Physikalisch-Technische Bundesanstalt
Braunschweig and Berlin
National Metrology Institute

Overview of the EMPIR project UHDpulse - “Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

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

WP2 EPTN, Workshop “Ultra-high dose rate dosimetry: what’s going on?”
6.5.21, virtual

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Overview of the EMPIR project UHDpulse - “Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

UHDpulse

Contents

- EMPIR program, Partners & Collaborators
- Ultra-high dose per pulse, metrological challenges
- Objectives, Work Package structure
- Current progress in ultra-high dose rate dosimetry

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

UHDpulse Partners and Collaborators

Metrology Institutes

Irradiation facility provider

Radiation detector developer

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

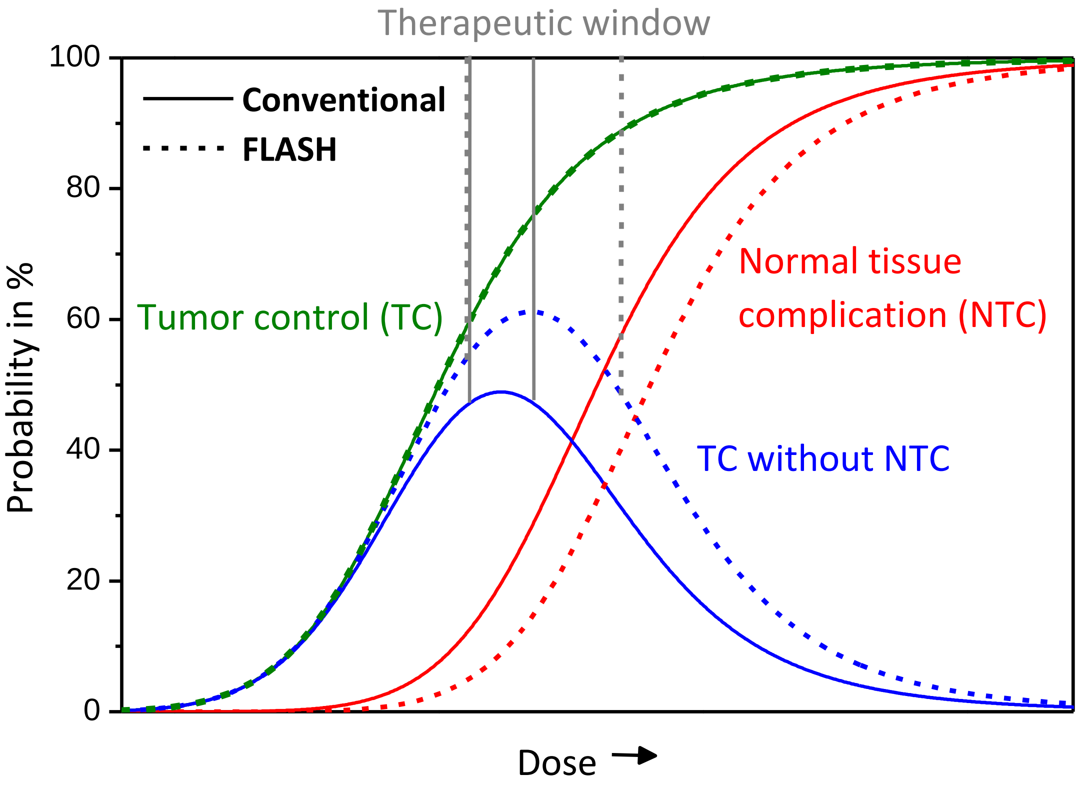
Interested institutes that want to contribute to the goals of the project may join the as **collaborator**

FLASH radiotherapy

ultra-high dose rate →

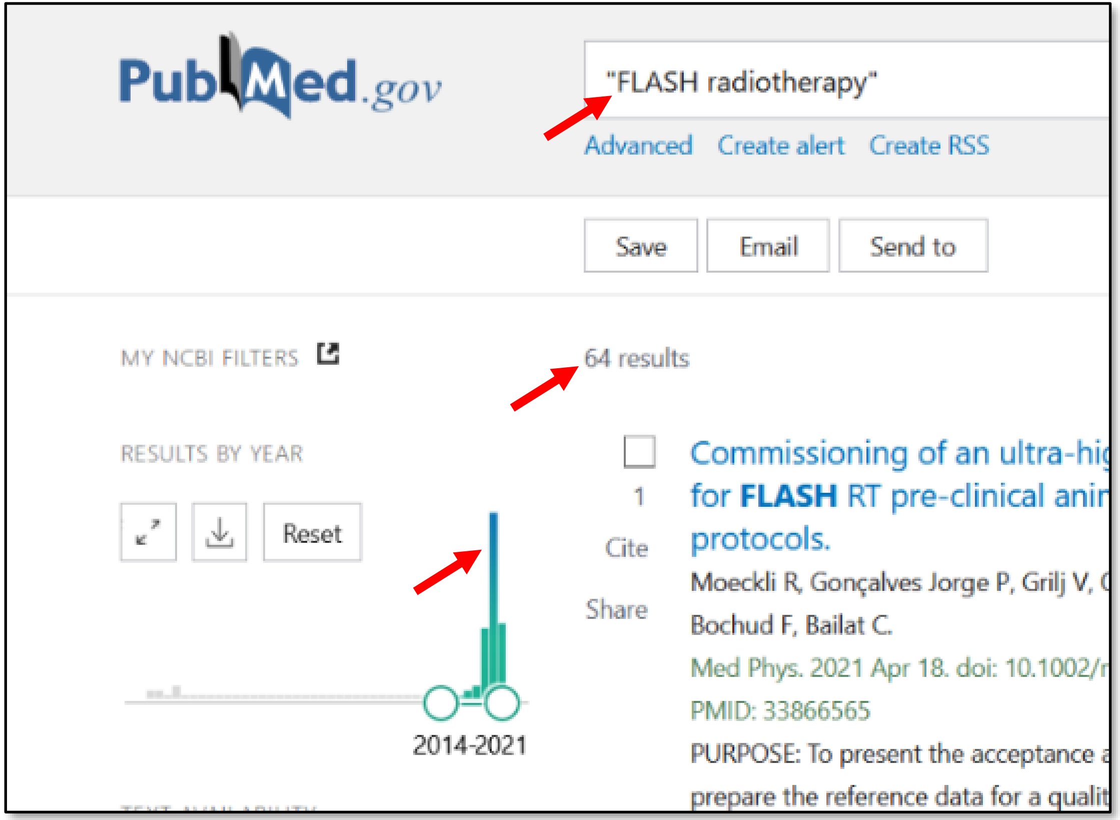
- reduction of the normal tissue complications (NTC)
- same tumour control level (TC)
- Less side effects, or higher dose for better chance of cur

→ FLASH effect



FLASH radiotherapy

- The number of institutes interested in FLASH radiotherapy and the number of FLASH papers published per year increasing exponentially.
- 2021: 1 paper/week
- Regardless of whether FLASH will play a significant role in radiotherapy in the future or not, there is just now an urgent need for tools for traceable dose measurements for FLASH

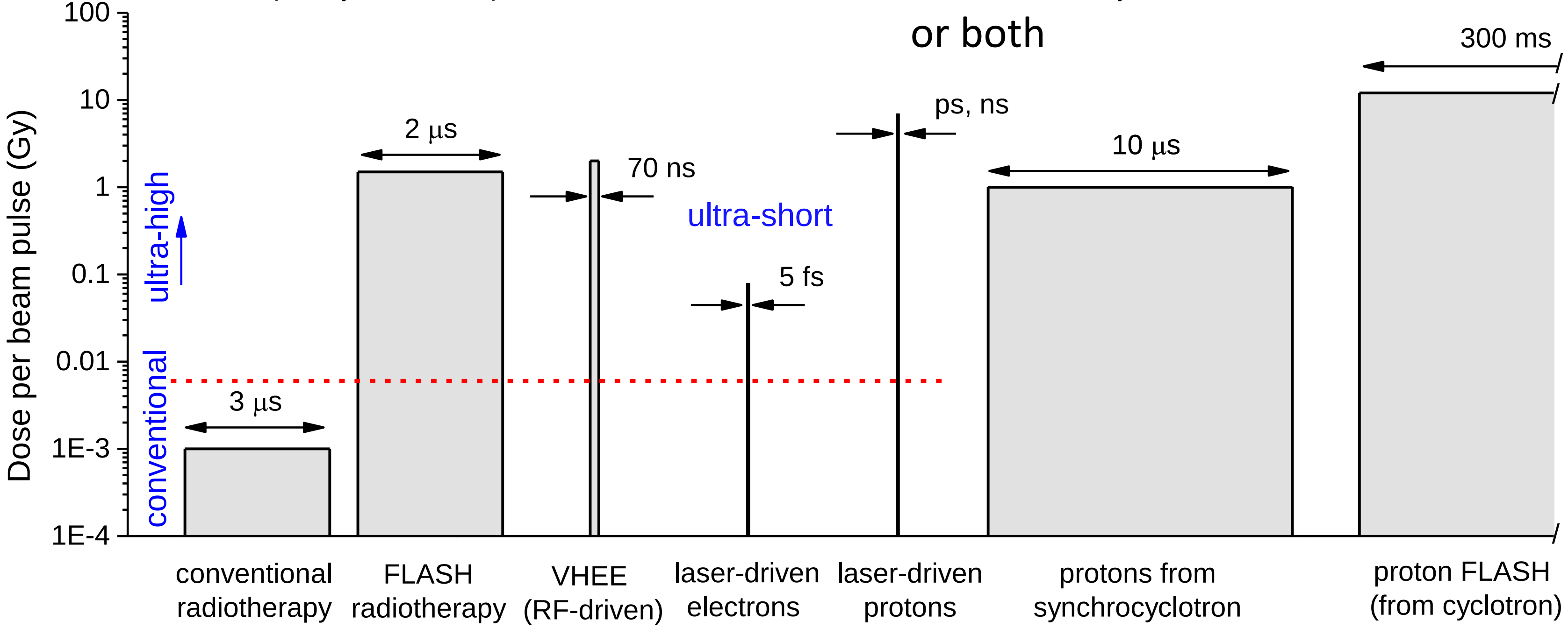


"Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates"

