Normal tissue sparing via proton FLASH, SFRT and beyond

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THE UNIVERSITY OF KANSAS
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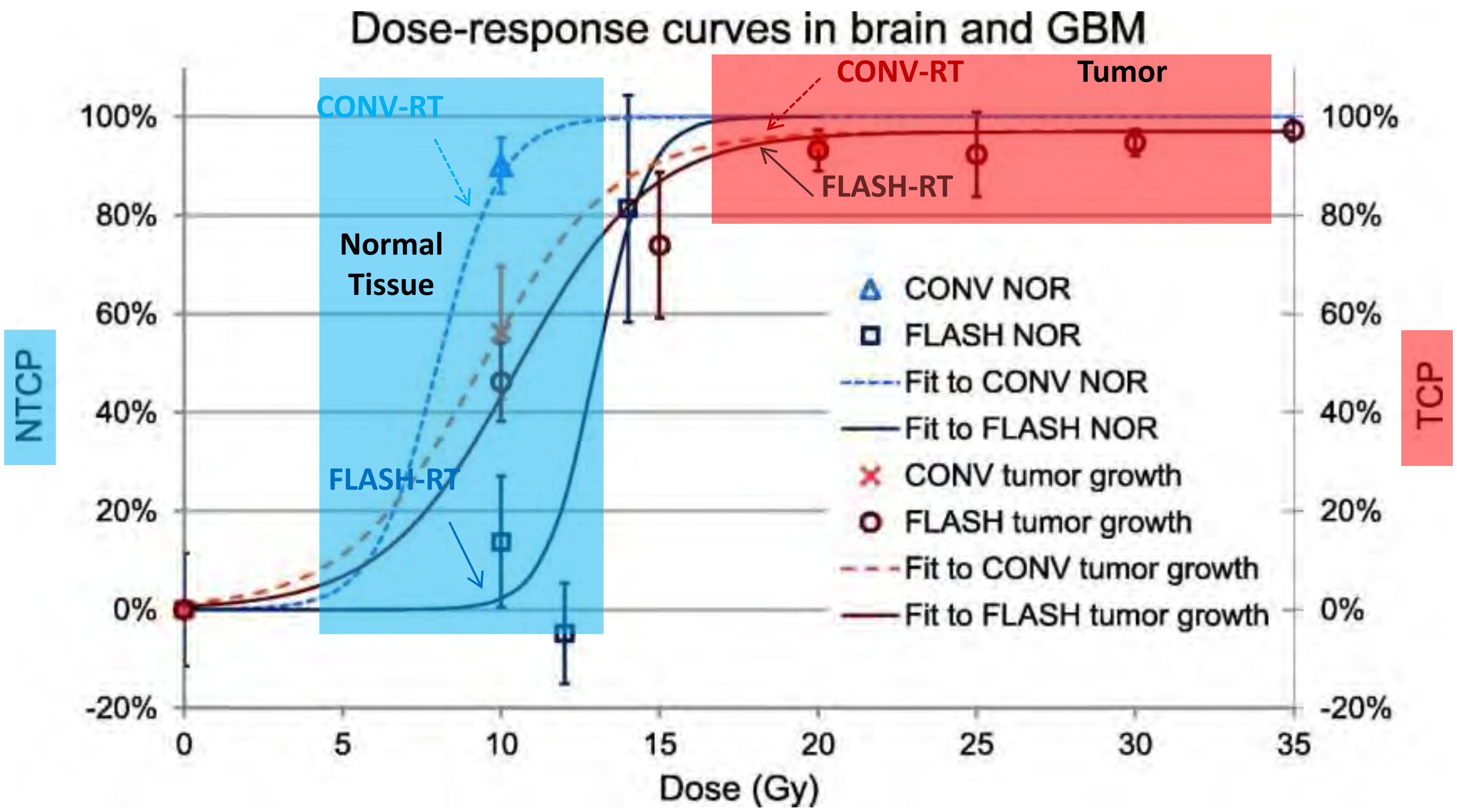
Disclosure

- Research collaborations with IBA and RaySearch
- FLASH research funding from IBA

FLASH enhances normal-tissue sparing



[Bourhis Radiother Oncol 2019]

Proton FLASH clinical trials

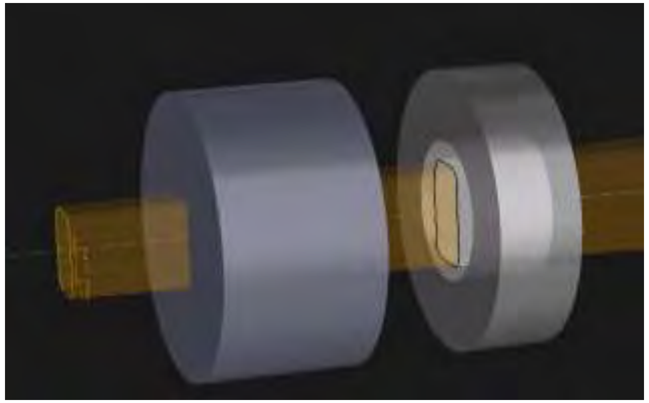
- FLASH *v.s.* VMAT
  - Does FLASH maintain the benefit of protons for OAR sparing?

- FLASH *v.s.* IMPT
  - Does FLASH improve the OAR sparing? (How to quantify? How much?)

ConformalFLASH planning via RayStation

IBA 2024 FLASH Treatment Planning Contest Award (1st Place)

IMPT plan
Multi-layer planning, with range shifter and aperture block



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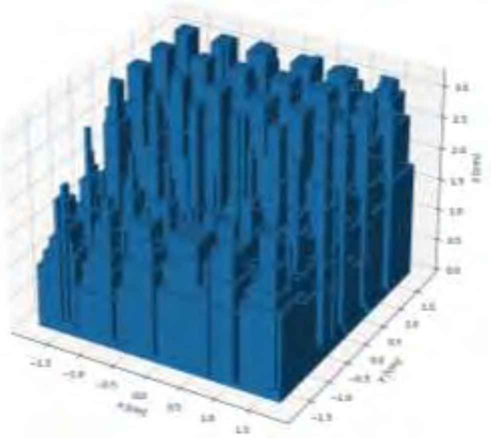
Hedgehog
Ridge filter is automatically created



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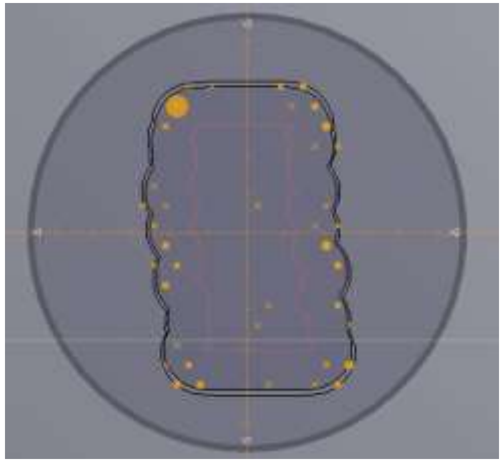
FLASH plan
Single-layer plan is optimized, and spots filtered to achieve FLASH dose rate

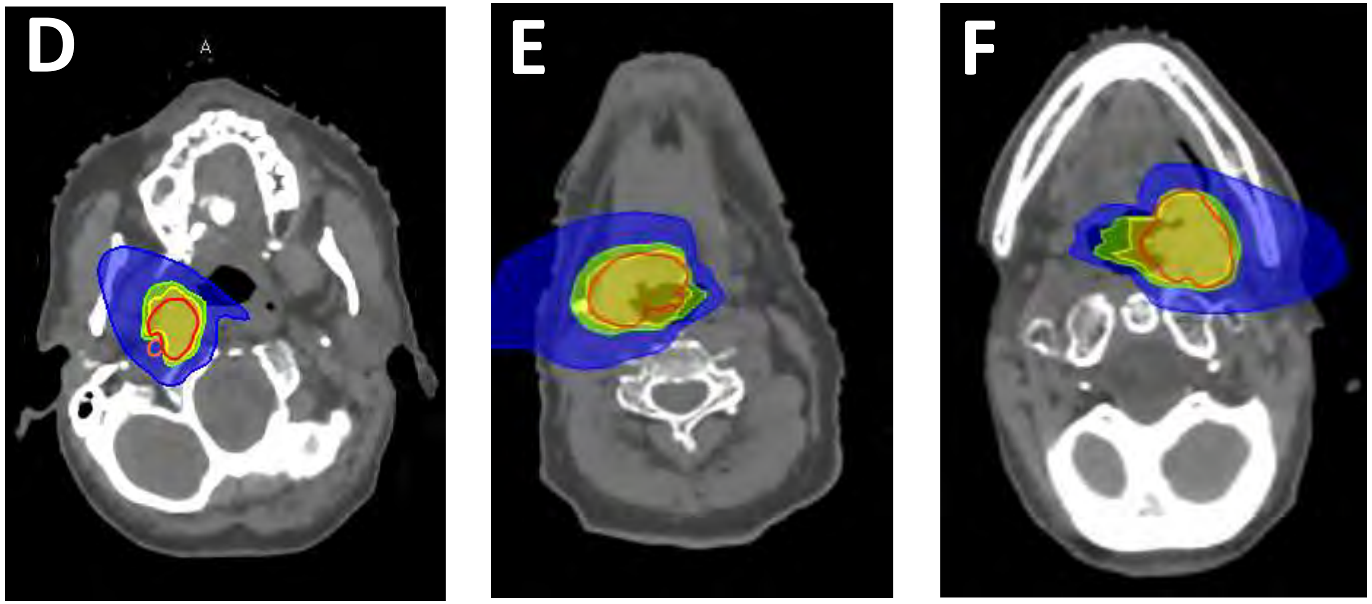


Clinical cases: reHN

FLASH vs IMPT vs VMAT

Multi-field: 3 re-irradiation HN
2 fields, SFO (8 Gy / field), ipsilateral

8 Gy @ 95% PTV / fx

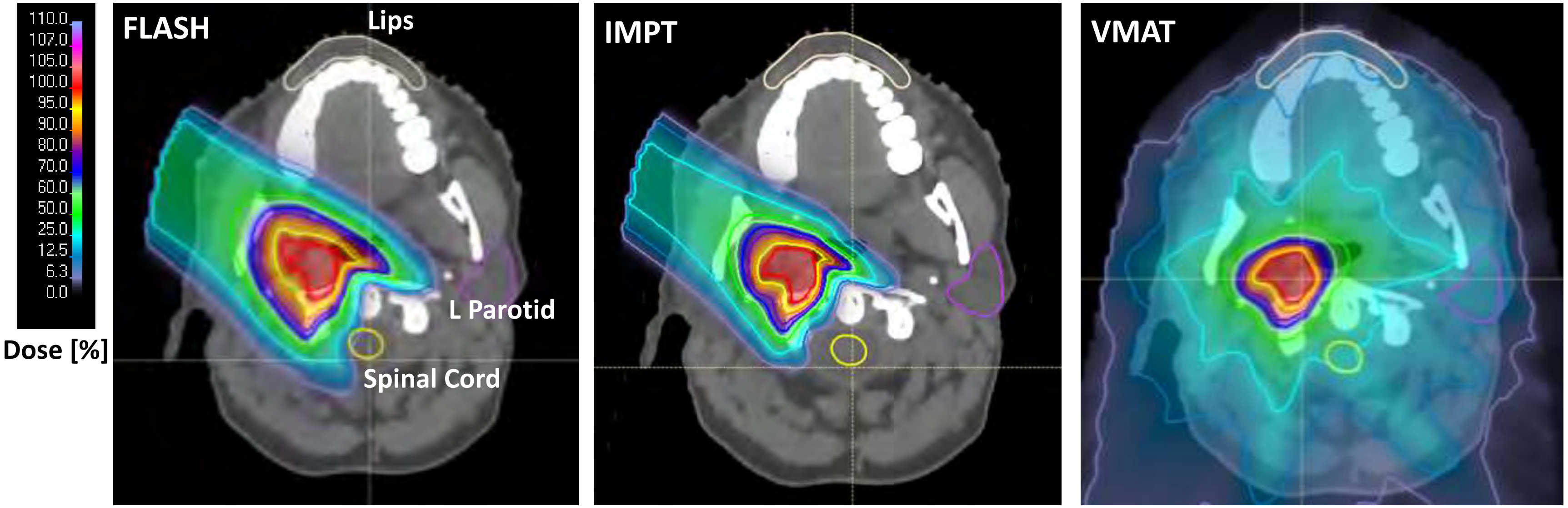


reHN 1
CTV: 6 cc

reHN 2
CTV: 10 cc

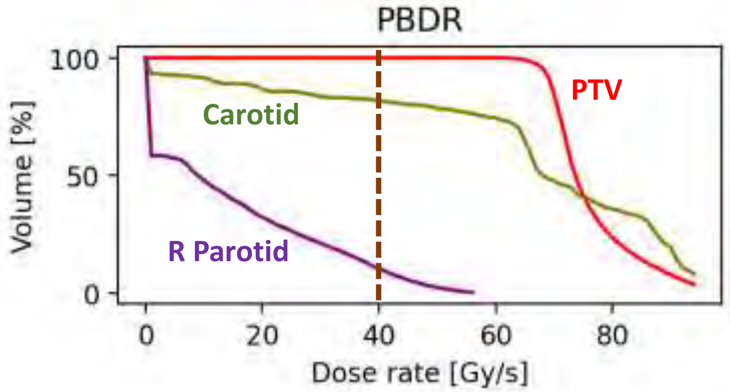
reHN 3
CTV: 13 cc

HN1: proton benefits



- Protons spare dose on contralateral OARs
- In terms of physical dose conformality, FLASH is degraded, compared to IMPT (larger penumbras)

