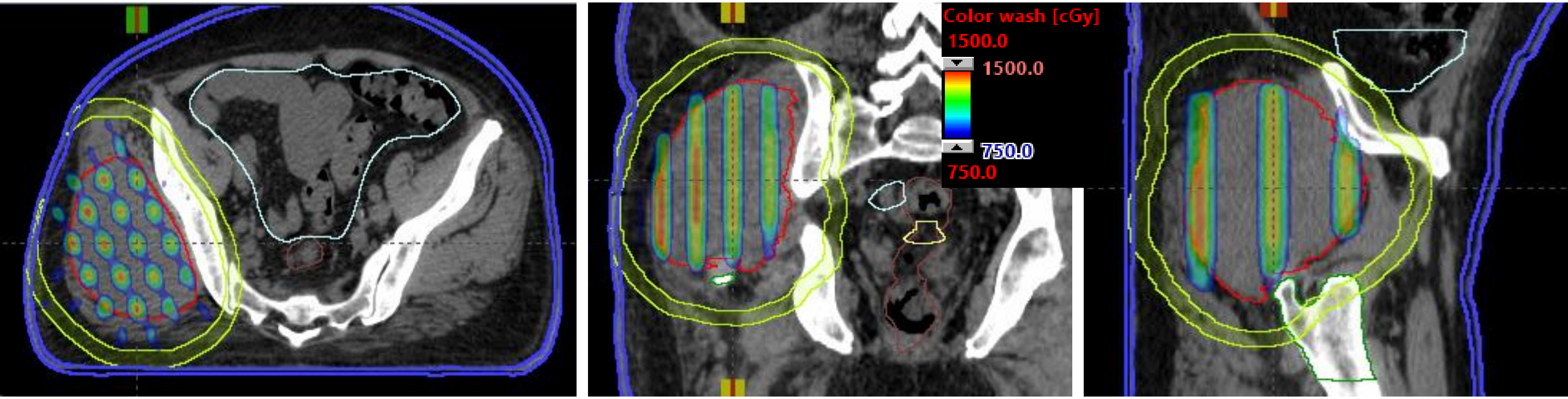
Clinical Implementation of SFRT: Same Day Treatment of Conebeam CT-Guided Novel MLC-Based SFRT for Very Large Bulky Masses



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An NCI-Designated Cancer Center

UK HealthCare
Markey Cancer Center

Motivation & Clinical Rationale

- **Traditional GRID therapy: de-bulking advanced bulky tumors (> 8 cm)**
  - ✓ Treatment of patients with advanced bulky tumors – curative/palliative intent
  - ✓ GRID therapy treatment started in orthovoltage era – a grid collimator
  - ✓ Managed skin & subcutaneous tissue toxicity – area blocked by the grid can regrowth
  - ✓ In MV-era: An open X-ray field is converted to a set of pencil beam type radiation fields using an external physical block – made up of Cerrobend or lead
  - ✓ Deliver a large single dose of 10-20 Gy before conventional RT

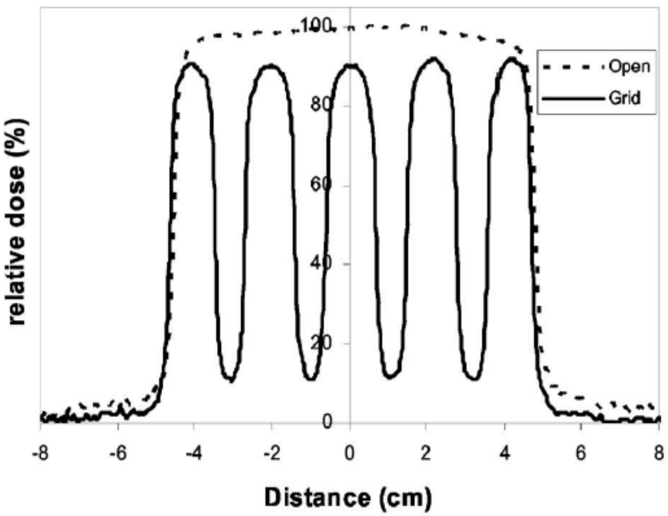
- **University of Kentucky – Pioneer for GRID therapy treatment**
  - ✓ Demonstrated great response of mass reduction (62 to 91%) ≥ 15 Gy followed by RT
  - ✓ 78% response rate of pain palliation and 73% rates of mass effect after GRID with/without conventional RT

Mohiuddin M *et al*. High-dose spatially-fractionated radiation (GRID): a new paradigm in the management of advanced cancers. Int J Radiat Oncol Biol Phys (1999); 45:721-727

How Does SFRT Treatment Work for Bulky Tumors?

- **Although, underlying mechanisms have not been fully explained, the following actions were speculated to contribute to the promising clinical outcomes of SFRT:**
- **Radiation-induced bystander effect (RIBE):**
  - ✓ RIBE – Response associated with the induction of radiation effects in low dose levels via signaling of hit ones (at high dose levels) – SFRT
  - ✓ PVDR could be responsible for RIBE…?
- **Damage of intratumor micro-vasculature structure:**
  - ✓ Immature tumor vessels are irregularly dilated, constricted and branched
  - ✓ Tumor blood vessels are rather fragile and susceptible to high single-dose
  - ✓ Contributing indirect cell-death, in addition to direct cell-kill
- **Increasing anti-tumor immune response:**
  - ✓ Ablative high-dose radiation upregulates various immunostimulatory cytokines, which then interacts with the tumor antigens released from the dying tumor cells thereby provoking an anti-tumor immune response (weeks, months…)

Motivation & Clinical Rationale (cont.)



Dosimetric characteristics of a newly designed grid block for megavoltage photon radiation and its therapeutic advantage using a linear quadratic model

Ali S. Meigooni,[a] Kai Dou, Navid J. Meigooni, Michael Gnaster, Shahid Awan, Sharifeh Dini, and Ellis L. Johnson
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Med. Phys. 33 (9), September 2006 revised 29 June 2006; accepted for publication 6 July 2006;)

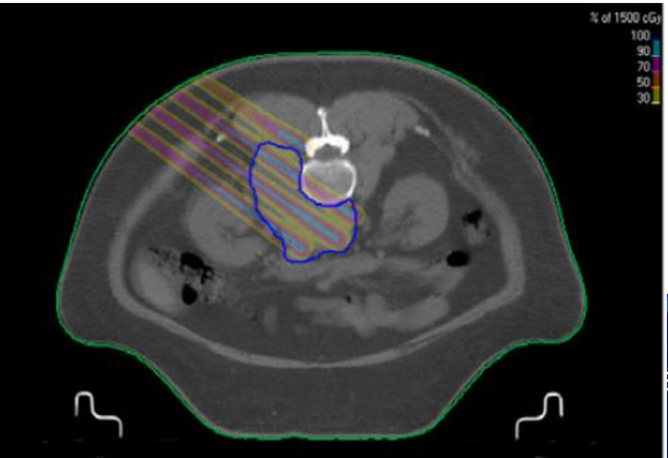
✓ Peak to valley dose ratio (PVDR) ~ 3-5

- **Major limitations of a traditional single-field GRID therapy:**
  - ✓ Deep-seated tumors may received only <u>1/3 or less of prescribed dose (15 Gy)</u>
  - ✓ Skin toxicity –a major concern <u>while escalating tumor dose</u>
  - ✓ <u>Difficult to spare other adjacent critical structures</u>
  - ✓ Physical GRID-block is not radially available to any radiotherapy clinics
  - ✓ GRID-block <u>poses a serious concern for patient safety</u> at slanted angles
  - ✓ Dosimetric detail <u>may not be always available</u> in user's TPS

Motivation & Clinical Rationale (cont.)

- **Modern GRID therapy approaches:**
  - ✓ MLC-based step-and-shoot – single field Tx (U of Maryland)
  - ✓ Optimized VMAT <u>or</u> Tomotherapy plan (U of Arkansas, John Hopkins)
  - ✓ MLC-based inversely-optimized plan (Augusta U, GIT)
  - ✓ CyberKnife GRID plan (U of Miami)
  - ✓ Proton GRID therapy (Stockholm U, Sweden) & MSK Cancer Center (NY)

- **Difficulties of modern GRID therapy approaches:**
  - ✓ Needed a 3rd party software to re-contour GRID target – <u>3D lattice structure</u>
  - ✓ MLC-based or Tomotherapy inversely-optimized plans – <u>days of planning time</u>
  - ✓ Needed <u>extensive physics QA</u> time
  - ✓ Much longer treatment time – <u>potential chance of patient movement</u>
  - ✓ Highly modulated MLC/Tomotherapy plan – <u>higher leakage dose</u>
  - ✓ Inaccessible to expensive Cyberknife or proton therapy units to every patient



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Spatially fractionated (GRID) radiation therapy using proton pencil beam scanning (PBS): Feasibility study and clinical implementation

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(Received 14 September 2017; revised 10 January 2018; accepted for publication 25 January 2018; published 1 March 2018)

Motivation & Clinical Rationale (cont.)

