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FLASH Experiments in Canada

Tania Karan
Medical Physicist
BC Cancer - Vancouver

Nothing to disclose

Some of what will be presented here is in 2 manuscripts pending publication

History of Dose rate effects

1990s

THE DOSE-RATE EFFECT REVISITED: RADIOBIOLOGICAL CONSIDERATIONS OF IMPORTANCE IN RADIOTHERAPY

ERIC J. HALL, D.SC. AND DAVID J. BRENNER, PH.D.

2000s

Dose-rate effects in external beam radiotherapy redux

C. Clifton Ling [a,b,*,1], Leo E. Gerweck [c,**], Marco Zaider [b], Ellen Yorke [b]

[a] Varian Medical Systems, Palo Alto, CA, USA; [b] Department of Medical Physics, Memorial Hospital, New York, NY, USA; [c] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

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2010s

FLASH

Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a Clinical Linear Accelerator

Emil Schüler, PhD,* Stefania Trovati, PhD,* Gregory King, PhD,* Frederick Lartey, PhD,* Marjan Rafat, PhD,* Manuel Villegas,* A. Joe Praxel,* Billy W. Loo, Jr, MD, PhD,*,† and Peter G. Maxim, PhD*,†

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2]* Laura Caplier,[3]† Virginie Monceau,[4,5]‡ Frédéric Pouzoulet,[1,2]§ Mano Sayarath,[1,2]¶ Charles Fouillade,[1,2] Marie-France Poupon,[1,2]‖ Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]

PHASER: A platform for clinical translation of FLASH cancer radiotherapy

Peter G. Maxim [a,**], Sami G. Tantawi [b,**], Billy W. Loo Jr. [c,d,*]

Modifying a clinical linear accelerator for delivery of ultra-high dose rate irradiation

Michael Lempart [a], Börje Blad [a], Gabriel Adrian [b], Sven Bäck [a,c], Tommy Knöös [a,c], Crister Ceberg [c], Kristoffer Petersson [a,*]

Ultra high dose rate Synchrotron Microbeam Radiation Therapy. Preclinical evidence in view of a clinical transfer

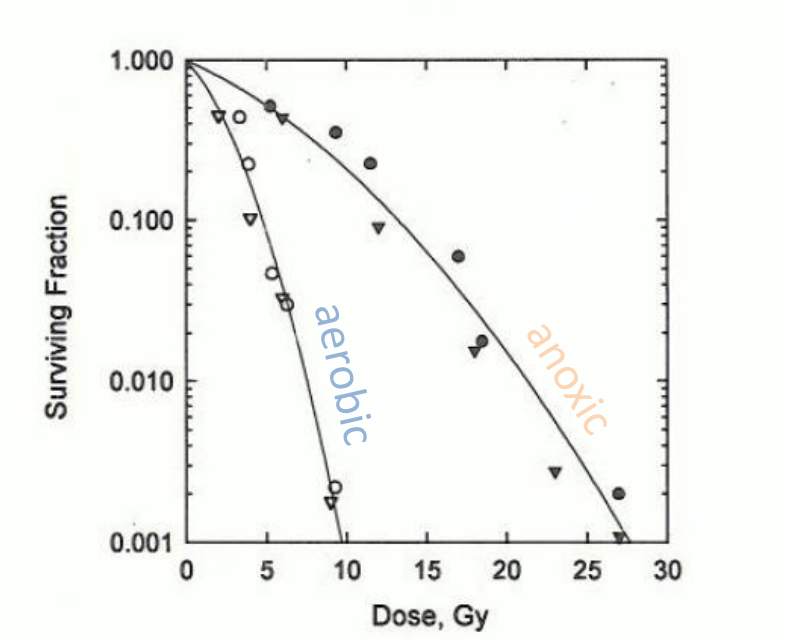
Laura Eling [a], Audrey Bouchet [a], Christian Nemoz [b], Valentin Djonov [c], Jacques Balosso [d], Jean Laissue [e], Elke Bräuer-Krisch [b], Jean Francois Adam [a], Raphael Serduc [a,*]

1990s

In vitro melanoma, glioma cells

Standard: ~0.025 Gy/s on ^{60}Co

20 MeV electrons – linear accelerator
Pulse duration = 3.2 µs
Each dose given in single pulse
High DR: **$5.7 \times 10^5 - 10^7$ Gy/s**



The Survival of Aerobic and Anoxic Human Glioma and Melanoma Cells after Irradiation at Ultrahigh and Clinical Dose Rates

Joanna Cygler,* Norman V. Klassen,† Carl K. Ross,† Tewfik J. Bichay* and G. Peter Raaphorst*

*Ottawa Regional Cancer Centre, Civic Division, Ottawa, Ontario K1Y 4K7, Canada; and †Institute for National Measurement Standards, Ionizing Radiation Standards Group, National Research Council of Canada, Ottawa, Ontario K1A 0R6, Canada

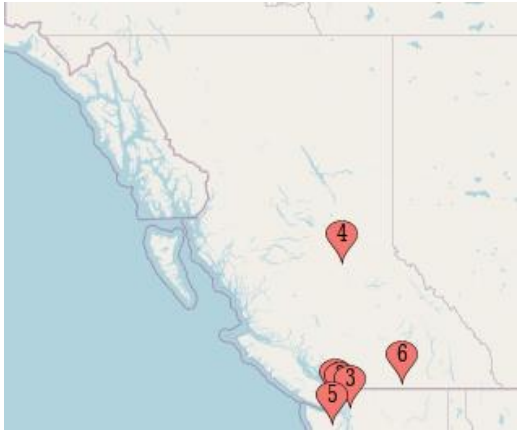
British Columbia: Machines / Dosimetry

Unique provincial multi-centre approach

BC Cancer: 6 centres, 32 linacs

In any given year, chances are one is being decommissioned

In 2019, in the months of July, October and December experiments were carried out in Vancouver, Fraser Valley and Abbotsford centres respectively on machines just prior to their decommissioning



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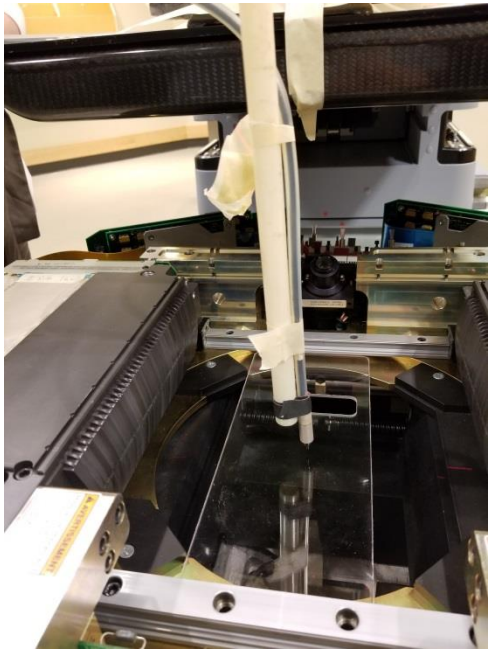
Experimental setup for Varian iX linear accelerator

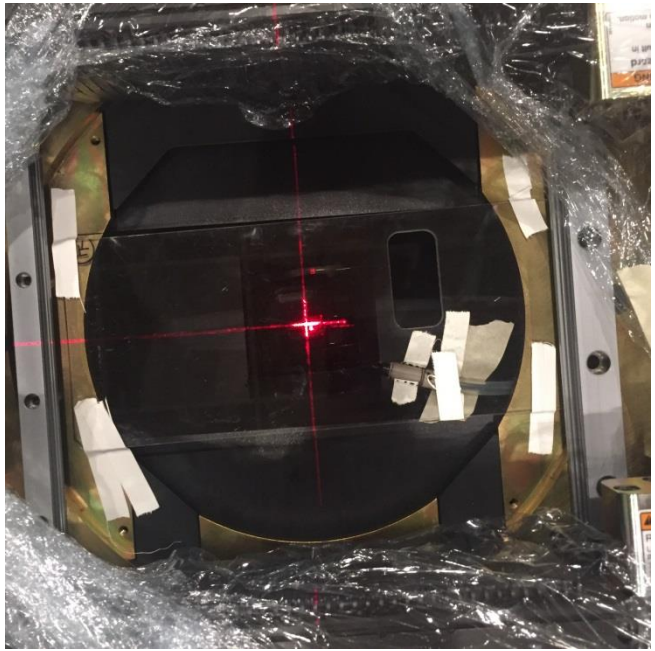
1. Photon beam tuned for maximum dose rate

2. Pneumatic switch system modified to prevent target from moving into path

3. Carousel rotated so electron foil in place in lieu of FF

4. Inverse square law leveraged by reducing SSD





40x40 field, gantry 180°, dose, PFN, steering servos OFF

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Several iterations of experiments:

Vancouver	Fraser Valley	Abbotsford
operating with 10MV parameters, with a 9MeV foil	operating with 18MV parameters, with 9 and 16MeV foils	operating with 15MV parameters, with a 9MeV foil
Arduino timer based delivery	MU-based delivery	Pulse counting based delivery