Structure	Quantity	FLASH	IMPT	VMAT
L Parotid	D 1%	0	0	21%
	D mean	0	0	14%
Spinal Cord	D 1%	13%	0	33%
	D mean	1%	0	3%
Lips	D 1%	0	0	14%
	D mean	0	0	4%



FLASH dose rate/effective dose via in-house TPS codes

- **Pencil-beam dose rate** (PBDR): [Folkerts Med Phys 2020]

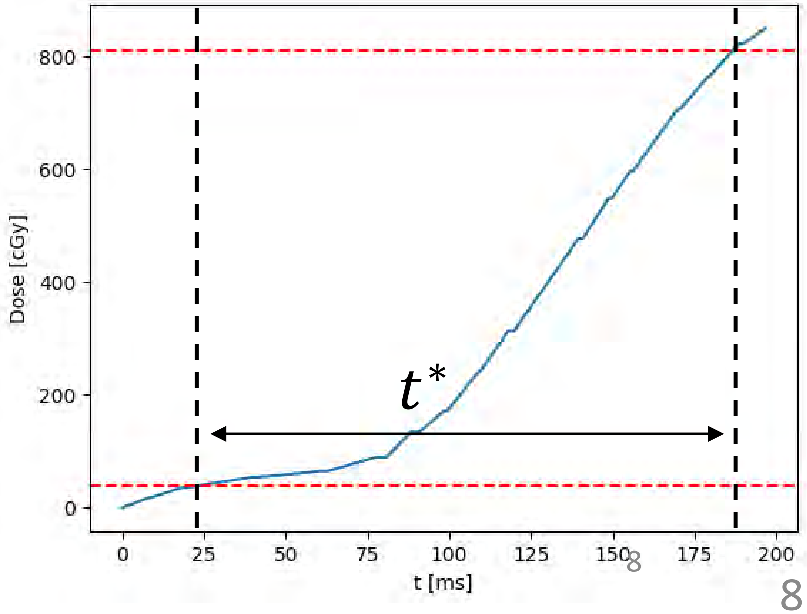
Depends on spot delivery pattern,

D_i: Total dose at voxel *i*
d_{th}: Dose threshold (5% of prescription)
t^*: Delivery time between thresholds

$$PBDR_i = \frac{D_i - 2d_{th}}{t^*}$$

I_{nozzle} = 500 nA @ 226 MeV
V_{scan} = 1 cm / ms
t_{spot}[ms] = 0.044·MU

Total dose at voxel *i*



- **Effective dose:** [Gao Med Phys 2022]

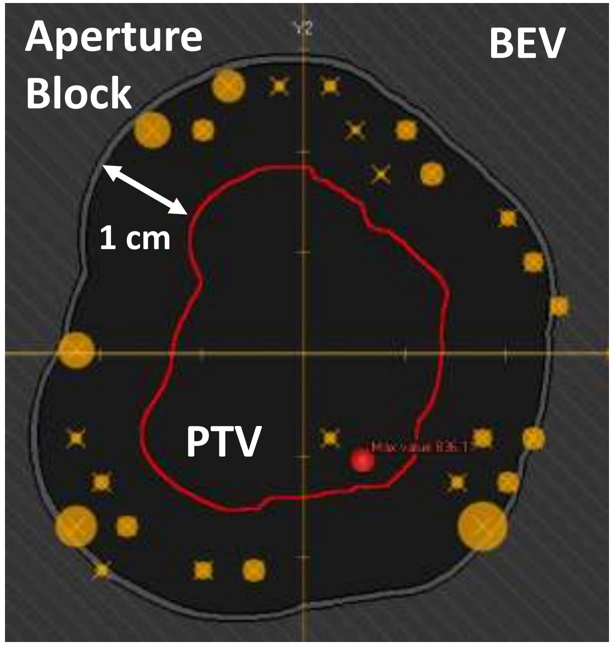
Flash regime is reached above **dose and dose rate** threshold,

d_0: 5 Gy
d_{r0}: 40 Gy/s (PBDR)

$$D_{eff} = \begin{cases} 0.7D, & D > d_0 \cap D_r > d_{r0} \\ D, & \text{CTV, or below thrsld.} \end{cases}$$

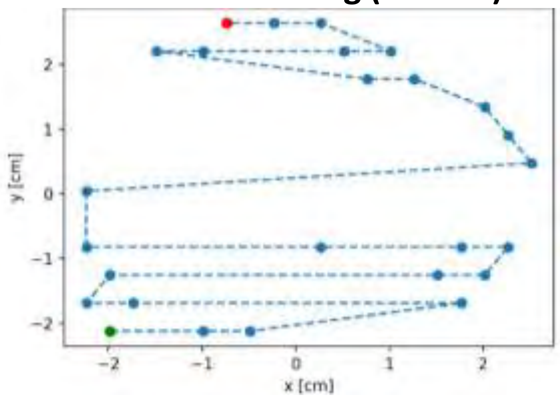
Dose rate optimization

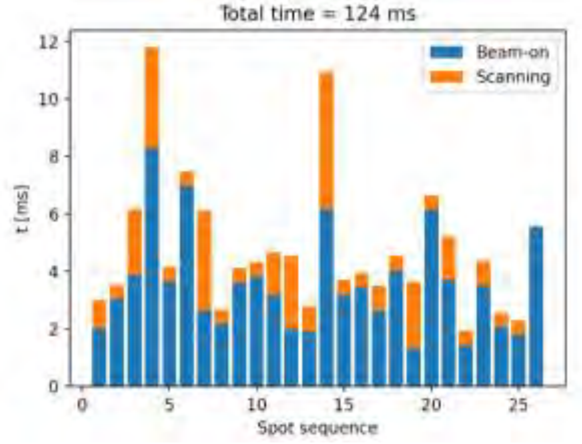
- After filtering, spots are mostly left on the edges,



Min/max spot weight: 30/190 MU

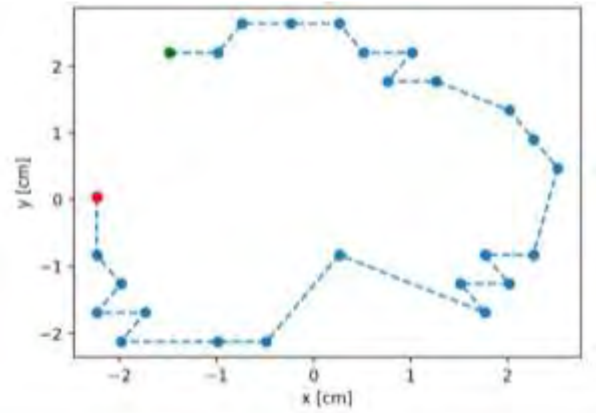
Raster scanning (default)

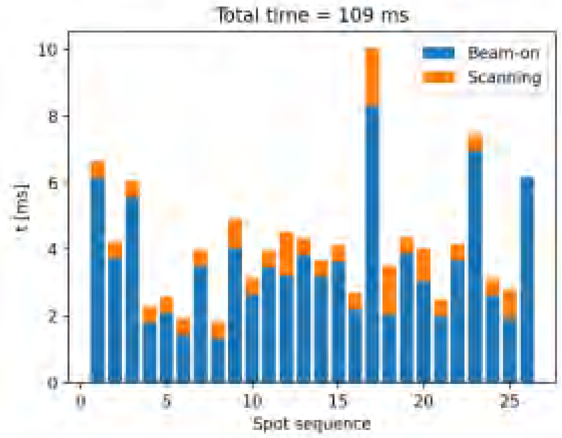




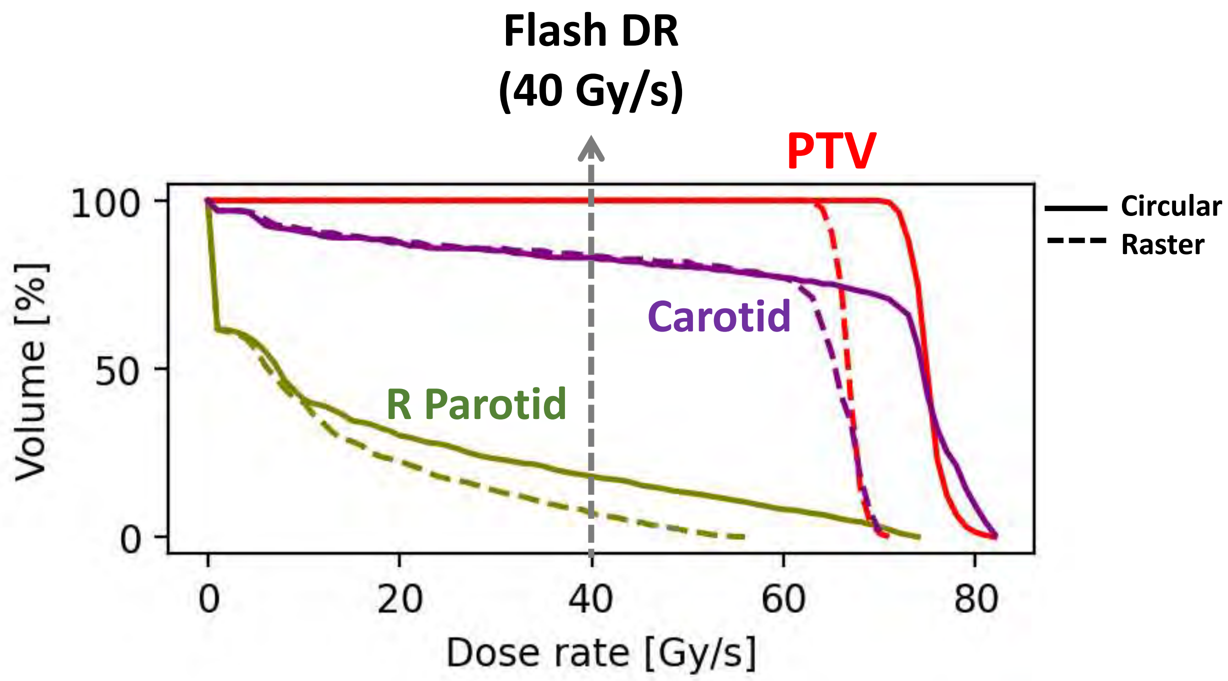
- Scanning pattern is optimized to increase PBDR via in-house codes

Circular scanning

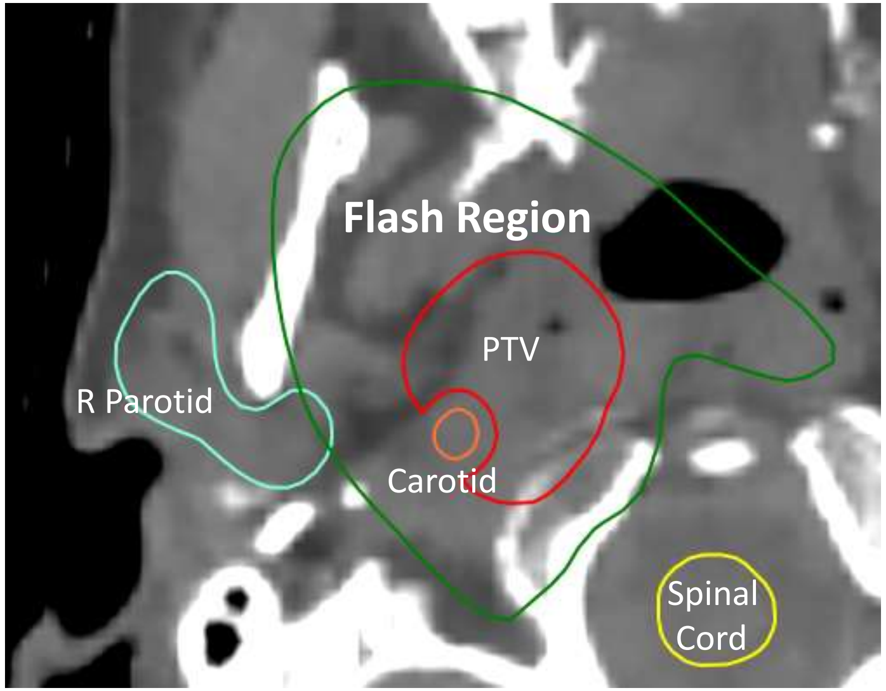




Dose rate optimization



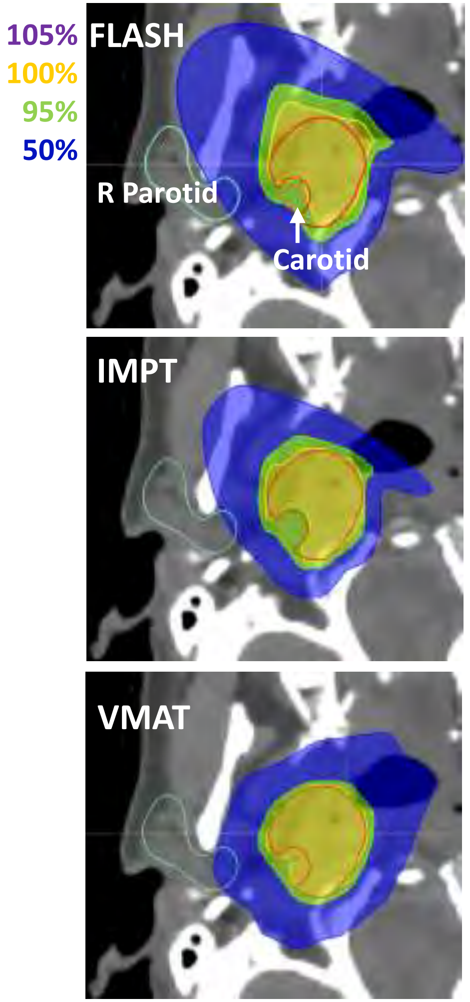
- Flash regime is **achieved** close to the PTV



