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Physics, Dose Metrics and Clinical Implementation of Spatially Fractionated and Microbeam Radiation Therapy

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Conflict of Interest

Hualin Zhang is the co-chair of The Radiosurgery Society (RSS) GRID/Lattice/Microbeam/Flash Radiation Therapy Working Groups.

Otherwise, the contents presented today **do not** have any conflict of interests.

The papers selected in this presentation are mainly based on the level of my familiarity, not because they are more important than others.

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Outlines

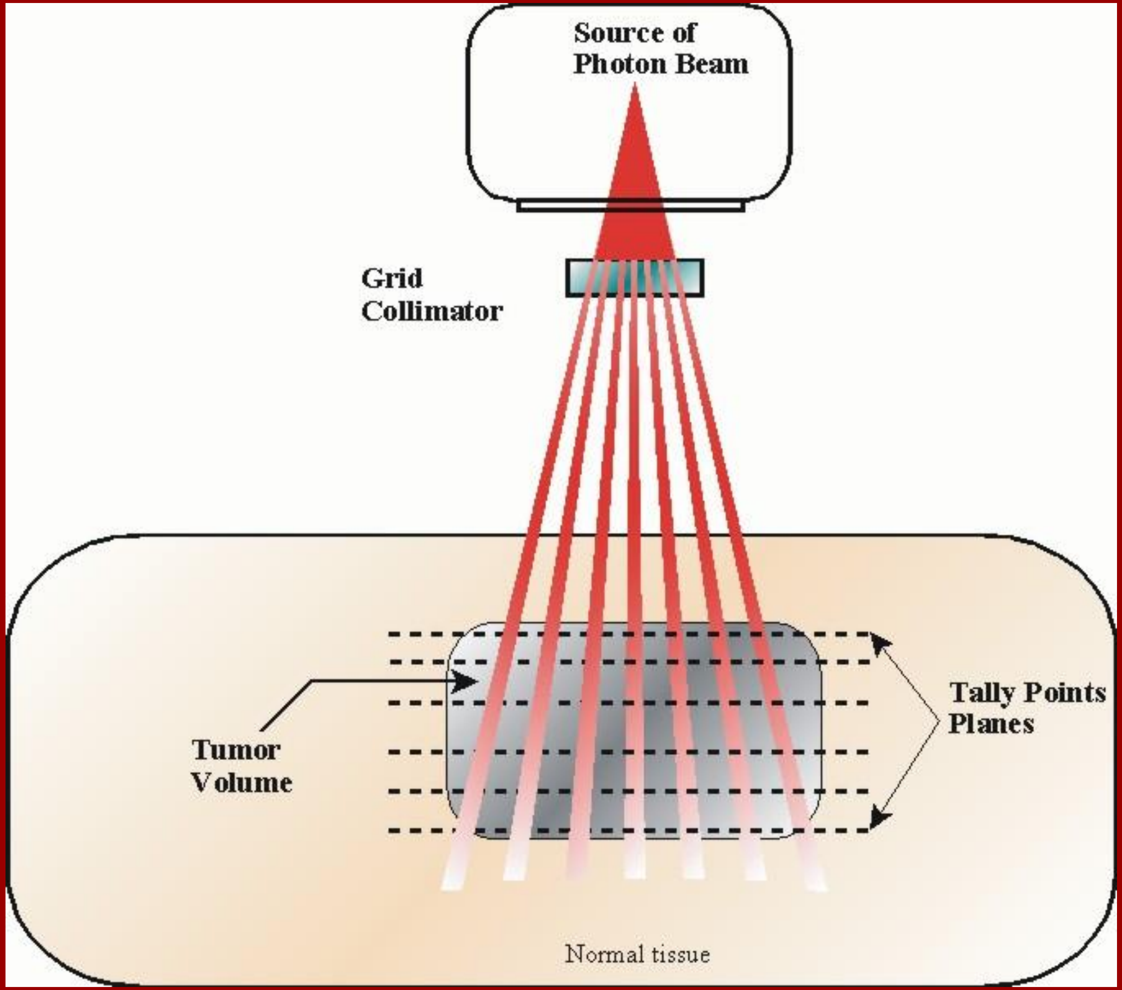
1. Introduction of Spatially Fractionated Radiation Therapy
2. Dose metrics of GRID and Lattice therapy
3. How to implement an SFRT program in clinic
4. Clinical practice pattern of SFRT
5. Advances in GRID, Lattice, and microbeam Therapy

1. Introduction of Spatially Fractionated Radiation Therapy

- **Spatially fractionated radiation therapy evolved from GRID therapy**
- **GRID** therapy was proposed as early as 1950’s, initially for skin cancer treatment to increase tolerance
- **GRID** therapy deliberately creates hot and cold spots (dose heterogeneity) via a GRID collimator
- **Dose intensity modulations happen** in 2D- or 3D-space of tumor target volume, which were referred as GRID or Lattice therapy. Official name is **Spatially fractionated radiation therapy** (SFRT)
- **SFRT** uses a large peak dose (or called nominal dose), originally only used for one fraction before starting conventional EBRT

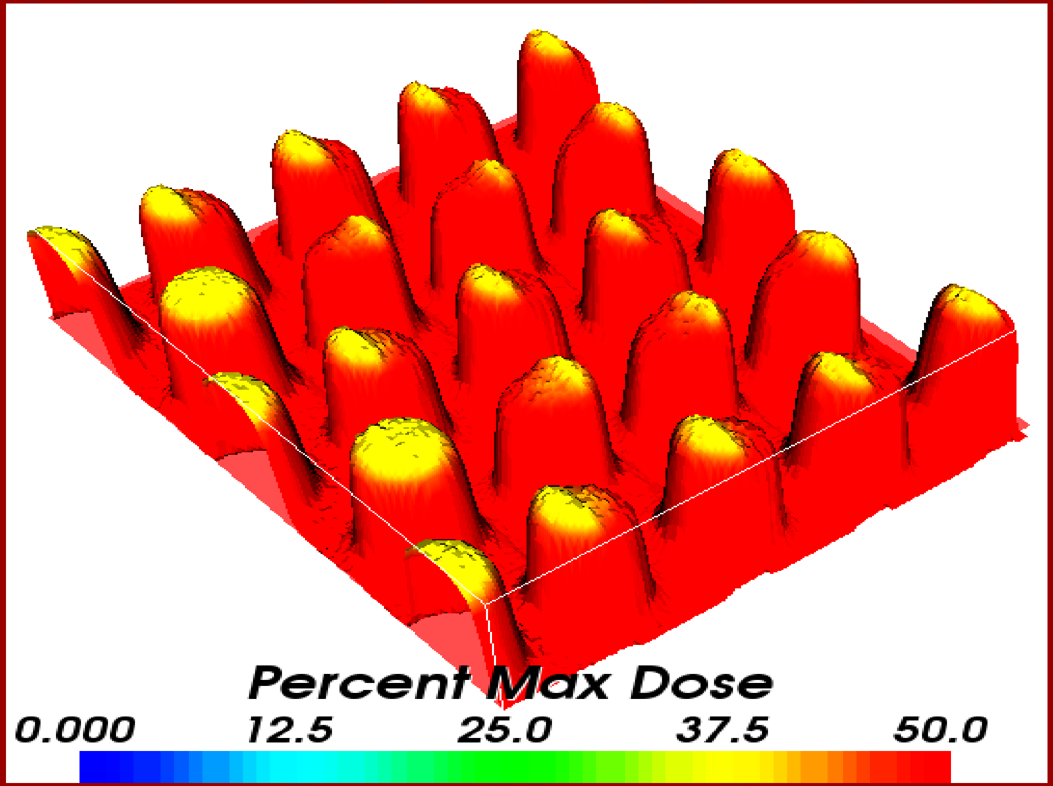
Marks H. A new approach to the roentgen therapy of cancer with the use of a grid. J Mt Sinai Hosp N Y. 1950;17(1):46-48.

Dose Properties of GRID Fields



Schematic diagram

Film dose measurement



Zhang, *IJROBP, 2006*

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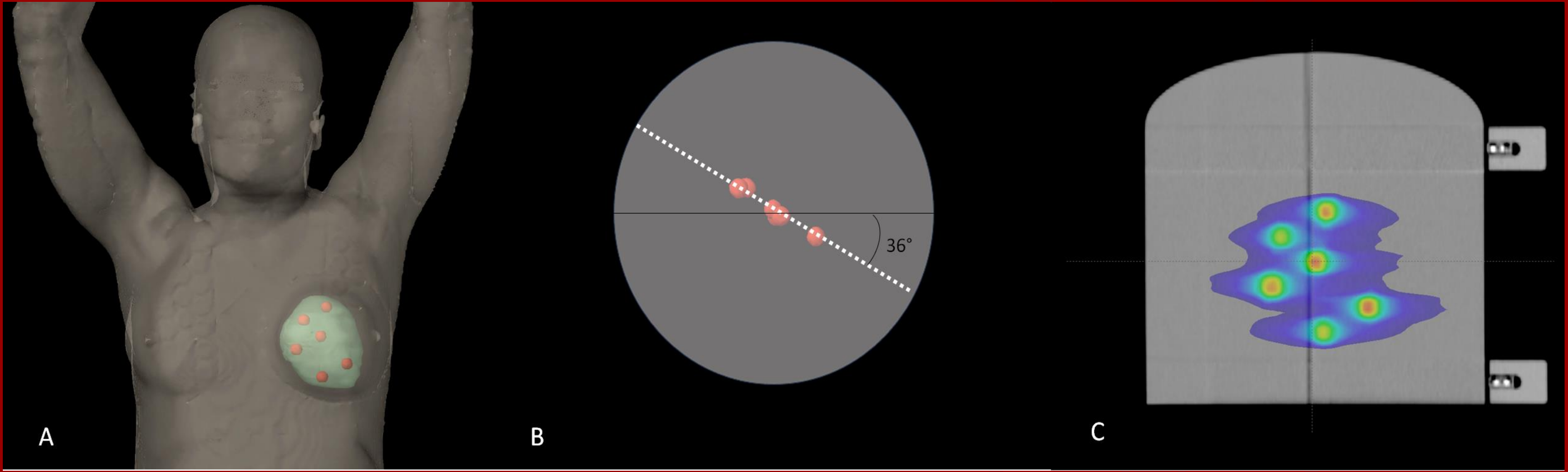
Lattice Radiation Therapy



Michael Grams, Hualin Zhang. Chapter 15: SFRT Field Calibration. In Book: Zhang H, Mayr N, editors. Spatially Fractionated, Microbeam and Flash Radiation Therapy: A Physics and Multi-disciplinary Approach. IOP Publishing; 2023. ISBN 978-0-7503-4046-5

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Lattice Vs GRID

Lattice therapy

- Can effectively spare normal structures,
- Can put high dose vertices to desired locations,
- Cannot maintain large dose modulation, peak/valley dose ratio is smaller than GRID.

GRID therapy

- Can maintain large dose modulation, peak/valley dose ratio is greater than Lattice.
- Can maintain similar dose pattern for different patients,
- Cannot effectively spare normal structures.

The real reasons for improved responses by SFRT remain unclear, biologists believe following effects may have contributed the favorable outcomes.