Experiments repeated multiple times at each centre
Dosimetry with ion chamber, film and OSLDs
Point of measurement 47-49cm SSD
Resultant dose rates were ~300 Gy/s

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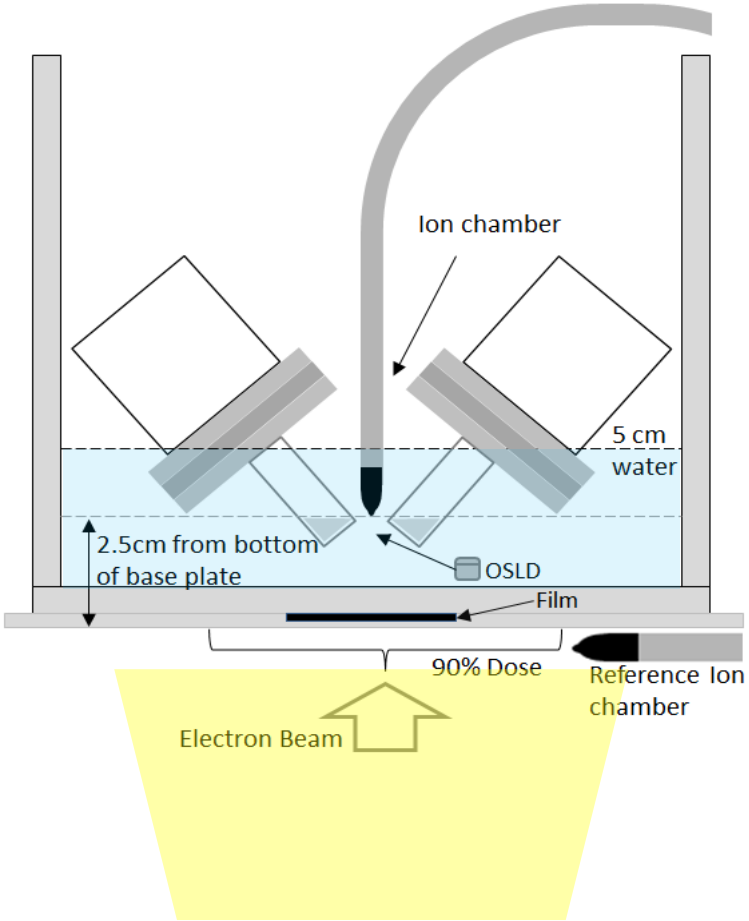
IC: calibrated at standard conditions, relied on cross-calibration with passive dosimeters

Experiments repeated with matched electron energies:

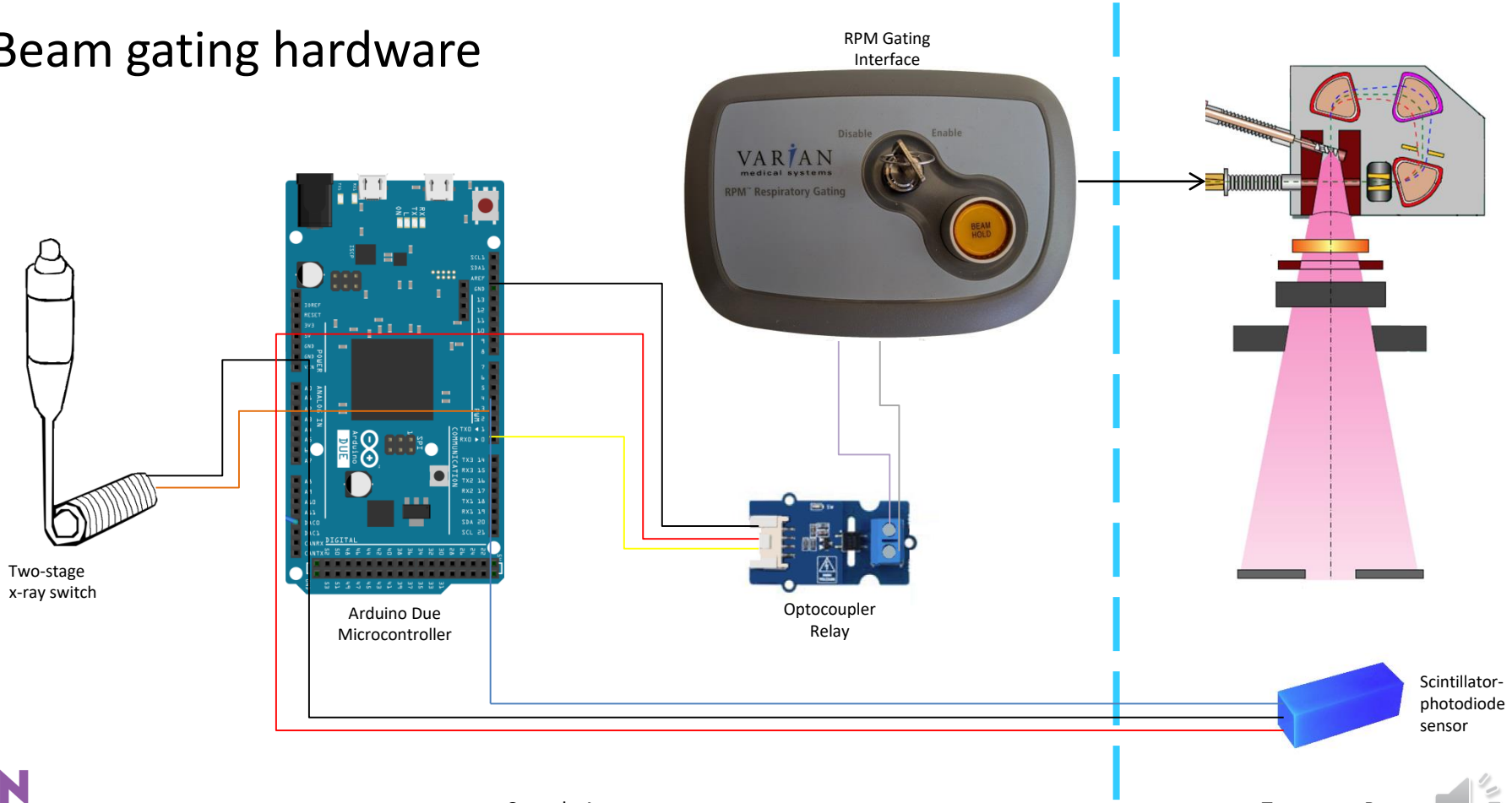
100cm SSD

600MU/min

standard linac settings



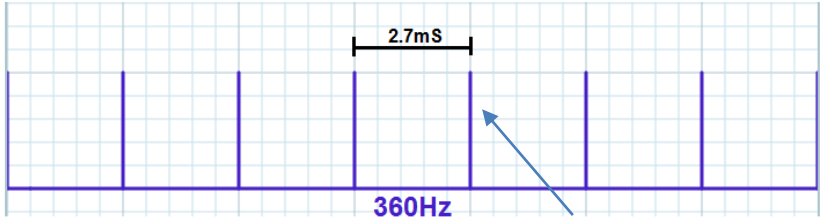
Beam gating hardware



Varian iX Clinac has two pulse repetition frequencies (PRF):

360Hz

Used only in low photons (6MV and 10MV) due to the limitations of the waveguide



180Hz

All other energies

5 µs/pulse

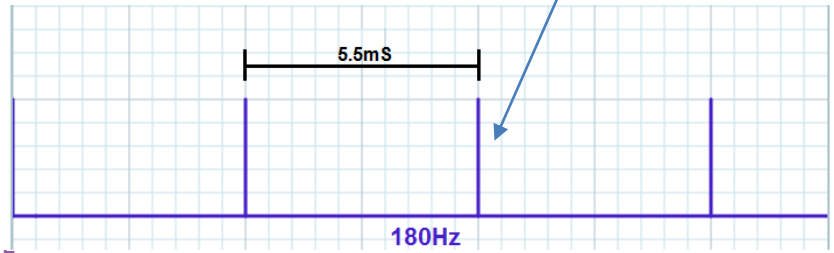
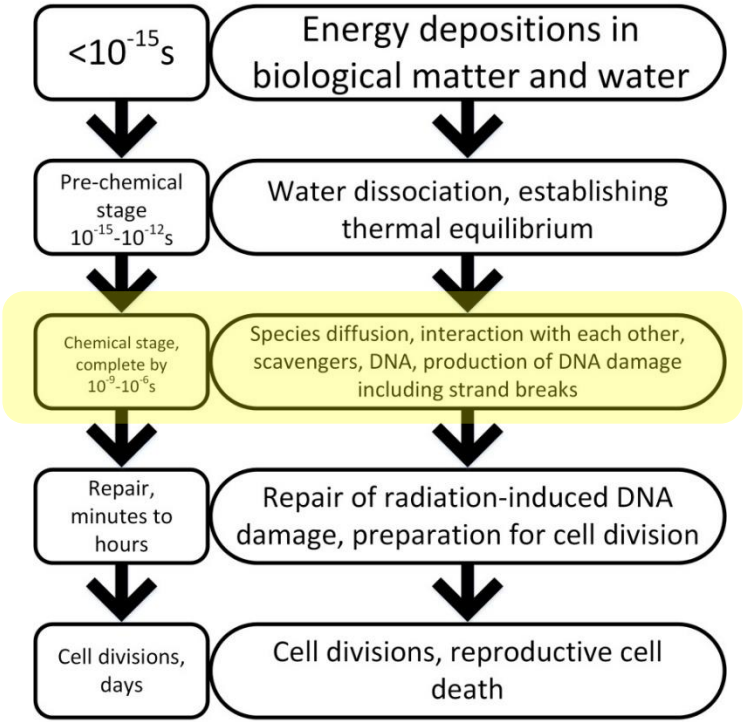


