Challenges in dosimetry of particle beams with ultra-high pulse dose rates

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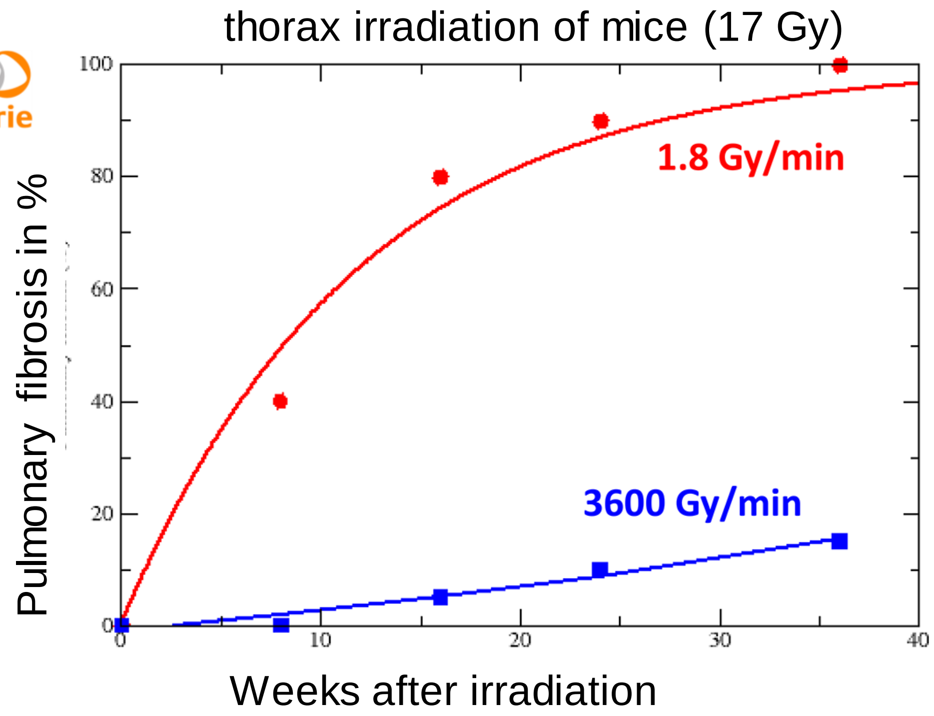
Outline

- FLASH effect and experimental evidences
- Peculiarities of ultra-high pulse dose rates
- Dosimetric challenges
- The EMPIR UHDpulse project
- First results
  - Challenges of ionization chamber dosimetry in UHPDR VHEE beams
  - First calorimetry measurements with laser-driven proton beams
- Summary and conclusions

FLASH Radiotherapy

- Radiotherapy currently used for over 50% patients diagnosed with cancer
- Improved the 3D dose conformation thanks to major advances in technologies.
  - therapeutic resistance to radiation can cause local disease progression
  - patients may still experience severe toxicity from radiation treatment

New radiotherapy strategies required for limiting toxicities maintaining tumour control

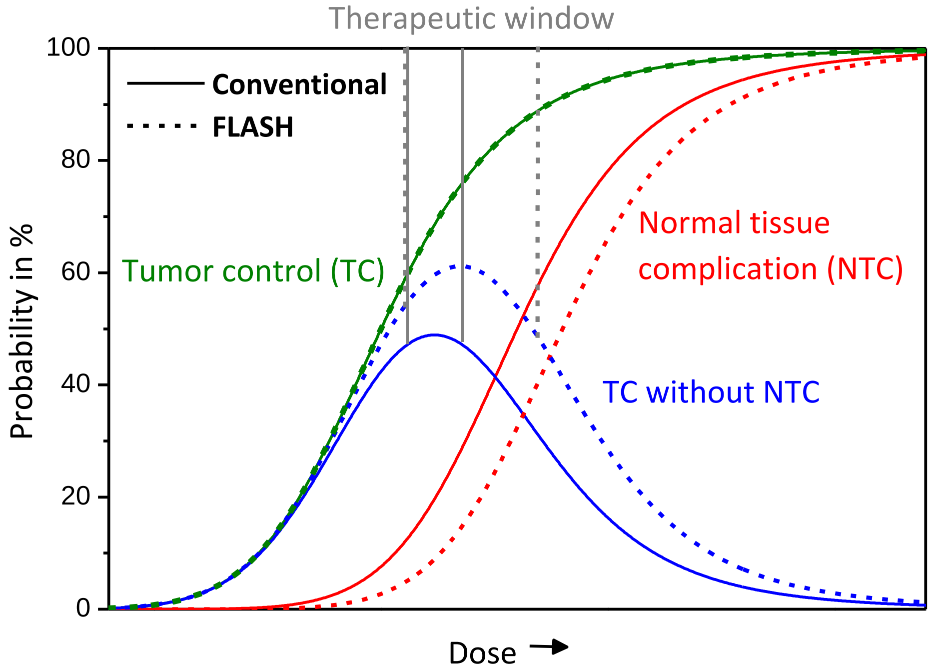


Favaudon et al., Sci Transl Med 6 (2014) 245ra93

Durante et al., Br J Radiol 91 (2018) 20170628

FLASH effect

ultra-high dose rates



FLASH Radiotherapy

- Most of the studies performed using electron beams accelerated by modified clinical LINAC or dedicated electron accelerators (E < 20 MeV)

36 weeks post-RT

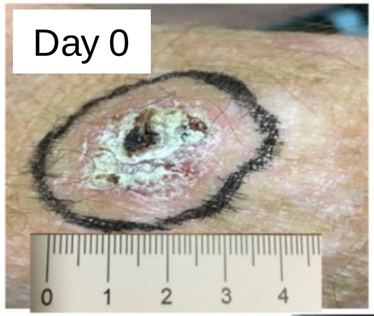
Conventional (5 Gy/min)

necrotic lesions

FLASH (300 Gy/s)

normal appearance of skin

Vozenin et al., Clin Cancer Res 25 (2019) 35



1a : Day 0

1b : 3 weeks

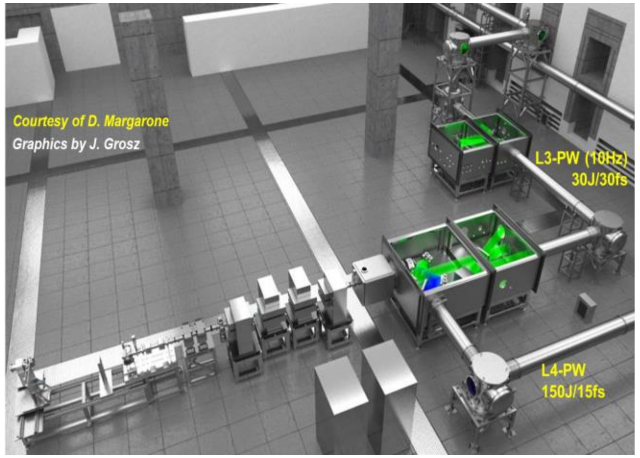
- lymphoma on skin
- FLASH-RT: 10 pulses (of 1 us duration) in 90 ms with 1.5 Gy/pulse