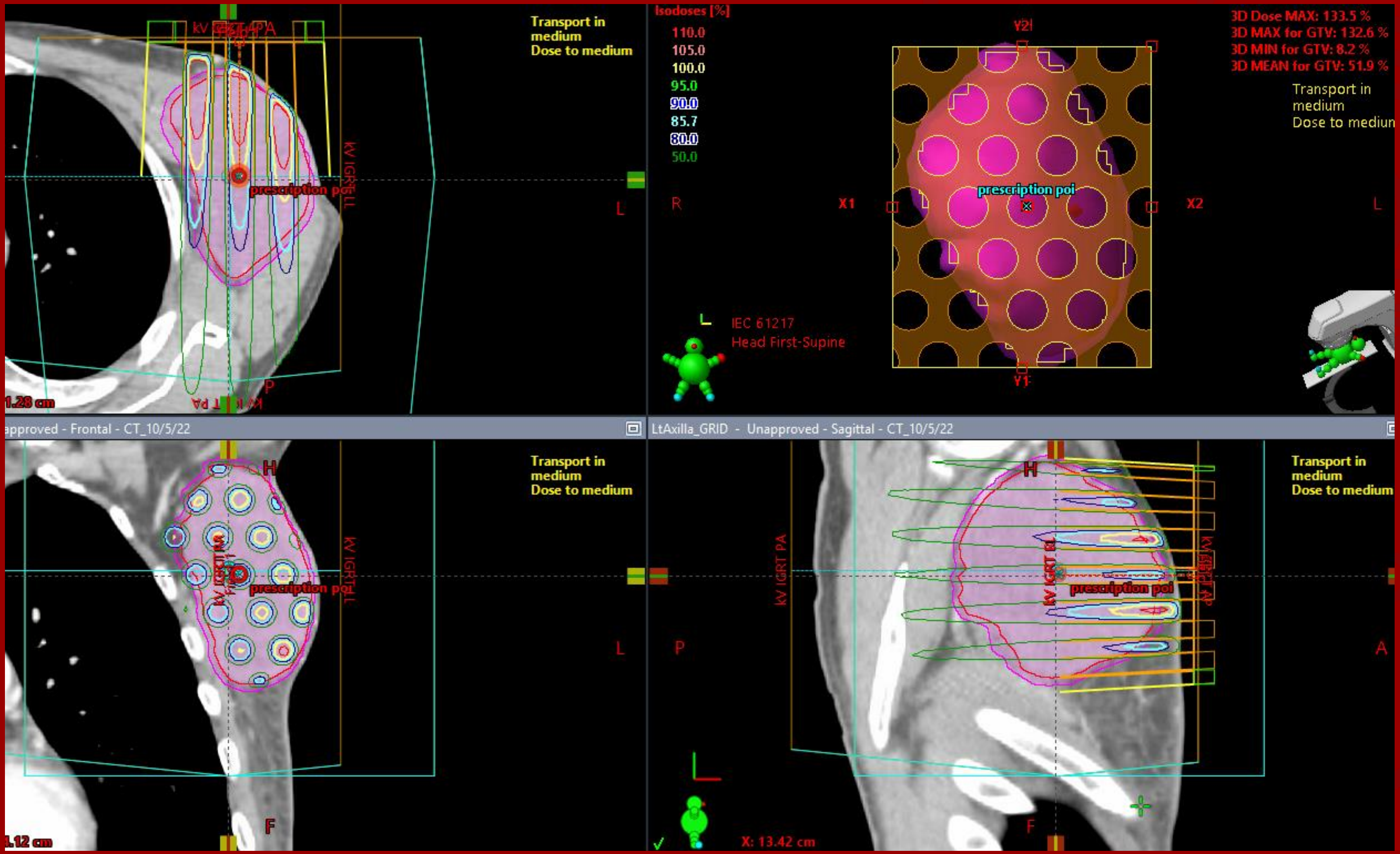
- SFRT Enhances the ability of normal tissues to repair (better than cancer cells) by additionally lowering normal tissue dose.
- SFRT achieves high tumor cell kill with high (ablative-fraction) dose, creates intensive killing islands, inhibits cancer cell communication.
- SFRT leverages the by-stander effects, abscopal effects and cohort effects, which are stronger in the heterogeneous fields.
- SFRT also manifests the early evidence of immuno-modulation effects (in low-dose regions).

2. Dose metrics of GRID and Lattice therapy

- ✓Lattice therapy was developed because of the success of GRID therapy,
- ✓Lattice therapy takes advantage of the advanced treatment planning system (TPS) and versatility of multileaf collimator (MLC) of modern medical linac machine,
- ✓The success of interstitial LDR or HDR brachytherapy may be translated to explain the Lattice, GRID therapy,
- ✓Lattice therapy shares many dose parameters with GRID therapy; but Lattice therapy has some unique dose parameters.

Dose Distribution of GRID Therapy

Some treatment planning systems, such as Eclipse, can handle GRID collimator for GRID therapy dose calculation



Axilla bulky tumor GRID therapy

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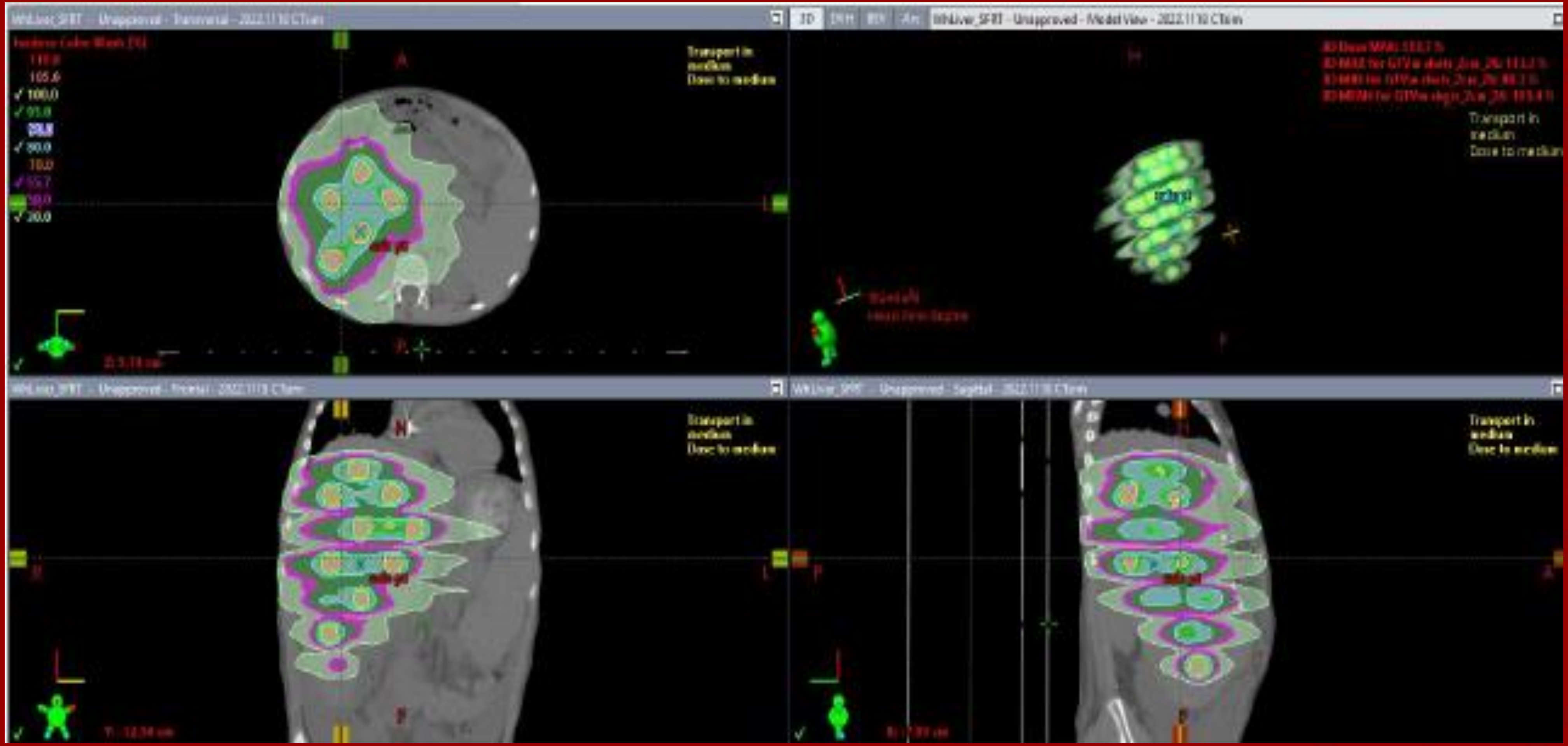
Dose Distribution of Lattice Therapy (LRT)



Liver bulky tumor Lattice therapy generated by VMAT at USC by Dr. Olch

Lattice therapy (LRT) can be designed for any bulky tumors

The RSS Working Groups recommended dose metrics for GRID and Lattice therapy

GRID therapy	Lattice therapy
Prescription dose (D_p, in Gy)	Prescription dose (D_p, in Gy)
Equivalent uniform dose (EUD, in Gy)	Equivalent uniform dose (EUD, in Gy)
Planning target volume (PTV, in cm^3)	Gross target volume (GTV, in cm^3)
Peak-peak distance at tumor center depth (cm)	Volume of Lattice, $V_{lattice}$
Secondary collimator margin (cm)	Volume of Vertices, $V_{vertices}$,
Dose covering 95% of target (D95, in Gy)	Dose covering 95% of target (D95, in Gy)
Dose covering 90% of target (D90, in Gy)	Dose covering 90% of target (D90, in Gy)
Dose covering 50% of target (D50, in Gy)	Dose covering 50% of target (D50, in Gy)
Dose covering 20% of target (D20, in Gy)	Dose covering 20% of target (D20, in Gy)
Dose covering 10% of target (D10, in Gy)	Dose covering 10% of target (D10, in Gy)
Dose covering 5% of target (D5, in Gy)	Dose covering 5% of target (D5, in Gy)
Valley/peak dose ratio at the tumor center depth (VPDR) (from 0.1 to 0.5)	D95/D5 (from 0.2 to 0.5)
D10/D90, PVDR (from 2 to 7)	D10/D90, PVDR (from 2 to 5)
High dose core number (>3)	High dose core number (>3)

Zhang, et al. *Rad Research.* 194: 665-677 (2020)
Wu, et al. *Rad Research*. 194:737-746 (2020)

3. How to implement an SFRT program

Implementing SFRT needs a lot of physics preparation, it will be easier for you to start with GRID therapy …

(a). GRID collimator commissioning

(b). functionality, safety check, MU delivery limit adjustment, conformality check.