- **To overcome these difficulties, at University of Kentucky, we have developed a fast, safe, effective and accurate 3D-MLC based forward planning and treatment delivery approach for SFRT patients.**
- **It generates a highly non-uniform, sieve-like dose distribution that can be delivered via image-guided SFRT, similar to SBRT!**
- **Major advantages of our approach:**
  - ✓Eliminates all the major difficulties of single-field GRID-block
  - ✓Avoids other difficulties/complexities of modern GRID therapy approaches
  - ✓Potential for escalating tumor dose while sparing adjacent organs, including skin
  - ✓Offer same day GRID therapy to our patients – fast, safe, accurate & effective Tx
  - ✓Provide all the dosimetry information's to treating physicians for plan review…

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RADIATION ONCOLOGY PHYSICS | Open Access

A novel, yet simple MLC-based 3D-crossfire technique for spatially fractionated GRID therapy treatment of deep-seated bulky tumors

Damodar Pokhrel, Matthew Halfman, Lana Sanford, Quan Chen, Mahesh Kudrimoti

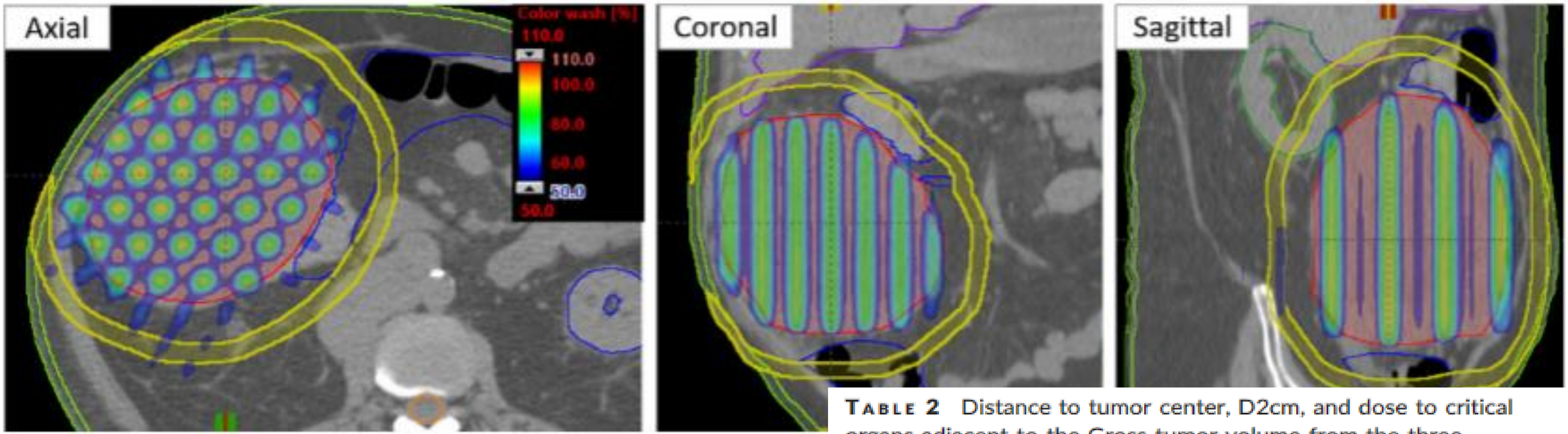
First published: 08 February 2020 | https://doi.org/10.1002/acm2.12826 | Citations: 6

Validation Study of MLC based 3D-Crossfire Approach

Table 1 Main tumor characteristics of the patients included in this study.

Pt. #	Treatment site	GTV vol. (cc)	GTV diameter (cm)	Primary disease site
1	Left lung	554	10	Connective and soft tissue of thorax
2	Left neck	129	6	Squamous cell carcinoma of neck
3	Right axilla	503	10	Malignant neoplasm of axilla
4	Left kidney	856	12	Malignant neoplasm of kidney
5	Right neck	512	10	Malignant neoplasm of neck
6	Right kidney	1486	14	Malignant neoplasm of kidney
7	Thyroid	224	8	Malignant neoplasm of thyroid gland
8	Chest	442	9	Squamous cell carcinoma of chest
9	Chest	551	10	Malignant neoplasm of neck/chest
10	Abdomen	467	10	Intra-abdominal lymph nodes
11	Liver	366	9	Intra-abdominal lymph nodes
12	Right adrenal	1678	15	Neoplasm of cortex of adrenal gland
13	Right thigh	530	10	Neoplasm of urinary organ

3D MLC-based SFRT: Dose Distribution & Sparing Critical Organs



$$PVDR = GTVD10\% \div GTVD90\%$$

- **Mimicking brachytherapy like heterogenous dose-distribution**
- **Enhanced deep-seated bulky tumor dose tunneling**
- **Achieved PVDR ~ 3.0, on average**
- **Reduced skin toxicity**
- **Spared adjacent OAR by tweaking MLC**
- **Allow for image-guided SFRT**

TABLE 2 Distance to tumor center, D2cm, and dose to critical organs adjacent to the Gross tumor volume from the three-dimensional-multileaf collimator (3D-MLC) plan for the patients included in this study.

Pt. #	Treatment site	Distance from skin to tumor center (cm)	D2cm (%)	Maximal dose to immediately adjacent critical structures (Gy)
1	Left lung	9.9	70.9	6.7 (spinal cord)
2	Left neck	4.3	61.1	5.9 (spinal cord)
3	Right axilla	7.5	64.6	7.3 (ribs)
4	Left kidney	10.4	72.1	6.4 (bowel)
5	Right neck	6.2	63.6	8.0 (spinal cord)
6	Right kidney	9.9	75.1	5.6 (spinal cord)
7	Thyroid	5.0	55.2	6.8 (spinal cord)
8	Chest	7.0	71.1	5.6 (spinal cord)
9	Chest	6.9	62.6	5.9 (spinal cord)
10	Abdomen	8.0	73.6	5.7 (stomach)
11	Liver	5.9	70.1	5.6 (spinal cord)
12	Right adrenal	8.7	71.3	7.9 (large bowel)
13	Right thigh	6.6	72.1	6.7 (bowel)

3D MLC-based SFRT: Potential for Escalating Dose to Bulky Masses

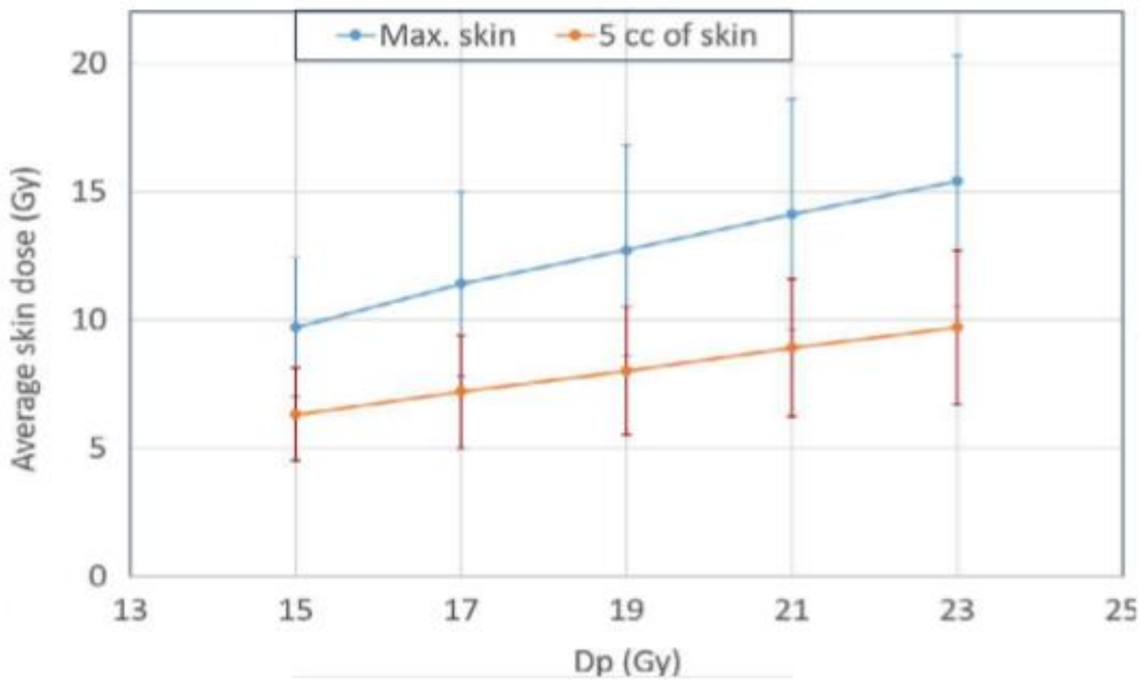
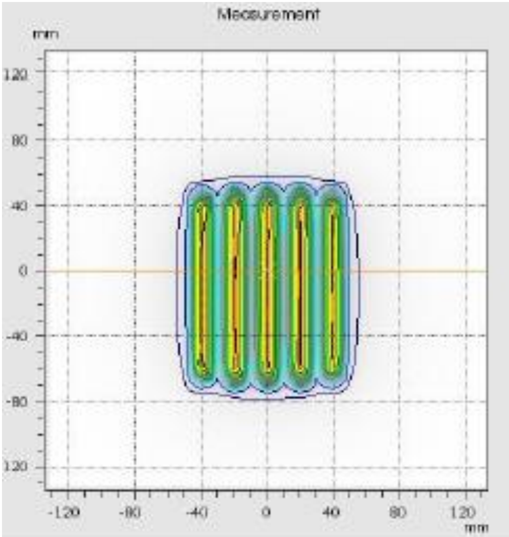
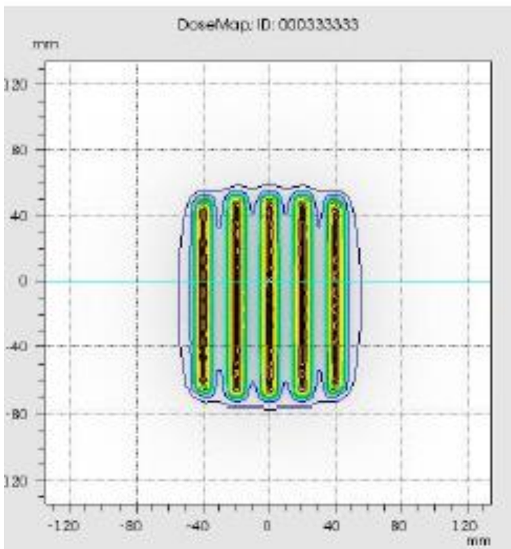