- Scanning pattern can increase PBDR on OARs and PTV
- Not all OARs will be at Flash regime

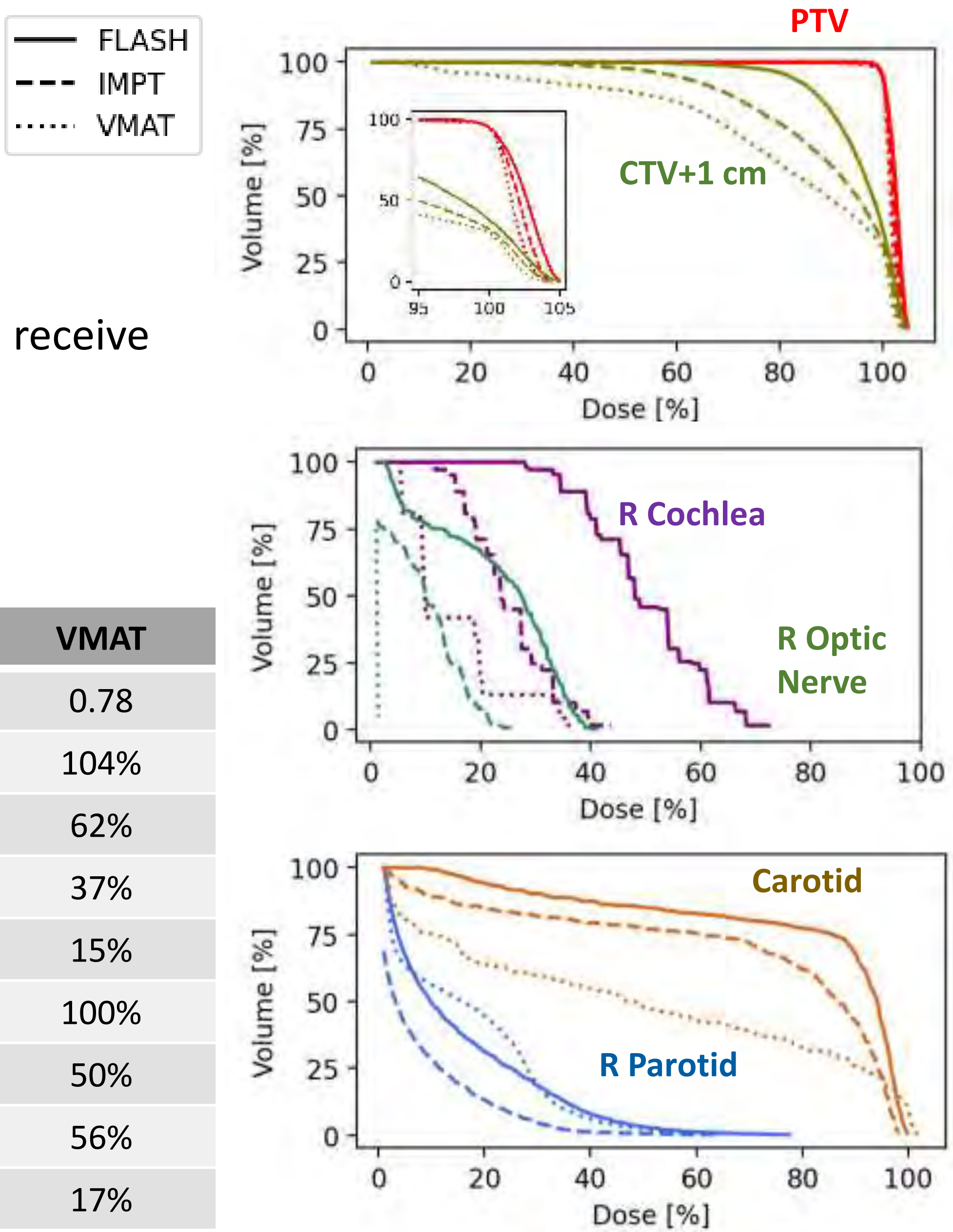
HN1

Physical dose (RBE)



- OARs that are within the proton beam path receive higher doses than with VMAT
- FLASH conformity is poorer

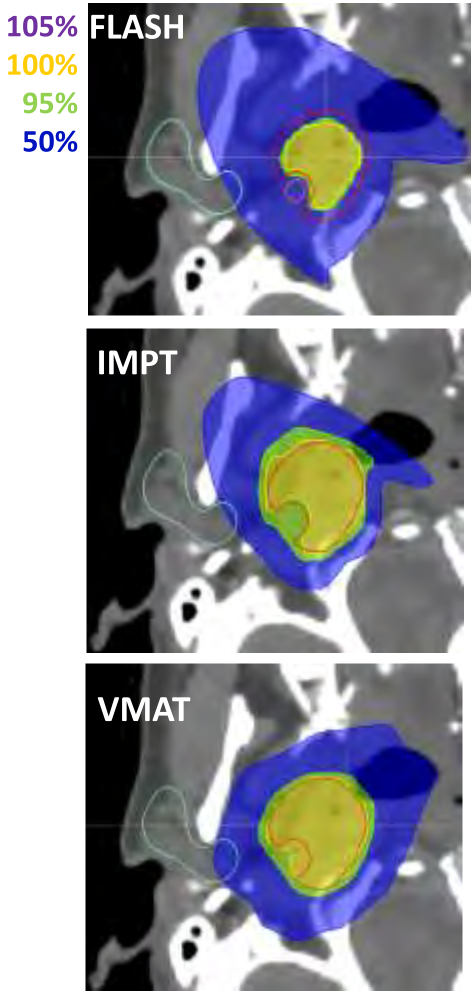
Structure	Quantity	FLASH	IMPT	VMAT
PTV	CI	0.62	0.73	0.78
	D 1%	105%	104%	104%
CTV+1cm	V 80%	96%	77%	62%
R Cochlea	D 1%	73%	44%	37%
	D mean	50%	25%	15%
Carotid	D 10%	98%	97%	100%
	D mean	82%	72%	50%
R Parotid	D 1%	62%	44%	56%
	D mean	16%	8%	17%



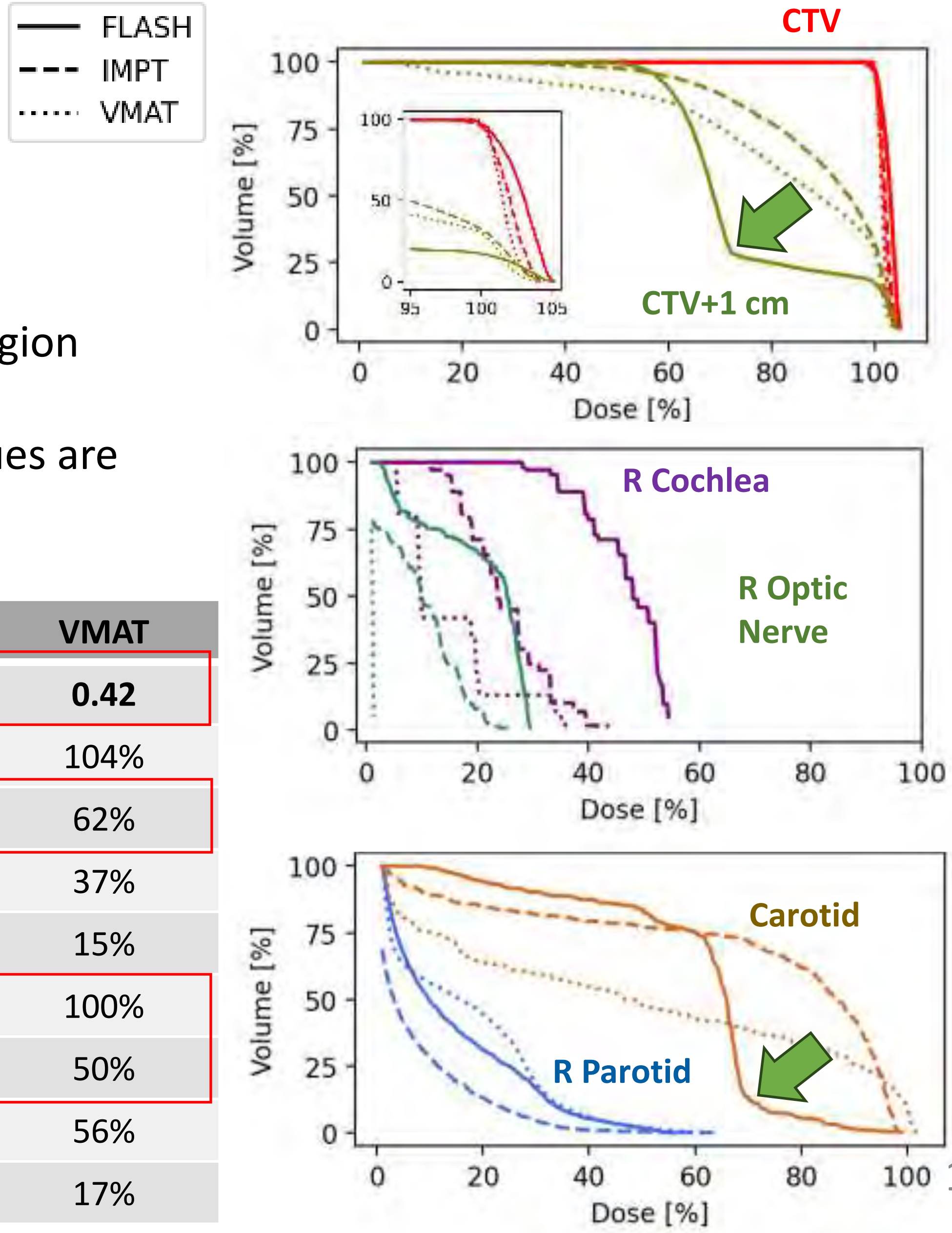
HN1

Effective dose (RBE)

- Effective dose: correction factor on Flash region
- OAR high doses are reduced, but mean values are still higher than VMAT



Structure	Quantity	FLASH	IMPT	VMAT
CTV	CI	**0.71**	**0.37**	**0.42**
	D 1%	105%	104%	104%
CTV+1cm	V 80%	**25%**	77%	62%
R Cochlea	D 1%	55%	44%	37%
	D mean	47%	25%	15%
Carotid	D 10%	**72%**	97%	100%
	D mean	**60%**	72%	50%
R Parotid	D 1%	53%	44%	56%
	D mean	15%	8%	17%



