Initial Experience with an Electron FLASH System

Kyuhak Oh, Ph.D and Su-Min Zhou, Ph.D

Department of Radiation Oncology

Disclosure

- Great Plains IDeA-CTR-Pilot Project Program
- University of Nebraska Collaboration Initiative Program.

Content

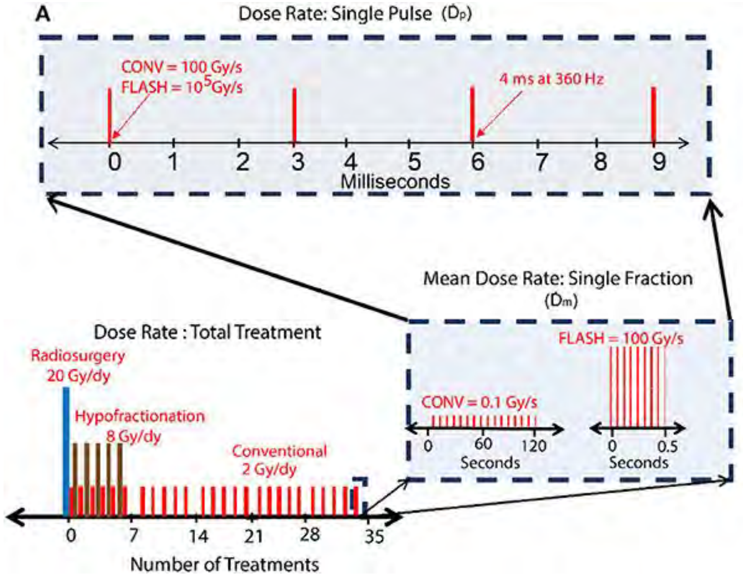
- What is the FLASH RT?
- eFLASH System Commissioning in Norfolk
- eFLASH Research at UNMC

What is the FLASH RT?

University of Nebraska Medical Center

Definition of FLASH Therapy

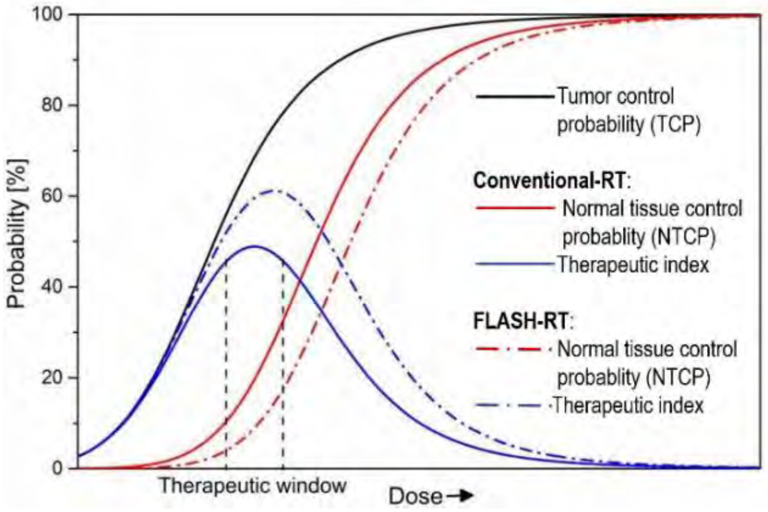
- Ultra-high dose rate radiation (>40 Gy/s) that is a thousand times faster than conventional dose rate radiation
- Reducing radiation induced normal tissue side effects
- While maintaining similar tumor control



B

Beam Characteristics	CONV	FLASH
Dose Per Pulse Dp	~0.4 mGy	~1 Gy
Dose Rate: Single Pulse Ḋp	~100 Gy/s	~10^5 Gy/s
Mean Dose Rate: Single Fraction Ḋm	~0.1 Gy/s	~ 100 Gy/s
Total Treatment Time T	~days/minutes	< 500 ms

Muhammad et al. (2020)



Moekli et al. (2022)

History of FLASH Radiation Therapy

1959
- FLASH effect was firstly reported by Dewey and Boag.

1966
- The reduction in normal tissue toxicity was demonstrated in mouse models by Hornsey and Alper.

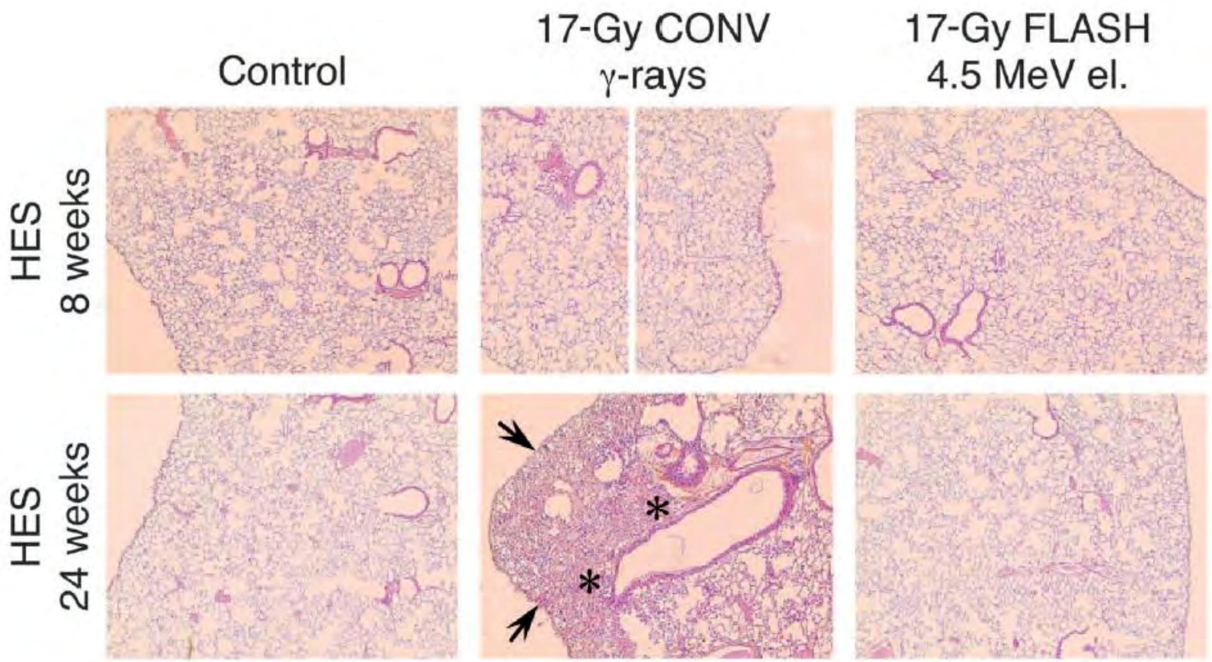
1971
- Hendry et al. demonstrated that hypoxia was induced by high dose rate electron beams.

2014
- Favaudon et al. revealed the differential response to high dose rates between normal and tumor tissue irradiated with FLASH RT.

