Pr Raphaël Moeckli
Institute of Radiation Physics

Medical physics of ultra-high dose rate electron beams

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Conflicts of interest

Grant from Accuray
(nothing to do with FLASH)

Collaborations with
PMB Alcen
IntraOp
CERN

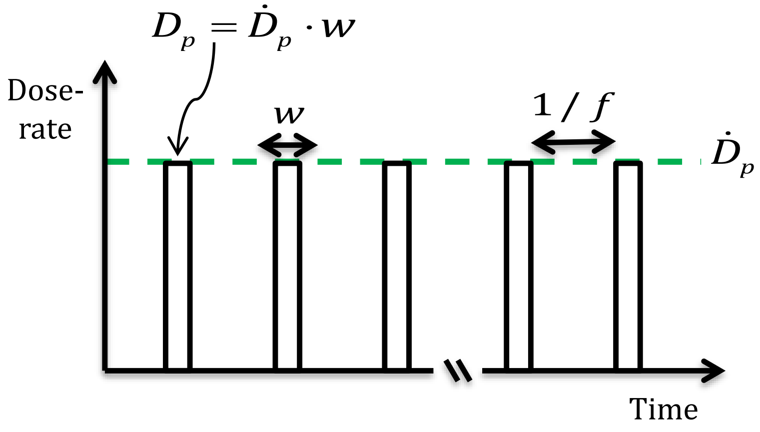
A word of caution

Difference between High Dose rate (HDR) and FLASH

FLASH effect is a biological effect that may happen when the dose is delivered in a very short time duration and therefore high dose rate (HDR) beams are used to trigger FLASH effect

FLASH effect is a biological effect and as long as one talks about physics, one should talk about HDR that may trigger FLASH effect

Beam structure



1/f >> w

w	pulse width	$[0.5 - 2.2]\ \mu s$
f	pulse repetition frequency	$[10 - 200]\ Hz$
$\dot{D}_p$	dose-rate in pulse	$[10^3 - 5 \cdot 10^6]\ Gy/s$
$D_p = \dot{D}_p \cdot w$	dose per pulse	$[10^{-3} - 5]\ Gy$
$\dot{D}_m = \dot{D}_p \cdot w \cdot f$	mean dose-rate	$[10^{-2} - 1000]\ Gy/s$

Flash RT

Conventional	Flash (HDR)
Mean dose-rate ~ 4 Gy/min	Mean dose-rate ~100 Gy/s
Treatment time ~ minutes	Treatment time < 1 s

Flash is really a flash

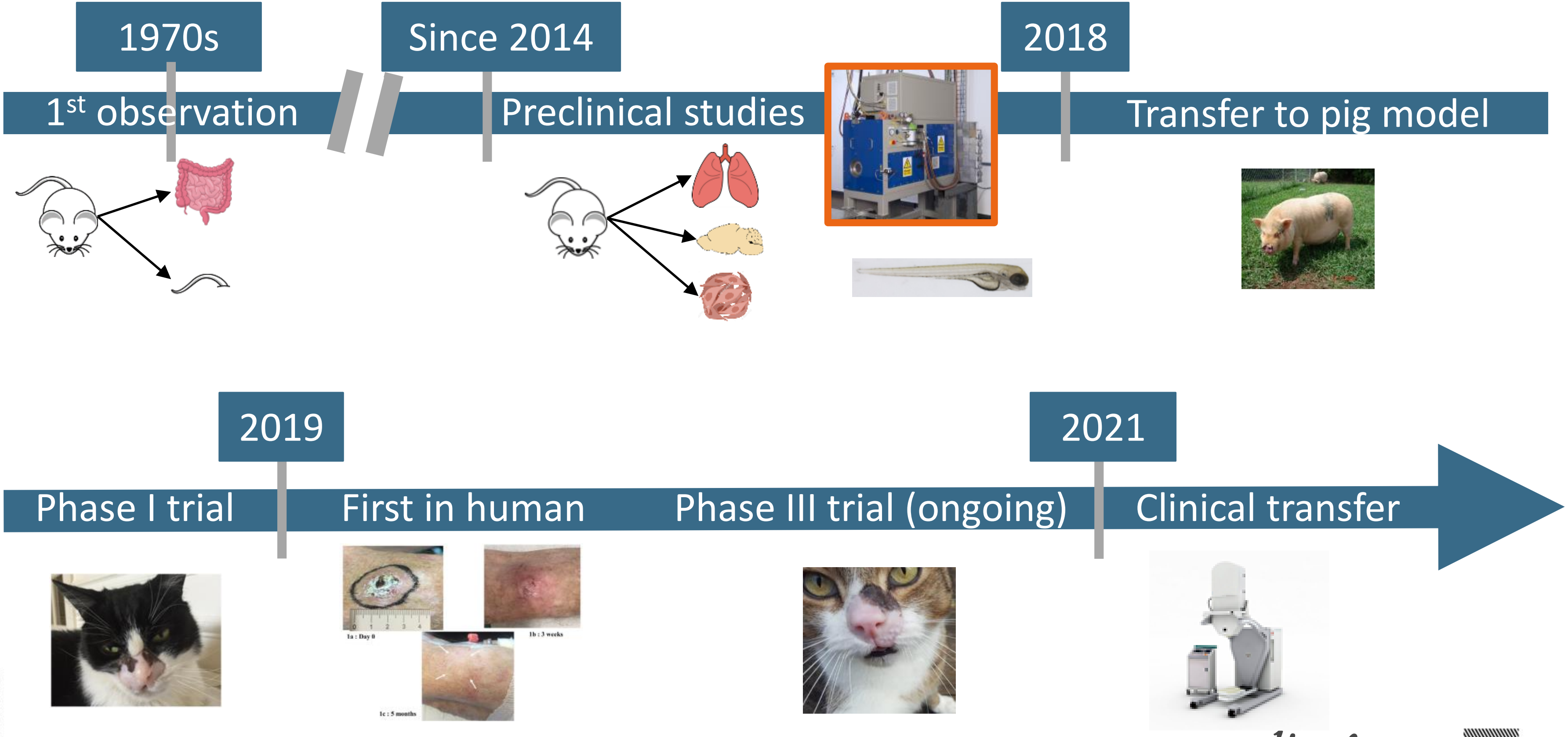
Why is Flash RT of interest?

Increase in differential response between normal tissue and tumors

Short treatment times (<1s)

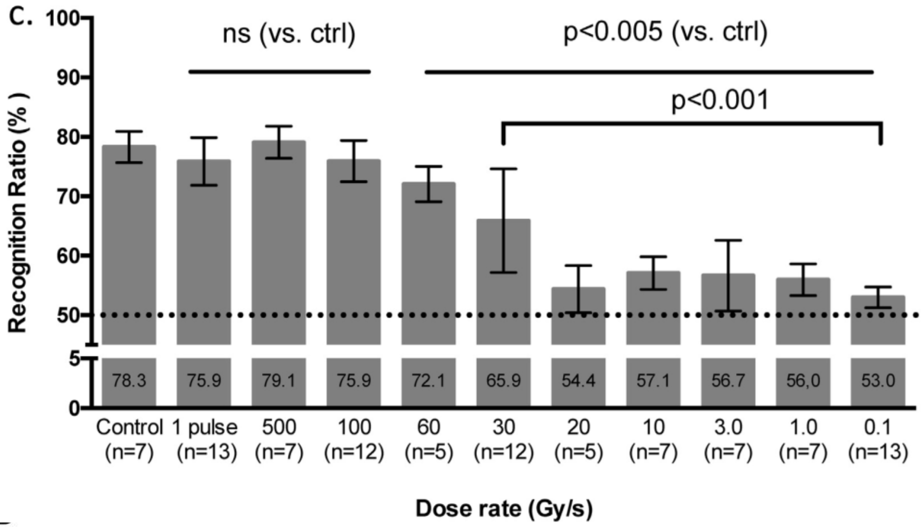
- Motion management, i.e. remove intra-fraction motion
- Patient comfort
- Improved treatment

FLASH timeline



Two important experiments

Memory testing in mice
(whole brain irradiation)



Pig skin irradiation

34 Gy 31 Gy 28 Gy

Montay-Gruel 2017; Vozenin 2018

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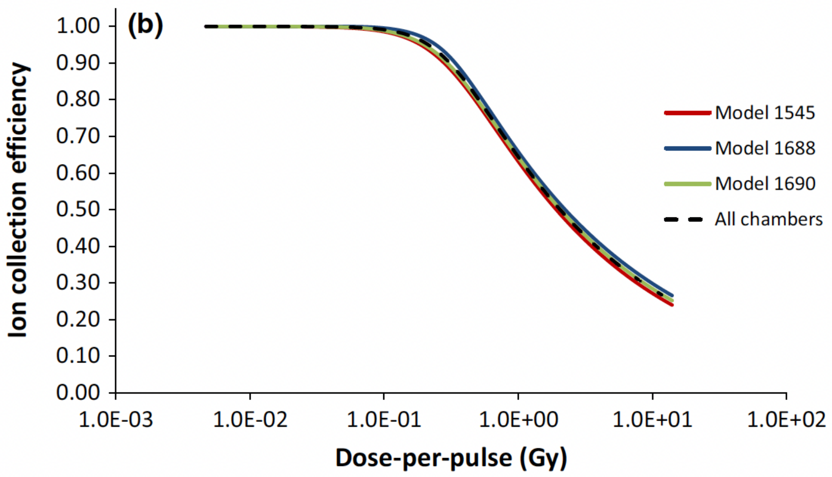
Metrology

