PAB 2024
Particle Accelerators and Beams Conference
11–12 June 2024 | Cumbria

FLASH and VHEE and studies at CLEAR facility

Manjit Dosanjh

University of Oxford

Cancer is a growing global challenge

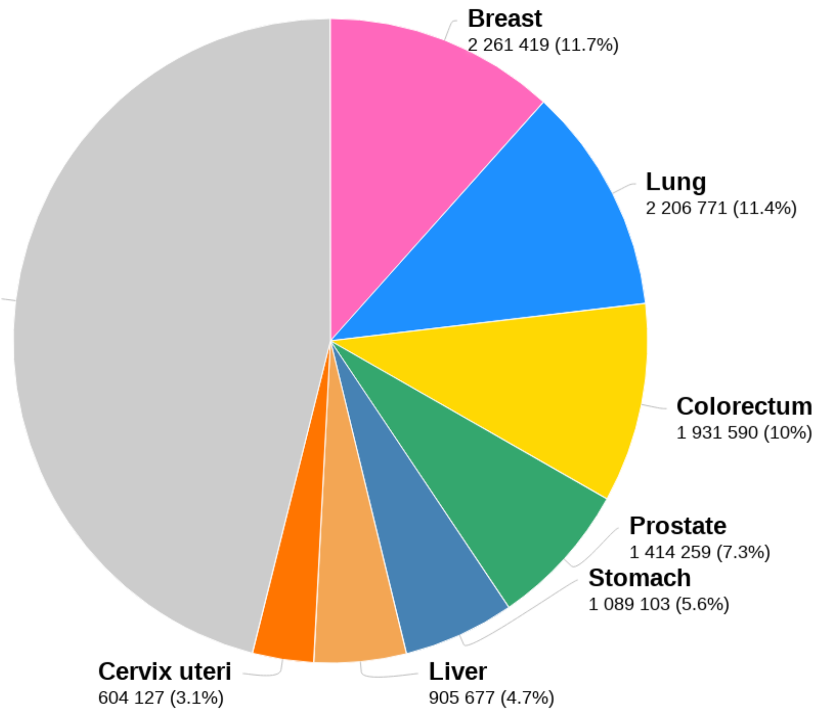
Globally **19.3** million new cases per year diagnosed and **9.96** million deaths in **2020**

This will increase to **27.5** million new cases per year and **16.3** million deaths by **2040**

In the UK, one in two people will get cancer in their lifetime

Radiation therapy is considered a key tool for treatment for about 50-60% patients

Yet in UK only around 25% received RT



Total : 19 292 789

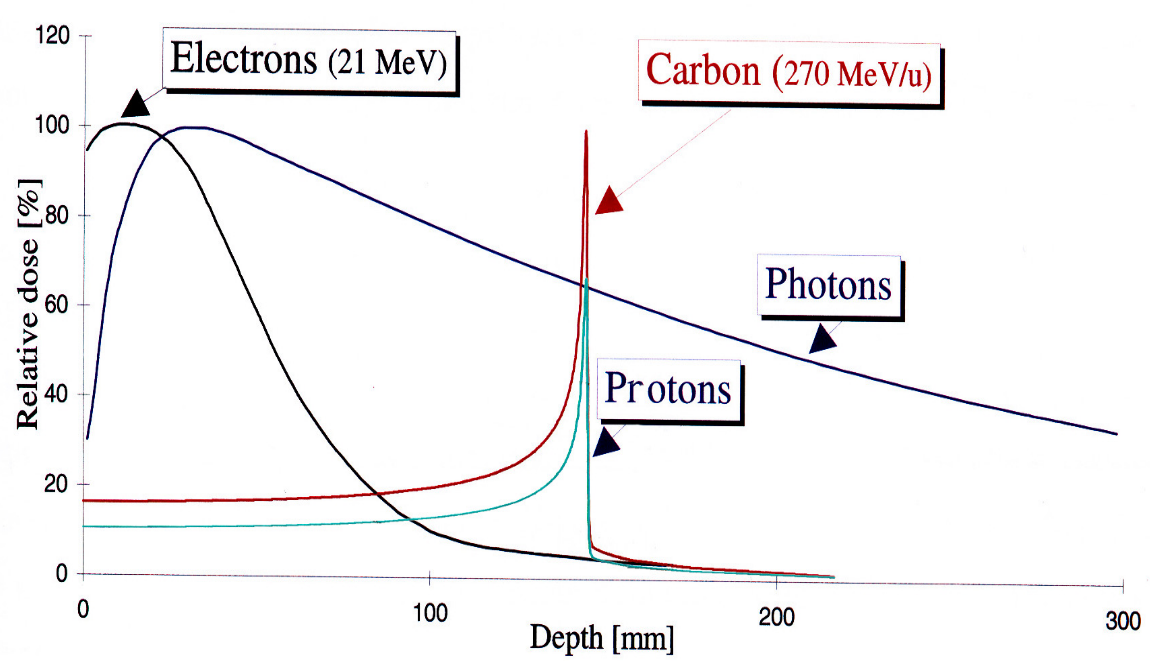
Data source: GLOBOSCAN 2020

Aims of Radiotherapy:

- Irradiate tumour with sufficient dose to **stop cancer growth**
- **Avoid complications** and **minimise** damage to surrounding tissue

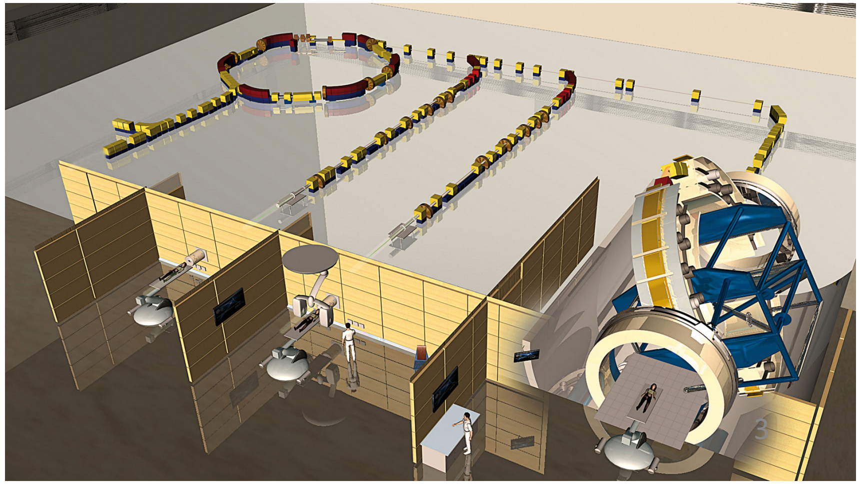
Current radiotherapy methods:

- 5-25 MV photons
- 5 - 25 MeV electrons
- 50 - 400 MeV/u hadrons



Varian True Beam e- linac

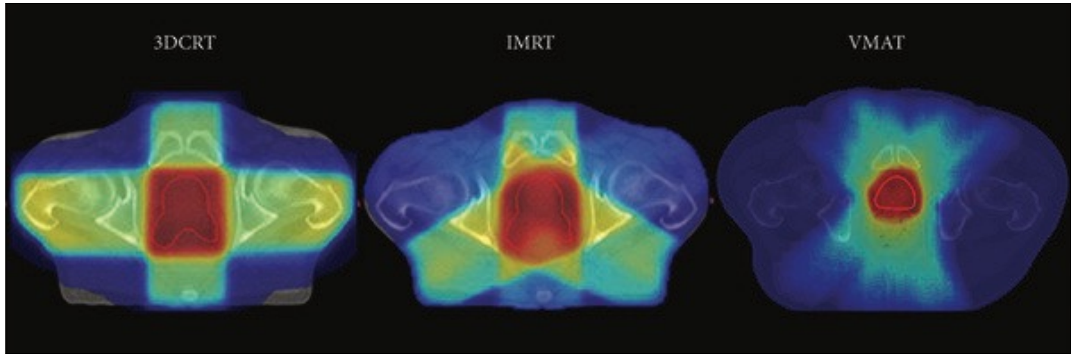
Heidelberg Ion Therapy Centre

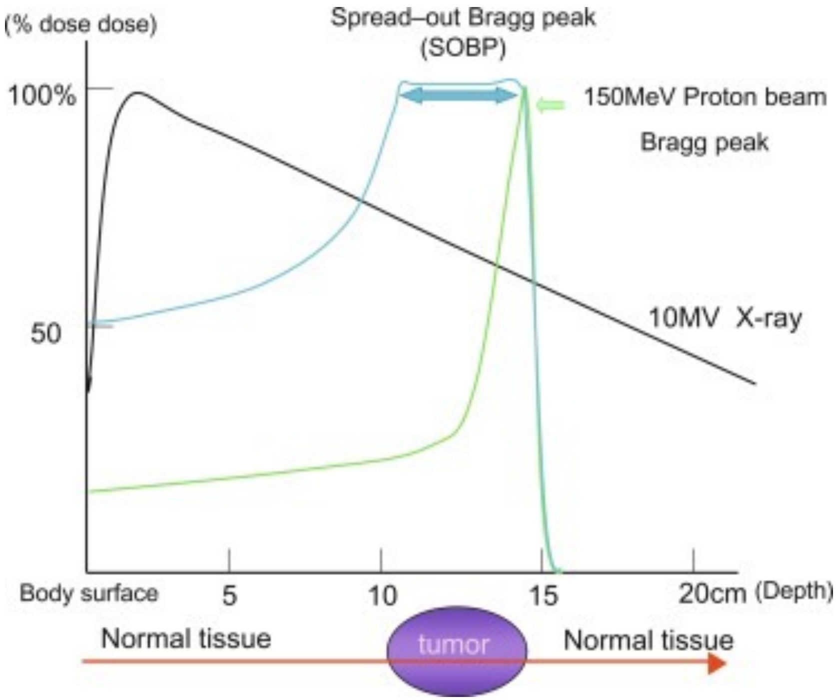


Goal of Radiotherapy

Holy Grail: Deliver as much radiation dose to the tumour whilst minimising the dose to normal healthy tissue

- Better targeting – improved imaging
- Improving dose conformality to tumour through
- IMRT (Intensity Modulated Radiation Therapy)
- VMAT (Volumetric-Modulated Arc Therapy)
- MRI-Linac, treat while you image
- Using the Bragg Peak in hadron therapy.
- Fractionation – delivering treatment across 20-30 fractions.

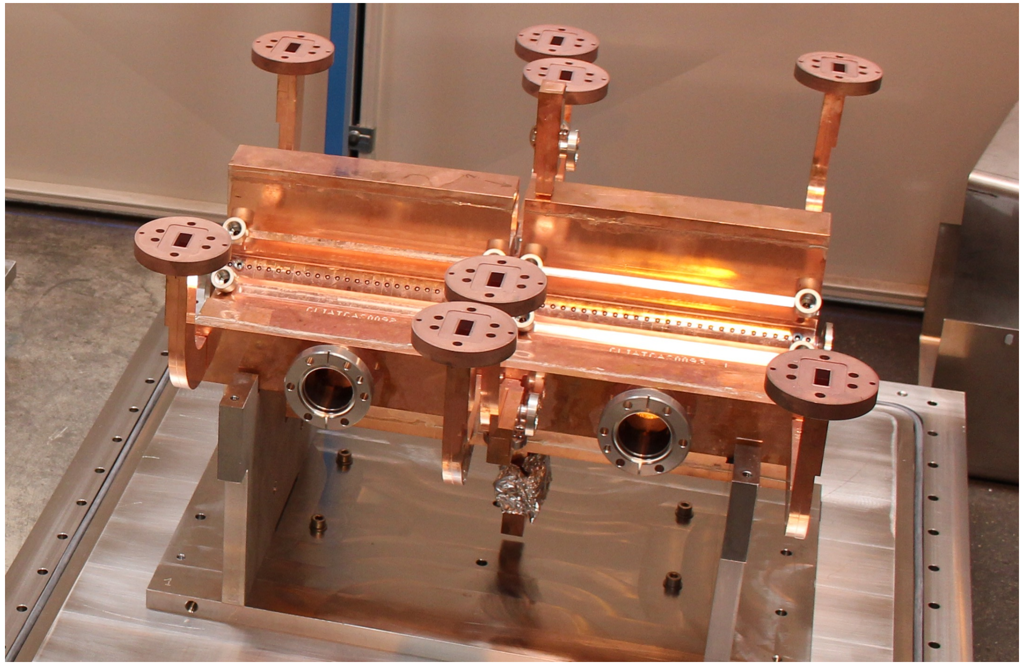




VHEE: New State of the art for RT?

With High-Gradient linac technology and Laser-Wakefield acceleration developments, **Very High Energy Electrons (VHEE)** in the range 50–250 MeV are possible in a clinical setting offering the promise to be a cost-effective option for RT

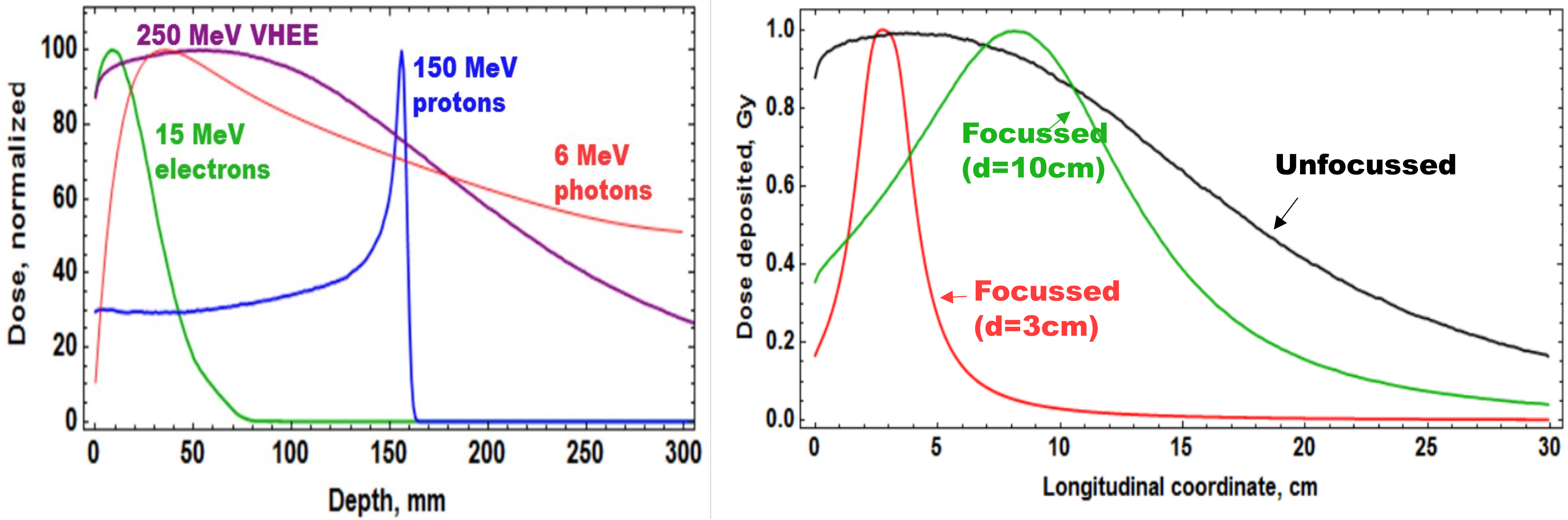
Recently revived interest in using VHEE (50-250 MeV e-) for RT



CLIC RF X-band cavity prototype (12 Ghz, 100 MV/m)

Very High Energy Electron (VHEE)

- Their ballistic and dosimetric properties can surpass those of MV photons, which are currently the most commonly used in RT.
- Their position compared to protons need to be further evaluated, but they can be produced at a reduced cost.