Figure courtesy of Vitali Moiseenko



Vitali Moiseenko, Jimm Grimm, James D. Murphy, David J. Carlson, Issam El Naqa. Analytical and mechanistic models. In: A Guide to Outcome Modeling in Radiotherapy and Oncology: Listening to the Data. Editor: Issam El Naqa. CRC Press, ISBN 9781498768054, 2018, 65-84

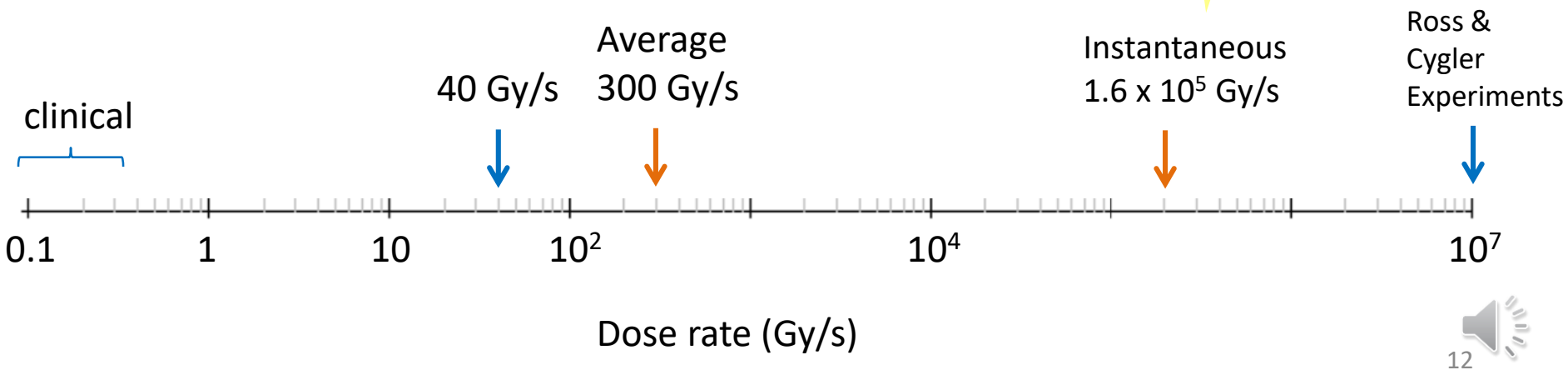
At 300 Gy/sec, for 360 repetition rate:

10 Gy in 33 ms in 12 pulses

0.8 Gy / pulse

5 µs/pulse → 160 000 Gy/s *instantaneous*

Within each pulse, instantaneous dose rate is ~1430x higher in FLASH than in *standard* delivery



Dosimetry results detailed by another group member:

Implementation and Dosimetry of EFLASH Radiotherapy

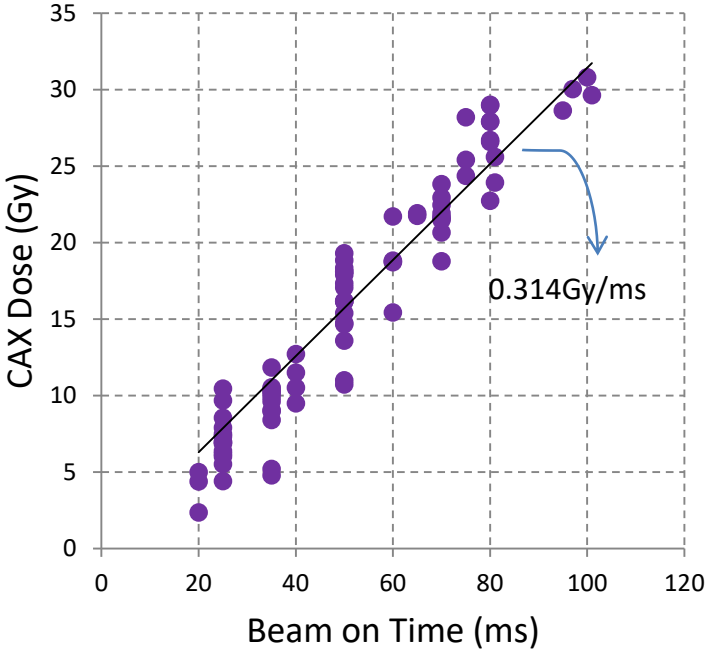
C Mendez[1]*, T Karan[1], M Petric[1], A Bergman[1], D Ta[1], J Sweeney[1], A Kyle[2], J Baker[2], C Duzenli[1], A Minchinton[2], (1) BC Cancer, Vancouver, BC (2) Bc Cancer Research Centre, Vancouver, BC

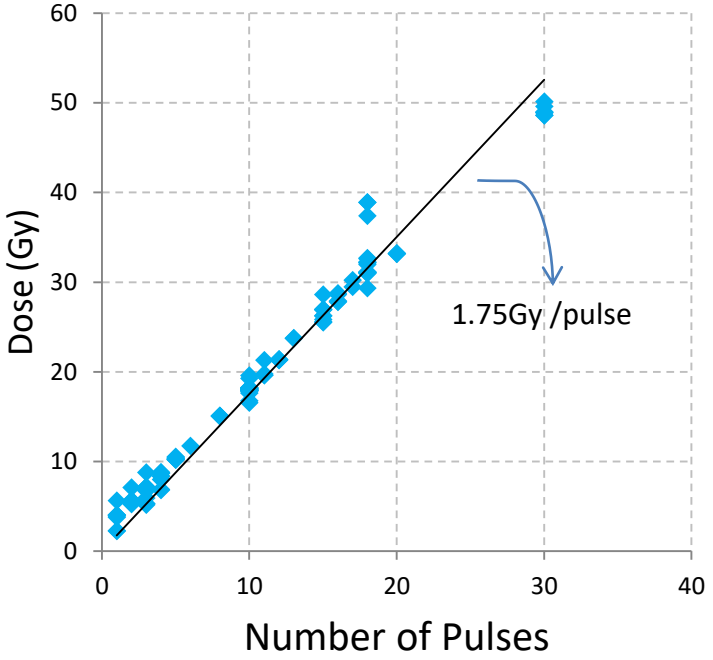
Presentations

(Monday, 7/13/2020) 3:30 PM - 5:30 PM *[Eastern Time (GMT-4)]*

Room: Track 3

Purpose: A feasibility study of modifying a standard clinical linear accelerator to deliver electron FLASH (eFLASH) dose rates (>50 Gy/second) for irradiation of cell suspensions and 3D spheroids as well as in vivo irradiations of tumour-bearing mice.