Fig. 4. Calculation of predicted average skin doses (maximal and dose to 5 cc of skin) as a function of escalated prescription doses (Dp) for all 13 GRID therapy patients. A simple three-dimensional-multileaf collimator crossfire GRID planning technique allowed for escalation of tumor doses up to 23 Gy while maintaining the skin toxicity.

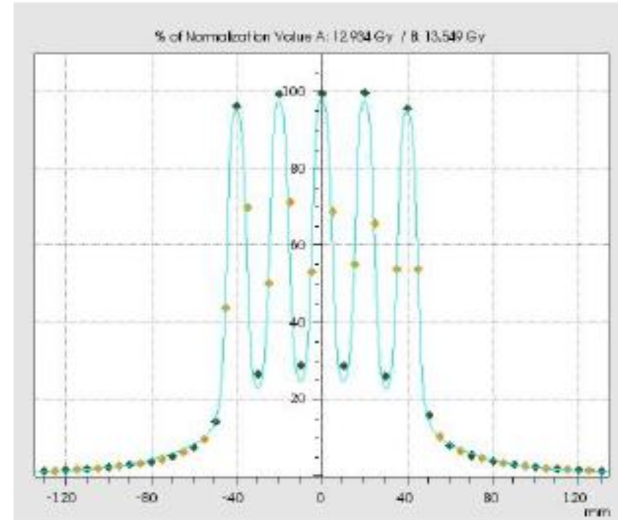
- **<u>Plan Evaluation</u>: RTOG-0915, single-dose compliance criteria were used for OAR**

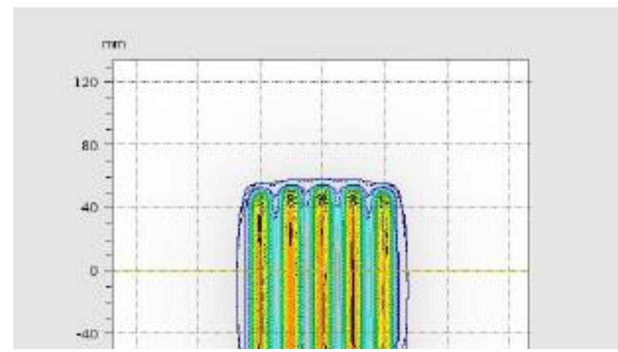
3D MLC-based SFRT: Phantom Measurement & Validation





- **PVDR**: ~4.0 (single field)
- **Dots**: measured
- **Continue line**: calculated





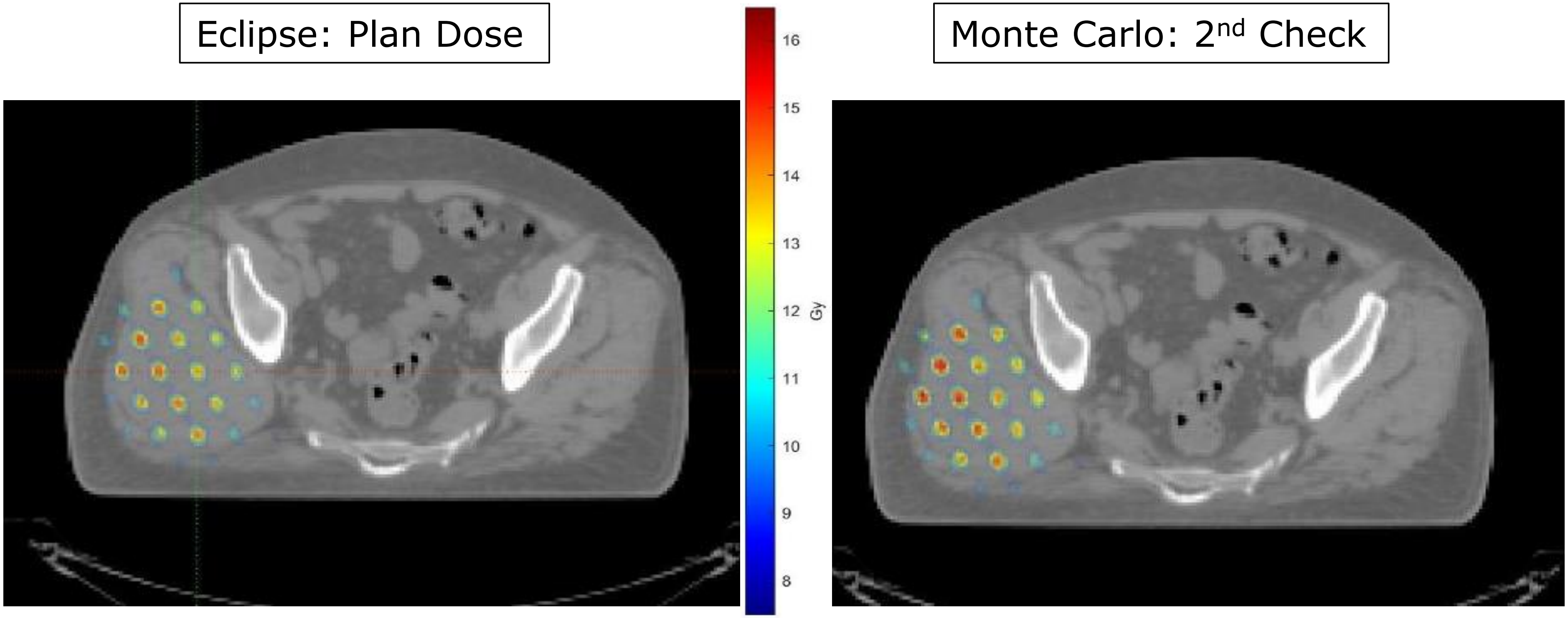
Gamma 2D - Parameters

3.0 mm Distance- To- Agreement
3.0 % Dose difference with ref. to max. dose of calculated volume
Suppress dose below 5.0 % of max. dose of calculated volume
Option "Use 2nd and 3rd pass" selected

Statistics

Number of Dose Points	1,405
Evaluated Dose Points	400 (28.5 %)
Passed	400 (100.0 %)
Failed	0 (0.0 %)
Result	100.0 % (Green)

3D MLC-based SFRT: Independent Dose Verification



MU required by Monte Carlo to match planned dose would be **97.5% of planned MU**

Monte Carlo Code, Courtesy of Dr. Quan Chen (University of Kentucky)

3D MLC-based SFRT: Independent Field-by-Field MU Verification

UK Department of Radiation Medicine - Plan Review Worksheet

MU Verification Section

PlanID: A2A5 MLC-GRID

	Field 1	Field 2	Field 3	Field 4
Field ID	A2	A3	A4	A5
Machine ID	21PLAT6X	21PLAT6X	21PLAT6X	21PLAT6X
Calc. Type	Heterogeneous	Heterogeneous	Heterogeneous	Heterogeneous
SSD	93.2	96.1	96.3	95.0
Depth	6.8	3.9	3.7	5.0
Eff. Depth	6.8	4.0	3.7	5.0
X Collimator	6.7	6.5	6.5	6.2
Y Collimator	4.5	4.5	6.5	5.0
BlkEqSq @ Depth	2.5	2.5	3.0	2.5
Sc	0.974	0.973	0.983	0.975
Sp	0.923	0.923	0.923	0.923
TPR	0.926	1.042	1.055	1.000
Inverse Square	1.000	1.000	1.000	1.000
Tray Factor	1.000	1.000	1.000	1.000
Wedge ID	None	None	None	None
Wedge Factor	1.000	1.000	1.000	1.000
OAR	0.893	0.909	0.909	0.909
Other Trans. Factor	1.000	1.000	1.000	1.000
Dose	535.9	297.7	148.9	506.1
Calc. MUs	757.9	367.6	180.0	649.8
TPS MUs	731.0	367.0	178.0	644.0
Agreement	3.7	0.2	1.1	0.9
Type	% Diff.	% Diff.	% Diff.	% Diff.