$\underbrace{\text{particle beams}}_{\text{electrons, protons (no photons)}}$ with $\underbrace{\text{ultra-high pulse dose rates}}_{\text{ultra-high dose per pulse, ultra-short pulse duration or both}}$

electrons, protons
(no photons)

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



Ultra-high dose per pulse at FLASH radiotherapy

UHDpulse

institutCurie

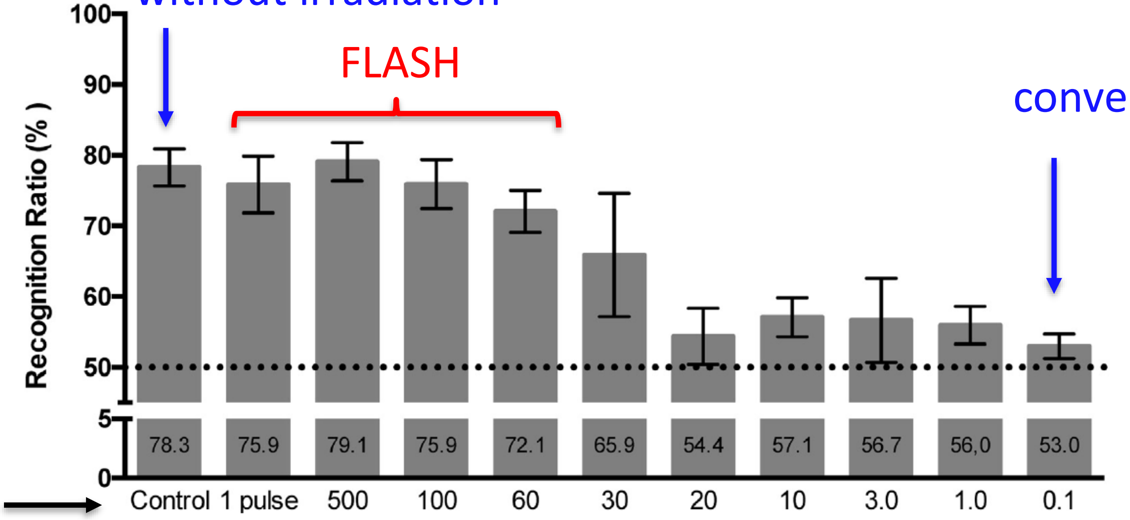
CHUV Centre hospitalier universitaire vaudois

mice brain irradiation with 10 Gy

without irradiation

FLASH

conventional



Mean dose rate [Gy/s]

Dose per pulse [Gy] 10 5 1 0.6 0.01 0.0003

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

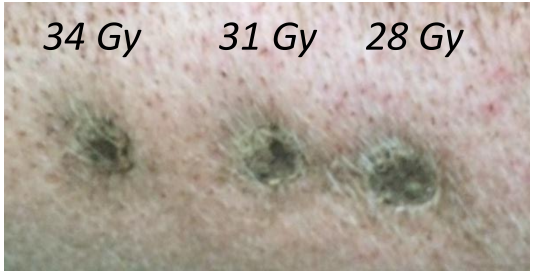
Ultra-high dose per pulse at FLASH radiotherapy

Centre hospitalier universitaire vaudois

Conventional and FLASH Irradiation (with same total dose)

36 weeks post-RT

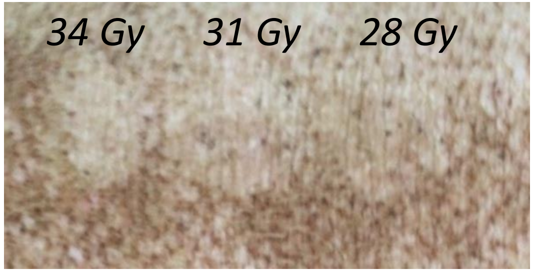
Conventional (5 Gy/min)



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

Ultra-high dose per pulse at FLASH radiotherapy

Centre hospitalier universitaire vaudois

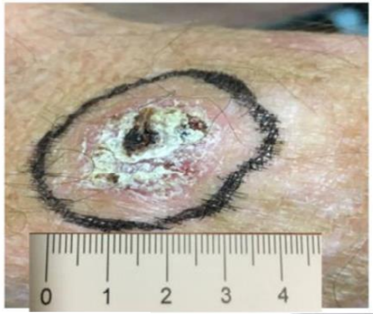
<u>human Patient:</u>

lymphoma on skin

<u>FLASH-RT:</u>

10 pulses (of 1 μs duration) in 90 ms

with **1.5 Gy/pulse**



Day 0

3 weeks

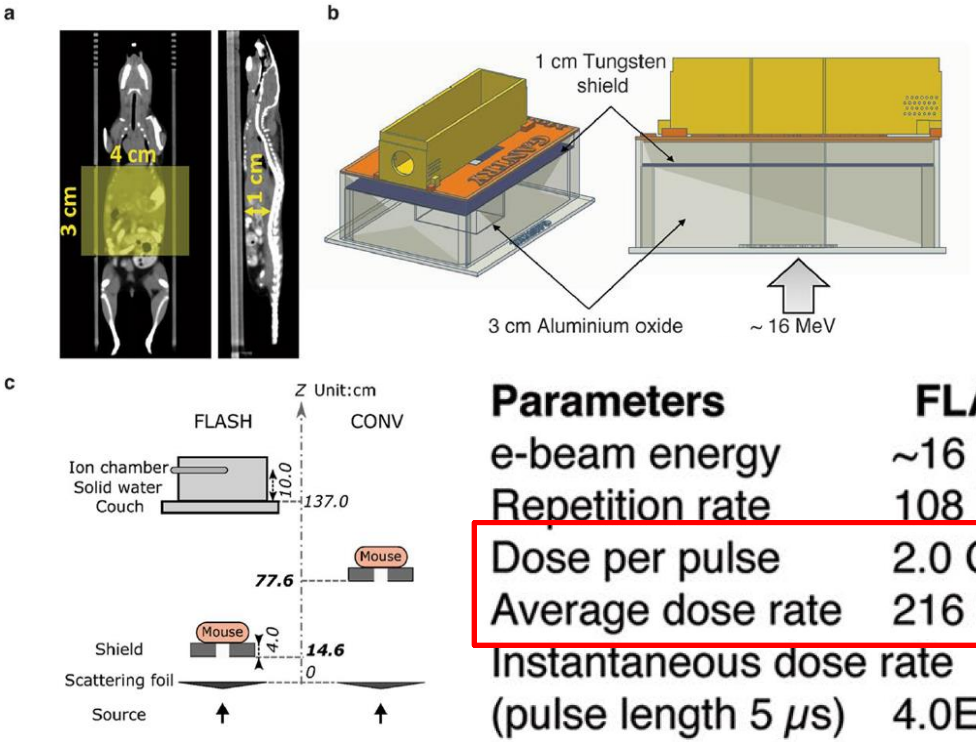
(max. of skin reactions)

5 months

Bourhis et al., Radiother. Oncol. (2019)

