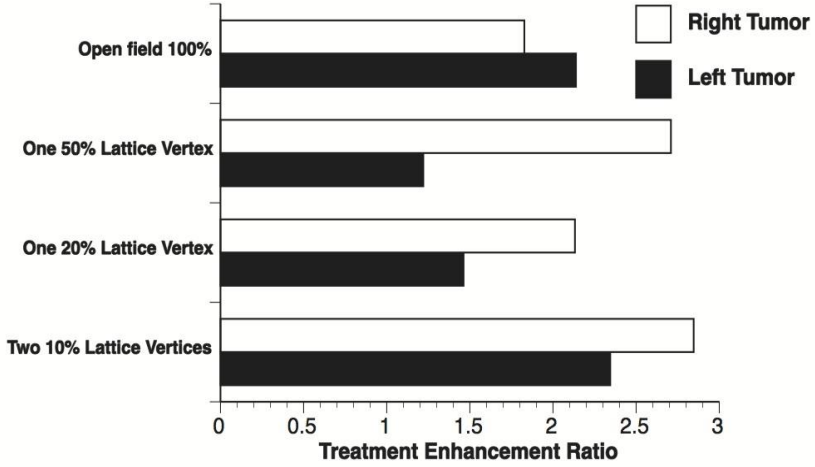
LEFT IRRADIATED TUMOR

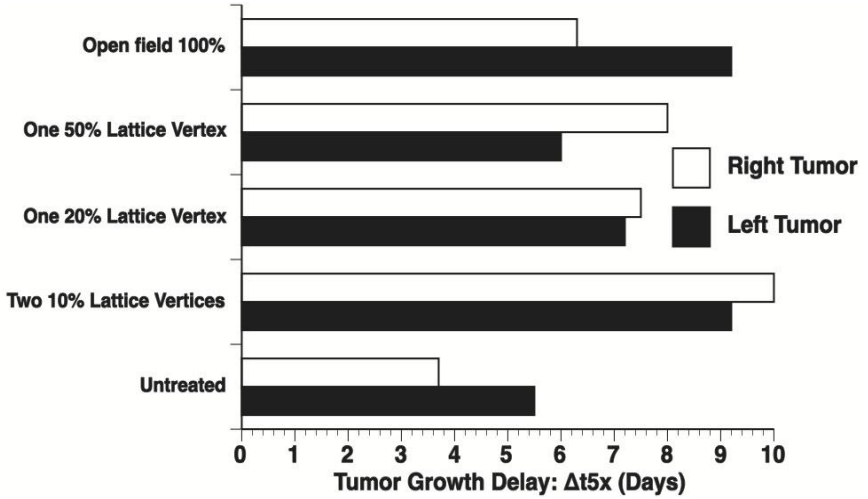


RIGHT UNTREATED TUMOR



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





Immunity enhanced:

