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

Dosimetry of particle beams with ultra-high pulse dose rates (in the context of VHEE)

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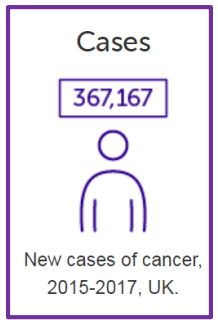
Very High Energy Electron Radiotherapy Workshop (VHEE'2020), 5-7 October 2020

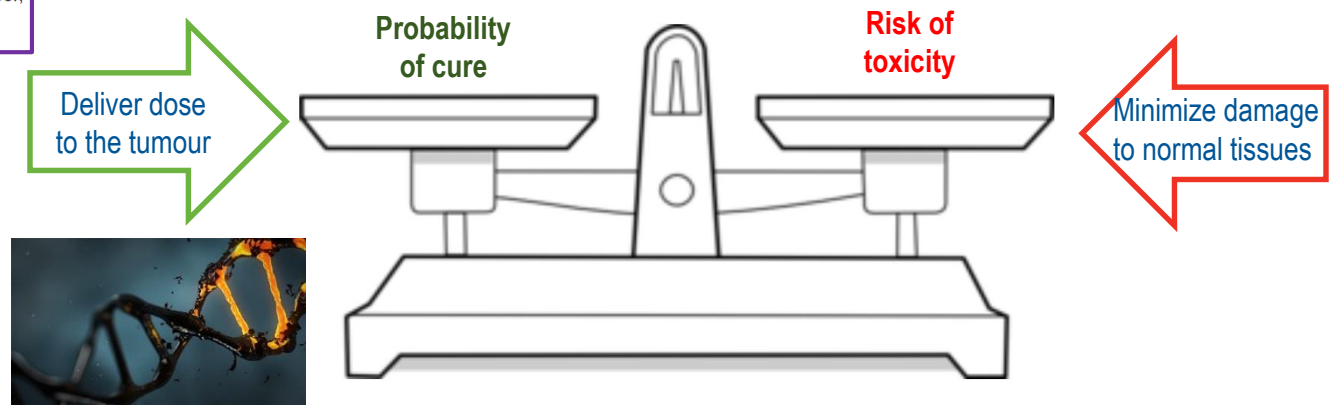
Outline

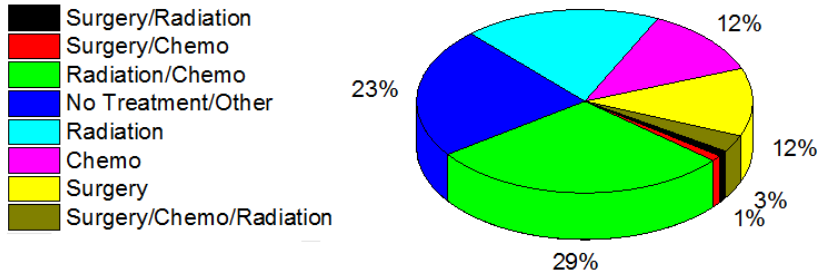
- Background/Motivation
- Interest in UHPDR RT
- Recap on dosimetry
- Challenges of dosimetry of UHPDR beams
- First results
  - Calorimetry & ionization chamber dosimetry in UHPDR VHEE beams
- Conclusions

Motivation



- >360,000 new cancer cases/yr (70% rise over the next 2 decades)
- Radiotherapy is the most cost-effective methods responsible for ca. **50% of cancer survivals**





How can we increase efficacy of RT?

- Improved the 3D dose conformation (thanks to major technological advances)
- Use of radiosensitizers/radioprotectors
- Application of different beam modalities
- UHDRP…
- ….

Why are we interested in UHPDR RT?

FLASH!

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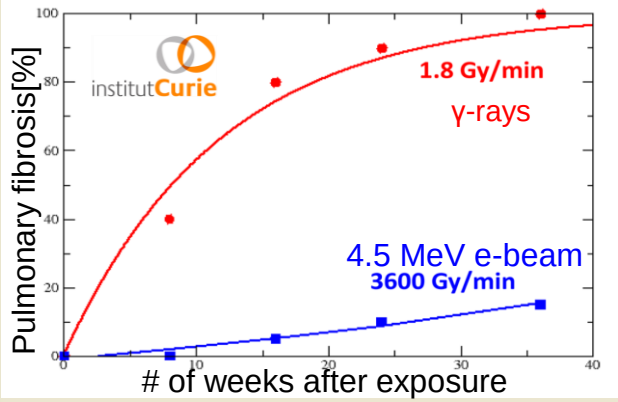
- First UDR studies – 1960s

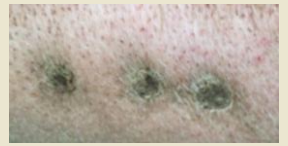


Favaudon, *et al. Sci Transl Med* 2014; 6

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

36 WEEKS POST-RT

Conv. (5 Gy/min)



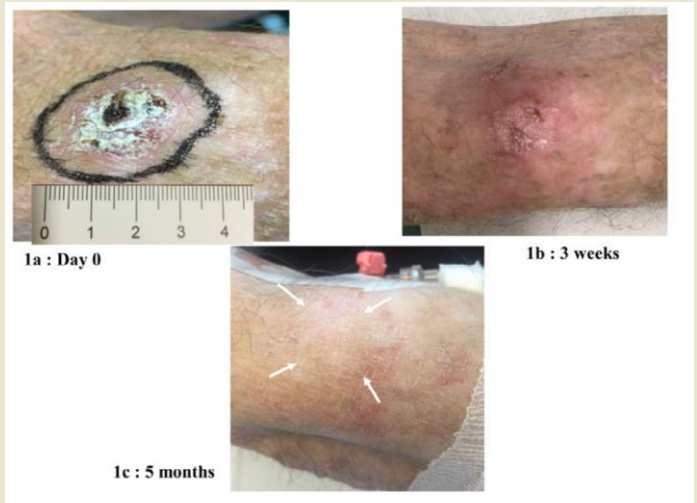
necrotic lesions

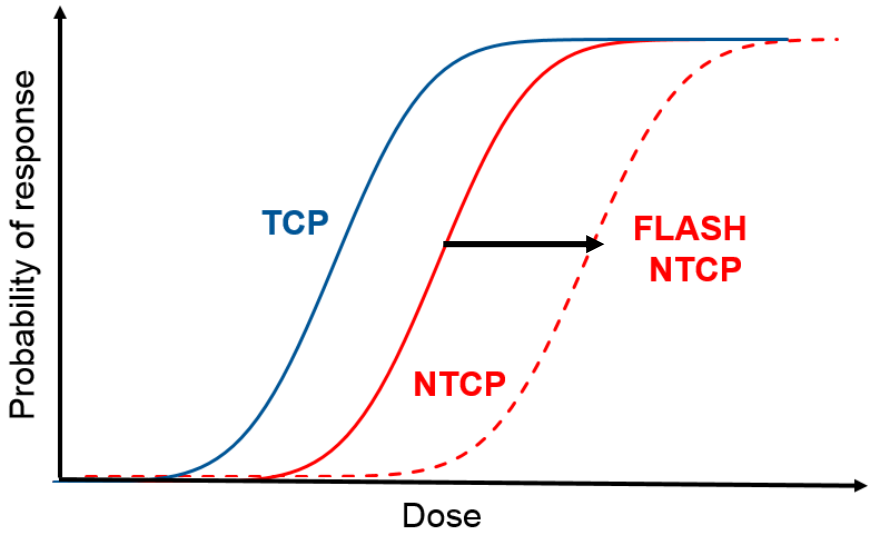
FLASH (300 Gy/s)