Centre hospitalier universitaire vaudois

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

FLASH proton therapy

- New generation of delivery systems (dose delivery by pencil beams) and proton accelerators (**synchrocyclotrons** and **laser-based** accelerators) further increase the interest towards UHPDR
- First studies with laser-driven proton (extremely short pulse duration → ps-fs → up to 10^9 Gy/s) beams did not show dose rate dependent effects for a variety of *in vitro* assays.
- **Dedicated facilities** have been developed in the perspective of exploring the potentialities of FLASH protontherapy
- A recent *in vivo* study with a **dedicated apparatus for passively scattering clinical proton beams** have more clearly demonstrated the FLASH effect with protons → <u>*see E. Diffenderfer's talk*</u>



FLASH studies…
…in a “FLASH”

Wilson et al.
Frontiers in Oncology
(2020)

In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if >1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Zebrafish embryo (16)	Fish length	**1.2–1.5**	10–12	10^6-10^7	Single pulse	Electron
Zebrafish embryo (29)	Fish length, survival, and rate of oedema	1	0–43	100	0.106×10^9	Proton
Whole body irradiation of mice (34)	LD50	**1.1**	8–40	17–83	400	Electron
Thoracic irradiation of mice (10)	TGFβ signaling induction	**1.8**	17	40–60	100–150	Electron
Thoracic irradiation of mice (18)	Number of proliferating cells, DNA damage, expression of inflammatory genes	**>1 Significant Differences**	17	40–60	100–150	Electron
Abdominal irradiation of mice (33)	Survival	<1 Significant Difference	16	35	Likely 300	Electron
Abdominal irradiation of mice (12)	LD50	**1.2**	22	70–210	100–300	Electron
Abdominal irradiation of mice (17)	Survival, stool formation, regeneration in crypts, apoptosis, and DNA damage in crypt cells	**>1 Significant Differences**	12–16	216	108	Electron
Whole brain irradiation of mice (25)	Novel object recognition and object location tests	**>1 Significant Differences**	30	200, 300	108, 180	Electron
Whole brain irradiation of mice (13)	Variety of neurocognitive tests	**>1 Significant Differences**	10	$5.6 \cdot 10^6$	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**>1 Significant Differences**	10	$30–5.6 \cdot 10^6$	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥1.4**	10	$5.6–7.8 \cdot 10^6$	single pulse	Electron
Whole brain irradiation of mice (24)	Novel object recognition test	**>1 Significant Difference**	10	37	1,300	X-ray
Total body and partial body irradiation of mice (32)	TD50	1	3.6–28	37–41	1,388	X-ray
Thoracic irradiation of mice (11)	lung fibrosis, skin dermatitis, and survival	**>1 Significant Difference**	15, 17.5, 20	40	?	Proton
Irradiation of mouse tail skin (49)	Necrosis ND50	**1.4**	30 and 50	17–170	50	Electron
Irradiation of mouse skin (27)	Early skin reaction score	**1.1–1.6**	50–75	2.5 mean, 3×10^4 in the pulse	23–80	Electron
Irradiation of rat skin (26)	Early skin reaction score	**1.4–1.8**	25–35	67	400	Electron
Irradiation of mini-pig skin (15)	Skin toxicity	**≥1.4**	22–34	300	100	Electron

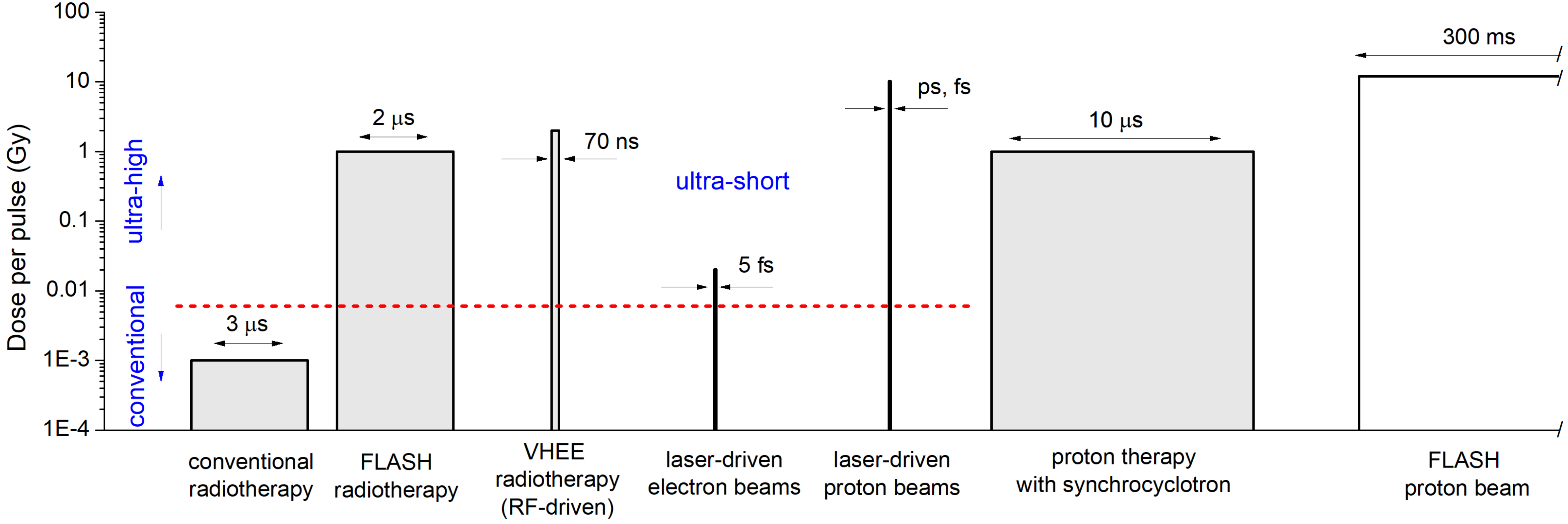
FLASH Radiotherapy: open questions

- Why FLASH effect? Several non-mutually exclusive hypothesis. Oxygen depletion?
- Is it only dependent on the dose-rate averaged on the irradiation duration?
- Are there other more relevant parameters? Dose-per-pulse? Dose rate in the pulse?
- Are there differences for different beam time structures?