PHYSICIST: Dennis Cheek DATE: 2/20/2020

3D-Conf Plan Review Worksheet, Courtesy of Dr. Lee Johnson (University of Kentucky)

Conebeam CT-guided MLC-based SFRT for Bulky Masses!

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TECHNICAL NOTE | Open Access

Conebeam CT-guided 3D MLC-based spatially fractionated radiation therapy for bulky masses

Damodar Pokhrel, Mark E Bernard, Richard Mallory, William St Clair, Mahesh Kudrimoti

First published: 21 April 2022 | https://doi.org/10.1002/acm2.13608

- Our previous proof-of-concept needed generating GTV GRID-lattice structure using a 3rd party algorithm, export/import CT data…
- Standard RT clinics including community centers may not have a 3rd party algorithm
- To avoid that extra step, and accelerate treatment planning process.
- We have developed an in-house MLC fitting algorithm with Millenium-120 leaves that were fitted to GTV generating 1 cm diameter holes at 2 cm center-to-center distance at isocenter.
- This configuration generated brachytherapy like dose-tunneling distributions without post-processing GTV-contour!
- In this algorithm, fitted MLCs parked outside jaws, minimized MLC tip leakage…
- Planning time: < 1 hour
- Promoting same day SFRT– Effectively managing bulky tumors in a timely manner!

In-house MLC-Fitting Algorithm for Rapidly Generating SFRT Plan!

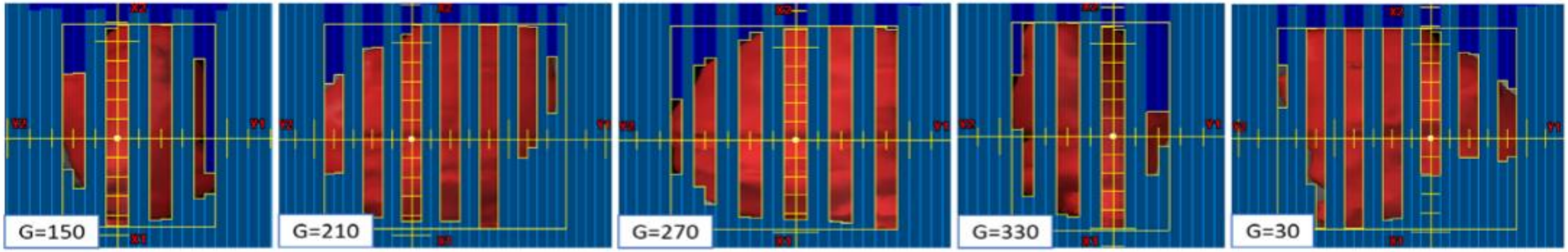

FIGURE 1 Illustration of the in-house 3D-MLC-fitting algorithm to the physician-delineated GRID GTV target (red) without post-processing the GTV contour. Five of six gantry angles were used to treat large and bulky (501 cm^3, 10-cm diameter) right pelvis mass for 15 Gy in one fraction. Some peripheral MLCs positions were adjusted to further minimize the dose to immediately adjacent critical organ, including small bowel. GTV, gross tumor volume

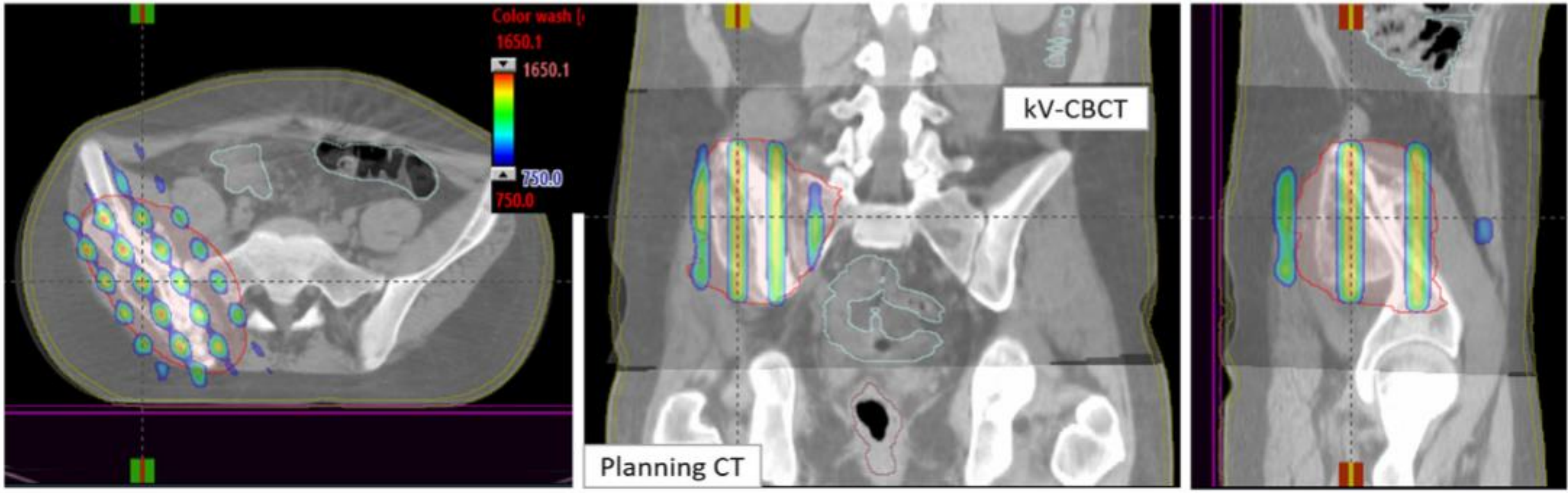

FIGURE 2 Demonstration of axial, coronal, and sagittal views of kV-CBCT images (see the inset) coregistered with planning CT images (see the back of coronal and sagittal views) used for CBCT-guided SFRT treatment on TrueBeam Linac. The overlaid planned isodose colorwash (50%–110%) with anatomical landmarks is shown for a patient treated with MLC-based 3D-conformal SFRT (15 Gy in one fraction) for a deep-seated bulky mass of 10.0-cm-diameter tumor in a right pelvis—malignant neoplasma of connective and soft tissue of trunk. CBCT images were acquired in the treatment position followed by performing automatic rigid-registration and manually fine-tuning the registration for tumor soft-tissue alignment before applying the couch correction. 3D, three-dimensional; SFRT, spatially fractionated radiation therapy

Example Head and Neck SFRT Plan via MLC-Fitting Algorithm!