normal appearance of skin

- subcutaneous lymphoma
- delivery: 10 pulses (1 us) in 90 ms with 1.5 Gy/pulse

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





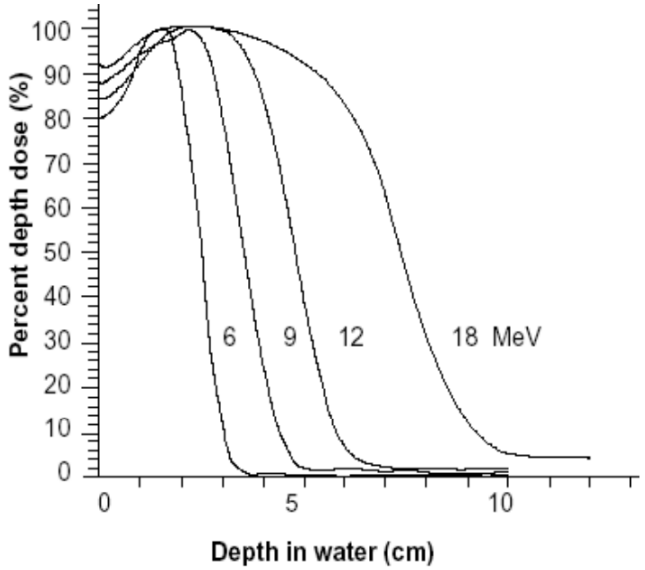
FLASH RT

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

DRAWBACKS

- Limitations of clinical electrons
- High relative surface dose
- Shallow penetration/short range
- Range straggling (no Bragg peak)
- High penumbra
- Bulging effect
- Spread of beam in air (why we have cones)

BEAM ENERGY



Radiation Oncology Physics, IAEA 2005

Limitations of electron beams due to energy – *what happens if the electron energy is increased??*

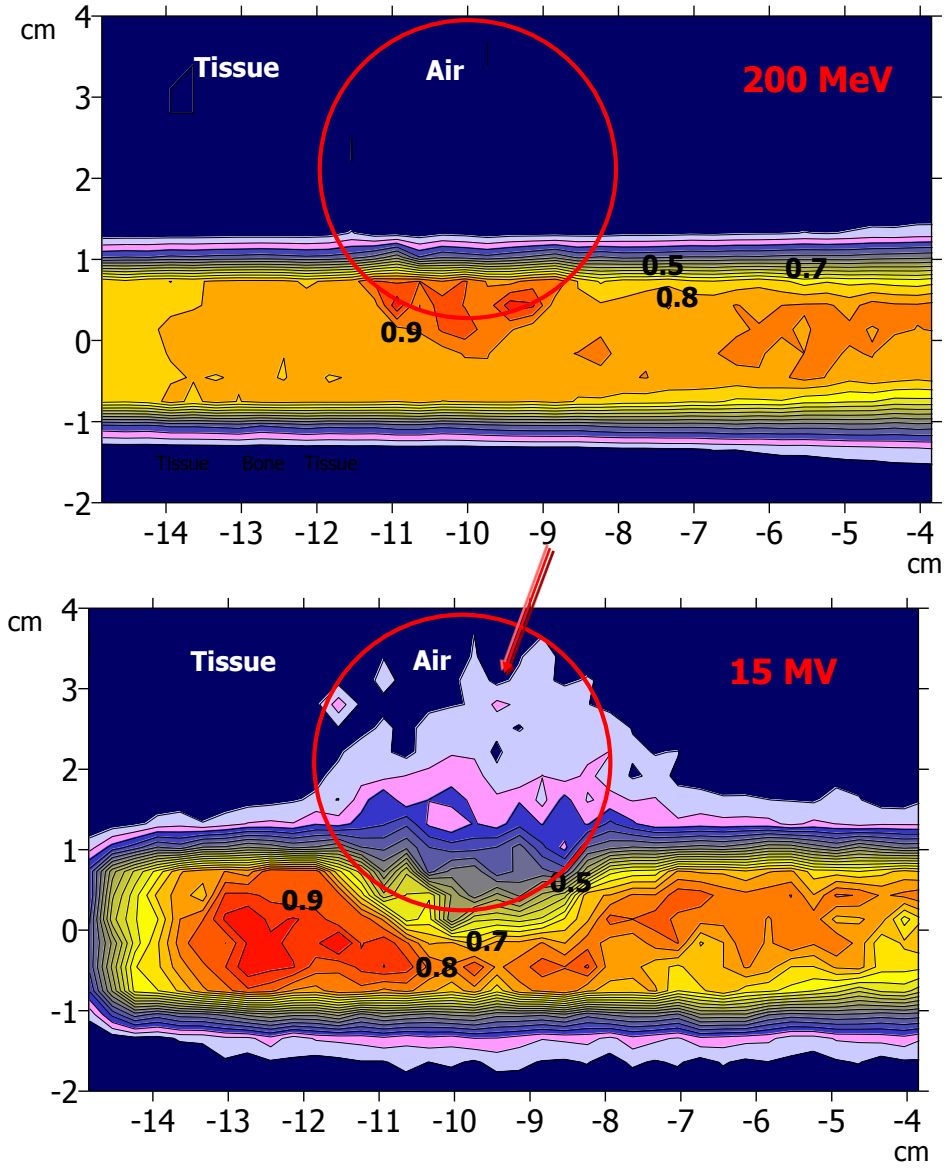
What happens if the electron energy is increased (100+ MeV)?

- Increases depth of penetration
- No range straggling if beam penetrates through patient
- Ability to control position electromagnetically
  - Scanning beams more easily done than heavy particles
  - Speed of electromagnetic scanning allows for ~ 100X more beams delivered in the same time as photons
- Lower beam spread and reduced bulging effect

While maintaining some low energy characteristics

- Can produce pencil beams
- Less costly than heavy particles
- High surface dose