Ion chamber

Usual tool not available
For traceability
For usual measurements



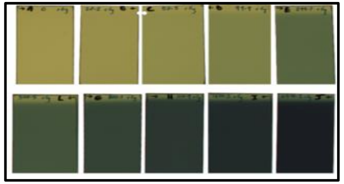
Petersson 2018

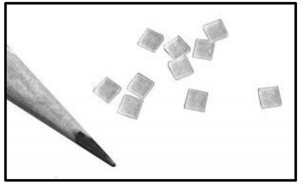
Traceability

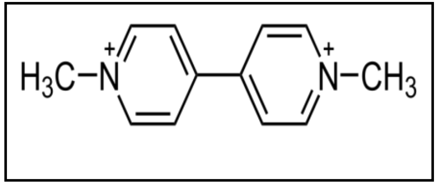
Absolute dosimetry

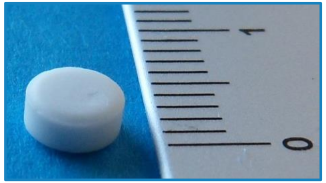
- Calibration to a national standard
- There is no standard for HDR beams
- No usual traceability possible

Use of redundancy





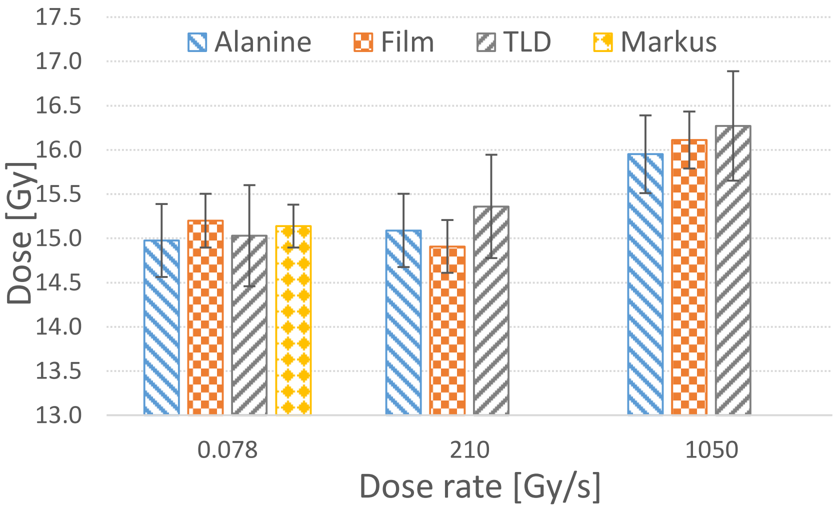




Redundancy of dosimetric measurements ⇨ traceability

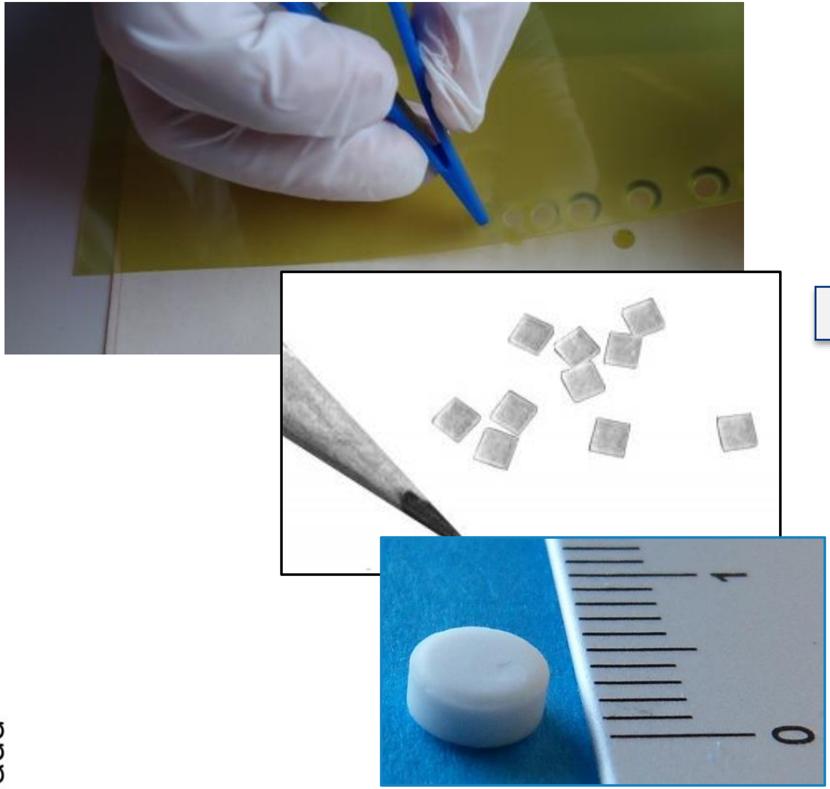
Take dosimeters with different detecting principles → different dose rate dependency

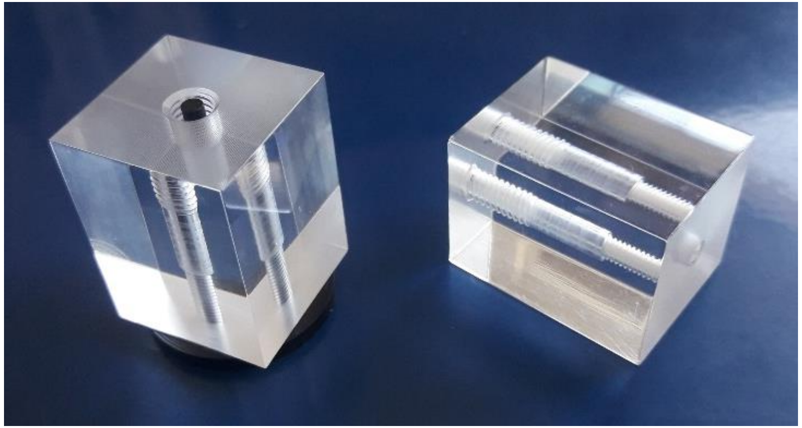
Start with reference conditions (conventional LINAC) → extrapolate to UHDR



Agreement within 3 % for UHDR and within 2 % for CONV

UHDR dosimetric intercomparison

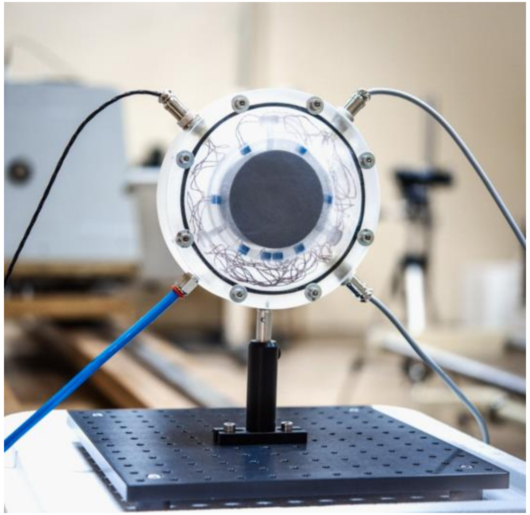


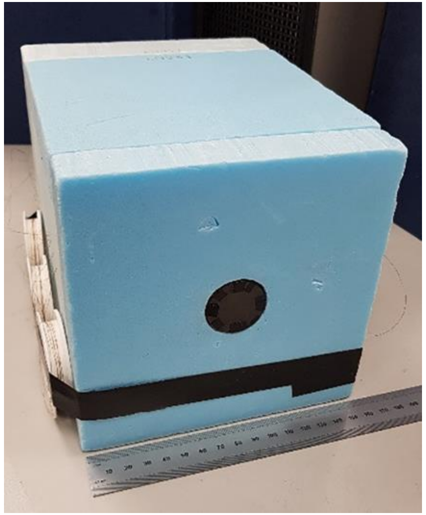


Towards primary standards

The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

Andreas Schüller [a,*], Sophie Heinrich [b], Charles Fouillade [b], Anna Subiel [c], Ludovic De Marzi [b,d], Francesco Romano [e,c], Peter Peier [f], Maria Trachsel [f], Celeste Fleta [g], Rafael Kranzer [h,i], Marco Caresana [j], Samuel Salvador [k], Simon Busold [l], Andreas Schönfeld [m], Malcolm McEwen [n], Faustino Gomez [o], Jaroslav Solc [p], Claude Bailat [q], Vladimir Linhart [r], Jan Jakubek [r], Jörg Pawelke [s,t], Marco Borghesi [u], Ralf-Peter Kapsch [a], Adrian Knyziak [v], Alberto Boso [c], Veronika Olsovcova [w], Christian Kottler [f], Daniela Poppinga [h], Iva Ambrozova [x], Claus-Stefan Schmitzer [y], Severine Rossomme [z], Marie-Catherine Vozenin [q]