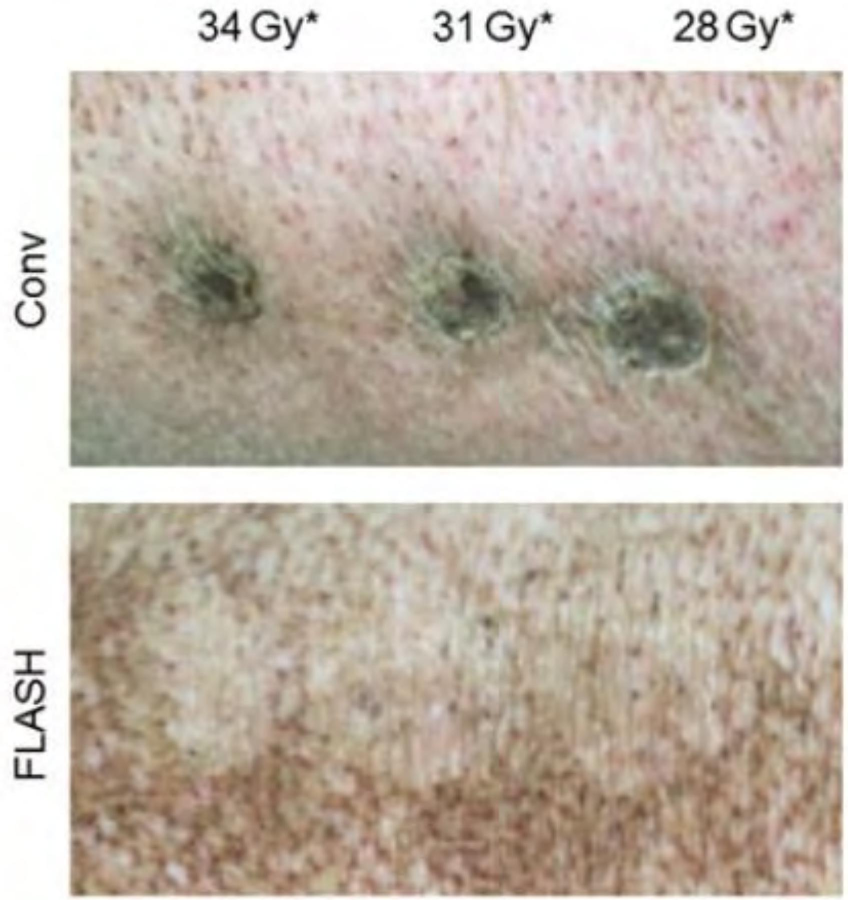
2018
- The first clinical implementation of electron FLASH radiotherapy was successfully conducted for the treatment of a patient with a skin lesion of recurrent cutaneous lymphoma.

2022
- Mascia *et al.*[10] reported the initial results from the first clinical trial, i.e., FAST-01, and have demonstrated the safe use of proton FLASH radiotherapy for the palliation of patients with bone metastasis.

FLASH Effect



Vozenin et al. (2019)



Favaudeon et al. (2014)

Pre-clinical and Clinical Evidence

System	Author	Year	Irradiation		Modality of radiation	models		Endpoint(s)	Main findings*	
			FLASH-RT	CONV-RT		Tumor	Normal tissue		Tumor	Normal tissue
Brain	Montay-Gruel P (26)	2020	12.5×103 -5.6×106 Gy/s	0.1Gy/s	electron	mice (glioblastoma)	–	tumor growth;cognitive function	similar antitumor effect	protective effect
	Montay-Gruel P (23)	2019	>100 Gy/s	0.07-0.1 Gy/s	electron	–	mice	cognitive function;ROS, neuronal structure, synaptic protein, neuroinflammation	–	fully preserved
	Simmons DA (24)	2019	200, 300Gy/s	0.13 Gy/s	electron	–	mice	cognitive function, neurodegeneration, neuroinflammation	–	protective effect
	Montay-Gruel P (21)	2018	37 Gy/s	0.05 Gy/s	X-ray	–	mice	cognitive function, Cell proliferation, GFAP	–	protective effect
	Montay-Gruel P (20)	2016	0.1,1, 3, 10, 30, 100,500 Gy/s, 5.6 MGy/s		electron	–	mice	cognitive function	–	protective effect above 30 Gy/s, fully preserved above 100 Gy/s
Intestine	Venkatesulu BP (28)	2019	35Gy/s	0.1 Gy/s	electron	–	mice	toxicity, survival	–	No protection effect
	Billy W. Loo (9)	2017	210 Gy/s	0.05 Gy/s	electron	–	mice	survival	–	protective effect
Lung	Fouillade C (29)	2020	40–60GY/S	?	electron	–	mice	cell proliferation, DNA damage, inflammatory genes		protective effect
	Buonanno M (22)	2018	0.025 Gy/s - 1500 Gy/s		proton	–	human lung fibroblasts	cell survival, b-gal, TGFb		protective effect
	Favaudona V (30)	2015	>40 Gy/s,	< 0.03Gy/s	electron	mice(lung tumor)	mice	tumor growth, apoptosis, lung fibrosis	similar antitumor effect	protective effect
	Favaudon V (19)	2014	≥40 Gy/s	< 0.03Gy/s	electron	mice(lung tumor)	mice	tumor growth, early and late complications	similar antitumor effect	protective effect
Skin	Bourhis J (10)	2019	166.7Gy/s	–	electron	patient (lymphoma)	–	tumor response; Soft tissue toxicity	complete response	grade 1 epithelitis, grade 1 oedema
	Vozenin MC (27)	2018	300 Gy/s	0.083 Gy/s	electron	cat (squamous carcinoma	pig	skin toxicity, PFS	PFS at 16 months was 84%	protective effect
Blood	Chabi S (25)	2020	200Gy/S	<0.072 Gy/S	electron	mice (leukemia)	mice	tumor growth, normal hematopoiesis	similar antitumor effect	protective effect
Other	Adrian G (31)	2020	600 Gy/s	0.233 Gy/s	electron	prostate cancer cells	–	survival	flash effect depends on oxygen concentration	
	Beyreuther E (32)	2019	100 Gy/s	0.083 Gy/s	proton	–	zebrafish embryo	survival	–	Similar toxicity except for pericardial edema at one dose point(23Gy)

*FLASH-RT, FLASH radiotherapy; CONV-RT, conventional dose-rate radiotherapy; *Effects of FLASH-RT compared with CONV-RT.*

Lin et al. (2021)

- FLASH increased normal tissue sparing compared to conventional dose rate
- Better tissue sparing with increasing dose rates
- Tumor control was the same or better with Flash compared to conventional dose rate

eFLASH System Commissioning

University of Nebraska Medical Center

Currently Used eFLASH system

Machine	Energy	Beam Output	Location	Reference
Oriatron eRT6	6 MeV	~200 Gy/s	100 cm SSD	Jaccard et al. (2017)
Elekta Precise	8 MeV	~1000 Gy/s	Wedge position (19 cm from target reference)	Lempart et al. (2019)
Varian Clinac 21EX	20 MeV	~900 Gy/s	Ion chamber position	Schuler et al. (2017)
Varian Clinac 2100 C/D	10 MeV	310 Gy/s	isocenter	Rahman et al. (2021)
Experimental LINAC	200 MeV	117 Gy/s	Not given	McManus et al. (2020)
Research LINAC	7 or 9 MeV	>1000 Gy/s	Not given	Gomez et al. (2022)
IORT NOVAC11	5 or 7 MeV	~4000 Gy/s	Not given	Di Martino et al. (2020)
IntraOp Mobetron	6 or 9 MeV	>800 Gy/s	17.3 cm SSD	Moeckli et al. (2021)
IORT NOVAC7	7 MeV	~540 Gy/s	1.6 cm SSD	Felici et al. (2020)
Eleckta Synergy	6 MeV	~633 Gy/s	13 to 15 cm SSD	Xie et al. (2022)
Varian Clinac iX	9 or 16 MeV	~20000 Gy/s	Internal monitor chamber	Szpala et al. (2021)
Varian Clinac 21EX	16 MeV	~2650 Gy/s	Monitor ion chamber	Poirier et al. (2021)
Kinetron LINAC	4.5 MeV	60 Gy/s	Not given	Favaudon et al. (2014)

- Several research laboratories have modified linear accelerators to produce ultra-high dose rates to study the FLASH effect.
- However, these custom linacs are scarce and resource intensive.
- Each FLASH machine has different energy level up to 200 MeV and different instantaneous dose rate up to 20000 Gy/s.

