Physikalisch-Technische Bundesanstalt
Braunschweig and Berlin
National Metrology Institute

Current state-of-the-art and coming developments on dosimetry for FLASH radiotherapy

Andreas Schüller
Department 6.2 “Dosimetry for Radiation Therapy and Diagnostic Radiology”
on behalf of the UHDpulse consortium

Workshop “FLASH radiation therapy in Brandenburg, Berlin and Northern Germany”
25.-26.8.21, DESY Zeuthen and virtual

Current state-of-the-art and coming developments on dosimetry for FLASH radiotherapy

UHDpulse

Contents

- Dosimetry for conventional clinical electron beams
- FLASH irradiation: Ultra-high dose rate / dose per pulse
- The UHDpulse project
- PTB reference field for ultra-high dose per pulse
- Coming developments on dosimetry for FLASH RT

Dosimetry for conventional clinical electron beams

Primary standard of the unit Gy for absorbed dose to water

$$D_w = d\varepsilon/dm$$

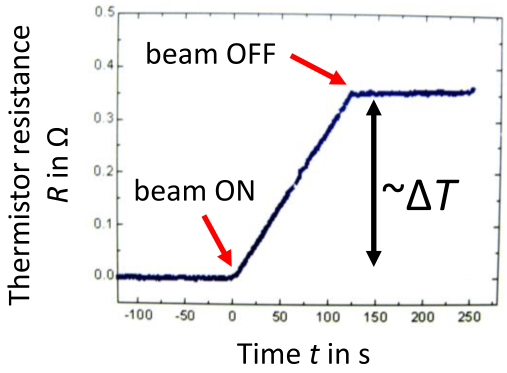
1 Gy = 1 J/Kg

ε: energy deposit in medium, *m:* mass of medium (water)

$$D_w = c_p \cdot \Delta T \cdot \Pi k_i$$

$\Delta T = 0.24$ mK/Gy

c_p: Heat capacity of water, ΔT: Radiation-induced temperature rise
Πk_i: corrections for perturbations (heat transport, etc.)

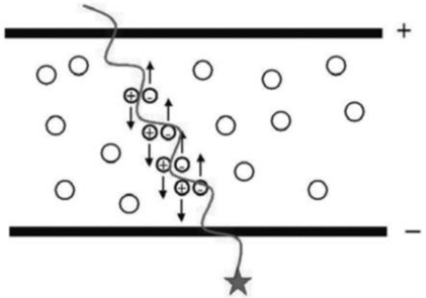


PTB water calorimeter at a medical LINAC

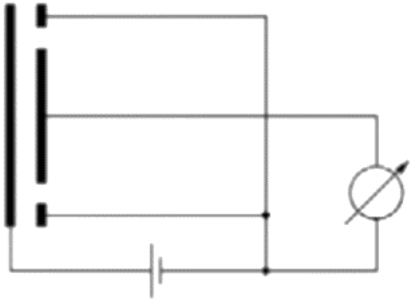
Clinical beams: 4 – 22 MeV, 100 – 400 Hz,
1 - 4 µs macropulse, mean dose rate < 5 Gy/min

Dosimetry for conventional clinical electron beams

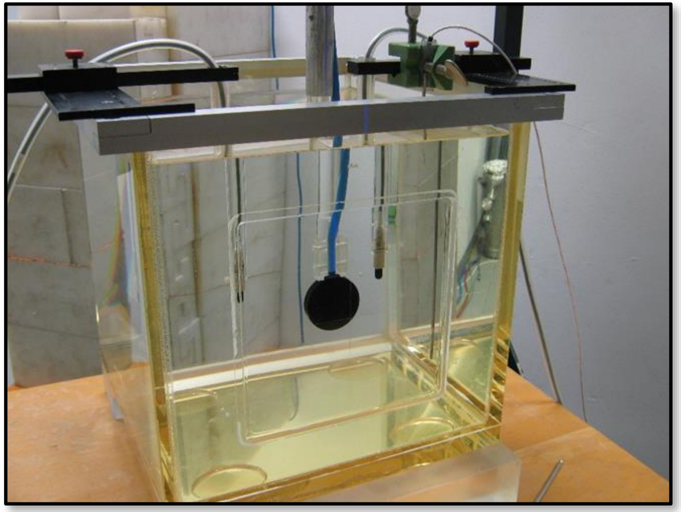
Ionization chambers: the standard for reference dosimetry in conventional radiotherapy



ionizing radiation creates ion pairs



high voltage   current



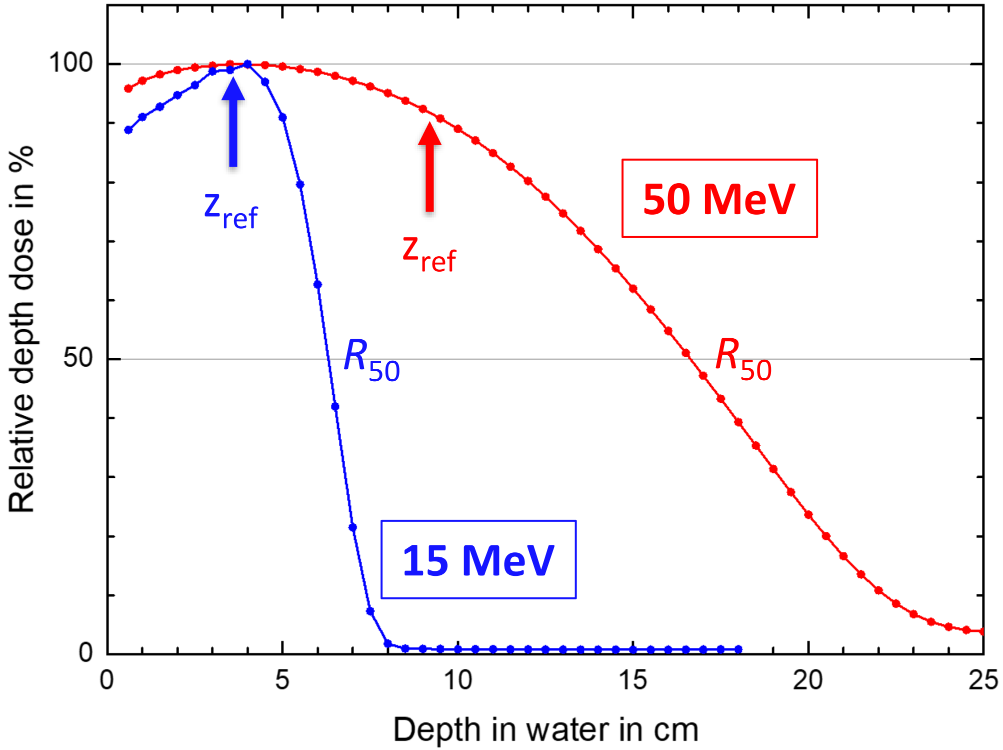
Plane-parallel ionization chamber in a water phantom (recommended for electron beams)

Codes of Practice:
Formalism for clinical reference dosimetry of high-energy electron beams (3 – 50 MeV)

→ IAEA's TRS 398, AAPM's TG-51, DIN 6800-2

Dosimetry for conventional clinical electron beams

Percentage depth dose curve (PDD)

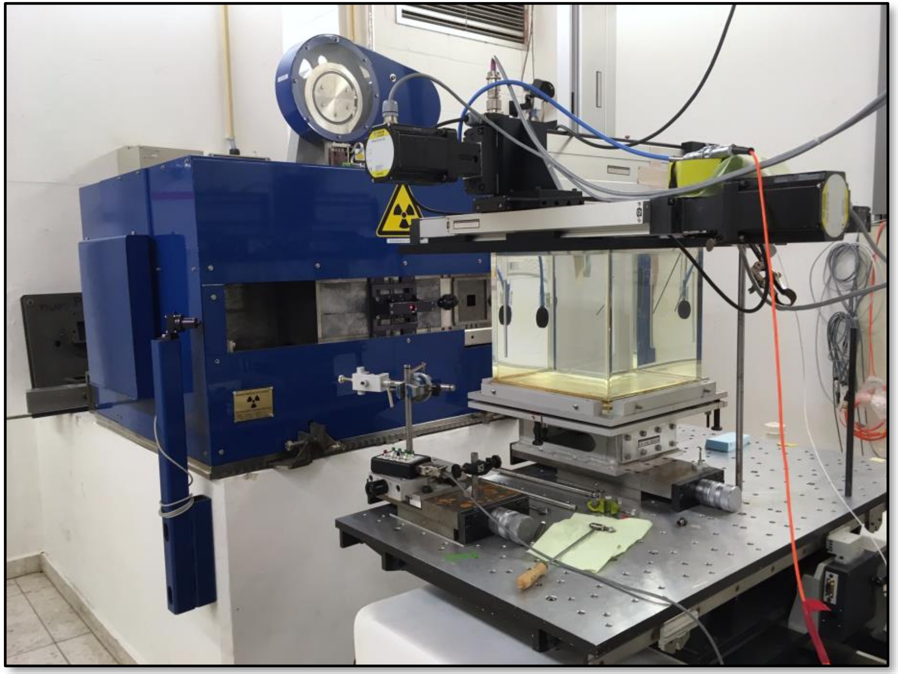


Dosimetry for conventional clinical electron beams

Absolute dose

$$D = (M\text{-}M_0)\ N\ k_\rho k_\mathrm{h} k_\mathrm{s} k_\mathrm{p} k_\mathrm{E}$$

D	absorbed dose (at $\boldsymbol{z}_{\mathbf{ref}}$)
M	reading
M_0	zero reading
$\boldsymbol{N}$	**calibration coefficient (Co-60)**
	correction due to
k_ρ	air density
k_h	humidity
$\boldsymbol{k}_\mathbf{s}(\dot{\boldsymbol{D}})$	**ion recombination**
k_p	polarity
$\boldsymbol{k}_\mathbf{q}(\boldsymbol{E})$	**radiation quality (electrons vs. Co-60 photons)**



^{60}Co Source of PTB's calibration service
(dose rate determined by means of water calorimeter)