Schueller 2021

Pre-clinical

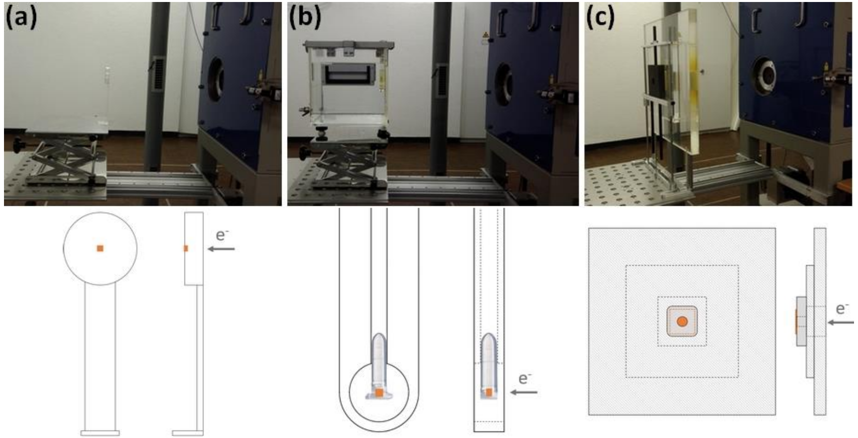
Dosimetric procedure for UHDR

Procedure developed for three setups

a) PMMA box (mice)

b) Water Tank (zebrafish)

c) Collimator (mini-pig)



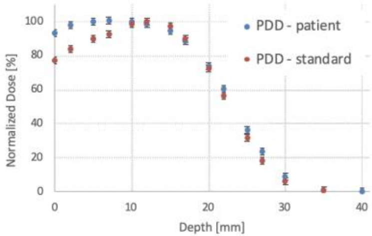
→ Procedure applied to biological irradiations with *in vivo* dosimeters

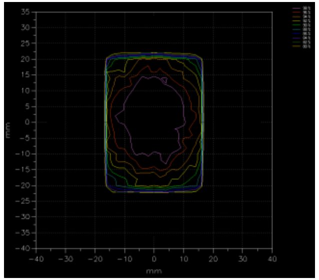
Without procedure : dose deviations up to 15%

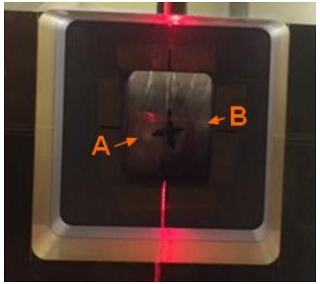
With procedure : dose deviations <3%

Dosimetry of first patient

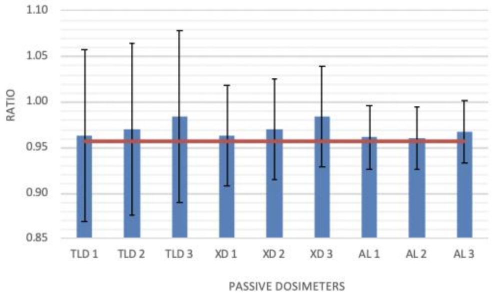
Pre-treatment	Treatment	Dosimetry check







	Pre-treatment [Gy]	Alanine A [Gy]	Alanine B [Gy]
Dose [Gy]	14.9	14.9	14.9



Additional safety measures
Pulses and time counter device (independent)

Clinical transfer

Electron UHDR

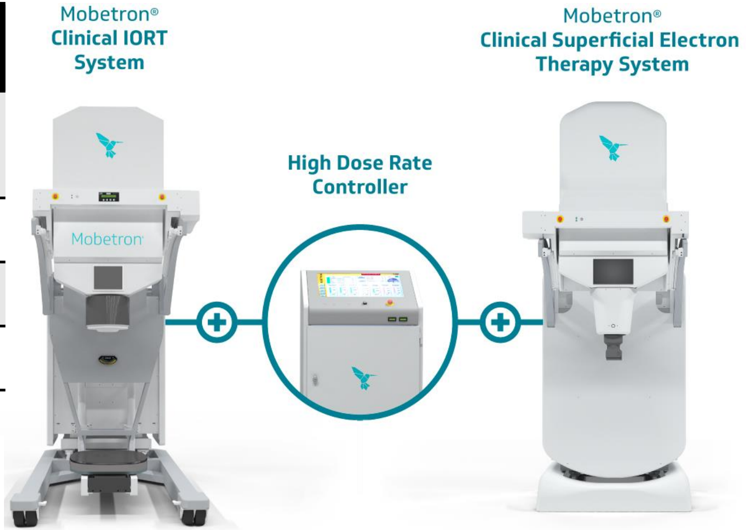
Table VI. Characteristics reported in the literature for electron UHDR devices.

Device	Mobetron® (IntraOp)	Oriatron eRT6 (PMB Alcen)	Kinetron (CGRMeV)	Modified Elekta	Modified Varian	Novac7 (Sordina)
Reference	This publication	Jaccard[14] Petersson[26]	Lansonneur [16]	Lempart[15]	Schüler[8,17]	Felici[25]
Available beam energy [MeV]	6 and 9	6	4.5	10	9, 16, and 20	7
Maximum average dose rate [Gy/s]	>700 @ 6 MeV >800 @ 9 MeV	1000	NA*	≥ 300	74 @ 9 MeV 300 @ 16 MeV 200 @ 20 MeV	540
Maximum dose per pulse [Gy]	>8 @ 6 MeV >9 @ 9 MeV	10	1	1.9	1.67 @ 16 MeV 1.85 @ 20 MeV	18.2
Max. beam size @ max. dose rate [cm]	4 @ 90% isodose	NA	NA	2 (5% flatness)	1 (90% isodose)	0.5 (FWHM)
Short-term stability [%]	0.8	< 1	NA	1 to 4**	NA	NA
Long-term stability	1.8 @ 6 MeV 2.3 @ 9 MeV	4.1%	NA	NA	NA	NA

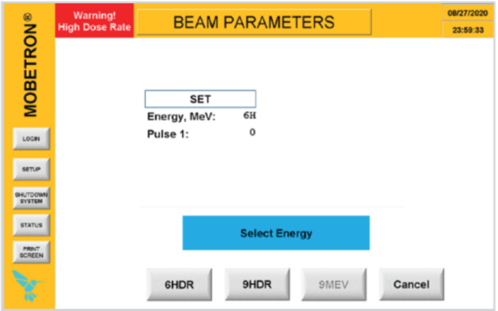
An example of commissioning

FLASH with Electrons at IntraOp

Attribute	Std Mode	FLASH (HDR) Mode
Energy config. (3 Modes)	6/9/12 MeV Conv (3)	6 & 9 MeV FLASH (2) 6 or 9 MeV Conv. (1)
Pulse Width	1.2μs	0.5 – 4.0 μs (manual adj.)
Pulse Frequency	30 pps	10 – 100 pps (manual adj.)
Dose Delivery	Monitor Units	# of Pulses and Distance



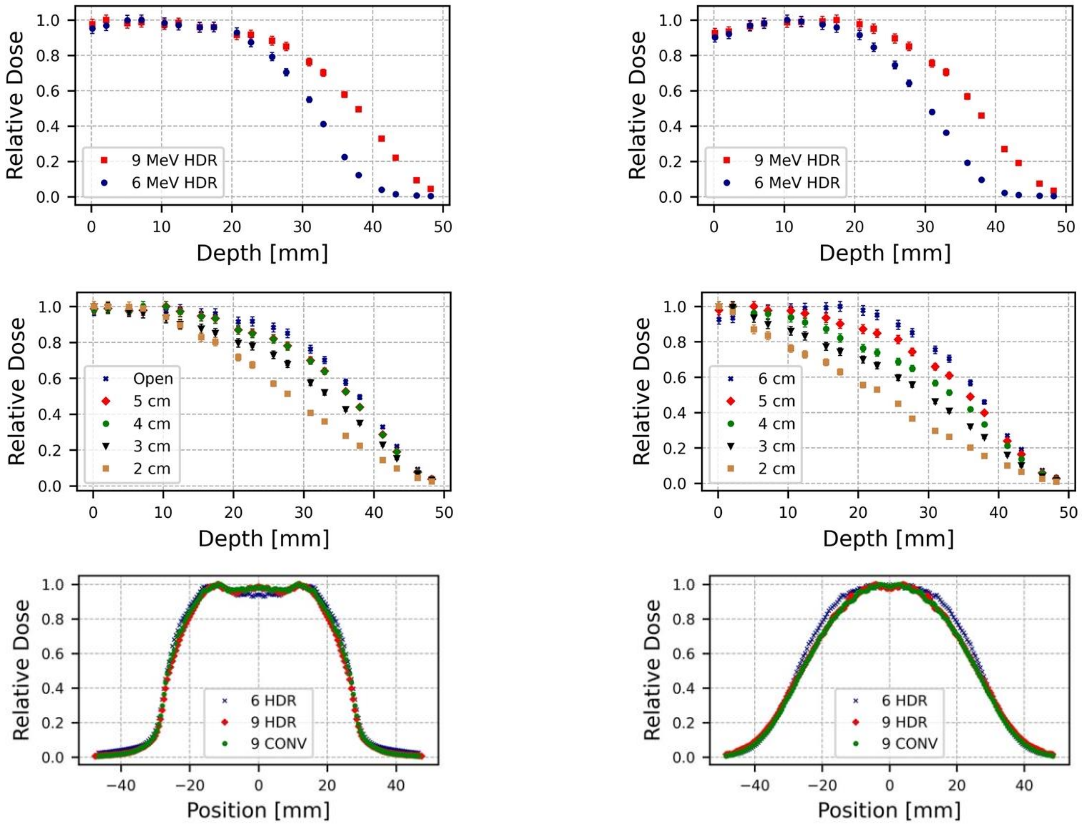
HDR Pulse Structure Control User Interface