….basic question:

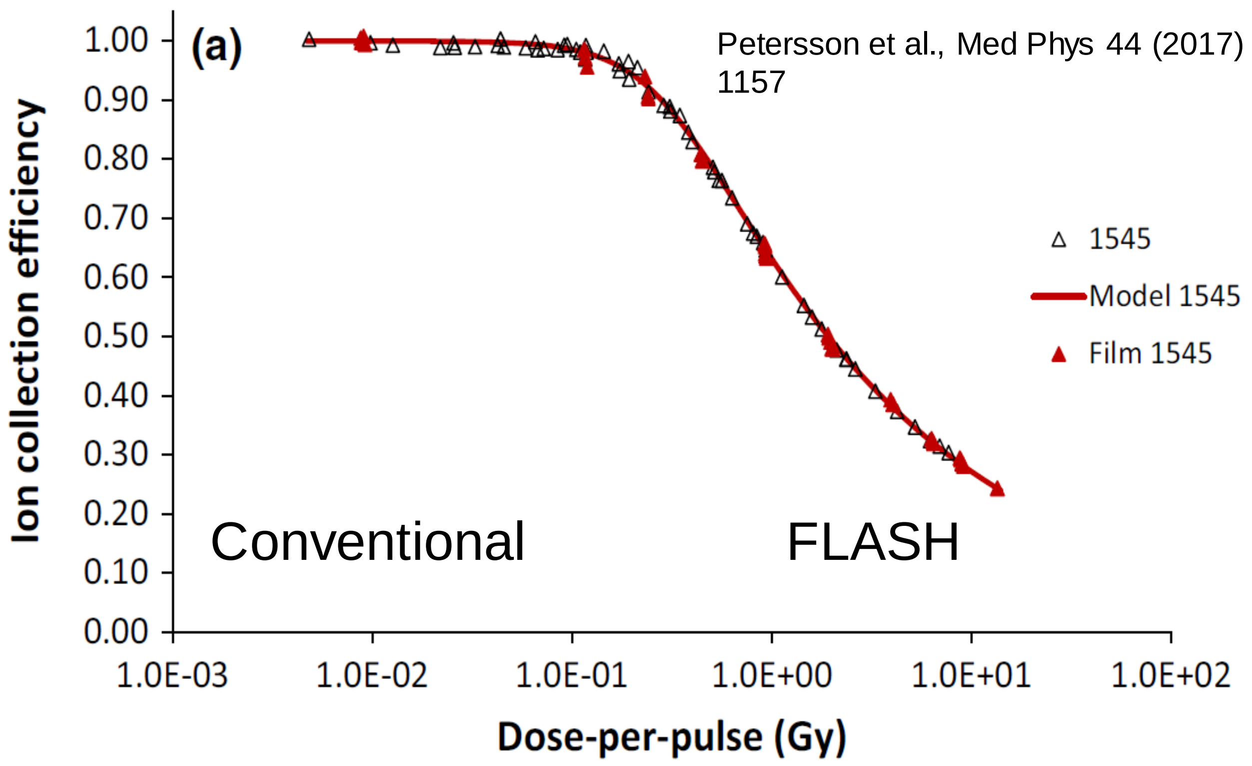
- *Are we able to properly perform precise absorbed dose measurements with **UHPDR beams**? With the level of accuracy required for clinical translations?*

Beams with ultra-high pulse dose rates



Courtesy of A. Schueller

FLASH Radiotherapy: dosimetric challenges



	FLASH	conventional
dose per pulse	1 – 10 Gy	0.3 mGy
pulse width	1 -2 us	3 us
dose rate during pulse	10^6 Gy/s	10^2 Gy/s
pulse repetition frequency	10 – 100 Hz	200 Hz
mean dose rate	40 – 1000 Gy/s	0.05 Gy/s
time for dose delivery	**100 ms**	**4 min**

tools and methods established in dosimetry for conventional RT are not suitable for FLASH-RT

UHDpulse EMPIRE project

EMPIR Call: 2018 / Health (JRP)
Coordinator: Andreas Schüller (PTB)
Duration: 2019-2022
Start: 1. Sept. 2019
Funding: 2.1 M €

Topic: tools for traceable dose measurements for:
- **FLASH radiotherapy**
- VHEE radiotherapy
- laser driven medical accelerators

https://www.euramet.org/research-innovation/search-research-projects/details/project/metrology-for-advanced-radiotherapy-using-particle-beams-with-ultra-high-pulse-dose-rates/

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

***UHDpulse**: Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates*

5 National Metrology Institutes
leading in the field of dosimetry

2 academic hospitals
pioneers in FLASH-RT

3 universities
experts in detector development
pioneer in laser-driven beams

3 national research institutes
pioneer in detector development
pioneer in laser-driven beams
dosimetry expert

1 European research institute
laser-driven beam research

2 companies
expert in detector development

NMI's		Irradiation facility provider		Radiation detector developer	
PTB Physikalisch-Technische Bundesanstalt Braunschweig und Berlin	WP6 (coordin.)	CHUV Centre hospitalier universitaire vaudois	WP3	ADVACAM Imaging the Unseen	WP4
NPL National Physical Laboratory	WP1	institut Curie		CSIC cnm	
METAS	WP2	eli beamlines		USC Universidade de Santiago de Compostela	
CZECH METROLOGY INSTITUTE	WP5 (impact)	Nuclear Physics Institute of the CAS public research institution		POLITECNICO MILANO 1863	
Central Office of Measures		QUEEN'S UNIVERSITY BELFAST		PTW THE DOSIMETRY COMPANY	
		HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF			

UHDpulse

UHDpulse EMPIRE project: WPs

WP1: Primary standards

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

WP2: Secondary standards, relative dosimetry

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

WP4: Detectors and methods outside primary beam

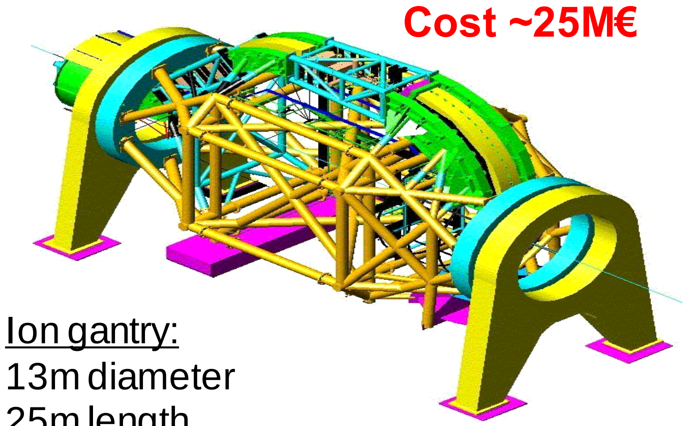
- Active detection techniques for pulsed mixed radiation fields of stray radiation
- Methods with passive detectors