DOI: 10.1016/j.radonc.2019.06.019

Ultra-high dose per pulse at FLASH radiotherapy



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 …

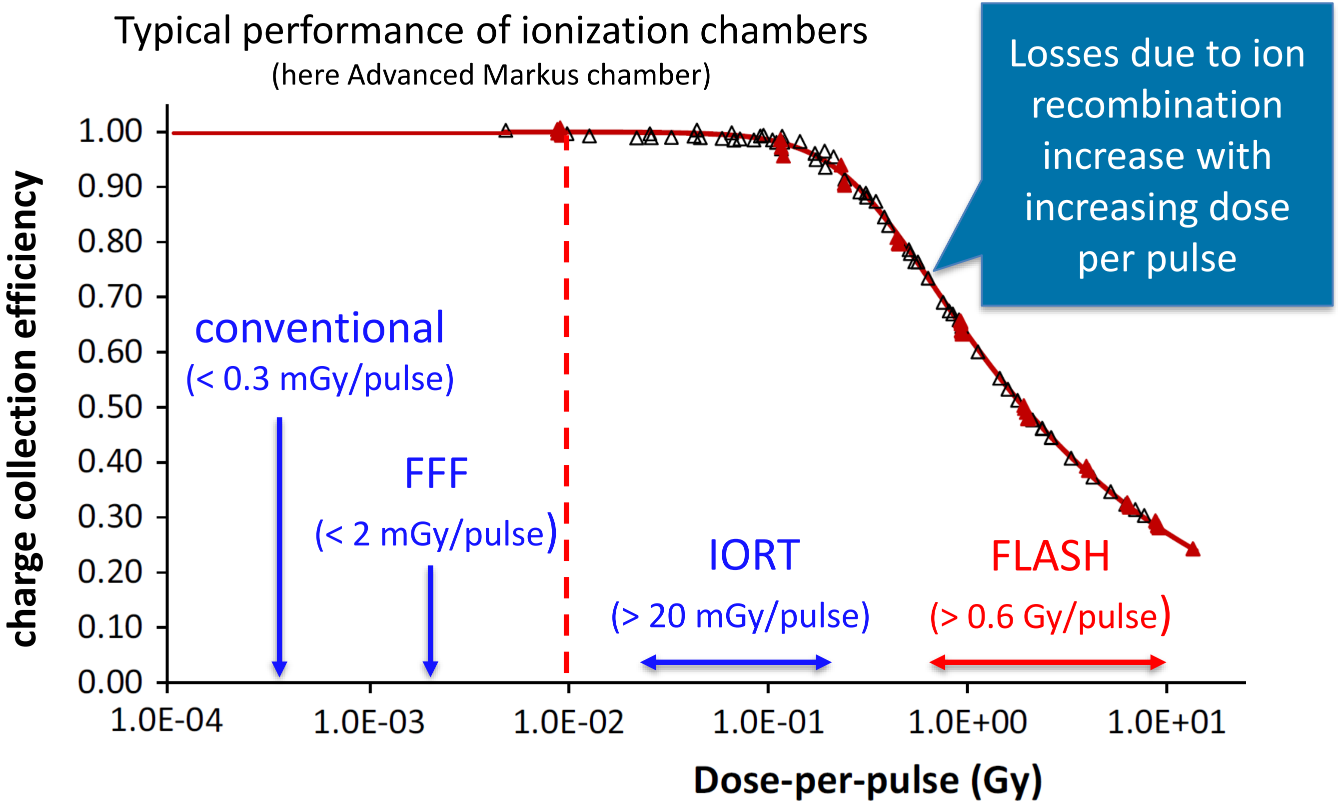
https://doi.org/10.1038/s41598-020-78017-7

Metrological challenge ultra-high dose per pulse

Due to ultra-high dose rates and pulsed structure of the beams, tools and methods established in dosimetry for conventional radiotherapy are not suitable for FLASH radiotherapy.

There are

- **no** active dosimeters for real-time measurements
- **no** formalism (Codes of Practice) for reference dosimetry
- **no** corresponding primary standards



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

Objectives, WPs

UHDpulse

to establish traceability in absorbed dose measurements of ultra-high pulse dose rate beams.

The specific aims of the project are:

- Development of primary and secondary absorbed dose standards and reference dosimetry methods
- Characterization of state-of-the-art detector systems
- Development of methods for relative dosimetry and for the characterization of of stray radiation
- Providing of input data for future Code of Practice

NPL National Physical Laboratory

WP1: Primary standards

- Definition of reference conditions
- Reference radiation fields
- Adapting primary standards (water calorimeter, Fricke dosimeter)
- Prototype graphite calorimeters

METAS

WP2: Secondary standards, relative dosimetry

- Transfer from primary standards
- Characterizing established detector systems
- Formalism for reference dosimetry for future Code of Practice

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WP5: Impact, WP6: Coordination

PTB Physikalisch-Technische Bundesanstalt Braunschweig und Berlin

WP4: Detectors and methods outside primary beam

- Active detection techniques for pulsed mixed radiation fields of stray radiation and pulsed neutrons
- Methods with passive detectors

WP3: Detectors for primary beam

- Novel and custom-built active dosimetric systems
- Beam monitoring systems

ADVACAM Imaging the Unseen

CHUV

Objectives, WPs

The UHDpulse consortium wrote an overview paper describing the goals of the project, providing details on the state-of-the-art of radiotherapy using particle beams with ultra-high pulse dose rates and introducing promising candidates as suitable dosimeters for ultra-high dose rate dosimetry to be investigated within UHDpulse.

(currently number 7 on the list of most downloaded articles of the last 90 days of this journal)


Outline

Highlights
Abstract
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1. Introduction
2. Overview of novel radiotherapy techniques using ultra-...
3. Metrological challenges and possible solutions for dosi...
4. The UHDpulse project
5. Conclusion
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ELSEVIER

Physica Medica
Volume 80, December 2020, Pages 134-150

Original paper

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] ... Marie-Catherine Vozenin [q]

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https://doi.org/10.1016/j.ejmp.2020.09.020 Get rights and content

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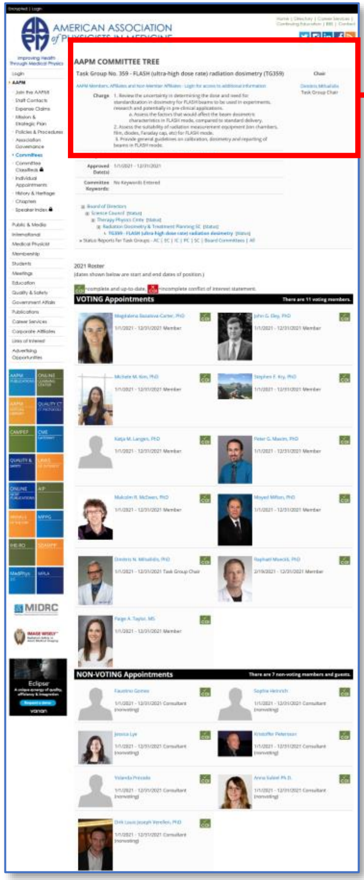
Highlights

- Ultra-high dose rate reduces adverse side effects in radiotherapy (FLASH effect).
- Studies and implementation in practice requires accurate dose measurements.
- An European joint research project was started to develop a measurement framework.
- Tools for dosimetry of ultra-high pulse dose rate beams will be provided.

https://doi.org/10.1016/j.ejmp.2020.09.020

AAPM-ESTRO joint Task Group No. 359

“FLASH (ultra-high dose rate) radiation dosimetry”



TG359

- 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.
- Assess the suitability of radiation **measurement equipment** (ion chambers, film, diodes, Faraday cap, etc) for FLASH mode.
- Provide general **guidelines** on calibration, dosimetry and reporting of beams in FLASH mode.

UHDpulse

<u>Objective 5:</u>
to facilitate the uptake of the project’s achievements by **standards developing organizations** and end users

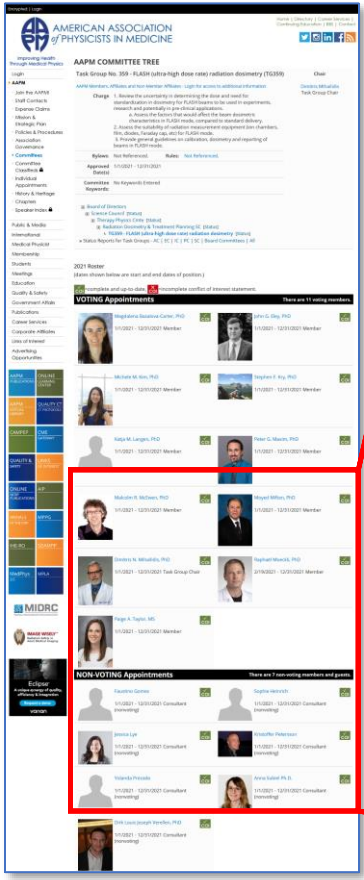
<u>Objective 2:</u>
to characterise the response of available **detector systems**