Unique Collaboration Structure

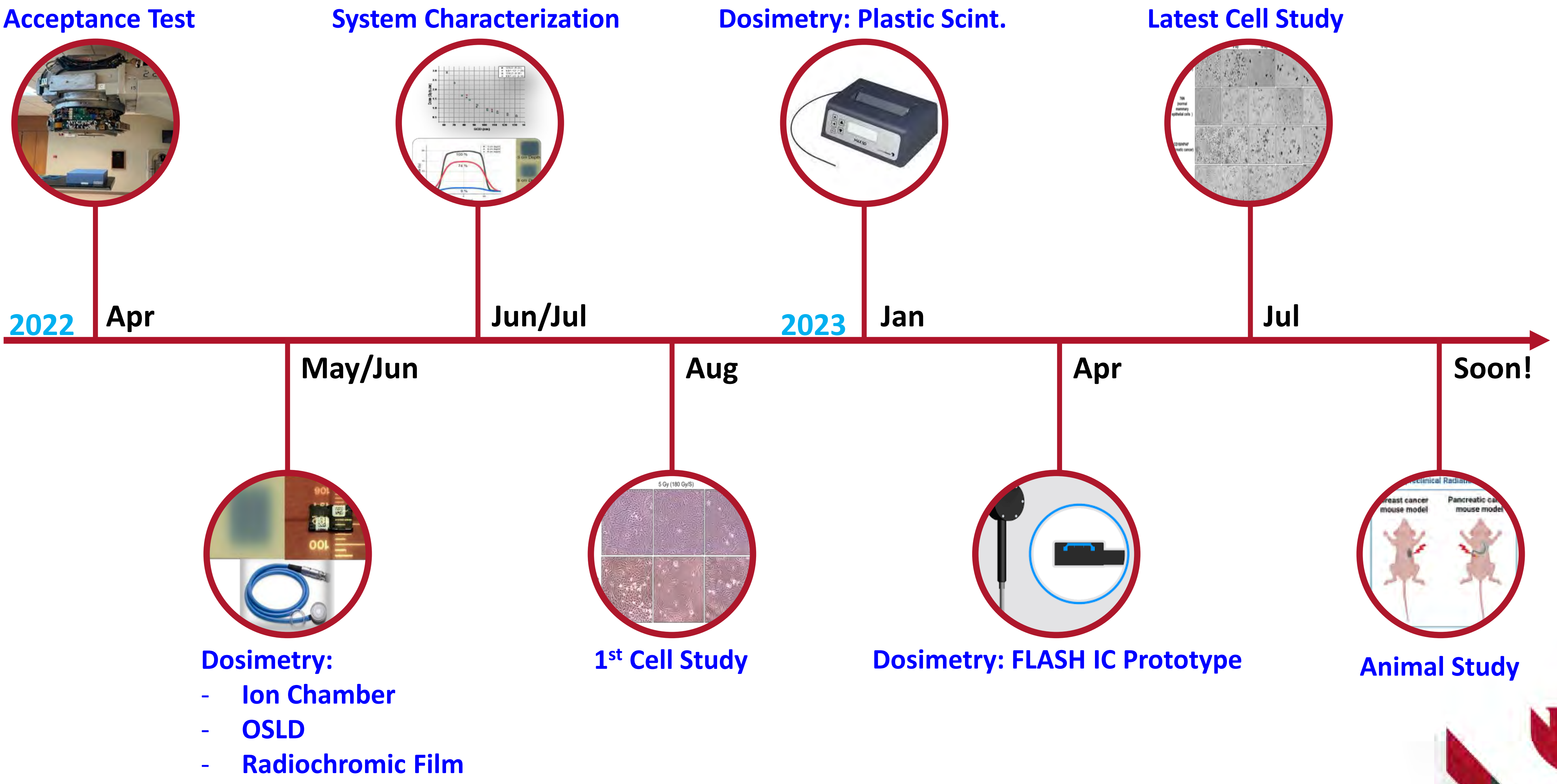
UNMC

VARIAN medical systems

FAITH REGIONAL HEALTH SERVICES

- The FLEX system is located in Norfolk, NE. about two hours (~113 miles) away from our main campus.

Timeline of UNMC eFLASH Project



Installation for 1st Clinac-FLEX machine

Dose Rate > 180 Gy/s at isocenter
under a 10x10 cm^2 board beam condition

Maximum Dose Rate > 680 Gy/s at gantry head
under a 10x10 cm^2 board beam condition

*** FLEX: FLASH Research Extension**

Radiation Safety for eFLASH Facility

Survey Process

Gantry = 0°, No Scatter

Dose Point	Dose Rate
Vault Door	30 cm = 1.0 mR/hr
Console	Highest = 1.2 mR/hr

Gantry = 270°, No Scatter

Dose Point	Dose Rate
Vault Door	30 cm = 3.6 mR/hr
Console	Highest = 6 mR/hr
West Wall (Outside)	Highest = 50 mR/hr

Gantry = 90°, No Scatter & Scatter

Dose Point	Dose Rate, No Scatter	Dose Rate, Scatter
Vault Door	30 cm = 1 mR/hr	30 cm = 0.5 mR/hr
Console	Highest = 3.2 mR/hr	Bkg all areas
Block Room Hallway Outside Block Room	30 cm @ Wall = 150 mR/hr Hallway Outside Room; 38 mR/hr	30 cm @ Wall = 34 mR/hr

Gantry = 180°, No Scatter

Dose Point	Jaws Open (Photon)
Vault Door	30 cm = 0.4 – 0.6 mR/hr
Console	Highest = 2.4 mR/hr
Block Room (East)	Highest = 1.4 mR/hr
Break Room (South)	Bkg
Outside (West)	Highest = 0.6 mR/hr
North Wall of Vault	Bkg
Supply Room (Above Vault)	Floor = 30 mR/hr 3 ft Above Floor = 16 mR/hr

Safety Report

No.	Stage	Description	Check	Note
1	Set-up	Turn on all monitors		
2		Turn on OBI and 4DCT systems		
3		Turn on power key switch • Horizontal: On / Vertical: Off		
4		Turn on the Angle R and T servos for conventional beam delivery • Toggle switches to the right side		
5		Make gantry angle 0 degree and collimator 0 degree		
6		Turn on the MLC and park the MLC		
7		Enter service mode		
8		Set beam parameters - Mode: Fixed - Treatment Mode: New Treatment - Beam Energy: 6, 9, 12, or 16 MeV ** 20 MeV is only for FLASH mode* - Repetition Rate: 1000 MU/Min - Monitor Units: 500 - Time: 1.0 - Applicator: 10 × 10 Applicator		
9	Conversion to FLASH mode	Turn off the Angle R and T servos for FLASH beam delivery • Toggle switches to the left side		
10		Set beam parameters - Mode: Fixed - Treatment Mode: New Treatment - Beam Energy: 20 MeV - Repetition Rate: 1000 MU/Min - Monitor Units: 150 - Time: 1.0 - Applicator: 10 × 10 Applicator		
11		Override interlocks - DS12, XDP1, XDP2, XDRS, XDR1, XDR2, EXQ1, EXQ2, EXQT, UDRS, UDR1, UDR2, ACC		
12		Set the number of pulses on the Varian beam pulse counter		
13	Daily QA / Dosimetry Measurement / Cell Experiment	Check the number of pulses		
14		Check the repetition rate		
15		Check the SSD		
16		Check the field size		
17		Check the build-up		