WP3: Detectors for primary beam

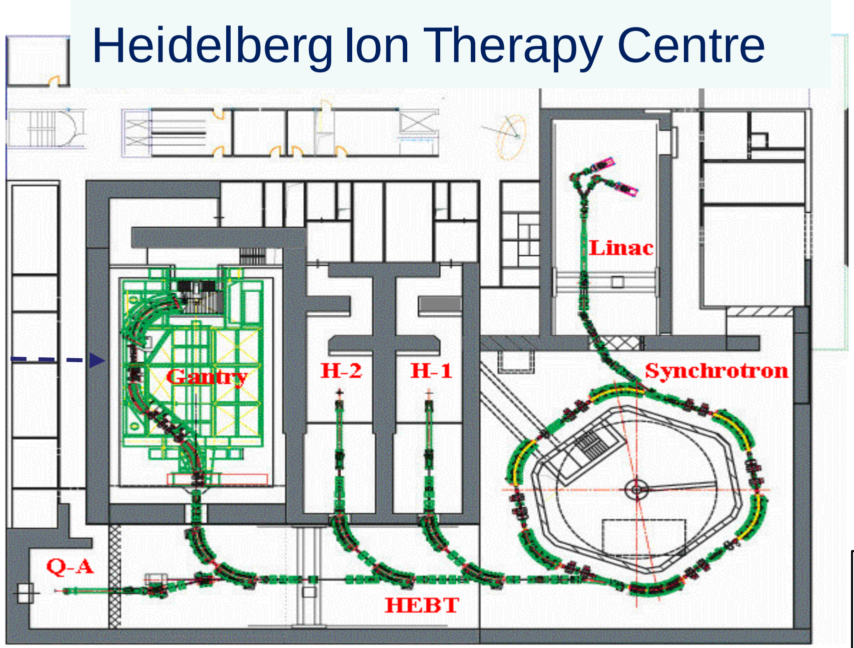
- Novel and custom-built active dosimetric systems
- Beam monitoring systems

Laser-driven ion beams

Cost ~25M€



Ion gantry:
13m diameter
25m length
600ton overall weight
420ton rotational



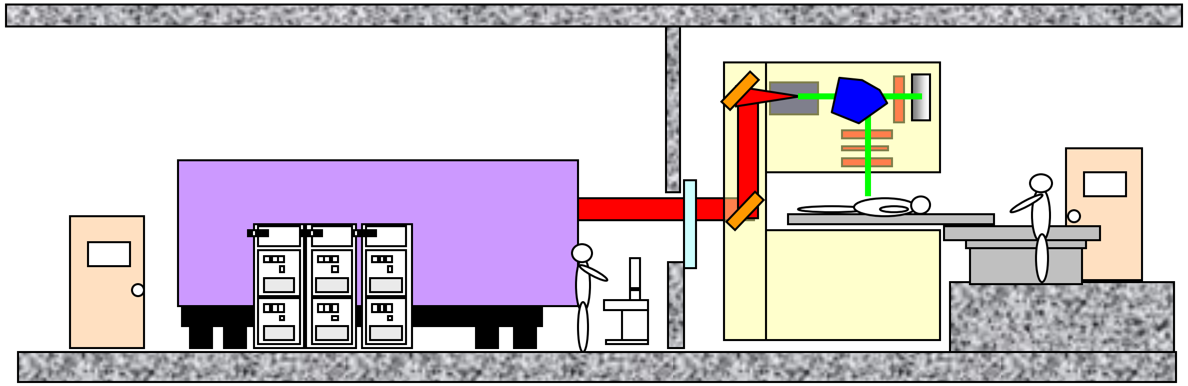
Accelerator
4m diameter
60 tons
500nA,
250MeV

Cost ~10-20M€

***Vision* first proposed in** :

S.V. Bulanov *et al*, Phys. Lett. A, **299**, 240 (2002)
E. Fourkal et al, Med Phys., **30**, 1660 (2003)
V. Malka, *et al*, Med. Phys., **31**, 1587 (2004)

- Laser transport rather than ion transport **(reduced shielding**)
- Possibility to **reduce size** of gantry
- Possibility of **controlling output energy** and spectrum
- Spectral shaping for direct "painting" of tumour region
- varying accelerated species (**Mixed fields**: x-ray + e- + ions)
- In-situ diagnosis



Laser-driven ion projects for medical applications

onCOOPtics (Jena, HZDR) → PW system coupled to cancer treatment centre. Development of beam lines, gantry design

ELIMAIA @ ELI Beamlines (IoP, Cz)
ELIMED (INFN, Italy) → High-rep medical beamline on PW laser. Use of conventional modules

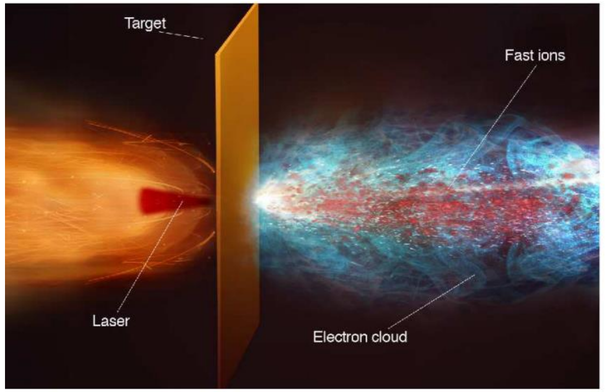
LIGHT (GSI Darmstadt) → High-flux beam capture/ transport

MAP/CALA (Munich) → Biomedical beamline for radiobiology/dosimetry

SAPHIR (LOA, Amplitude. Fr) → 200 TW system, biomedical beamline

A-SAIL (UK ion acceleration consortium. Uk) → Queen's University Belfast
University of Strathclyde Imperial College London
CLF RAL -STFC