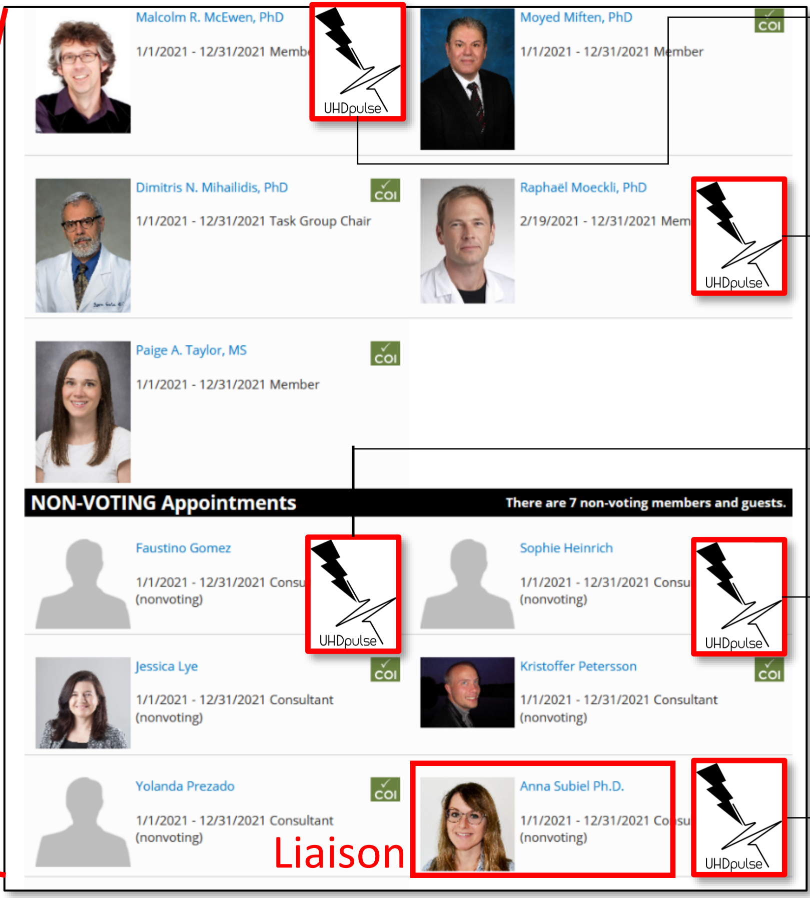
<u>Objective 4:</u>
provide the input data for **Codes of Practice**

https://www.aapm.org/org/structure/default.asp?committee_code=TG359

AAPM-ESTRO joint Task Group No. 359

UHDpulse





UHDpulse members:

NRC·CNRC Canada

CHUV Centre hospitalier universitaire vaudois

USC Universidade de Santiago de Compostela

institut Curie

NPL National Physical Laboratory

SIT

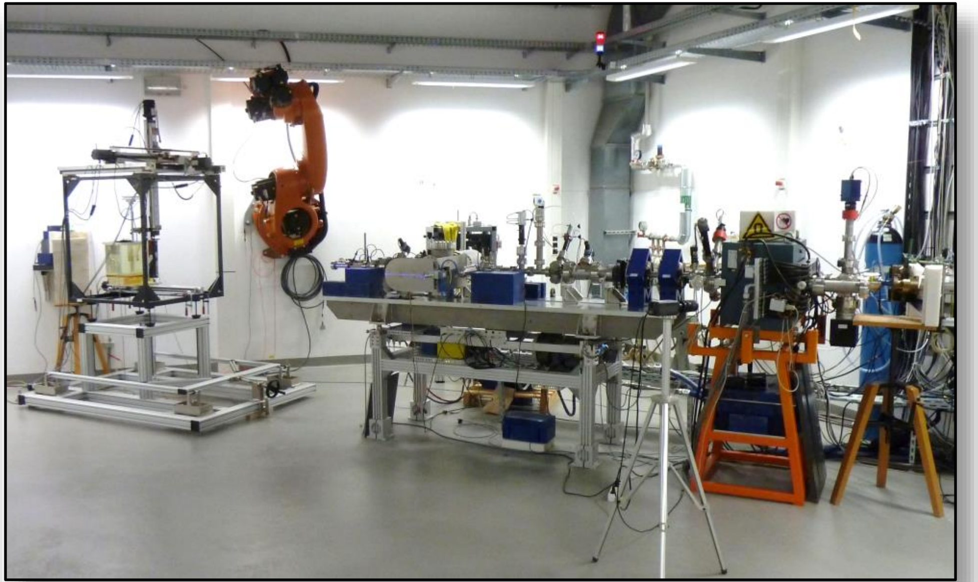
netwerk iridium Topzorg in radiotherapie

PTW THE DOSIMETRY COMPANY

iba Dosimetry Protect, Enhance and Save Lives

https://www.aapm.org/org/structure/default.asp?committee_code=TG359

PTB's electron reference field for UHD dosimetry



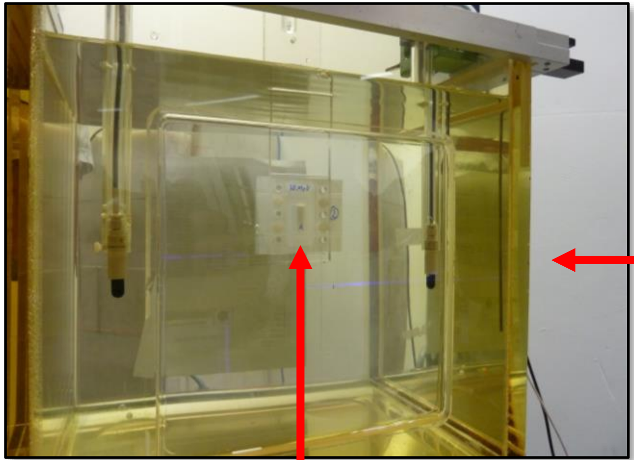
PTB's Research electron accelerator

Beam line with water phantom

E = 0.5 – 50 MeV

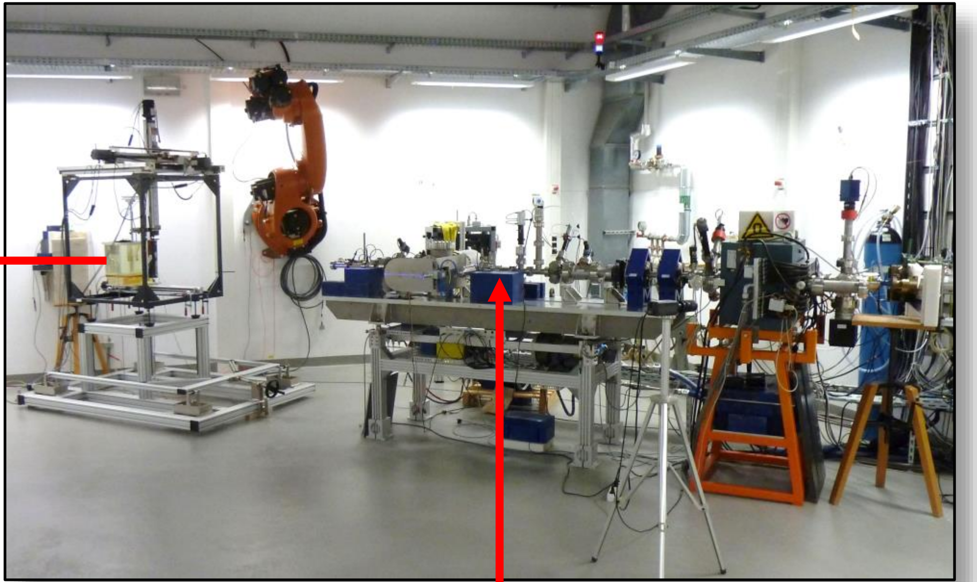
up to 7 Gy/pulse (SSD 0.7 m, 20 MeV)

PTB's electron reference field for UHD dosimetry



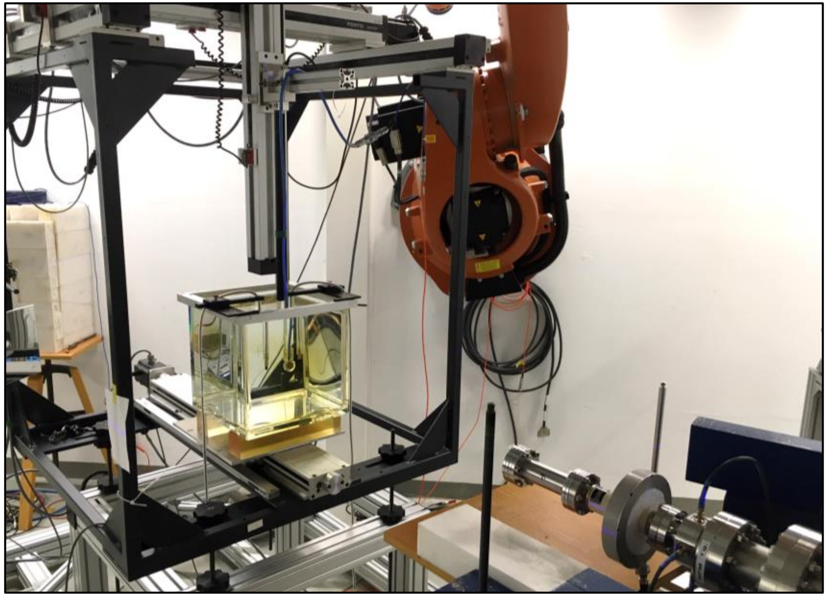
Alanine pellets at reference depth in water phantom