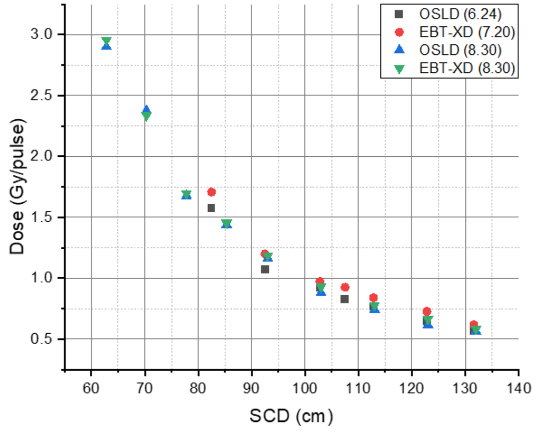
Check List

eFLASH Research at UNMC

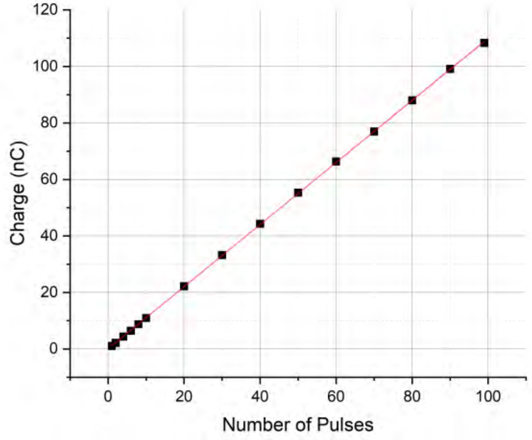
University of Nebraska Medical Center

System Characterization

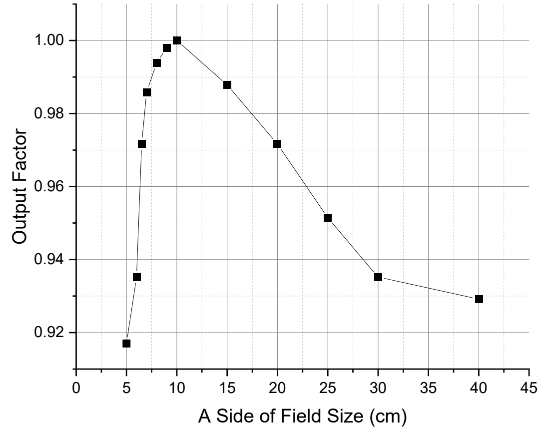
Dose Vs. SCD



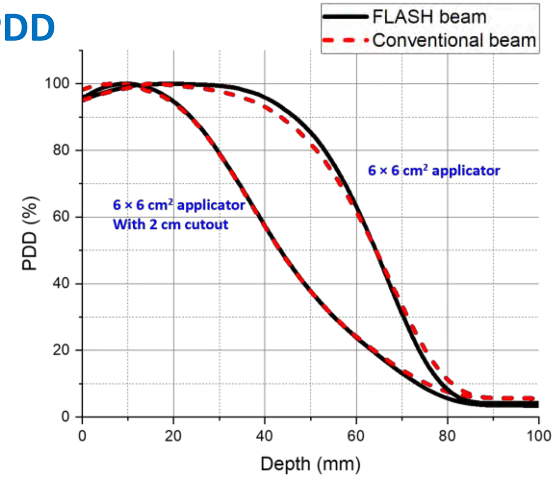
Linearity



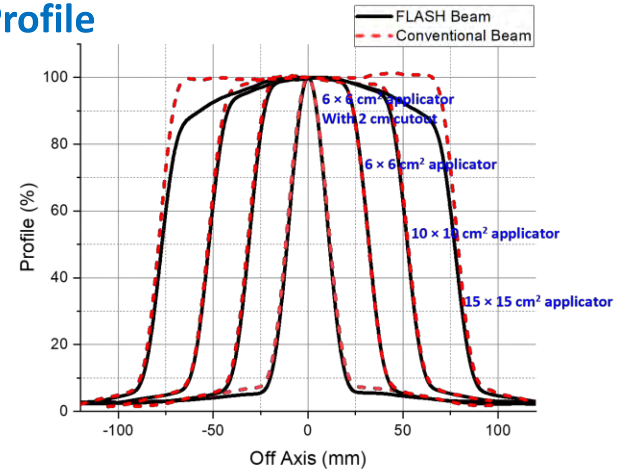
Output Factor Vs. Field Size



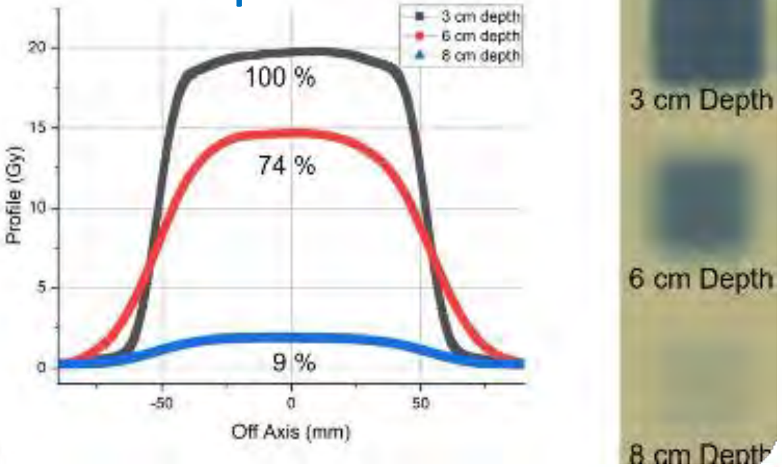
PDD



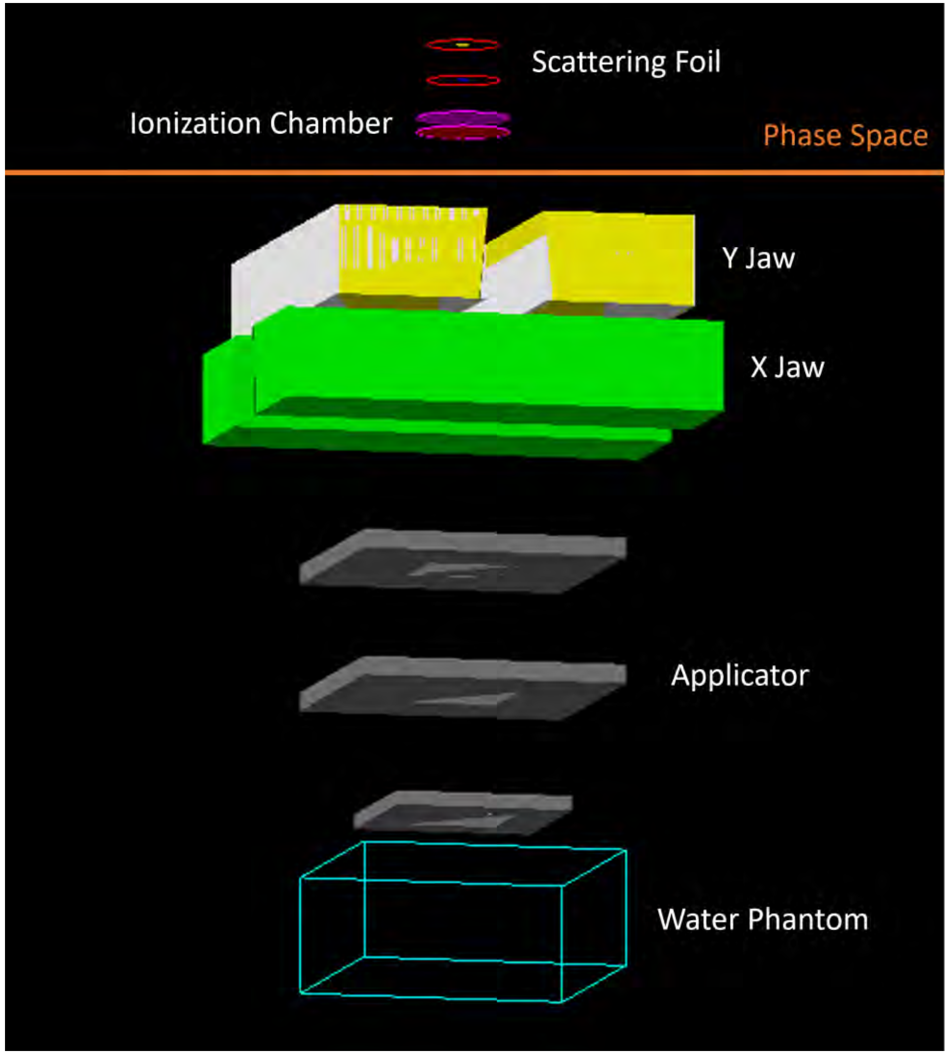