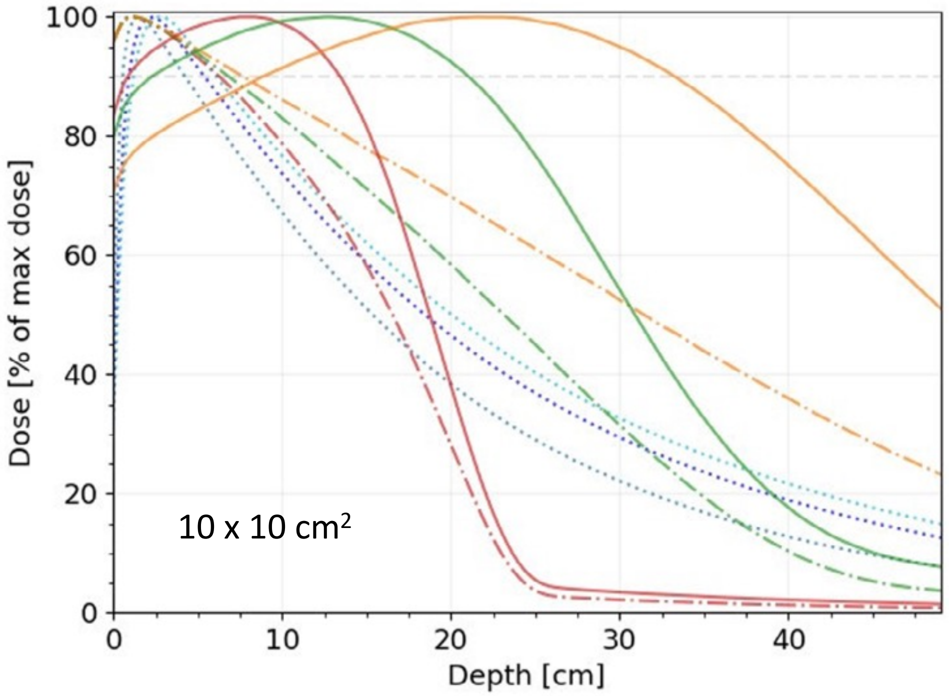


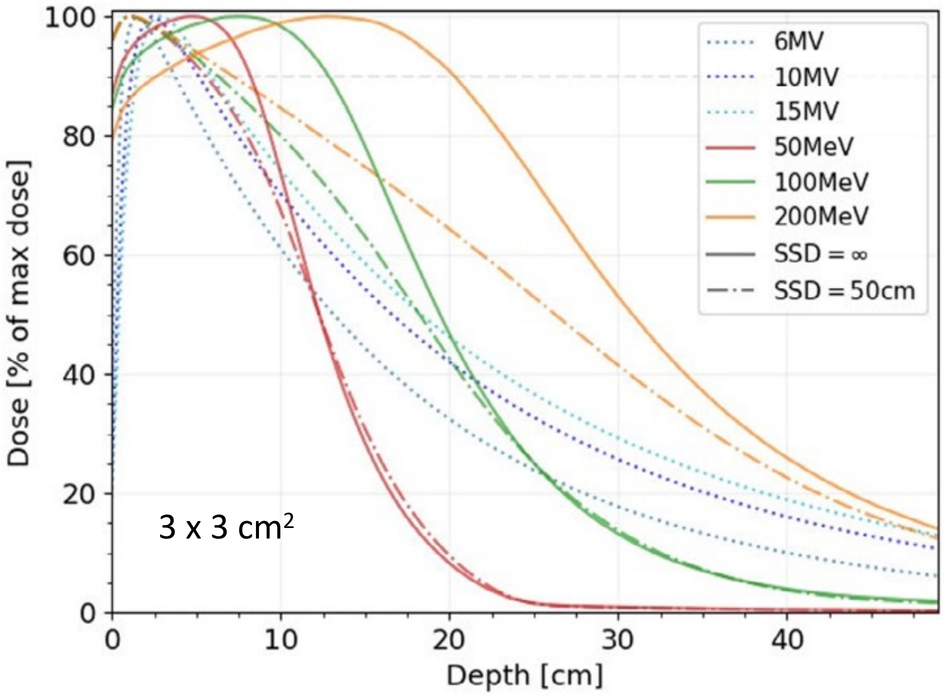
Depth Dose curve for various particle beams in water (beam widths r=0.5 cm)

A. Lagzda et al: VHEE Beams, 2017

VHEE for Radiotherapy

- Study by Bohlen et al, 2021 assessed the performance of VHEE beams and offered a first estimate of treatment indications
- Beam energies of 100 MeV and above are needed to cover common tumours (5–15 cm in-depth) conformally. Higher energies provide an additional benefit specifically for small and deep-seated lesions due to their reduced lateral penumbrae.

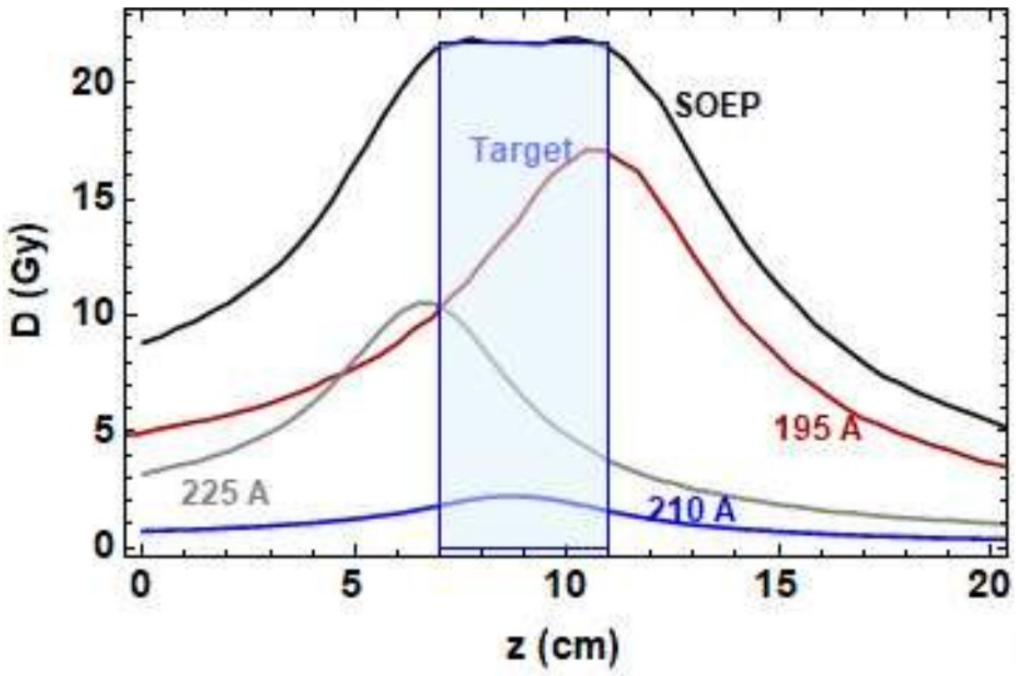




Böhlen et al: Characteristics of VHEE Beams, 2021

Very High Energy Electron (VHEE) Radiotherapy

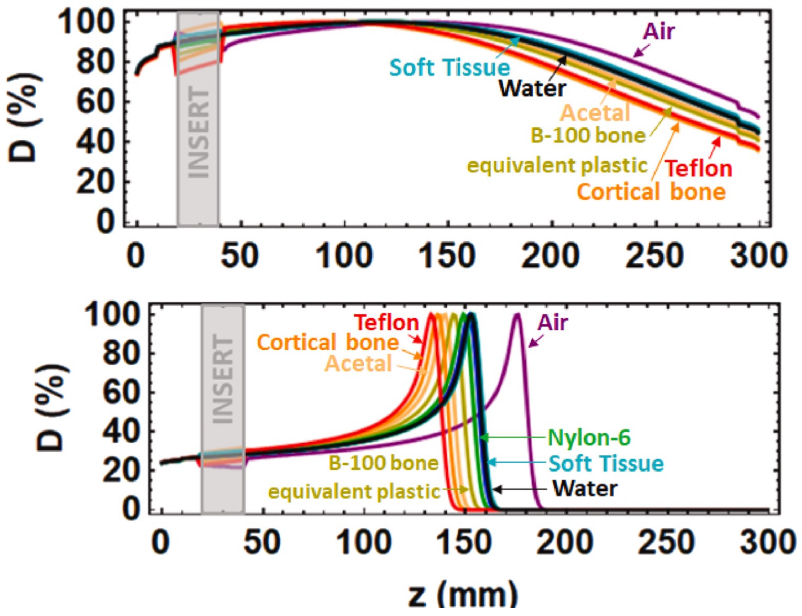
- Favourable characteristics compared to clinical electron beams such as :
  - Increased range within the patient
  - Sharper lateral penumbra
  - Relative insensitivity to tissue heterogeneities
- Possibility for pencil beam scanning or strong focussing (to create an 'electron peak')
- Numerous studies show VHEE can provide generally superior treatment plans compared to state-of-the-art photon RT.
- VHEE facilities would be more compact and cost-effective in comparison to proton and ion therapy facilities.



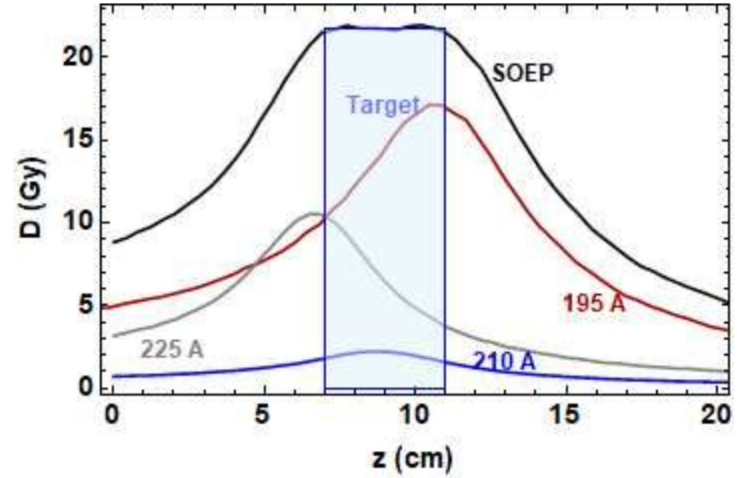
Whitmore et al: Focussed VHEE Beams, 2021

Very High Energy Electron (VHEE) RT: Future?

- VHEE beams offer favourable characteristics compared to clinical electron beams such as
  - Increased range within the patient
  - Sharper lateral penumbra
  - Relative insensitivity to tissue heterogeneities
- VHEE beams allow the possibility for pencil beam scanning or strong focussing (to create an 'electron peak')
- Numerous TPS studies conclude VHEE can provide generally superior dose distributions compared to state-of-the-art intensity modulated photon plans.
- VHEE facilities would be more compact and cost-effective in comparison to proton and ion therapy facilities.



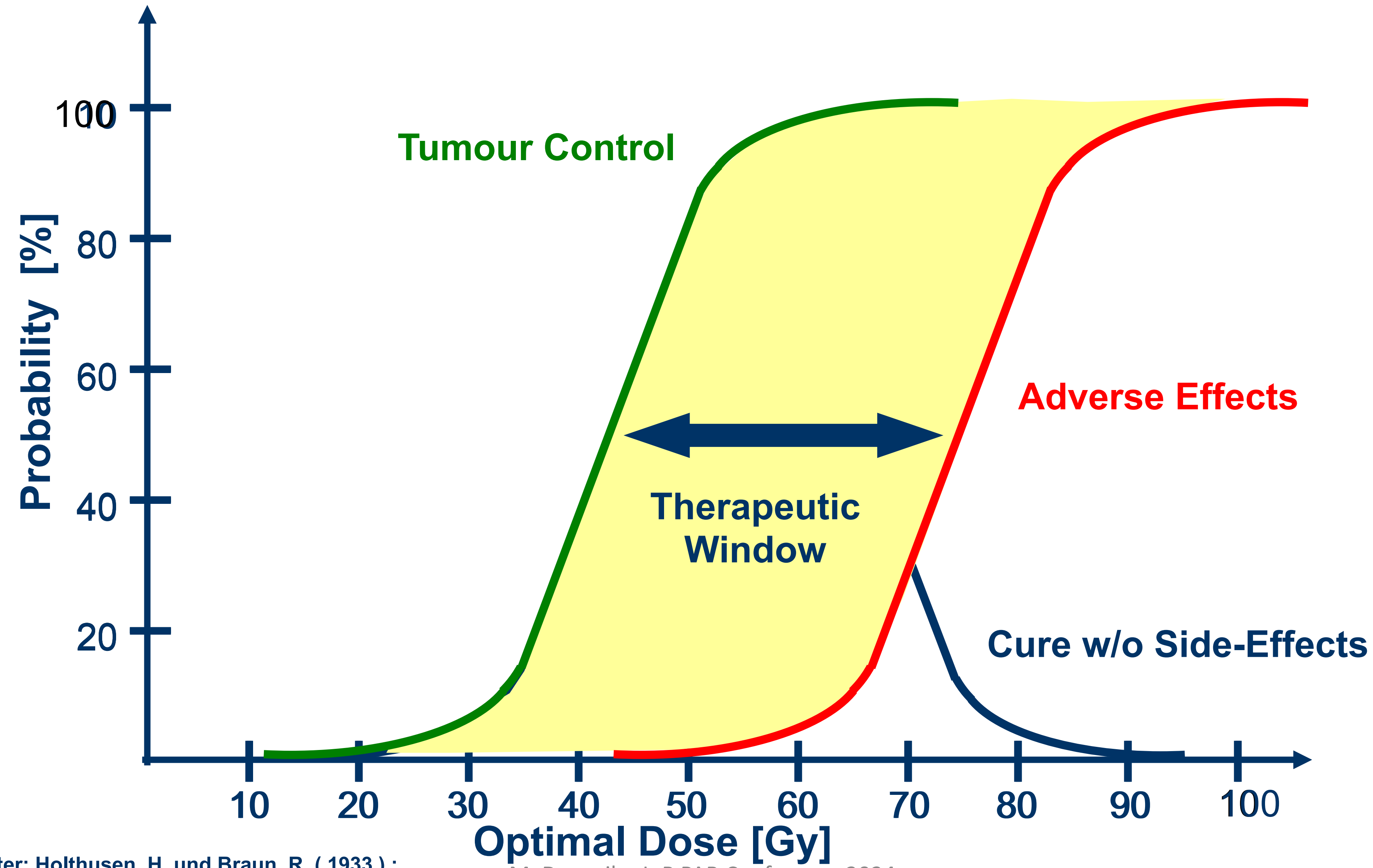
A. Lagzda et al, NIMS 2020



Whitmore et al, Sci. Rep. 2021

FLASH: a new way of delivering Radiotherapy for treating cancer?

Holthusen-Curve (1933): Dose-Response-Relationship



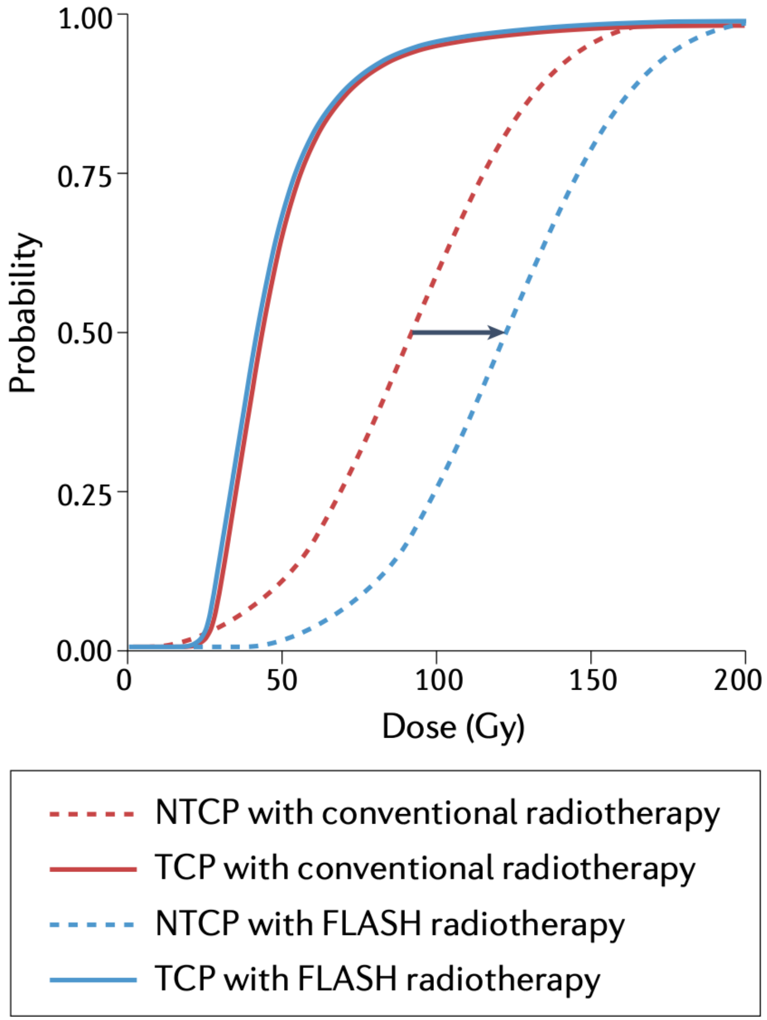
After: Holthusen, H. und Braun, R. (1933) : Grundlagen und Praxis der Röntgenstrahldosierung, Thieme Verlag, Leipzig

UHDR RT & FLASH Effect

- Increased differential response between healthy and cancerous tissues when dose delivered at ultrahigh dose rates (UHDR)
  - > 40 Gy/s compared to ~0.08 Gy/s.