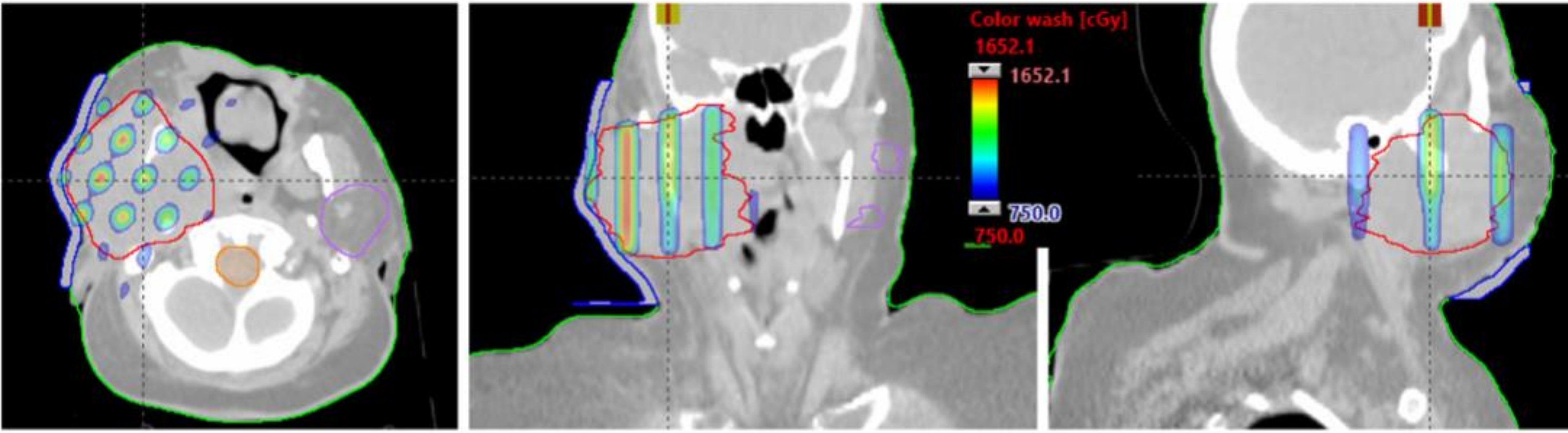

FIGURE 3 Axial, coronal, and sagittal views of an isodose colorwash of the MLC-based 3D-conformal SFRT plan in the treatment of Markel cell carcinoma of the large right neck mass (265 cm^3, equivalent to a 8.4-cm diameter) was treated for a single dose of 15 Gy, with a 110% hotspot inside the GTV. Immediately adjacent critical organs, such as spinal cord and brainstem, were spared. Moreover, to avoid contralateral parotid gland, 90° gantry angle was not used. 3D, three-dimensional; GTV, gross tumor volume; SFRT, spatially fractionated radiation therapy

Typical Example of Neglected Rt Breast Mass SFRT Plan via MLC-Fitting Algorithm!

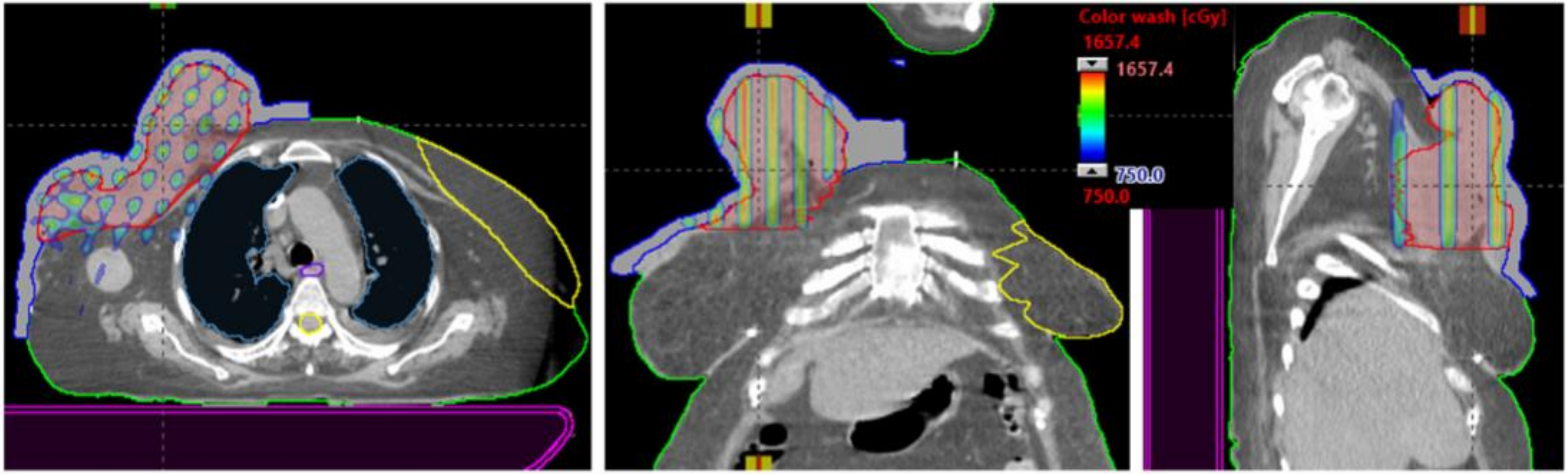

FIGURE 4 This is an example of the MLC-based 3D-conformal SFRT for the treatment of neglected female right breast patient of very large right breast mass. Due to the very large patient separation, 90° and 150° gantry angles were not used. Maximal dose to critical organs, such as spinal cord (1.9 Gy), left breast (1.6 Gy), heart (3.9 Gy), and mean lung dose (1.3) Gy, was achieved. 3D, three-dimensional; SFRT, spatially fractionated radiation therapy

Another Example of Large & Bulky Lt Chest Mass Treated with SFRT

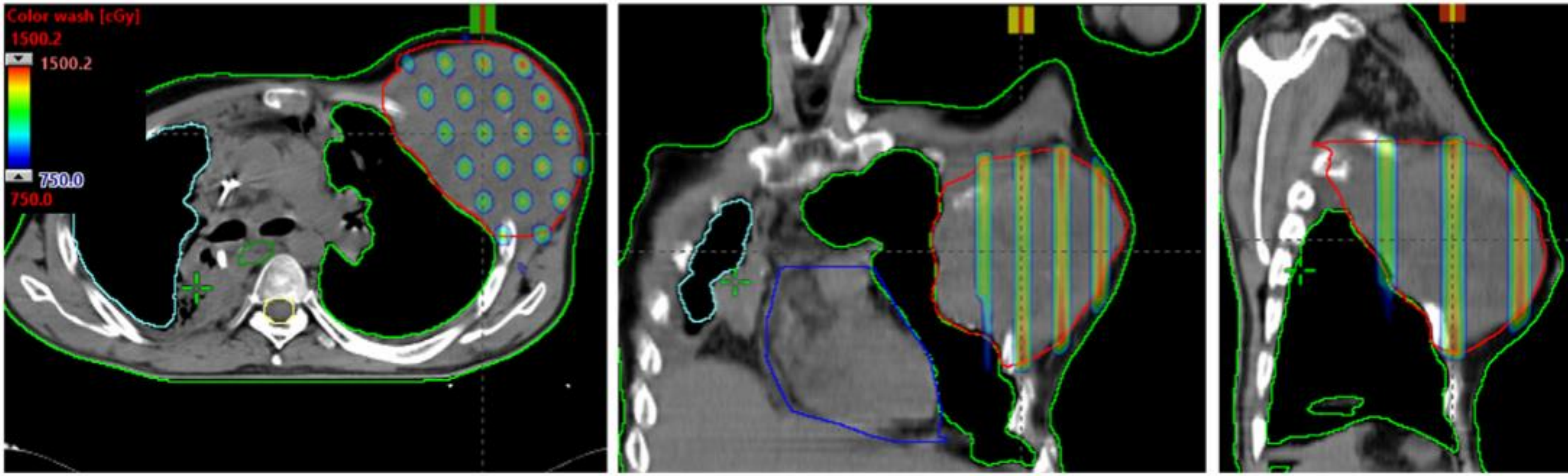

FIGURE 5 Demonstration of axial, coronal, and sagittal views of isodose colorwash (50%–110%) for very large and bulky adenocarcinoma of left lung mass that was delivered via novel 3D MLC-based SFRT. Due to the large patient separation, the 270° gantry angle was not used. Maximal dose to critical organs such as spinal cord (1.6 Gy), heart (4.8 Gy) and mean lung dose (1.7 Gy) was achieved. 3D, three-dimensional; SFRT, spatially fractionated radiation therapy