Profile



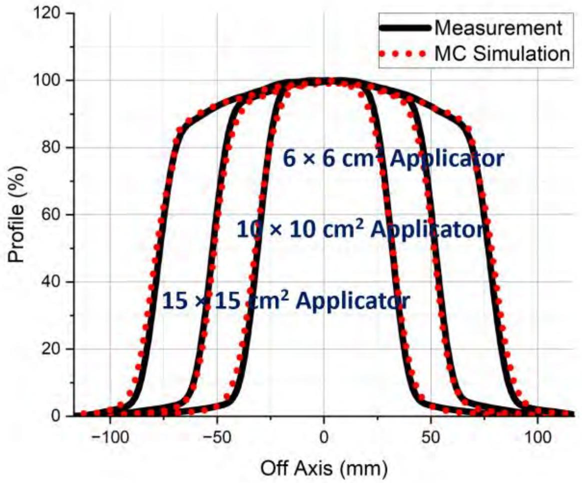
Profile Vs. Depth



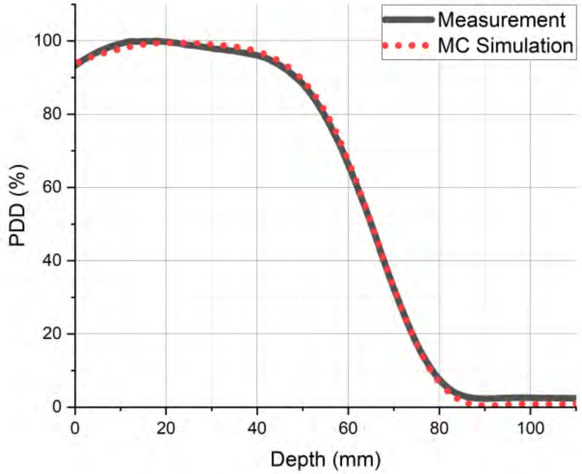
Monte Carlo Simulation



Profiles

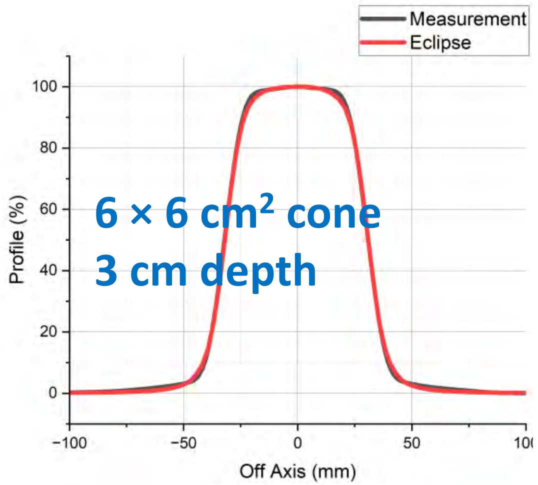


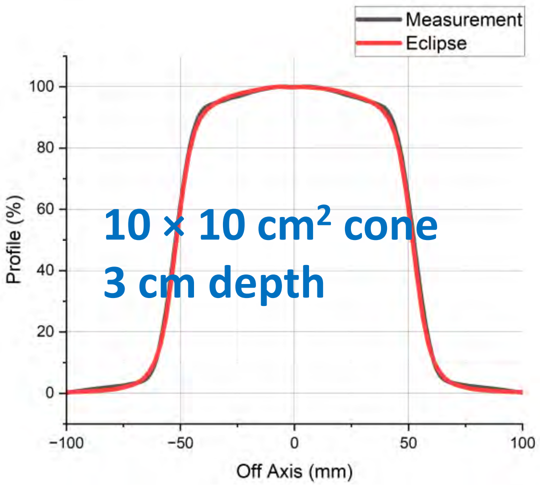
PDDs

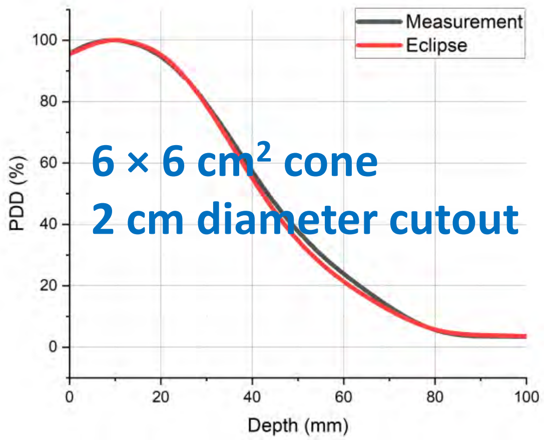


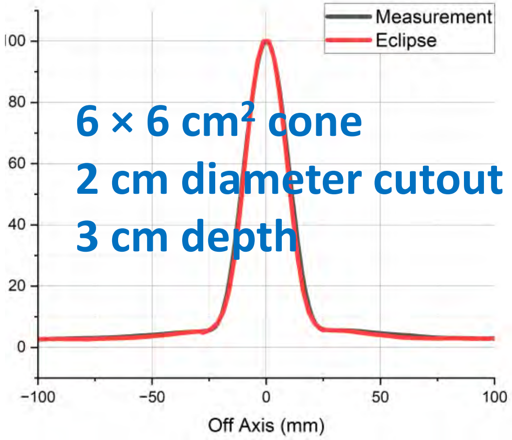
Applicator Size	R_{50} (cm)	
	Measurement	Monte Carlo Simulation
6 × 6 cm²	6.43	6.46
10 × 10 cm²	6.49	6.51
15 × 15 cm²	6.55	6.54