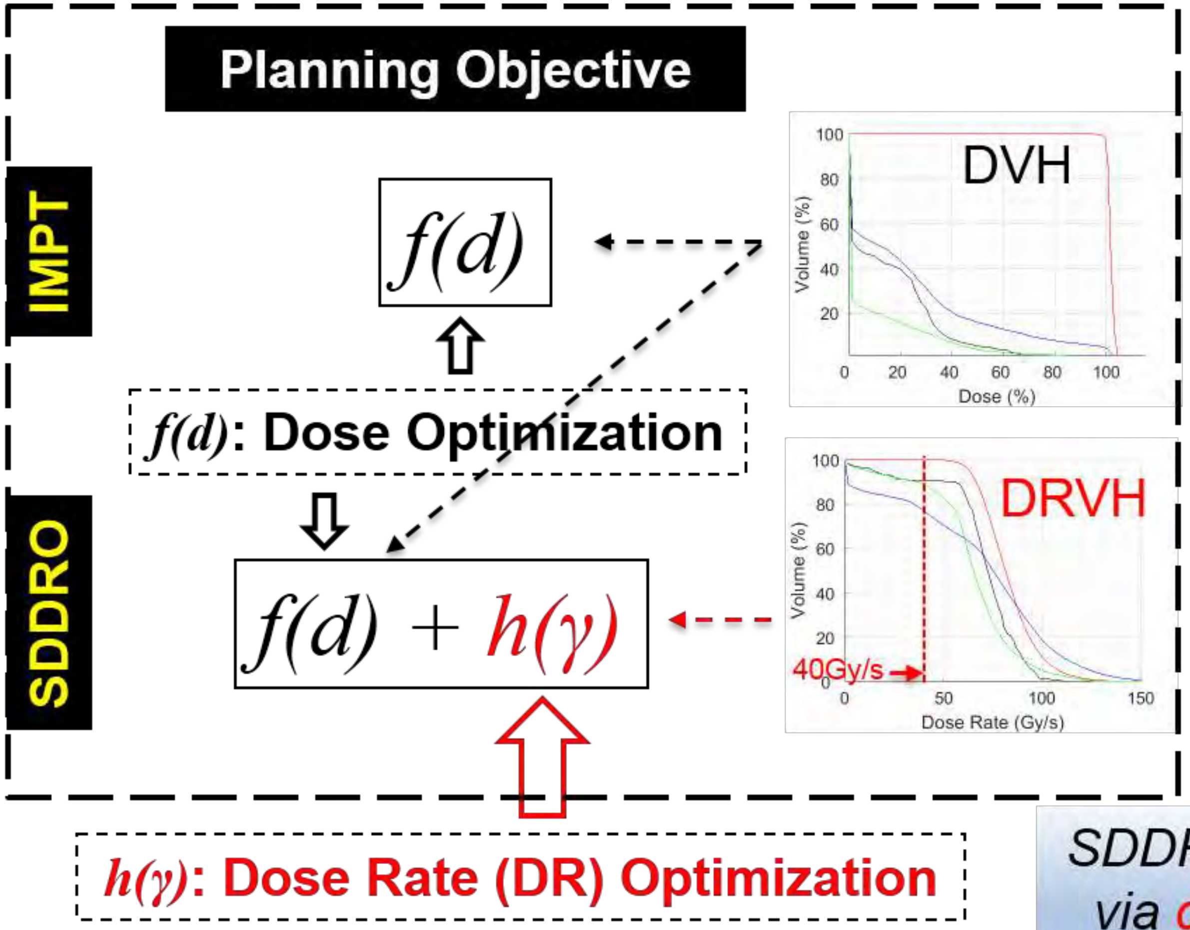
Conclusions

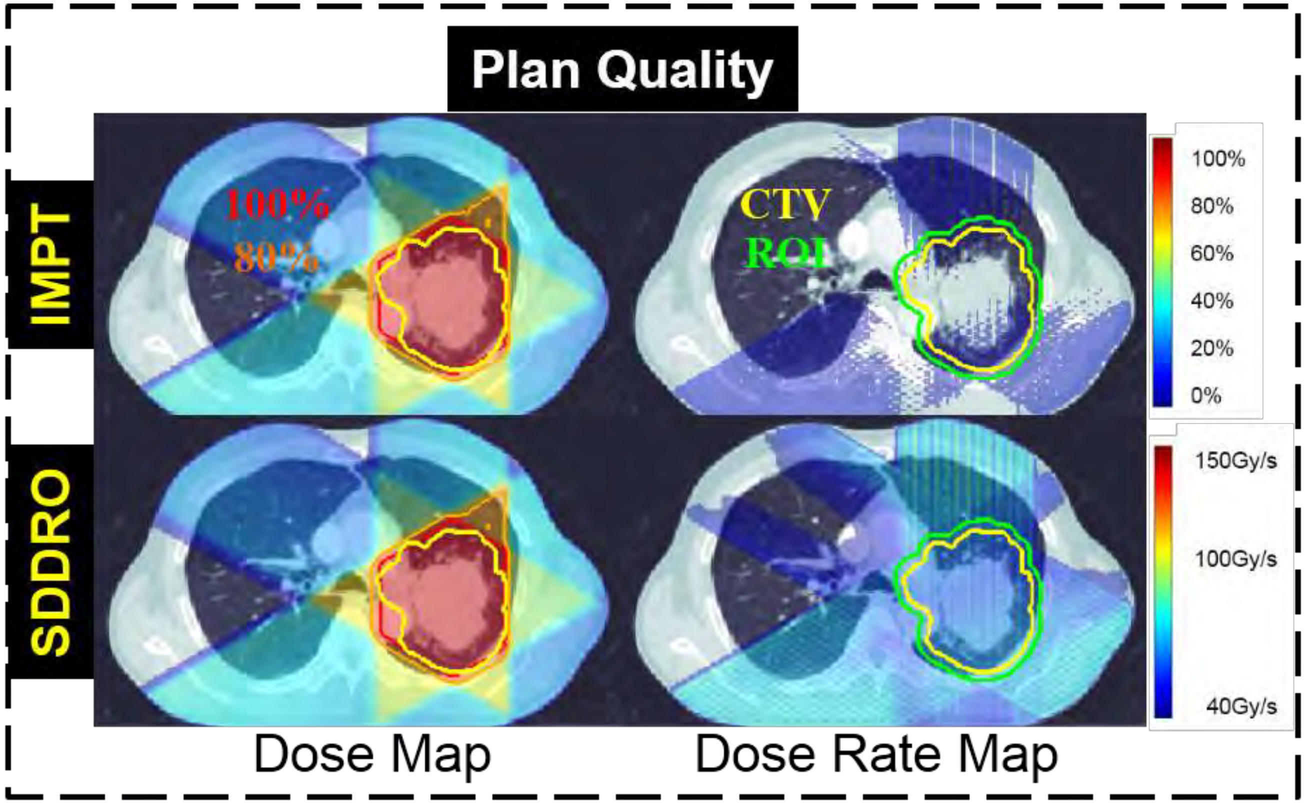
- Compared to VMAT, FLASH maintains the proton benefit for normal tissue sparing (e.g., contralateral OARs in reHN)
- Compared to IMPT, FLASH has degraded plan quality in terms of physical dose
- FLASH potentially improves the high-dose sparing (e.g., CTV1cm in terms of FLASH effective dose)
  - Scanning pattern can be optimized to improve PBDR

FLASH research

- Dose rate optimization
- FLASH effective dose (FED) optimization
- One-step ConformalFLASH optimization
  - Joint optimization of spot weights and CEF parameters
- Proteus®ONE based FLASH biology studies
- FLASH-SFRT

Simultaneous Dose and Dose Rate Optimization (SDDRO)





SDDRO improves the FLASH-dose-rate coverage from IMPT via dose rate optimization with preserved dose distribution.

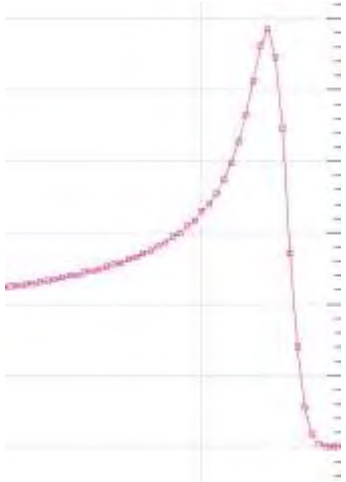
PTCOG 2021 Michael Goitein best abstract award in Physics

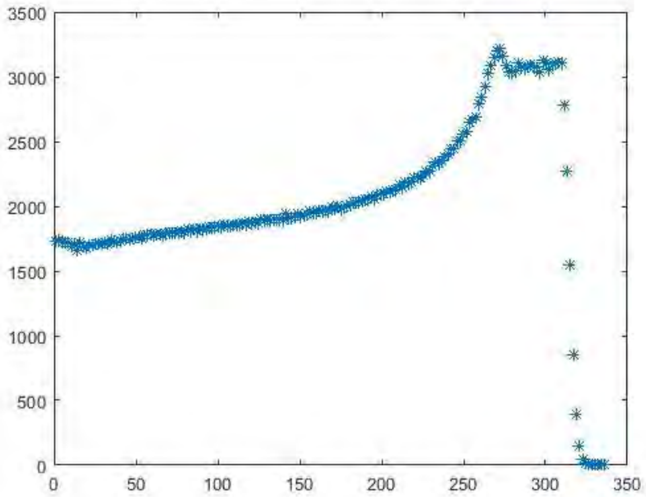
One-step ConformalFLASH optimization

FLASH plan
DIRECT pin optimization

Hedgehog
shape is part of optimization

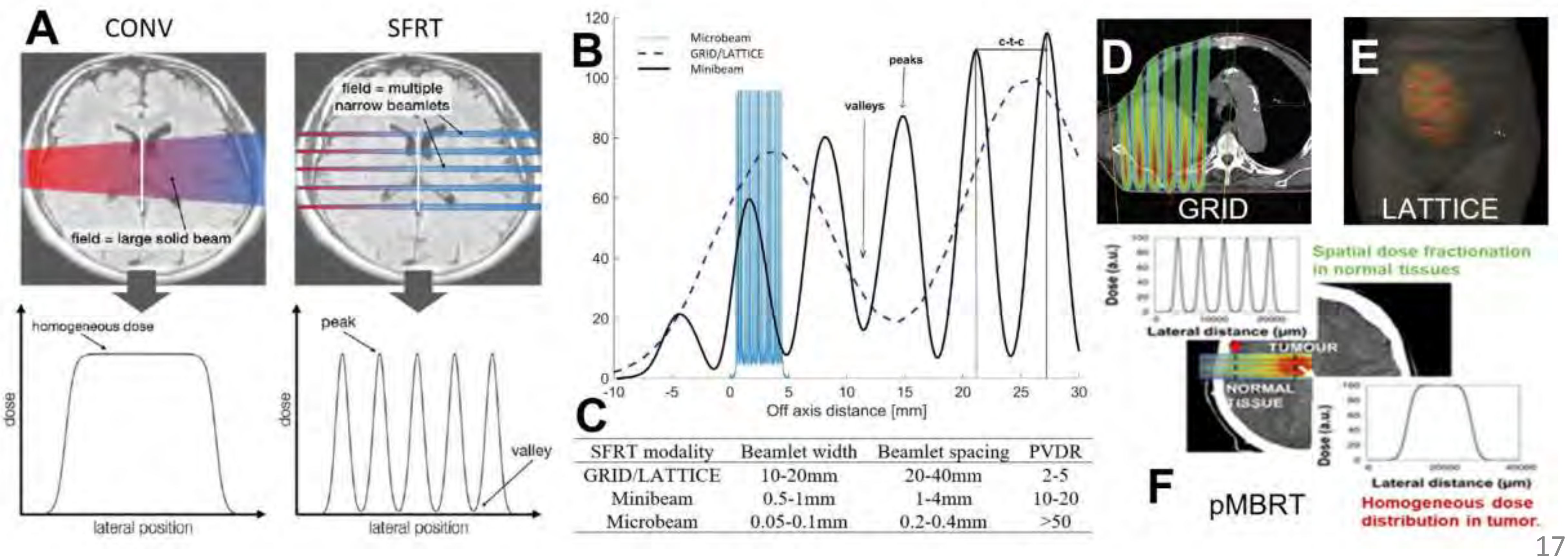
Preliminary Test: Using 226 MeV to achieve a 4 cm SOBP





SFRT

SFRT modality	Beamlet width	Beamlet spacing	PVDR
GRID/LATTICE	10-20mm	20-40mm	2-5
Minibeam	0.5-1mm	1-4mm	10-20
Microbeam	0.05-0.1mm	0.2-0.4mm	>50



SFRT: Clinical Use

- GRID [Mohiuddin Cancer 1990]
  - Head and neck cancer [Huhn TCRT 2006, Peñagarícano IJROBP 2010, Choi Cureus 2019]
  - Sarcoma [Mohiuddin IJROBP 2009, Kaiser J Radiat Oncol 2013, Snider Radiat Res 2020]
  - Melanoma [Kudrimoti IJROBP 2002]
  - Proton GRID [Gao MP 2018, Mohiuddin Brit. J. Radiol. 2020]

- LATTICE [Wu Cureus 2010]
  - Cervical cancer [Amendola Cureus 2010, Suarez Cureus 2015, Amendola Radiat Res 2020]
  - Lung cancer [Amendola ctRO 2018, Amendola Cureus 2019]

SFRT program at KUMC

- pMBRT
- LATTICE/GRID
  - Proton/photon
  - Clinical trials
  - Immunotherapy, targeted therapy
- Treatment planning
  - PVDR optimization
  - Lattice position optimization
  - Scissor beam based proton GRID
  - Proton ARC based proton LATTICE

pMBRT

- Compared to GRID/LATTICE
  - higher PVDR and very high therapeutic index,
  - beyond the simple difference in beam size and should be due to different biological mechanisms [Prezado22]
- Compared to microbeam
  - can reach deep-seated tumors
  - deliverable on clinical machines
- pMBRT is a synergy of proton and minibeam
  - proton Bragg peaks for sparing OAR
  - therapeutic index further enhanced when combined with proton RT, which is likely due to immune activation [Potez19, Tinganelli20]

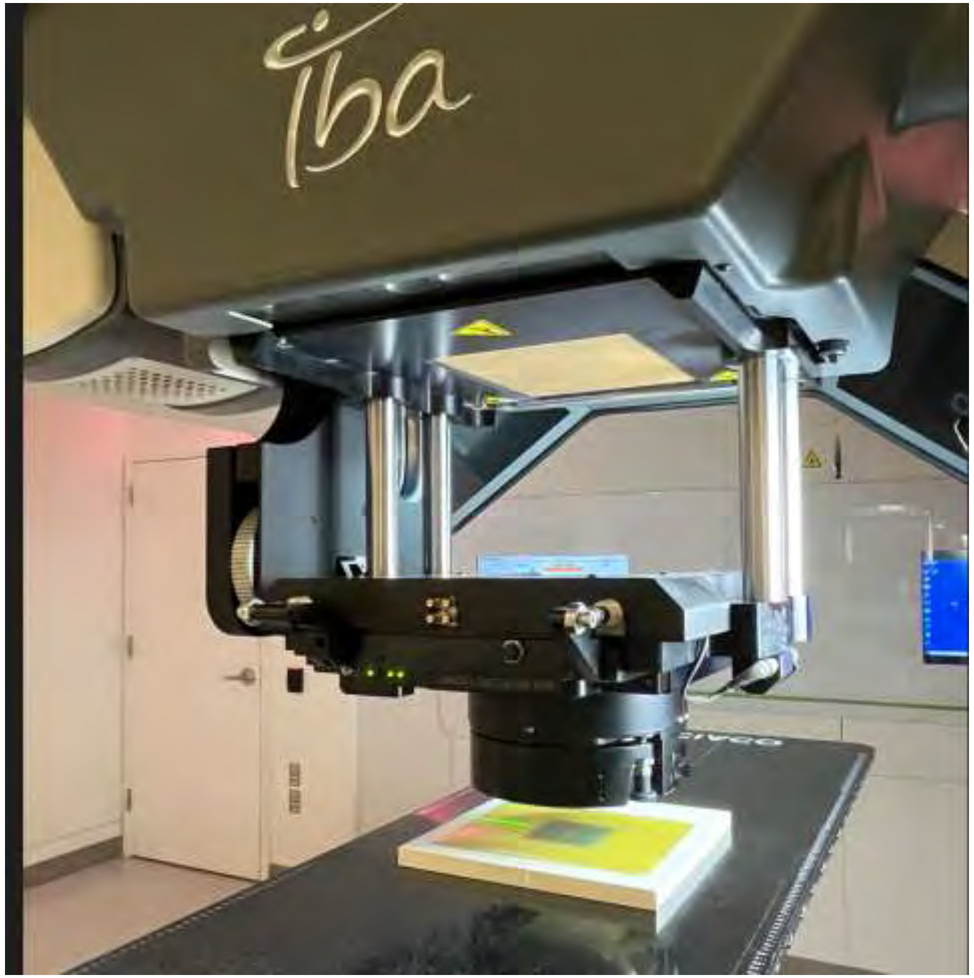
Our recent progress

- First clinical prototype
  - System development and validation
  - RayStation TPS
  - Animal experiment setup