A. Macchi et al., Rev. Mod. Phys. (2013)

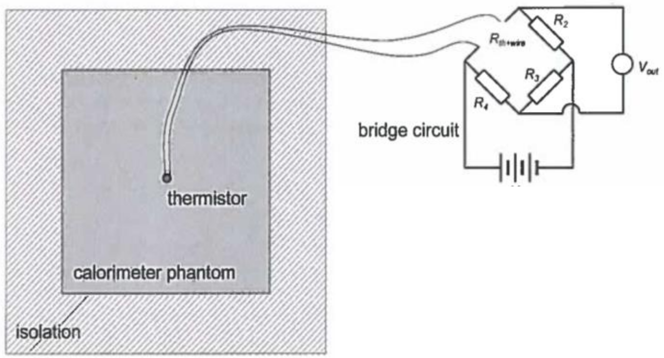


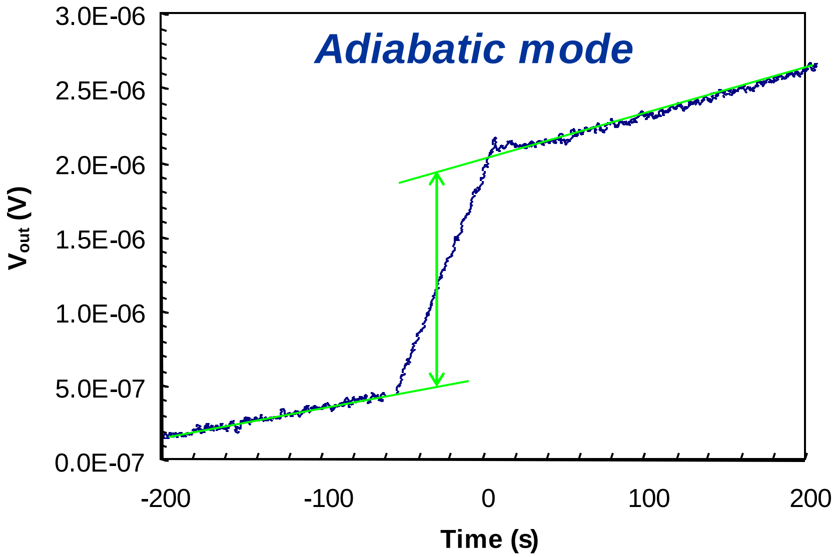
- Ultra-short pulse duration (ps-ns)
- Dose rate up to 10^{10} Gy/s
- Dose-per-pulse up to several Gys
- Harsh experimental environment due to electromagnetic pulse (EMP)

Calorimetry for proton dosimetry

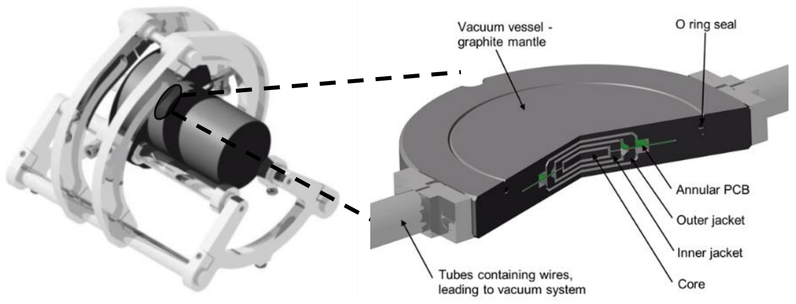
- Novel approach proposed by NPL never exploited so far for laser-driven beams based on **calorimeters**

- Water and graphite calorimeters have been demonstrated with p beams
- **Graphite calorimetry** at NPL (higher sensitivity)



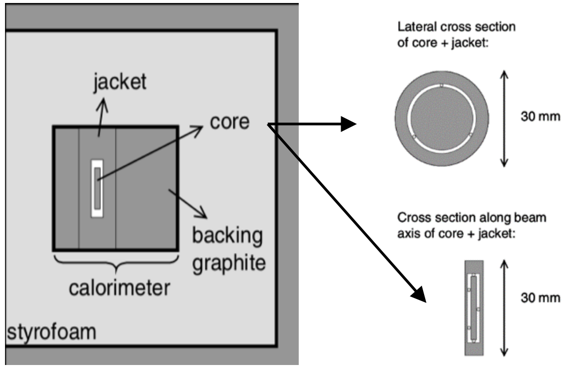


- **primary standard graphite calorimeter for absorbed dose in clinical proton beams**
- New IPEM UK code of practice to deliver an uncertainty on reference dosimetry for protons of approximately 2% (at 95% CL)

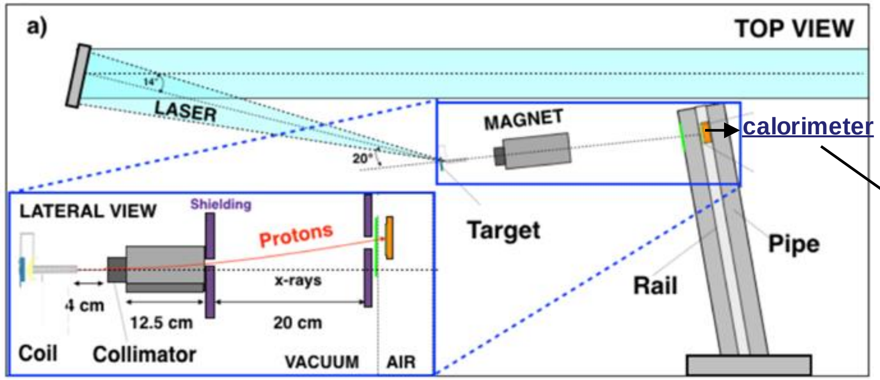


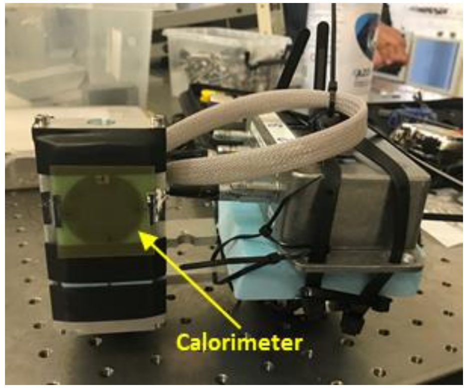
Calorimetry for laser-driven proton beams