- Normal tissue sparing can allow for dose escalation to treat radio-resistant tumours.

- Significantly reduces treatment times (< 200 ms for FLASH) and “freezes” organ motion.



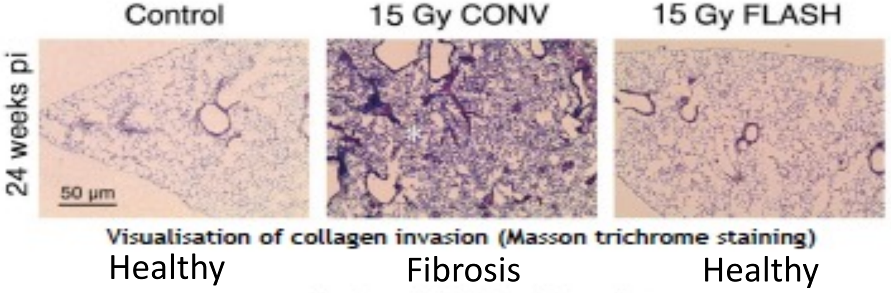
Vozenin, MC., Bourhis, J. & Durante, M. Towards clinical translation of FLASH radiotherapy. *Nat Rev Clin Oncol* **19**, 791–803 (2022).

Glimpse of FLASH THERAPY - 2014

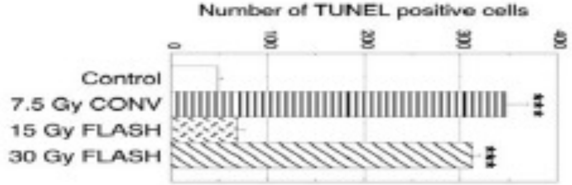
First Proof-of-Concept with low-energy e$^-$

Sci Transl Med 6: 245ra93, 2014

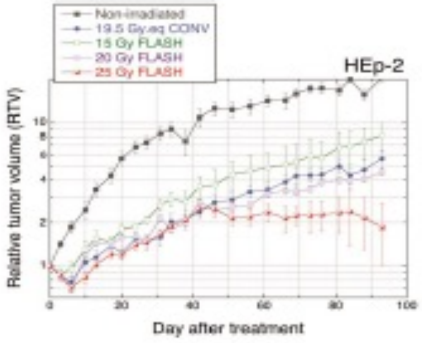
- ➢ FLASH spared normal lung tissue at doses known to induce fibrosis in mice exposed to conventional dose-rate irradiation (CONV).



- ➢ FLASH spared smooth muscle cells in arterioles from radio-induced apoptosis.



- ➢ No difference between FLASH and CONV with regard to tumor growth inhibition.
- ➢ However, normal tissue sparing by FLASH allowed dose escalation without complications, resulting in complete tumor cure in some xenograft models.



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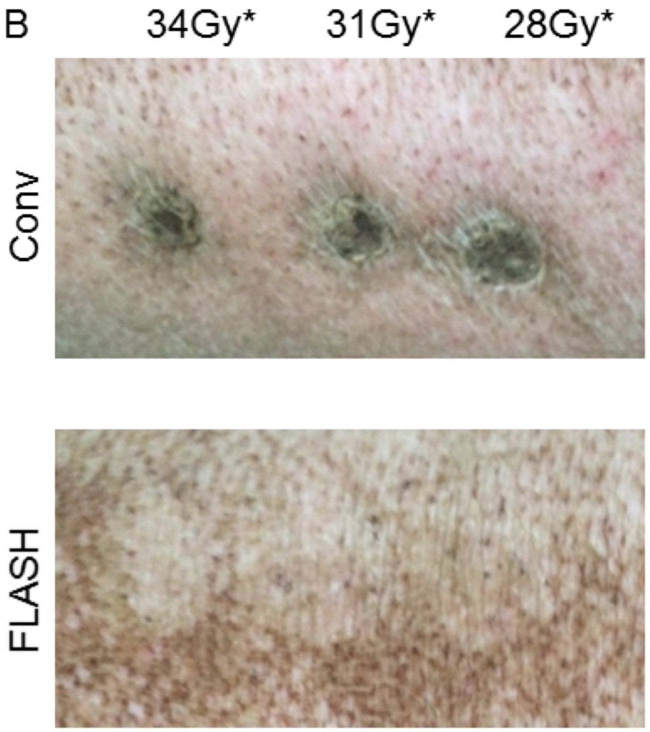
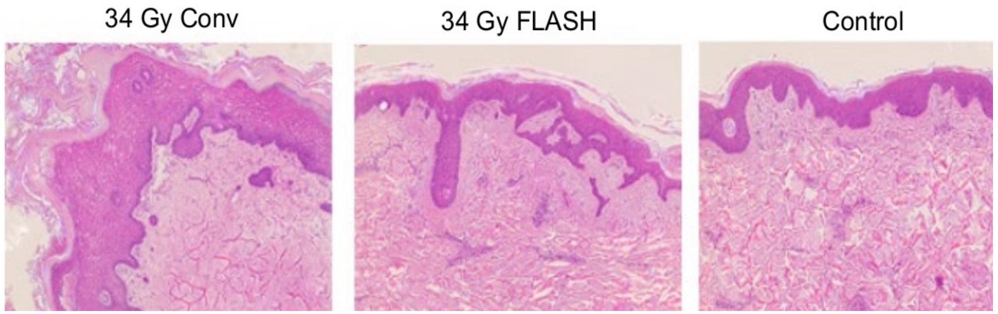
The FLASH Effect – gaining huge momentum



Vozenin MC, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond JF, Petit B, Burki M, Ferrand G, Patin D, Bouchaab H, Ozsahin M, Bochud F, Bailat C, Devauchelle P, Bourhis J. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. Clin Cancer Res. 2019 Jan



- Apparent sparing of healthy tissue when dose is delivered at **ultrahigh dose rates (UHDR) of > 40 Gy/s.**
- Healthy tissue sparing observed in virtually all radiation modalities.
  - ✓ Majority of experiments/trials with low energy electrons and shoot-through protons.
- So far, 2 human trials:
  - Skin lymphoma with 6 MeV electrons (CHUV, 2019).
  - Bone metastases with 250 MeV (shoot-through) protons (Cincinnati, 2020). Pain relief and not curative
  - Further trials are ongoing

FLASH mechanism is still not fully understood.

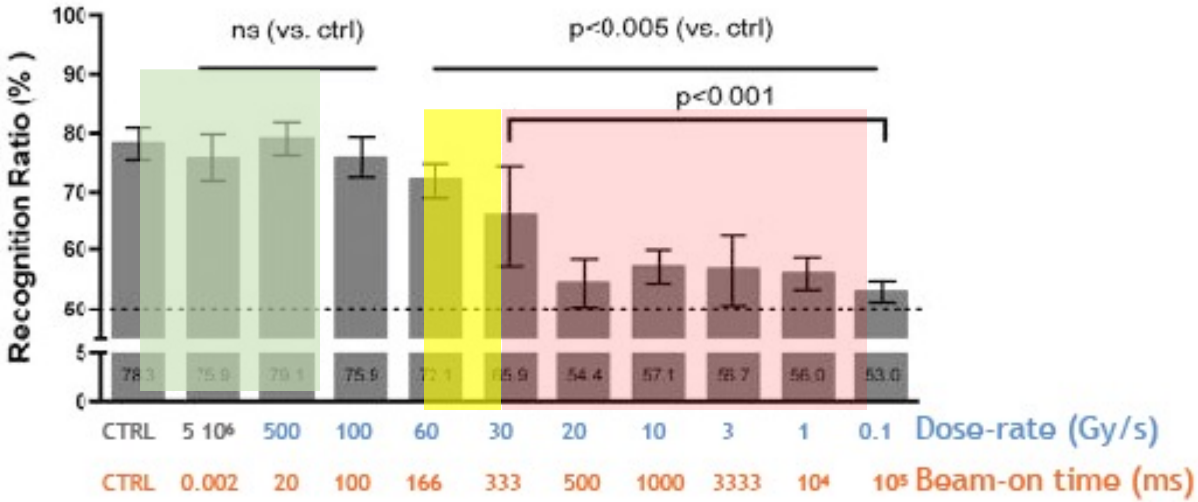
FLASH THERAPY

First Proof-of-Concept with low-energy e⁻

Whole brain irradiatio with 10 Gy in single dose

Montay-Gruel *et al*. Radiother Oncol 124: 365-9, 2017

FLASH preserves mouse memory and neurogenesis in the hippocampus provided the beam-on time does not exceed 100 ms



BrdUrd incorporation for visualisation of replicating progenitors (stem) cells (2 months pi)

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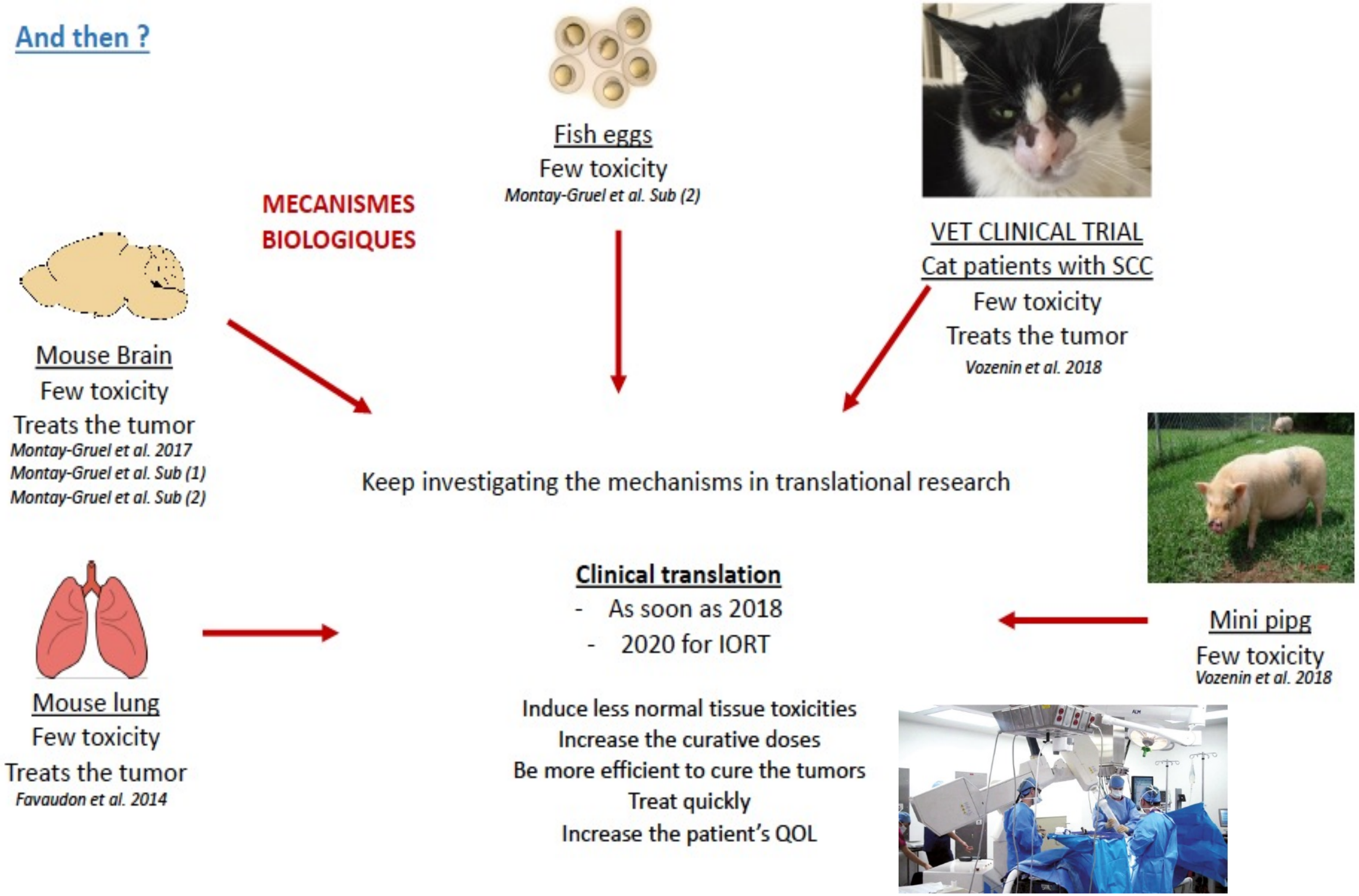
CHUV

FLASH THERAPY: Towards a clinical practice (Vozenin et al, CHUV)



Clinical Translation (2019): Treatment of a first patient with FLASH-radiotherapy,

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology. Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland

5.6 MeV linac adapted for accelerating electrons in FLASH mode

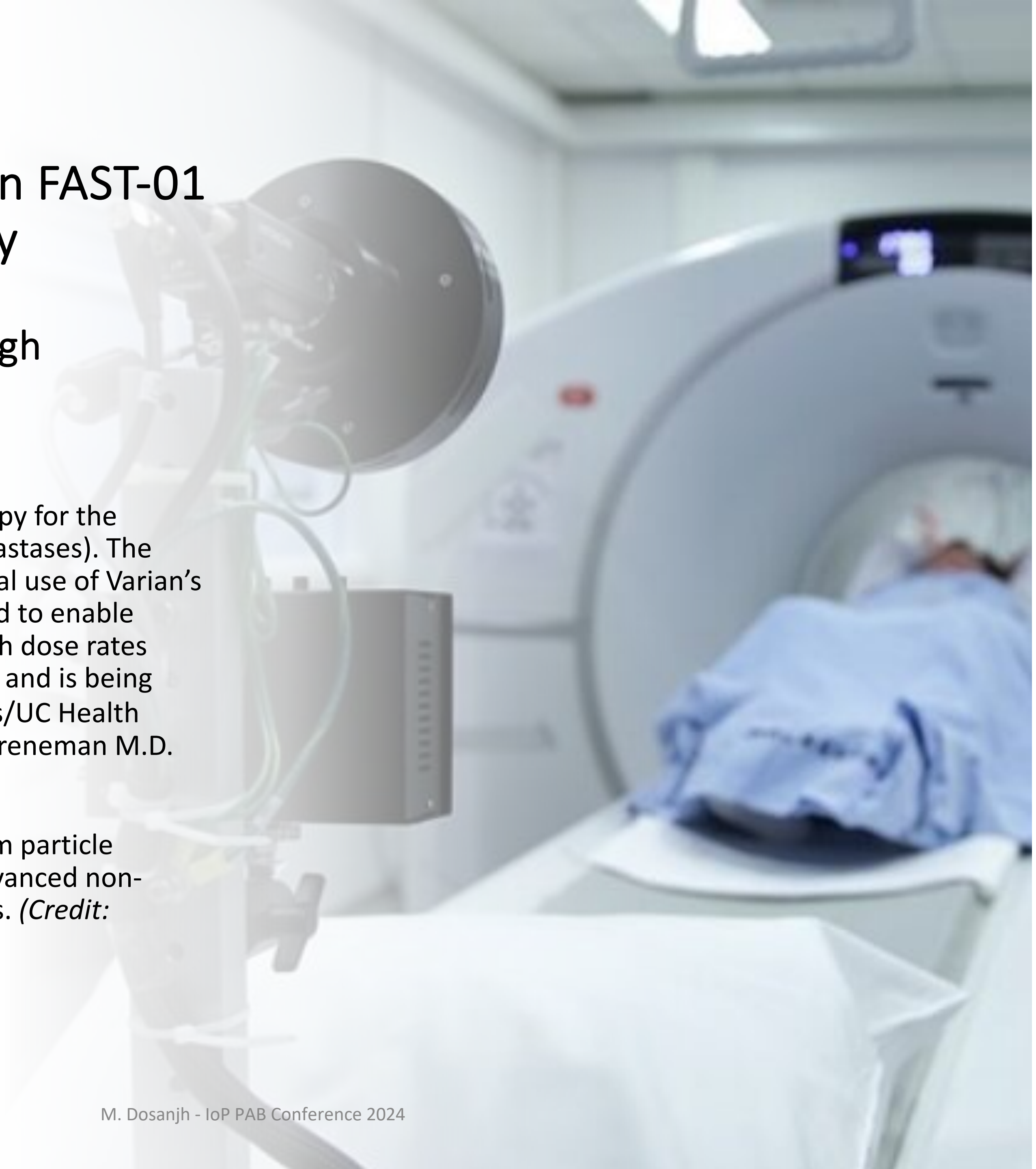
15 Gy with 10 pulses **in 90 ms**

3.5 cm diameter tumour, multiresistant cutaneous

Appears that instantaneous dose Induces a massive oxygen consumption and a transient protective hypoxia in normal issues