(c). GRID Dicom file importation

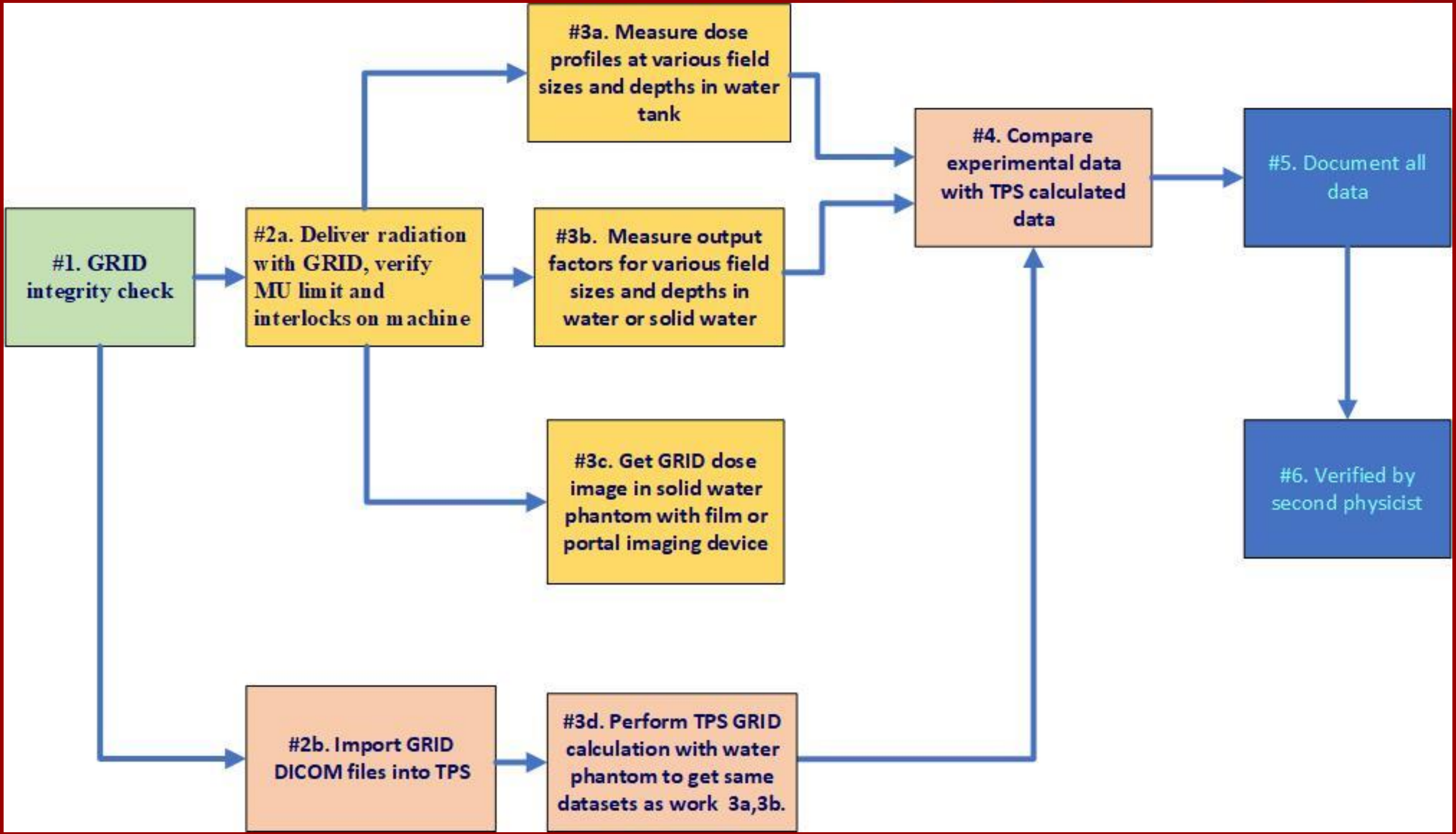
(d). Lattice plan creation

(e). Discussing with MD

(f). Discussing with experienced MDs and physicists from outside if felt necessary.

(g). Reading SFRT dosimetric white papers

GRID therapy implementation workflow at USC



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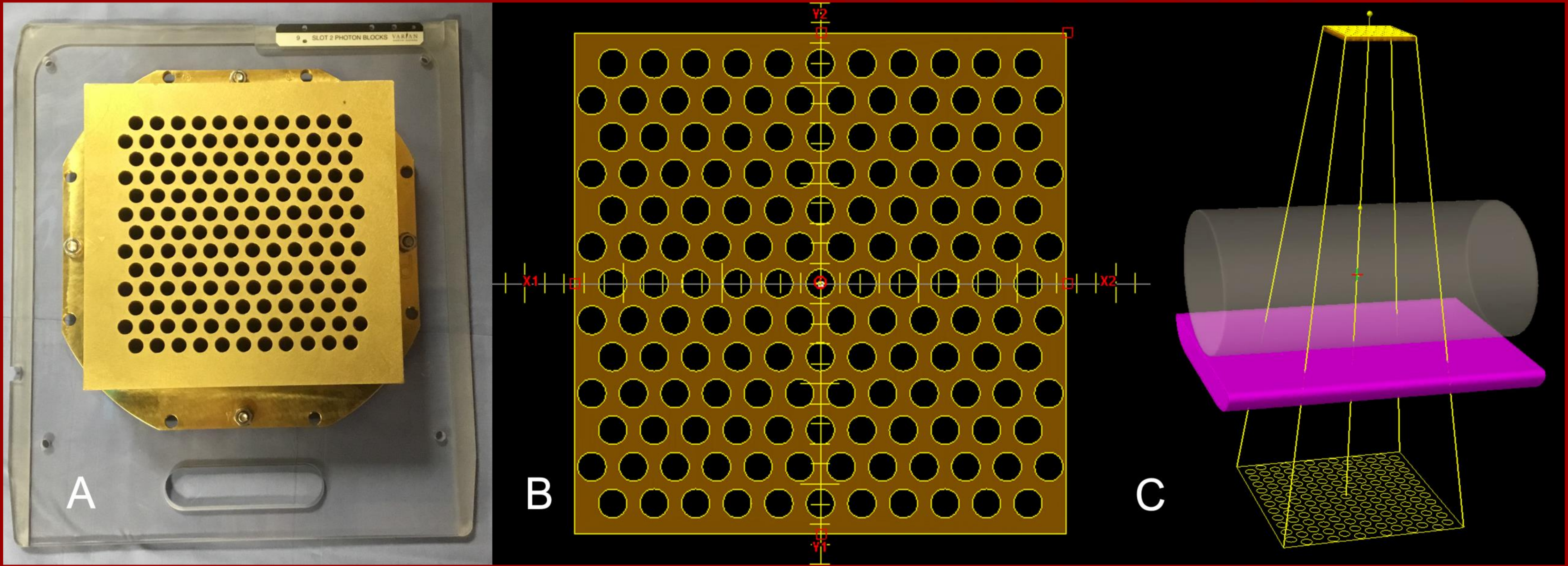
Measurement with a GRID collimator



Zhang, et al. Cancers, 14, 1037, 2022

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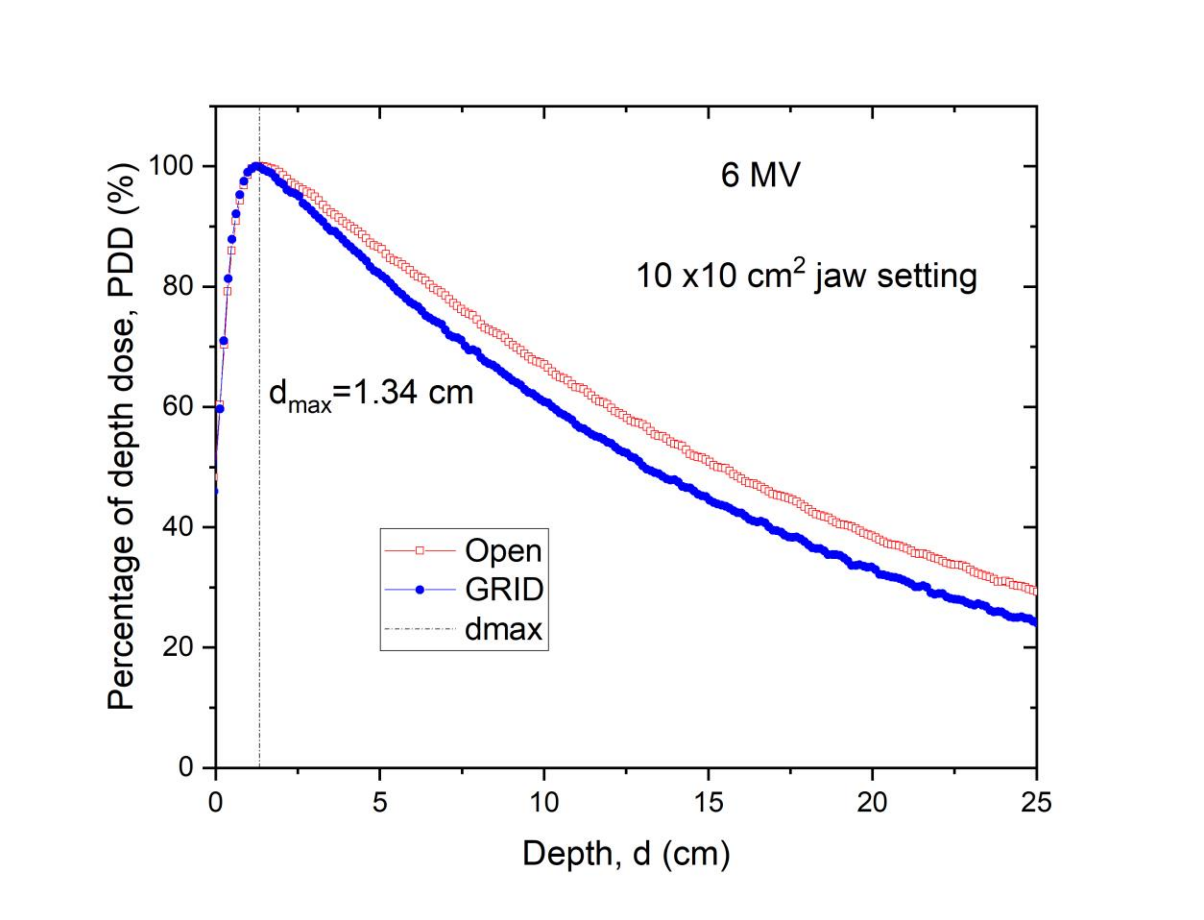
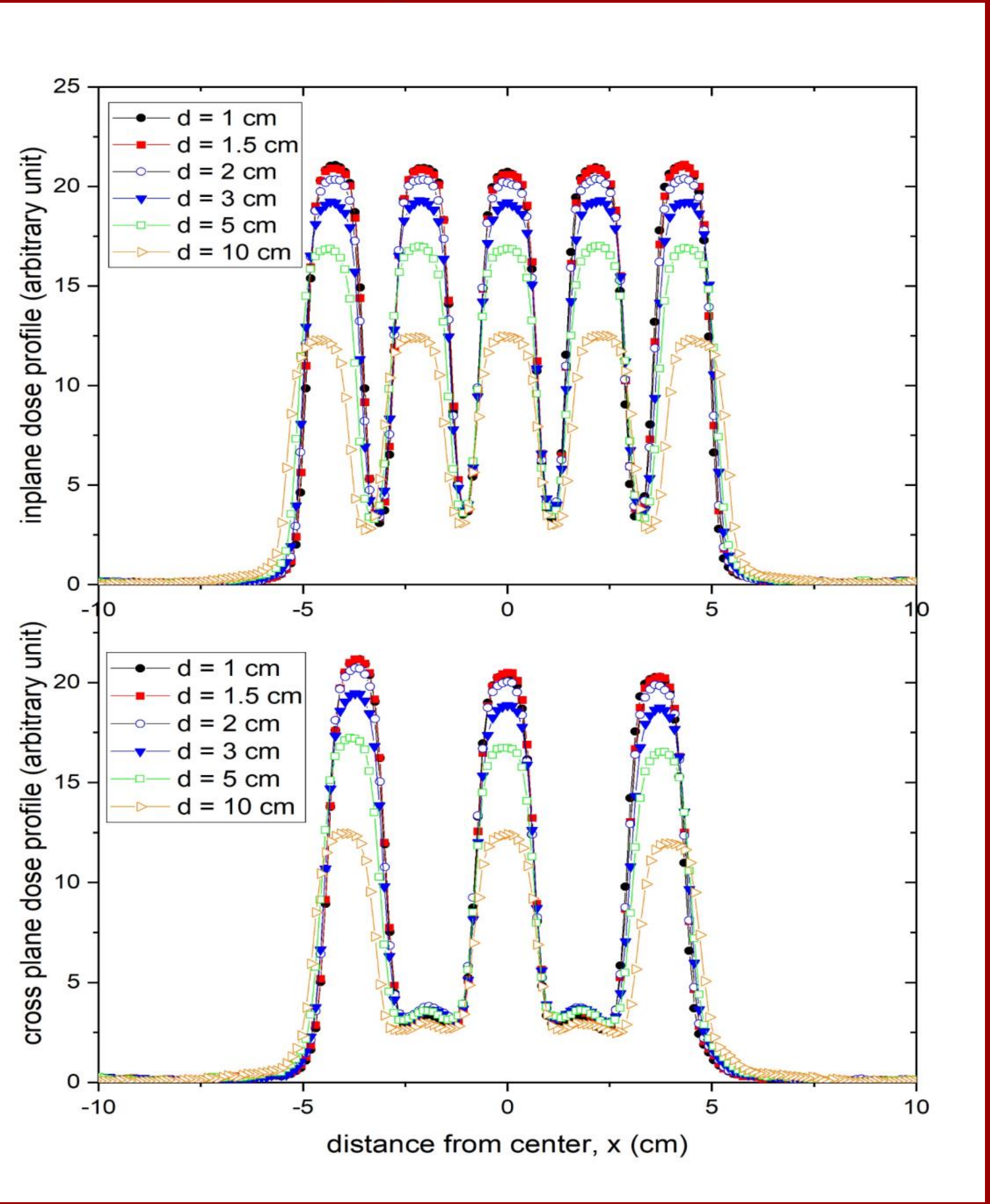
Percent depth dose and dose profiles at different depths