FLASH irradiation: Ultra-high dose rate / dose per pulse

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]

In vitro studies suggested that sub-millisecond pulses of radiation elicit less genomic instability than continuous, protracted irradiation at the same total dose. To determine the potential of ultrahigh dose-rate irradiation in radiotherapy, we investigated lung fibrogenesis in C57BL/6J mice exposed either to short pulses (≤500 ms) of radiation delivered at ultrahigh dose rate (≥40 Gy/s, FLASH) or to conventional dose-rate irradiation (≤0.03 Gy/s, CONV) in single doses. The growth of human HBCx-12A and HEp-2 tumor xenografts in nude mice and syngeneic TC-1 Luc+ orthotopic lung tumors in C57BL/6J mice was monitored under similar radiation conditions. CONV (15 Gy) triggered lung fibrosis associated with activation of the TGF-β (transforming growth factor–β) cascade, whereas no complications developed after doses of FLASH below 20 Gy for more than 36 weeks after irradiation. FLASH irradiation also spared normal smooth muscle and epithelial cells from acute radiation-induced apoptosis, which could be reinduced by admin-

treatment time

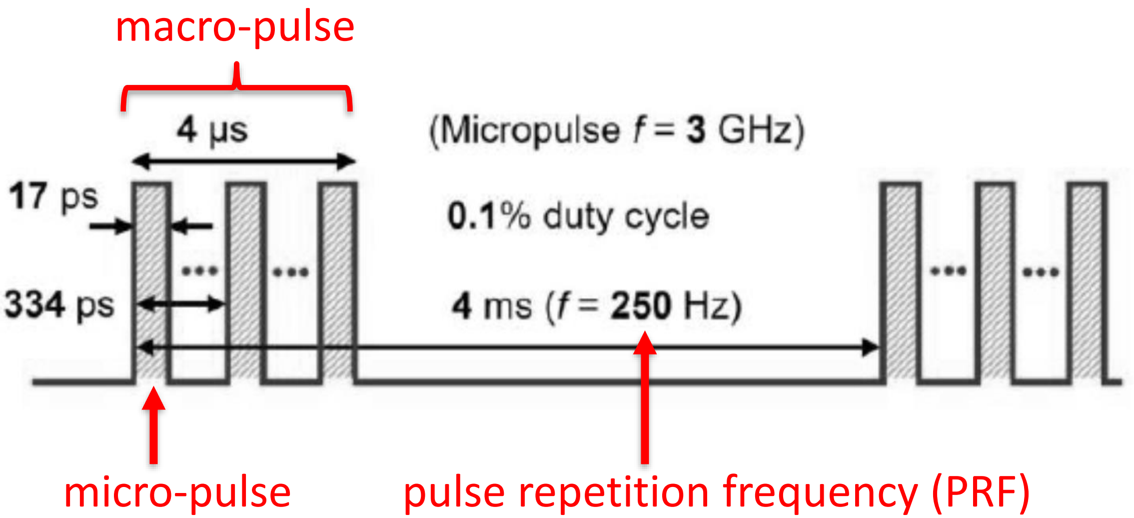
average dose rate
(dose/treatment time)

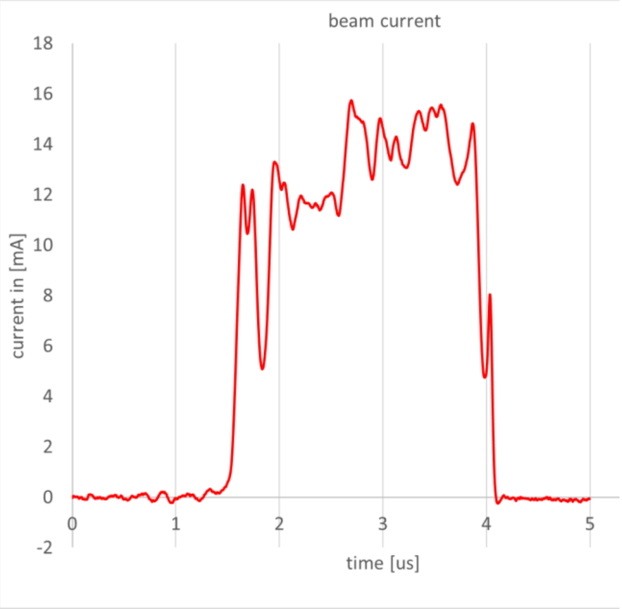
delivered total dose

Science Translational Medicine 6 (2014) 245, pp. 245ra93
http://dx.doi.org/10.1126/scitranslmed.3008973

FLASH irradiation: Ultra-high dose rate / dose per pulse

Pulse structure of a Linac beam





FLASH irradiation: Ultra-high dose rate / dose per pulse

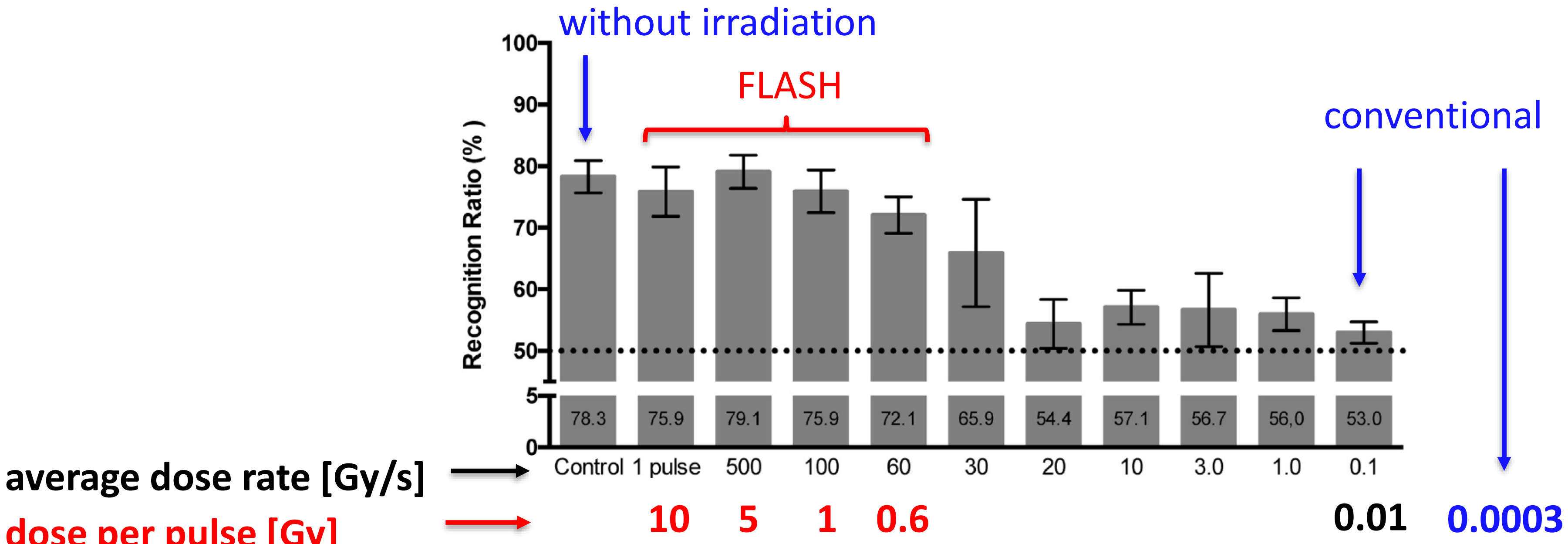
Comparison FLASH vs. conventional irradiation

	FLASH (linac beam)	conventional
average dose rate	**> 40 Gy/s**	**5 Gy/min**
treatment time	< 500 ms	4 min
macro pulse width	2 μs	4 μs
pulse repetition frequency	10 Hz	300 Hz
pulse dose rate (within macro-pulse)	~ MGy/s	< 100 Gy/s
dose per pulse (DPP)	0.6 – 10 Gy	0.3 mGy

ultra-high dose per pulse

FLASH irradiation: Ultra-high dose rate / dose per pulse

Mice brain irradiation with 10 Gy



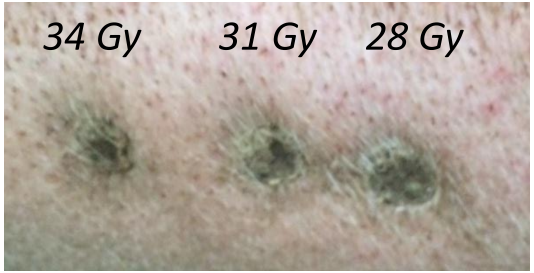
Montay-Gruel *et al.*, Radiotherapy and Oncology 124 (2017) 365
http://dx.doi.org/10.1016/j.radonc.2017.05.003

FLASH irradiation: Ultra-high dose rate / dose per pulse

<u>FLASH irradiation of the skin of a pig</u>

Conventional and FLASH Irradiation (with same total dose)

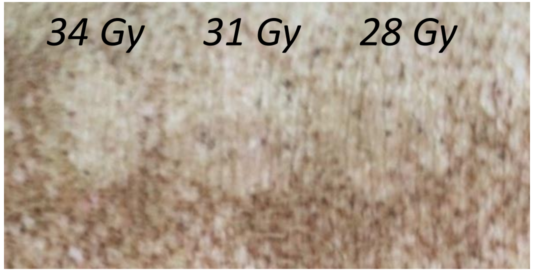
Conventional
(5 Gy/min)



necrotic lesions

FLASH
(300 Gy/s)

3 Gy/pulse



normal appearance of skin

Vozenin *et al.*, Clin Cancer Res 25 (2019) 35
http://dx.doi.org/10.1158/1078-0432.CCR-17-3375

FLASH irradiation: Ultra-high dose rate / dose per pulse

Treatment of a human Patient
(lymphoma on skin)

delivered total dose: 15 Gy
10 pulses (of 1 μs duration)
treatment time: 90 ms
dose per pulse: 1.5 Gy