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

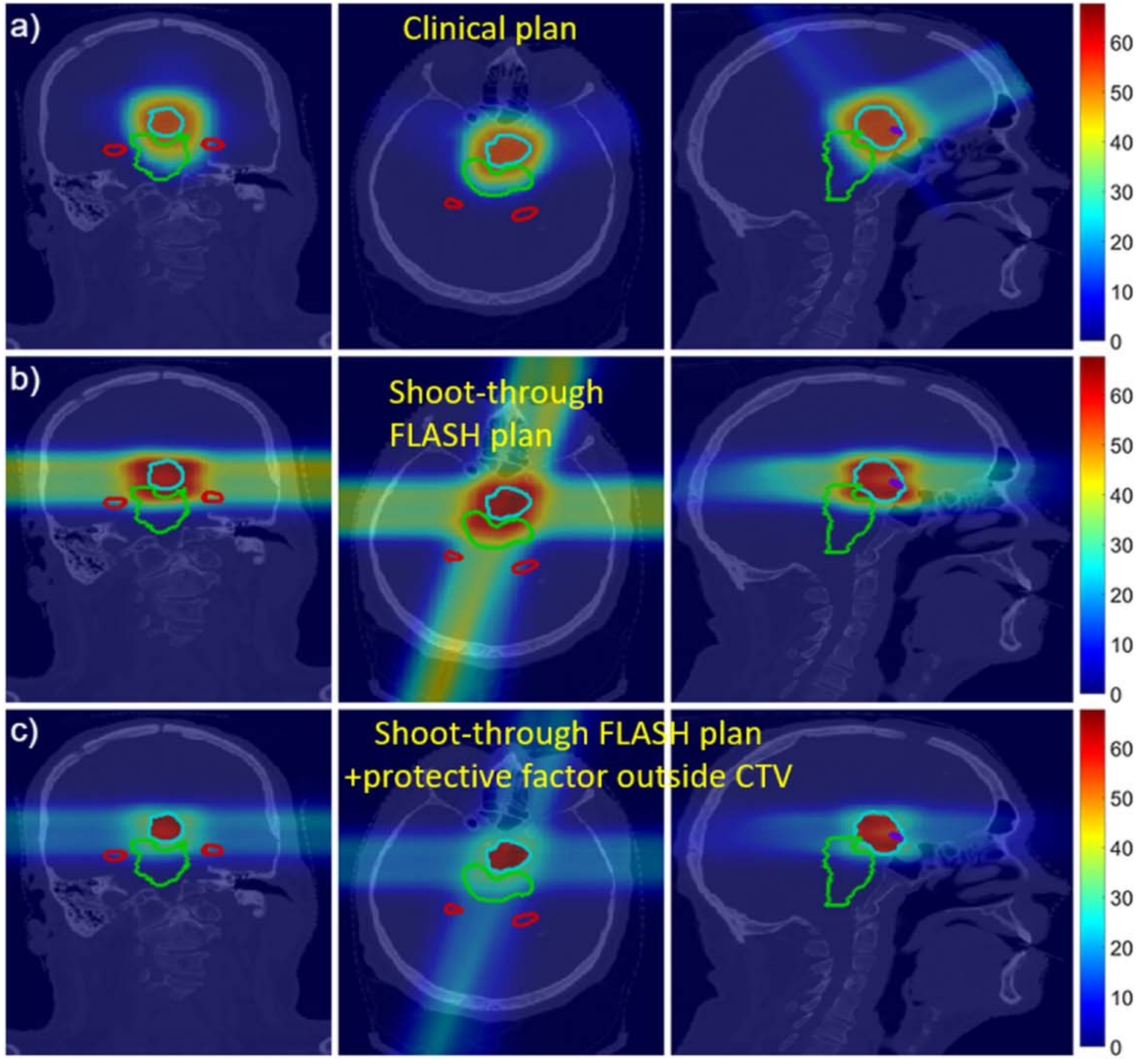
First Patient Treated in FAST-01 FLASH Proton Therapy (November 2020)
Transmission-shoot through



FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases). The clinical trial involves the investigational use of Varian’s ProBeam particle accelerator modified to enable radiation therapy delivery at ultra-high dose rates (dose delivered in less than 1 second) and is being conducted at the Cincinnati Children’s/UC Health Proton Therapy Center with John C. Breneman M.D.

The study will assess Varian's ProBeam particle accelerator modified to deliver an advanced non-invasive treatment for cancer patients. *(Credit: Bokskapet from Pixabay)*

Considerations for shoot-through FLASH proton therapy



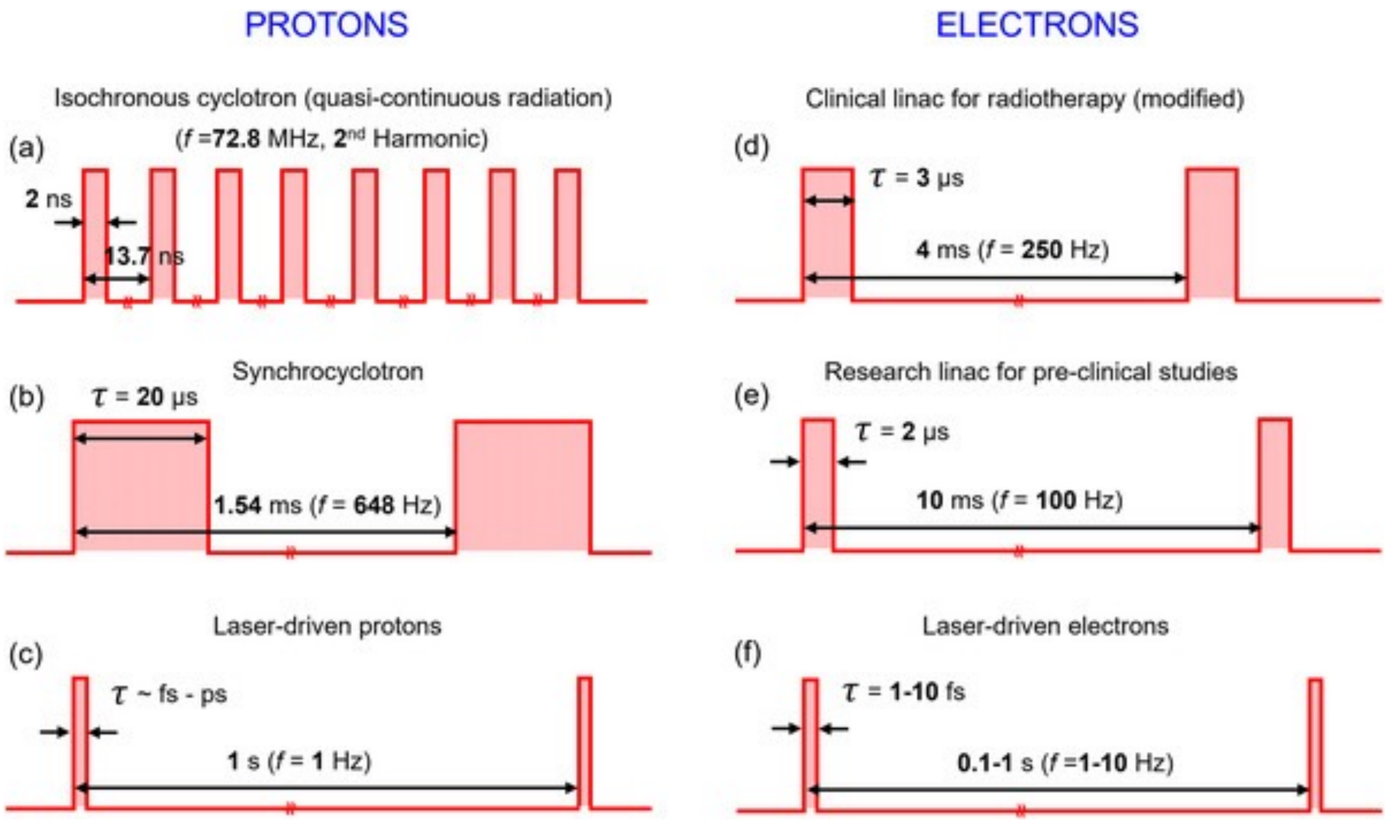
Frank Verhaegen et al, Phys. Med. Biol. 66, March 2021

Standard RT: Dose is delivered in several minutes

With FLASH, dose is delivered in milliseconds

In micro-seconds

Even in nano/pico-seconds

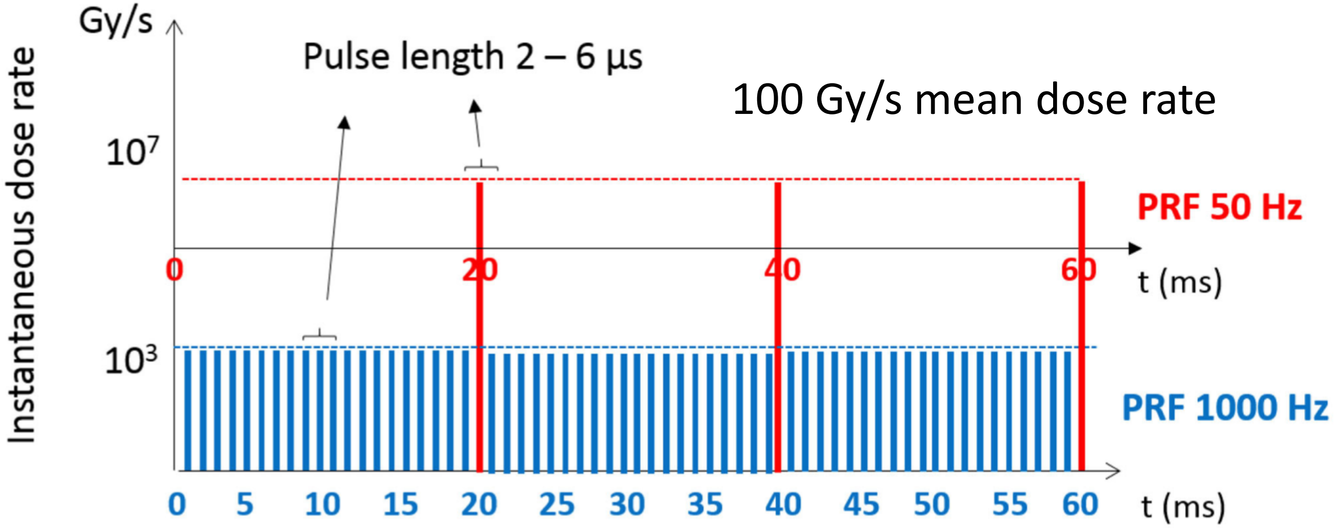


Romano, F et al. Med Phys, 2022. .

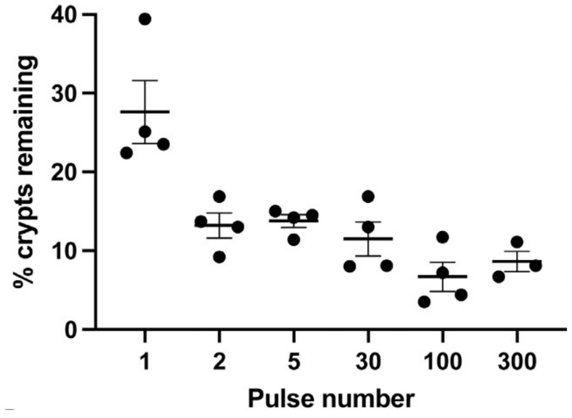
UHDR RT & FLASH Effect – Dose Rates

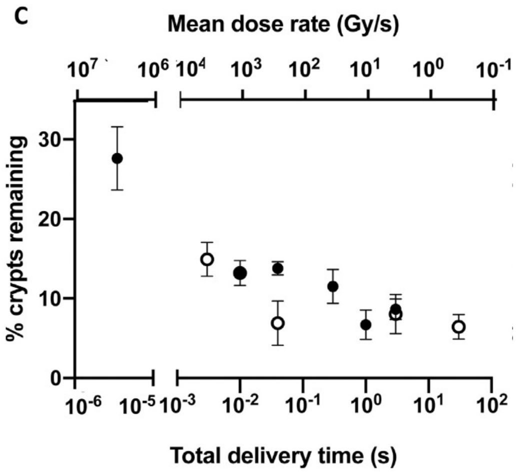
- Important parameters:
  - Mean dose rate
  - Total treatment time
  - Dose per pulse
  - Instantaneous dose rate

- Still not decided which parameters FLASH effect depend on.