GRID Field output factor

Normalized by 10x10 cm^2 GRID Field

6 MV Output Factors	Field Size (cm^2)					
	6x6	8x8	10x10	15x15	20x20	25x25
PTW Microdiamond (measured)	0.981	0.990	1.000	1.023	1.042	1.061
TPS (calculated)	0.977	0.990	1.000	1.013	1.024	1.034
% Difference	0.41%	0.00%	0.00%	0.98%	1.73%	2.54%
10 MV Output Factors	Field Size (cm^2)					
	6x6	8x8	10x10	15x15	20x20	25x25
PTW Microdiamond (measured)	0.975	0.986	1.000	1.027	1.049	1.069
TPS (calculated)	0.970	0.987	1.000	1.017	1.028	1.040
% Difference	0.51%	-0.10%	0.00%	0.97%	2.00%	2.71%

Table 1: Comparison of measured and Varian Eclipse TPS calculated 6 MV and 10 MV output factors for various field sizes using a brass GRID block. The OFs were normalized by the OF for a 10x10 cm^2 field size with the GRID block in place.

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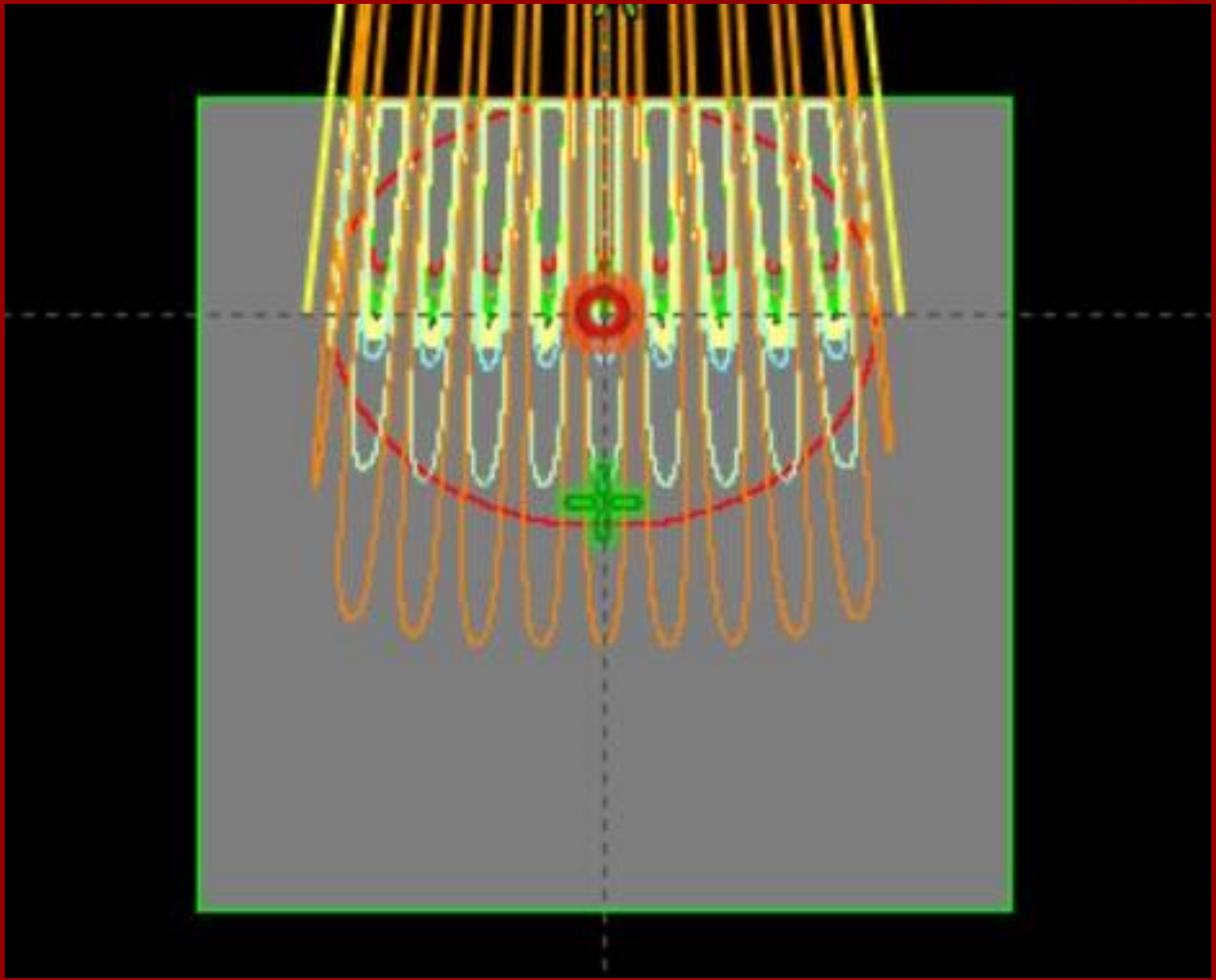
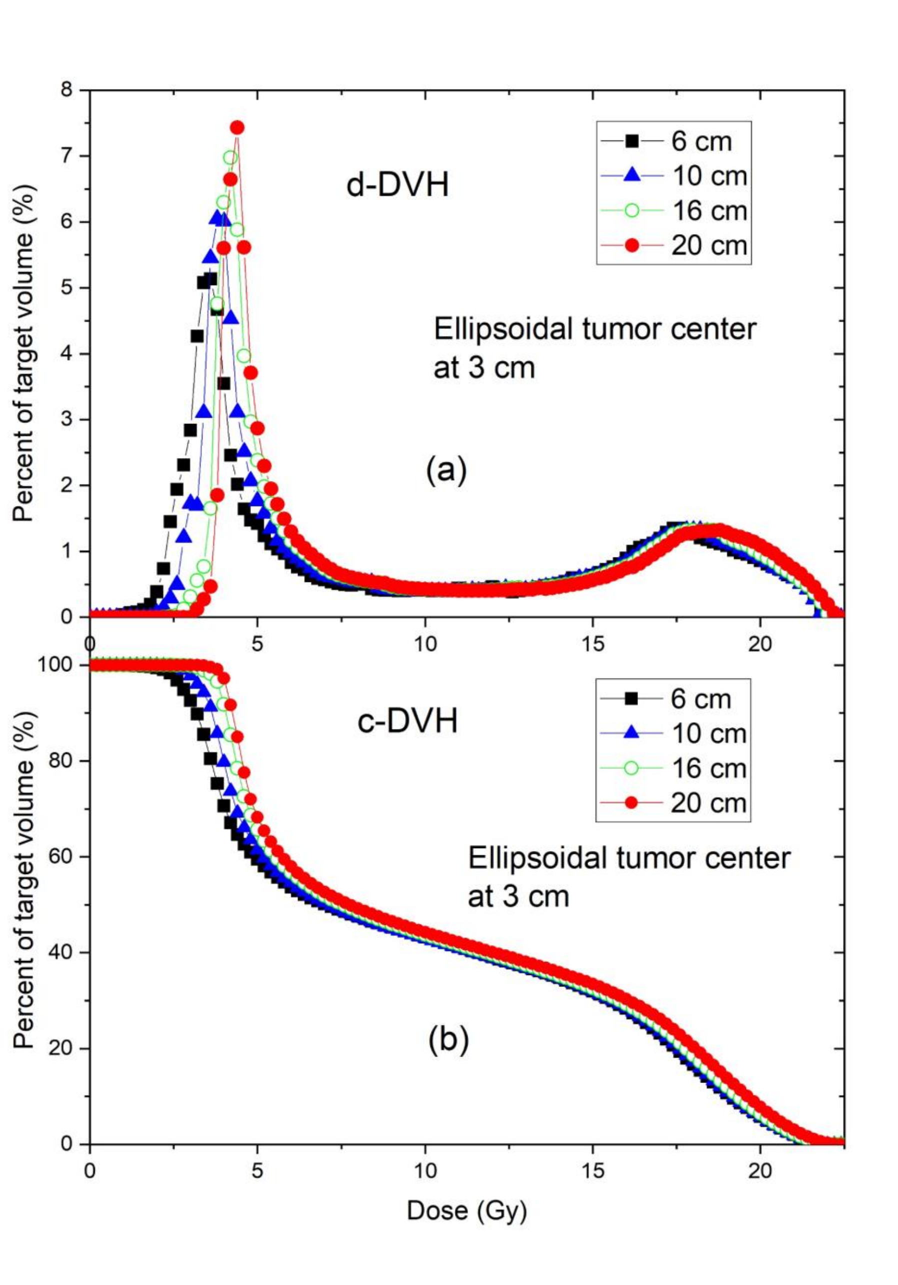
Treatment planning system (TPS) needs to be checked for Grid-collimator based SFRT calculation



Play GRID therapy with a flat-water phantom in TPS

Get DVH curves of target



Zhang, et al. Cancers, 14, 1037, 2022

GRID and Lattice therapy dosimetry white papers and dosimetry consensus.