Programmed MU method – very reproducible

Other shortcomings: linac timer precision = 0.1min

programmable whole MU only. 1MU~5Gy

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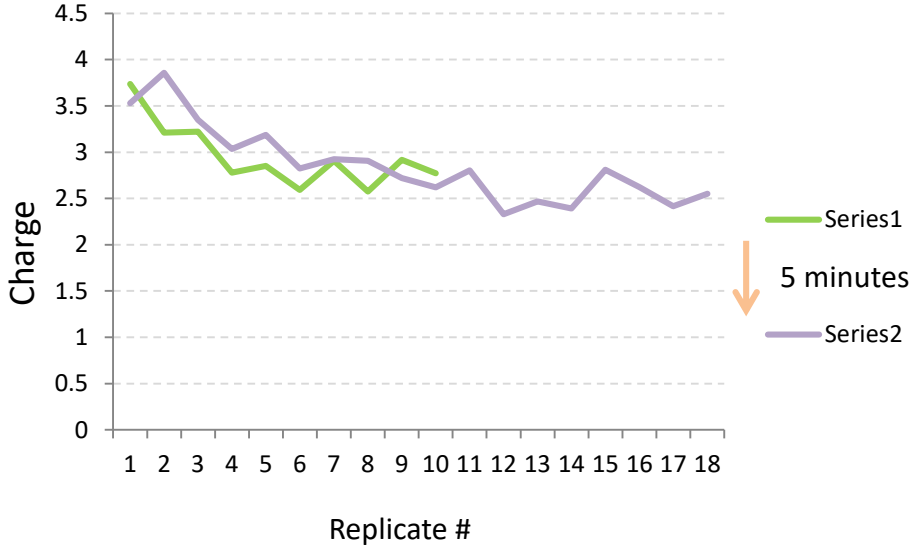
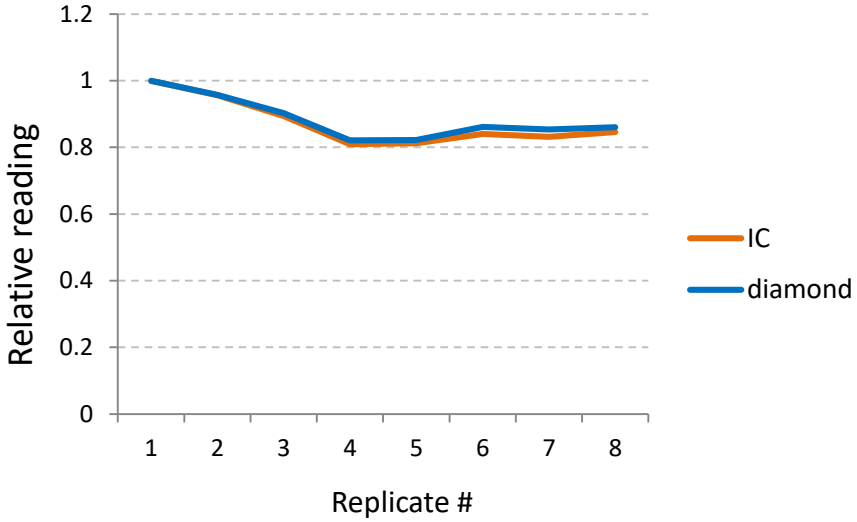
Sources of uncertainty





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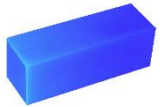
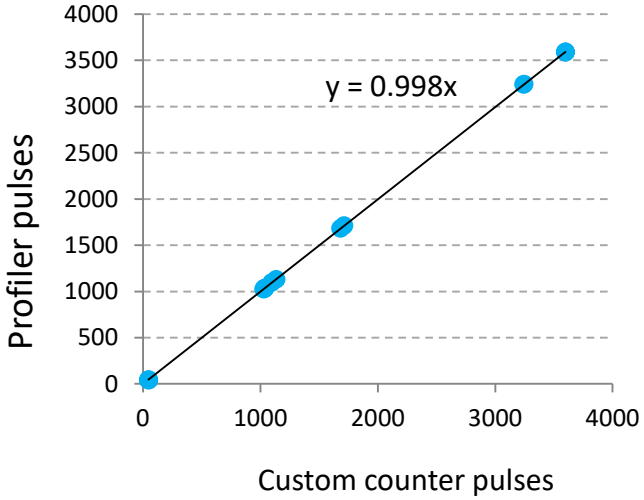




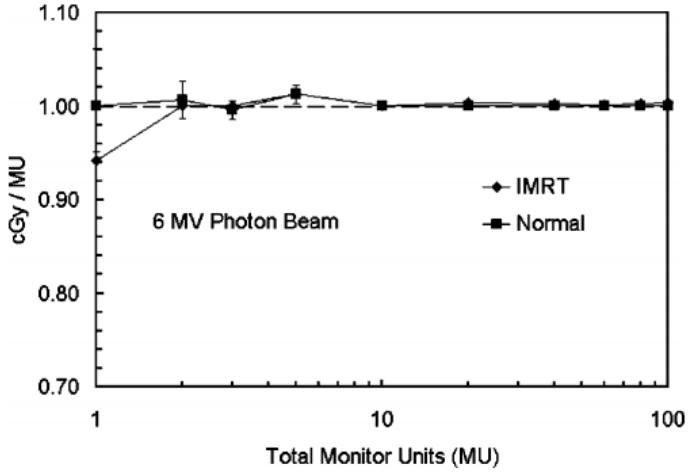


FIG. 2. Dose per monitor unit versus monitor units delivered through a subfield for the 6 MV photon beam.

Comparison of beam characteristics in intensity modulated radiation therapy (IMRT) and those under normal treatment condition

C.-W. Cheng[a)]
Morristown Memorial Hospital, Morristown, New Jersey

Dose linearity and uniformity of a linear accelerator designed for implementation of multileaf collimation system-based intensity modulated radiation therapy

Cheng B. Saw[a)]
Department of Radiation Oncology, UPMC Cancer Centers, Pittsburgh, Pennsylvania 15232



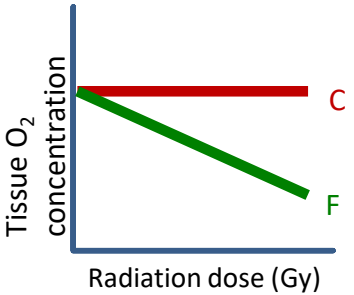
Radiobiology

Radiolytic oxygen depletion-induced hypoxia: dose & time dependent

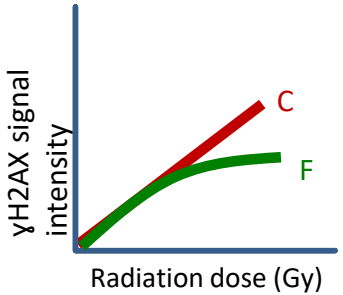
	O2 %	[O2] µM
Room air	20.3	215.1
physiological	5	53.0
hypoxic	1	10.6

Oxygen depletion estimates	
Micheals **0.44 µM/Gy**	Limoli **2.5 µM/Gy**

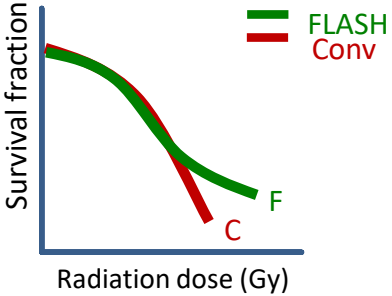
O_2 consumption rate exceeds re-supply at higher doses



If less O_2 then there is less DNA damage



If less DNA damage then there is less cell kill



Oxygen depletion in irradiated aqueous solutions containing electron affinic hypoxic cell radiosensitizers , International Journal of Radiation Oncology*Biology*Physics

Howard B. Michaels PH.D.

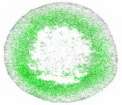
Volume 12, Issue 7, Part 1, July 1986, Pages 1055-1058

Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken

M.-C. Vozenin *†, J.H. Hendry ‡, C.L. Limoli §

Clinical Oncology

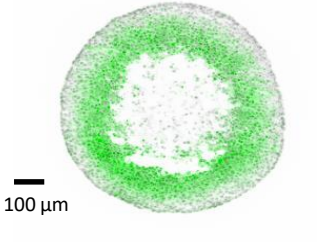
Volume 31, Issue 7, July 2019, Pages 407-415



3D Spheroid assays

A – Spheroid-microarray for assessing DNA damage

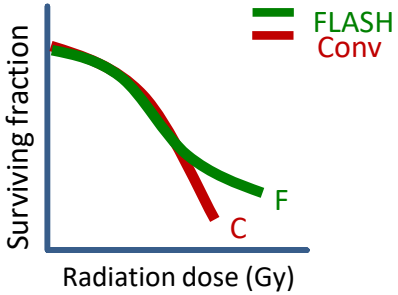
- 96 well plate format for full dose-response curves
- Spheroids collected, frozen, immunohistochemically stained for hypoxia & markers of DNA damage
- Analysis of cell damage is done as a function of distance from the edge of the spheroids, with cells closer to the inner necrotic area being more hypoxic than the outer cells



Pimonidazole-stained hypoxia gradient

B - Colony-assay for assessing surviving fraction

- Vials of spheroid irradiated in varying oxygen and dosing conditions
- Automated dissociation, plating & colony counting
- Full dose response curves are drawn



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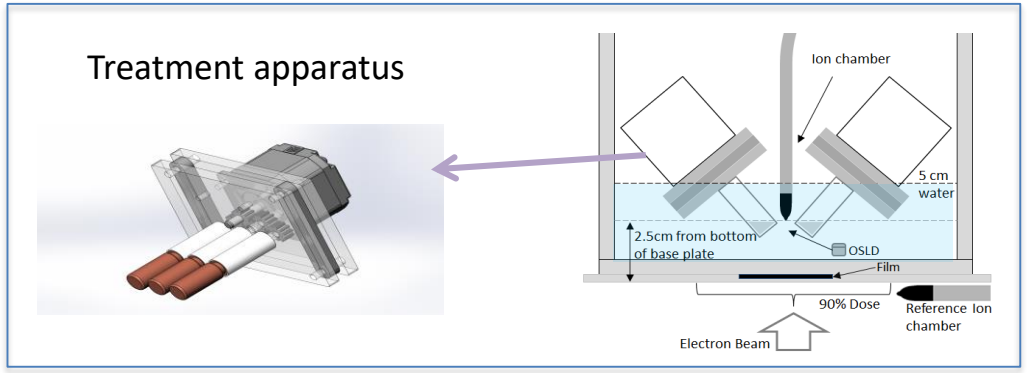
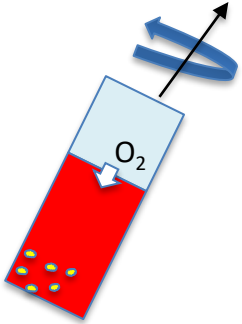
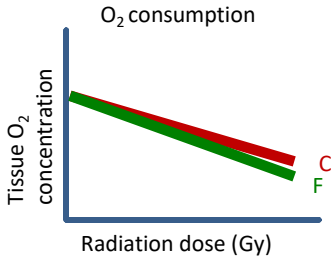
Experiment set-up:
2 possibilities to elucidate the oxygen-effect of FLASH