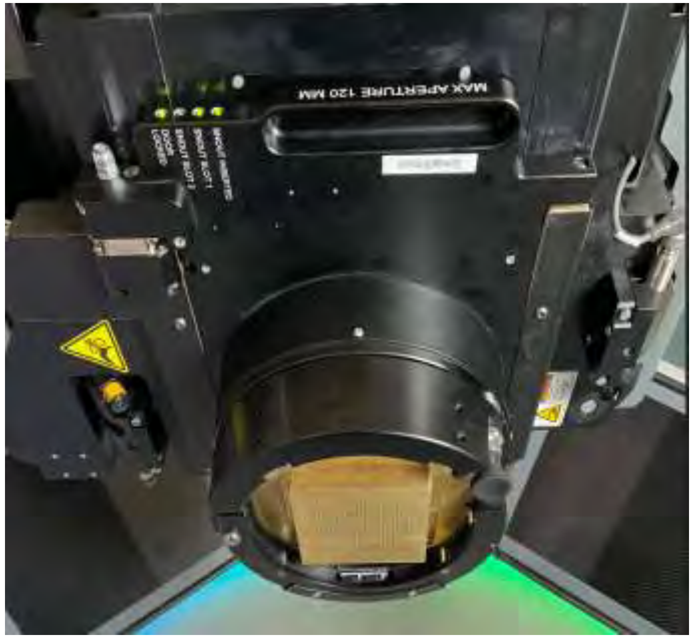
- pMBRT-specific treatment planning methods
  - Feasibility of PVDR in depth
  - Joint optimization of PVDR and dose objectives
  - Adaptive dose calculation
  - Multi-collimator optimization

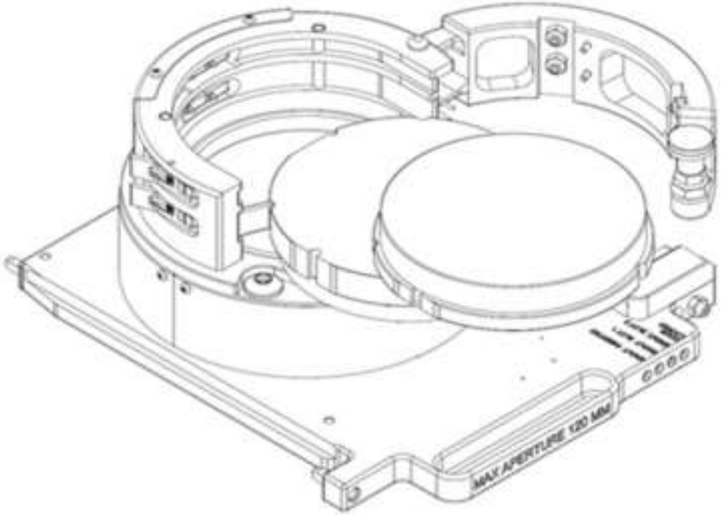
ASTRO 2023 Basic/Translational Science Award

IBA Proteus®ONE based pMBRT system



pMBRT aperture

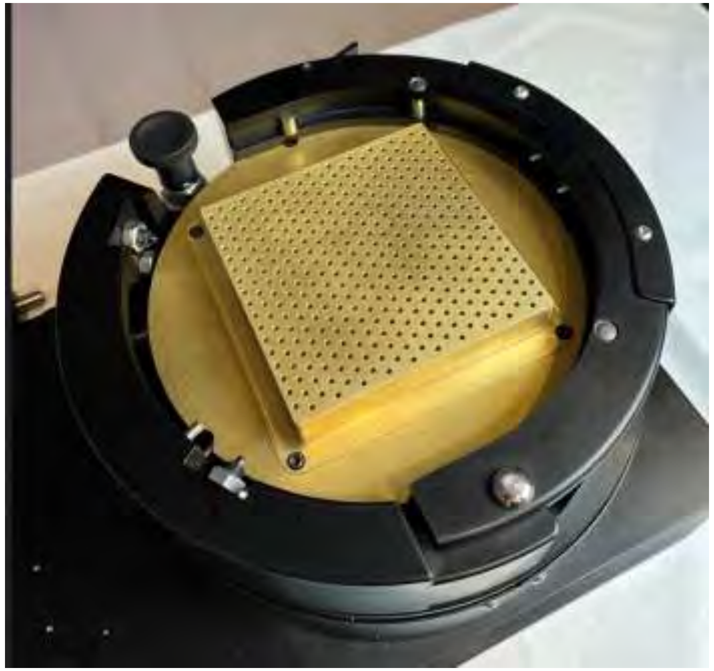


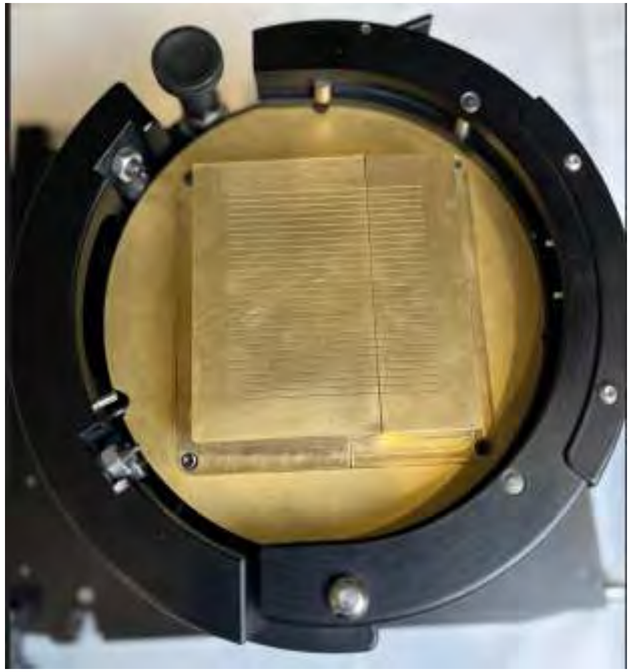


Stability

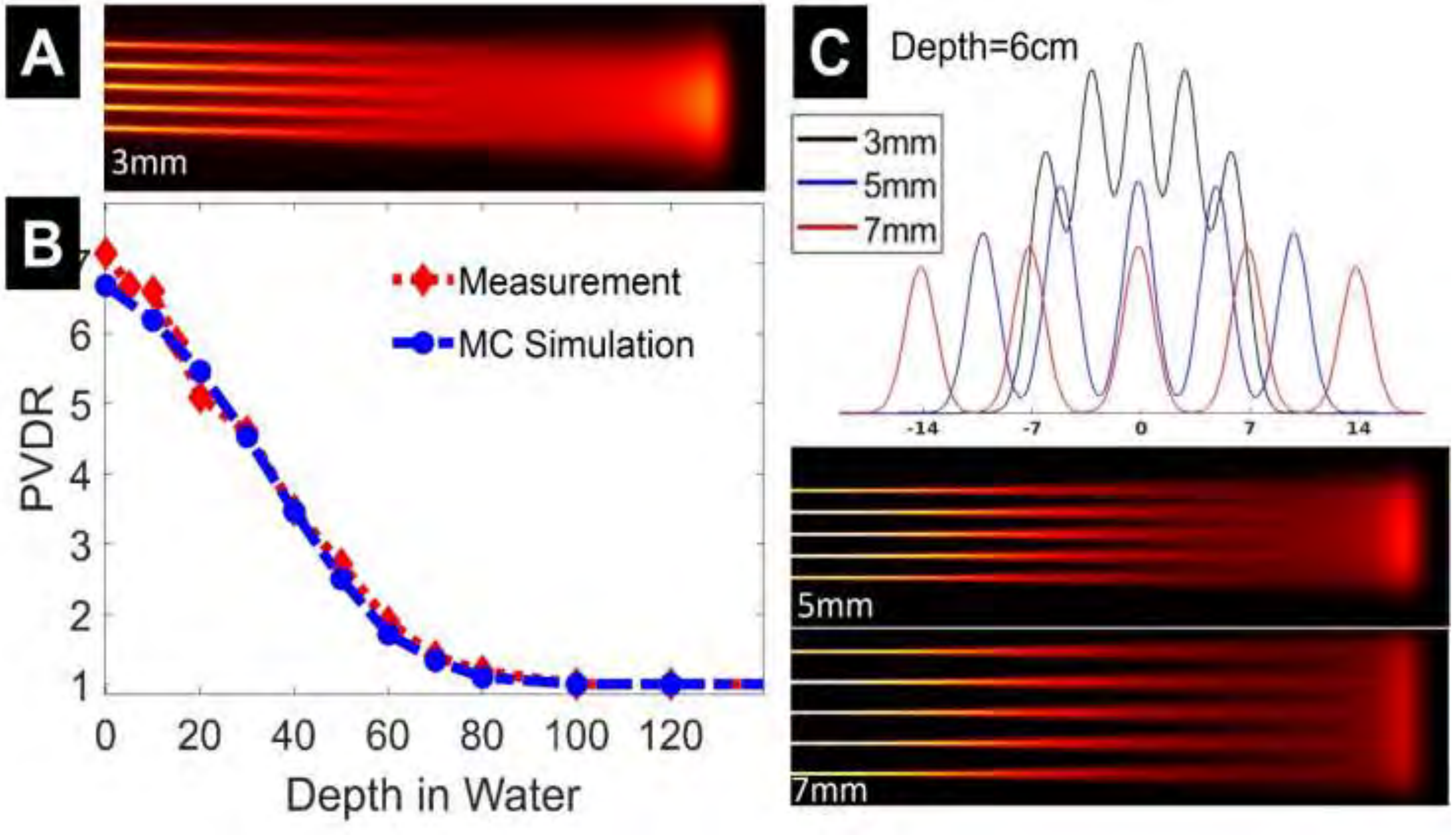
Reproducibility

Flexibility



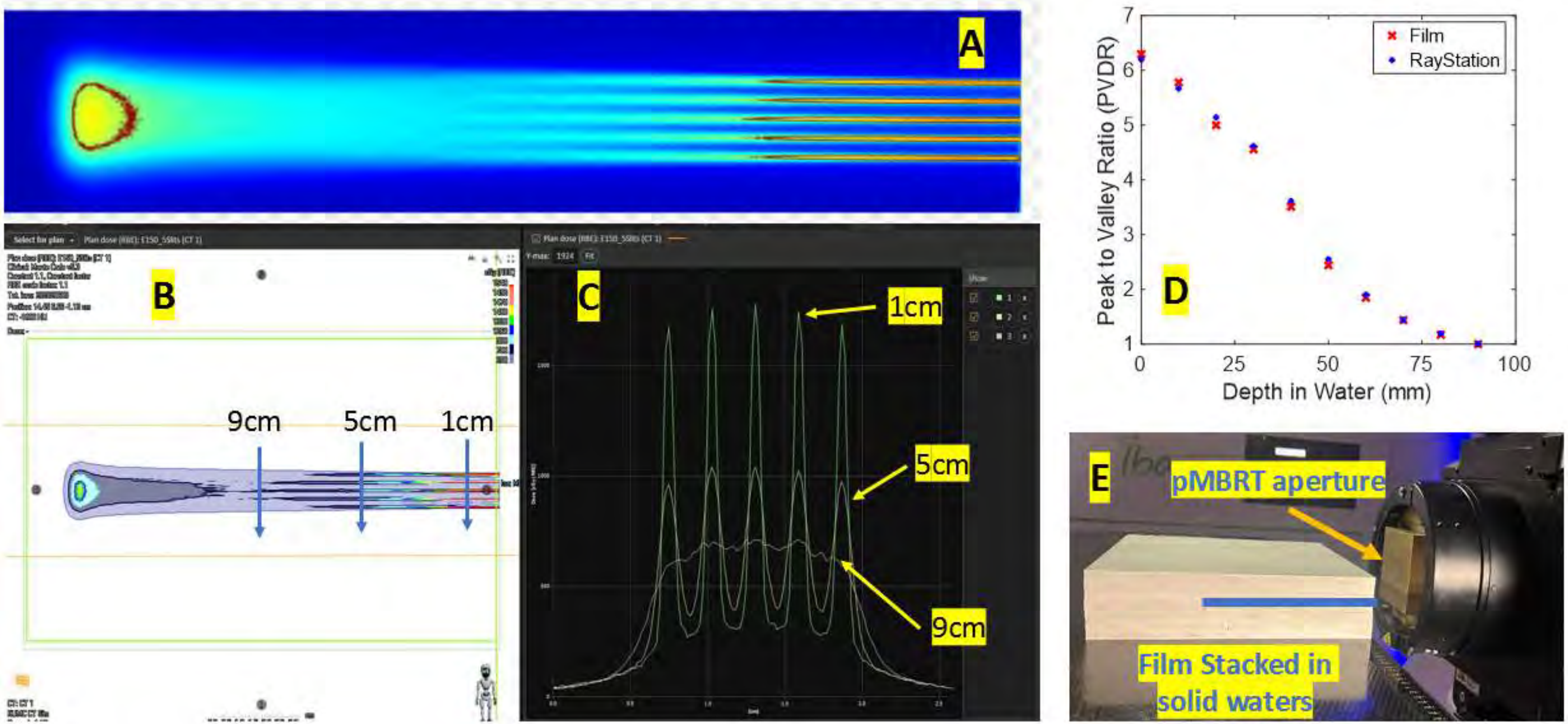


PVDR validation



A: Film measurement at 150MeV: film stacked in solid water and gantry at 90 degrees. **B**: PVDR at various depths: film measurement versus MC simulation for D_{ctc}=3mm. **C**: Dose profile at 6cm depth with D_{ctc}=3mm, 5mm, and 7mm, of PVDR=2, 7, and 12 respectively via MC simulations.