RADIATION RESEARCH **194**, 665–677 (2020)
0033-7587/20 $15.00

DOI: 10.1667/RADE-20-00047.1

Photon GRID Radiation Therapy: A Physics and Dosimetry White Paper from the Radiosurgery Society (RSS) GRID/LATTICE, Microbeam and FLASH Radiotherapy Working Group

Hualin Zhang,[a,1] Xiaodong Wu,[b] Xin Zhang,[c] Sha X. Chang,[d] Ali Megooni,[e] Eric D. Donnelly,[a] Mansoor M. Ahmed,[f,2] Robert J. Griffin,[g] James S. Welsh,[h] Charles B. Simone, II[i] and Nina A. Mayr[j]

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RADIATION RESEARCH **194**, 737–746 (2020)
0033-7587/20 $15.00

DOI: 10.1667/RADE-20-00066.1

The Technical and Clinical Implementation of LATTICE Radiation Therapy (LRT)

Xiaodong Wu,[a,b,c,d,1] Naipy C. Perez,[b] Yi Zheng,[a,d] Xiaobo Li,[d] Liuqing Jiang,[d] Beatriz E. Amendola,[b] Benhua Xu,[d] Nina A. Mayr,[e] Jiade J. Lu,[c] Georges F. Hatoum,[f] Hualin Zhang,[g] Sha X. Chang,[h] Robert J. Griffin[i] and Chandan Guha[j]

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Lattice therapy dosimetry white paper
Dosimetry consensus.

Wu, et al. Radiation Research, 2020.

WU *ET AL.*

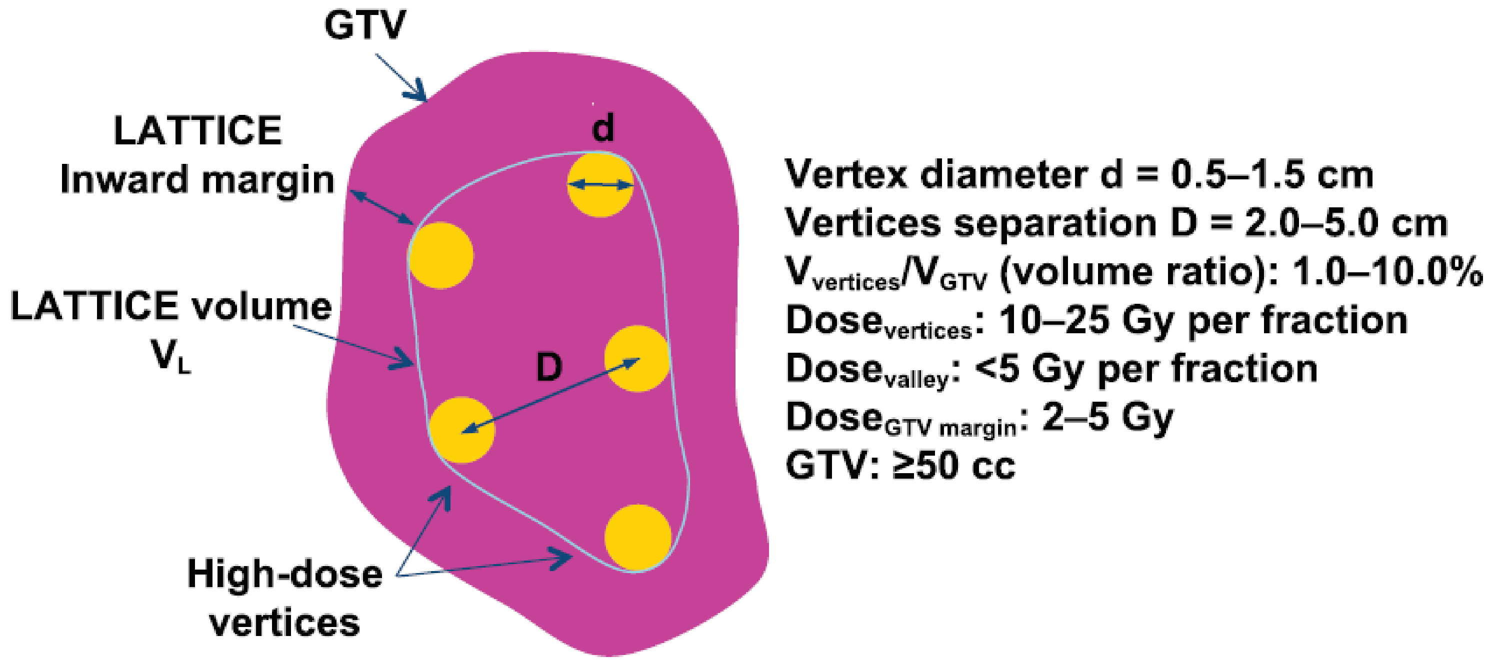
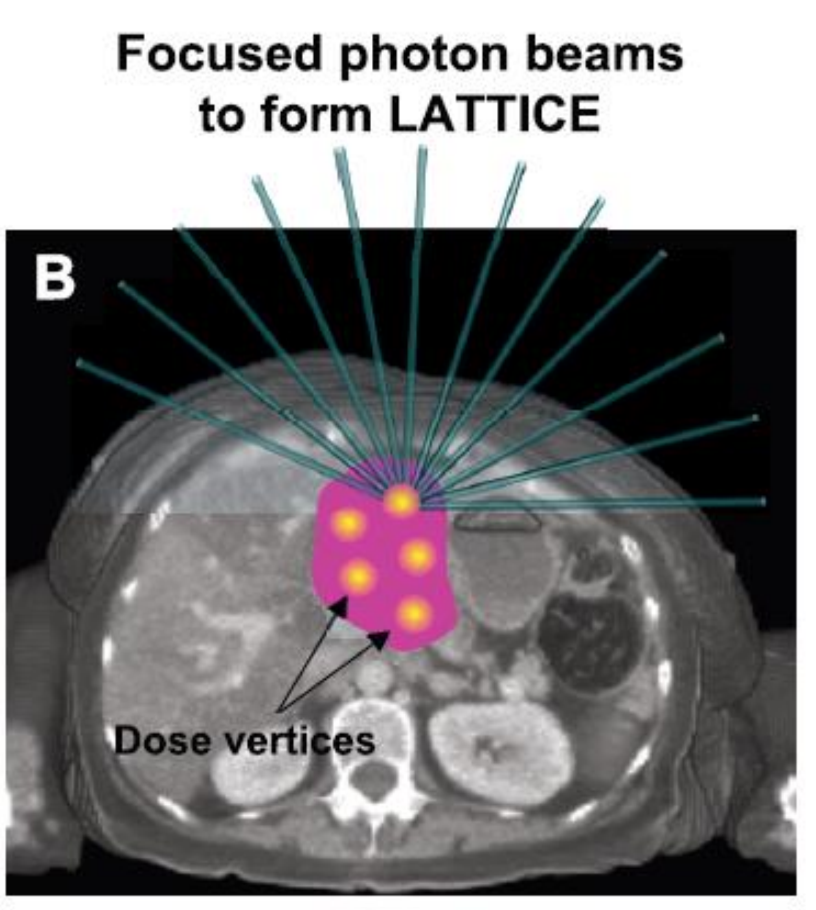


FIG. 4. Parameters and ranges of a typical LRT plan.



4. Clinical practice pattern of SFRT

Clinical practice is the SFRT's real driving force, new progress is made almost in every month

More than 3000 patients have been treated by GRID therapy.[1]

1000 patients have been treated by Lattice therapy [1]

SFRT has been used for both the definitive and palliative treatments [2]

Presently, the main goal for implementation of SFRT should be to ensure that plans are delivered with maximal safety.[3]

1) Spatially fractionated .. SFRT Book, Hualin Zhang, Nina Mayr, IOP 2023
2) Mayr NA, et al SFRT clinical practice pattern, Adv Rad. 2023
3) Grams M, et al. Clinical aspects of SFRT. Physica Medica, 2023

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Currently as our survey reported, half of SFRT patients are treated by GRID, another half by Lattice