Dose traceable to primary standard

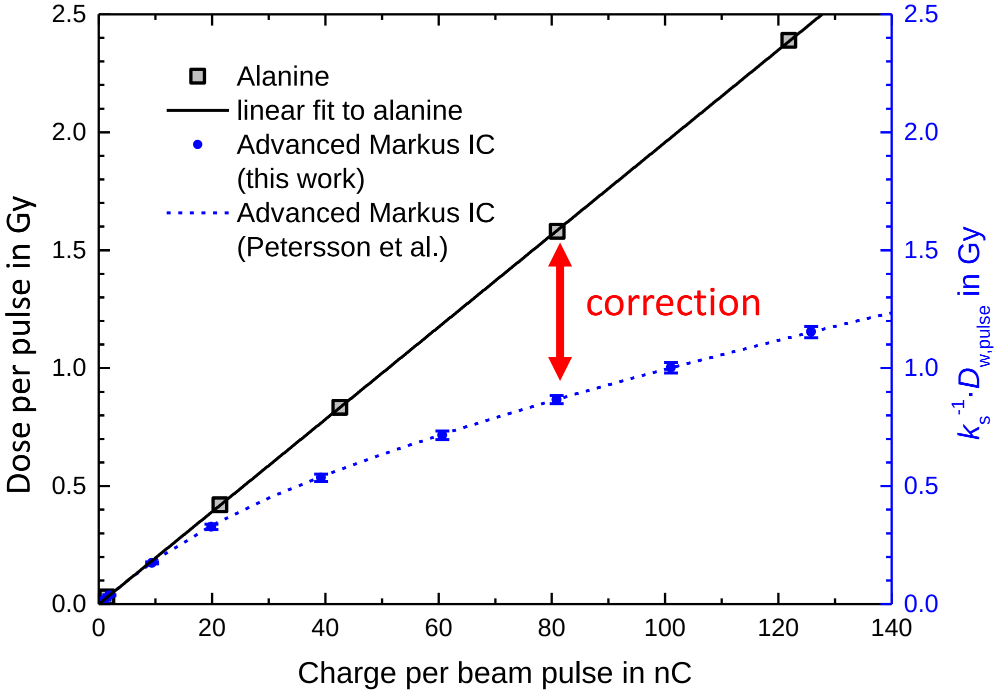


Non-destructive absolute beam pulse charge measurement (uncertainty < 0.1 % @70 nC/pulse)

PTB’s electron reference field for UHD dosimetry

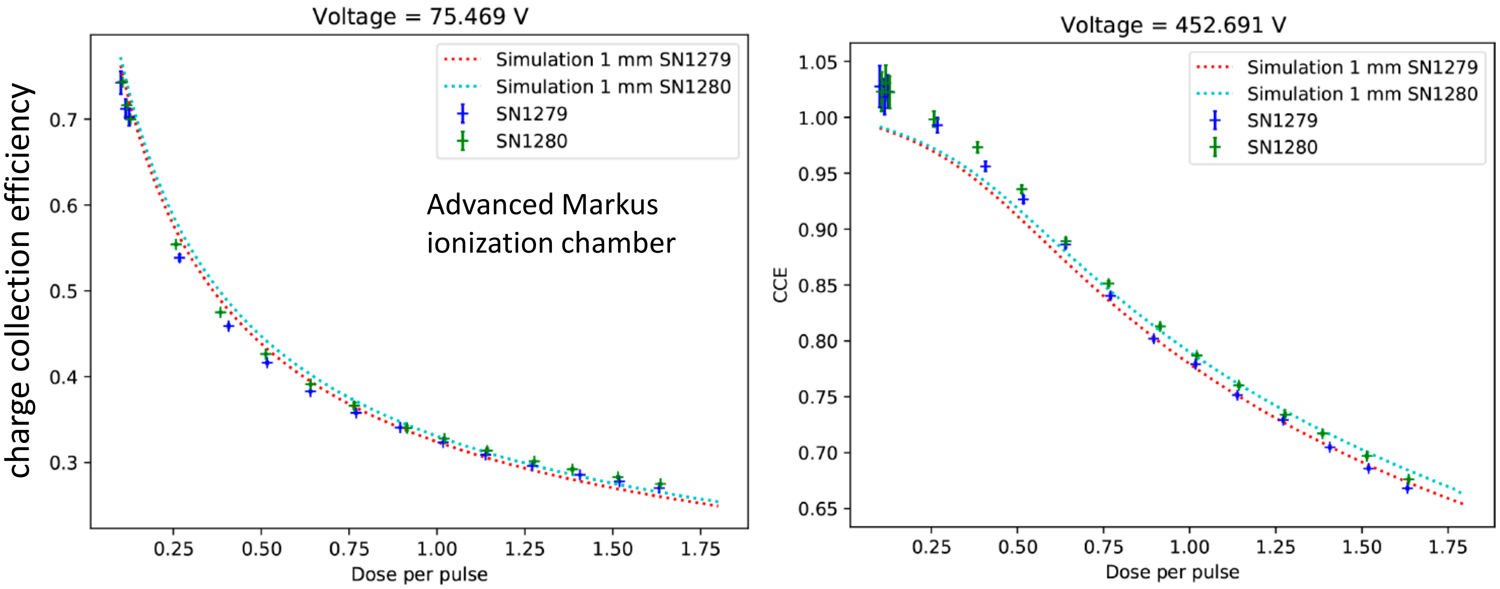


Detector under test at reference depth in water phantom



A Bourgouin et al., Calorimeter for Real-Time Dosimetry of Pulsed Ultra-High Dose Rate Electron Beams
https://doi.org/10.3389/fphy.2020.567340

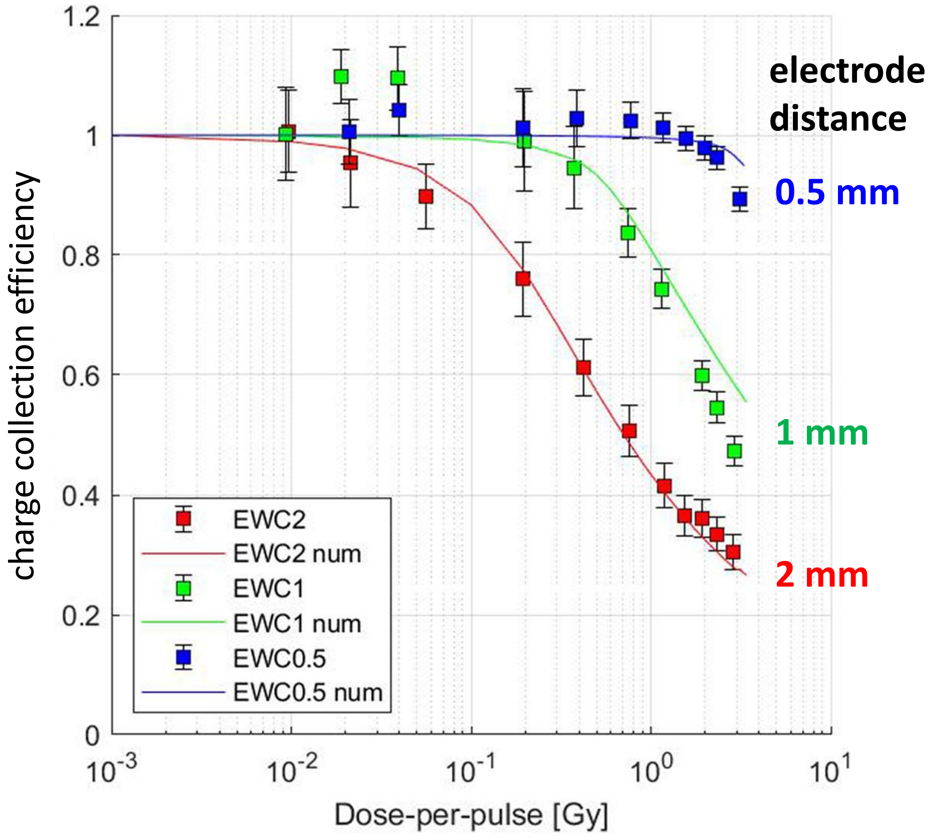
Dosimetry for FLASH RT with ion chambers



Within the framework of UHDpulse theoretical models for the calculation of the charge collection efficiency of plane parallel ionization chambers at ultra-high dose per pulse are developed, with the aim of to provide an ion recombination correction function.