Clinical Example of Enlarged Pelvis Lymph Node Treated with SFRT

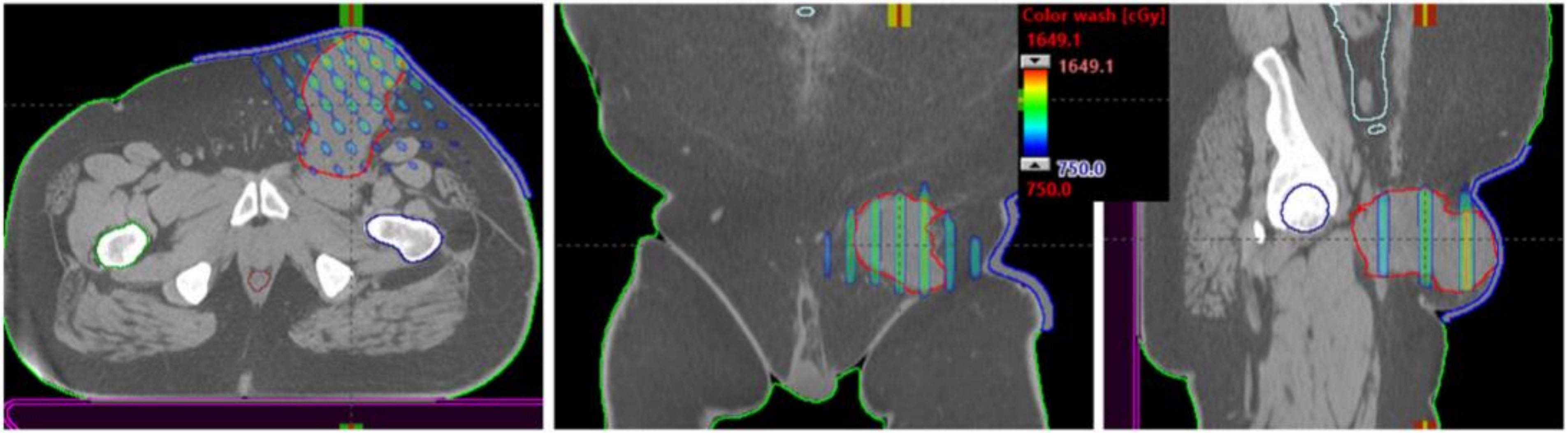

FIGURE 6 This is an example case of left enlarged pelvis lymph node of metastatic penis cancer patient treated with 3D MLC-based SFRT. Very large pelvis lymph node that was perturbing to the skin was treated for a large single-dose of 15 Gy with a 110% hotspot inside the GTV via 3D MLC-based SFRT. For four of six treatment fields with 10-MV beam, 5 mm bolus, a maximal dose rate of 600 MU/min was used. Gantry angles, 270° and 210°, were not used; Lower maximal dose to critical organs, left femoral head (4.3 Gy) and small bowel (1.3 Gy), was achieved. 3D, three-dimensional; GTV, gross tumor volume; SFRT, spatially fractionated radiation therapy

Clinical Example of Bulky Left Leg Sarcoma Treated with SFRT

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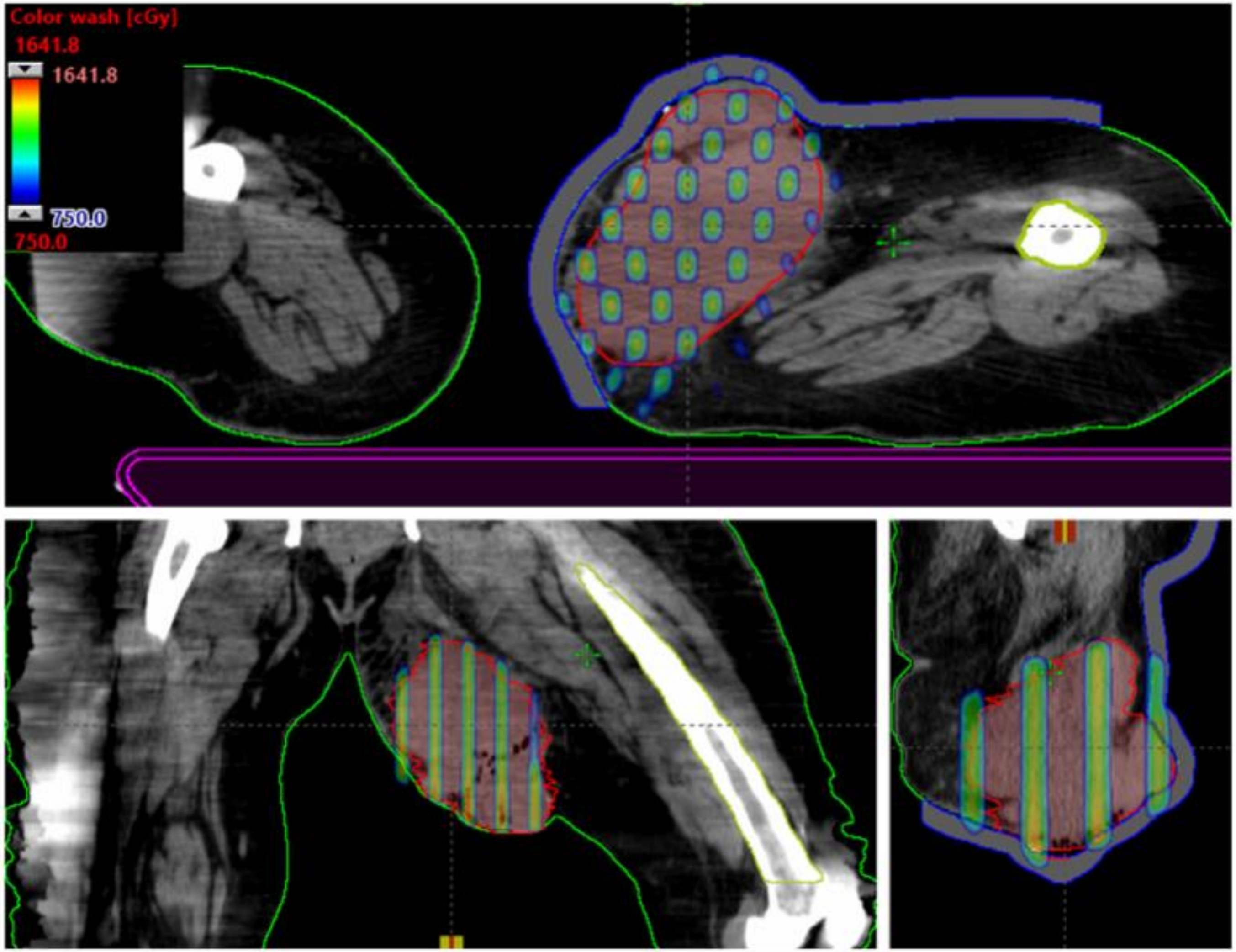
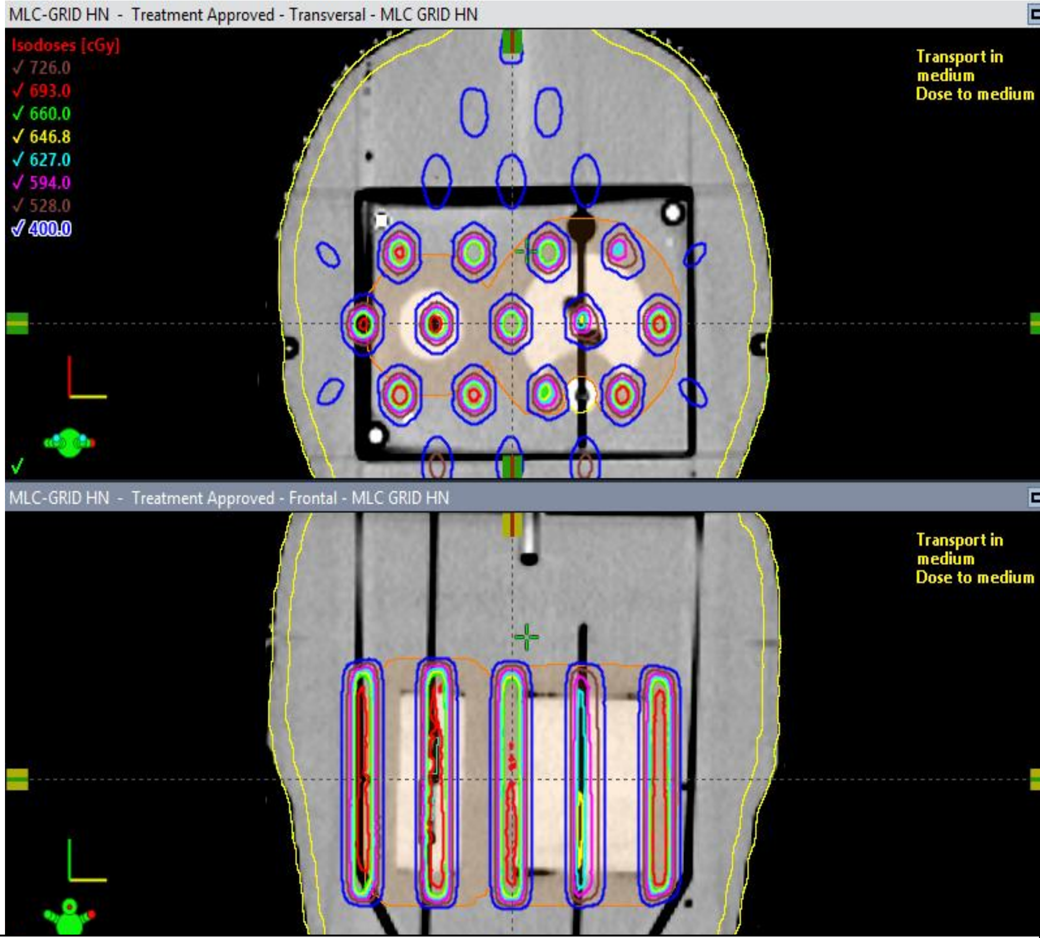


FIGURE 7 Demonstration of the axial, coronal, and sagittal views of isodose colorwash (50%–110%) for a patient treated for a bulky left upper leg soft tissue sarcoma using novel 3D MLC-based SFRT (15 Gy in one fraction) plan. To minimize the dose of left femur and right leg, 270° and 90° beams were not used. SFRT, spatially fractionated radiation therapy

Independent Dose Verification via IROC MD Anderson Head & Neck Phantom Irradiation!