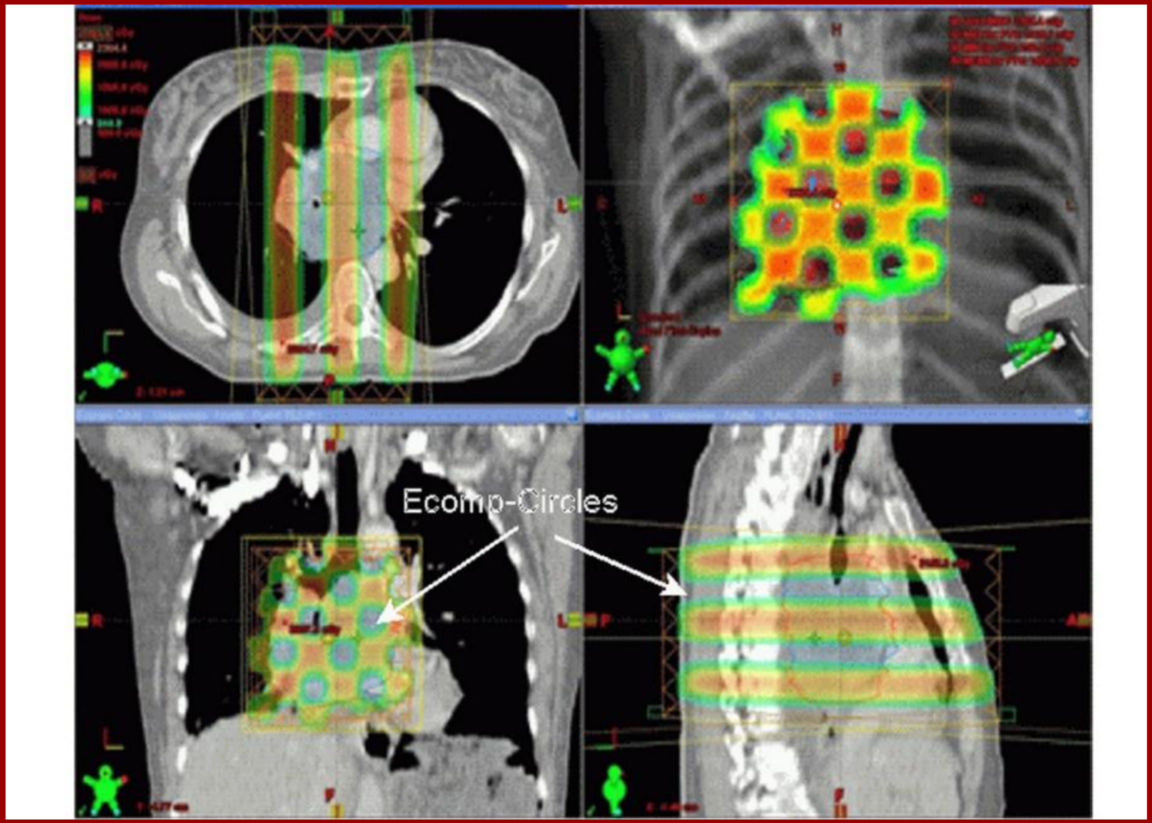

Figure from: Heather N et al. Med Dosim 2014; 39: 218-26

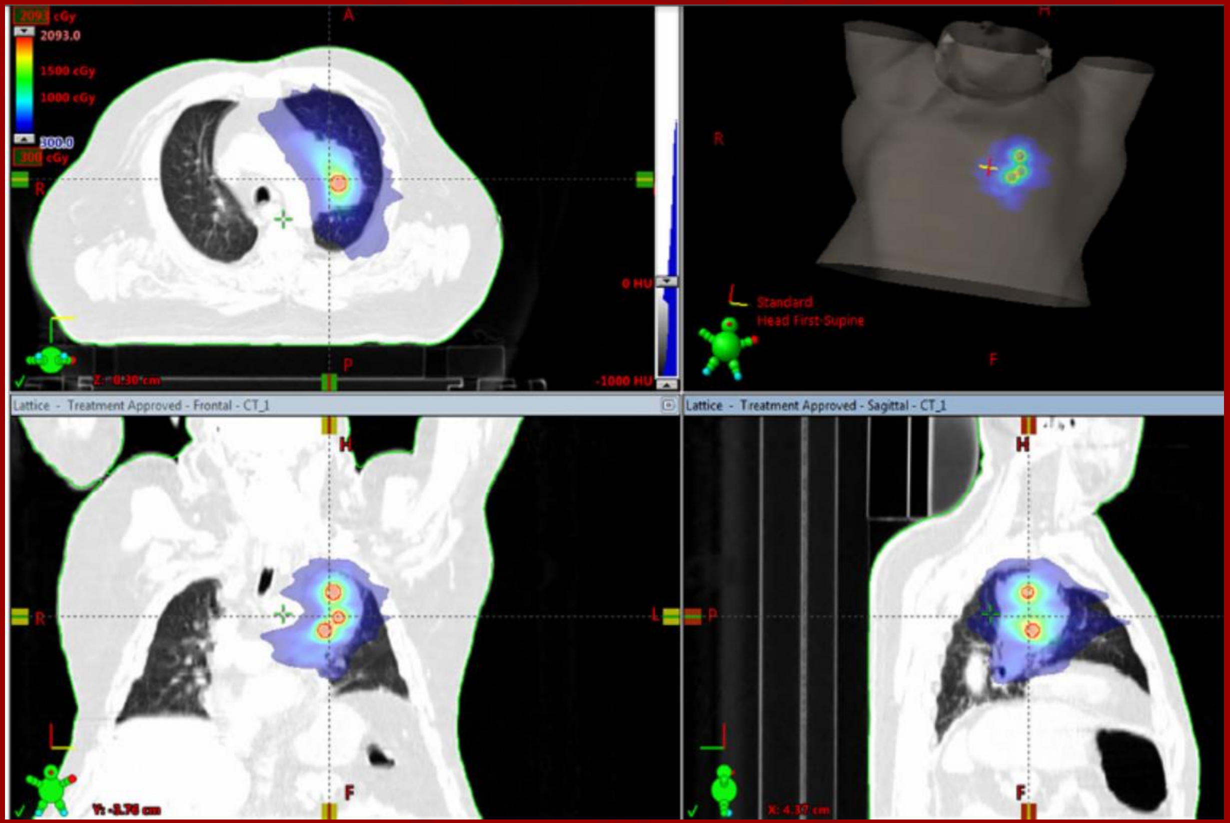

Figure from: Amendola BA et al. Clin Transl Rad Oncol 2018; 9: 68-71

In clinical SFRT practice, clinicians often want to know

a) What disease sites have been safely treated by SFRT?
b) What dose regimens (dose size, fraction number) have been used by practitioners?
c) When should we use GRID/Lattice, how long gap before or after conventional RT?
d) What treatment regimens should we use, solo or adjuvant?
e) How should we arrange following treatments?
f) How should we evaluate the SFRT responses?
g) Should we go through an IRB approval?

RSS Workgroups SFRT clinical effort #1: Head/neck, Sarcoma cancer SFRT clinical trial design consensus

Advances in Radiation Oncology (2022) 7, 100866

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Scientific Article

An International Consensus on the Design of Prospective Clinical–Translational Trials in Spatially Fractionated Radiation Therapy

Nina A. Mayr, MD,[a,b,*] James W. Snider, MD,[c] William F. Regine, MD,[d] Majid Mohiuddin, MD,[e] Daniel S. Hippe, MS,[f] José Peñagarícano, MD,[g] Mohammed Mohiuddin, MD,[h] Mahesh R. Kudrimoti, MD,[i] Hualin Zhang, PhD,[j] Charles L. Limoli, PhD,[k] Quynh-Thu Le, MD,[l] and Charles B. Simone, II, MD[m]

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RSS Workgroup SFRT clinical effort #2:
GYN cancer SFRT clinical trial design consensus

cancers MDPI

Guidelines

An International Consensus on the Design of Prospective Clinical–Translational Trials in Spatially Fractionated Radiation Therapy for Advanced Gynecologic Cancer

Beatriz E. Amendola [1], Anand Mahadevan [2], Jesus Manuel Blanco Suarez [3], Robert J. Griffin [4], Xiaodong Wu [5], Naipy C. Perez [1], Daniel S. Hippe [6], Charles B. Simone II [7], Majid Mohiuddin [8], Mohammed Mohiuddin [9], James W. Snider [10], Hualin Zhang [11], Quynh-Thu Le [12] and Nina A. Mayr [13,*]

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Citation: Amendola, B.E.; Mahadevan, A.; Blanco Suarez, J.M.; Griffin, R.J.; Wu, X.; Perez, N.C.; Hippe, D.S.; Simone, C.B., 2nd;

RSS Workgroup SFRT clinical effort #3: A survey report of clinical practice pattern of SFRT

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Advances in Radiation Oncology (2023) **000**, 101308

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Scientific Article

Practice Patterns of Spatially Fractionated Radiation Therapy: A Clinical Practice Survey

Nina A. Mayr, MD,[a,*] Majid Mohiuddin, MD,[b] James W. Snider, MD,[c] Hualin Zhang, PhD,[d] Robert J. Griffin, PhD,[e] Beatriz E. Amendola, MD,[f] Daniel S. Hippe, MS,[g] Naipy C. Perez, MS,[f] Xiaodong Wu, PhD,[h] Simon S. Lo, MD,[i] William F. Regine, MD,[j] and Charles B. Simone II, MD[k]

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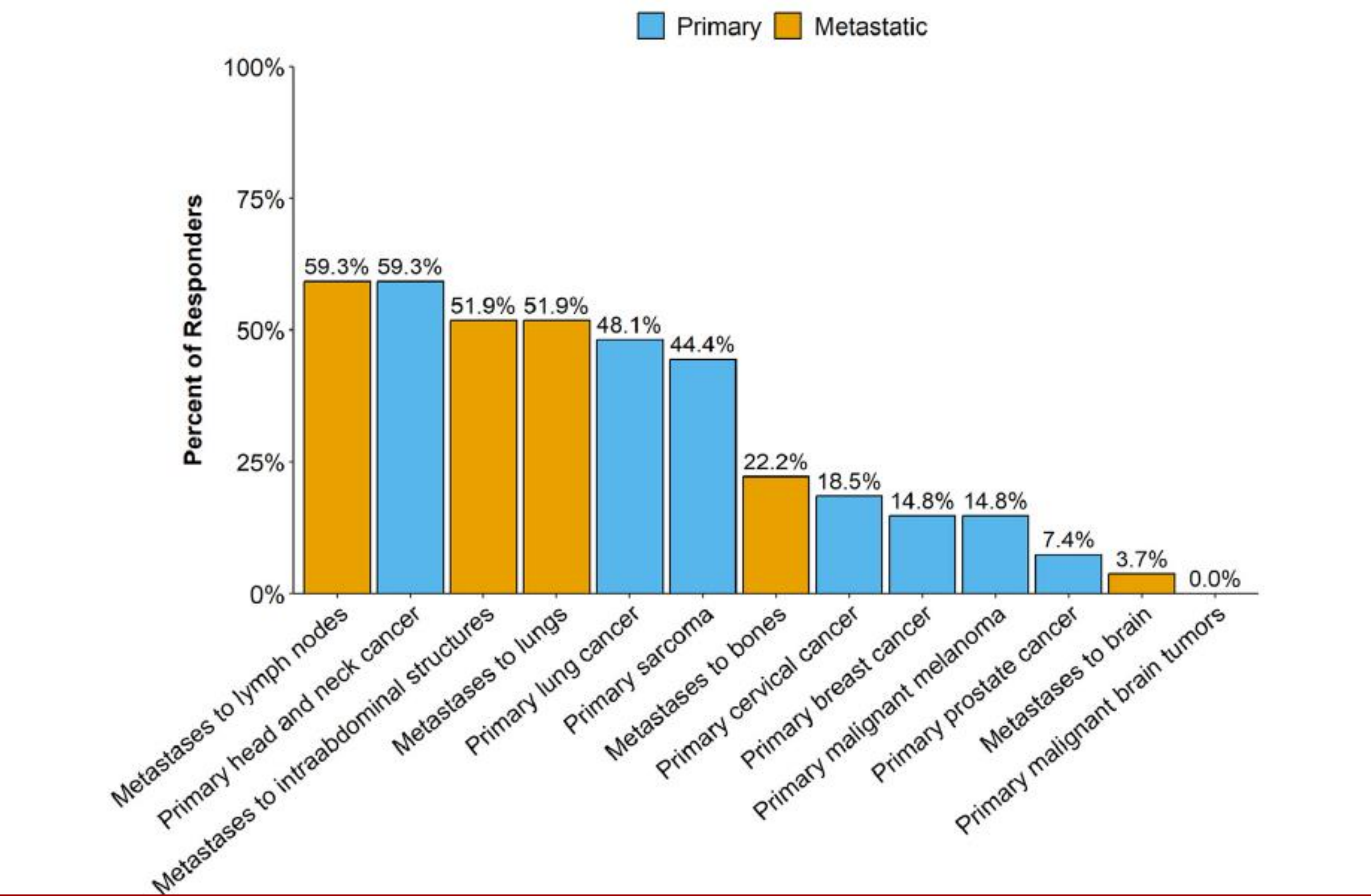
Disease sites and percentage of usage for SFRT

Figure shows the distribution of disease sites treated with spatially fractionated radiation therapy (SFRT). Proportions of radiation oncologists using SFRT for specific tumor types and tumor sites are presented.



SFRT clinical practice pattern

- The majority of practicing radiation oncologists (United States, 100%; global, 72.7%) considered SFRT an accepted standard-of-care radiation therapy option for bulky/advanced tumors
- Treatment of metastases/recurrences and nonmetastatic primary tumors, predominantly head and neck, lung cancer and sarcoma, was commonly practiced.

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SFRT clinical practice pattern _ cont.