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

Dosimetry for FLASH RT with ion chambers

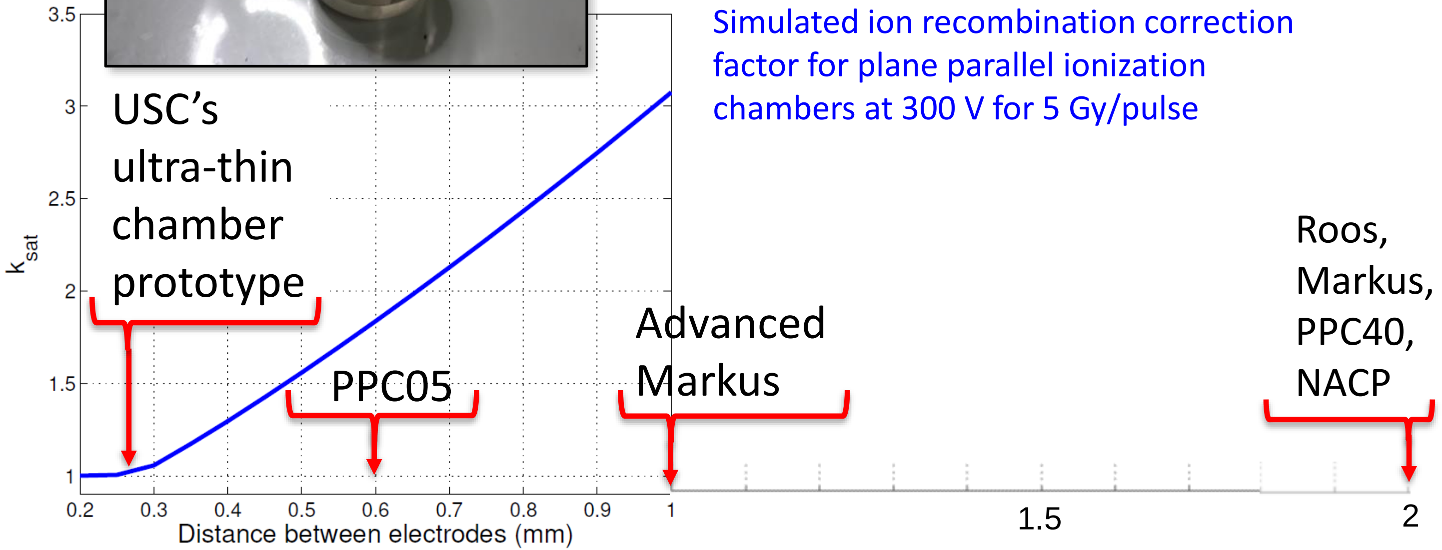


Within UHDpulse the performance of plane parallel ionization chamber prototypes with different electrode distance at ultra-high dose per pulse are investigated. Reduction of the electrode distance helps to increase the charge collection efficiency at ulta-high dose per pulse.

Rafael Kranzer et al., Medical Physics 2021, https://doi.org/10.1002/mp.14620

Dosimetry for FLASH RT with ion chambers

Within UHDpulse USC builds an ultra-thin plane parallel ionization chamber prototype in order to enable reliable ionization chamber measurements up to 5Gy/pulse.

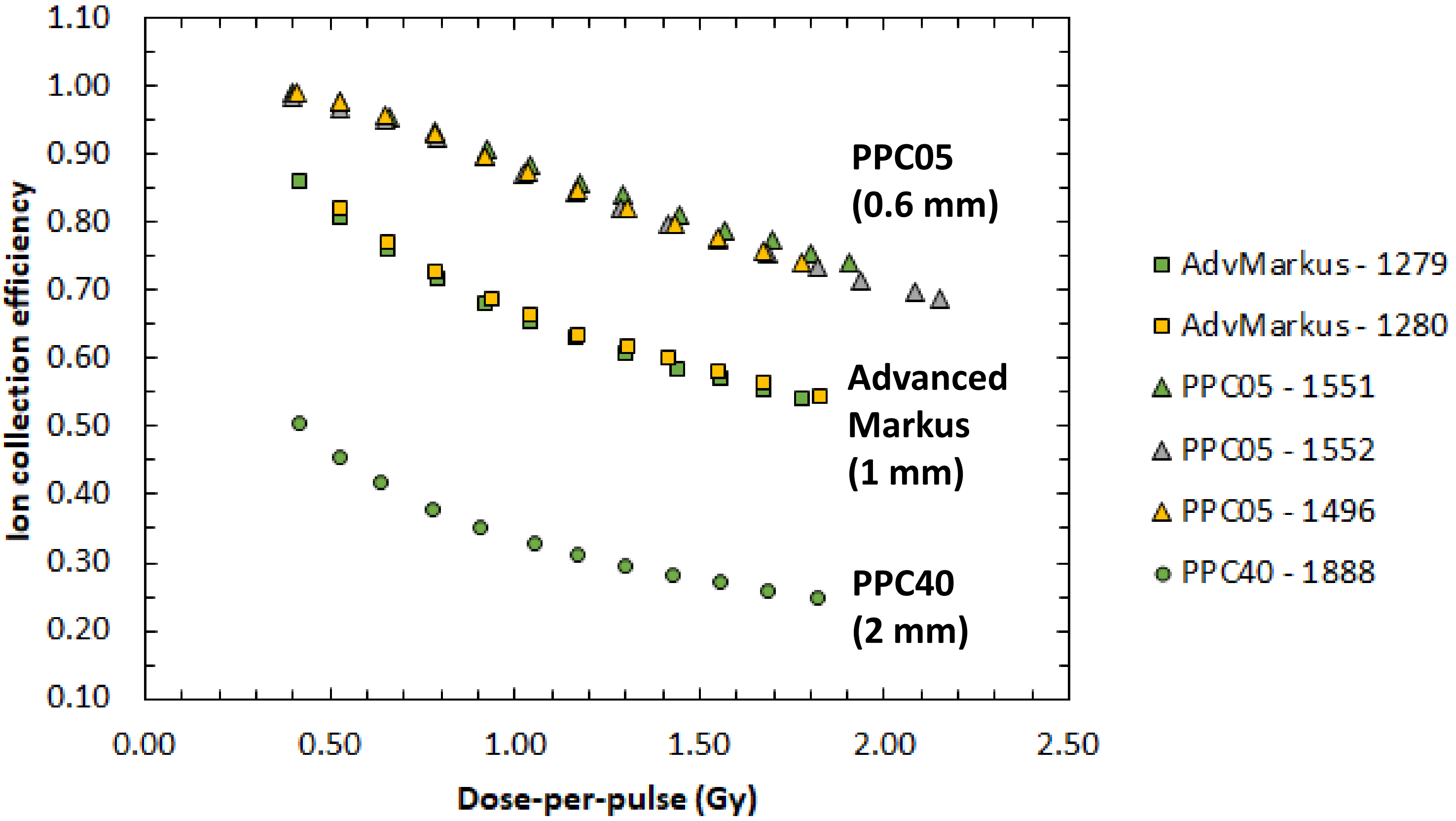


Simulated ion recombination correction factor for plane parallel ionization chambers at 300 V for 5 Gy/pulse

https://doi.org/10.1016/j.ejmp.2020.09.020

Dosimetry for FLASH RT with ion chambers

Within UHDpulse the response of different types of commercially available ionization chambers as well as their intra-type variations are characterized

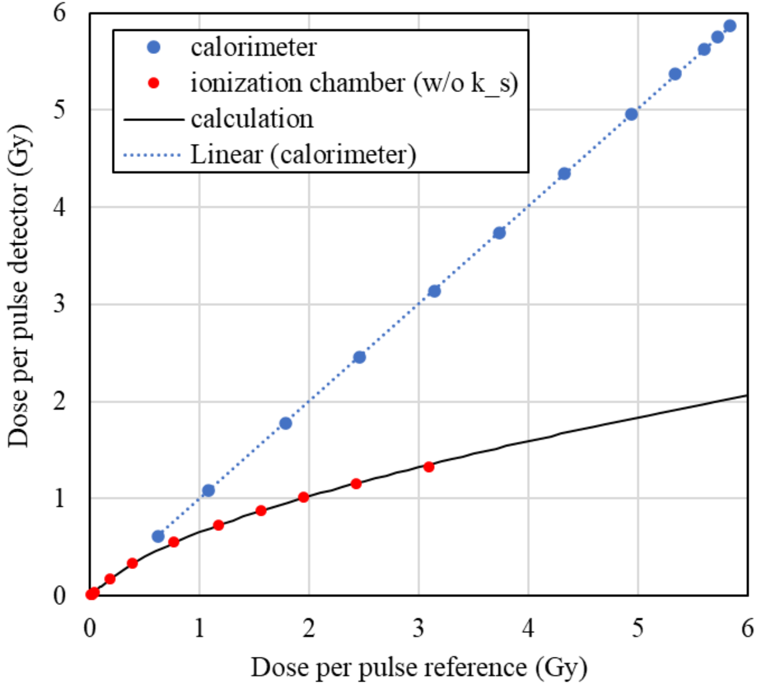


Alexandra Bourgouin et al., to be published

Dosimetry for FLASH RT by calorimeter

Within UHDpulse the performance of the Graphite Probe Calorimeter prototype "Aerrow" is investigated. The detector shows linear response in the FLASH range.