eMC Commissioning in Commercial TPS



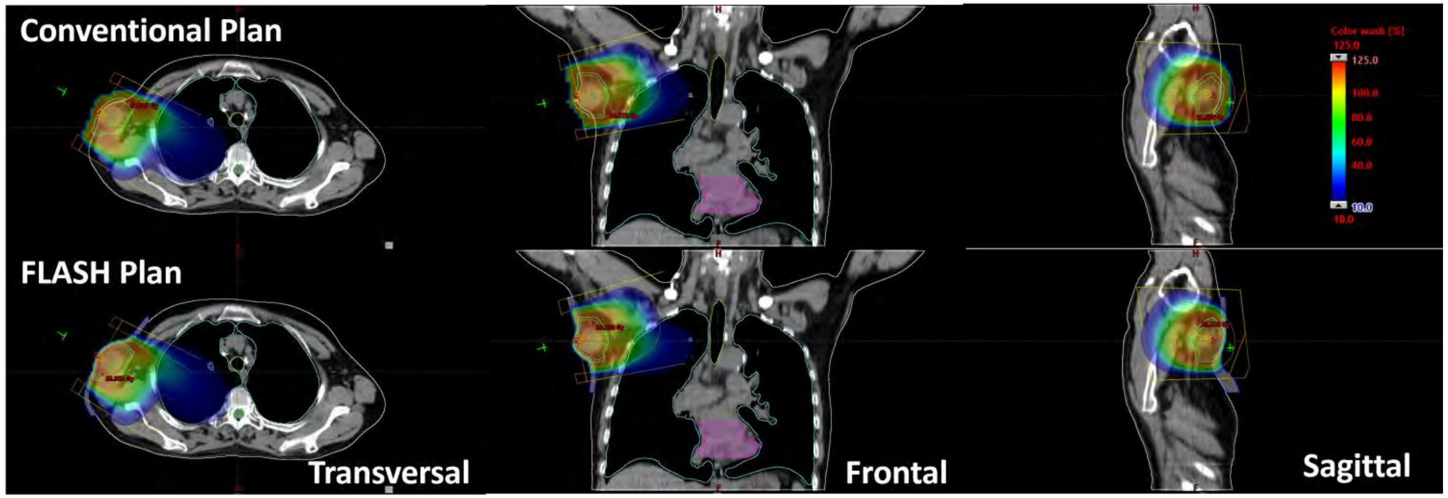


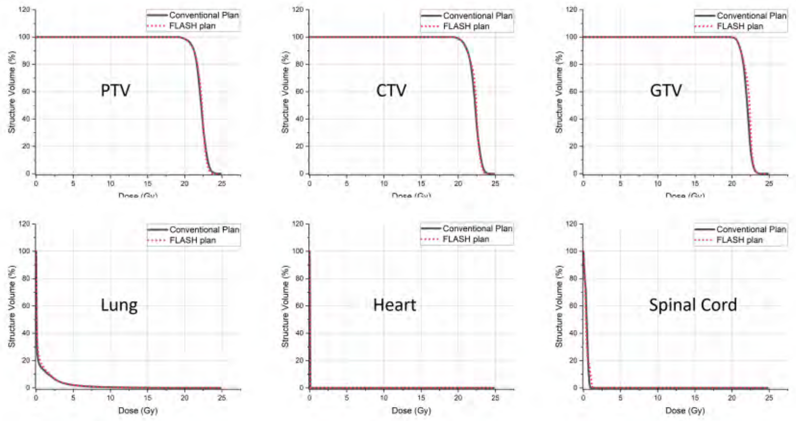




Applicator Size	**6 × 6 cm²**				**10 × 10 cm²**			
Method	eMC		Measurement		eMC		Measurement	
Depth (cm)	1	3	1	3	1	3	1	3
FWHM (cm)	6.1	6.3	6.1	6.3	10.2	10.4	10.2	10.4
Flatness (%)	3.0	9.6	3.1	9.2	3.2	5.5	3.3	4.9
Symmetry (%)	1.0	1.9	0.4	1.9	0.6	0.0	-0.2	-0.3
Penumbra (mm)	6.3	11.2	6.1	11.1	7.2	12.0	7.5	12.0