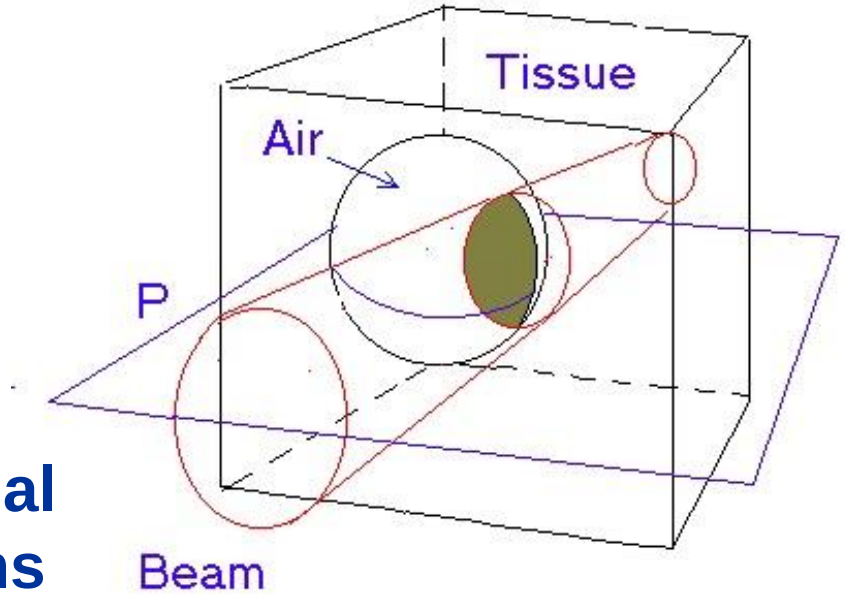
Advantages of VHEE RT



VHEE unlike X-ray photons maintain electronic equilibrium in tissues with varying densities

VHEE

conventional RT photons

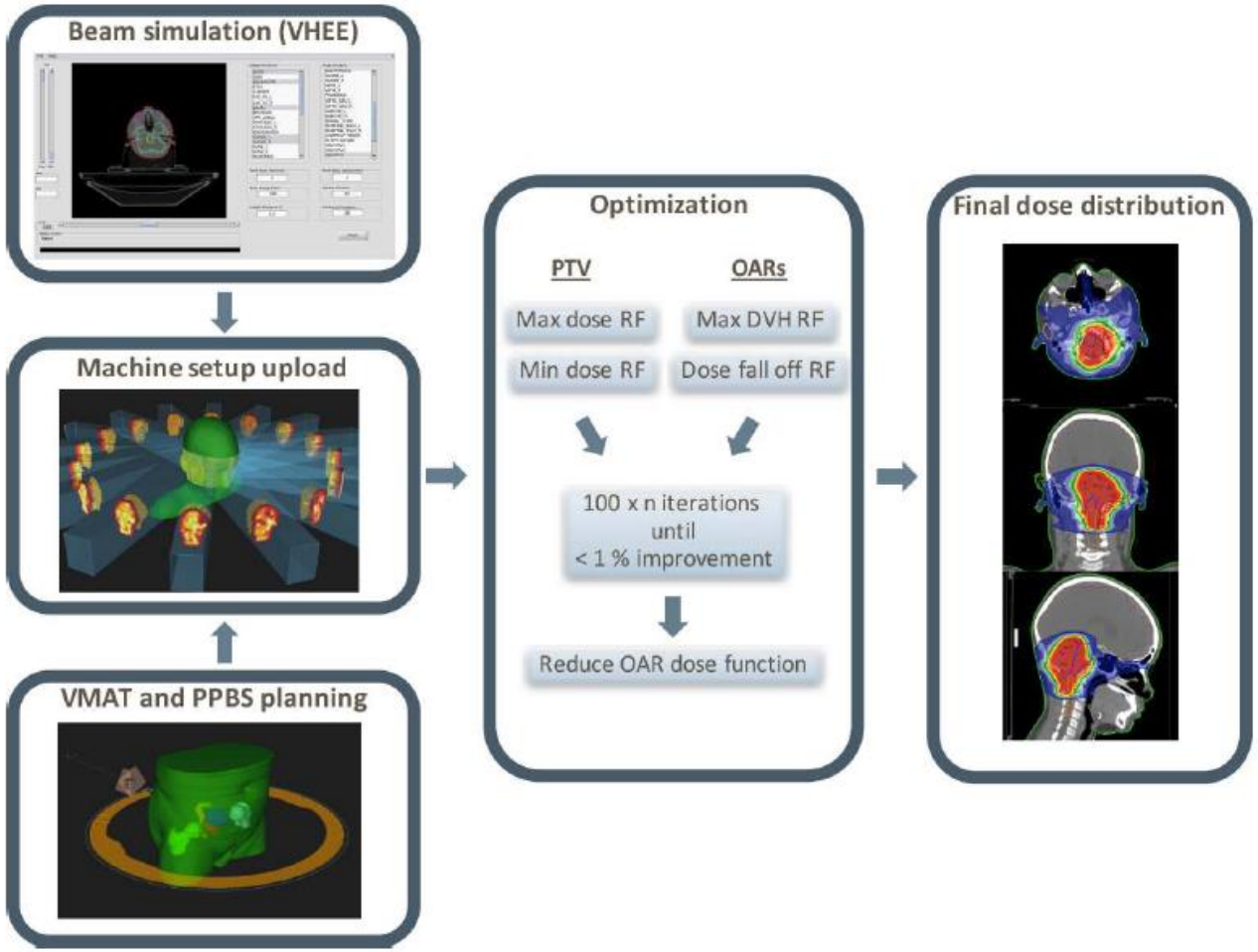


Perturbation of dose, - consequence - under or over dosage of tissue

Credit: C. DesRosiers

DesRosiers *et al.*, Proceedings of the SPIE, Vol. 6881, (2008)

TPS for VHEEs



Treatment planning for radiotherapy with very high-energy electron beams and comparison of VHEE and VMAT plans

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(Received 22 December 2014; revised 7 April 2015; accepted for publication 12 April 2015; published 29 April 2015)

Very high-energy electron (VHEE) beams in radiation therapy; Treatment plan comparison between VHEE, VMAT, and PPBS