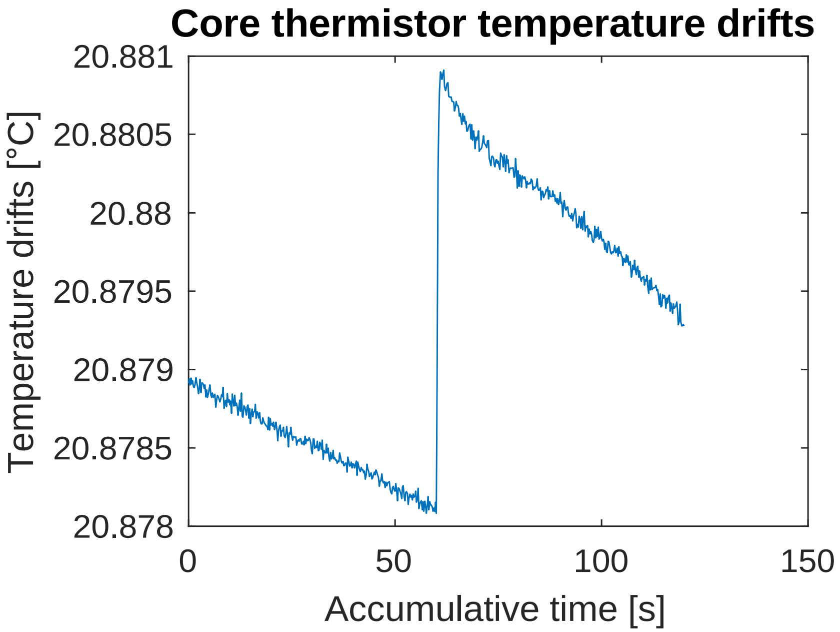
- Requirement: laser-driven proton energies of 15-60 MeV (→ WE range about 3-30 mm)
  - ***thin-walled calorimeter** in order to minimize divergence/absorption of the beam*
- A small graphite calorimeter originally developed for conventional low energy proton beams up to 60 MeV (Palmans *et al.* PMB **49** 2004) has been completely **refurbished**
  - **Cylindrical** shape (core nested in a three-piece jacket + additional graphite slabs)



- **First proof-of-principle test with laser-driven protons at RAL**



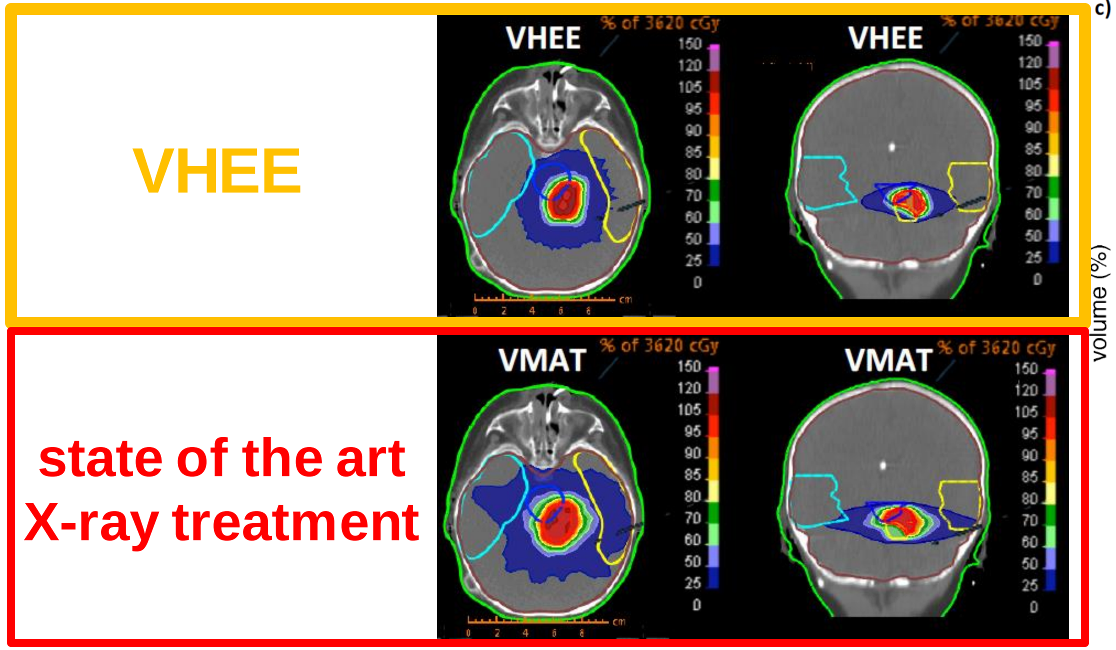


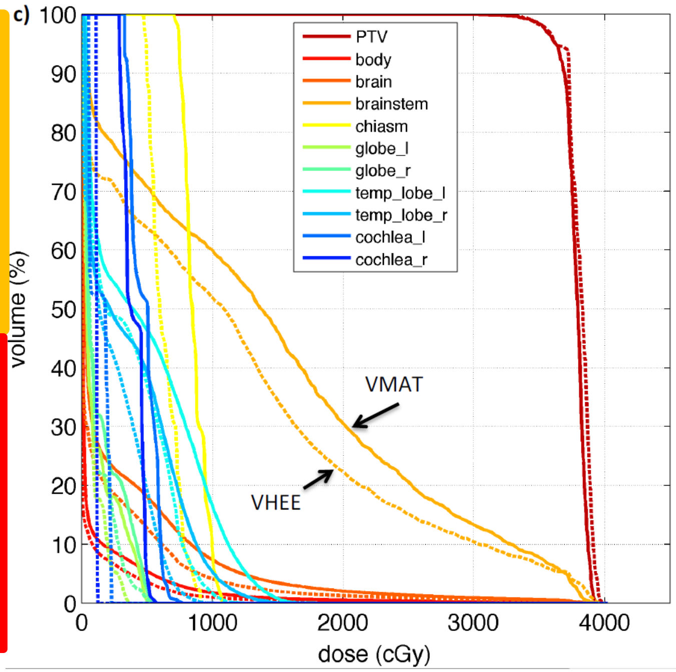


- **VULCAN PW** pulses of energy **600 J** and **~500 fs** durations
- focused to intensities > 10^{20} **W/cm²** onto **15 μm Au** targets
- Protons produced in the range **20– 45 MeV**
- high-energy component separated using a **0.9 T** dipole magnet
- doses between **1-3 Gy in one single pulse**

VHEE cons

- Most of studies carried out with low energy electrons (< 20 MeV) → only superficial tumours
- With the aim of treating deep-seated tumours → **Very High Energy Electron (VHEE)** beams (< 250 MeV)
  - Increased depth of penetration
  - Higher conformal dose distributions (vs photons) and low integral dose
  - Better sparing of organs at risk → enables dose escalation to the tumour
  - Ability to control position electromagnetically → Scanning beams more easily done than heavy particles