Screen for Entering Number of Pulses in High Dose Rate mode

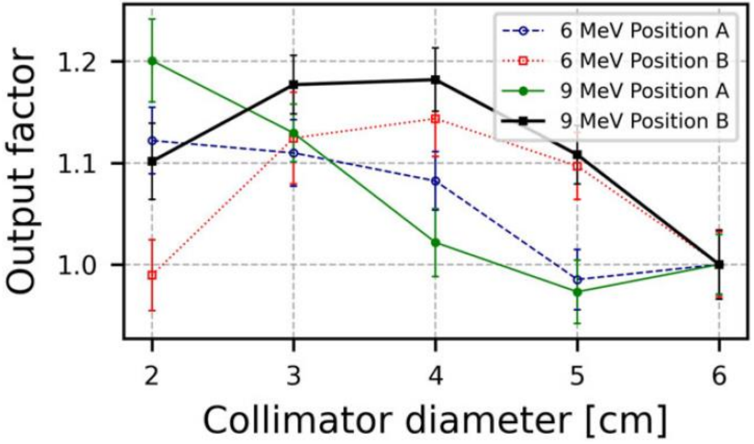
Courtesy of IntraOp

Beam commissioning



Beam commissioning

Position	A (PW: 4 μs; PRF: 60 Hz; 2 pulses)		B (PW: 4 μs; PRF 60 Hz; 7 pulses)	
Energy [MeV]	6	9	6	9
Film dose [Gy]	16.9 ± 0.2	18.7 ± 0.1	20.9 ± 0.2	23.4 ± 0.4
Alanine dose [Gy]	16.6 ± 0.2	18.3 ± 0.1	20.9 ± 0.3	22.9 ± 0.2
Difference [%]	1.8	2.2	0	2.2
Dose per pulse [Gy]	8.3	9.2	3.0	3.3



FlashKnife, PMB/CHUV

FlashKnife – PMB/CHUV

- Pre-clinical prototype
  - Partly commisioned
- Next
  - Clinical prototype for IORT end of 2022
  - Commissioning
  - Start clinical protocol in IORT

AAPM – ESTRO joint WG

AAPM COMMITTEE TREE

Task Group No. 359 - FLASH (ultra-high dose rate) radiation dosimetry (TG359)

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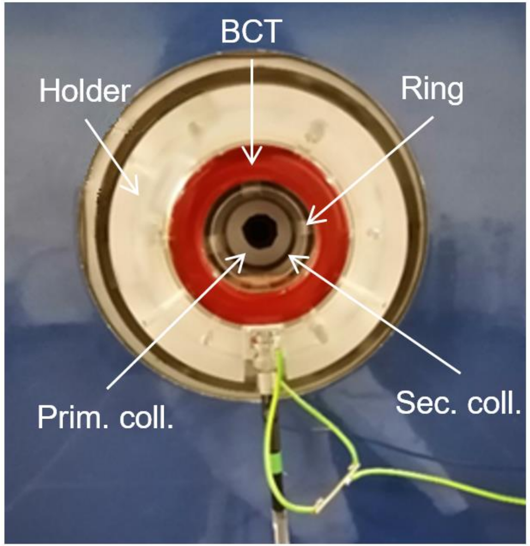
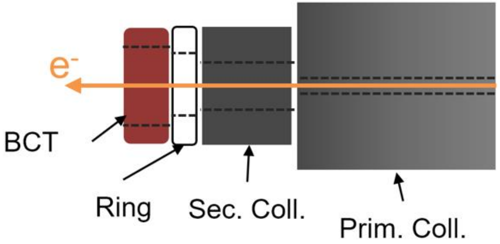
Committee Website | **Directory:** Committee | Membership

Email	You may send email to this group now using gmail or outlook. - or - You may save the address *2021.TG359@aapm.org* to your local address book. This alias updates hourly from the AAPM Directory.
Charge	1. Review the uncertainty in determining the dose and need for standardization in dosimetry for FLASH beams to be used in experiments, research and potentially in pre-clinical applications. a. Assess the factors that would affect the beam dosimetric characteristics in FLASH mode, compared to standard delivery. 2. Assess the suitability of radiation measurement equipment (ion chambers, film, diodes, Faraday cap, etc) for FLASH mode. 3. Provide general guidelines on calibration, dosimetry and reporting of beams in FLASH mode.
Bylaws:	Not Referenced. **Rules:** Not Referenced.
Approved Date(s)	1/1/2021 - 12/31/2021
Committee Keywords:	No Keywords Entered
Most recent status update:	- Click to view more or update.

Beam monitoring

Beam monitoring / eRT6

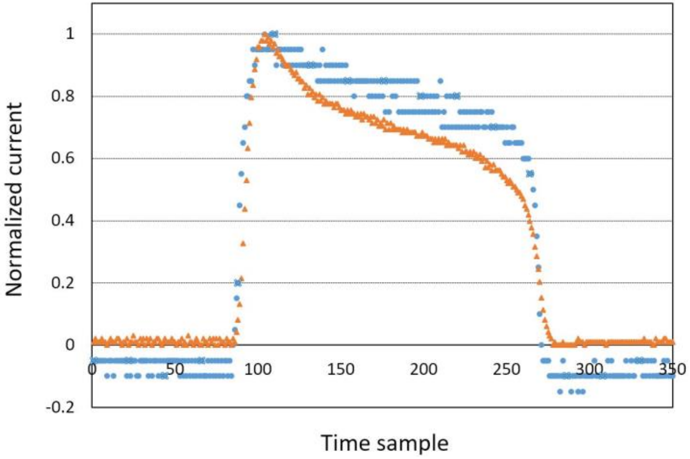




Jorge, submitted

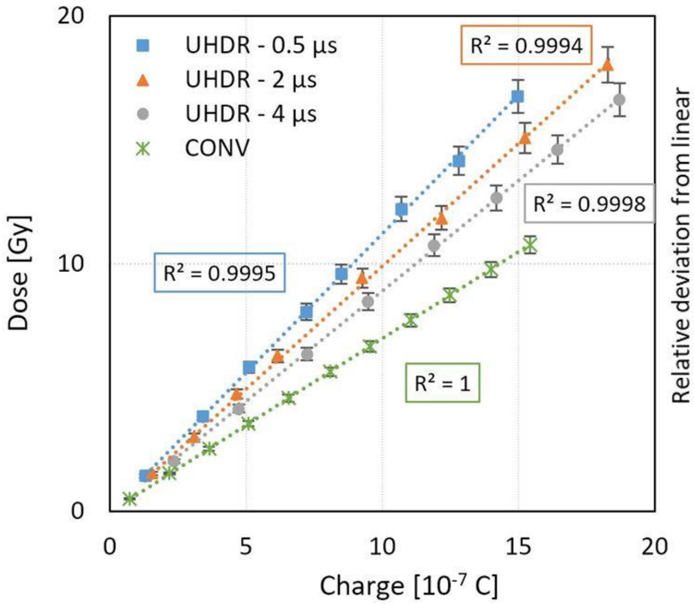
Beam monitoring / eRT6

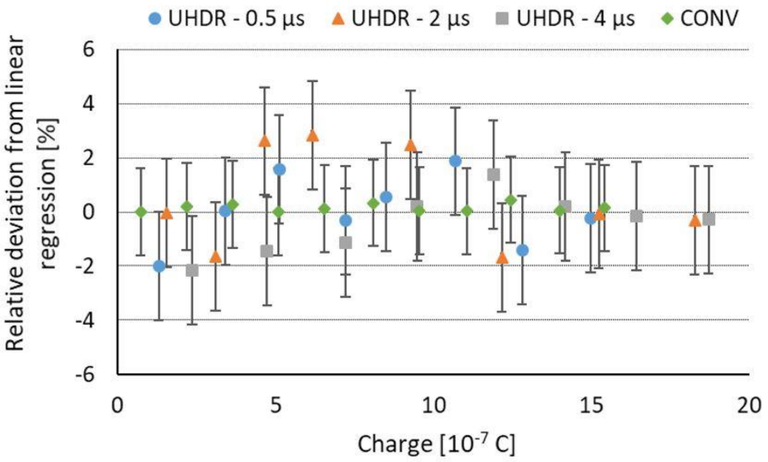
Parameter investigated	GT [V]	PW [µs]	PRF [Hz]	N_p
PRF	300	2	10	1 - 8
			100	
			250	
PW	300	0.5	100	3 - 35
		2		1 - 12
		4		1 - 8