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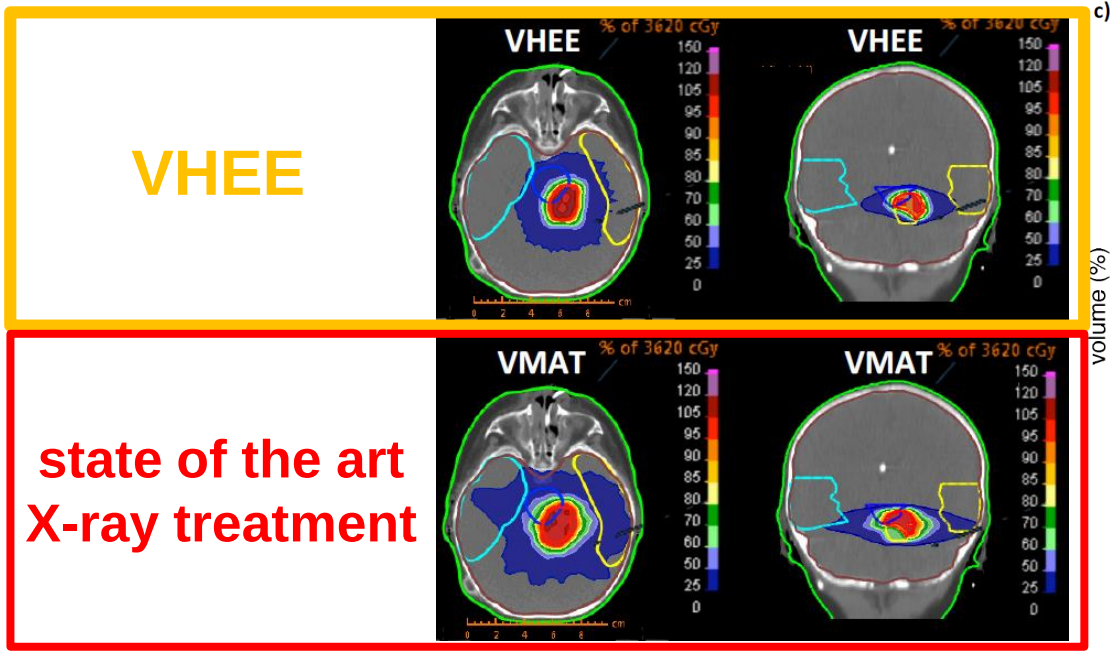
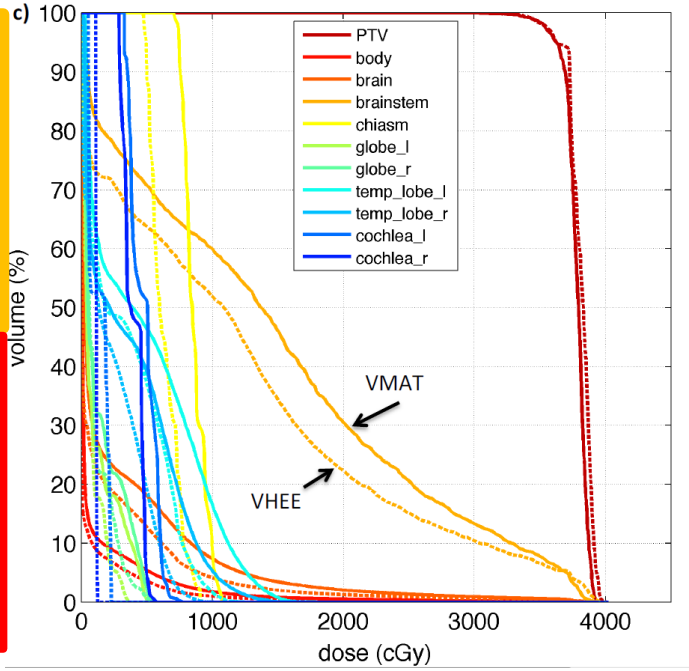
(Received 19 August 2016; revised 15 March 2017; accepted for publication 15 March 2017; published 4 May 2017)

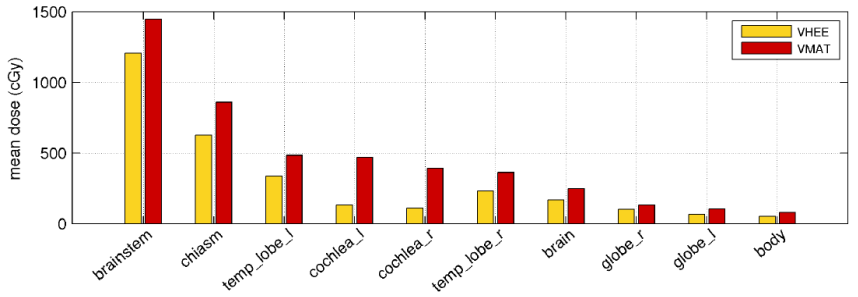
Schueller, Med Phys. 2017 Jun;44(6)

VHEE plan vs VMAT plan (H&N case)

- VHEE can achieve superior dose distributions (vs photons), can provide **better sparing of organs at risk** and enable **dose escalation** to the tumour







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

Review of FLASH studies (Wilson et al. Frontiers in Oncology 2020)

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Summary of irradiation parameters and outcomes for in vivo studies investigating the FLASH effect

normal tissues

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	5.6·10^6	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**>1 Significant Differences**	10	30–5.6·10^6	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥1.4**	10	5.6–7.8·10^5	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

tumour tissues

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**
Thoracic irradiation of orthotopic engrafted non-small cell lung cancer (Lewis lung carcinoma) in mice (36)	Tumor size and T-cell Infiltration	**>1 Differences in tumor size (significant) and T-cell infiltration**	18	40	?	Proton
Thoracic irradiation of orthotopic engrafted mouse lung carcinoma TC-1 Luc+ in mice (10)	Survival and tumor Growth Delay	1	15-28	60	100–150	Electron
Abdominal irradiation of mice (17)	Number of tumors, tumor weights	1	12–16	216	108	Electron
Whole brain irradiation of nude mice with orthotopic engrafted H454 murine glioblastoma (8)	Tumor Growth Delay	1	10–25	2.8–5.6·10^6	Single pulse	Electron
Local irradiation of subcutaneous engrafted Human breast cancer HBCx-12A and head and neck carcinoma HEp-2 in nude mice (10)	Tumor Growth Delay	1	15–25	60	100–150	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (8)	Tumor Growth Delay	1	0–35	125–5.6·10^6	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (19)	Tumor Growth Delay	1	10–30	125–5.6·10^6	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted Human hypopharyngeal squamous cell carcinoma ATCC HTB-43 in nude mice (35)	Tumor Growth Delay in irradiated Mice and RBE	1	20	0.008 mean, ≈10^9 in pulse	<<1	Proton
Treatment of locally advanced squamous cell carcinoma (SCC) in cat patients (15)	Tumor response and survival	1 Similar response as in published studies with CONV-RT	25–41	130–390	100	Electron
Treatment of CD30+ T-cell cutaneous lymphoma T3 N0 M0 B0 in human patient (9)	Tumor response	1 Similar response as previous treatments with CONV-RT	15	167	100	Electron

FLASH – a biological effect

- **NOT defined** by physical beam parameters
- BUT it is dependent on beam parameters

How FLASH effect is influenced by:

- Mean dose-rate (averaged on the irradiation duration)?
- Dose-per-pulse?
- Dose rate in the pulse?
- Temporal beam structures?

} systematic studies required

….What about dosimetry?

The importance of dosimetry:

- Successful radiotherapy depends on delivering the correct dose to the treatment volume and sparing surrounding healthy tissues

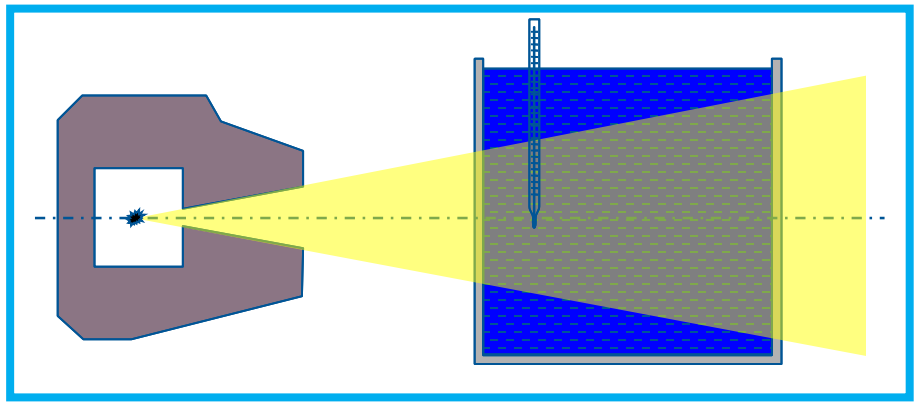
*Are we able to perform accurate absorbed dose measurements with **UHPDR beams** with the level of accuracy required for clinical translations?*