Day 0

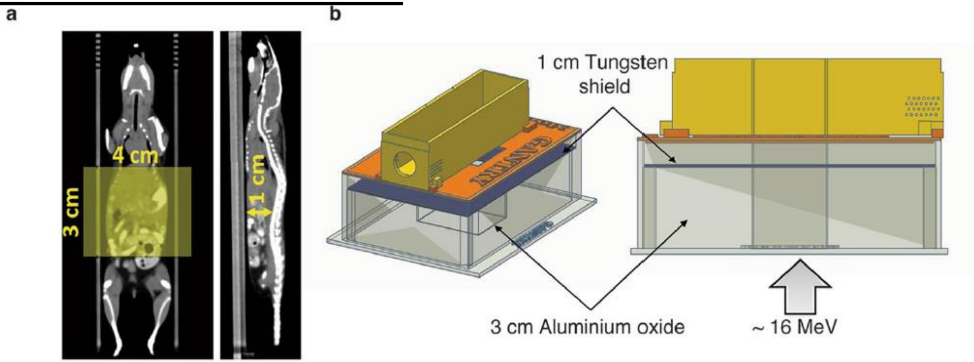
3 weeks

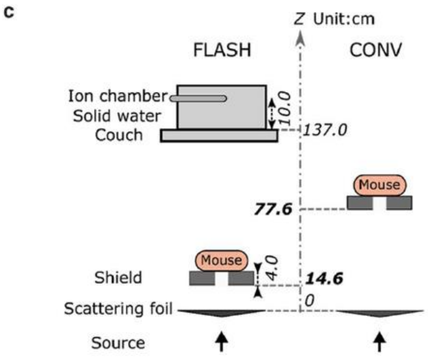
5 months

Bourhis et al., Radiother. Oncol. (2019)
http://dx.doi.org/10.1016/j.radonc.2019.06.019

FLASH irradiation: Ultra-high dose rate / dose per pulse

Treatment of cancer at mice





Parameters	FLASH	CONV
e-beam energy	~16 MeV	~16 MeV
Repetition rate	108 Hz	72 Hz
Dose per pulse	2.0 Gy	0.00109 Gy
Average dose rate	216 Gy/s	0.07863 Gy/s (4 Gy/min)
Instantaneous dose rate (pulse length 5 μs)	4.0E5 Gy/s	218.5 Gy/s

Levy et al. Scientific Reports (2020) “Abdominal FLASH irradiation …”
https://doi.org/10.1038/s41598-020-78017-7

FLASH irradiation: Ultra-high dose rate / dose per pulse

<u>Treatment of cancer at dogs</u>

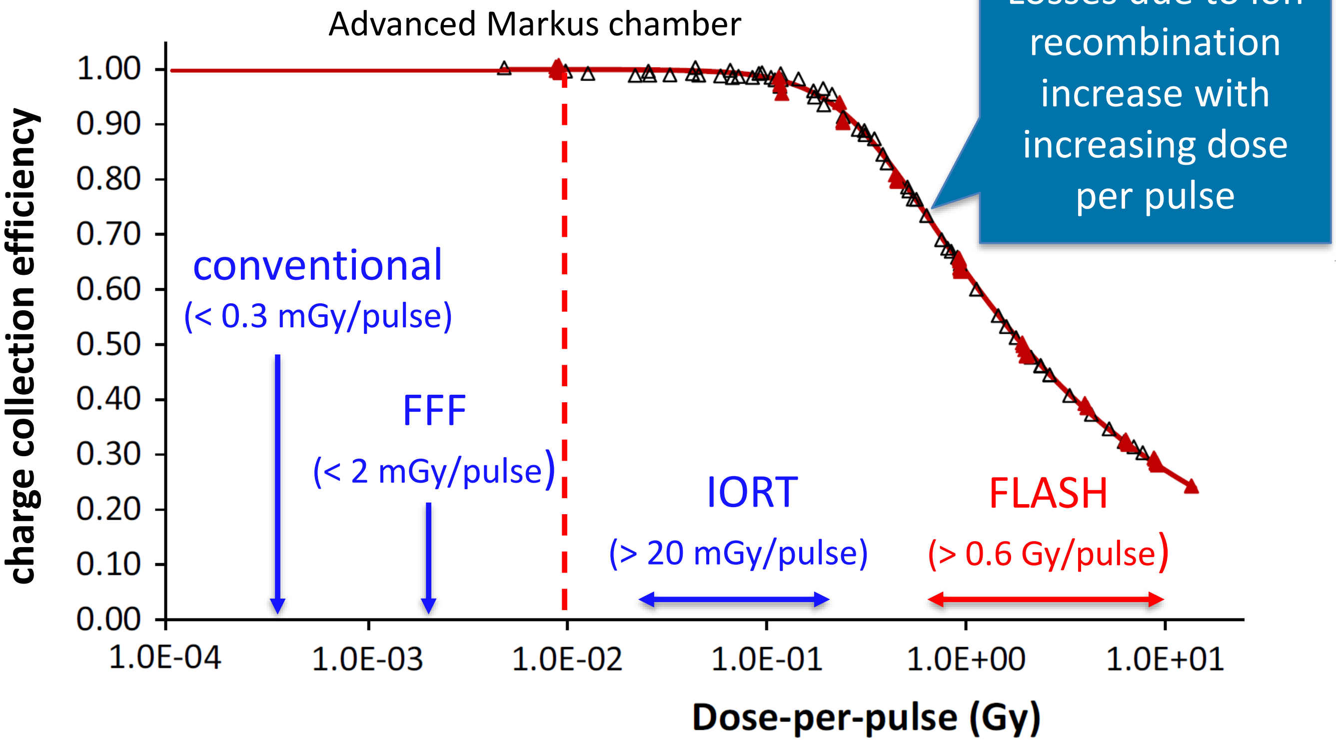
delivered total dose: 15 – 35 Gy
7-16 pulses
Average dose rates: 400-500 Gy/s
pulse dose rates: ~0.7 MGy/s
treatment time: 30 ms to 75 ms
dose per pulse: 2 Gy

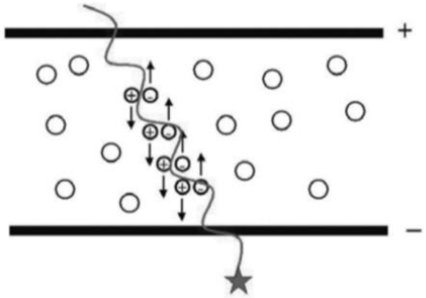
treatment of the leg with in vivo dose measurements by radiochromic film

Konradsson et al., Front. Oncol. (2021) 11:658004
https://doi.org/10.3389/fonc.2021.658004

FLASH irradiation: Ultra-high dose rate / dose per pulse

Behavior of ionization chambers





high ion density: ion pairs recombine before reaching the electrodes

Petersson *et al.*, Med Phys 44 (2017) 1157
https://doi.org/10.1002/mp.12111

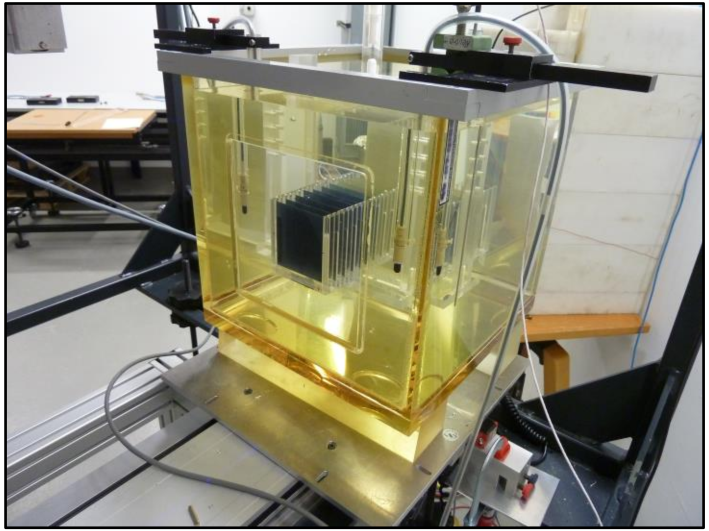
FLASH irradiation: Ultra-high dose rate / dose per pulse

Passive detectors:

OSLD (Optically Stimulated Luminescence detectors), TLD (Thermoluminescent dosimeter), alanine pellets, radiochromic film

Advantage:
- independent of dose rate, suitable for FLASH

Disadvantage:
- not real-time measurement, takes hours or days to get a dose value
- relatively large measurement uncertainty (> 5 %)