Jorge, submitted

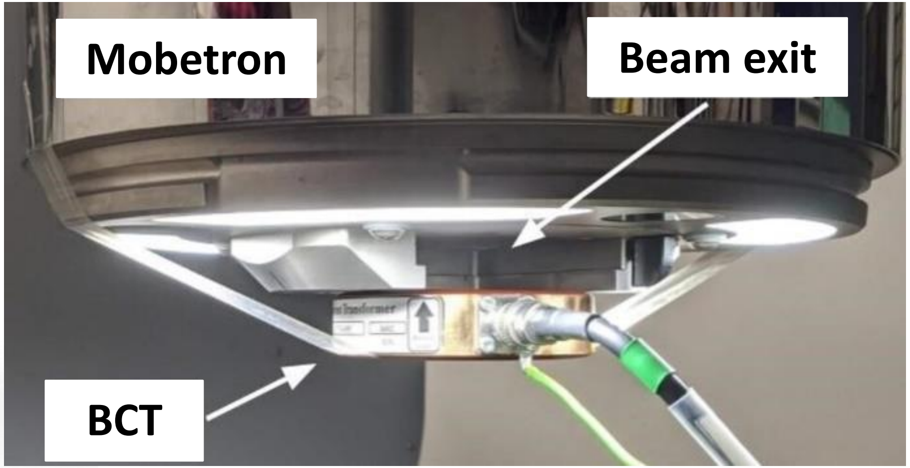
Beam monitoring / eRT6



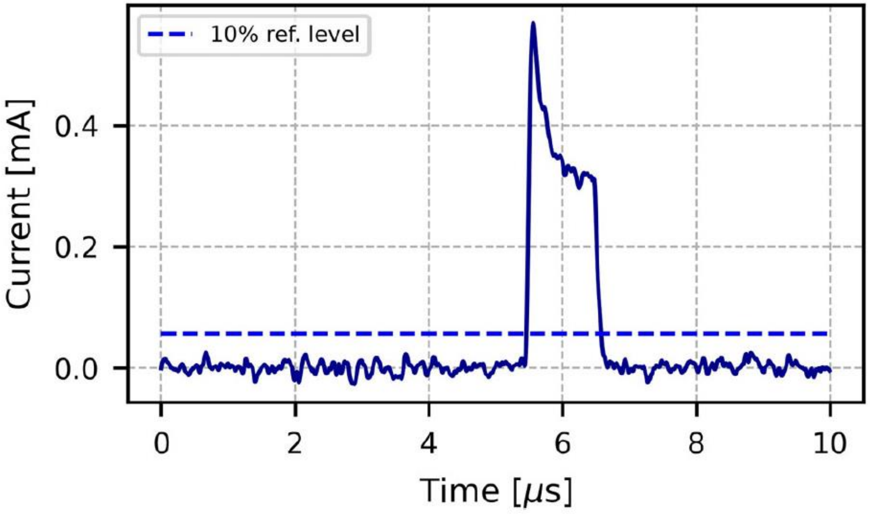


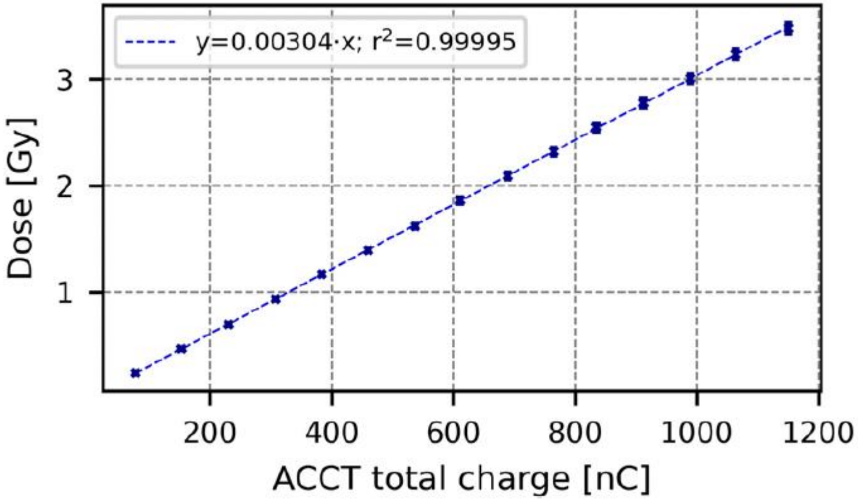
Jorge, submitted

Beam monitoring / Mobetron

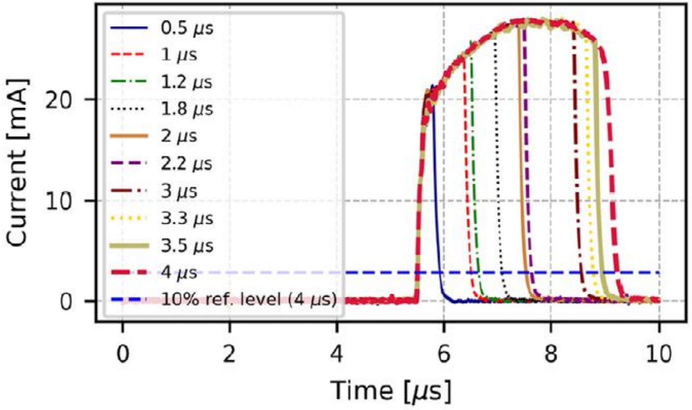


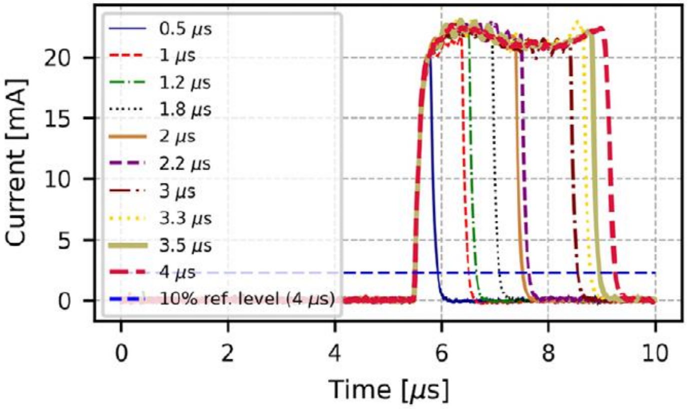
Linearity CONV





Pulse shape and monitoring



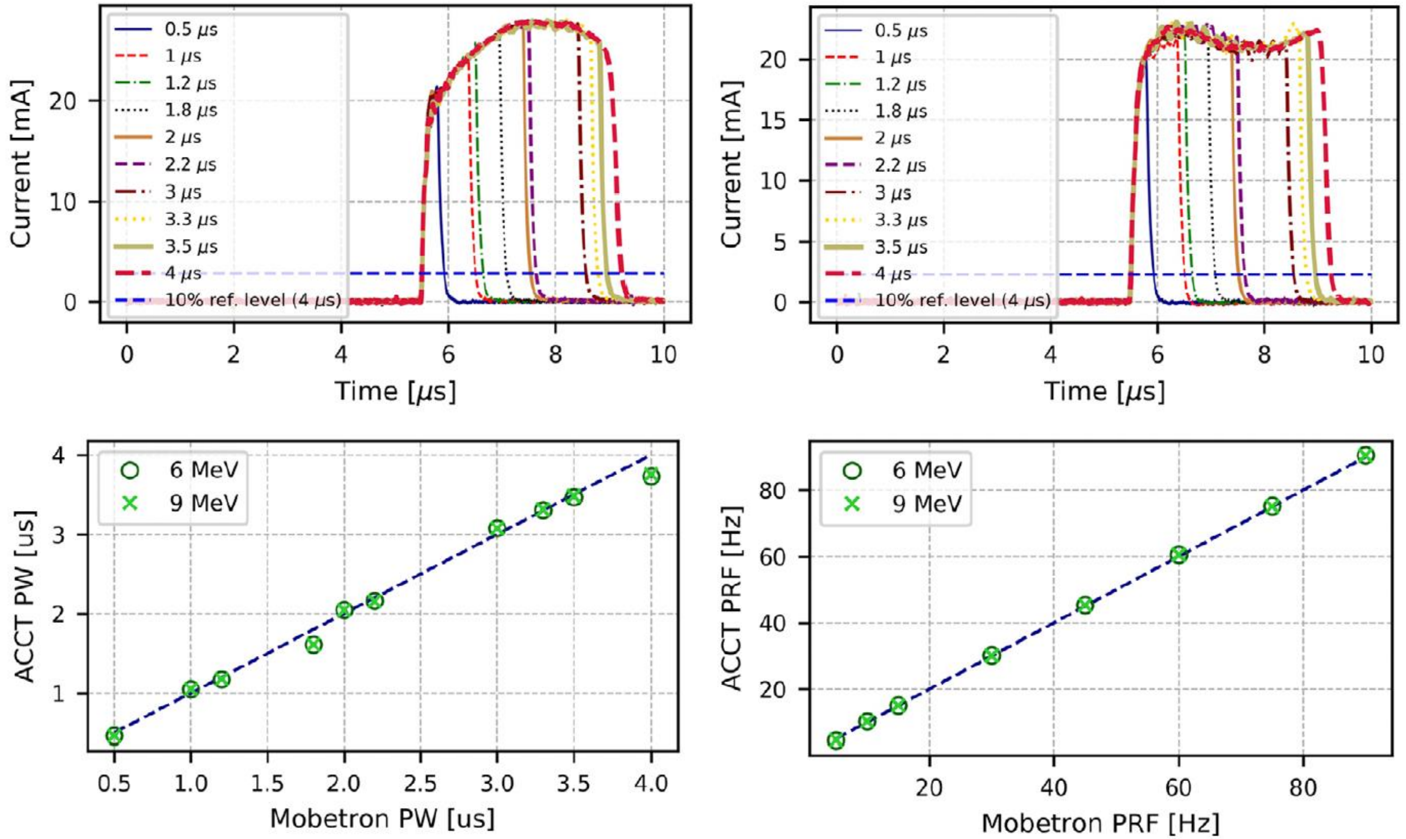


	Nominal values	ACCT values
PW [μs]	1.2	1.14 ± 0.02
PRF [μs]	30	30.3 ± 0.1
Number of pulses []	180	179 ± 3

Abbreviations: ACCT, AC current transformer; PW, pulse width; PRF, pulse repetition frequency.

Oesterle, 2021

Linearity with PW and PRF



Oesterle, 2021

Stability

	9 MeV CONV	6 MeV UHDR	9 MeV UHDR
Short-term stability [%]	0.43	1.79	2.09
Long-term stability [%]	2.38	2.85	3.98

Abbreviation: UHDR, ultra high dose rate.

canton de vaud

Oesterle, 2021

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Clinical trial

Clinical trial

IntraOp Announces First Patients Enrolled in FLASH Clinical Trial

July 08, 2021

IntraOp Medical Corporation announced today that Lausanne University Hospital (CHUV, Switzerland) enrolled the first patients in the **Impulse Trial: A phase I dose-escalation study of high dose rate radiotherapy with electrons in patients with skin metastases from melanoma**. The trial is a key milestone for the groundbreaking research collaboration agreement between IntraOp and the CHUV, executed in 2020. The Impulse Trial is the first in the world to evaluate the potential of leveraging the biological phenomenon known as the "FLASH Effect" to provide radiotherapy with curative intent to radio-resistant cancers.