Vignati, A. et al. Beam Monitors for Tomorrow: Challenges for Electron and Photon FLASH RT (2020)





Jia-Ling Ruan, et al. rradiation at Ultra-High (FLASH) Dose Rates Reduces Acute Normal Tissue Toxicity in the Mouse Gastrointestinal System (2021)

Technological Challenges of Clinical Translation of FLASH

Dose Delivery

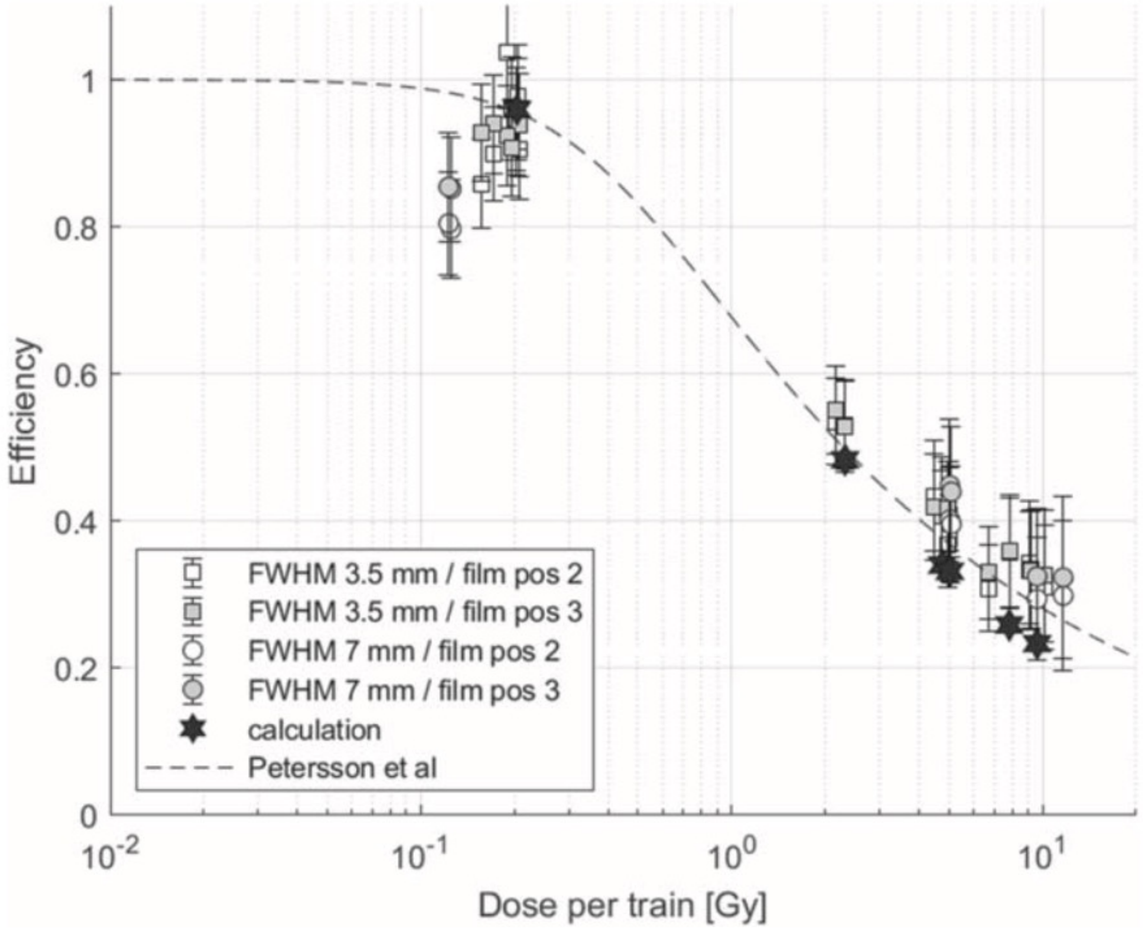
- Large majority of UHDR studies performed with low energy electrons – easy to produce.
- Photons – ‘bottleneck’ at target for trying to produce MV photons at UHDR
- Protons and Heavy Ions - ‘shoot through’ since lower energies reduce intensities below FLASH requirements – lose benefit of Bragg Peak.
- VHEE – answer to this issue? But need to be able to produce conformal dose distributions in <100 ms

Real-time Dosimetry

- Ionisation chambers saturate in UHDR conditions required for FLASH…

Challenge for Dosimetry of UHDR Beams

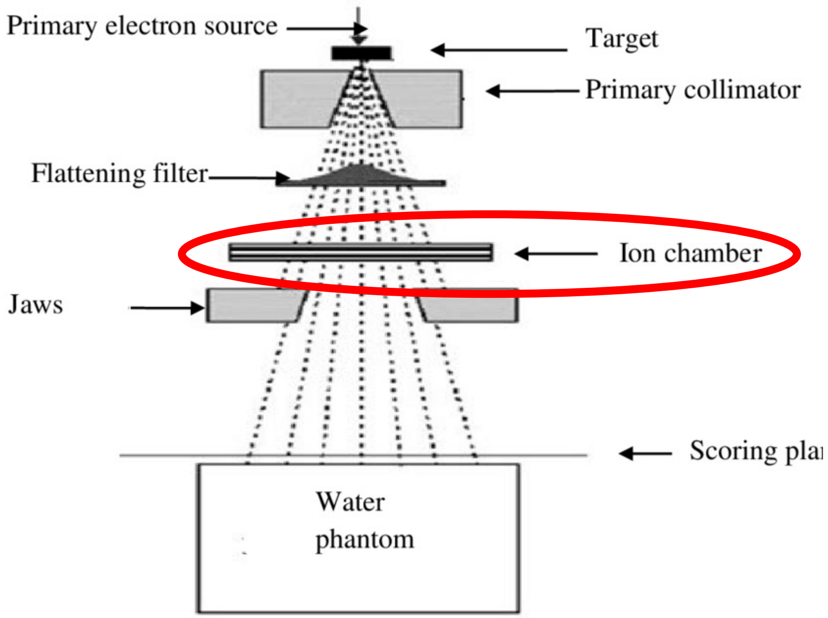
- Ionisation chambers saturate in UHDR conditions required for FLASH.
- Particularly an issue for pulsed radiation modalities i.e. VHEE.
- Correction factors introduce large uncertainties.
- Collection time of transmission ICs too slow for beam interception.
- **Promising alternatives:** ultra-thin ion chambers, solid-state detectors, scintillators, Cherenkov sensors

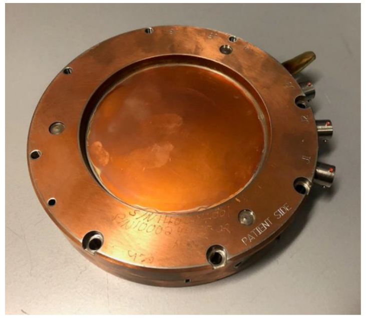


Poppinga et al. (2021)

UHDR Beam Monitor Wishlist

1. A response that covers a large dynamic range up to FLASH dose rates.
2. High temporal resolution.
3. High spatial resolution.
   a) Beam profile monitoring could be a necessity given additional uncertainties associated with FLASH – particularly with other novel delivery methods such as PBS and SFRT.
4. Minimal perturbation on the beam.
5. Large transverse area to cover entire beam.



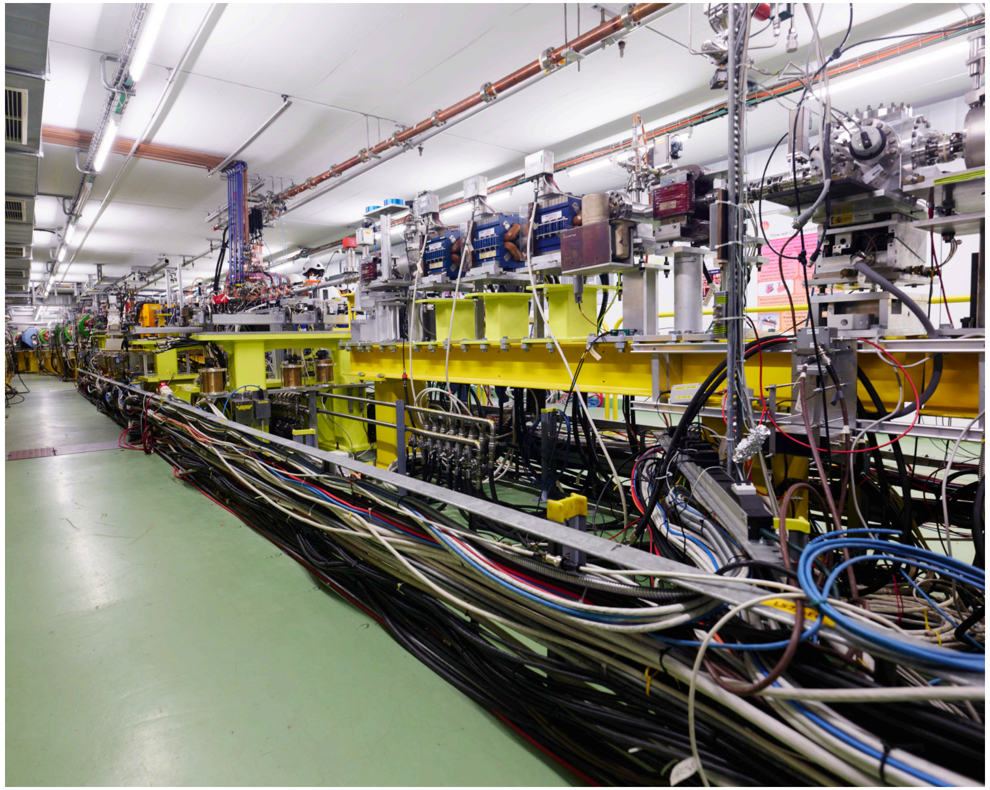


Clinical in-transmission ionisation chamber

CLEAR Facility

CERN Linear Electron Accelerator for Research

- Experimental beamline, as a multi-purpose user facility
- high quality e-beams
- 60 – 220 MeV electron beam.
- User facility detached from LHC complex
- 10 pC – 70 nC / pulse
- 0.833 Hz - 10 Hz pulse rep. freq.
- Pulse length 1 ps – 50 ns
- Used for accelerator and component R&D, electronics irradiations and medical applications.
- Significant focus on FLASH-UHDR VHEE RT research.
- A new beam line to provide additional test areas for users
- A permanent C-Robot 2.0 installation for dedicated medical studies

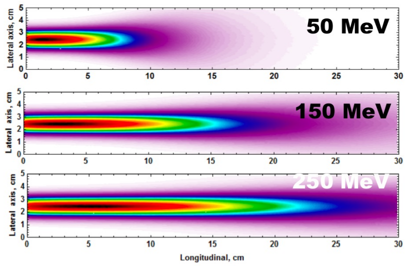


VHEE @ CLEAR - an outline

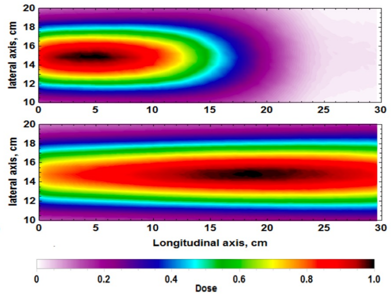
VHEE

- Rapid advances in compact high-gradient (~ 100 MV/m) accelerator technology in recent years
  - CLIC
  - NLC
  - W-band*
- Superior dose deposition properties compared to MV photons
- High dose-reach in tissue
- High dose rate (compared to photons)
- More reliable beam delivery around inhomogeneous media
- Better sparing of surrounding healthy tissue
- Particle steering

*V. Dolgashev, HG2016

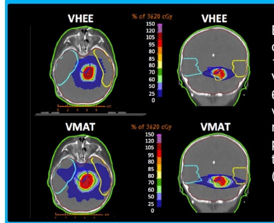


Dose maps of narrow () VHEE beams in water

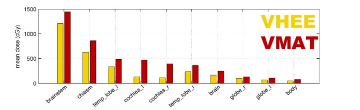


Dose maps of wide () VHEE beams in water

- Clinical studies by M. Bazalova-Carter *et al.* (2015) have compared 100 MeV VHEE with conventional (and MV) VMAT (Volumetric Modulated Arc Therapy) photon radiotherapy plans
- *Pediatric brain tumour, lung* and *prostate cases*
- VHEE therapy plan showed a **decrease of dose** up to **70%** in surrounding organs-at-risk (**OARs**)
- *VHEE plan was found to be more conformal than VMAT plan*



Brain tumour dose maps for 100 MeV VHEE and 6 MV volumetric modulated arc photon therapy (VMAT) .



Absorbed dose histograms for surrounding organs-at-risk.

M. Bazalova-Carter *et al*, «Treatment planning for radiotherapy with very high-energy electron beams and comparison of VHEE and VMAT plans», Medical Physics, vol. 42(5), **2015**.

Manchester University: A. Lagzda, R. Jones and other
- Project to characterize VHEE irradiation on radiosensitive films

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Activities:

- Experimental verification of dose deposition profiles in water phantoms
- Calibration of operational medical dosimeters – nonlinear effects with short pulses
- Demonstration of "Bragg-like peak" deposition with focused beams

Initial interest: Manchester Univ. *(A. Langzda, R. Jones)*

- Three measurements campaigns (2017-2018)

Further requests from:

Nat. Phys. Lab. UK *(A. Subiel et al.)*

- Two measurement campaigns (end 2018, spring 2019)

Strathclyde University *(K. Kokurewicz et al.)*

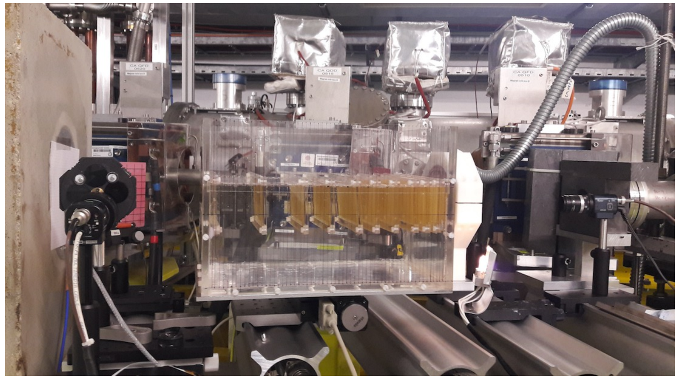
- One campaign completed (end 2018)

Oldenburg University and PTW *(B. Poppe, D. Poppinga et al.)*

- Two campaigns completed (end 2018, September 2019)

CHUV Lausanne *(M.C. Vozenin, C. Bailat, R. Moeckli et al.)*

- Preliminary tests (end 2018, spring 2019)



Relative Insensitivity to Inhomogeneities on Very High Energy Electron Dose Distributions

IPAC 2017 Proceedings • May 19, 2017

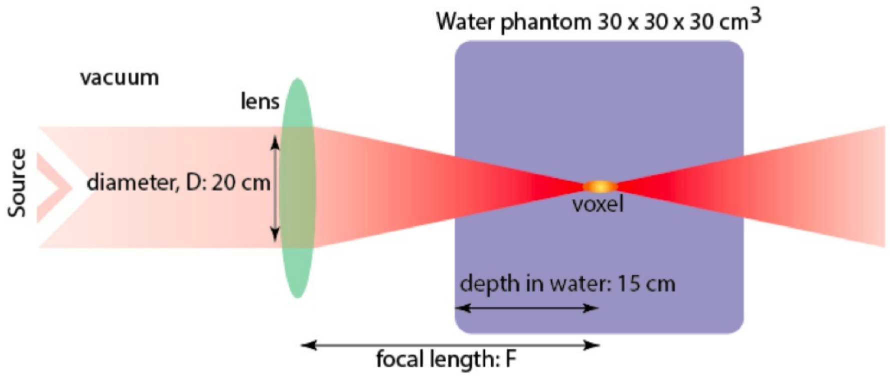
Agnese Lagzda, R.M. Jones, D. Angal-Kalinin, J. Jones, A. Aitkenhead, K. Kirkby, R. MacKay, M. van Herk, W. Farabolini, S. Zeeshan

Very-High Energy Electron (VHEE) Studies at CERN's CLEAR User Facility

IPAC 2018 Proceedings • 2018

Agnese Lagzda, R.M. Jones, A. Aitkenhead, K. Kirkby, R. MacKay, M. van Herk, R. Corsini, W. Farabolini

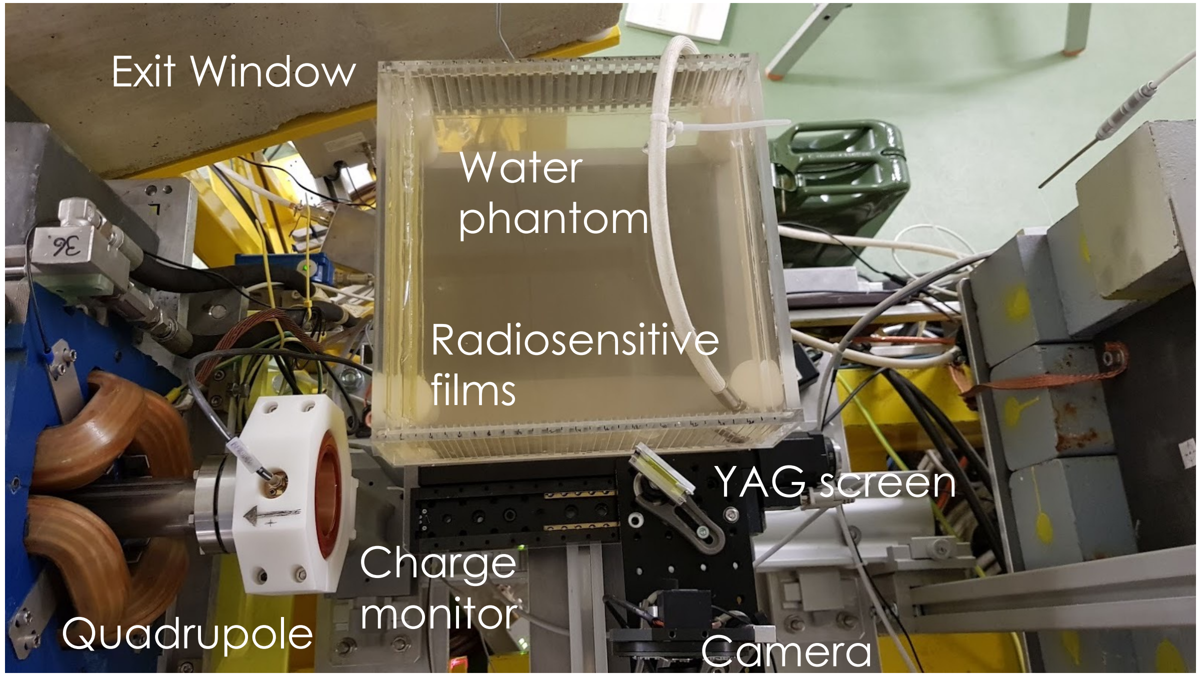
VHEE strong focusing



Aim:

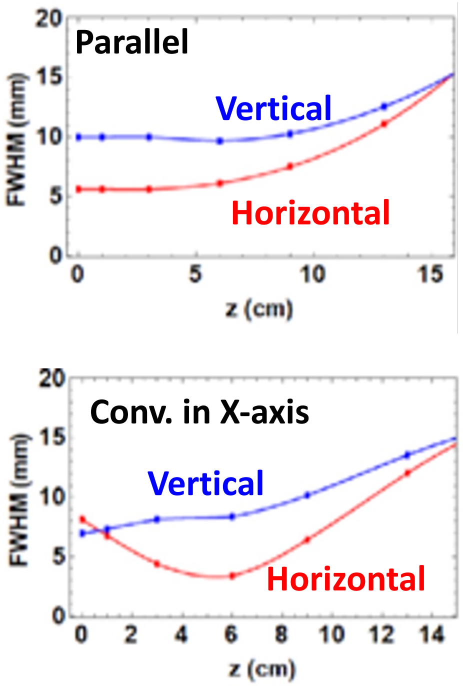
Focus the beam on the tumour to minimize the dose on the nearby healthy tissues

- Main activity in October 2019
- Two groups (Strathclyde and Manchester) Two full week of testing (plus installation and dismounting)
- Required rearrangement of beamline, with a temporary dump.