Recap on dosimetry

DETECTOR CATEGORIES

- Directly measure the quantity of absorbed dose (e.g. calorimeters)
- Measure ionisations (e.g. free-air chamber)
- Quantify in direct or indirect way the number of produced radicals (e.g. Fricke)

Radiation energy turns into heat



heat is tiny, but measurable

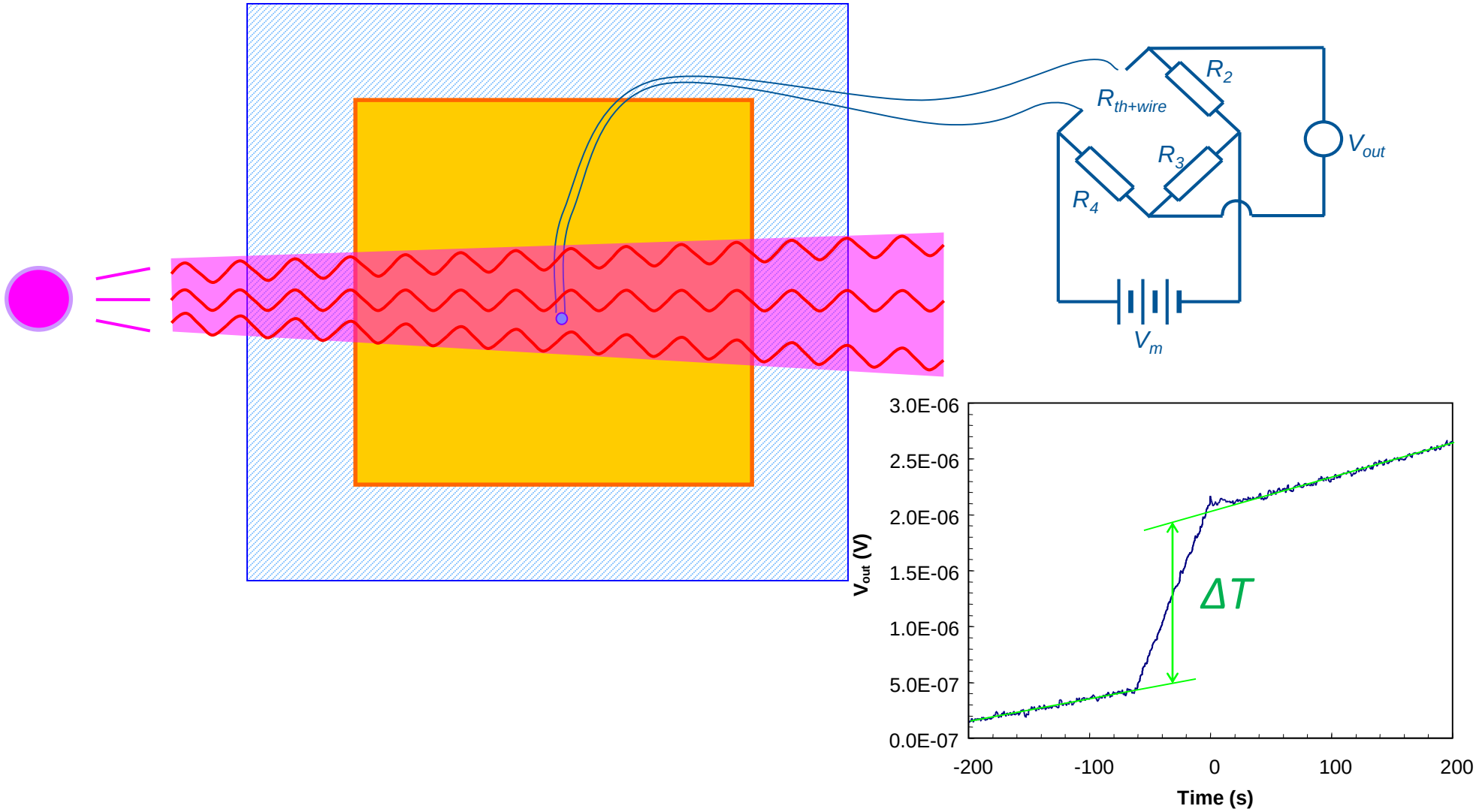
primary standards for absorbed dose are calorimeters