Clinical protocole

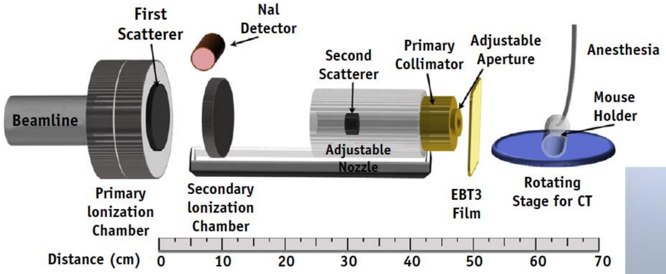
A phase I dose finding study of high dose rate radiotherapy in patients with skin metastases from melanoma

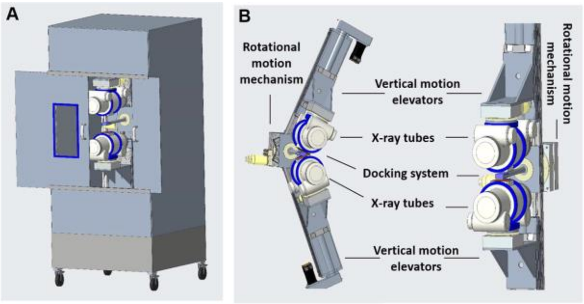
Dose level	**Level 1**	**Level 2**	**Level 3**	**Level 4**	**Level 5**	**Level 6**	**Level 7**
FLASH dose	22 Gy	24 Gy	26 Gy	28 Gy	30 Gy	32 Gy	34 Gy

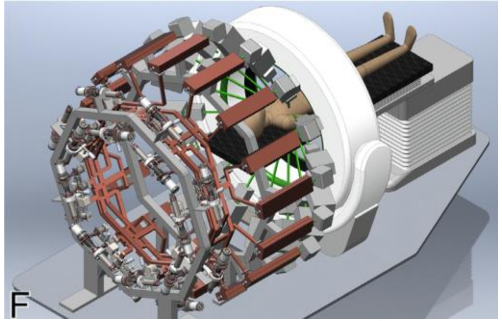
Duration of Dose Limiting Toxicity (DLT) period: 4 weeks post-irradiation

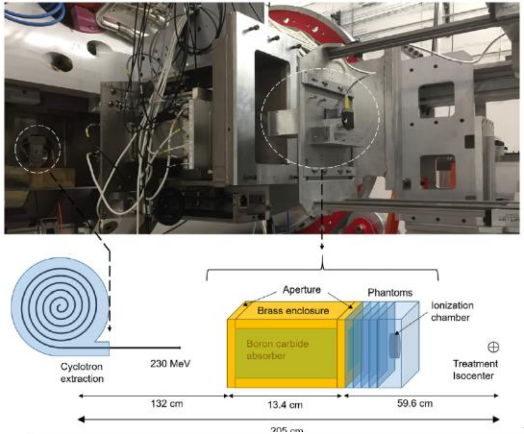
OTHER DEVICES

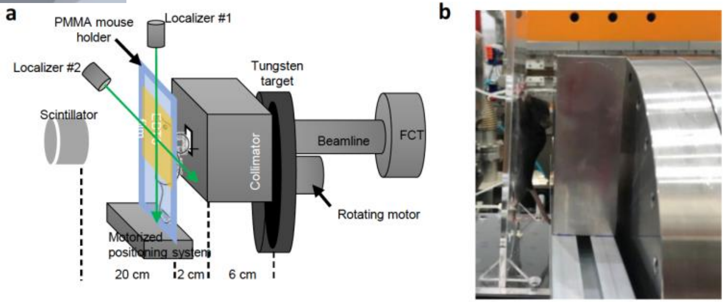
Non electron UHDR











Maxim 2019 ; Gao 2020 ; Diffenderfer 2020 ; Darafsheh 2020 ; Resaee 2021

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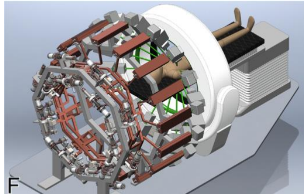
The future

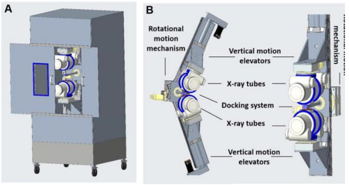
Which beam ?

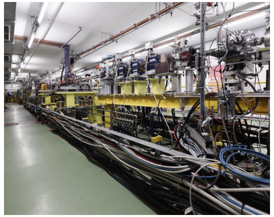
The «dream beam»

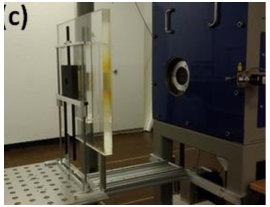
So what is the "dream beam" for FLASH

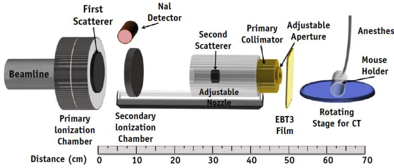
- Able to treat superficial and deep seated tumours
- Cheap with a compact design (fit in to space of a conventional linac)
- Move the beam not the patient
- Not sensitive to tissue heterogeneity or air gaps
- Able to treat in conventional and FLASH modes?
- Treatment planning system in place or under development
- Treatment Workflow can be integrated in to clinic
- Commercial system exists now or can be reterofitted
- Optimised to key FLASH parameters
  - Dose
  - Dose rate
  - Fractionation