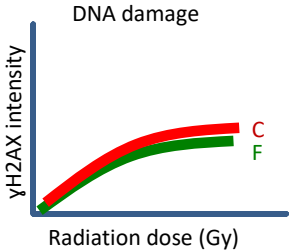
Tubes with media, air reservoir & spheroids

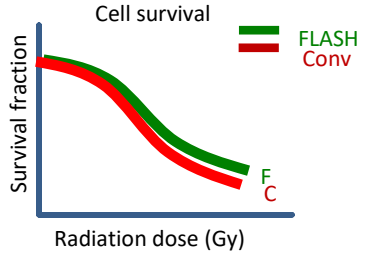


1. *Minimal stirring conditions* limits re-oxygenation even during conventional dosing

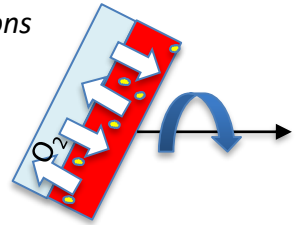


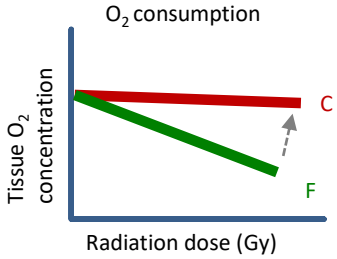


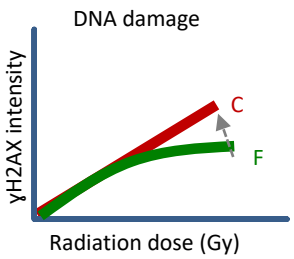


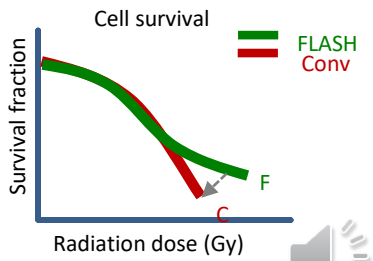


2. *Tumbling stirring conditions* maximizes re-oxygenation opportunity









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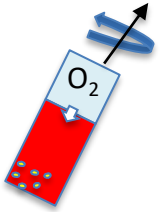
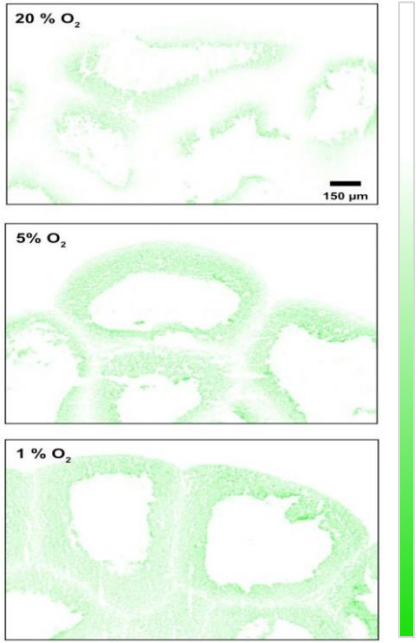
3D Spheroid microarray: DNA damage staining (gH2AX)



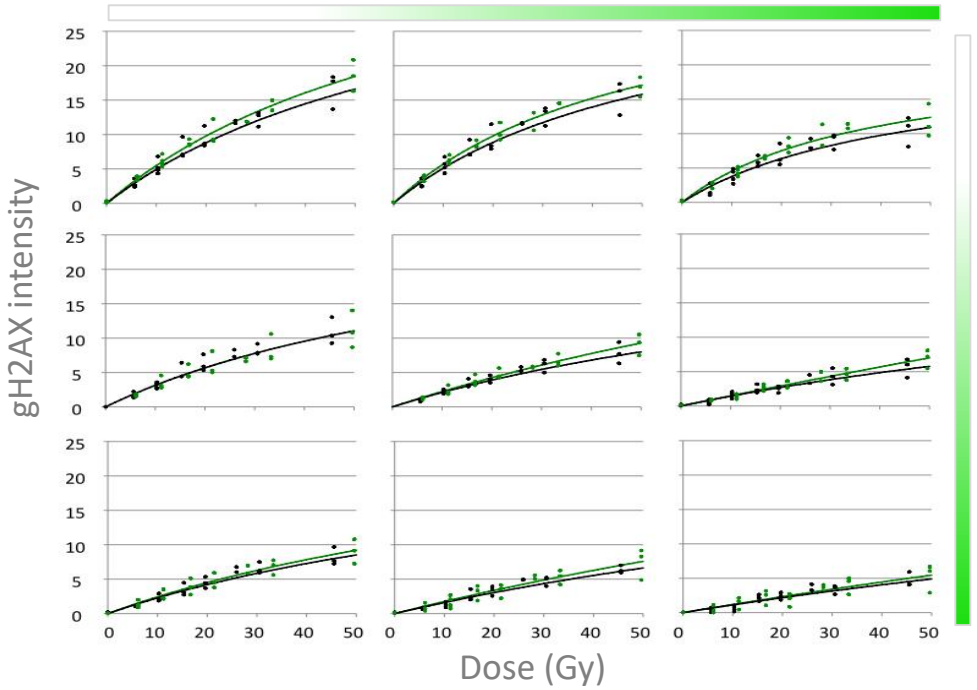
Hypoxia (pimonidazole)