RayStation pMBRT TPS commissioning

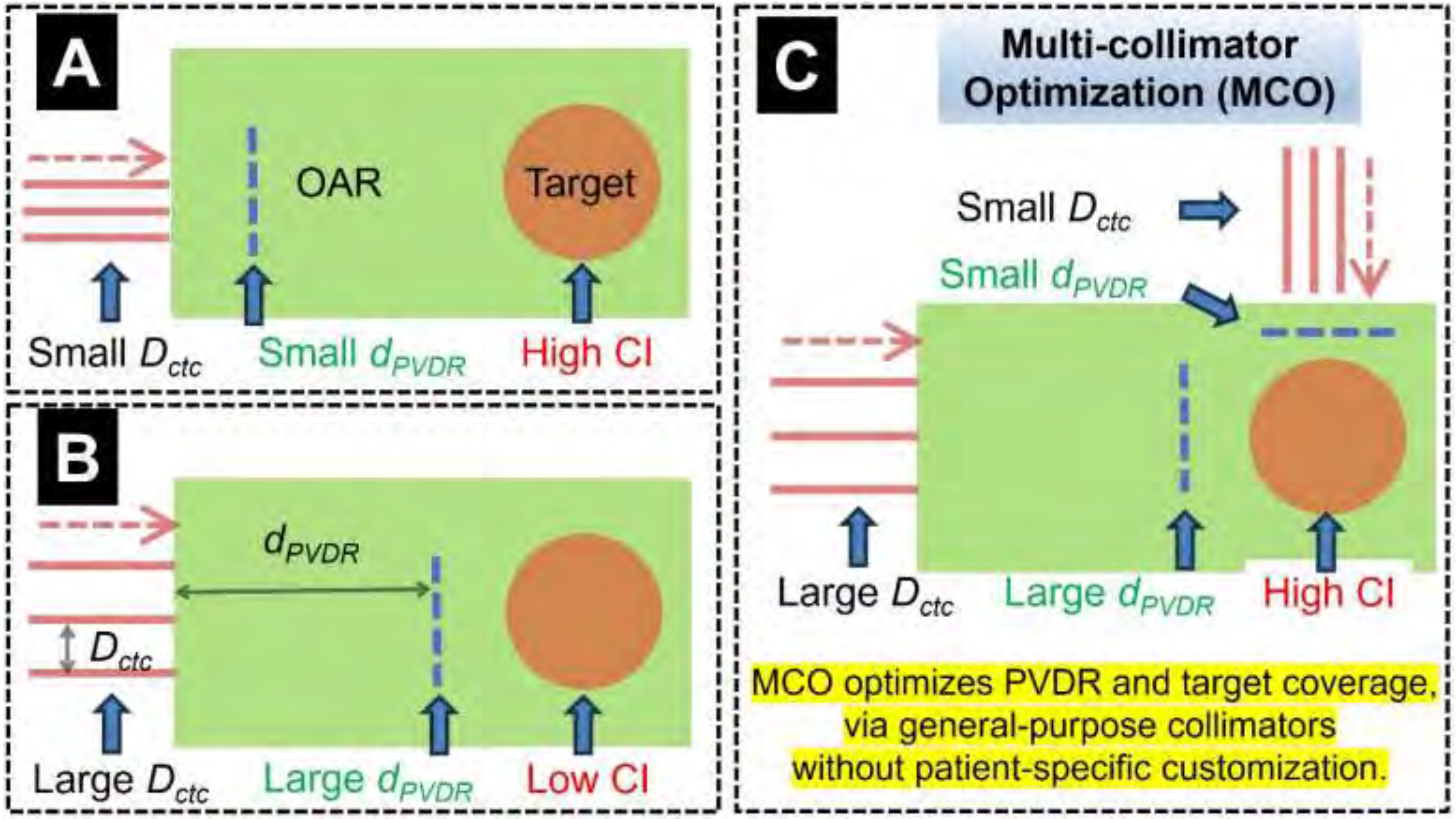


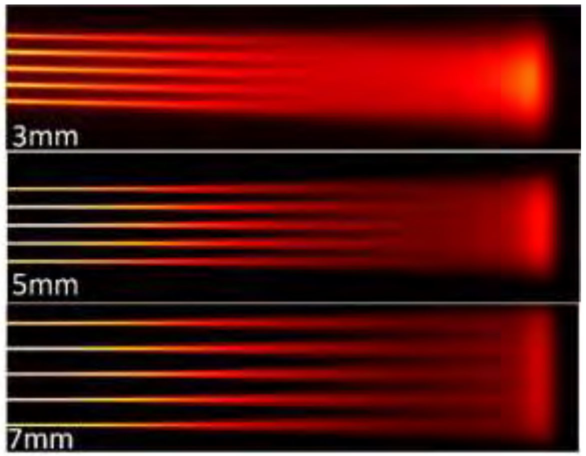
Towards clinical pMBRT

- Clinical pMBRT
  - Uniform target dose; PVDR in normal tissues
  - Need multi-field for target uniformity and OAR sparing

- How to deliver pMBRT with sufficient PVDR in patients?
  - One collimator does not work for all
  - Patient-specific collimator is costly
  - Our solution: multi-collimator (MC) planning and delivery

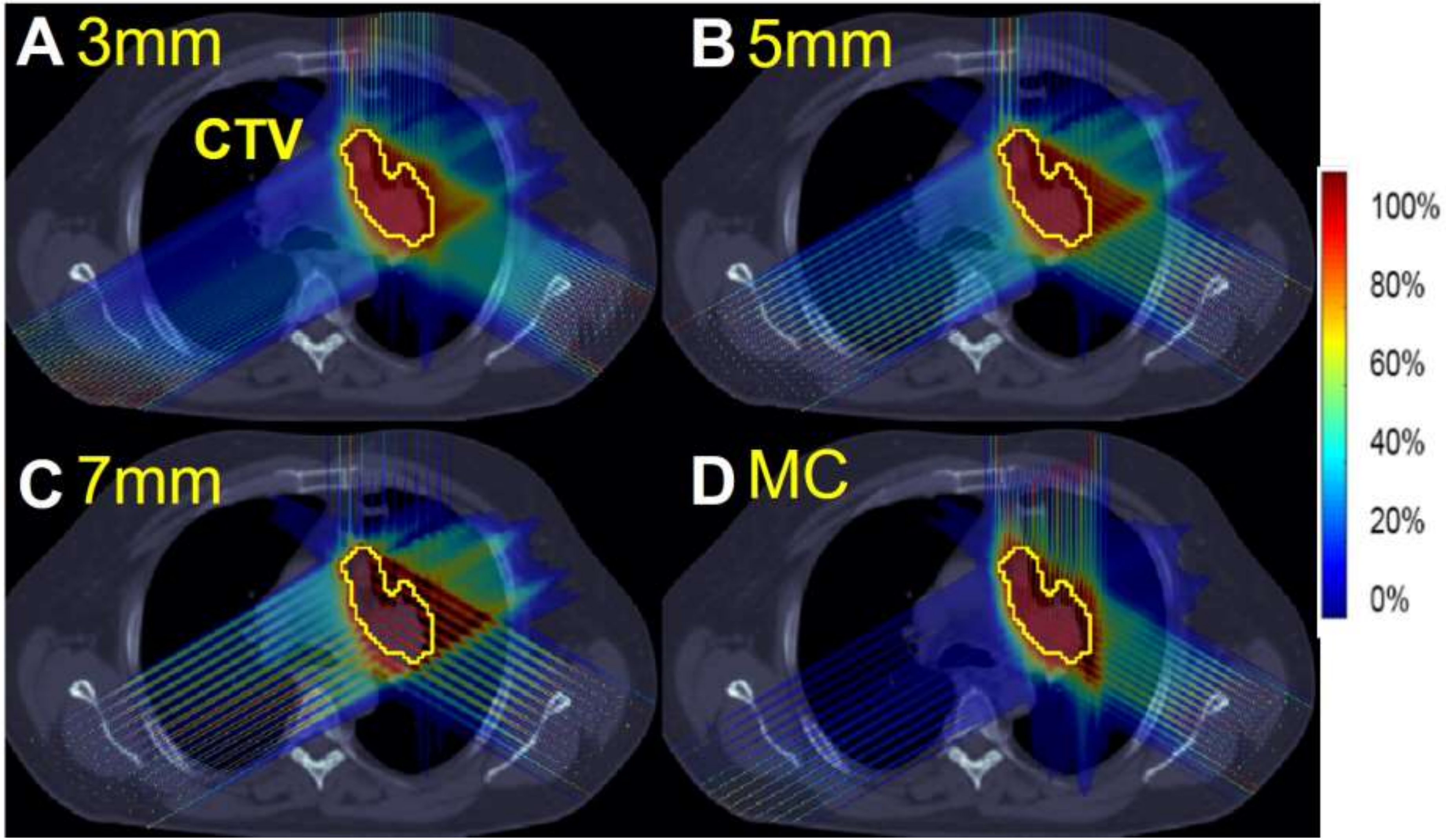
MC-pMBRT



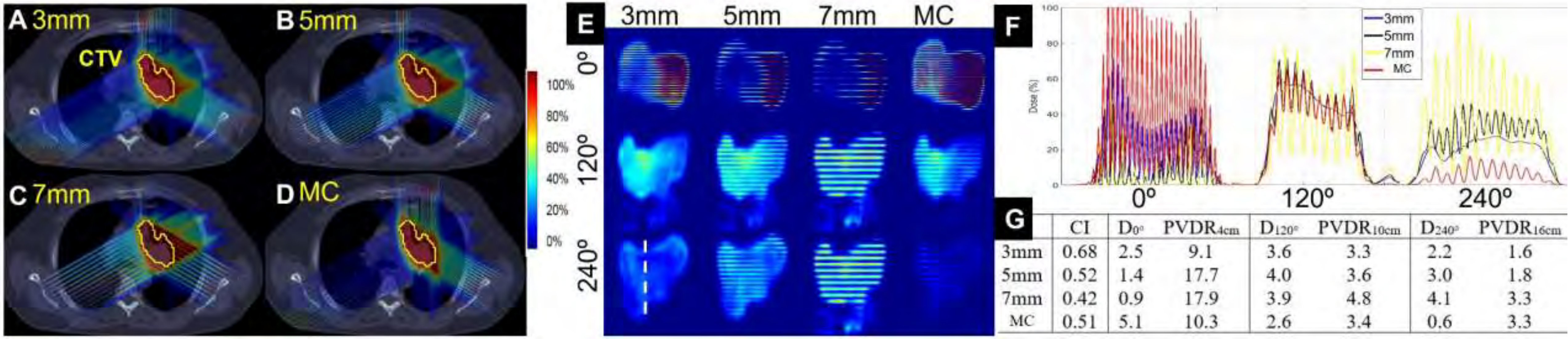


A: pMBRT with small D_{ctc} has shallow depth of high PDVR (d_{PVDR}) for OAR sparing, but high conformity index (CI) for target coverage. **B**: pMBRT with large D_{ctc} has deep d_{PVDR}, but low CI. **C**: MCO optimizes PVDR and target coverage, via general-purpose collimators.

MC v.s. SC



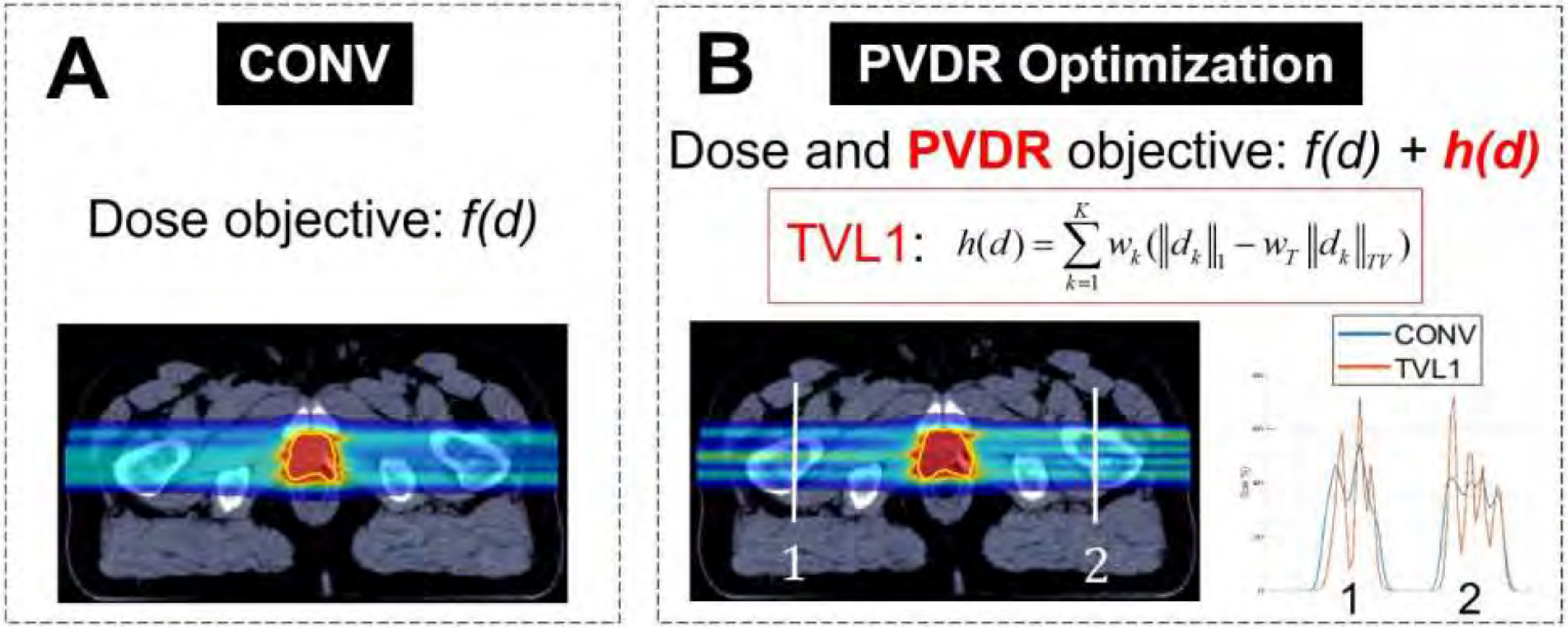
MC v.s. SC



	CI	$D_{0°}$	$PVDR_{4cm}$	$D_{120°}$	$PVDR_{10cm}$	$D_{240°}$	$PVDR_{16cm}$
3mm	0.68	2.5	9.1	3.6	3.3	2.2	1.6
5mm	0.52	1.4	17.7	4.0	3.6	3.0	1.8
7mm	0.42	0.9	17.9	3.9	4.8	4.1	3.3
MC	0.51	5.1	10.3	2.6	3.4	0.6	3.3

A-D: dose map for 3, 5, 7mm and mixed D_{ctc}'s respectively. **E**: BEV 2D dose slices. **F**: BEV 1D dose profiles. **G**: Plan parameters, including conformity index (CI), mean dose D_i of 2D slice (**E**) at angle i and $PVDR_d$ at depth d.