Kanagavelu..Ahmed et al, Rad Res 2014

Lattice irradiation tends to increase T cell infiltrate in remote tumor

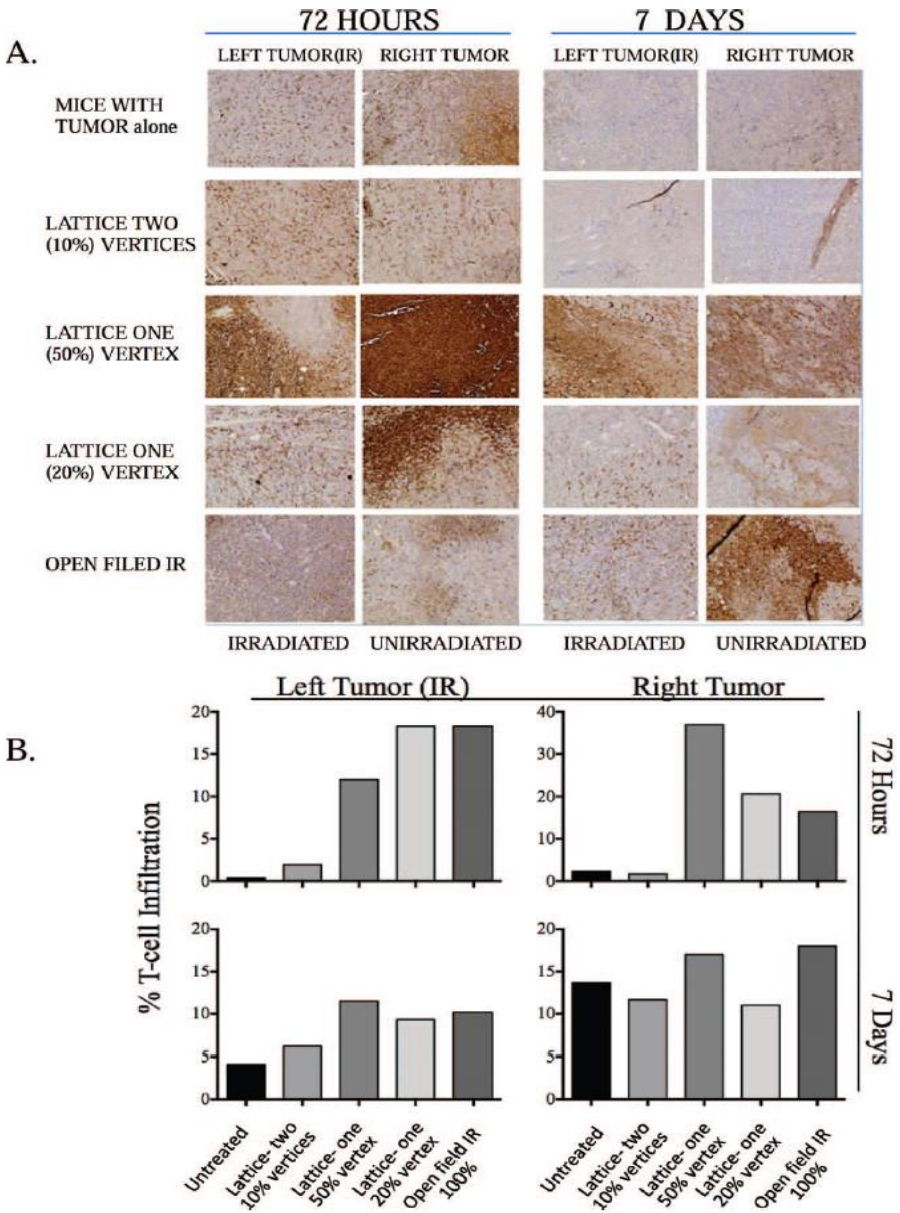
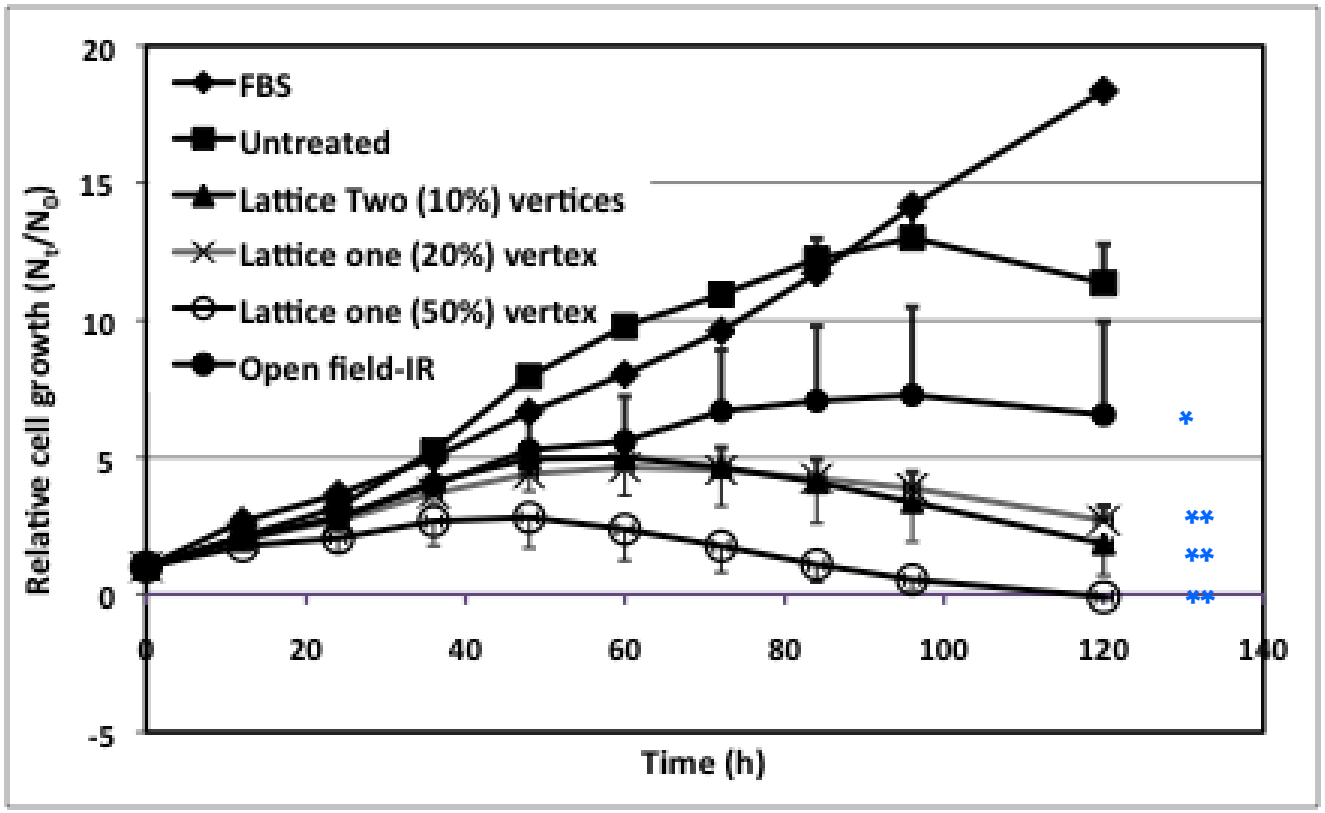
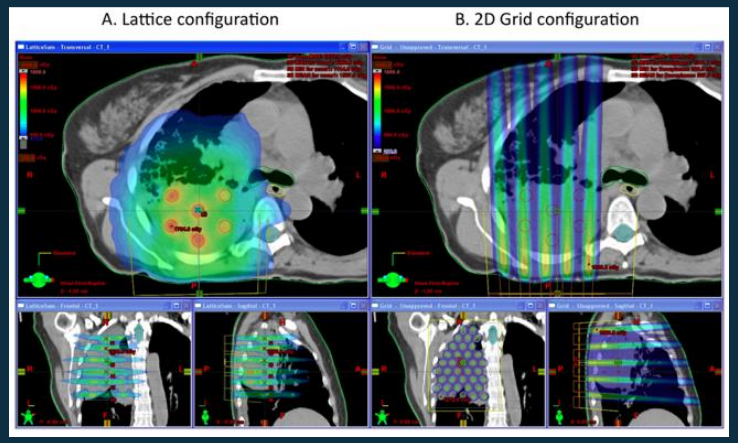