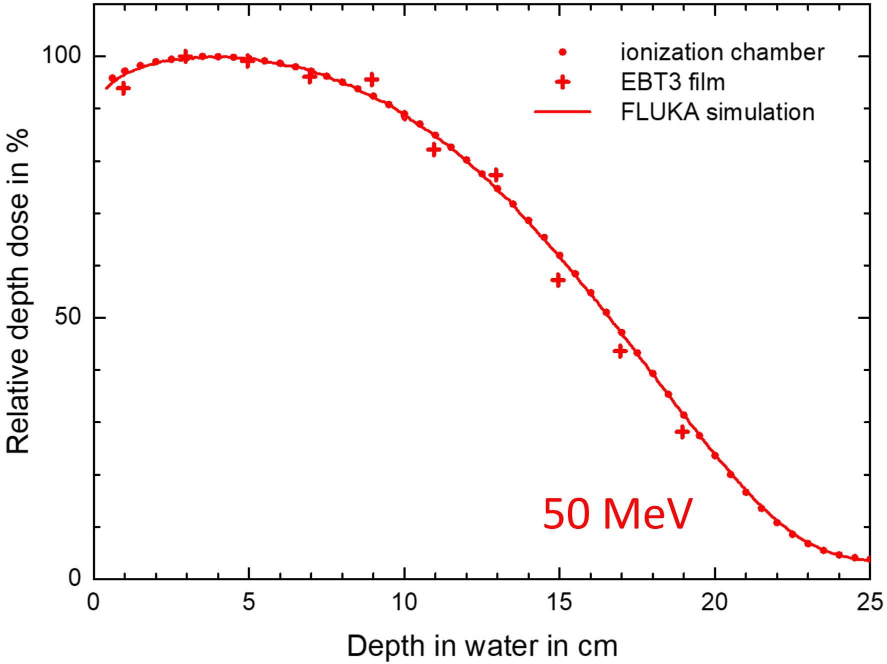


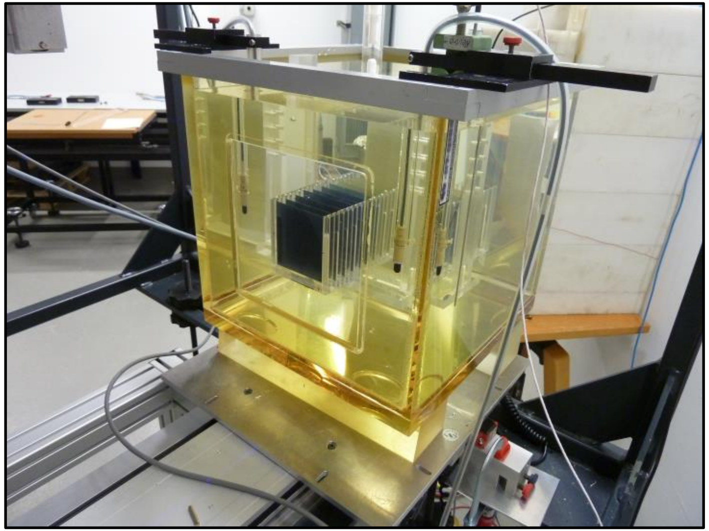
Stack of equispaced EBT3 films after exposure to 50 MeV electron beam

Kokurewicz et al., Front. Phys. (2020) 8:568302
https://doi.org/10.3389/fphy.2020.568302

FLASH irradiation: Ultra-high dose rate / dose per pulse

Passive detectors: radiochromic film





Stack of equispaced EBT3 films after exposure to 50 MeV electron beam

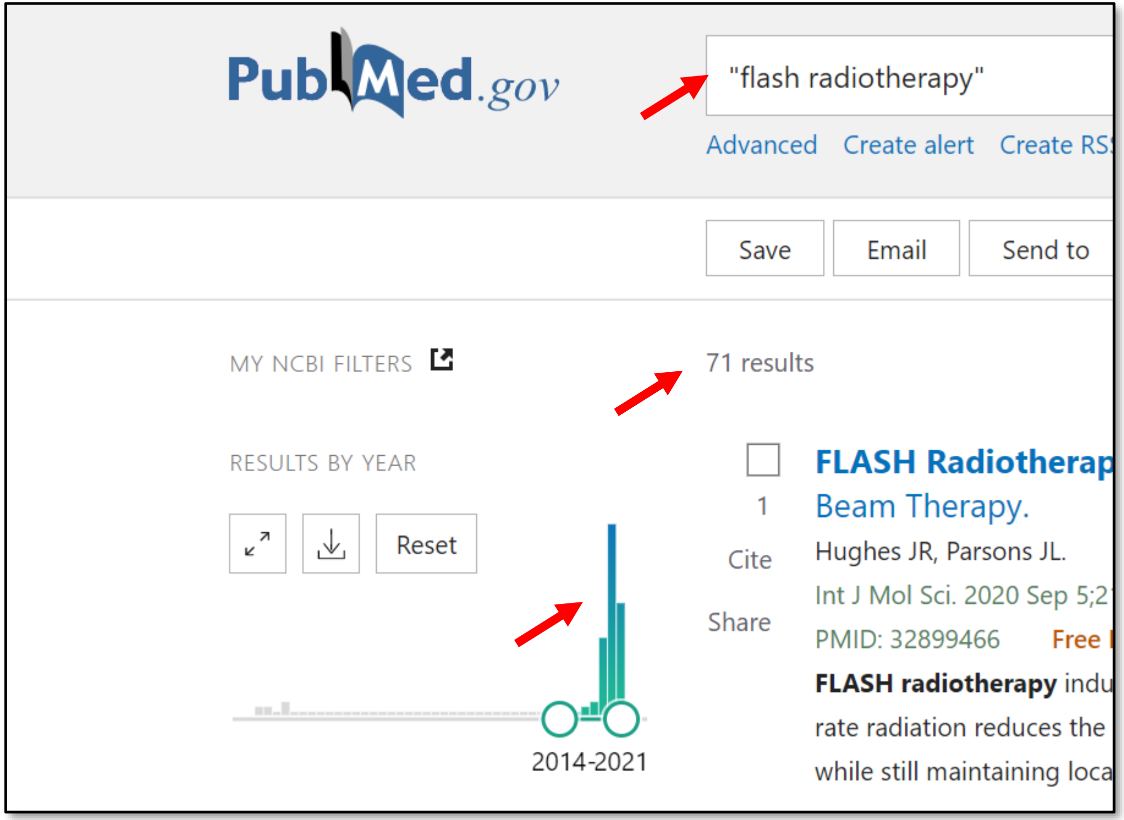
Kokurewicz et al., Front. Phys. (2020) 8:568302
https://doi.org/10.3389/fphy.2020.568302

FLASH radiotherapy

- number of institutes interested in FLASH RT and the number of FLASH papers published per year is increasing.

- currently: 3 paper/month

- urgent need for tools for traceable dose measurements for FLASH RT and real-time dosimeter for ultra-high dose per pulse



EMPIR project UHDpulse

Type: Joint Research Project

Duration: Sep/2019-Feb/2023

Start: 1. Sept. 2019

Funding: 2.1 M €

Coordinator: Andreas Schüller (PTB)

Topic: tools for traceable dose measurements for:

- **FLASH radiotherapy**
- VHEE radiotherapy
- laser driven medical accelerators

http://uhdpulse-empir.eu/

The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

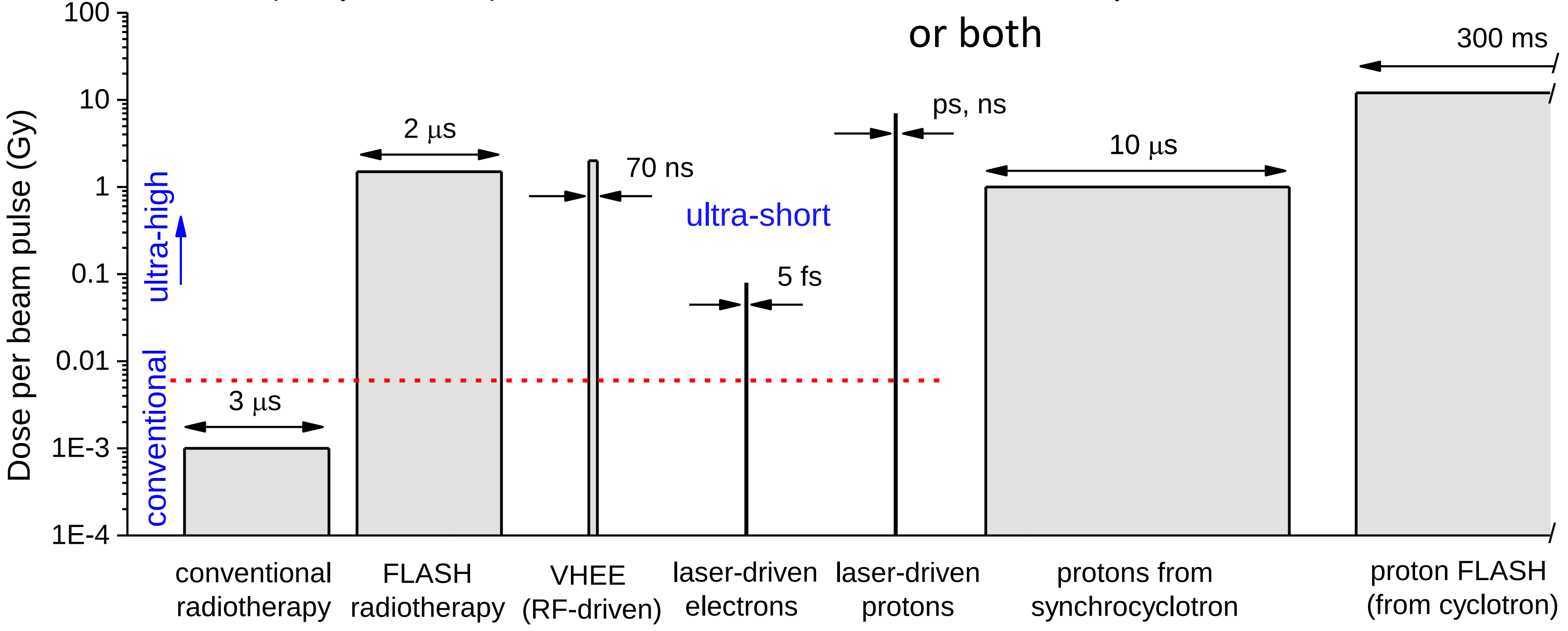
The European Metrology Programme for Innovation and Research (EMPIR):

- metrology-focused programme of coordinated R&D
- enables European metrology institutes, industrial and medical organisations, and academia to collaborate

“Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

electrons, protons (no photons)

ultra-high dose per pulse, ultra-short pulse duration or both



Partners and Collaborators

Metrology Institutes

Irradiation facility providers

Radiation detector developers

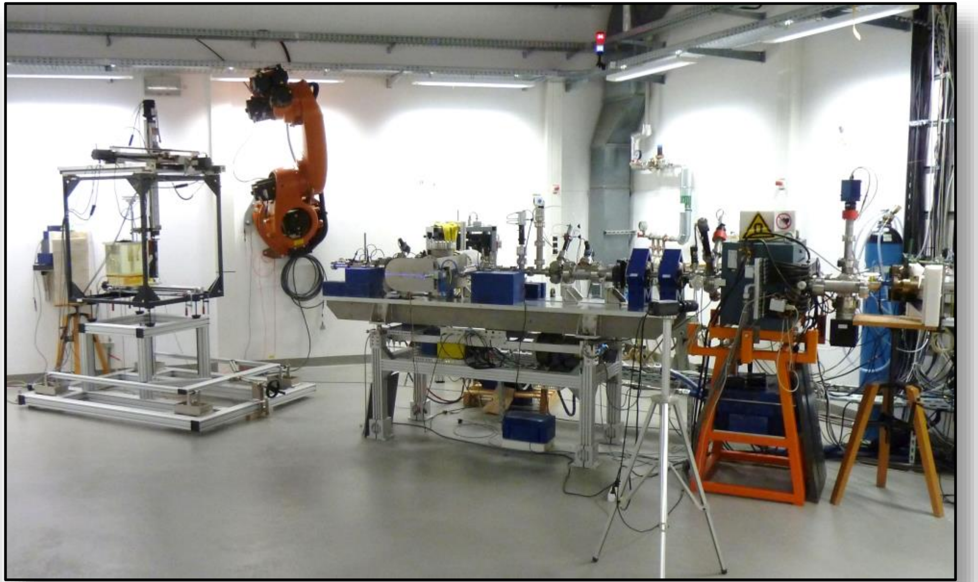
7 Metrology institutes
5 Hospitals
7 Universities
6 Research institutes
7 Companies
+ Proton therapy network

Interested institutes may join the as “collaborator”

PTB reference field for ultra-high dose per pulse

PTB's Research electron accelerator

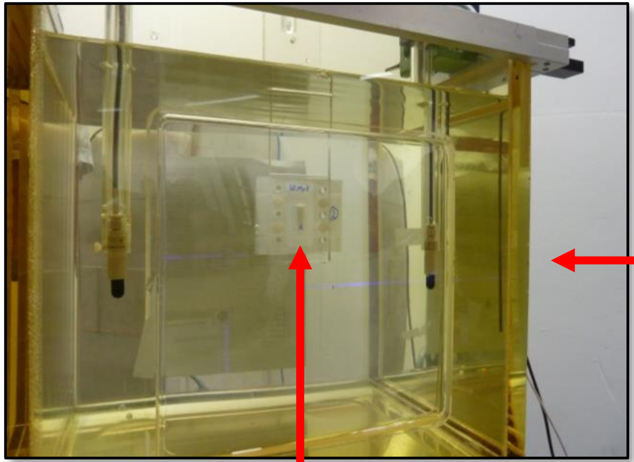
E = 0.5 – 50 MeV



Beam line with water phantom

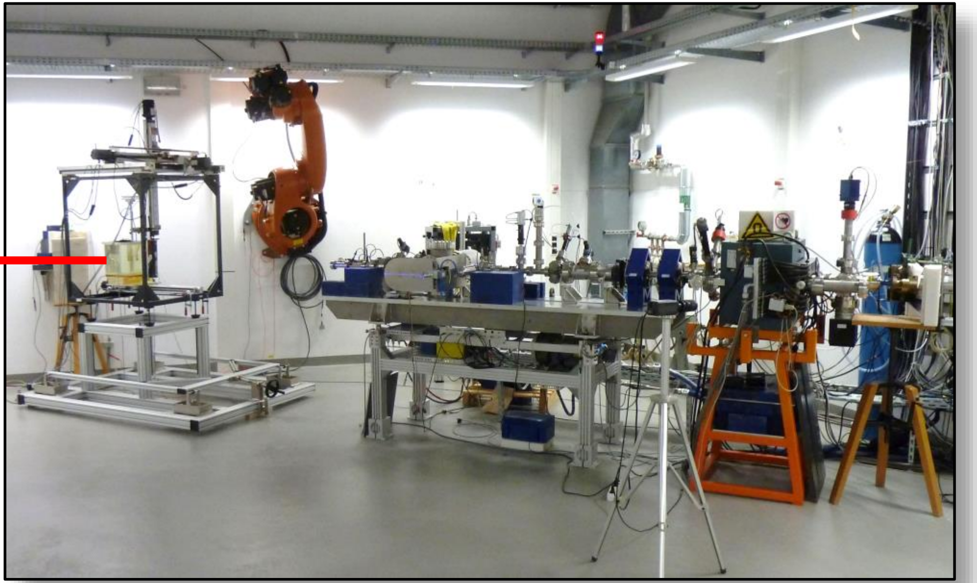
up to 7 Gy/pulse (SSD 0.7 m, 20 MeV)

PTB reference field for ultra-high dose per pulse



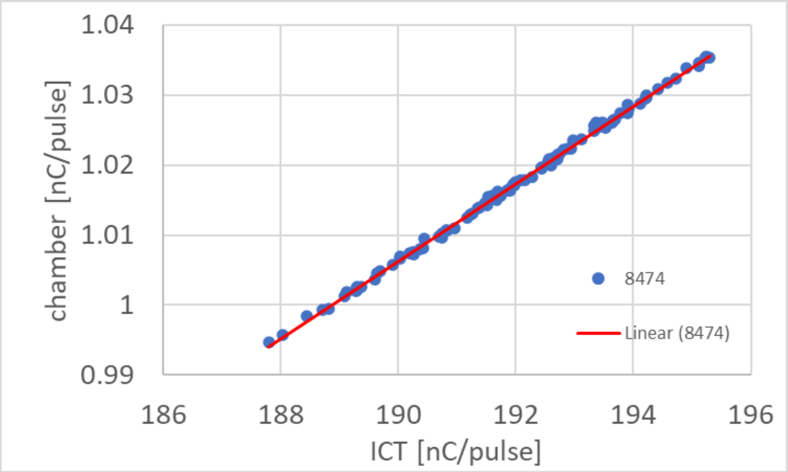
Alanine pellets at reference depth in water phantom

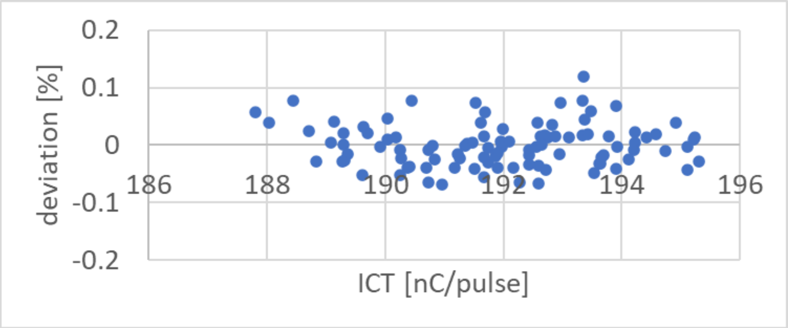
Dose traceable to PTB's primary standard

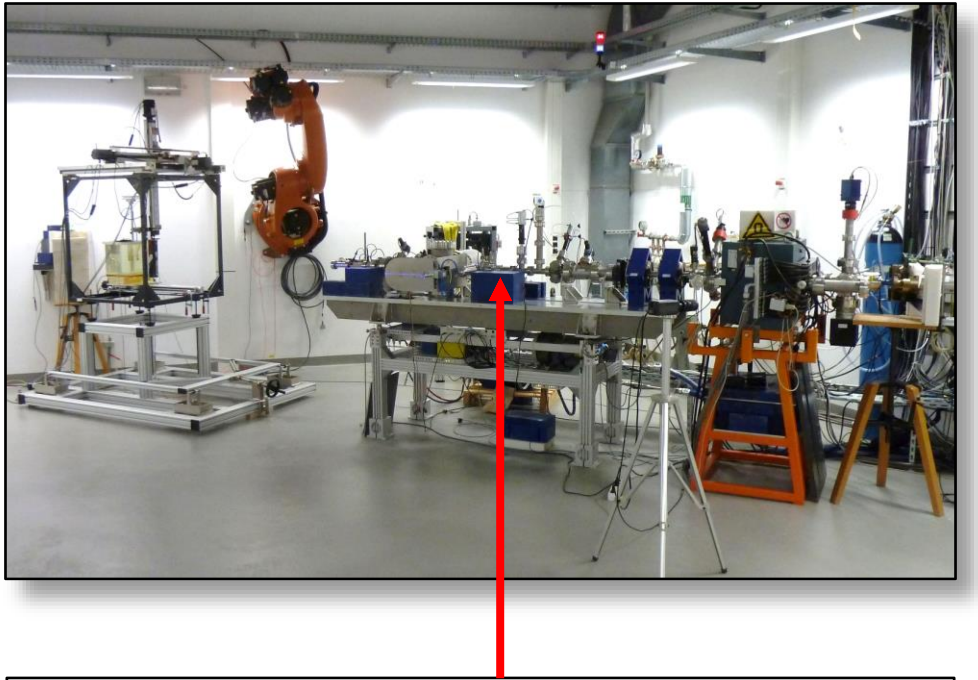


Beam line with water phantom

PTB reference field for ultra-high dose per pulse

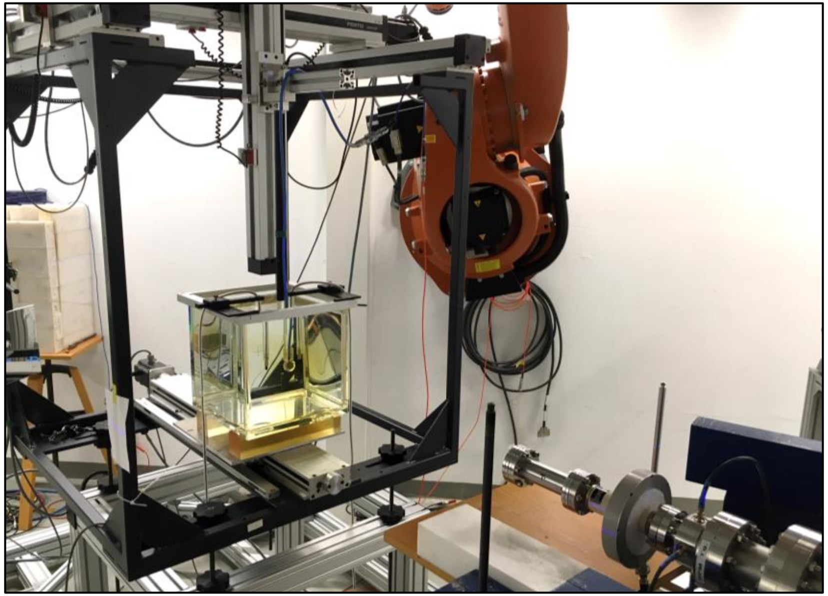






ICT: Non-destructive absolute beam pulse charge measurement (uncertainty < 0.1 % @70 nC/pulse)