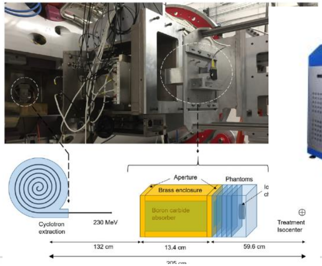


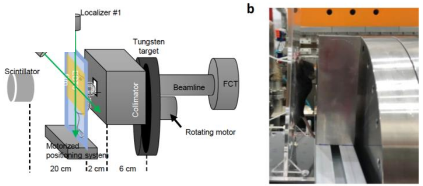




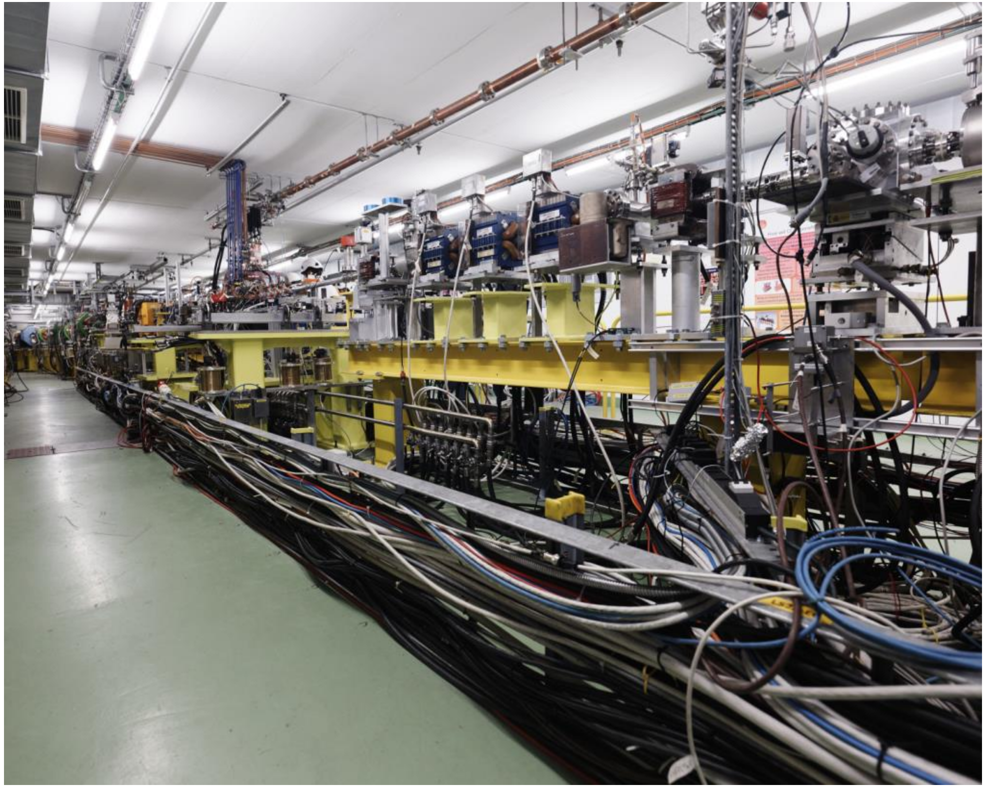


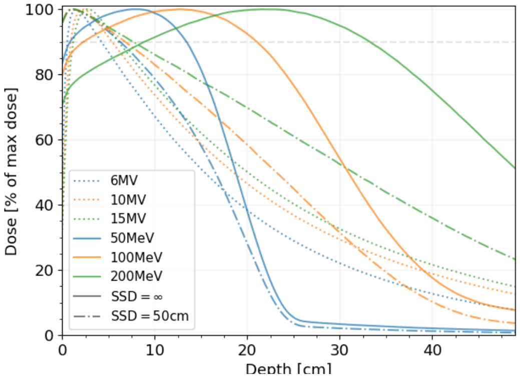


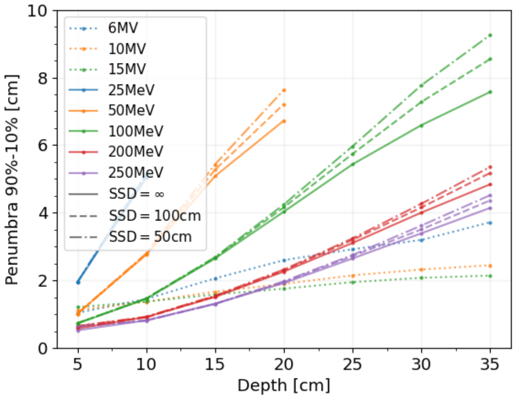




VHEE CHUV/CERN project







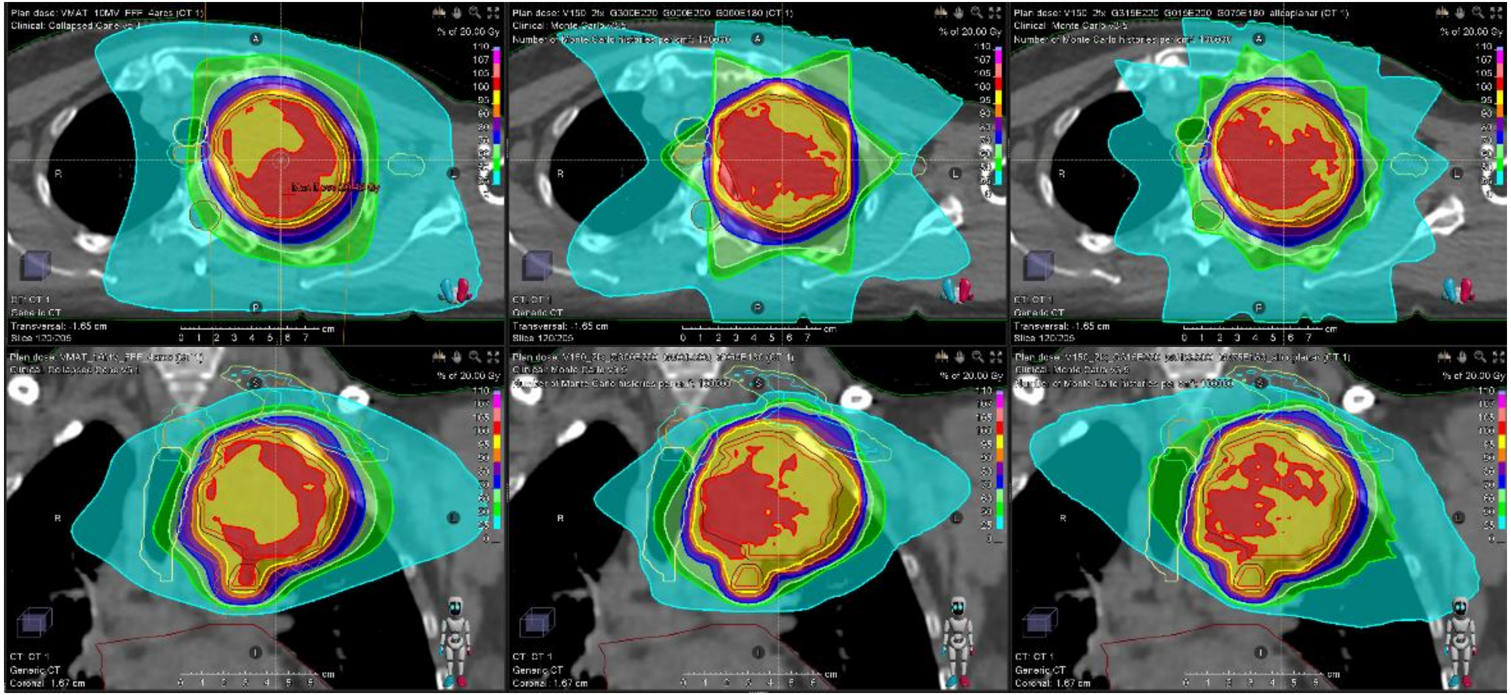
Boehlen 2021

Lung T4 190cc, spherical shape

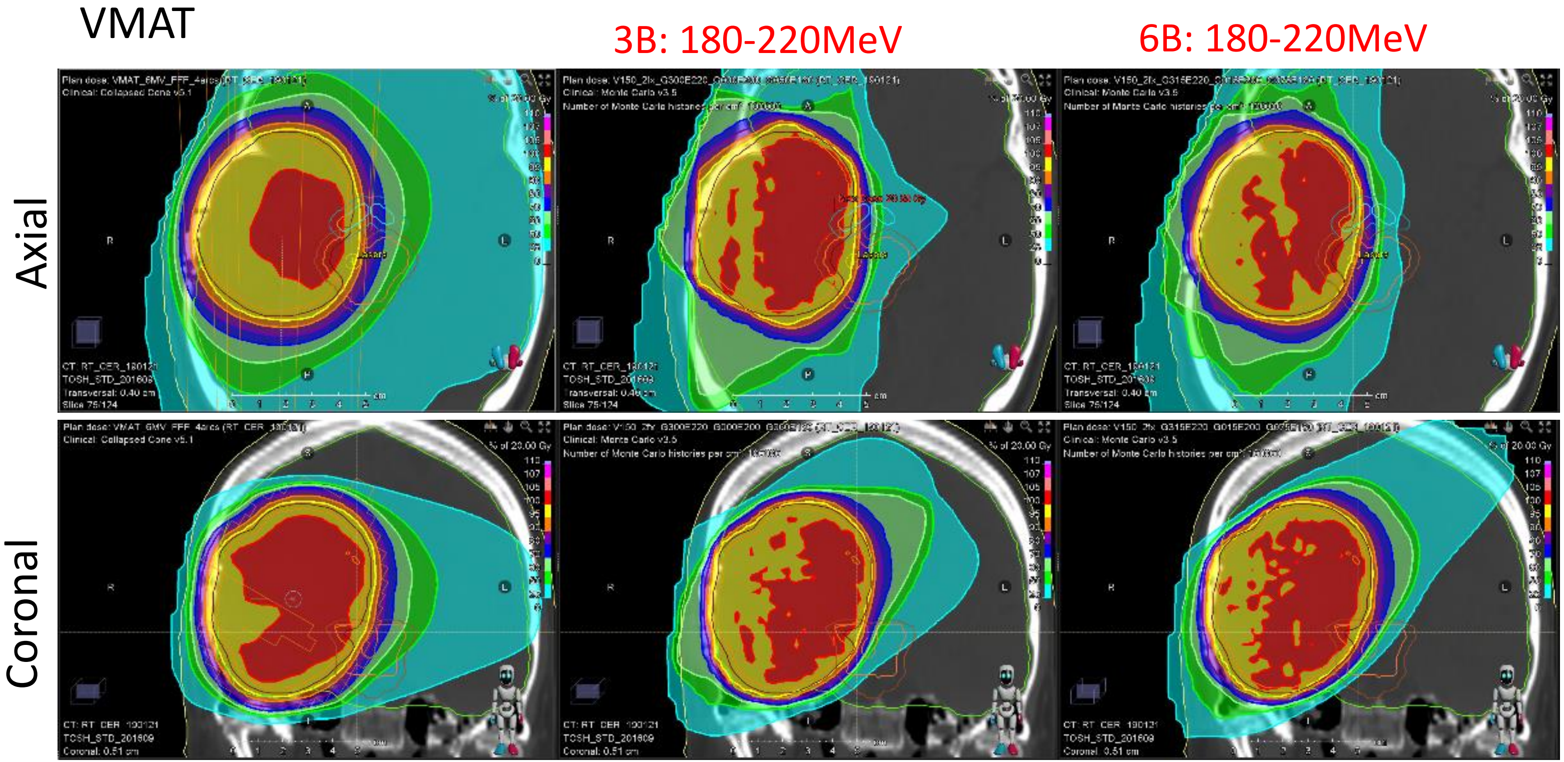
VMAT | 3B: 180-220MeV | 6B: 180-220MeV

Axial

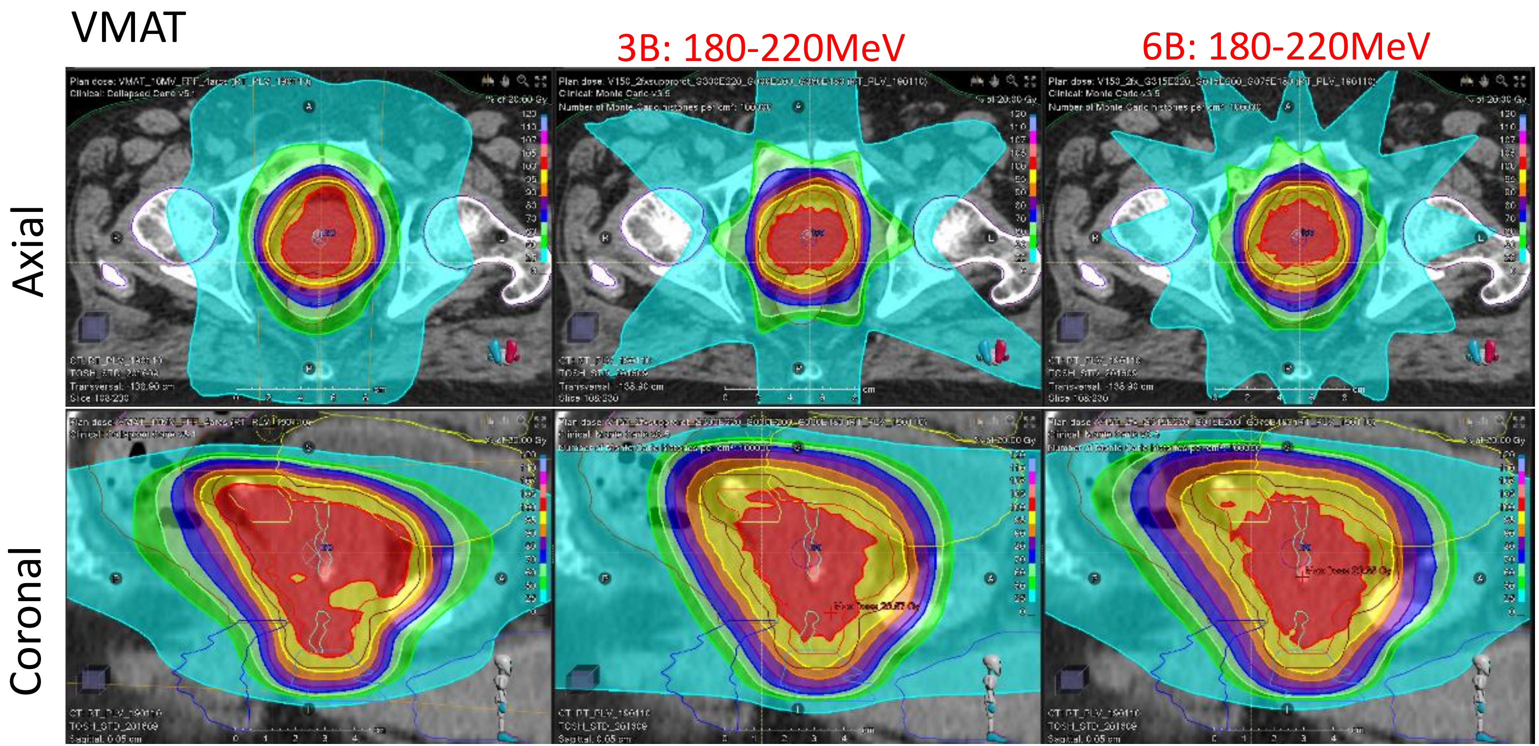