FIG. 5. Panel A: Immunohistochemistry staining for CD3 infiltration in tumors obtained from mice irradiated with high-dose radiation at days 3 and 7 post treatment. Antibody positive regions are brown. Panel B: Entire slides were digitally scanned and analyzed by the AperioImageScope Viewer software. The positive pixel count v9 algorithm was used to measure positive tumor regions for CD3 and shown as percent T-cell infiltration.

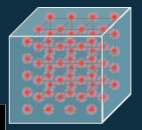
HUVEC growth was significantly reduced in response to all the LRT groups compared to cells that were grown in the serum obtained from either untreated or open field IR groups.

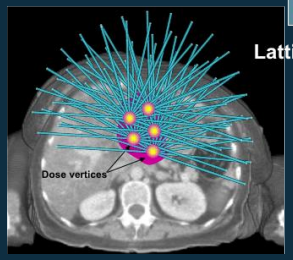


Grid versus Lattice



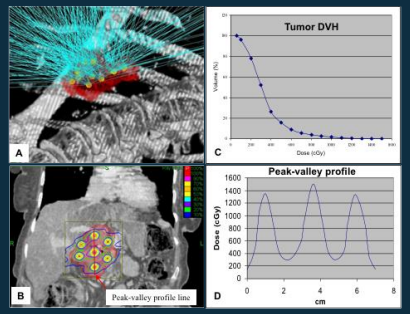
3D Dose Lattice by focused beam

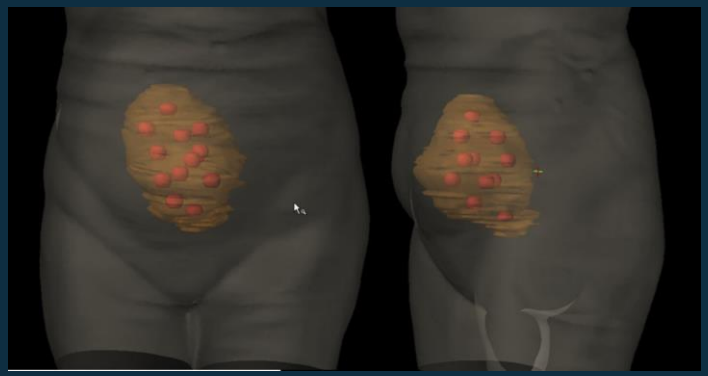


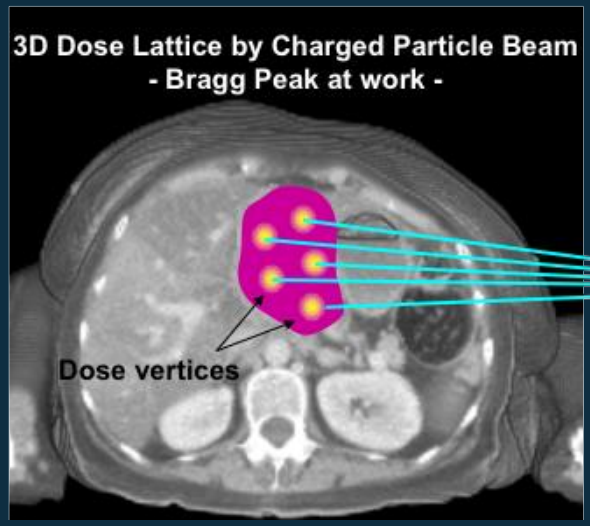


Lattice Radiotherapy

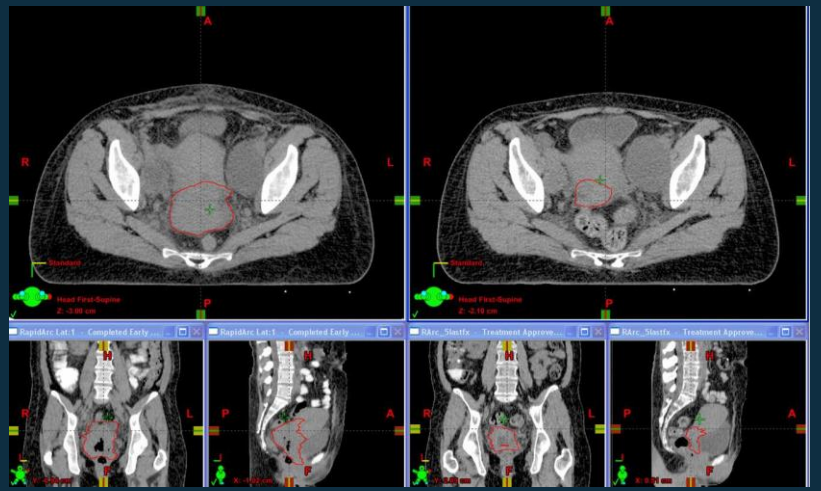
LRT with Cyberknife:
Multiple isocenter delivery