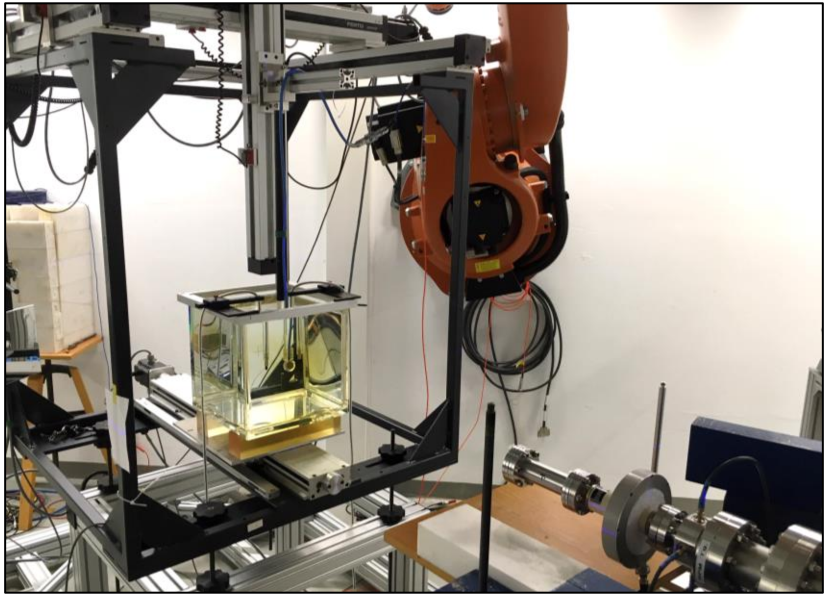
PTB reference field for ultra-high dose per pulse



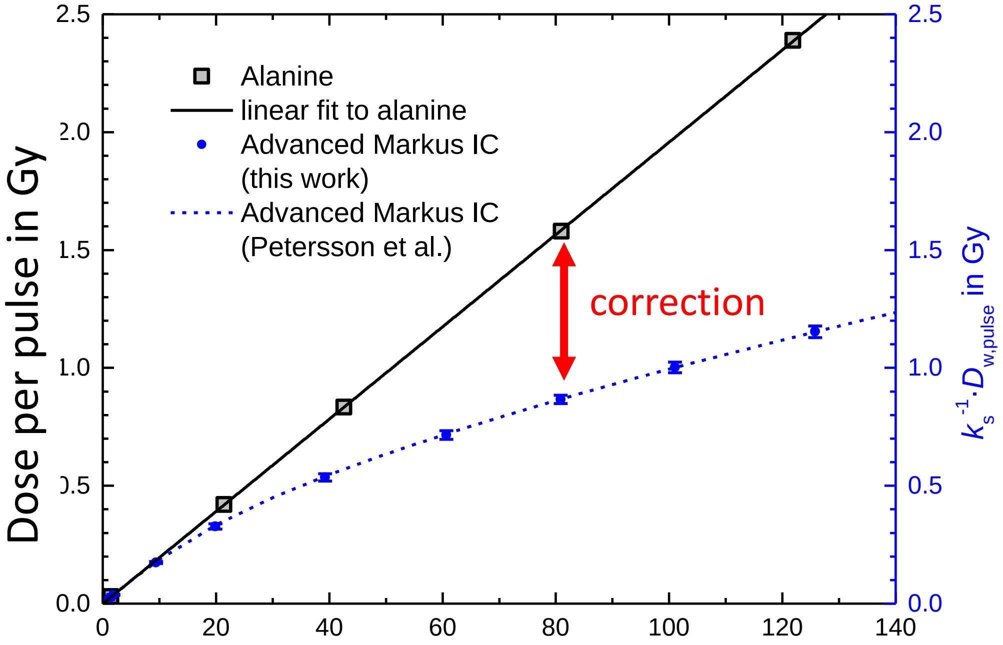
Detector under test at reference depth in water phantom

Video: Flashes of Cherenkov light in water phantom during ultra-high dose per pulse irradiation (PRF = 5 Hz)

PTB reference field for ultra-high dose per pulse



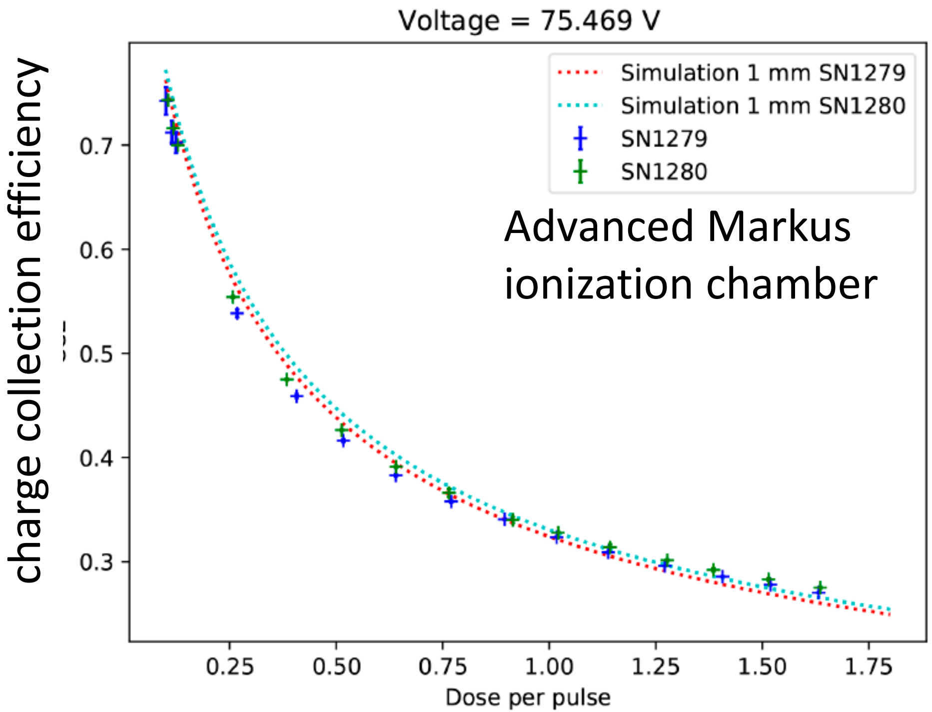
Detector under test at reference depth in water phantom

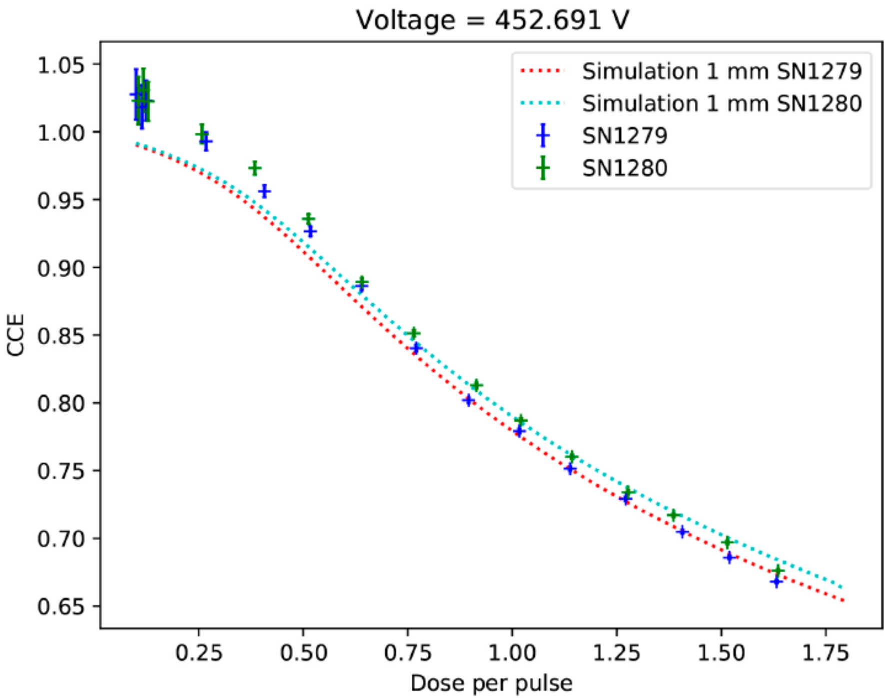


A Bourgouin et al., Front. Phys. (2020) 8:567340
https://doi.org/10.3389/fphy.2020.567340