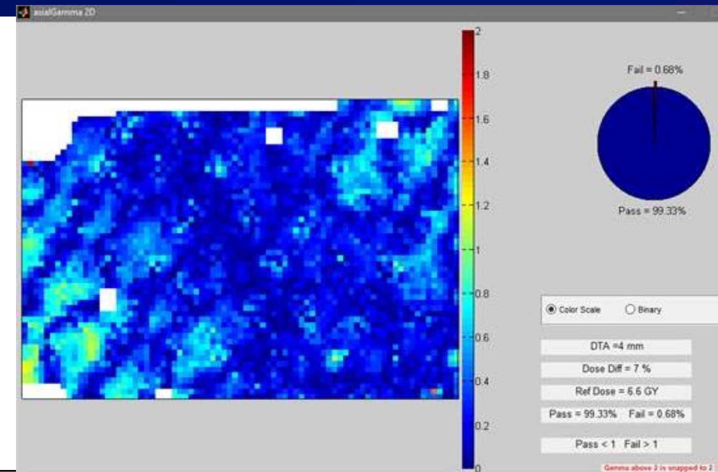
- **MD Anderson's head and neck credentialing phantom with dosimetry inserts containing 2 targets was imaged, planned and treated via 3D-MLC SFRT plan!**
- **Both PTV54 and PTV66 targets were contoured**
- **To generate a large and bulky mass (> 8.0 cm) both targets were added together and added 1 cm expansion around it – for SFRT planning**
- **Critical organs and TLDs were delineated per MD Anderson's standard**
- **Prescription: 6.6 Gy in 1 fraction.**

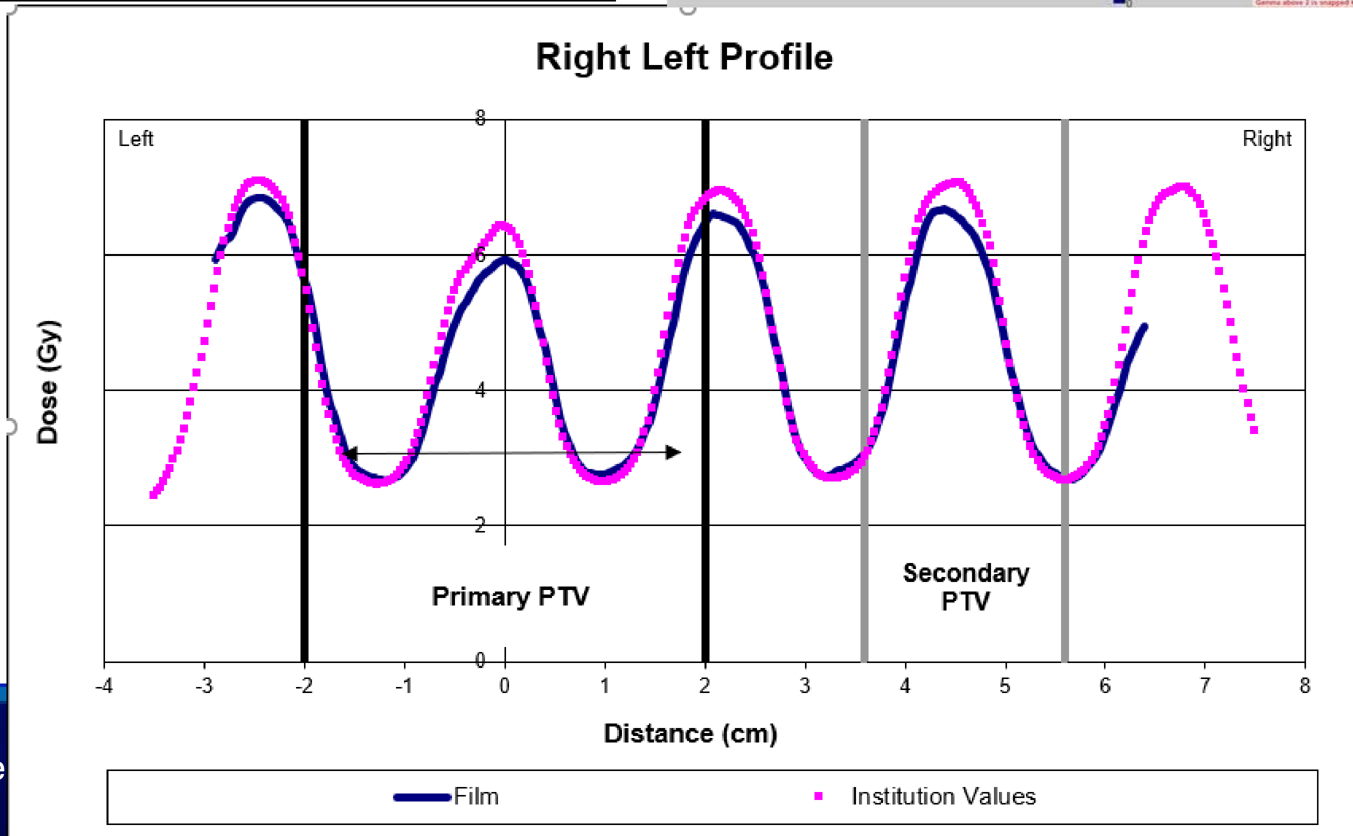


Head & Neck phantom, Courtesy of **Andrea & Nadia** from IROC MD Anderson (University of Texas, Houston TX)

Independent Dose Verification via IROC MD Anderson Head & Neck Phantom Irradiation!

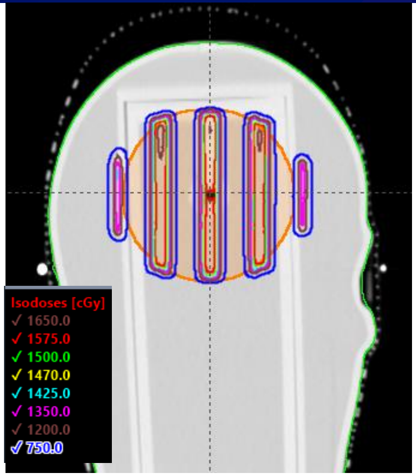
Location	Institution Reported Mean Dose	TLD Dose (cGy)	Measured/Institution
Primary PTV sup. ant.	446	460	1.03
Primary PTV inf. ant.	443	444	1.00
Primary PTV sup. post.	494	465	0.94
Primary PTV inf. post.	530	488	0.92
Secondary PTV sup.	669	677	1.01
Secondary PTV inf.	657	682	1.04
Organ at risk sup.	268	271	1.01
Organ at risk inf.	275	269	0.98