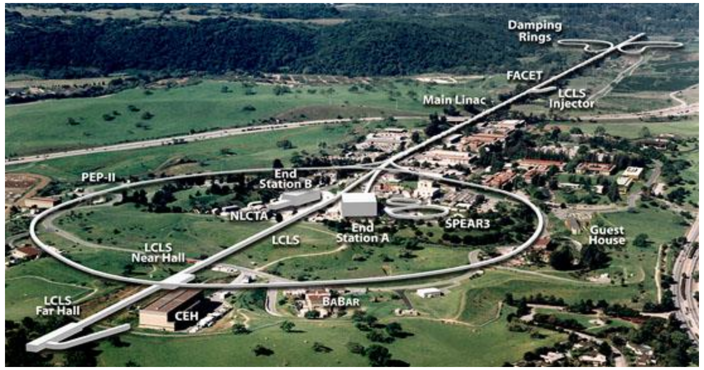


Bazalova *et al.*,
Med.Phys. 42 (2015)

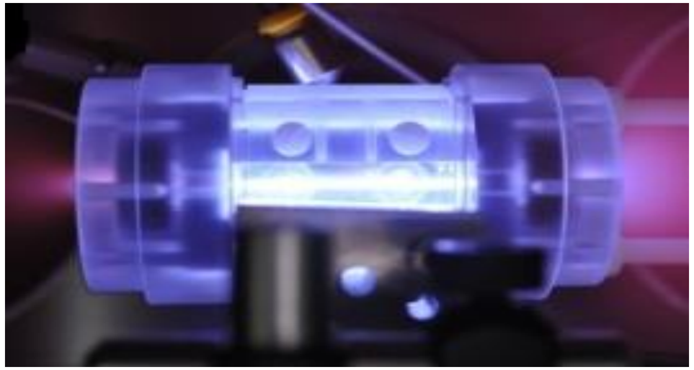
VHEE generation and challenges

- Conventional accelerators (RF cavities); Limit ≈ **100 MV/m** → acceleration gradient limits maximum energy obtained
- Laser-plasma accelerators: compact, cheaper, higher acceleration gradient ≈ **100 GV/m**

↳ **Under development**



SLAC - **3,3 km**
50 GeV e-beam

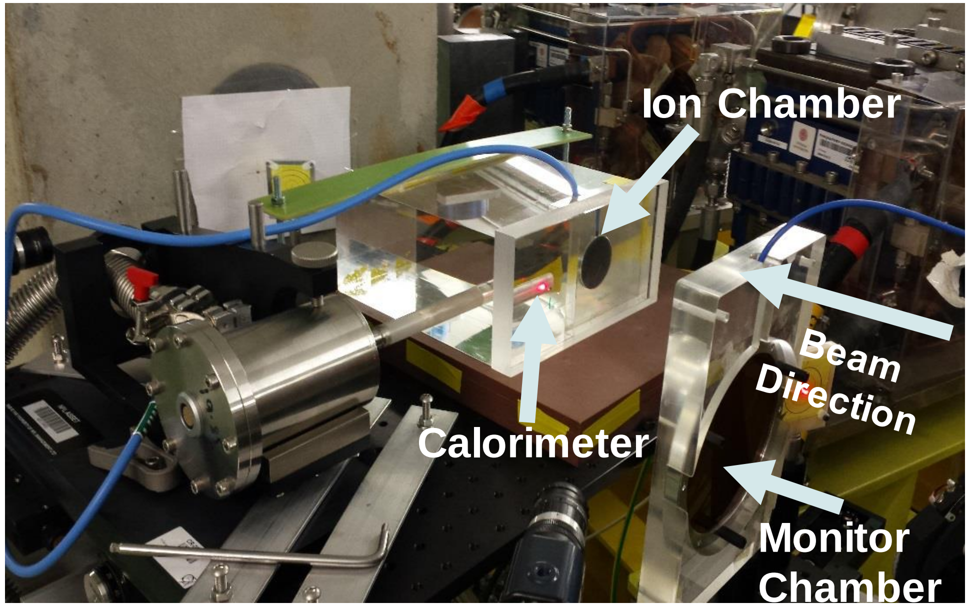


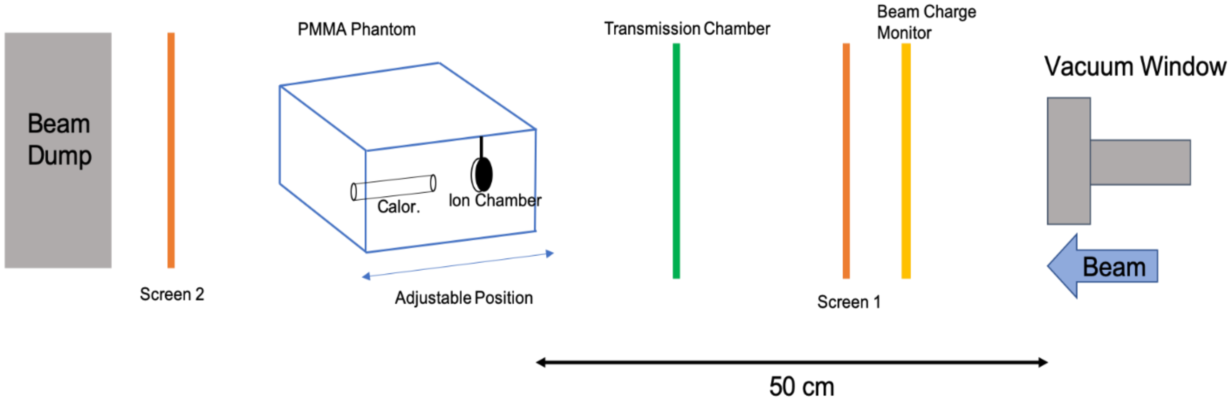
Plasma capillary - **3 cm**
3 GeV e-beam

- Very short nature of electron pulse duration: fs – ps → dose rate up to 10^9 Gy/s
- For clinical translation of VHEE beams accurate dosimetry must be performed, addressing the challenges related to these very high dose rates.