Outer edge (0-50 µm) *most oxic*

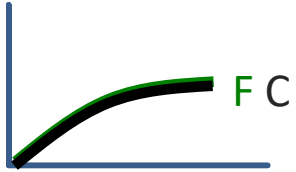
Middle (50-100 µm) *O_2 gradient*

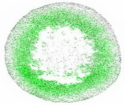
Inner edge (100-150 µm) *most hypoxic*



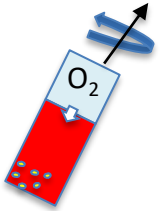
FLASH effect

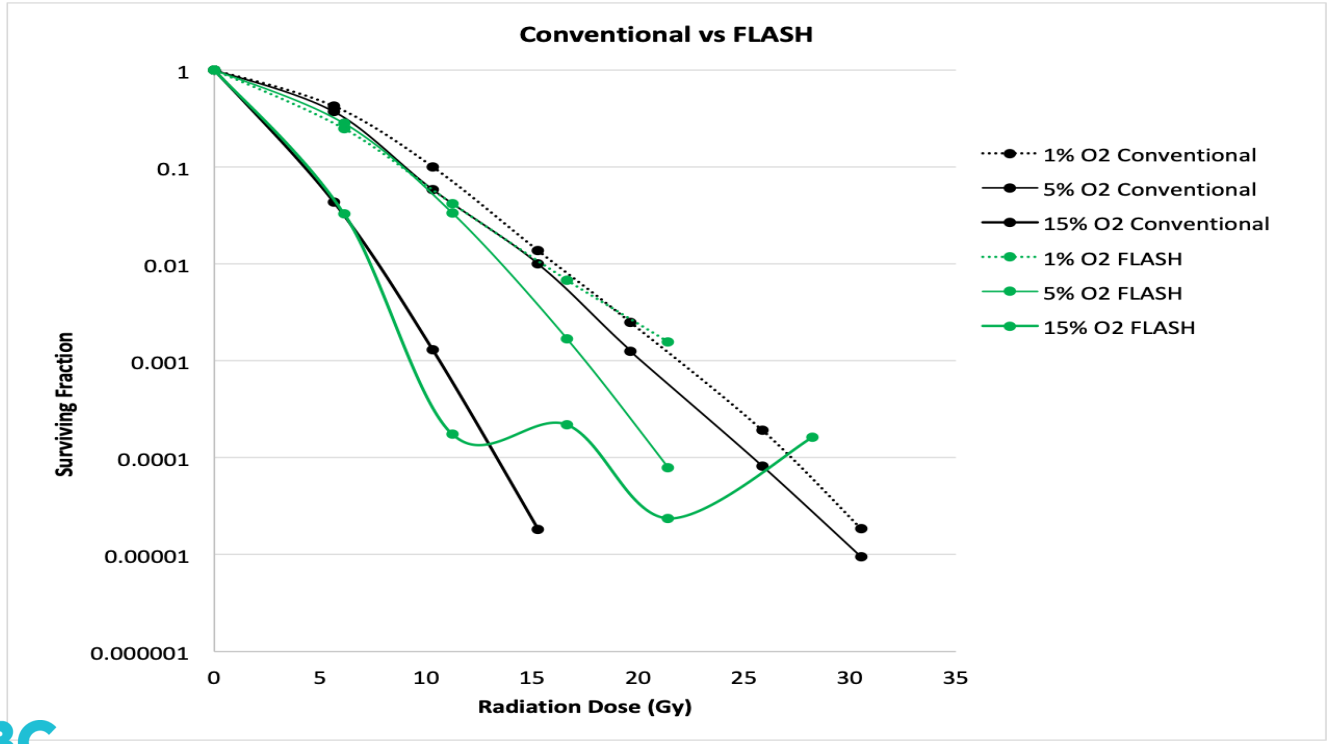
No effect

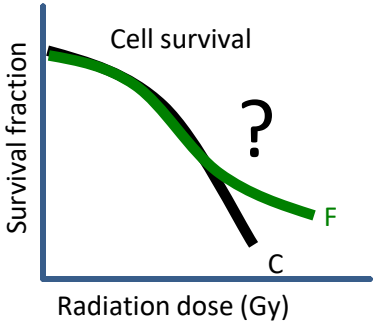


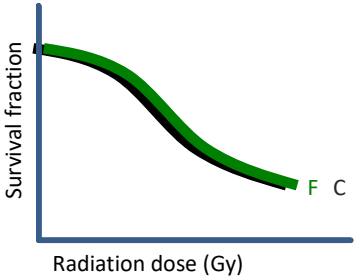


3D Spheroid Colony forming endpoint









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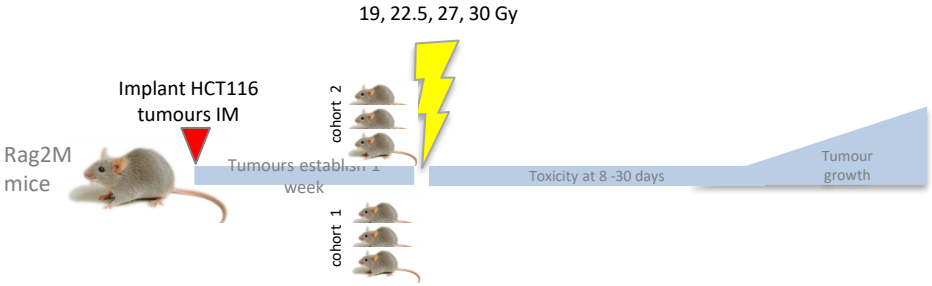
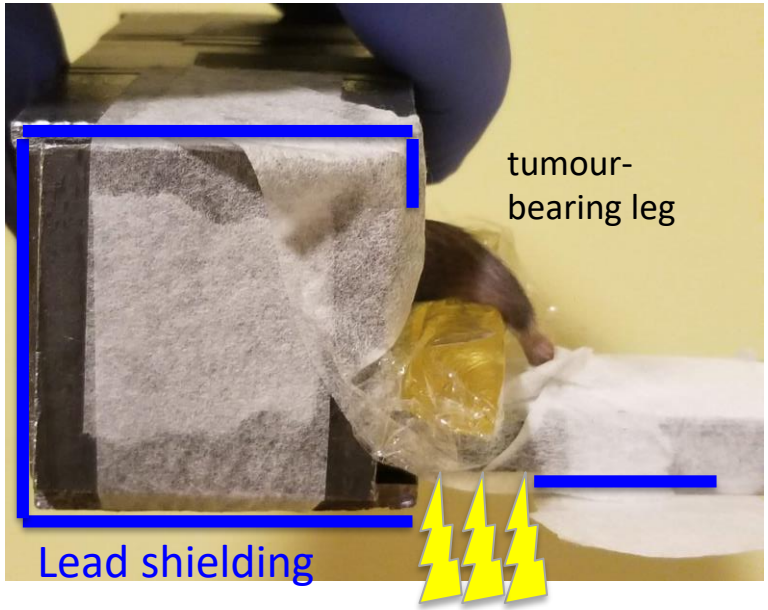
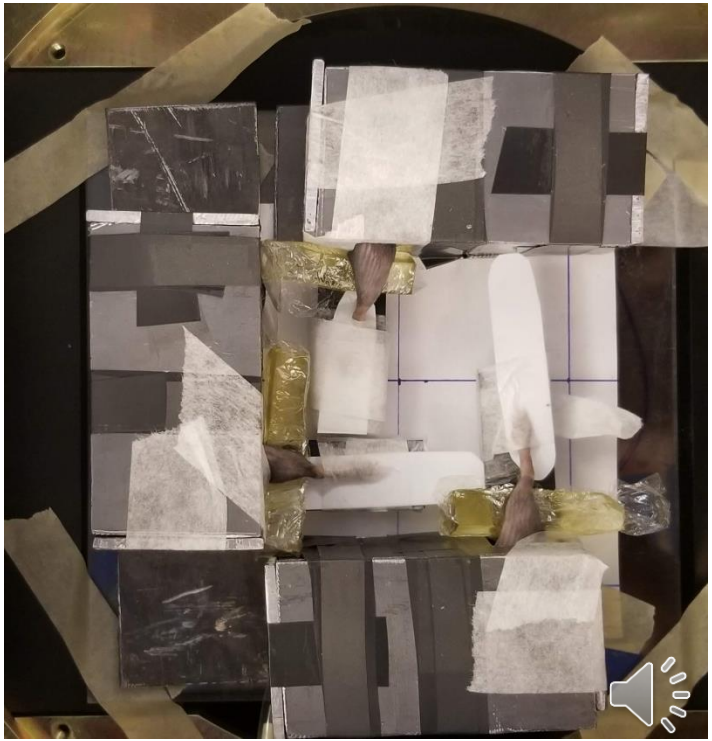
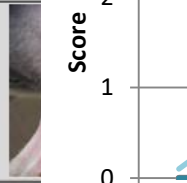
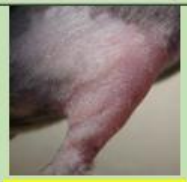
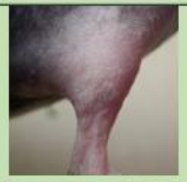
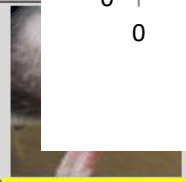
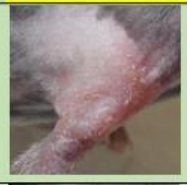
In Vivo Skin Toxicity