- In palliative SFRT, regimens of 15 to 18 Gy/1 fraction predominated (51.3%), and in curative-intent treatment of nonmetastatic tumors, 15 Gy/1 fraction (28.0%) and fractionated SFRT (24.0%) were most common.
- SFRT was combined with cERT commonly but not always in palliative (78.6%) and curative-intent (85.7%) treatment. SFRT–cERT time sequencing and cERT dose adjustments were variable.

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SFRT clinical practice pattern _ cont.

- In curative-intent treatment, concurrent chemotherapy and immunotherapy were found acceptable by 54.5% and 28.6%, respectively.
- Use of SFRT dosimetric parameters was highly variable and differed between GRID and LRT. SFRT heterogeneity dosimetric parameters were more commonly used (P = .008) and more commonly thought to influence local control (peak dose, P = .008) in LRT than in GRID therapy.

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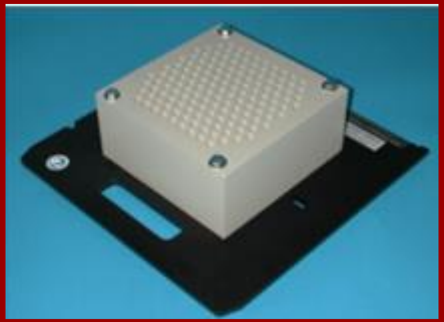
5. Advances in GRID and Lattice Therapy

Over the past seven decades, GRID therapy developed slowly but steadily. Before 2010, GRID therapy was used in a simple way, Lattice therapy had not been developed.

Before 2010,

- We only knew the peak dose and valley dose at the prescription depth.
- DVHs of target and OARs were unknown.
- TPS could not handle dose calculations of multiple apertures or GRID fields
- Most cases were for palliative treatments



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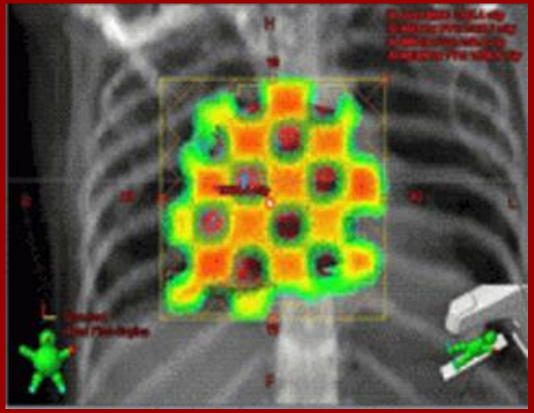
Nowadays, GRID and Lattice therapy has been significantly improved

After 2010, GRID therapy can be planned by TPS, Lattice therapy is increasingly used….



Some TPS can calculate the DVHs of target and OARs in GRID therapy. You can adjust a GRID/Lattice therapy plan based on the dose calculation results

We can use MLC to form a GRID or Lattice therapy.

GRID and Lattice therapy is used for both the palliative and definitive treatments.

Many different beams (photon, proton, electron, microbeam) can be used to deliver GRID/Lattice therapy.

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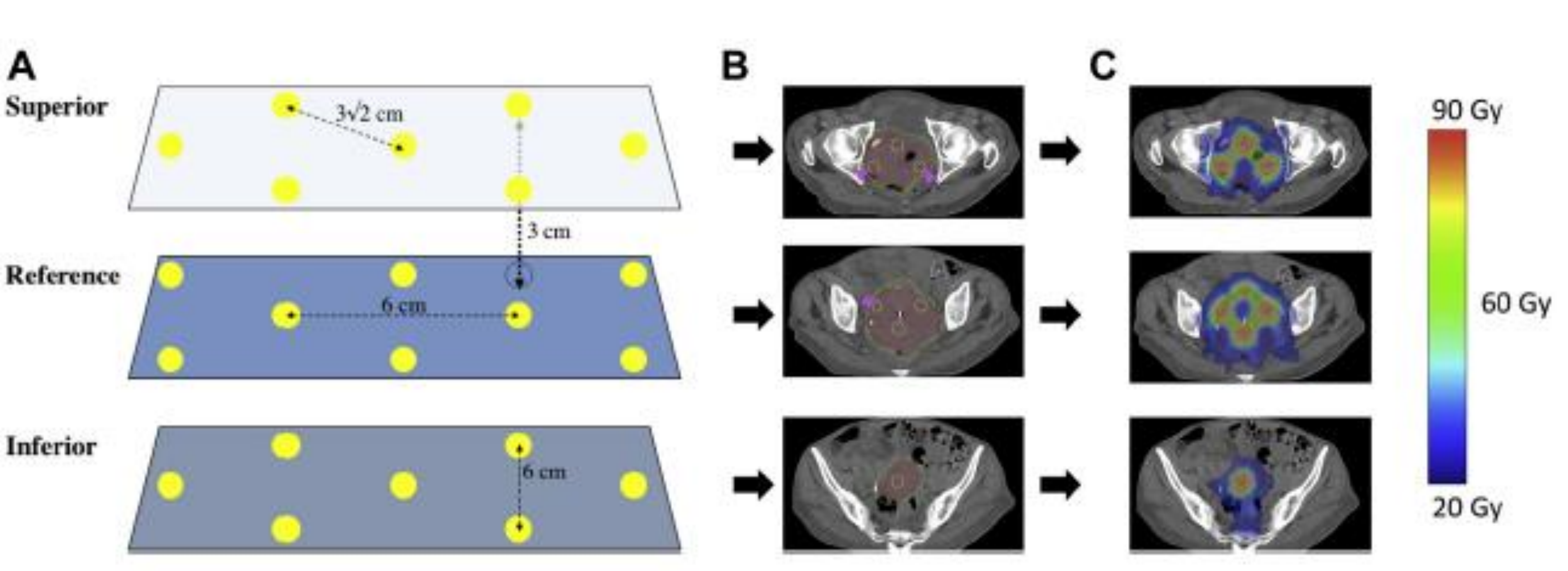
Pilot study 1: Combine LRT with conventional SBRT

LRT was split into multiple fractions, combined with the SBRT, so a very low valley dose was not particularly pursued.

Advantage:After multiple fractions of LRT, there is no need for additional EBRT.
Disadvantage: Spatial dose modulation is limited, SFRT benefits need to be clinically verified.
The pilot study was carried out by Washington University Group.



Sai Duriseti, MD, PhD, James Kavanaugh, MS, et al, Advances in Radiation Oncology: May-June 2021 Lattice ablative

Pilot study 2: mix multiple fractions of LRT into conventional EBRT

Cancer Management and Research

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CASE REPORT

Neoadjuvant Radiation Therapy with Interdigitated High-Dose LRT for Voluminous High-Grade Soft-Tissue Sarcoma

Georges F Hatoum[1,*], H Thomas Temple[2,*], Silvio A Garcia[1], Yi Zheng[1,3], Fouad Kfoury[4], Jill Kinley[5], Xiaodong Wu[1,3]

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Neoadjuvant radiation therapy

multi-fractions of LRT + multi-fractions of cEBRT

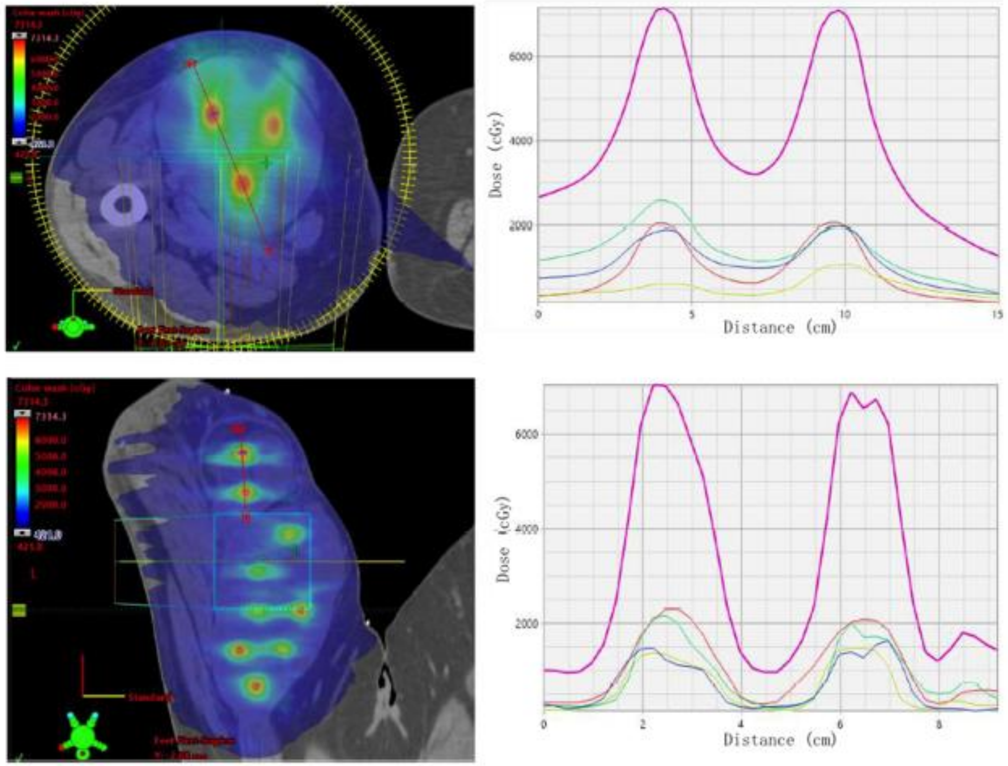


Figure 1 LRT plan. Upper left: dose distribution in an axial plane. Upper right: peak-valley dose profiles defined by the red line across the two dose vertices. Lower left: dose distribution in a coronal plane. Lower right: peak-valley dose profiles defined by the red line across the two dose vertices. The dose profiles contain individual arcs (lower 4 curves) and combined-arcs (upper curve).

RT Mode	Treatment Fractions																								
EBRT (VMAT)		2	3	4	5		7	8	9	10		12	13	14	15		17	18	19	20	21	22	23	24	25
LRT (VMAT)	1					6					11					16									

Figure 2 LRT↓EBRT delivery sequence.

First fraction LRT was given 7 days before starting c-EBRT

4 fractions of LRT were given between 21 fractions of cEBRT

Question #1: when should we start c-EBRT after SFRT?

Question #2: if it is still or more beneficial when multiple fractions of SFRT are given during c-EBRT?