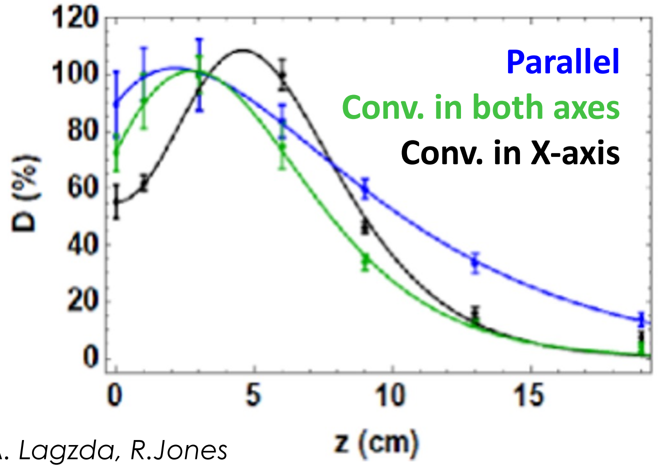


W. Farabolini, E. Senes, K. Kokurevicz

Beam size

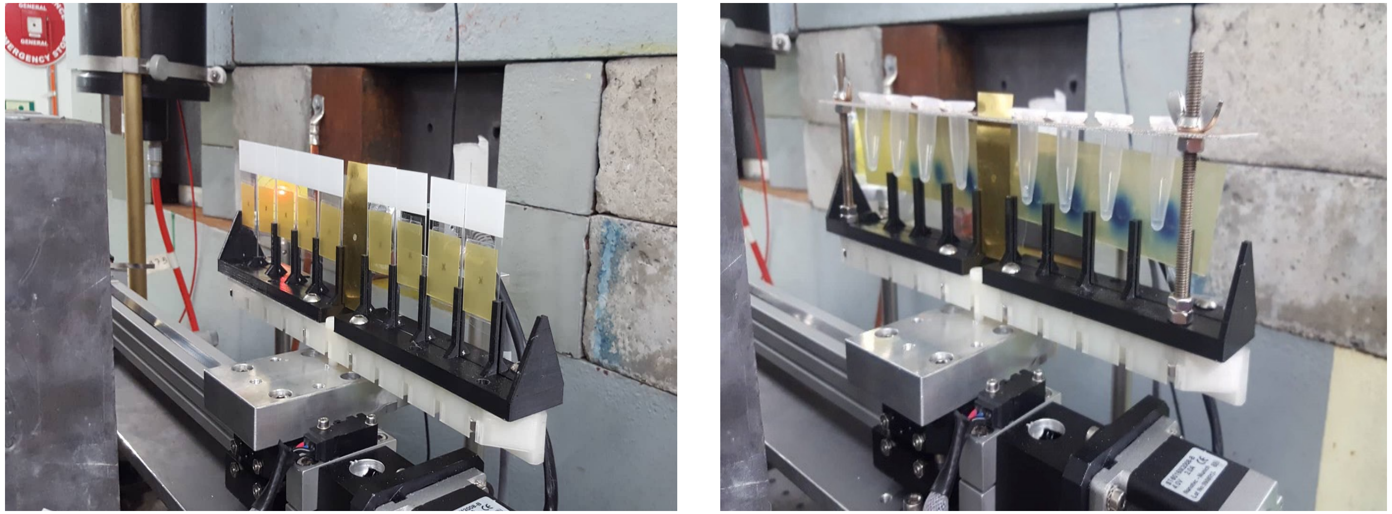


Dose deposition

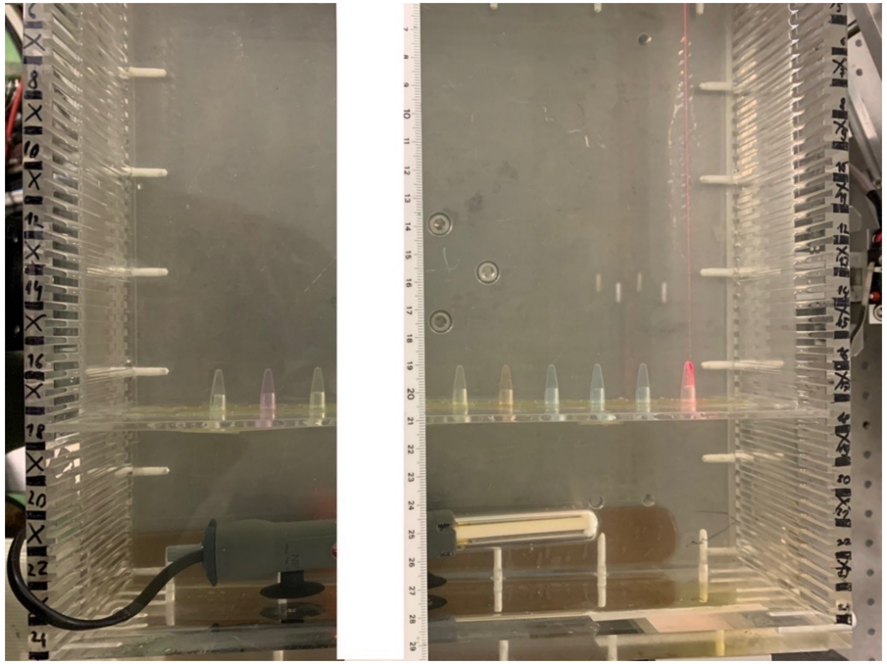


A. Lagzda, R.Jones

Biological effects of high dose rates



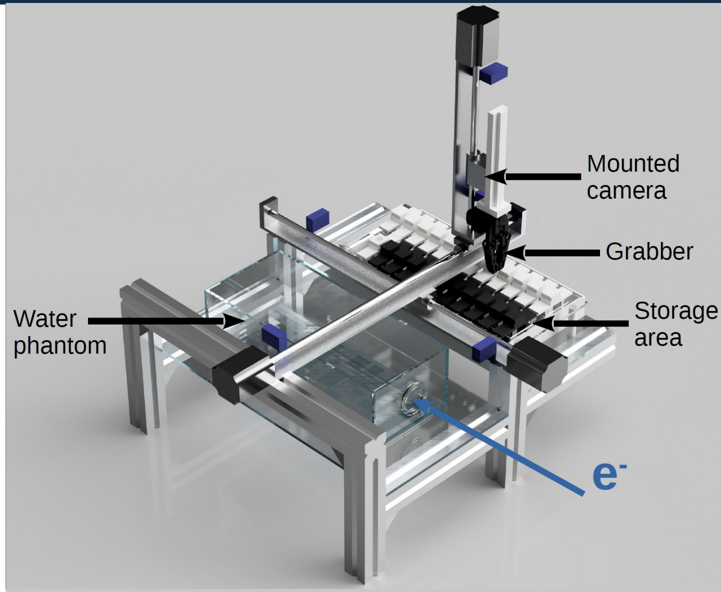
Left: dry plasmid samples on glass microscope slides.
Right: wet plasmid samples in Eppendorf tubes.
EBT-XD film placed behind samples, Manchester University
(K. Small, R. Jones et al.)

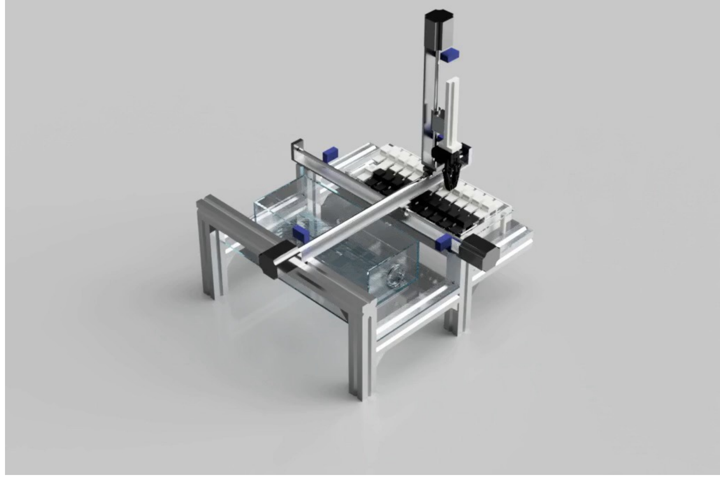


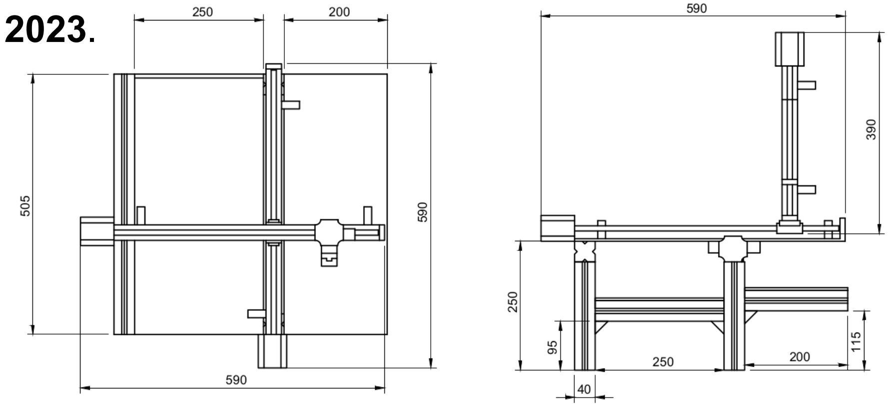
Set-up in the water tank. Zebra fish eggs, alanine pellets, gafchromic films,
CHUV Lausanne
(M.C. Vozenin, C. Bailat, R. Moeckli et al.)

The C-Robot

- In order to **facilitate** the **precise control** of **samples** for **multiple irradiations**, the CLEAR-Robot (**C-Robot**) was designed and built by members of the CLEAR Operation Team.
- It consists of **3 linear stages**, **6 limit switches**, a **3D-printed grabber**, **two water tanks** and an **Arduino board**.
- It has a **precision in position** in 3 axis of **50 µm**.
- It is **fully remotely controllable** from the **CERN Technical Network**.
- Thanks to a **mounted camera**, it can also measure the **beam sizes** and **transverse positions** at the longitudinal position of the sample.
- It is an **open-source project**: **pictures**, **3D renders**, **drawings** and all the **codes** for the **Arduino** and the **Graphical User Interface** can be found on: https://pkorysko.web.cern.ch/C-Robot.html
- Used for **100% of Medical Applications** in CLEAR in **2023**.

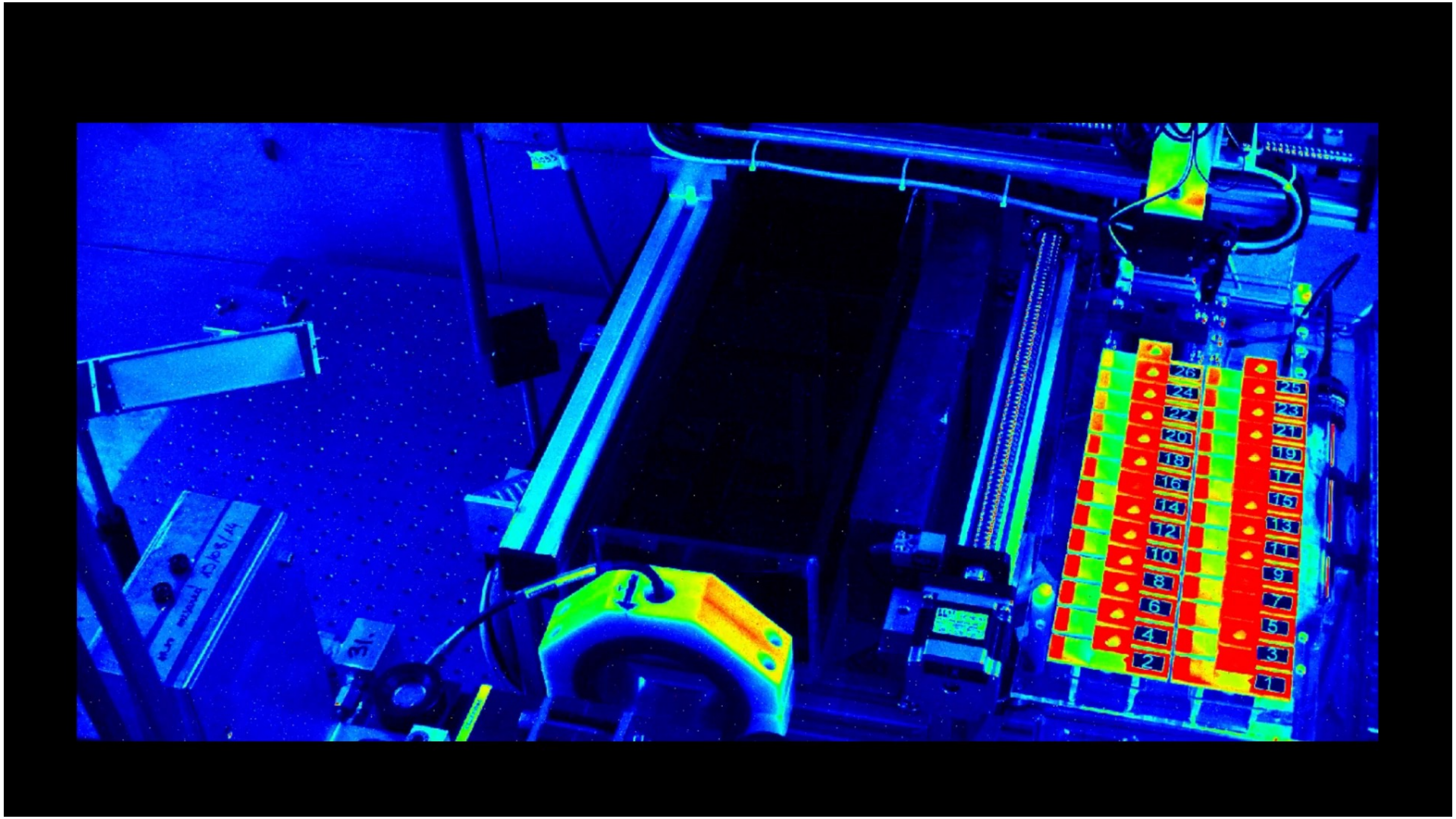






C-ROBOT

The C-Robot in action with beam

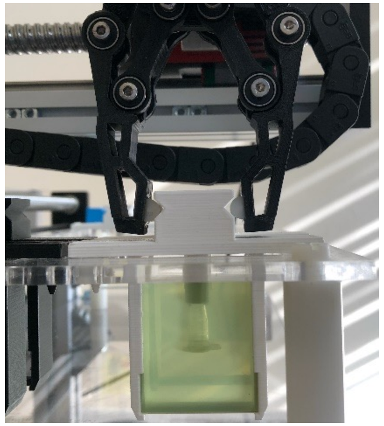


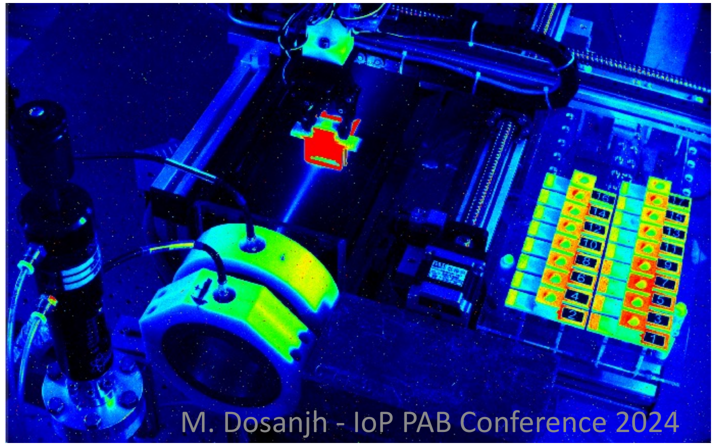
Collaboration with Prof Vozenin's group HUG (prev. CHUV)