Coming developments on dosimetry for FLASH RT

Corrections k_s at ultra-high DPP for available chambers

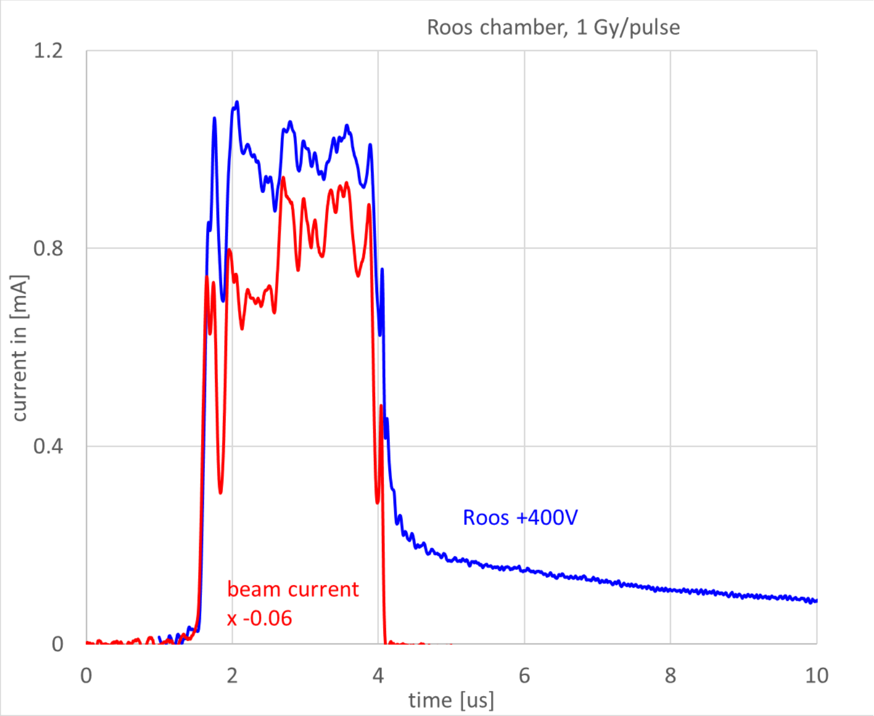


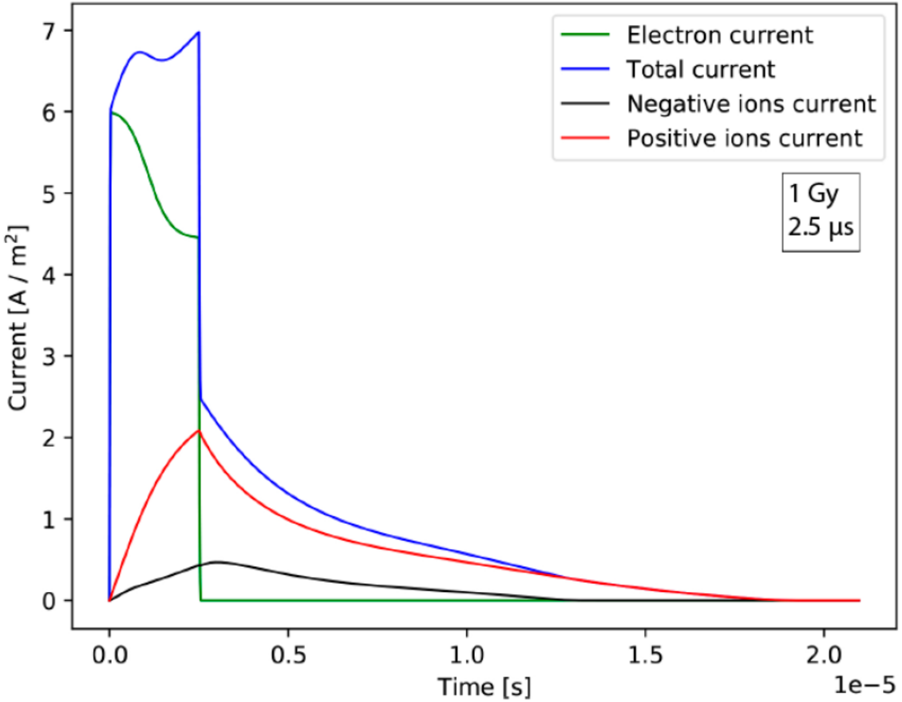


F. Gomez et al., The Challenge of Dosimetry in Flash Radiotherapy
https://indico.ific.uv.es/event/5983/contributions/13896/

Coming developments on dosimetry for FLASH RT

Corrections k_s at ultra-high DPP for available chambers: **Experiment for PITZ?**





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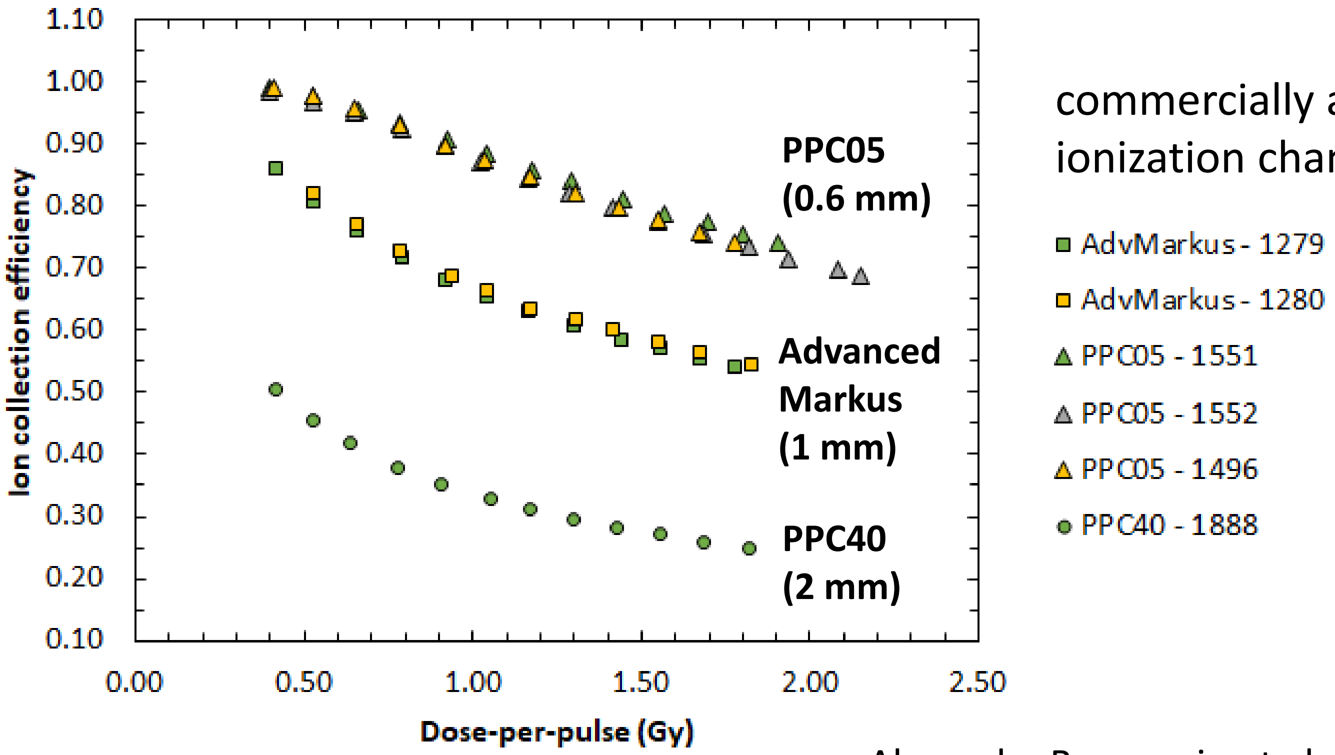
Coming developments on dosimetry for FLASH RT

Corrections k_s at ultra-high DPP for available chambers

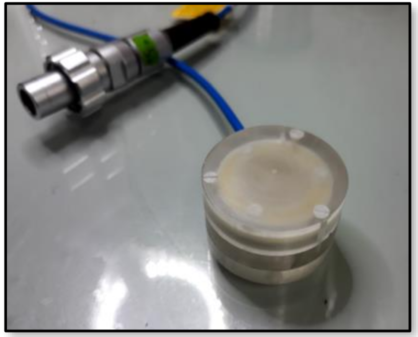


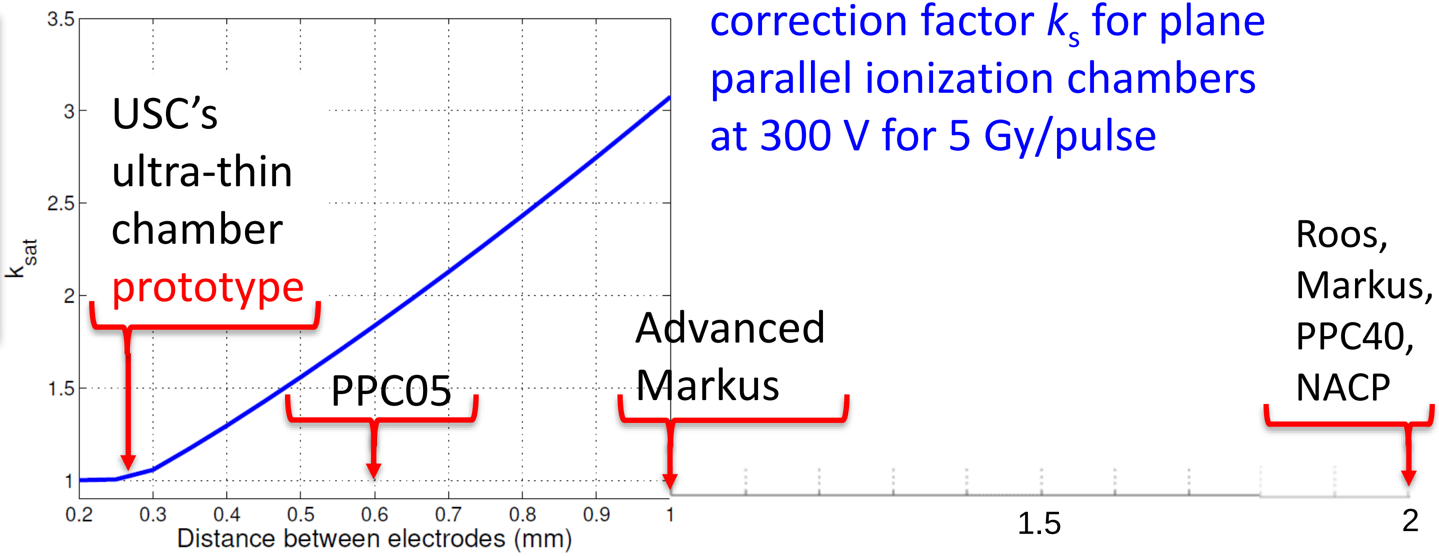
Alexandra Bourgoin et al.

http://uhdpulse-empir.eu/wp-content/uploads/2021-04_CIRMS2021_ABourgoin_Abstract.pdf