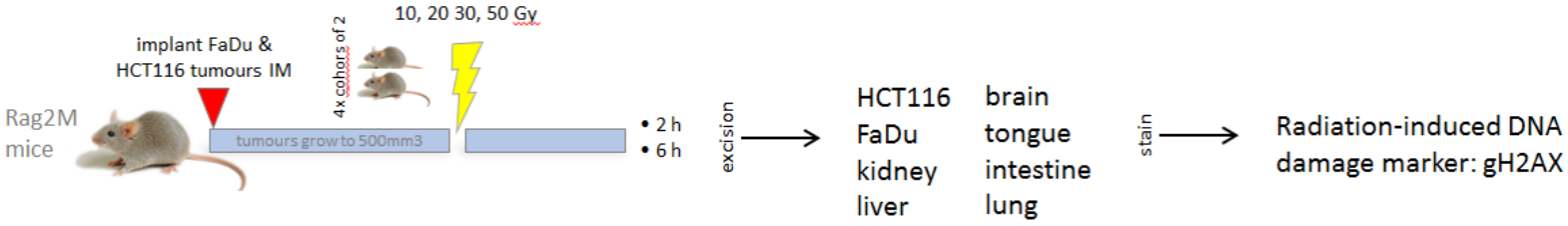
Photographs & scores noted daily

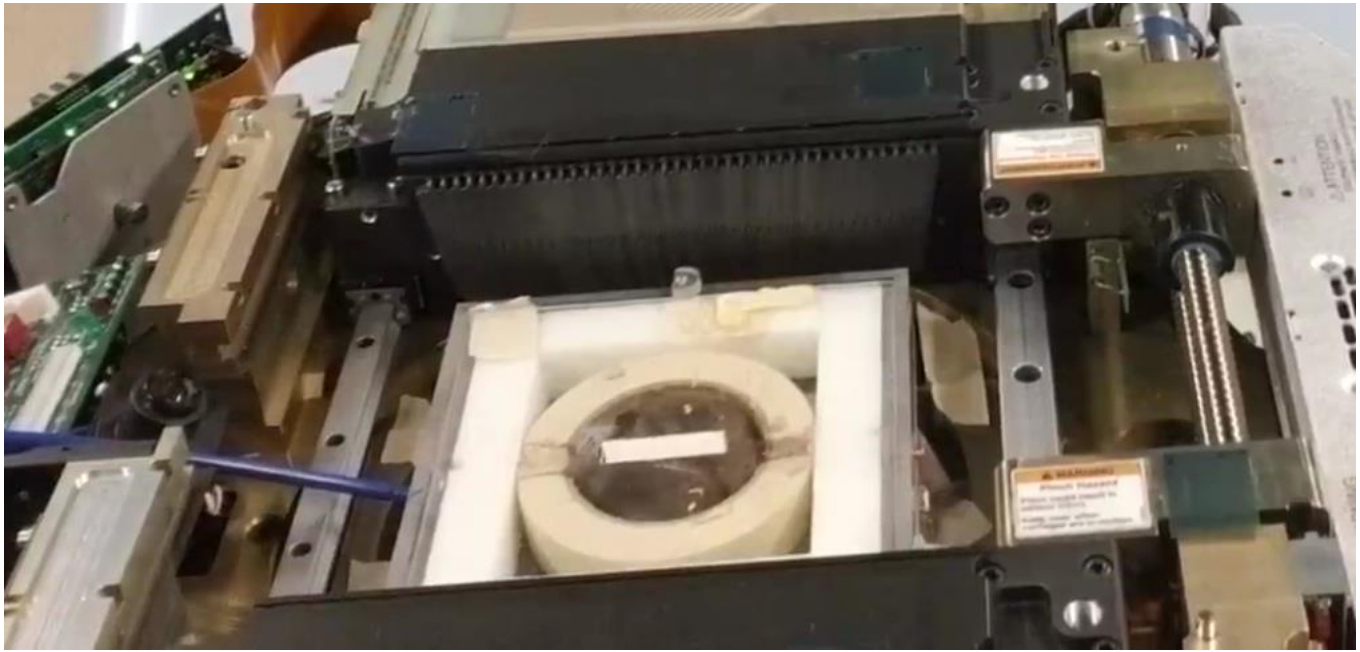




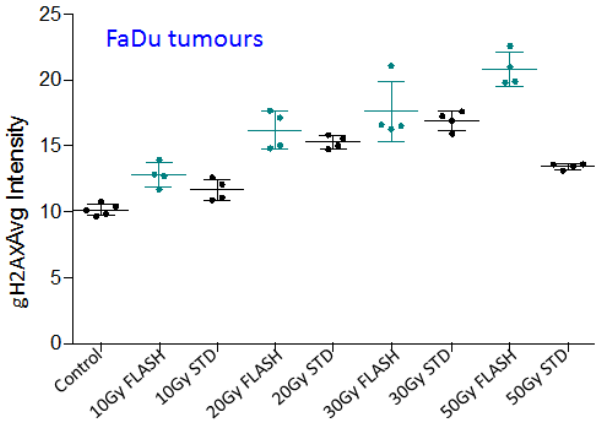
	Rag2m 19 Gy FLASH			Rag2m 19 Gy Std		
	382-b1	382-b2	382-b3	690-b1		
2020-01-17 Day 5						
2020-01-20 Day 8						
2020-01-22 Day 10						
2020-01-23 Day 11						
2020-01-24 Day 12						

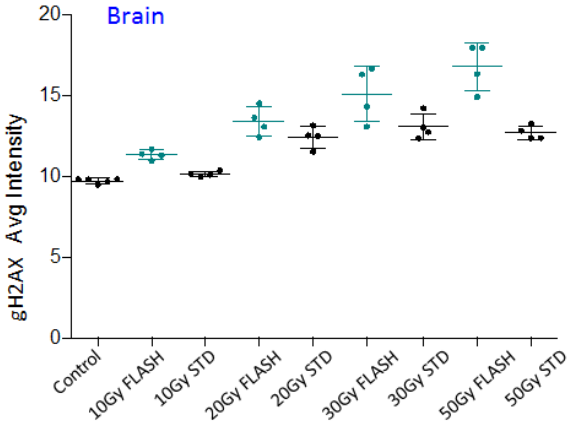
Tissue sensitivity: DNA damage

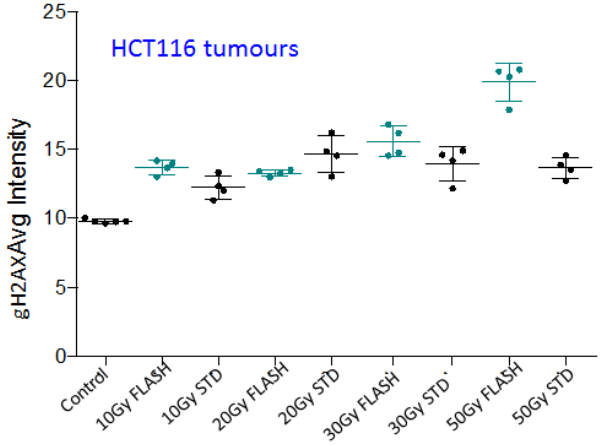


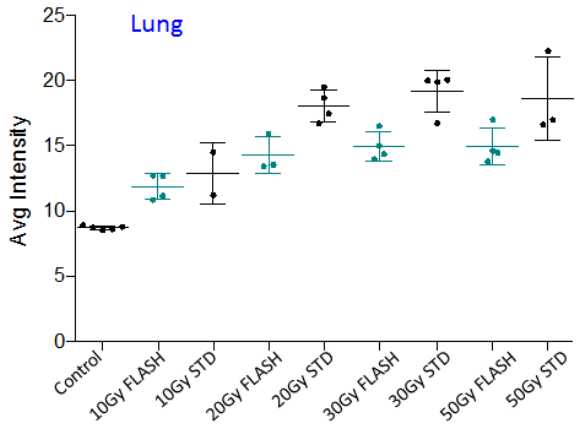


Radiation-induced DNA damage at 2 hours

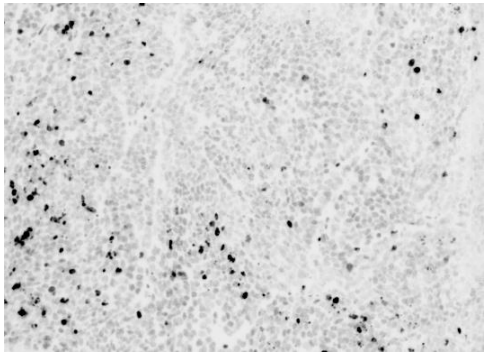




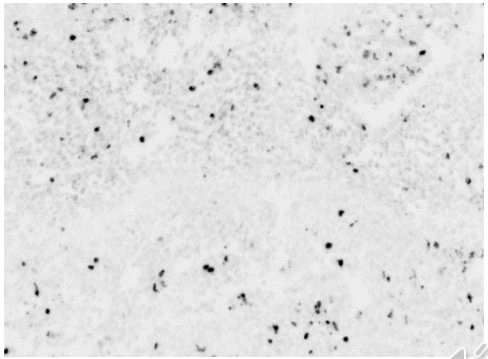




gH2AX staining of cell nuclei in HCT116 tumours



50 Gy FLASH



50 Gy STD

Future: Lessons

1. We switched a previously clinical machine from standard → FLASH mode in ~15 minutes using a reversible process

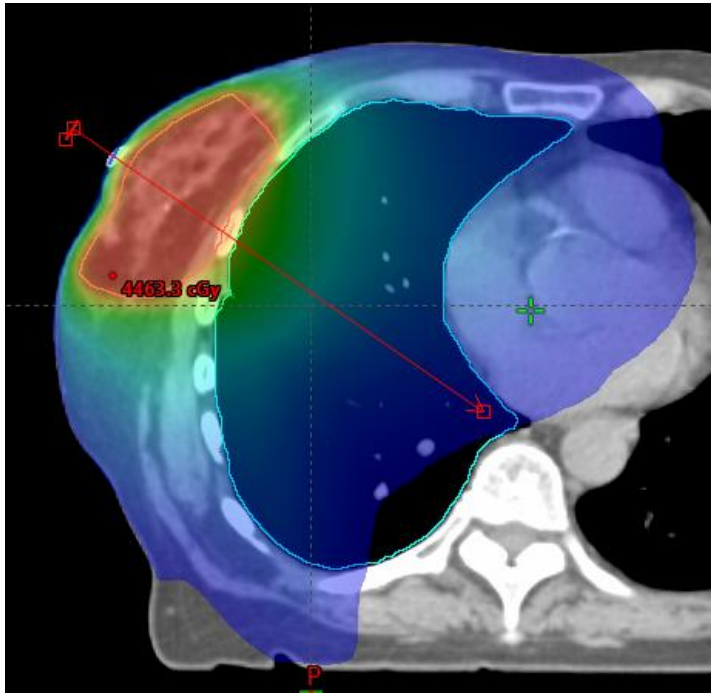
2. Machine set-up: Pulse counting circuitry results in most consistent results, but further look into beam generation is needed to quantify uncertainty

3. The similarity of DNA damage and survival response between FLASH & conventional dosing in the *in vitro* models where reoxygenation was not optimal suggests the crucial role of oxygen-depletion for the FLASH effect, and upcoming experiments will investigate this further