VHEE FLASH Radiobiology and Physico-Chemistry Experiments

VHEE FLASH Radiobiology studies investigating mechanisms behind FLASH effect using:

- Chemistry experiments measuring ROS generation in water for FLASH and CONV
- Plasmid irradiations to measure DNA damage
- Zebrafish eggs as biodosimeters to measure FLASH sparing effect
- Normal and cancerous cell irradiations



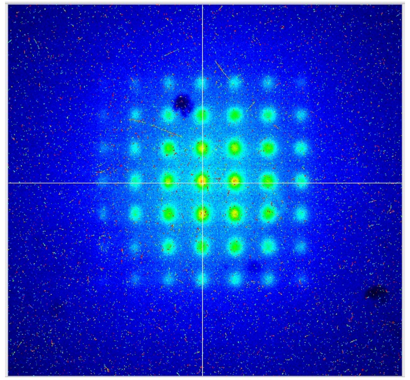


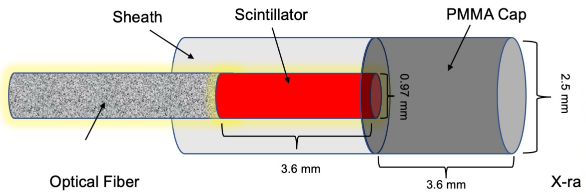
Prof. M. C. Vozenin
Head of Radiobiology and Radio-oncology, HUG, Geneva

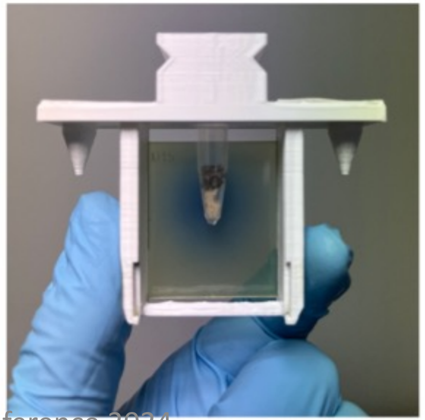
Collaboration with Prof Bazalova-Carter's group Victoria Uni

VHEE Spatial Fractionation – Scintillator Dosimetry – Drosophilae Biodosimeters

- VHEE Spatial Fractionation using tungsten GRID collimator.
  (paper published in Phys. Med. Bio.)
- VHEE UHDR Real-time dosimetry using plastic scintillator-coupled fibres at MedScint™ CCD spectrometer.
  (paper published in IEEE Sensors)
- *In vivo* radiobiology studies on drosophila melanogaster larvae as biodosimeters to investigate VHEE RBE and FLASH mechanisms/parameter space.



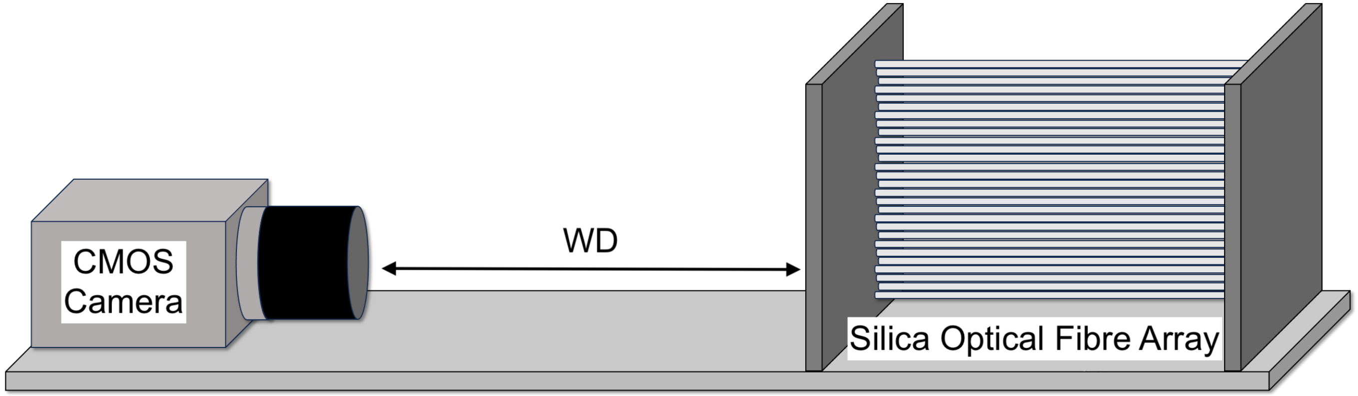


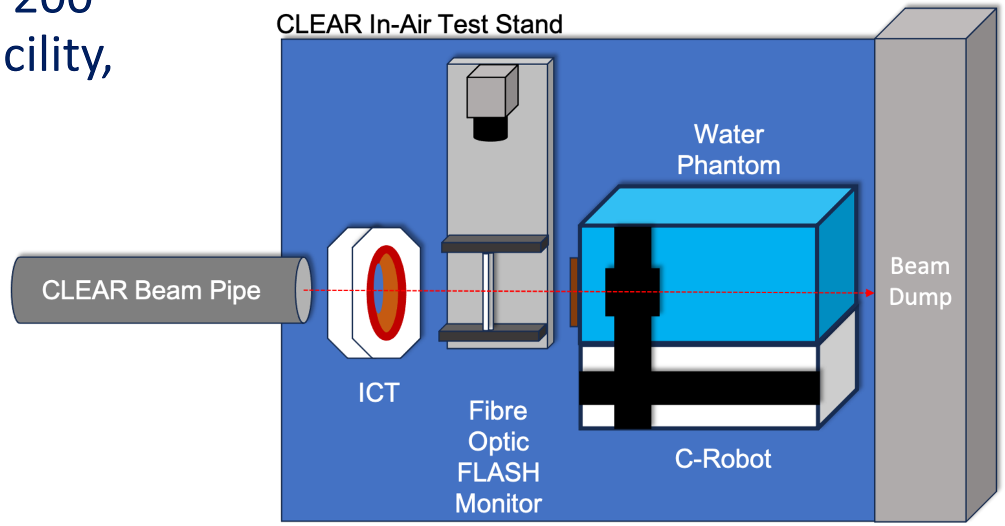


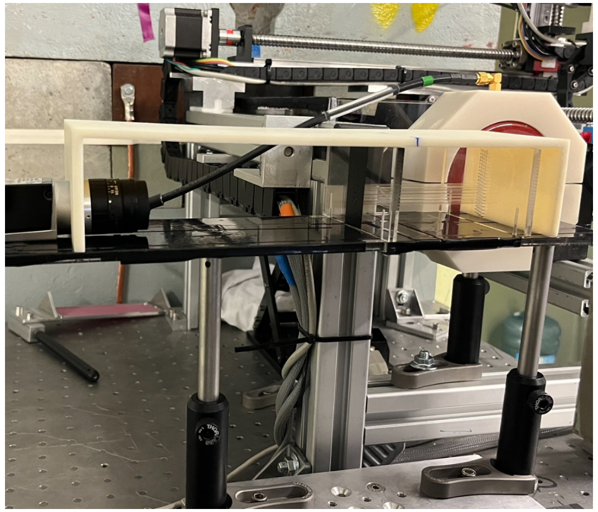
Prof. M. Bazalova-Carter
Head of XCITE Lab, UVic, Canada

Fibre Optic FLASH Monitor (FOFM)

- Novel detector for beam profile and dose monitoring for VHEE at UHDR.
- Array of fused silica fibre Cherenkov sensors (0.4 mm diameter, 10 cm length).
- Entire array readout using CMOS camera.
- Tested and characterised using 160 – 200 MeV electron beams the at CLEAR Facility, CERN.



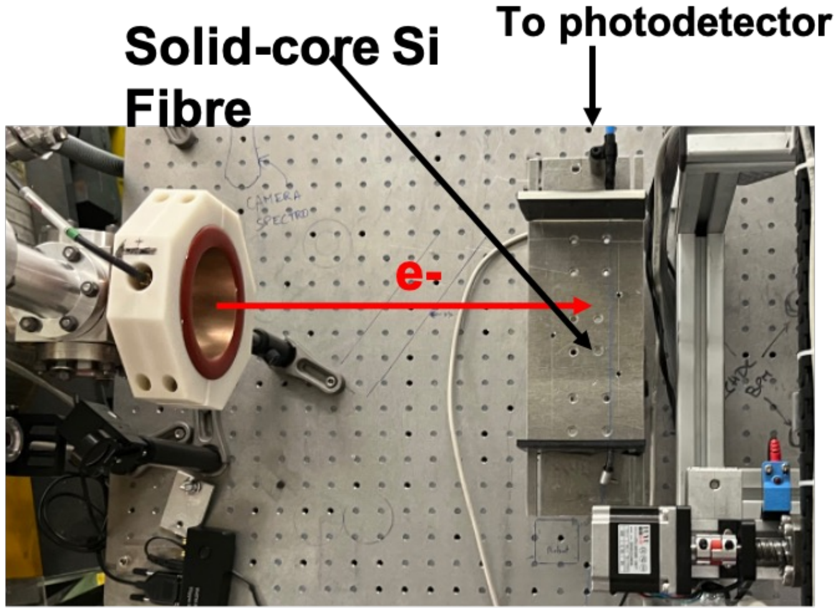


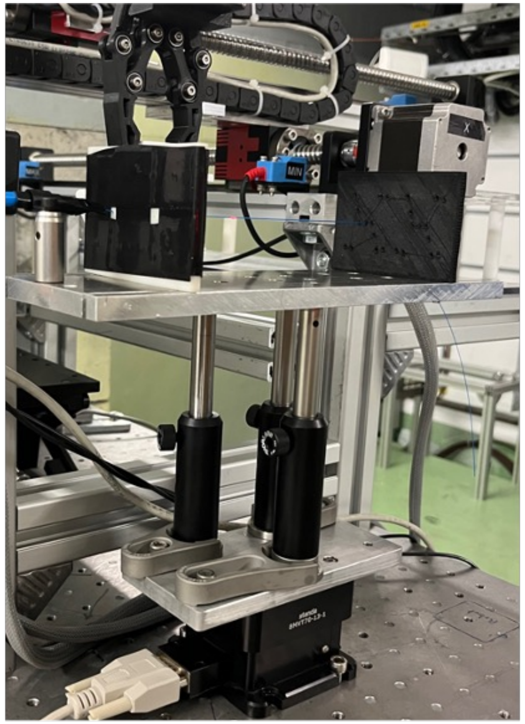


J. Bateman
JAI Oxford DPhil

Initial Single Fibre Experiments at CLEAR

- Initial experiments carried out with single 200 um Thorlabs multi-modal fibre to determine optimal photodetector setup with SiPM, PMT and CCD camera.

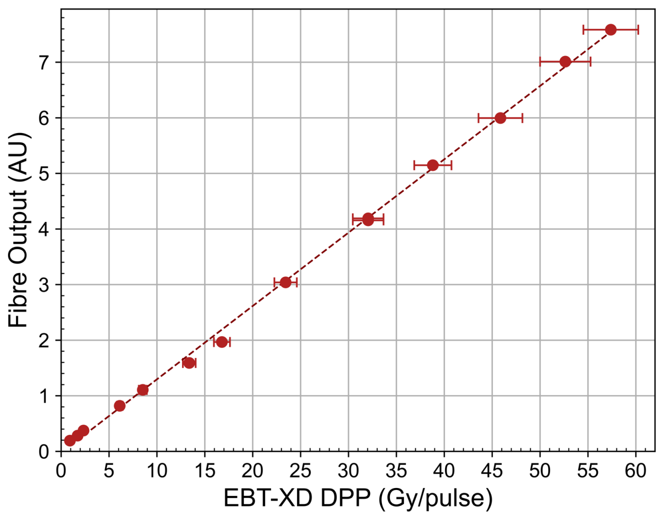


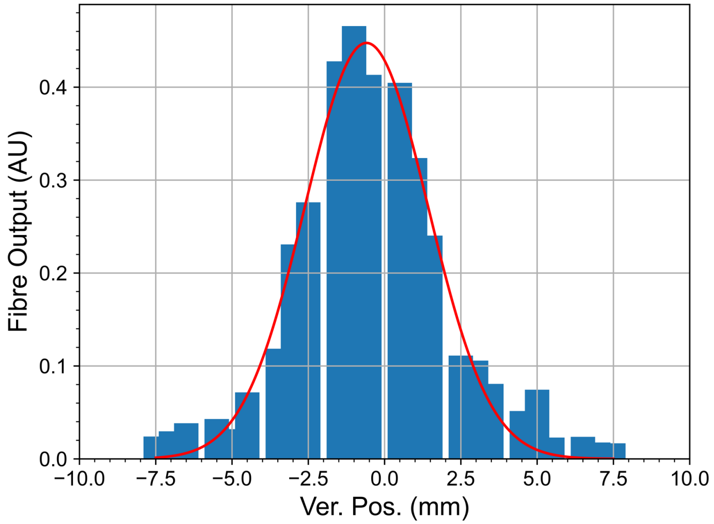


Fibre Optic FLASH Monitor Development

- First prototype (30 cm length fibres) characterisations at CLEAR using VHEE gaussian pencil beam:
  - Dose-per-pulse response linearity measurements (up to 58 Gy/pulse).
  - Profile measurements.
  - Energy and instantaneous dose rate dependence.