Coming developments on dosimetry for FLASH RT

Prototype ionization chambers for ultra-high DPP



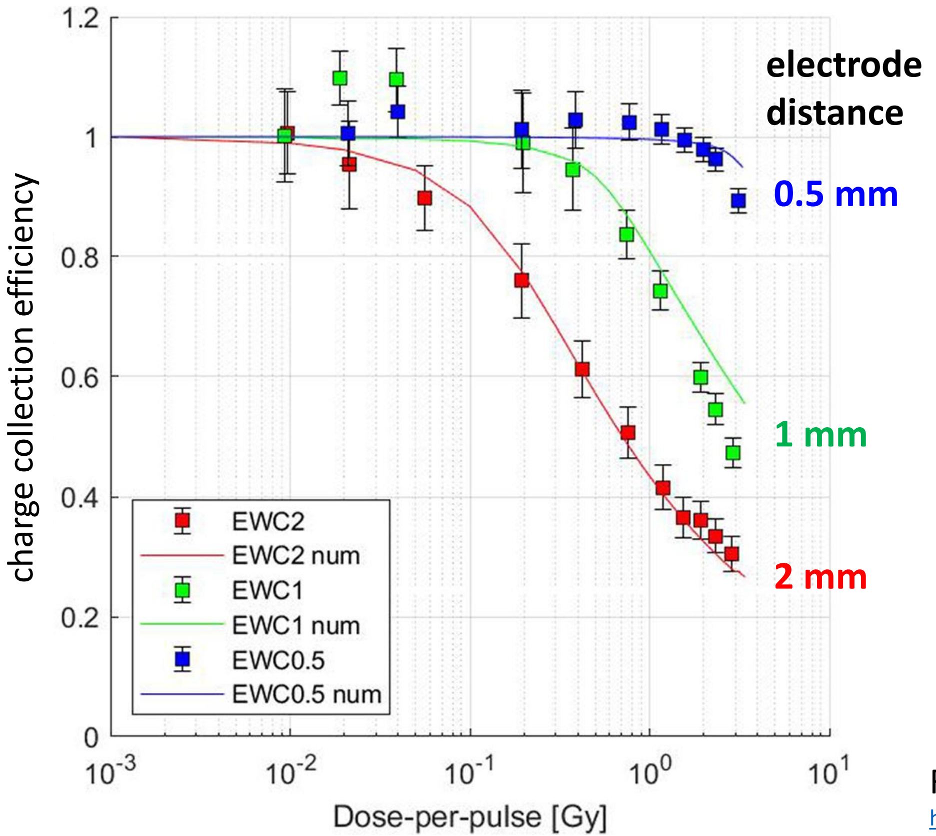


Simulated ion recombination correction factor k_s for plane parallel ionization chambers at 300 V for 5 Gy/pulse

Faustino Gomez et al., to be published

Coming developments on dosimetry for FLASH RT

Prototype ionization chambers for ultra-high DPP

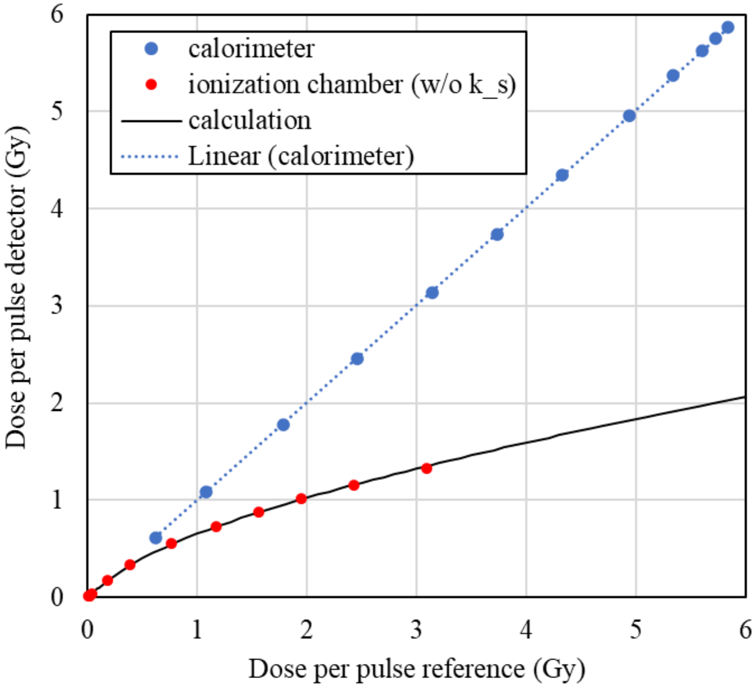


Rafael Kranzer et al., Med. Phys., (2021) 48: 819-830
https://doi.org/10.1002/mp.14620

Coming developments on dosimetry for FLASH RT

Prototype calorimeter

Aerrow (and Exradin A12 ionization chamber for size reference). The internal structure of Aerrow is shown as a blended rendering.

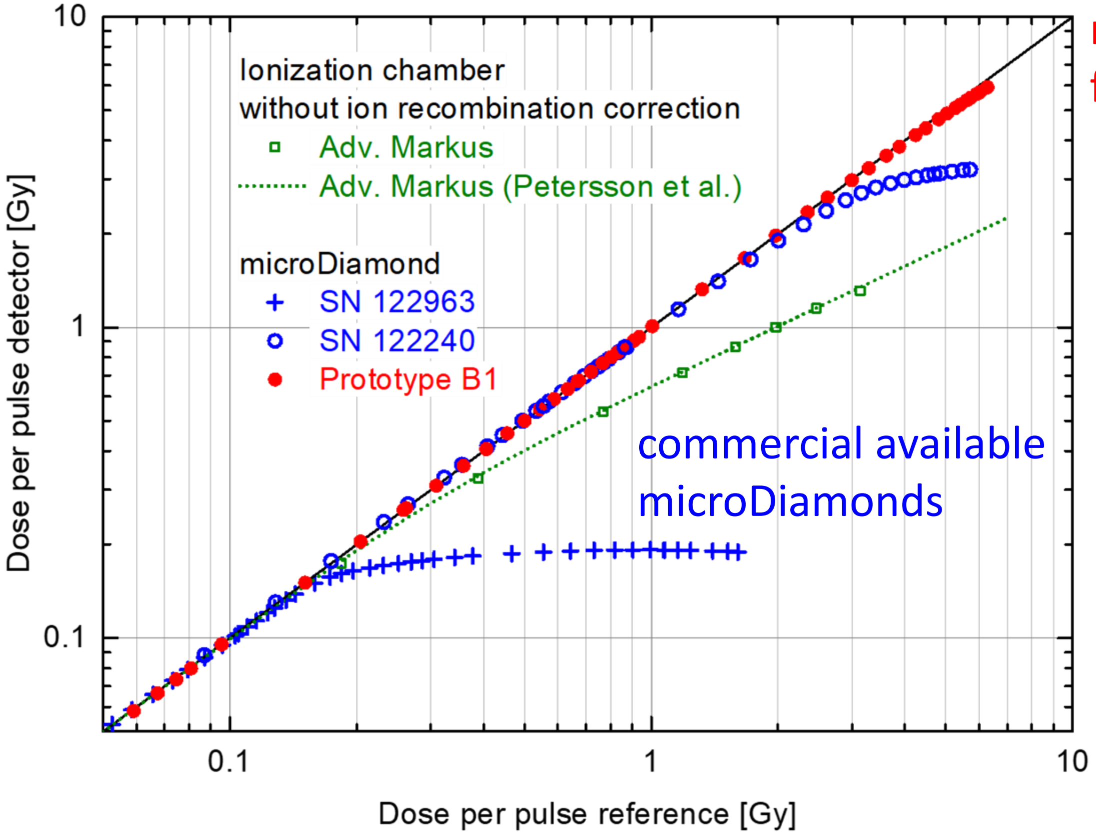


Detector response vs. dose reference from alanine/monitor.

Alexandra Bourgouin et al., to be published

Coming developments on dosimetry for FLASH RT

Prototype solid state detectors



microDiamond prototype for FLASH RT*

*Diamond prototypes are produced at the Industrial Engineering Department of Rome Tor Vergata University in cooperation with PTW.

Rafael Kranzer et al., to be published

Conference

UHDpulse

UHDpulse co-organizes the conference “FLASH Radiotherapy & Particle Therapy” (FRPT2021).

The conference will include the 3rd FLASH Workshop, the workshops of UHDpulse and INSPIRE (integrating activity for European research in proton therapy).

There will be FRPT2021 special issues in “Radiotherapy & Oncology” and in “Physica Medica”.

https://frpt-conference.org/

UHDpulse

Conference FRPT2021

All abstracts accepted to FRPT 2021 will be published in a supplement of the *"Physica Medica"* Journal.

Moreover, **the full papers of the best abstracts** presented at the Conference will be published in a special issue of:

- ***The "Physica Medica"*** Journal – for technology/dosimetry related work
- The ***"Radiotherapy and Oncology"*** Journal – for clinical application and biology related research

Submit your abstract and gain maximum exposure for your work.

LATE-BREAKING ABSTRACT SUBMISSION IS OPEN UNTIL 22 SEPTEMBER 2021

Conference FRPT2021

FRPT 2021 will be held at the Austria Center Vienna **and Online**

Sponsors:

varian A Siemens Healthineers Company | iba Dosimetry Protect, Enhance and Save Lives | SIT | PMB ALCEN

"A wealth of future studies are waiting to be done at all levels of physical, chemical, molecular, biological, and clinical endeavors."

Jolyon Hendry, Taking Care with FLASH Radiation Therapy
https://doi.org/10.1016/j.ijrobp.2020.01.029

However, if there is an error in dosimetry, then the difference in tissue response between conventional and ultrahigh-dose rate irradiation at seemingly equal total dose may be due to this error and not due to the FLASH effect.

http://uhdpulse-empir.eu/

This project (18HLT04) has received funding from the EMPIR programme co-financed by the Participating States and from the European Union's Horizon 2020 research and innovation programme.