VHEE dose measurements at CERN

- The response of **plane-parallel ionization chambers** to UHPDR (RF) VHEE beams at 200 MeV studied
- Experimental campaign at the CLEAR user facility at CERN:
  - measurements obtained with a **PTW Roos** Type-34001 chamber and **graphite calorimeter** developed at NPL (UK)
- Ratio of the two doses → recombination factor $\boldsymbol{k_{s,abs}}$ for the Roos chamber for various V (75 V – 600 V)
- Aim: *relationship* $k_{s,abs}$ *vs dose-per-pulse at instantaneous dose rates never used so far (<* 10^8 *Gy/s)*



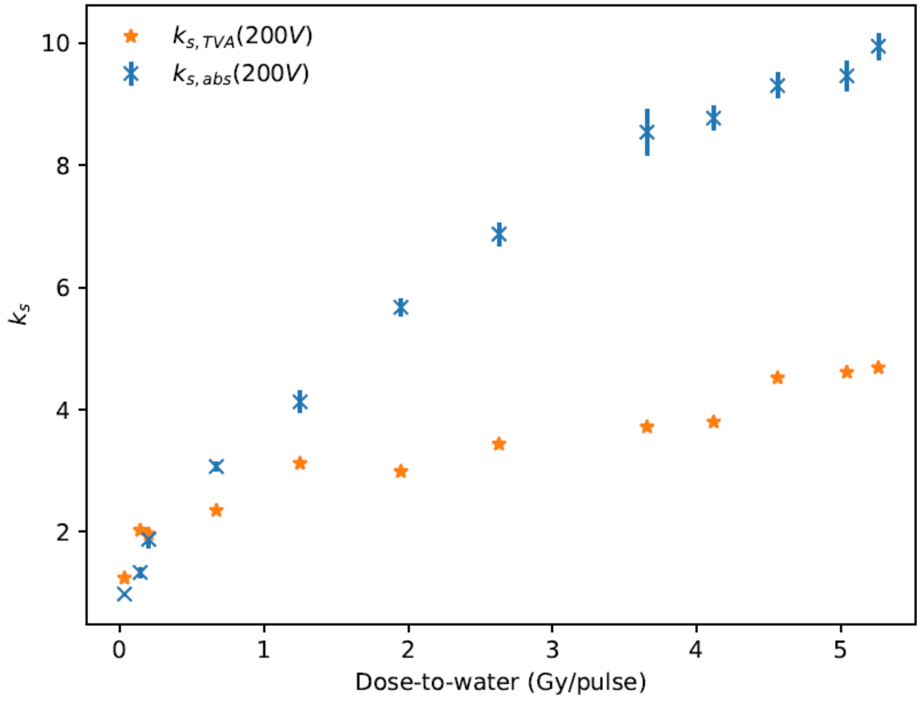


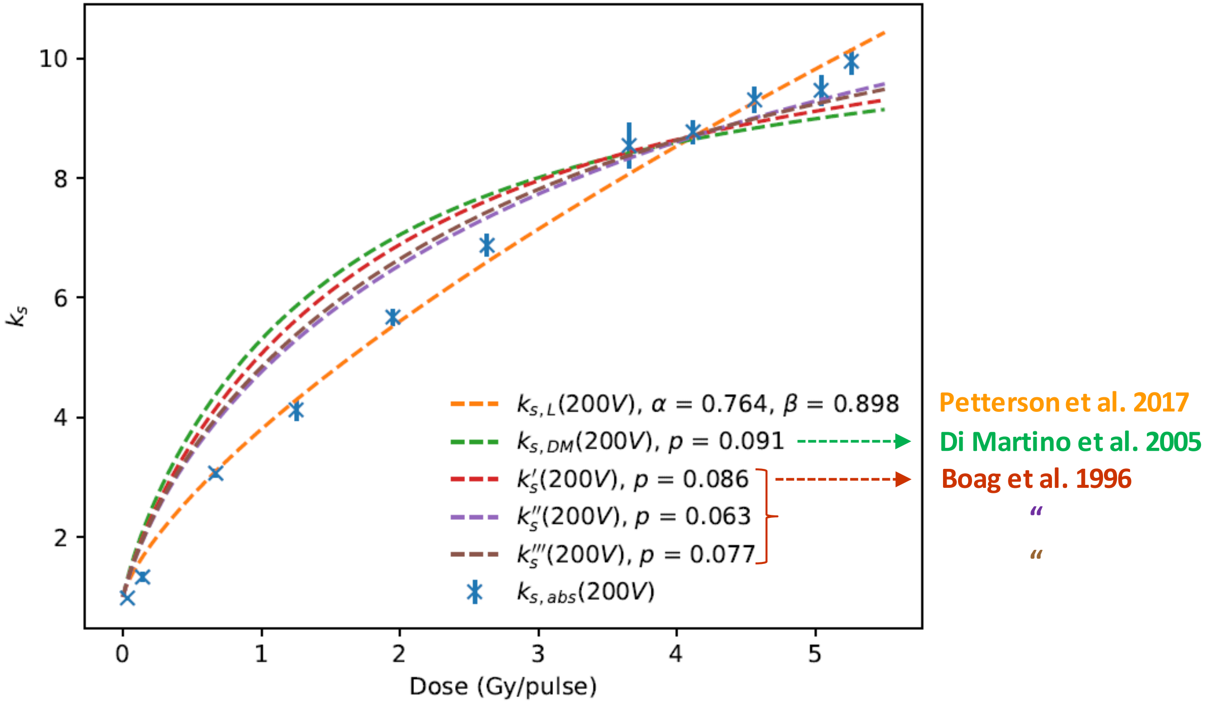
- energy spread between 0.25% and 6.5% (Gamba et al. 2017) .
- circular field with x and y σ of approximately 5 mm.
- chamber and calorimeter enclosed in PMMA phantom on moveable stand.

VHEE dose measurements at CERN

- Dose-per-pulse: few cGy up to several Gy
- k_s up to 10 (V = 200V) → collection eff. 10%
- $k_{s,abs}$ compared with $k_{s,TVA}$ (two-voltage method)

- No accepted ion recombination model for UHPDR to date
- Analytical (Boag 1996, Di Martino 2005) and logistic (Petterson 2017) models tested at these regimes





Submitted to *Sci. Rep*. (under review)

Utilization of chambers with smaller sensitive volumes and higher electric fields?

Summary and conclusions

- Challenges of dosimetry for ultra-high pulse dose rate have been discussed
- The objectives of the EMPIR project UHDpulse have been described
- Some first results have been showed for laser-driven proton beams and VHEE, describing the alternative approaches adopted for UHPDR beams.
- Results from the project activities will contribute to address metrological challenges of dosimetry at ultra-high dose rates
- The achieved outcomes will be promoted to standard organizations and international agencies
- Metrological and validated tools will be provided to support accurate preclinical studies and to enable future clinical applications of these emerging techniques

Thank you

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