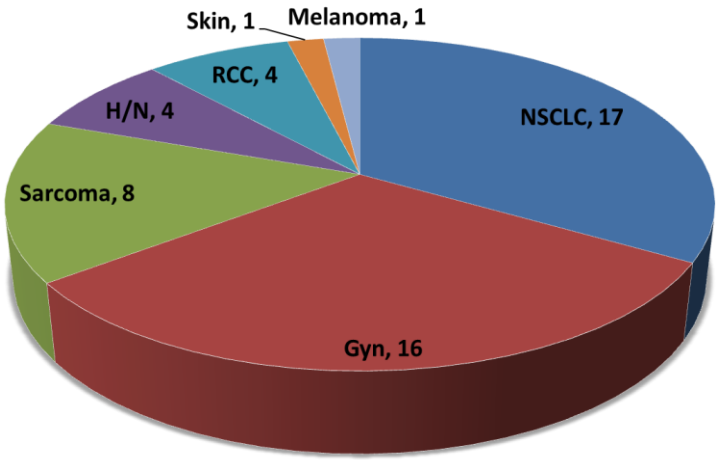


Particle Beam
Scanning Nozzle



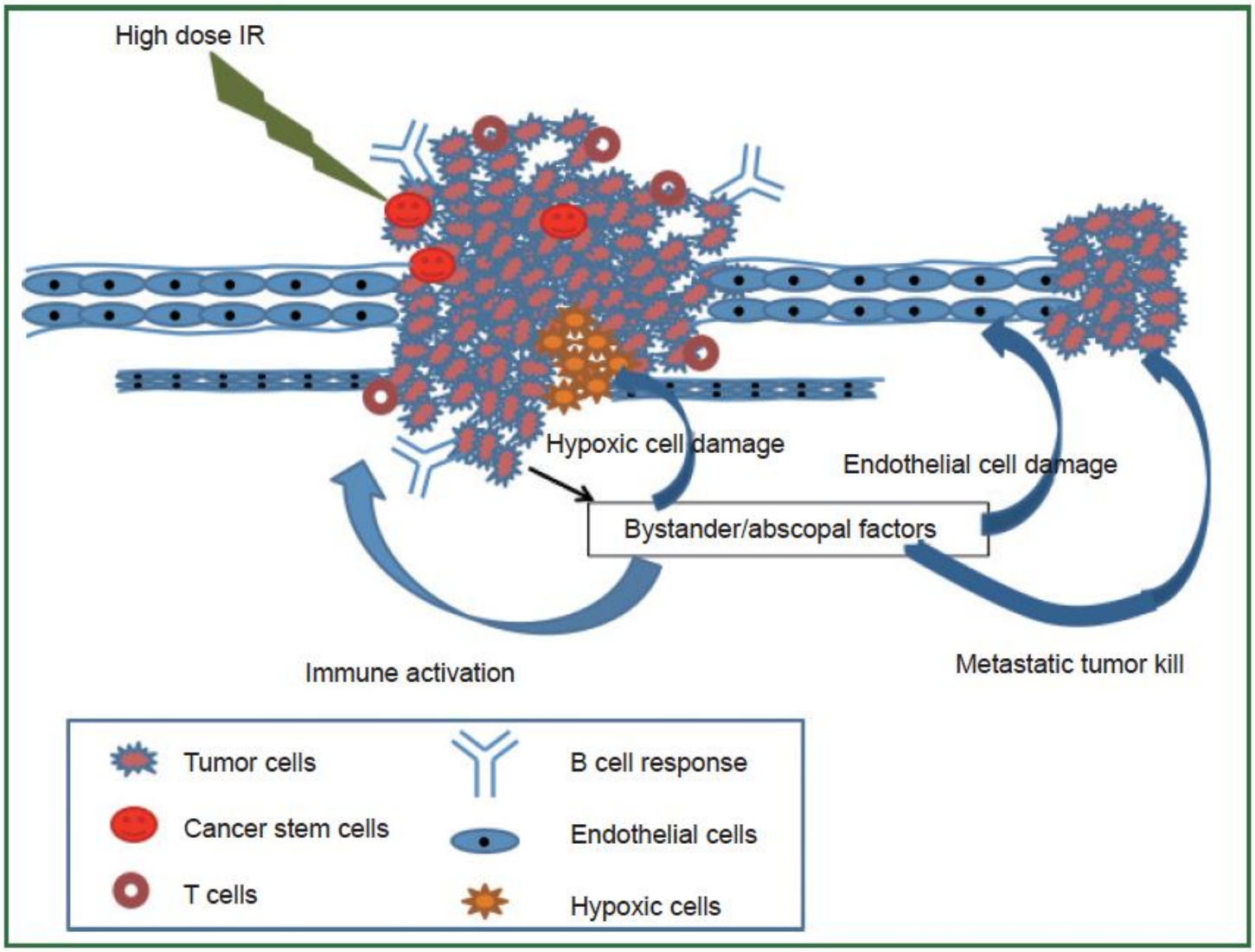
ICI Experience

Pathologic Diagnosis	n
NSCLC	17
Gynecological	16
Sarcoma	8
Head and neck	4
RCC	4
Skin	1
Melanoma	1
TOTAL	51