Joint dose and PVDR optimization (JDPO)



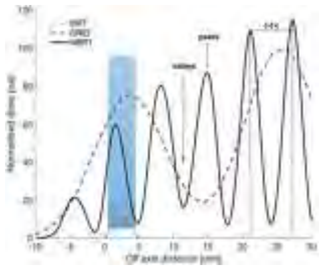
A: Conventional SFRT treatment planning (CONV) optimizes only dose objective. **B**: New SFRT treatment planning (e.g., our TVL1 method [Zhang2023]) optimizes both dose and PVDR objectives. The comparison of dose profiles at 1 and 2 shows that while PVDR is minimal via CONV, PVDR is substantially increased via TVL1 with lower valley dose.

pMBRT program at KUMC

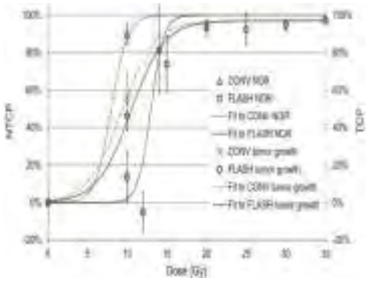
- Goal
  - Clinical pMBRT prototype
  - Pilot patient treatment

- Progress
  - pMBRT system with IGRT and RayStation TPS
  - pMBRT-specific treatment planning methods
    - Joint optimization of PVDR and dose objectives
    - Multi-collimator multi-field optimization
    - Adaptive dose calculation and treatment planning
  - Animal experiments

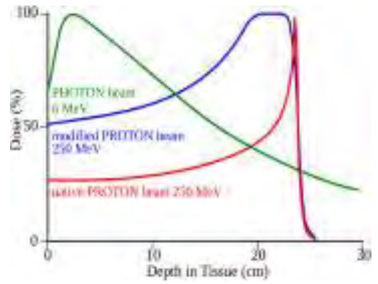
Motivation for FLASH+SFRT



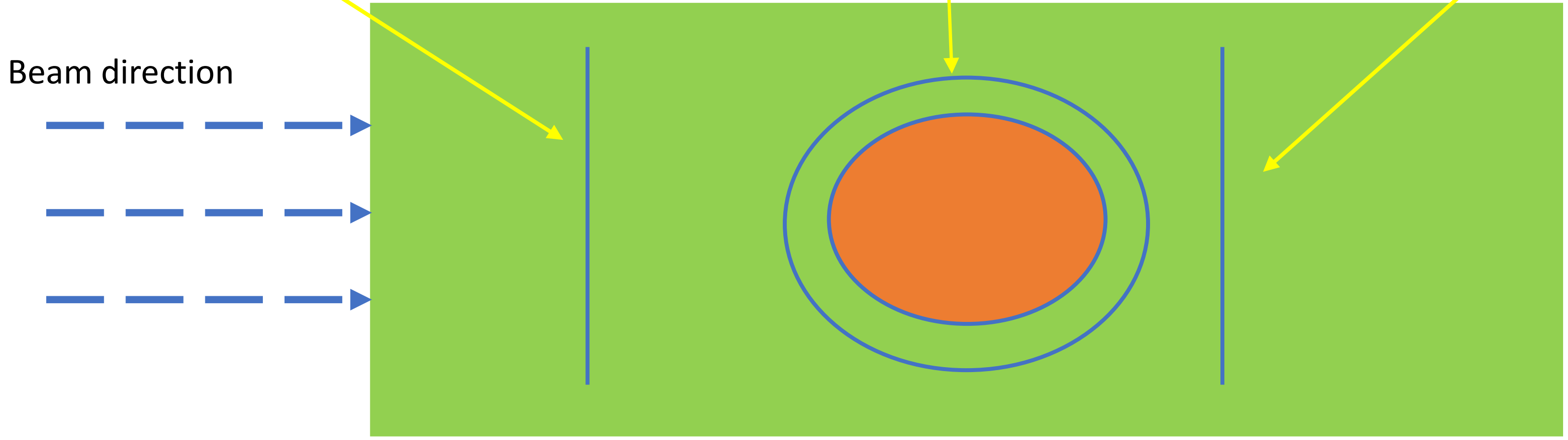
SFRT → **Shallow-to-Intermediate depth with high PVDR**



FLASH → **CTV1cm ring with UHDR**

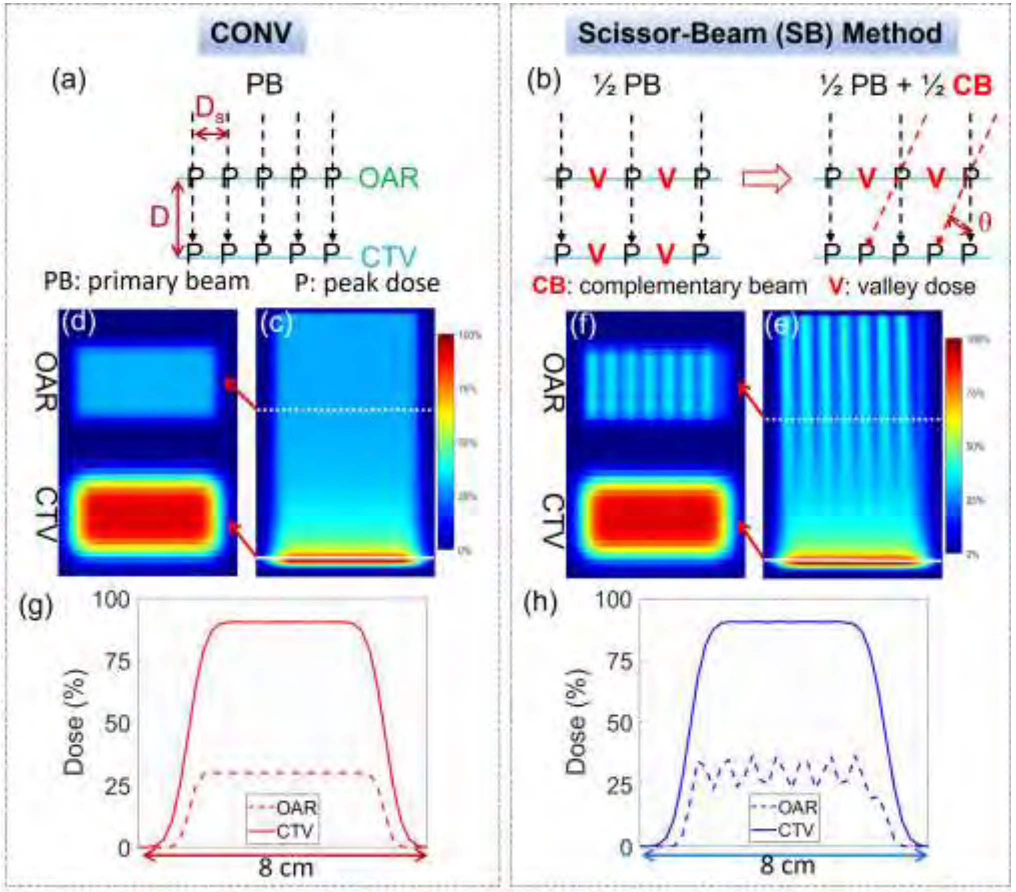


Proton → **Beyond the target with minimal exit dose**

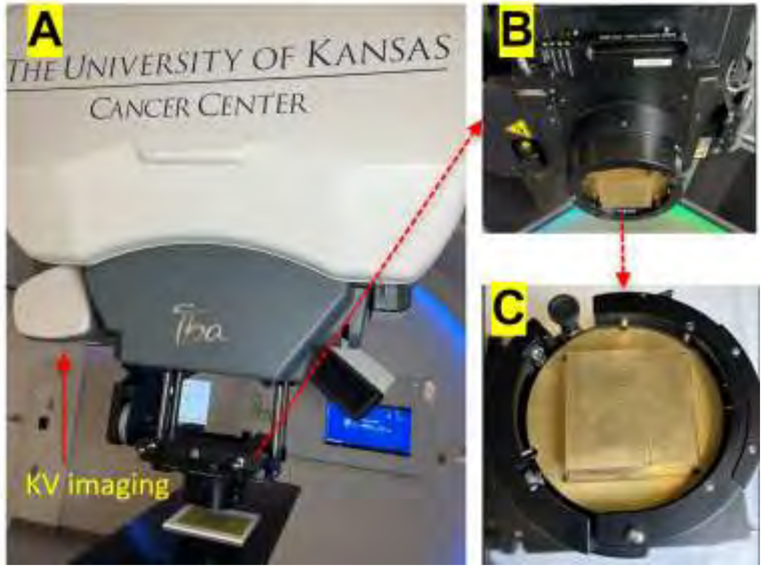


SFRT

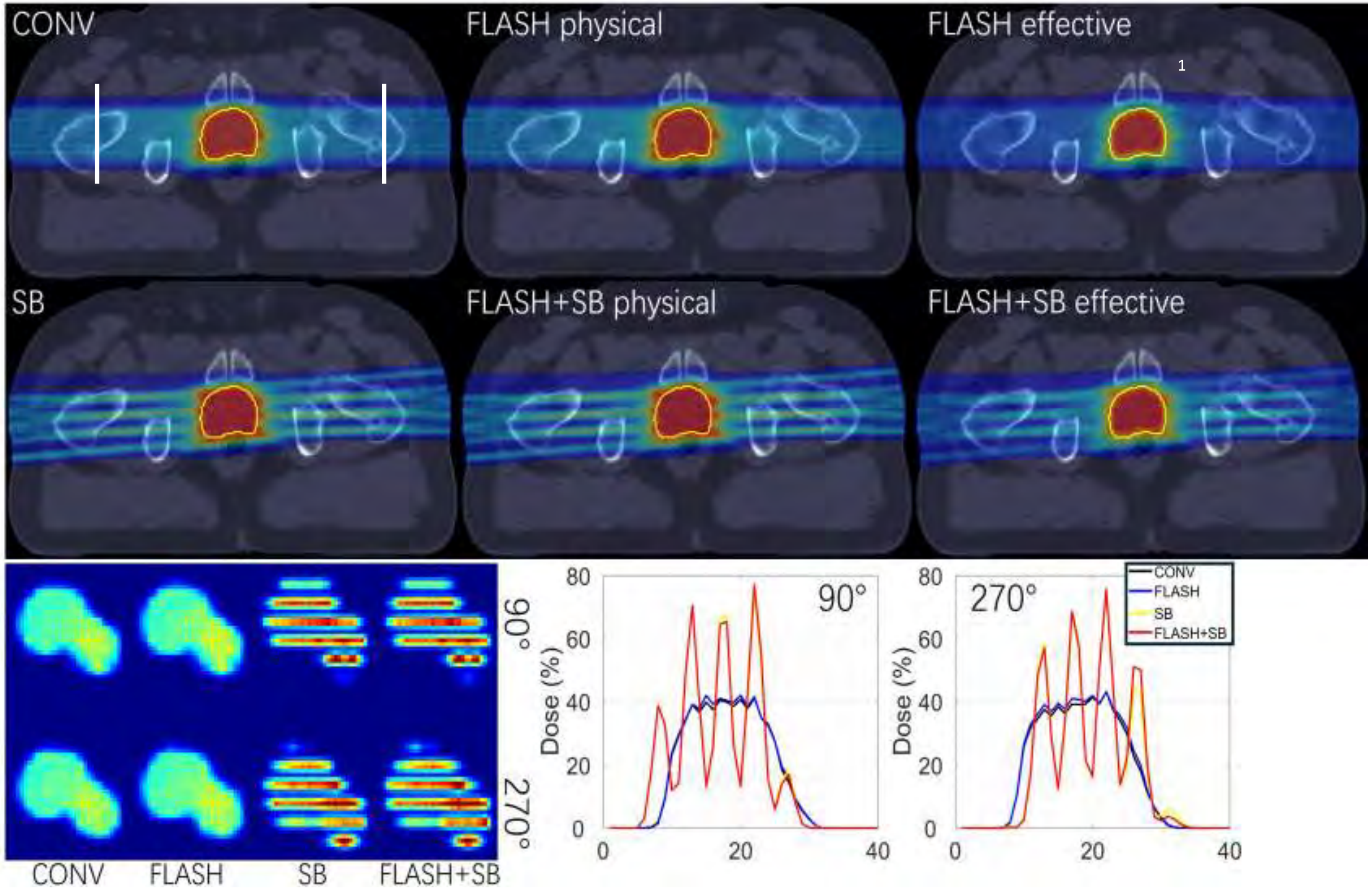
- Proton GRID via scissor beam (SB)
  - No collimator