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

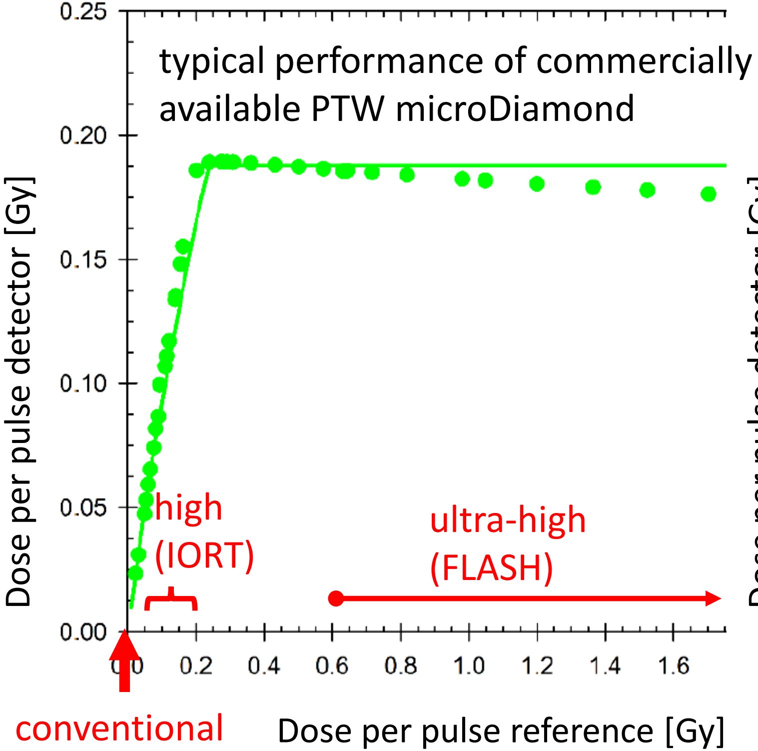


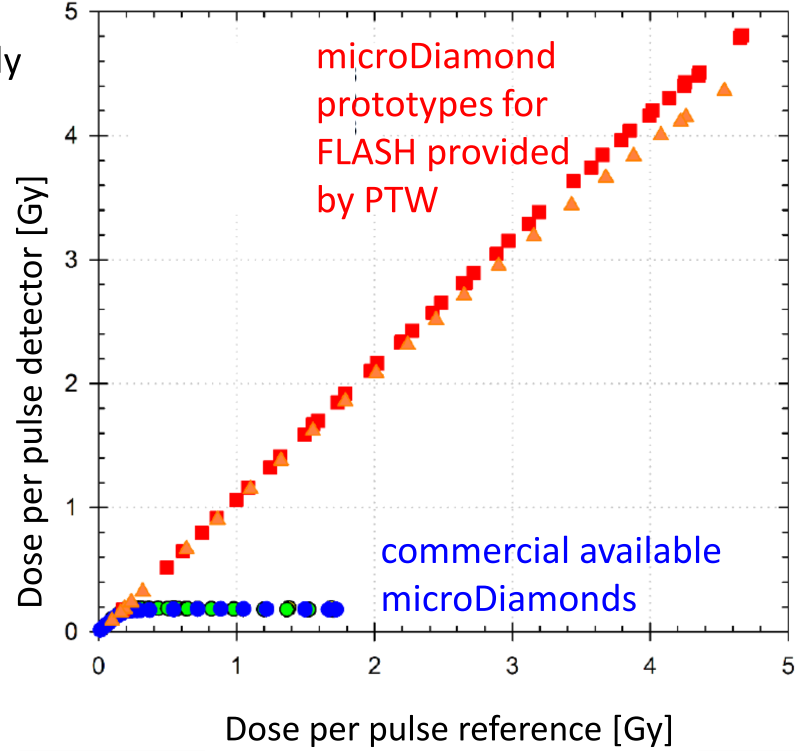
Detector response vs. dose reference from alanine/monitor.

Alexandra Bourgouin et al., to be published

Dosimetry for FLASH RT by diamond detectors

Within UHDpulse the performance of microDiamond detectors are investigated at ultra-high dose per pulse. Adapted prototypes show linear response in the FLASH range.

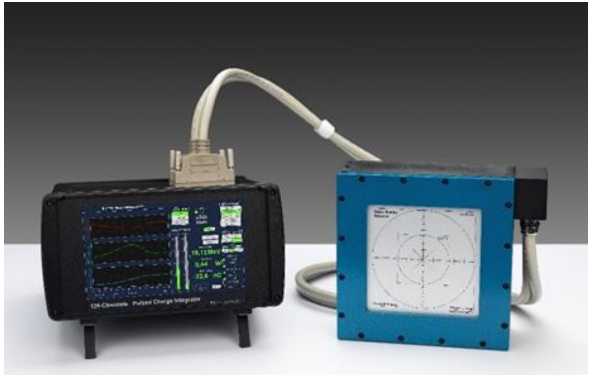




-> currently under test at PTB's **proton beam** at UHD

Rafael Kranzer et al., to be published

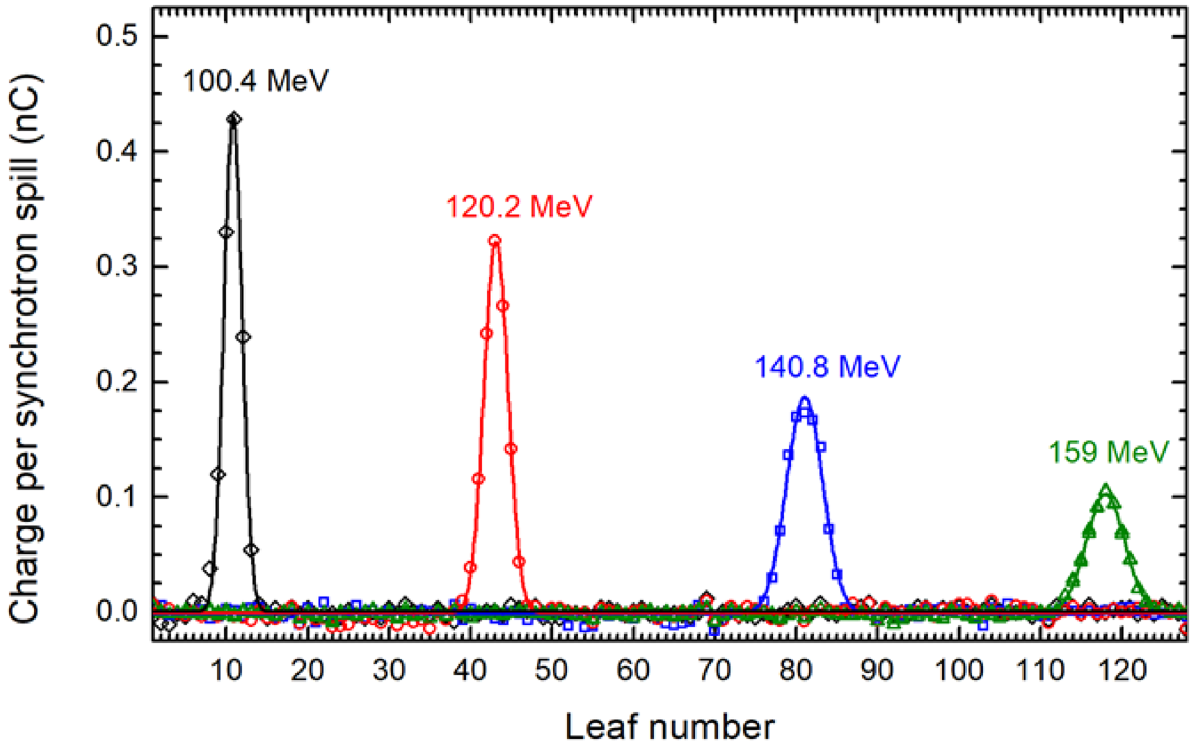
Dosimetry for proton FLASH by ML Faraday Cup



- PTB developed a portable Multi-leaf Faraday Cup (MLFC)
- Measuring principle is independent of the dose rate
- to be used in FLASH proton beams

Dosimetry for proton FLASH by ML Faraday Cup

- A test of the MLFC for proton beams was carried out at UHDpulse Collaborator MedAustron (at conventional dose rates)
- From energy and charge the dose rate can be determined