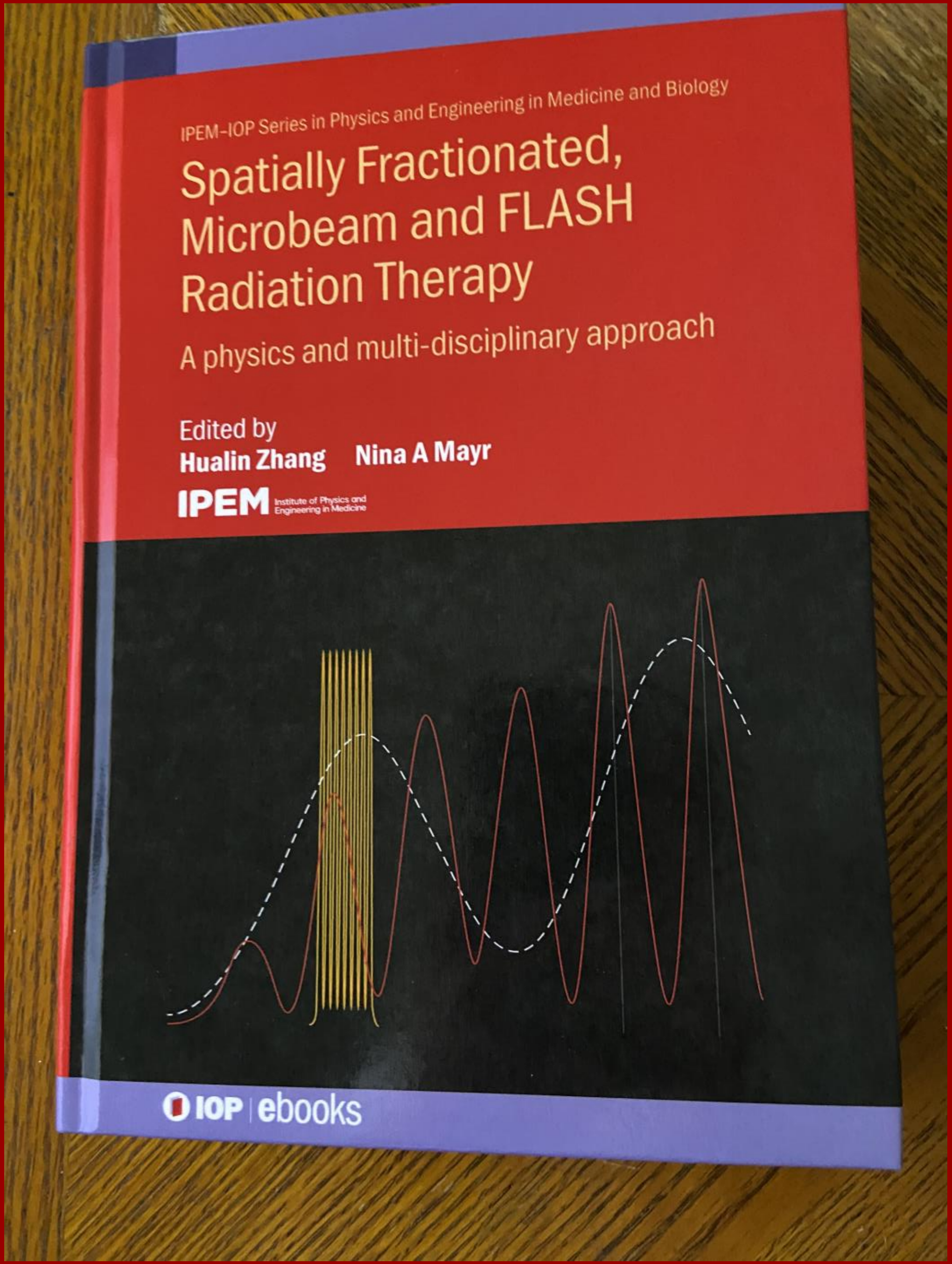
Answers remain unknown. The questions will be answered through more clinical trial data.

Hatoum, et al. Cancer Management and Research, 2023.

First SFRT Textbook was published in June of 2023

A Physics textbook in the multi-disciplinary (clinical and biology) context

ISBN 978-0-7503-4046-5



A Textbook of GRID/Lattice/Flash Radiation Therapy

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Spatially Fractionated, Microbeam and Flash Radiation Therapy: A Physics and Multi-disciplinary Approach.

I: Biology and Clinical Use

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Potential applications of microbeam, minibeam and FLASH

Photon microbeam and proton mini-beam SFRT

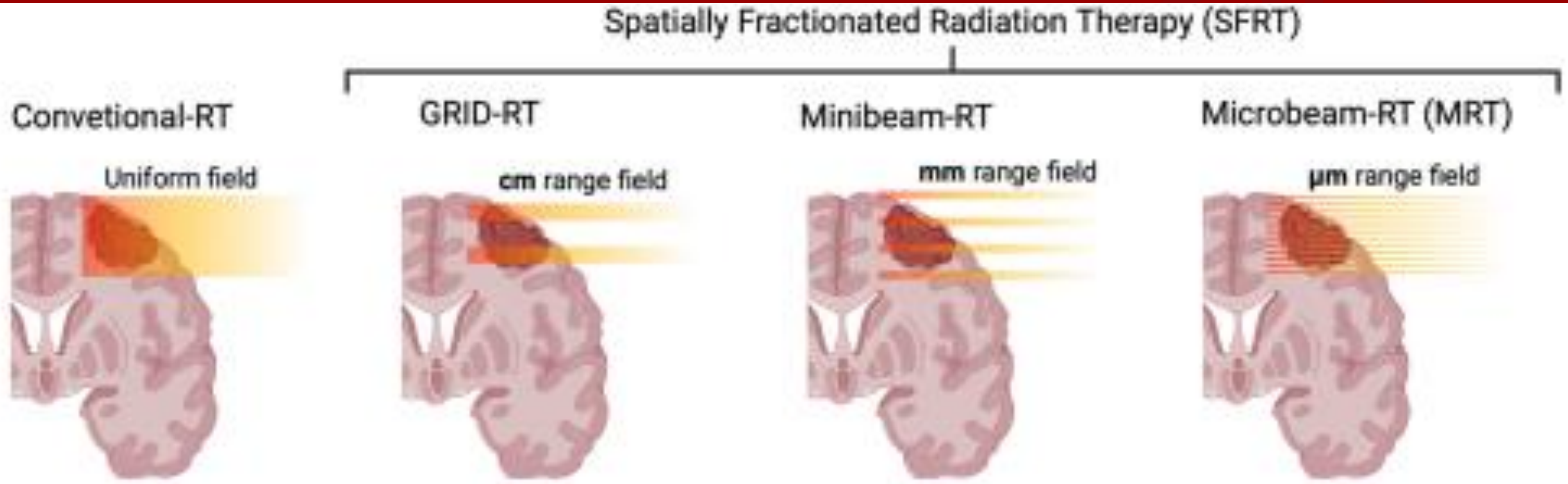

Figure 20.1. The evolution of SFRT from a uniform field to an array of micron-wide microbeams. Created with BioRender.com.

Preclinical mini- and micro-beam based SFRT studies have shown a drastic increase of radiation response

Picture from: Valentin Djonov, Cristian Fernandez-Palomo and Paolo Pellicioli. Chapter 20: Microbeam SFRT with photons. In Book: Zhang H, Mayr N, editors. Spatially Fractionated, Microbeam and Flash Radiation Therapy: A Physics and Multi-disciplinary Approach. IOP Publishing; 2023. ISBN 978-0-7503-4046-5

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The reasons of drastically increased radiation response of micro- and mini-beam based SFRT are likely due to

- There are more high-dose and cold-dose cores than MV GRID
- Dose rate is higher than MV GRID
- PVDR is much higher than MV GRID
- Bystander, abscopal effects are stronger in micro- and min-beam based SFRT because of many more high-dose and cold dose cores

Min- and Microbeam-based SFRT has become a hot research topic of radiation biology

Potez M,, et al. Synchrotron X-Ray boost delivered by microbeam radiation therapy after conventional X-Ray therapy fractionated in time improves F98 glioma control. Int J Radiat Oncol Biol Phys 2020;107(2):360–9.

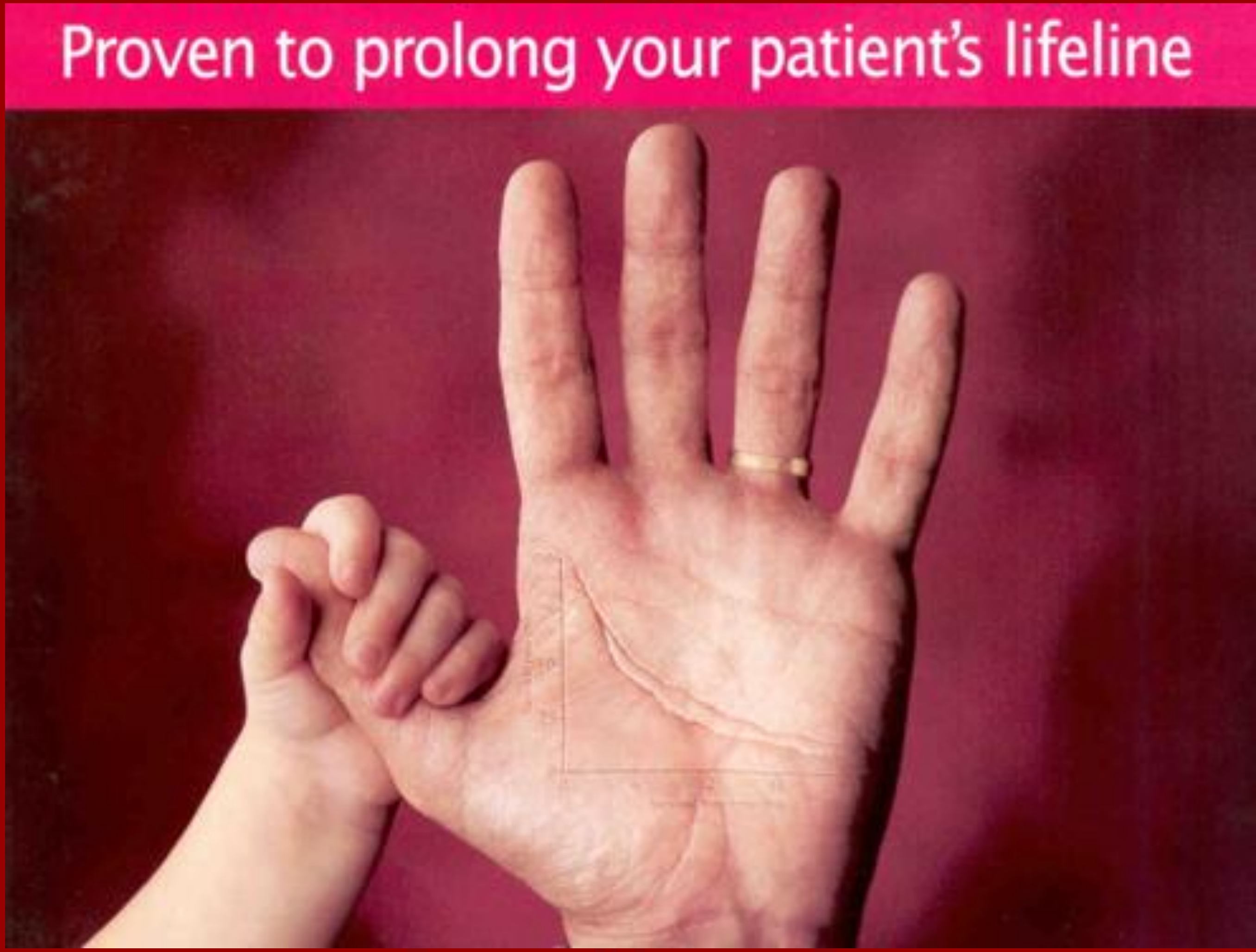
Our mission is

to provide a better way to **cure** or **control** cancers, and eventually to prolong our patients' lives.

Can we make a difference with SFRT?

We optimistically say "Yes"!

Our ongoing and new SFRT clinical trials will bring new hopes to our patients.



Picture from Tarceva INC. 2005

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Thanks for your attention!

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Questions or comments?