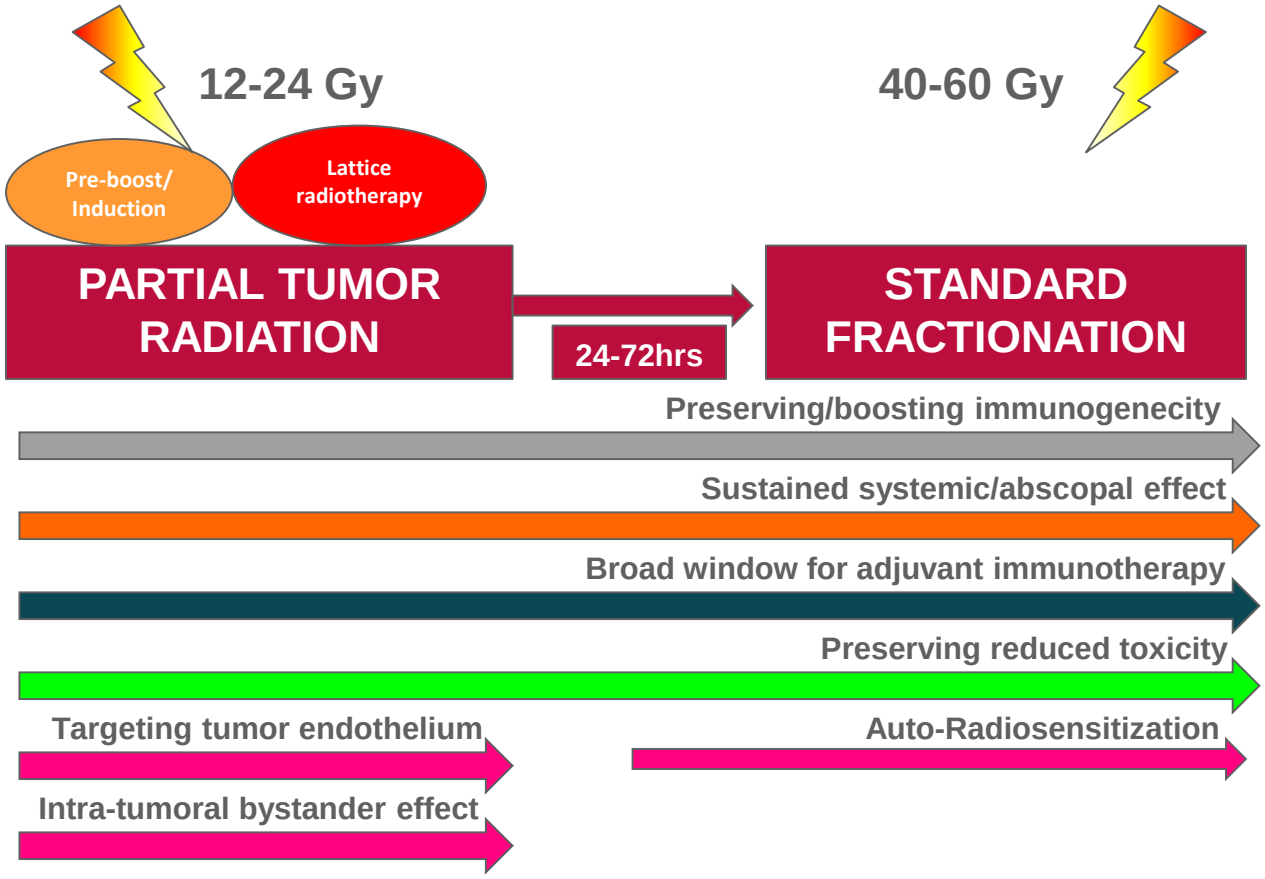
This shows that LRT is tolerable for various disease sites

Complex Biology Exists
Both immune and non-immune bystander / events are elicited



Exploitation of spatial fractionation and non-targeted radiotherapy in clinic

(based on limited pre-clinical data)



NCI-RRP initiatives

On August 20-21, 2018, a workshop held by the Radiation Research Program, National Cancer Institute and the Radiosurgery Society reviewed the proposed radiobiological mechanisms and existing clinical data on SFRT, emphasizing areas for further research.

The group identified a need for guidelines and standards for institutions to incorporate SFRT, addressing the need to standardize appropriate SFRT peak-valley dose and center-to-center spacing, the interval of SFRT fractions if more than 1 fraction is planned, the scheduling and sequencing of SFRT and conventional EBRT combinations, and more.

Further biological experiments using animal models as well as phase 1 and 2 trials are essential to clarify optimal dosing and regimens. It is equally important that the dosimetry of SFRT can be reliably validated.

Biomarkers, including the tumor, serum, and other signaling molecules mentioned earlier, should be measured to correlate with radiobiological data.

Three Working Groups on Grid/Lattice, microbeam and Flash Radiotherapy

- Clinical
  - Quyhn-thu Lei (Advisor)
  - Mohammed Mohiuddin
  - Charles Simone
  - Nina Myer
    - Majid Mohiuddin
    - J. W. Snider
- Physics
  - Xiaodong Wu
  - Hualin Zhang
- Biology
  - Robert Griffin
  - Charlie Limoli
  - Soren Bentzen

Thanks

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