- Proton minibeam radiation therapy
  - Multi-slit collimator
  - 2D planar minibeam dose
  - *s*=0.7mm, ctc=3mm
    - γ=30% at 6cm depth
    - Slightly reduced PVDR

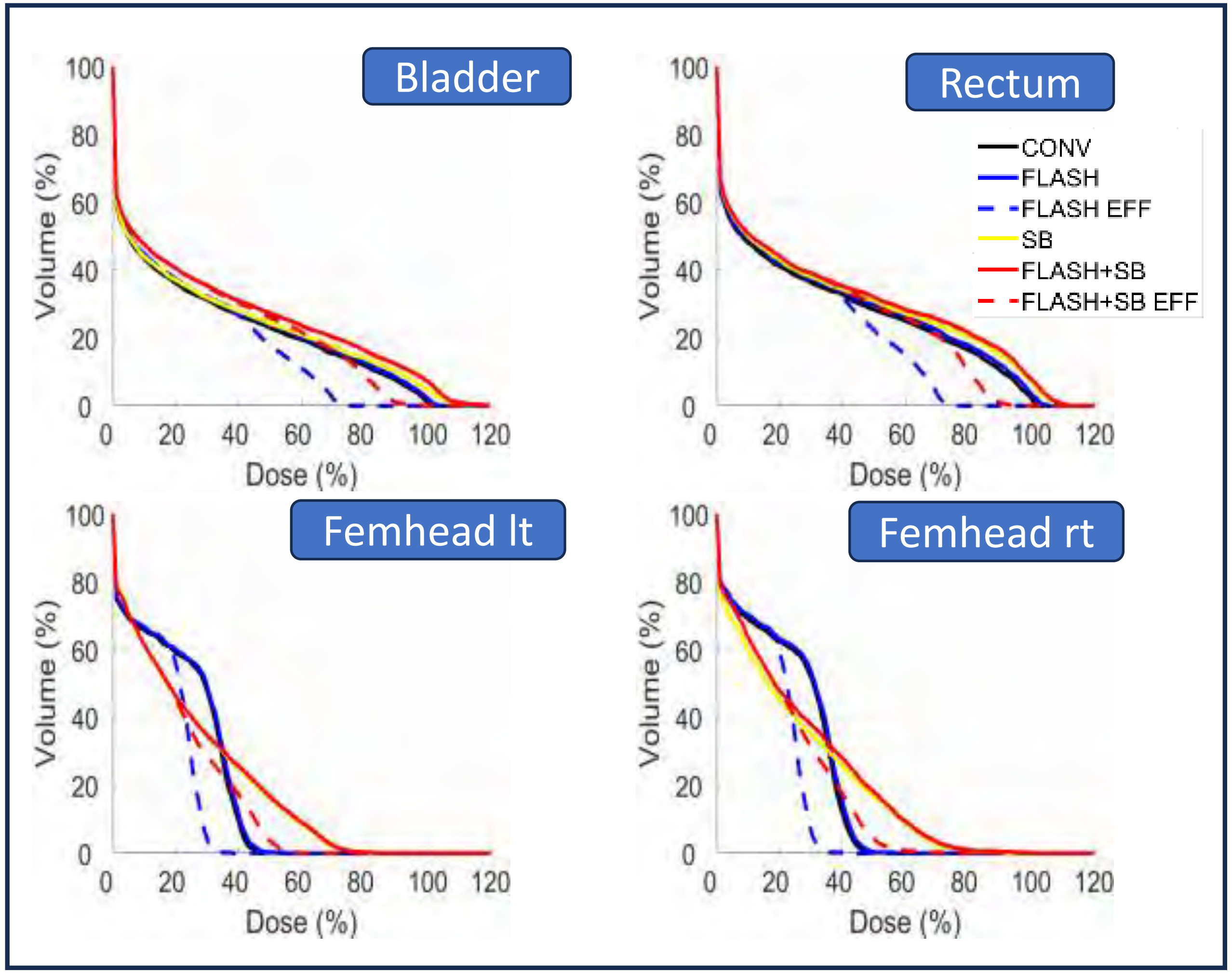


Prostate: GRID + FLASH



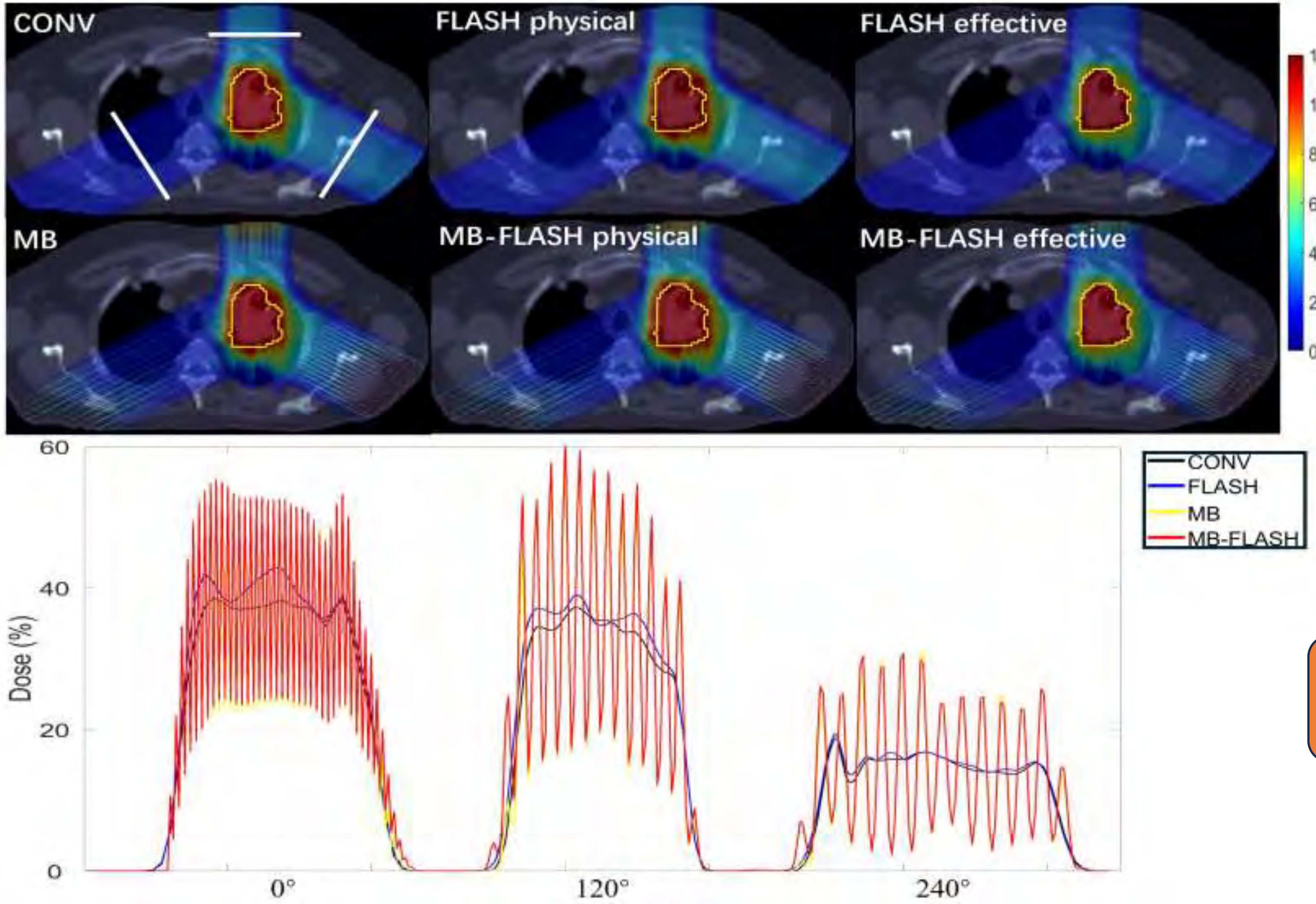
Spatially fractionated dose in shallow-to-intermediate depth

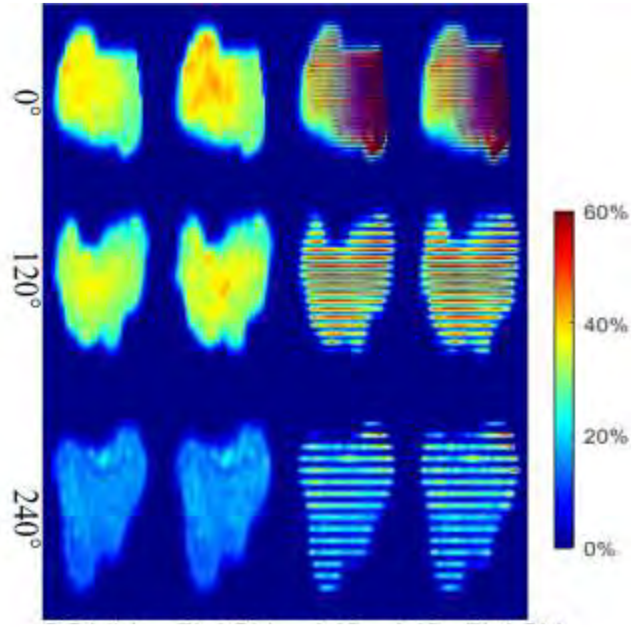
Prostate: GRID + FLASH



Reduce effective dose in OARs

Lung: Minibeam + FLASH





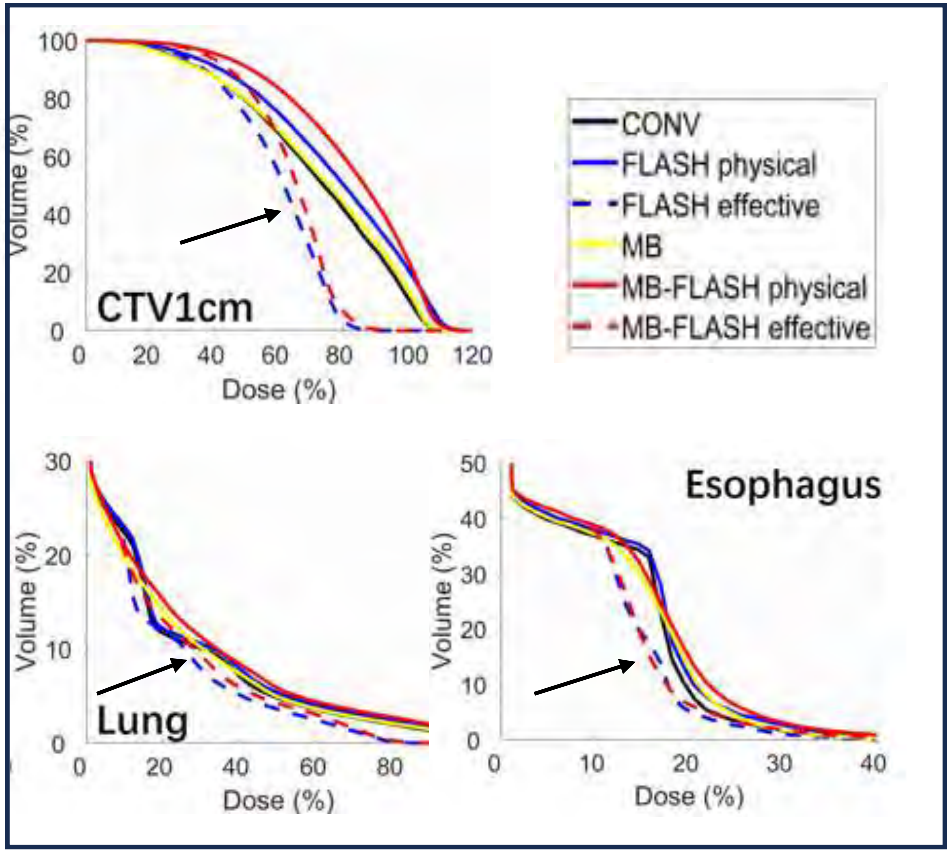
CONV FLASH MB MB-FLASH

Minibeam dose pattern in shallow-to-intermediate depth

Lung: Minibeam + FLASH

Structure	Quantity	CONV	FLASH (d/d-eff)	MB	MB-FLASH (d/d-eff)
CTV	CI	0.83	0.73/0.99	0.79	0.70/0.98
CTV1cm	V 80%	41.9	50.4/3.3	44.2	60.1/6.7
	D 5%	41.5	43.6/31.4	41.8	43.0/32.6
Spinal Cord	D 10%	19.5	20.8/16.2	19.8	21.9/17.8
	D mean (Gy)	3.2	3.4/2.7	3.2	3.6/2.9
Small Bowel	D 10%	7.8	8.2/7.0	8.4	8.8/7.0
	D mean (Gy)	2.9	3.1/2.6	3.0	3.2/2.7

	angle	CONV	FLASH (d/d-eff)	MB	MB-FLASH (d/d-eff)
PVDR	0°	1.3	1.4	2.2	2.2
	120°	1.1	1.2	3.3	6.1
	240°	1.1	1.1	3.4	6.1



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  - IBA
- Awards
  - 2021 PTCOG Michael Goitein Best Abstract Award in Physics
  - 2022 ASTRO Basic/Translational Science Award
  - 2023 PTCOG-NA The Best Abstract Award in Physics
  - 2023 ASTRO Basic/Translational Science Award
  - 2024 IBA ConformalFLASH Treatment Planning Contest Winner
- Research
  - Imaging (diagnostic, on-board)
  - Therapy (treatment planning, multi-modality RT)
  - Particle (proton, multi-ion)
  - Data (safety/quality, PRO)
  - Multidisciplinary (FLASH, SFRT)