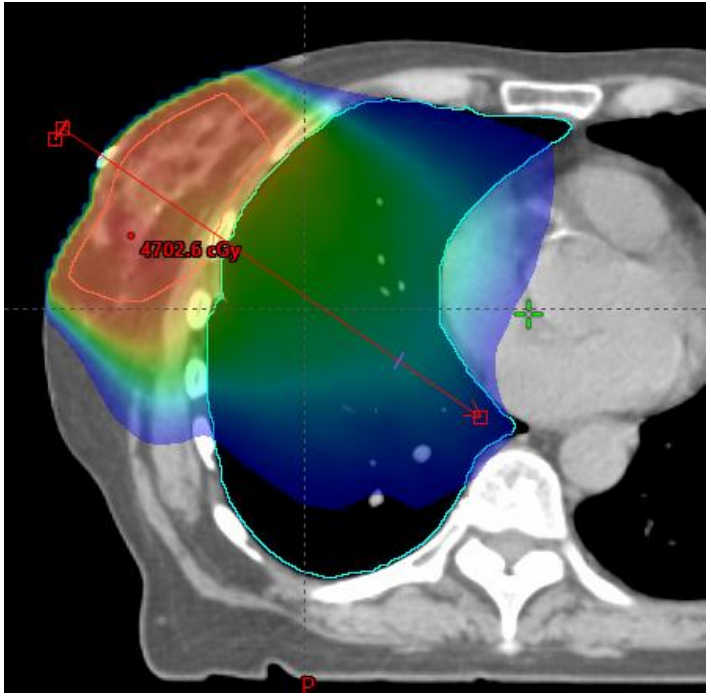
4. Mouse experiments: we did not observe an effect on skin toxicity at our dose rates, however some intriguing observations in the whole body irradiation experiments will prompt further investigation using more targeted fields

FLASH clinical use in future?

VMAT, 2 arc 6X plan



Electron, 16MeV plan



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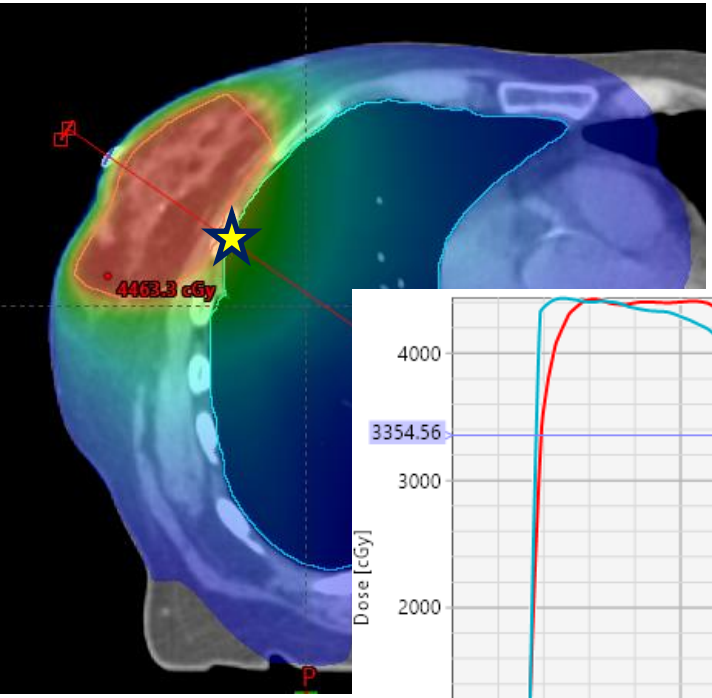

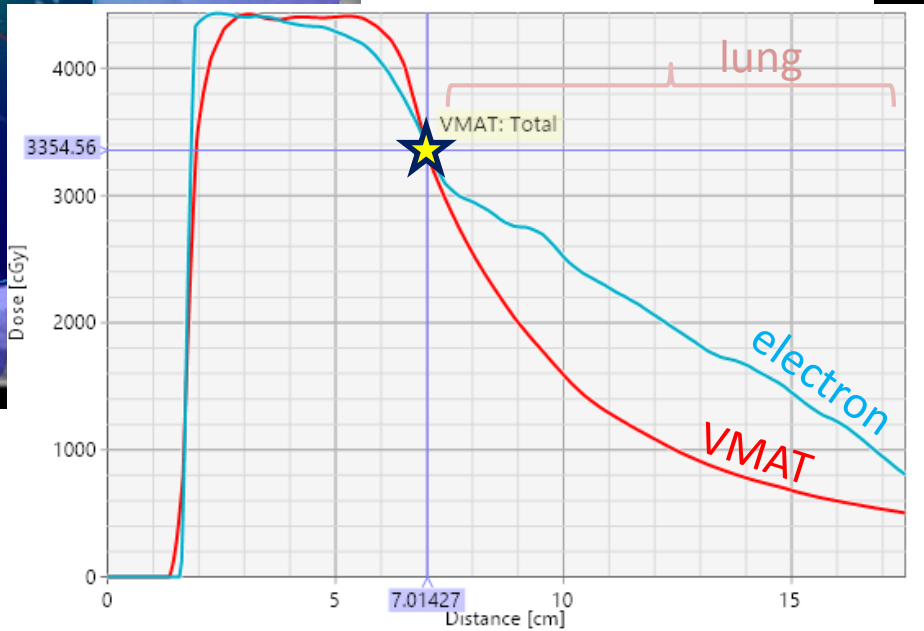

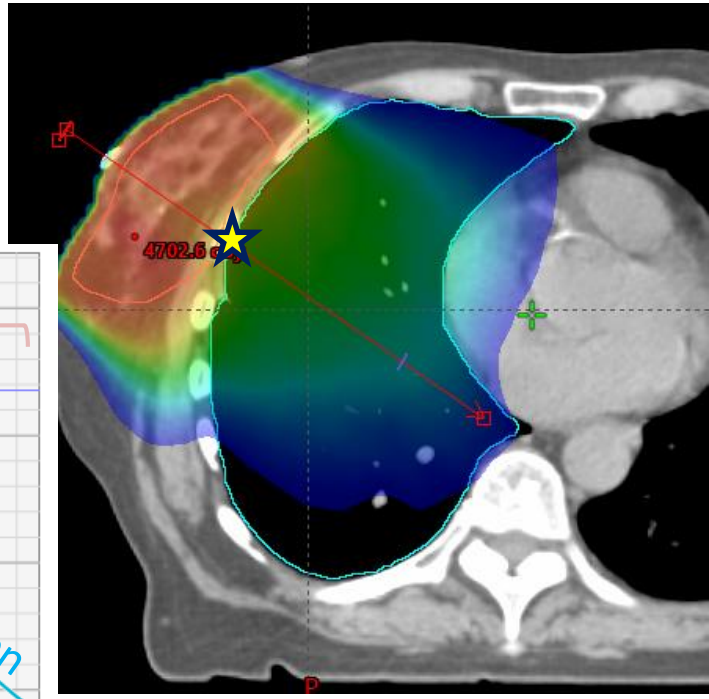

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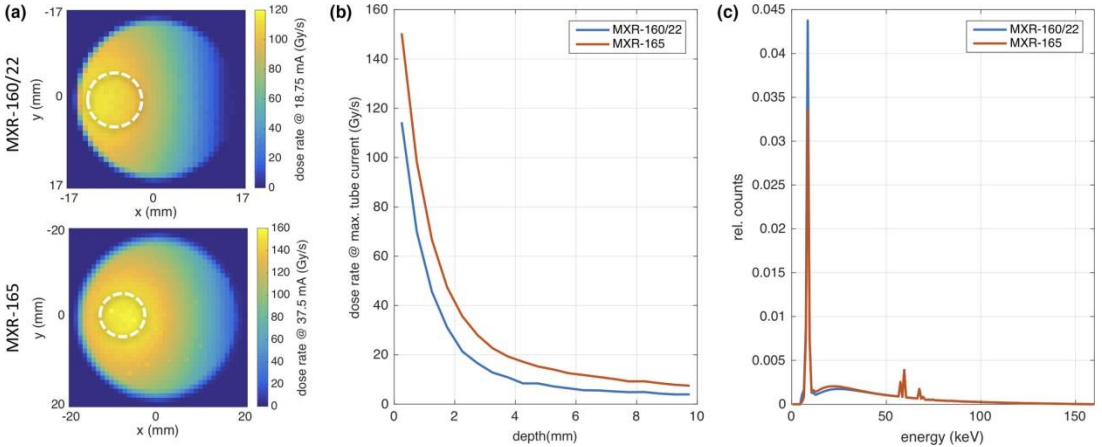
160 kV X-ray tubes: 2 models

Monte Carlo simulations

114-160 Gy/sec at surface of water phantom



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Editor's Choice

On the capabilities of conventional x-ray tubes to deliver ultra-high (FLASH) dose rates

Magdalena Bazalova-Carter, Nolan Esplen

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