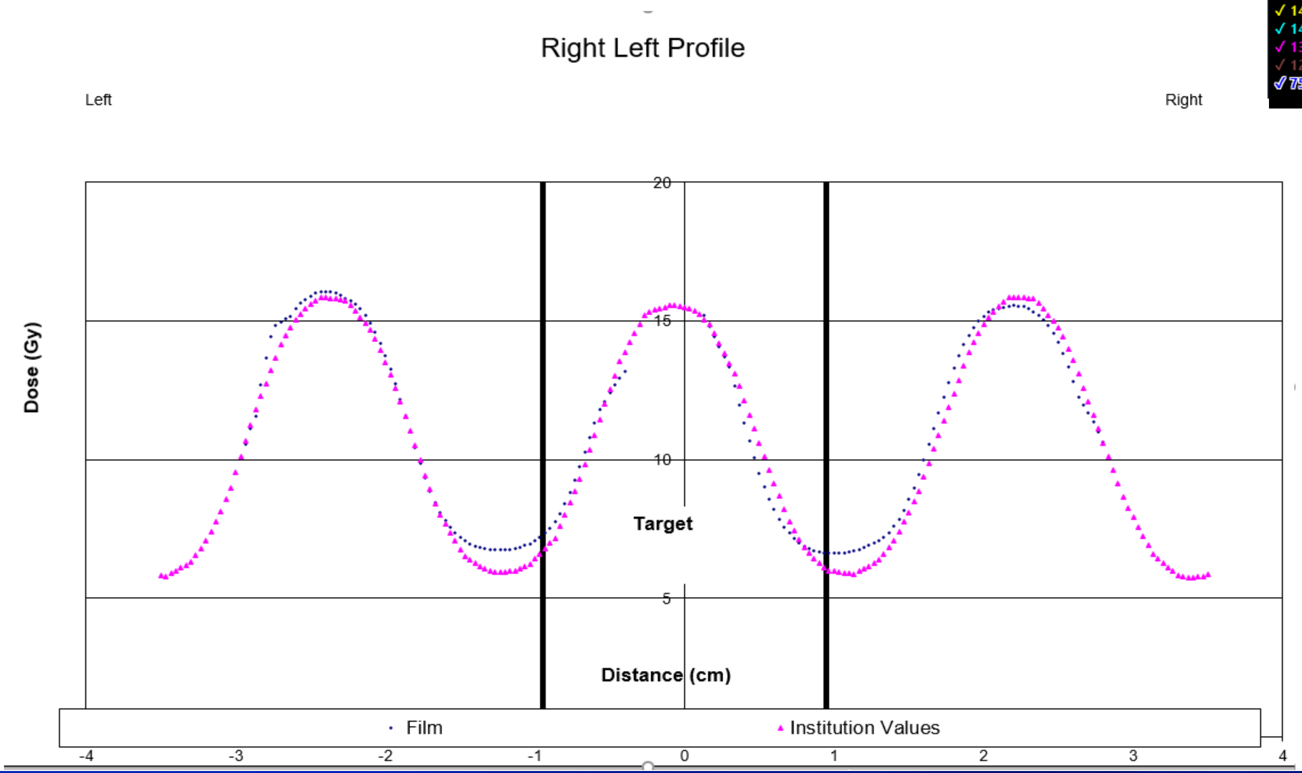




Independent Dose Verification via IROC MD Anderson SRS head Phantom Irradiation!

- **MD Anderson's SRS head credentialing phantom with dosimetry inserts was imaged, planned and treated via 3D-MLC SFRT plan!**
- **Prescription was 15 Gy in 1 fraction.**
- **1.9 cm PTV target, critical organs and TLDs were delineated.**
- **To generate a large and bulky mass (> 8.0 cm) added 3 cm expansion around it – for SFRT planning**





SRS head phantom, Courtesy of **Andrea & Nadia** from IROC MD Anderson (University of Texas, Houston TX)

Summary/Conclusions

- **We clinically implemented fast, safe, effective and accurate 3D-MLC based forward planning and treatment delivery approach for SFRT patients –debulking deep-seated unresectable large masses**
- **This novel, yet clinically useful treatment delivery method was extensively validated and used for SFRT patient's treatment at the University of Kentucky**
  - ✓ So far, we have already treated more than 60 patients of different treatment sites, except brain!
  - ✓ Other cancer centers can easily adopt this simple method for their patient care.
- **This simple and clinically useful SFRT method:**
  1. Eliminates all the major difficulties of single-filed traditional GRID-block
  2. Avoid major difficulties of modern inversely-optimized GRID therapy planning
  3. Allow for fast and effective treatment delivery–patient convenient
  4. Allow image-guided SFRT therapy–patient images data in ARIA for matching
  5. Allow potential for escalating tumor-dose while sparing adjacent OAR and skin
  6. Offer same day SFRT therapy to our patients–fast, safe, accurate & effective Tx
  7. Provides all dosimetry information's to treating physicians for plan review…

3D MLC-based SFRT: Future Research Directions

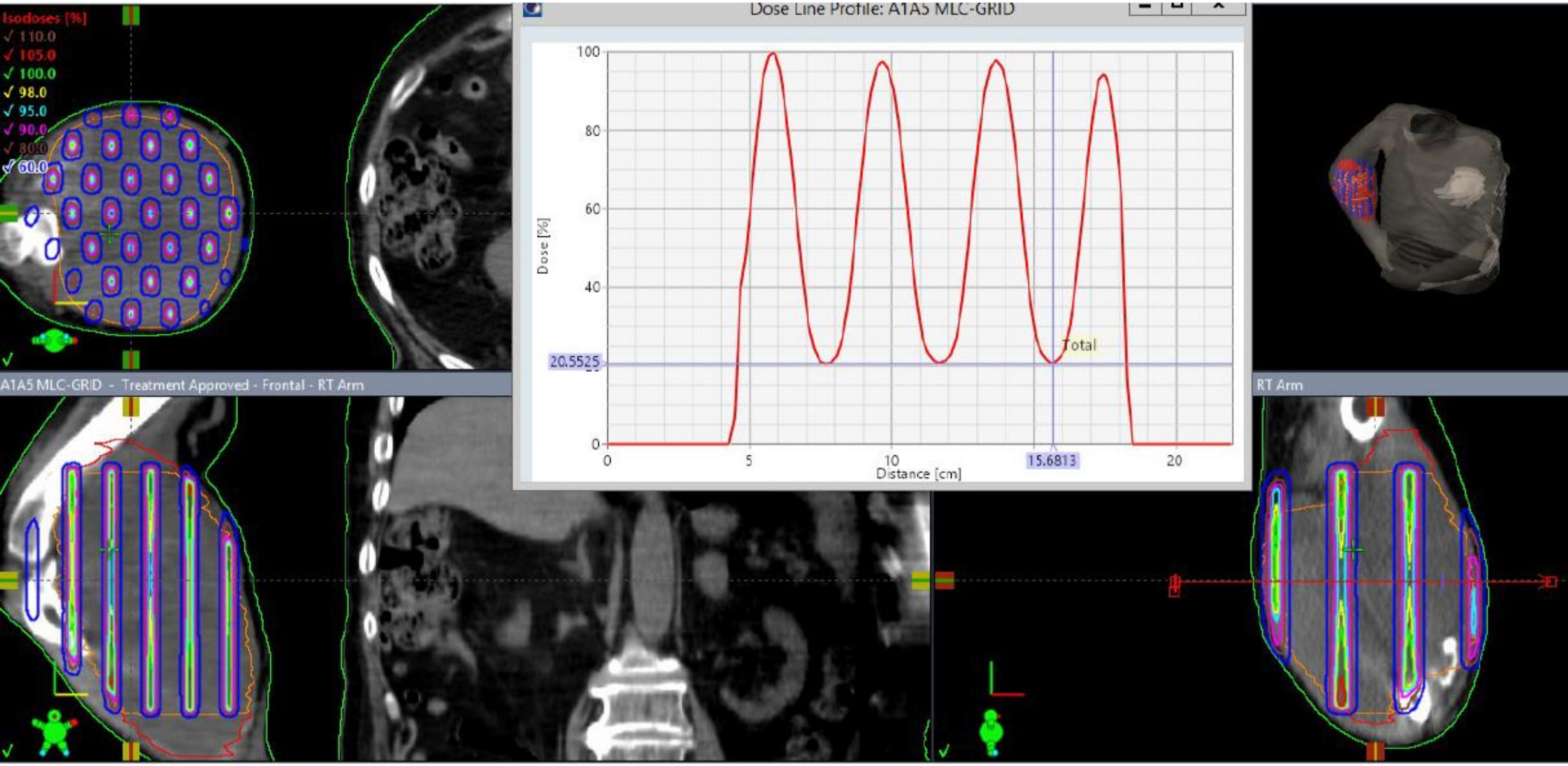
1. **Clinical follow up results & dose-escalation trial is ongoing!**
2. **Fully <u>automate MLC-based SFRT module</u> in Eclipse TPS**
   - ✓ *Research Grant Proposal to support a PhD student in medical physics*
3. **For thoracic/abdominal tumors motion management is important!**
   - ✓ *Develop a departmental protocol for patient CT simulation/immobilize patients*
   - ✓ *Evaluate clinical potential of DIBH treatment via rapid delivery of SFRT*
4. **Radiobiological modeling of different size GRID-holes**
   - ✓ *To improve the PVDR of each hole*
   - ✓ *To quantify improvement of <u>therapeutic gain via different hole-sizes & spacing</u>*
   - ✓ *Potential for escalating tumor-dose & further sparing adjacent critical structures*
5. **Further improve/optimize 3D-MLC SFRT planning approach for highly concave irregular large targets**
   - ✓ *Utilize <u>mix-beams & differential hole-sizes</u> to further optimize the dose coverage to large concave targets*
   - ✓ *Search for more optimal cross-fire angles to improve PVDR, if applicable.*

Acknowledgements!

- I would like to express my sincere thanks to all faculty and staff at U of Kentucky, Radiation Medicine for their support & contributions.
- IRB approved protocol #43272 (University of Kentucky, Dr. Pokhrel (PI))
- Andrea Molineu and Nadia Hernandez from IROC MD Anderson, TX
- Special thanks to Dr. Wei Luo, PhD, FAAPM (U of Kentucky)

3D MLC-based SFRT: Rt Arm Sarcoma (1203 cc, d = 13.2 cm)

Treated for 15 Gy with 6MV beam on TrueBeam Linac



Thank you for your time!