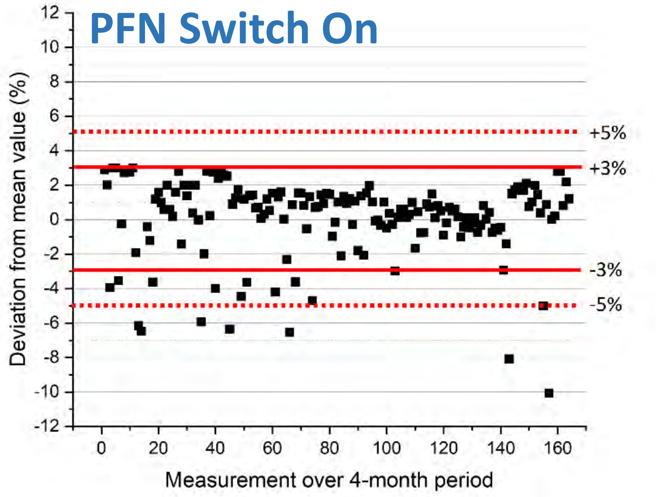
Treatment Planning Study

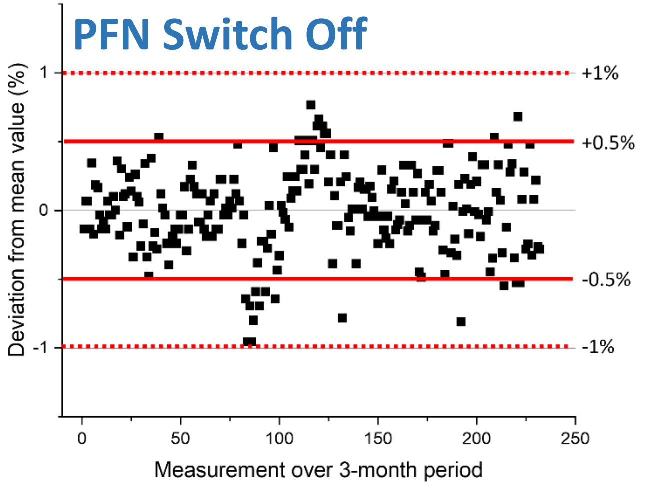


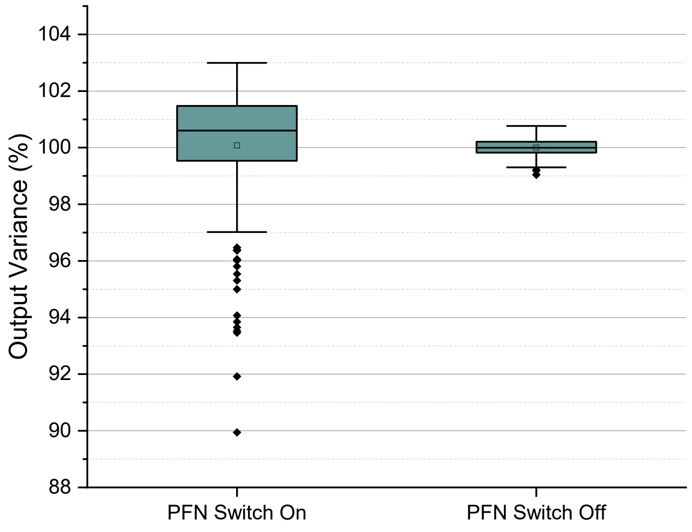


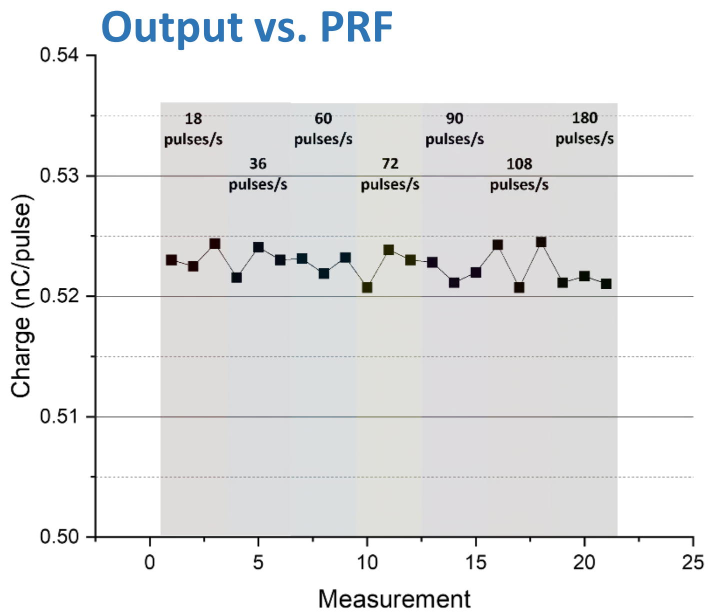
	Structure	Constraint	Conventional Plan	FLASH Plan
Target	GTV	$V_{95\%}$	100 %	100%
	CTV	$V_{85\%}$	100 %	100 %
OAR	Spinal cord	$D_{max} < 45$ Gy	1.1 Gy	1.4 Gy
	Lung	$V_{20Gy} <= 30\%$	0 %	0 %
	Heart	$V_{25Gy} <= 10\%$	0 %	0 %
		$V_{30Gy} <= 46\%$	0 %	0 %
		$D_{mean} < 26$ Gy	0.01 Gy	0.02 Gy

Stability Test

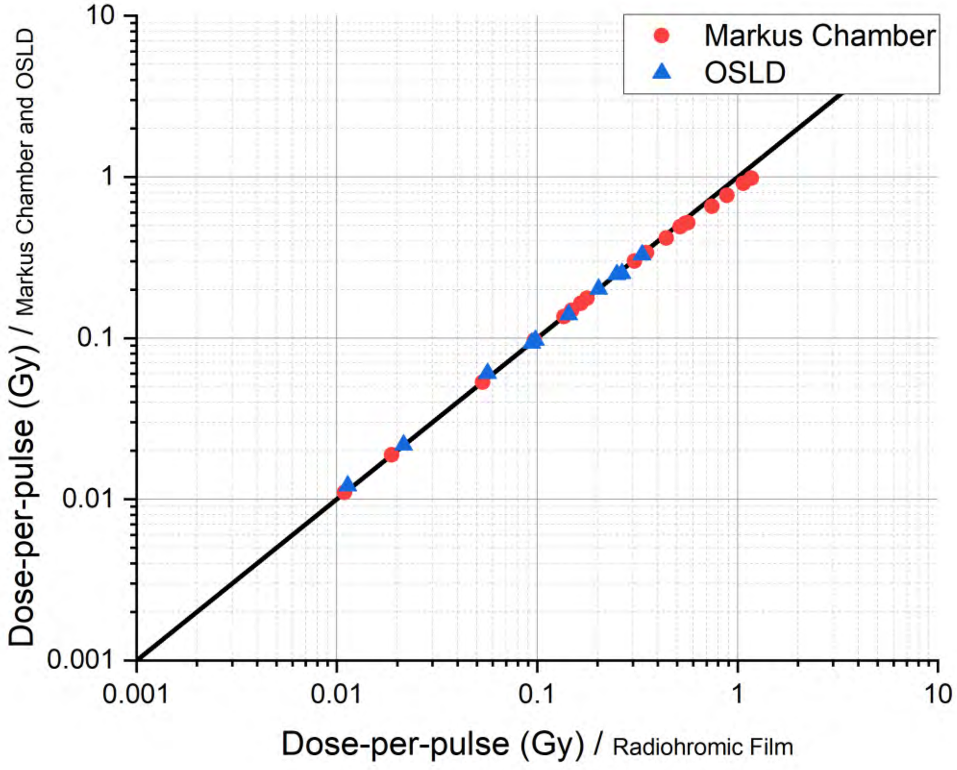






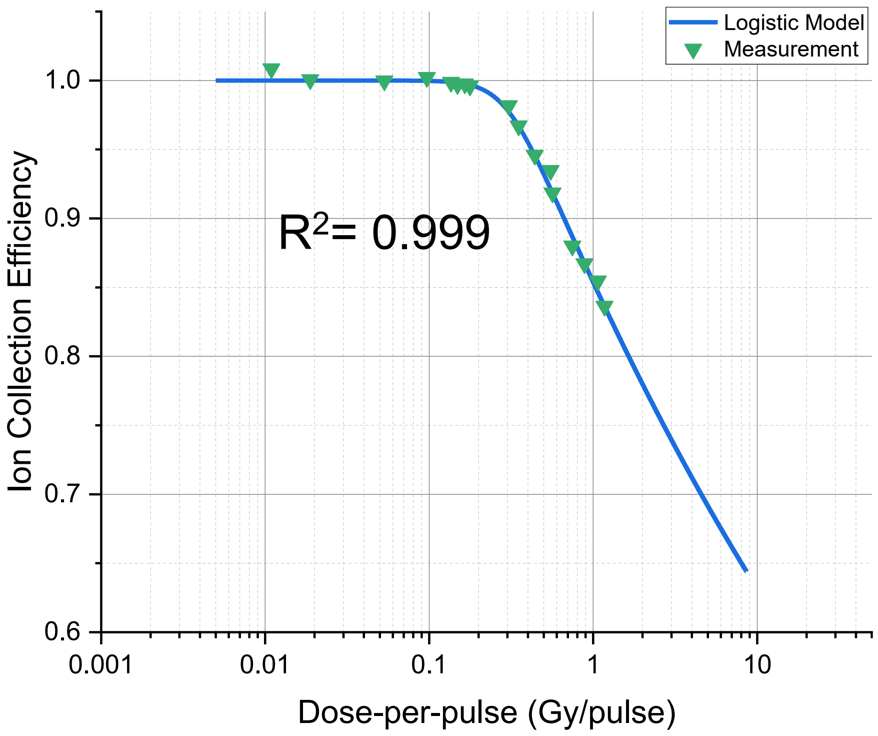


Ionization Chamber Recombination



Cross-calibration of the radiochromic film against parallel-plane chamber or OSLD