Coronal



Brain 190cc, spherical shape



Prostate 104cc, spherical shape

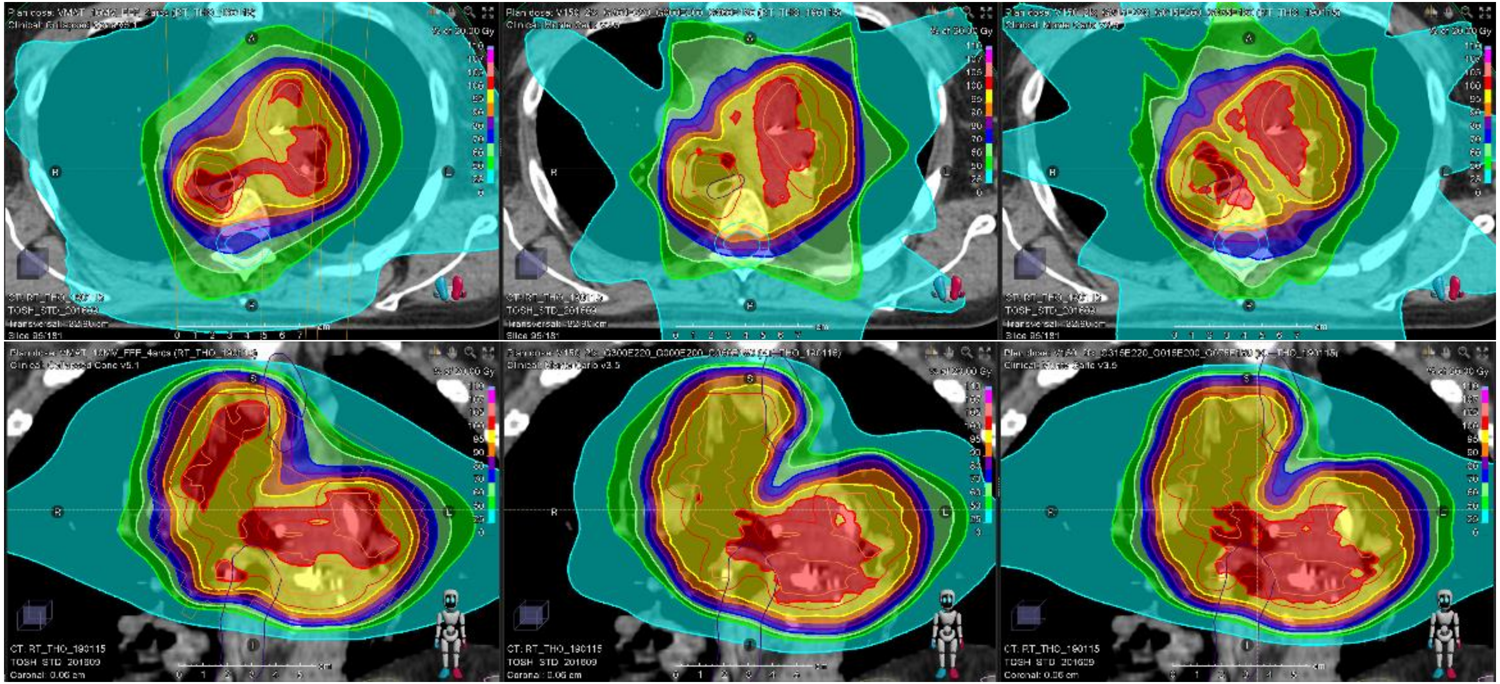


Mediastinum 173cc, concave

VMAT | 3B: 180-220MeV | 6B: 180-220MeV

Axial

Coronal



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Conclusions

FLASH-RT is a promising technique

Imprvement needed in

- Metrological traceability
- Monitoring and control of the beam
- Safety issues to be solved
- Capability to treat deep seated tumors