Calorimetry: principle

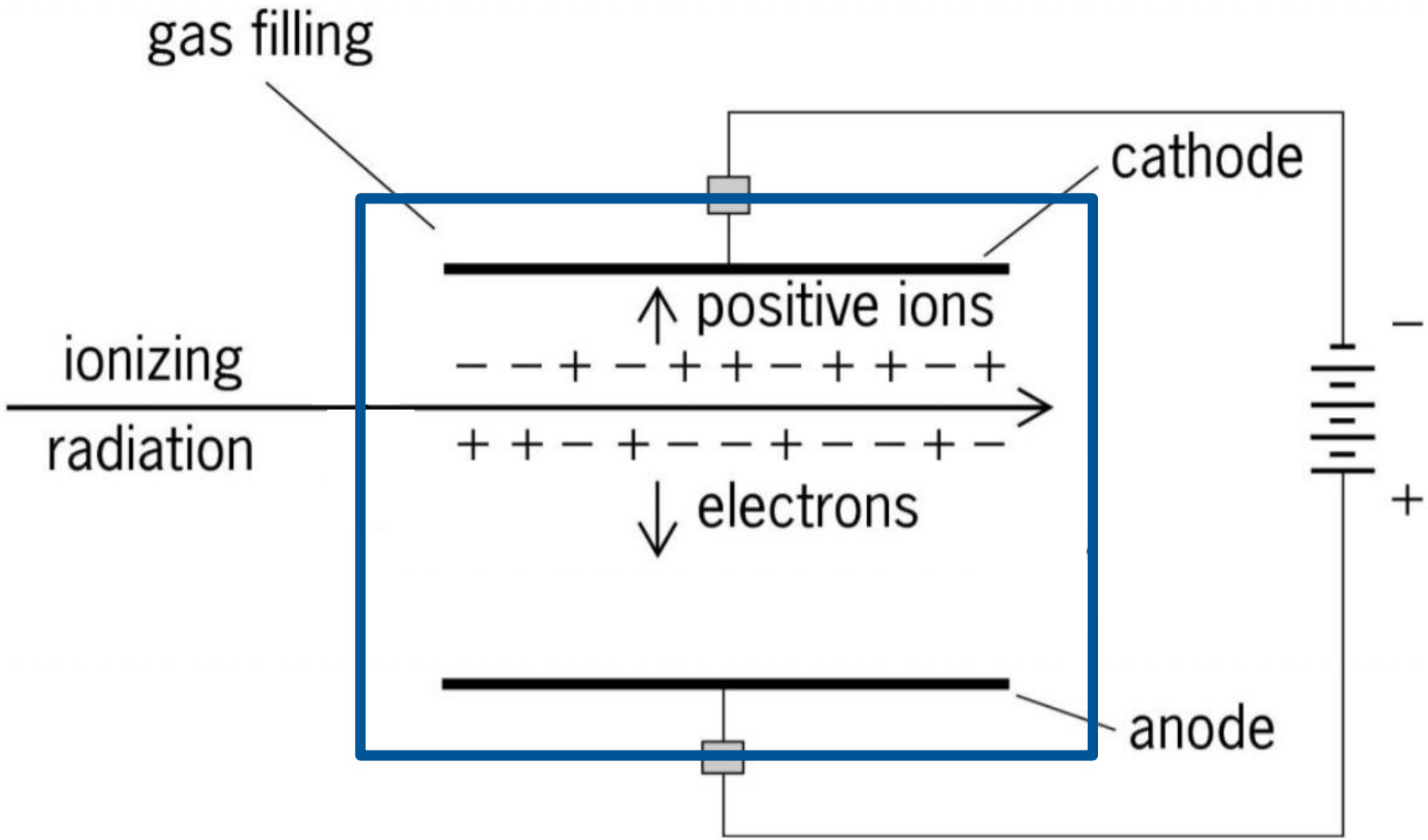
$$D = c \cdot \Delta T$$

	c ($J \cdot kg^{-1} \cdot K^{-1}$)	$\Delta T/D$ ($mK \cdot Gy^{-1}$)
water	4180	0.24
graphite	710	1.41

Calorimetry

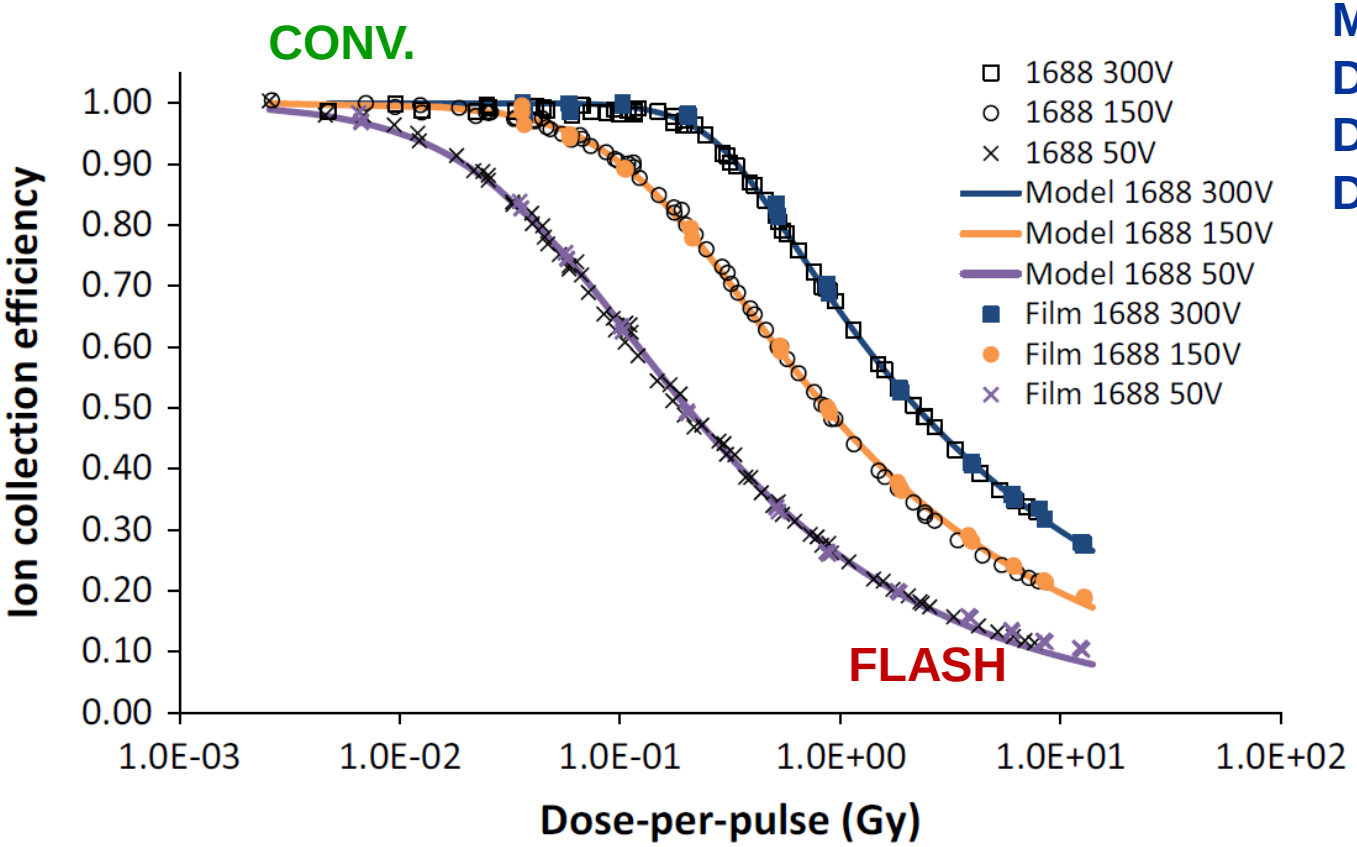


Ion chamber


gas filling
cathode
positive ions
ionizing
radiation
electrons
anode
–
+

Challenges of dosimetry of UHPDR beams

Loss of collection efficiency in IC



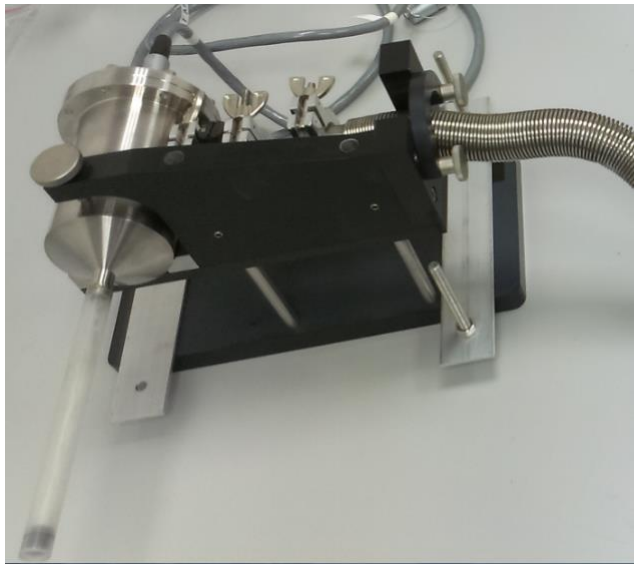
Petersson et al., Med Phys 44 (2017) 1157