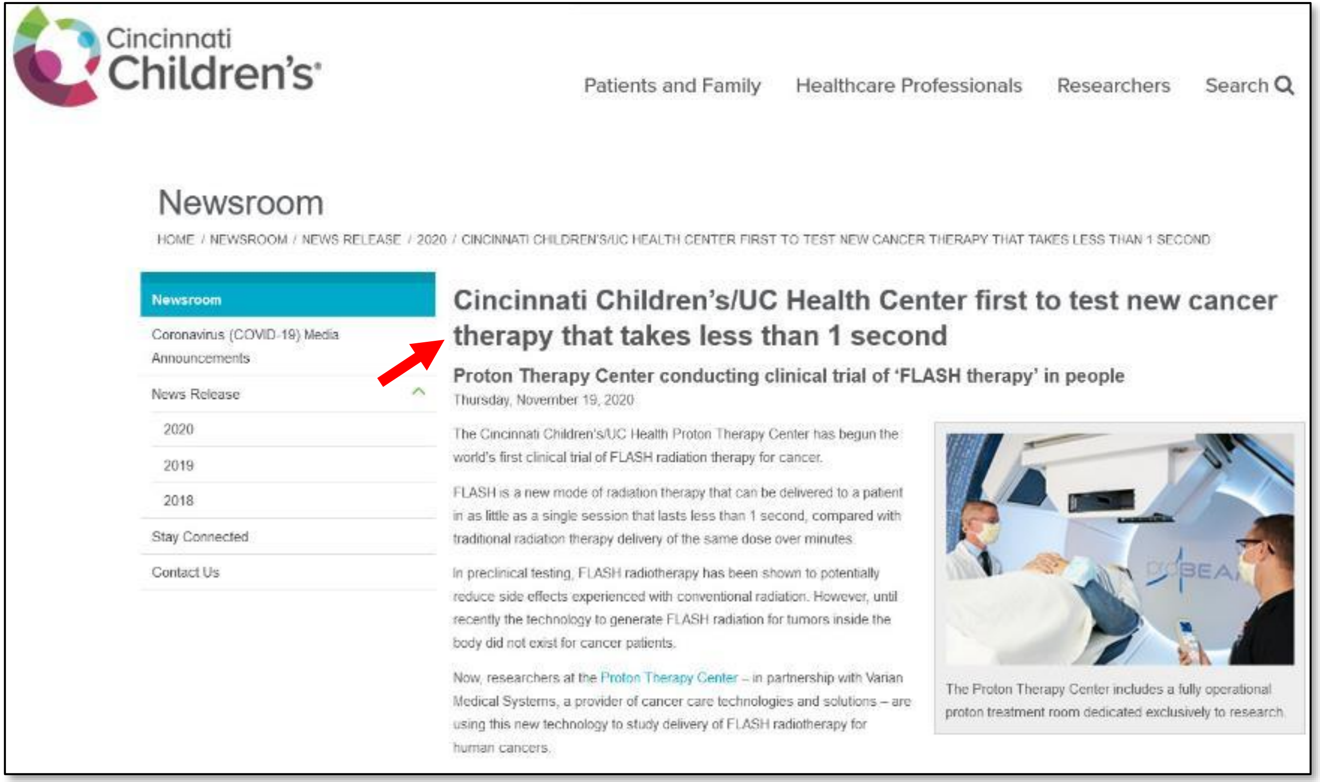
Makowski et al., to be published

Dosimetry for proton FLASH by ML Faraday Cup

UHDpulse

NPL National Physical Laboratory

- Within the framework of UHDpulse NPL has conducted an experimental campaign at Cincinnati's Children Proton Therapy Centre, where traceability to the NPL portable graphite primary standard has been provided for their FLASH proton beam. The centre was then allowed to start the first clinical trial of FLASH proton therapy in human patients.



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HOME / NEWSROOM / NEWS RELEASE / 2020 / CINCINNATI CHILDREN'S/UC HEALTH CENTER FIRST TO TEST NEW CANCER THERAPY THAT TAKES LESS THAN 1 SECOND

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Cincinnati Children's/UC Health Center first to test new cancer therapy that takes less than 1 second

Proton Therapy Center conducting clinical trial of 'FLASH therapy' in people

Thursday, November 19, 2020

The Cincinnati Children's/UC Health Proton Therapy Center has begun the world's first clinical trial of FLASH radiation therapy for cancer.

FLASH is a new mode of radiation therapy that can be delivered to a patient in as little as a single session that lasts less than 1 second, compared with traditional radiation therapy delivery of the same dose over minutes.

In preclinical testing, FLASH radiotherapy has been shown to potentially reduce side effects experienced with conventional radiation. However, until recently the technology to generate FLASH radiation for tumors inside the body did not exist for cancer patients.

Now, researchers at the Proton Therapy Center – in partnership with Varian Medical Systems, a provider of cancer care technologies and solutions – are using this new technology to study delivery of FLASH radiotherapy for human cancers.

The Proton Therapy Center includes a fully operational proton treatment room dedicated exclusively to research.

NPL primary standard graphite calorimeter

- developed to facilitate calibration in proton beams primarily for scanned (but also for scattered beam) delivery modes
- Graphite core 2 mm thick and 16 mm diameter
- Surrounded by a graphite inner and outer jacket, and a graphite mantle, arranged in a nested construction
- New UK IPEM code of practice is being delivered to deliver an uncertainty on reference dosimetry for protons of approx. 2% (k=2)
  → against 4.6% (k=2) for proton beams currently suggested by IAEA TRS-398 and based on an ionization chamber calibrated in a ^{60}Co beam → ***beam quality correction factor.***

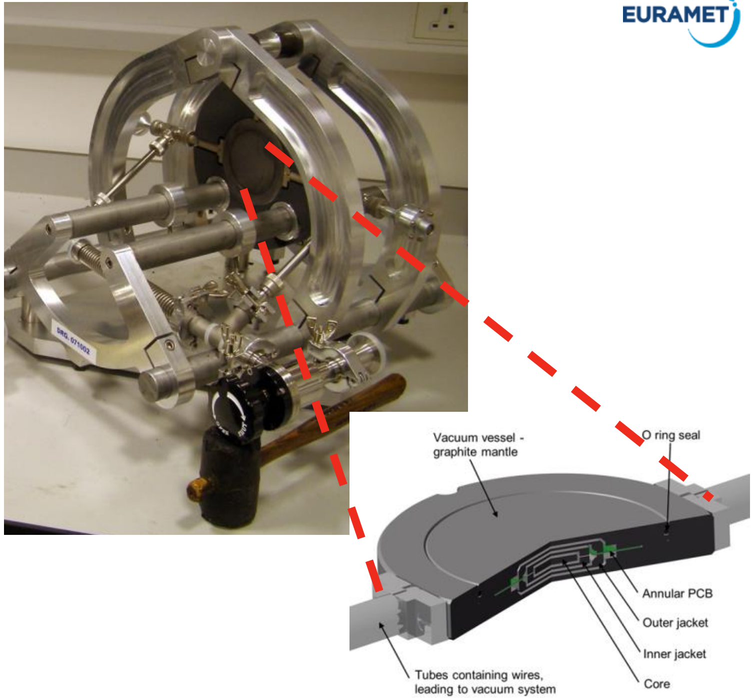


Fig. 1: NPL's primary standard graphite calorimeter.

Traceable graphite calorimetry of UHDR proton beam

to be published

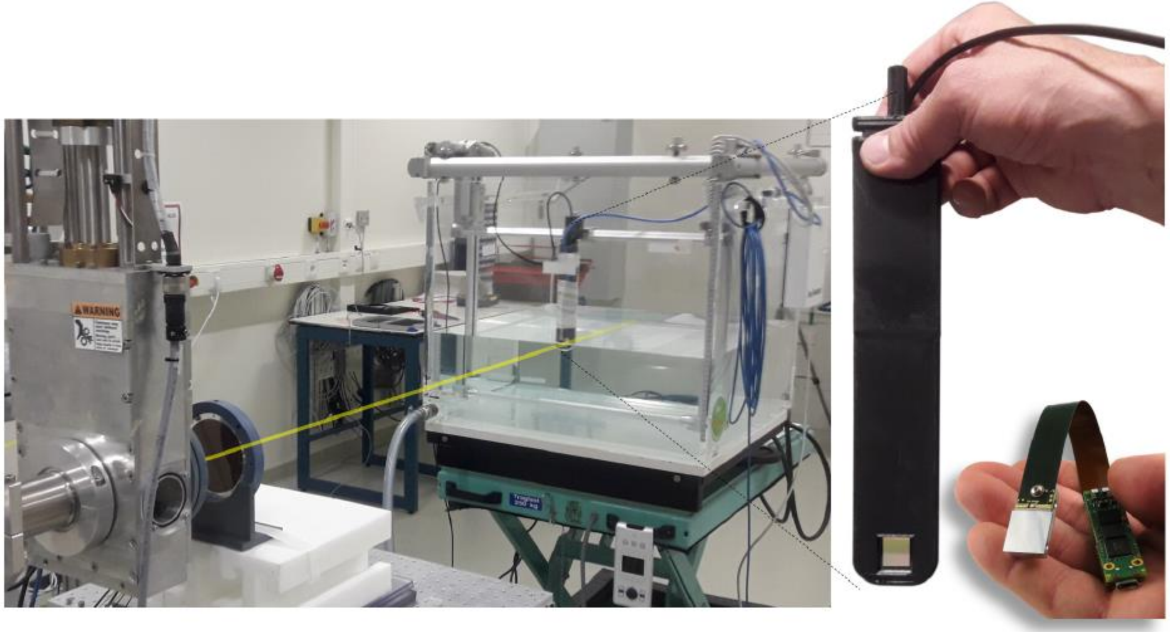
Dosimetry for proton FLASH stray radiation

ADVACAM
Imaging the Unseen

CZECH METROLOGY INSTITUTE

HZDR
HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

- ADVACAM developed a new prototype detector for the real-time measurement of pulsed stray radiation. The device was tested in a FLASH proton beam at HZDR (pencil PB, 160 Gy/s, 220 MeV, 2 ms pulseduration).



MiniPIX TPX3 Flex in a water phantom in an ultra-high dose rate proton beam

to be published

FRPT Conference

UHDpulse co-organizes the 3-day 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 dedicated Sessions for dosimetry and QA at ultra-high dose rates.

https://frpt-conference.org/

FRPT Conference

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.

Deadline: 12 May 2021

FRPT Conference

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

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“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

UHDpulse

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.