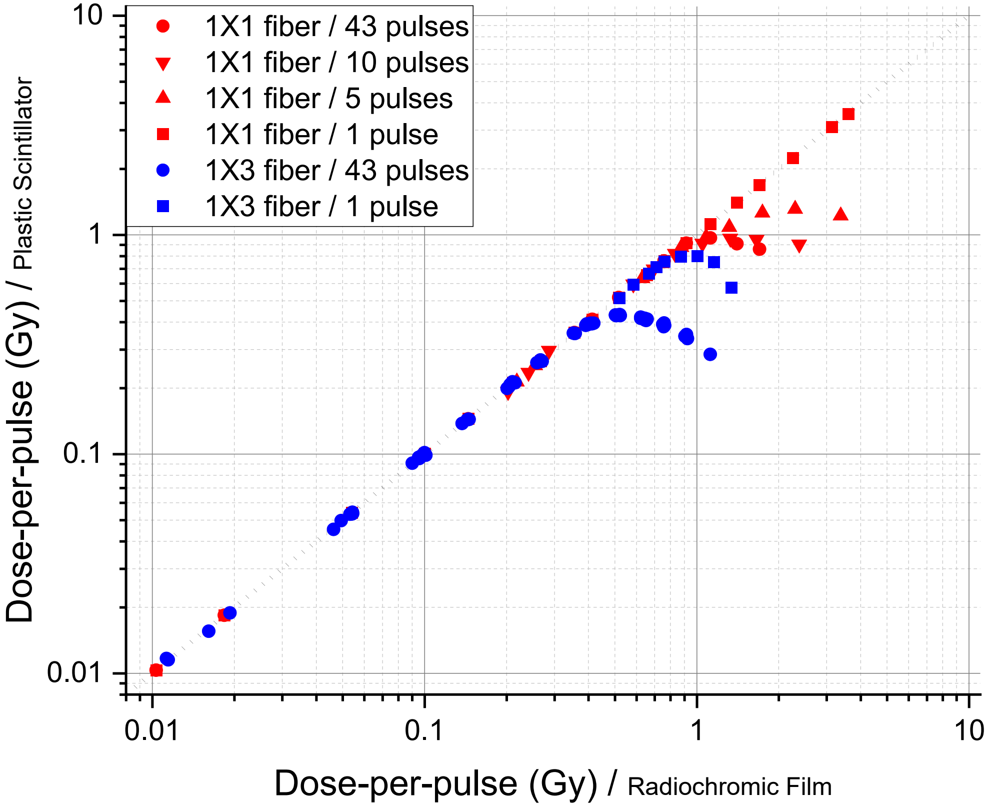
Ion collection efficiency for the plane-parallel chamber as a function of dose rate



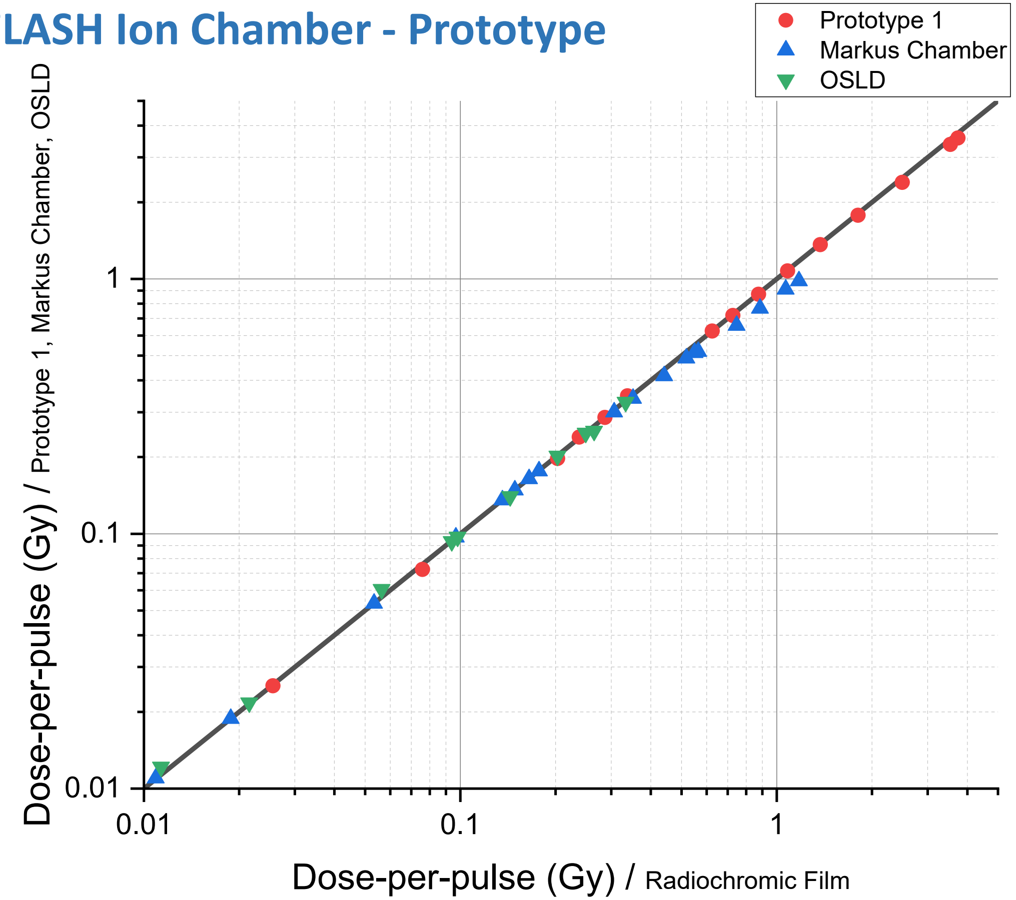
Logistic Model: Petersson et al. (2017)

Other Dosimetry Systems

Plastic Scintillator – W2



FLASH Ion Chamber - Prototype



Limitation / Future Work

Limitation	Future Work
• Coarse adjustment of the selected delivering dose set by the beam pulse counter (the number of pulses) • No accurate real-time monitoring	• Dosimetry system development under the eFLASH environment • eFLASH irradiation of small animal using the FLEX machine (Mice)

Conclusion

- The University of Nebraska Medical Center (UNMC), Faith Regional Health Services, and Varian collaborated to implement Varian's FLEX conversion for eFLASH research.
- This system is capable of delivering the ultra-high dose rate electron beam that is much faster than conventional dose rate beam.
- Dosimetric characteristics of the 16 MeV eFLASH and conventional electron beams were similar for all applicators and field sizes evaluated in this study except for the profiles because of the difference in the scattering foil designs.
- Clinac-FLEX system has the potential to significantly increase the access to ultra-high dose rate capabilities for scientists and clinicians and further promote multi-institutional research on the FLASH effect.

Acknowledgements

UNMC Medical Physic Group

Su-Min Zhou, Ph.D (PI)

Kyuhak Oh, Ph.D

Kyle Gallagher, Ph.D

Megan Hyun, Ph.D

Diane Schott, Ph.D

Yu Lei, Ph.D

Shuo Wang, Ph.D

Ellie Bacon, M.S

Sumudu Katugampola, Ph.D

UNMC Biology Group

Ying Yan, Ph.D (PI)

Brendan Graff

Christopher Jenkins

Radiation Safety

Frank Rutar, MS

VARIAN medical systems

Varian Service Engineer

Schmidt, Marty

UNMC

FAITH REGIONAL HEALTH SERVICES

Under the leadership of Dr. Charles Enke

Thank You!

HDR © 2017 Dan Schwalm

University of Nebraska Medical Center