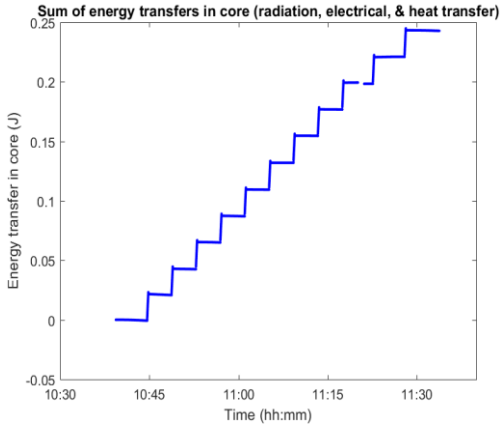
	CONV.	FLASH
Mean dose rate →	0.05 Gy/s	*vs* 40-1000 Gy/s
Dose per pulse →	0.3 mGy	*vs* 1-10 Gy
Dose in a pulse →	10^2 Gy/s	*vs* 10^6 Gy/s
Delivery time →	few min	*vs* <1s

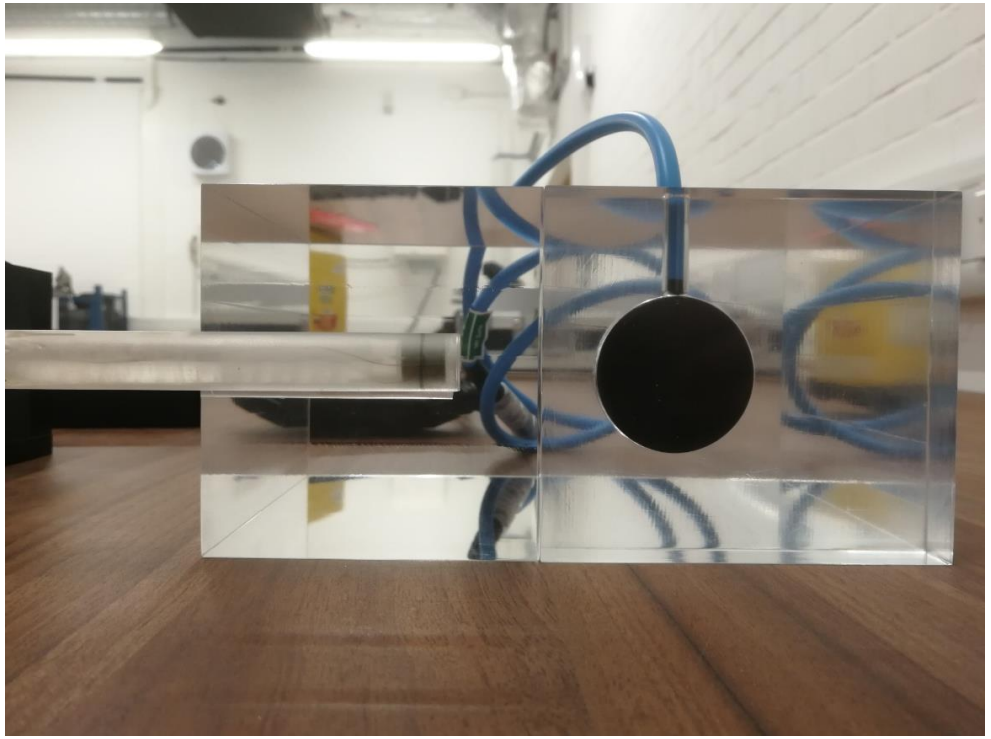
NEW DOSIMETRY TOOLS & METHODS NEEDED

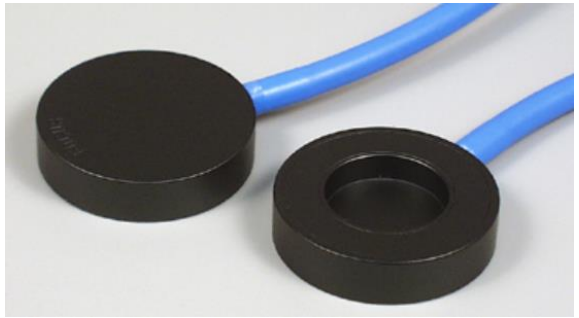
USE THE RIGHT TOOL FOR THE RIGHT JOB

First experimental results: UHPDR VHEEs





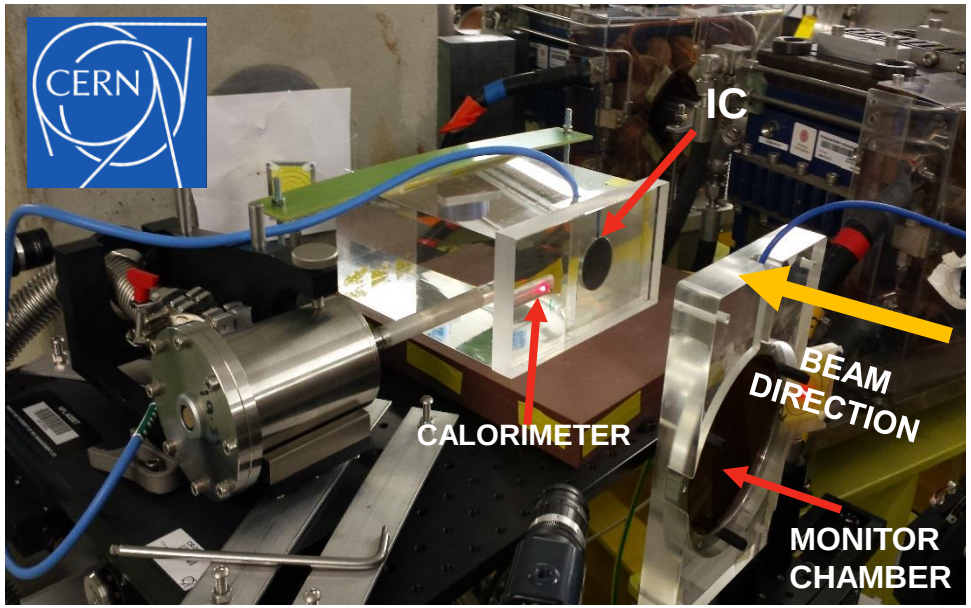




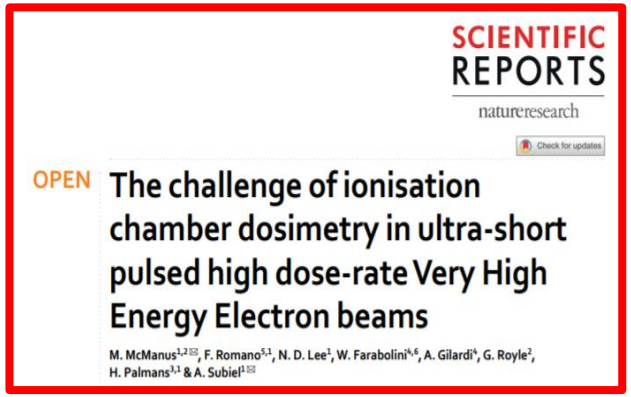
First experimental results: UHPDR VHEEs

OBJECTIVE: To study ion collection efficiency as a function of dose-per-pulse at instantaneous dose rates 5.0×10^6–3.1×10^8 Gy/s for VHEE beams (→ energies suitable for deep-seated tumours)

- BEAM PARAMETERS: 200 MeV, x and y σ of 5 mm, ΔE between 0.25 and 6.5%
- side-by-side measurements: **PTW Roos** chamber and NPL's **graphite calorimeter**
- quantification of the recombination factor $k_{s,abs}$ for the Roos chamber for a range of collecting voltages: 75 V – 600 V



The test-stand at the CLEAR facility, with the calorimeter, ion chamber and monitor chamber placed along the beam line with the beam travelling from right to left.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The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams

M. McManus, F. Romano, N. D. Lee, W. Farabolini, A. Gilardi, G. Royle, H. Palmans & A. Subiel

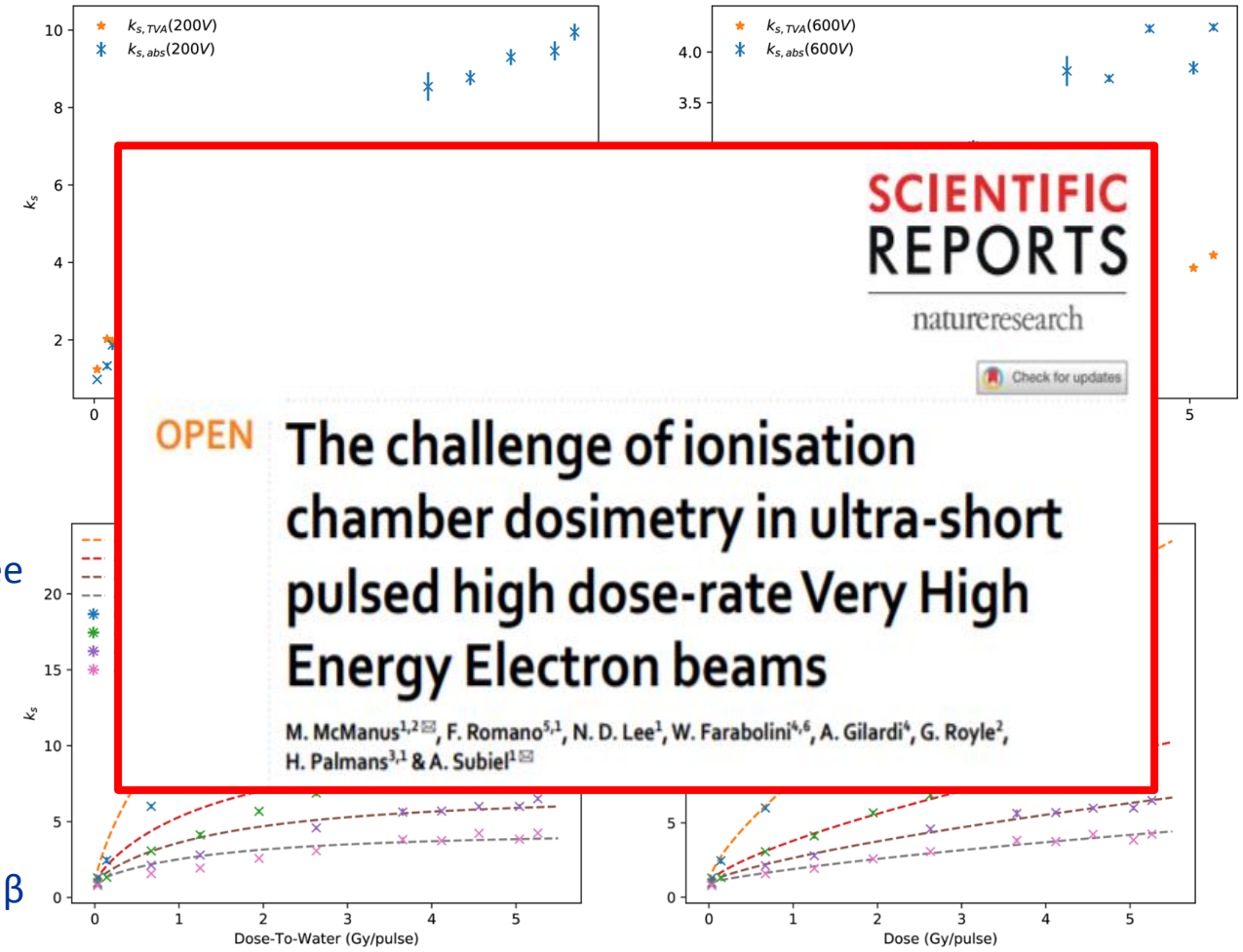
Nominal Beam Charge (nC/pulse)	Dw,cal (Gy/pulse)	ks,abs			
		75 V	200 V	350 V	600 V
0.05	0.03	1.3	0.98	0.89	0.78
0.2	0.20	3.41	1.87	1.56	1.14
0.25	0.14	2.46	1.33	2.05	-
1	0.67	6.00	3.07	2.12	1.58
2.2	1.25	8.80	4.12	2.80	1.94
3	1.95	11.96	5.67	-	2.58
4.5	2.63	14.99	6.87	4.59	3.07
6	3.66	18.94	8.54	5.63	3.81
7.5	4.12	19.54	8.77	5.69	3.74
9	4.56	21.38	9.30	5.99	4.23
10.5	5.26	22.99	9.95	6.50	4.24

$$k_{s,abs} = \frac{D_{w,cal}}{M k_{pol} k_{TP} k_{Q,Q_0} N_{D,w,Q_0}}$$

Results cont.

- k_s up to 10 (V = 200V) → collection eff. 10%
- k_s up to 4 (V = 600V) → collection eff. 25%
- $k_{s,abs}$ compared with $k_{s,TVA}$ (two-voltage method)

- Available recombination models include Boag's free-electron fraction models (Boag 1996)
- By optimising the free-electron fraction parameter in these equations, we were able to determine a best fit of our data.
- All analytical models of Boag and Di Martino show similar predictions of the recombination factor and estimations of the free electron fraction
- Analytical (Boag 1996, Di Martino 2005) and logistic (Petterson 2017) models tested
- The logistic model from Petersson shows the best fit to data over the whole dose-per-pulse range, however this model has no physical meaning and simply relies on two fitting constants α and β



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The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams

M. McManus[1,2], F. Romano[5,1], N. D. Lee[1], W. Farabolini[4,6], A. Gilardi[4], G. Royle[2], H. Palmans[3,1] & A. Subiel[1]

Credit: M. McManus

Conclusions & final statements

- Tools and methods established for dosimetry of conventional RT sources are not suitable for UHPDR beams (lack of primary standards, CoPs & reliable active dosimeters for real time dosimetry)
- Challenges of dosimetry for ultra-high pulse dose rate to be addressed within EMPIR UHDpulse project, which aims to provide metrological and validated tools will be provided to support accurate preclinical studies and to enable future clinical applications for UHPDR beams → Introduced by Andreas Schueller
- Plane-parallel Roos chamber exposed to UHPDR VHEE suffers from significant collection loses which cannot be described with available analytical ion recombination models
- Accurate absolute dosimetry is paramount in translational FLASH studies (given the uncertainties in biological response)

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- **Michael McManus**
- **Francesco Romano**
- Nigel Lee
- Hugo Palmans
- **Wilfrid Farabolini**
- **Antonio Gilardi**

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