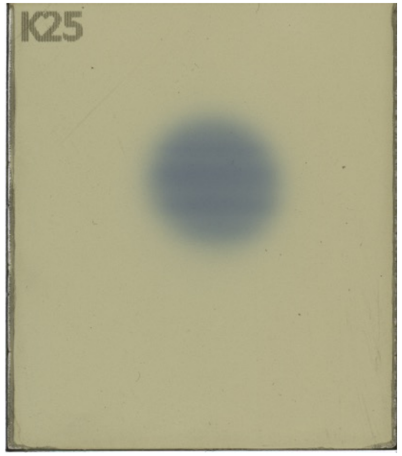
- Results published: Bateman, J. J., *et al* (2024). Development of a novel fibre optic beam profile and dose monitor for very high energy electron radiotherapy at ultrahigh dose rates. *Phys. Med. Biol*. https://doi.org/10.1088/1361-6560/ad33a0

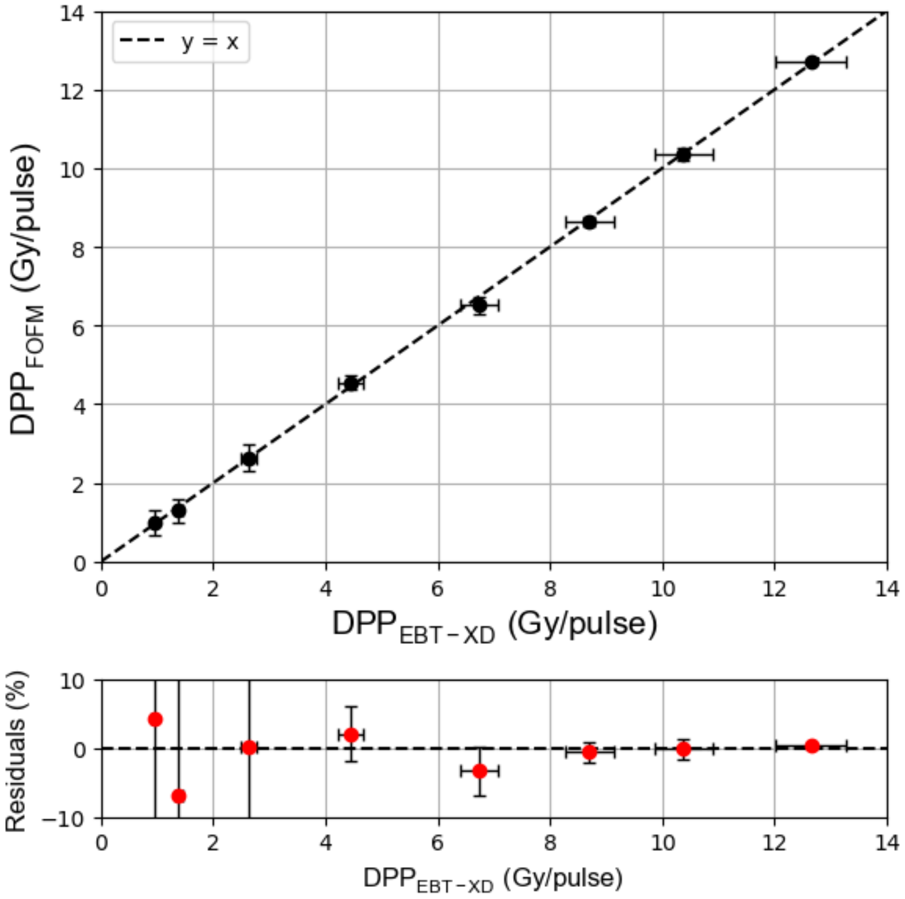




Uniform Beam Dose Monitoring

- Calibration function obtained for FOFM response to dose deposited at reference depth (25 mm).
- Calibrated FOFM measurements compared to EBT-XD dose measurements.
- Able to predict dose measured on EBT-XD films within 5%.

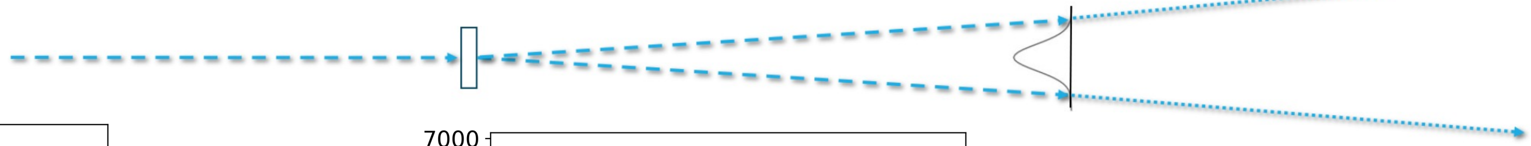


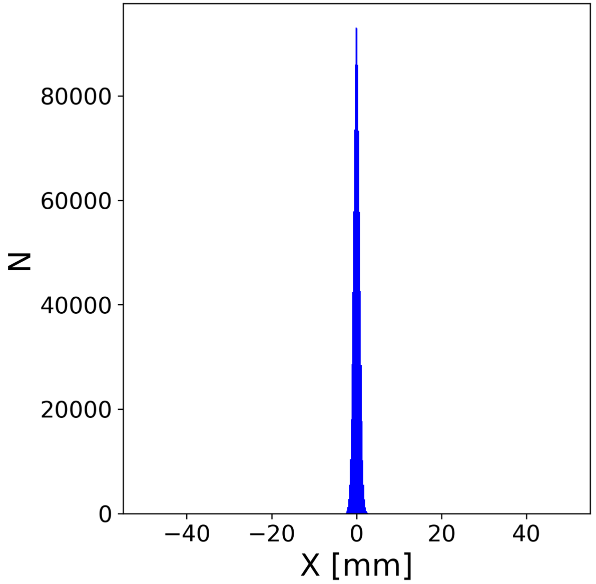


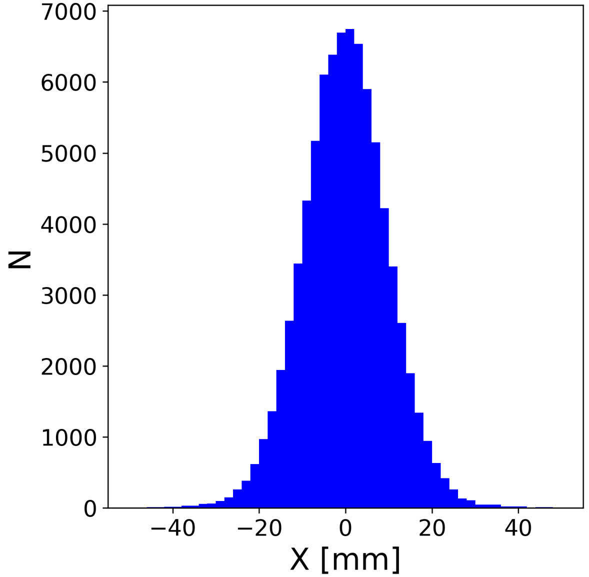
VHEE Dual-Scattering Systems

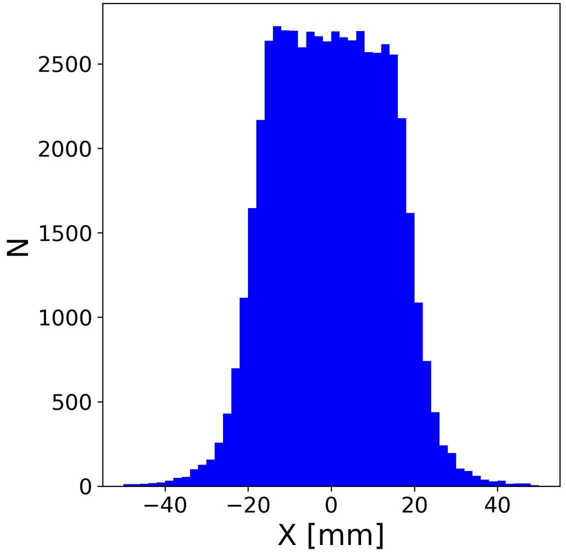
C. Robertson
JAI Oxford DPhil

- Beam magnification and flattening for conformal VHEE Radiotherapy - passive scattering commonly used in other modalities
  - Regained interest due to dose rate independence for FLASH - few studies for VHEE







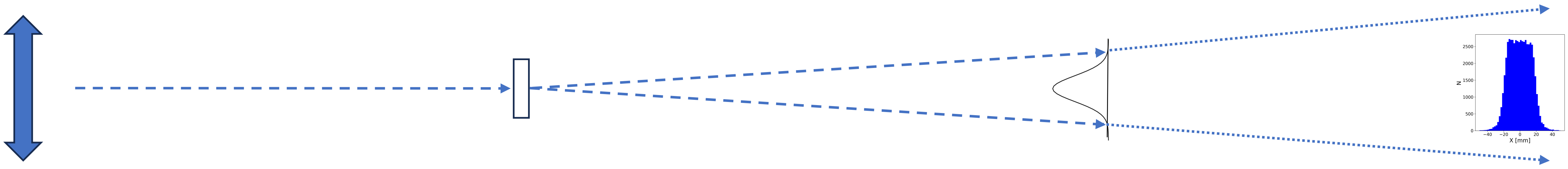


Scattering Foil Design

Initial Beam
- Energy
- Twiss parameters
- Emittance

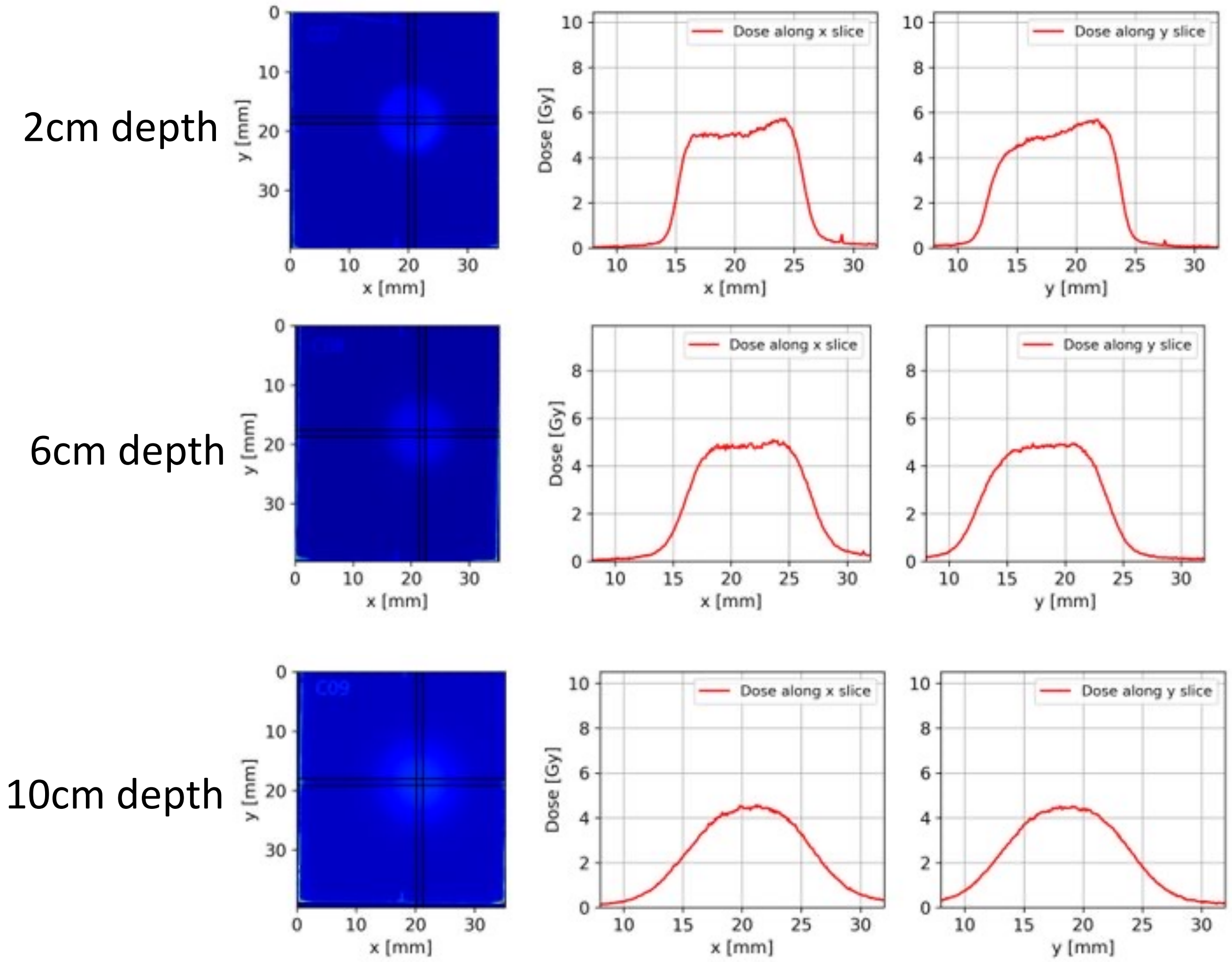
Spatial constraints
- Distance between scatterers
- Transverse space available
- Material choice

Desired Final Beam
- Radius
- Uniformity
- Transmission after collimation



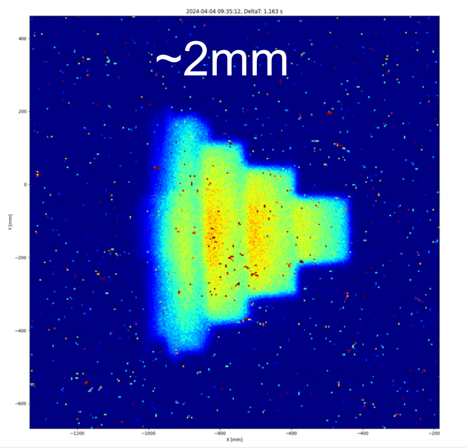
Beam Evolution

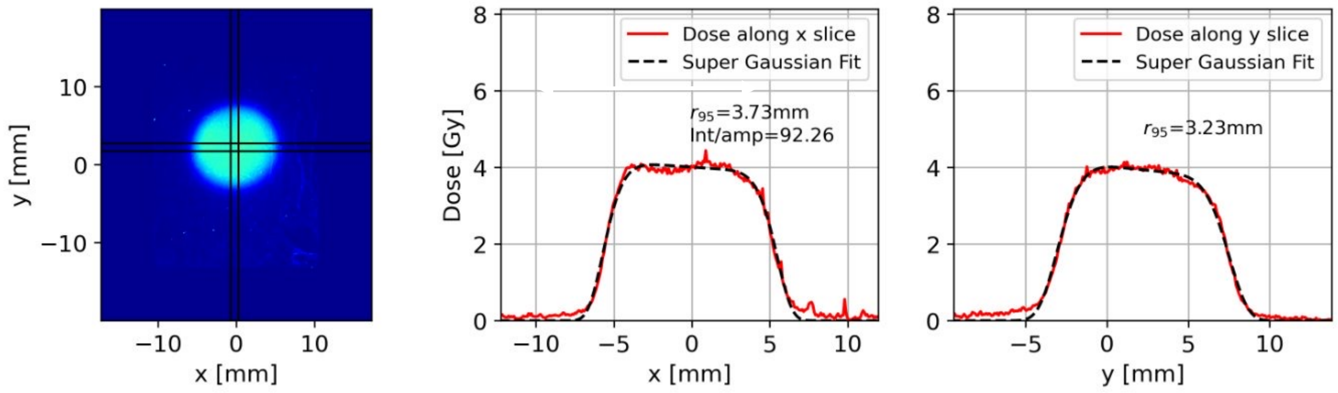
- Uniformity can be retained deep into water phantom
- Asymmetries from initial misalignment reduced
- **Initial beam can be modified to change shape**



Beam Evolution

- Successful experiments demonstrating magnified, flattened dose distributions at CLEAR
- **Permanent** in-vacuum CLEAR dual-scattering system developed and installed by operators in beamline
- System well characterised and operational with collimator to provide up to 1cm uniform beam profile for sample irradiations and conformal VHEE dose studies – now used as standard for CLEAR radiobiological studies.





VHEE-FLASH Dose Delivery and Dosimetry: Next Steps

Dosimetry & Beam Monitoring

- Fibre Optic FLASH Monitor currently under development has demonstrated a large dynamic range and ability to provide accurate pulse-by-pulse beam profile measurements – further optimisation needed once realistic clinical parameters for VHEE-FLASH become realised.
- Next steps…. Develop full prototype with two orthogonal arrays

Dose Delivery

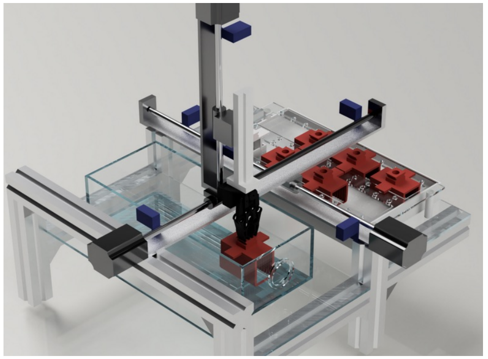
- Dual-scattering foil now realised for ~ 1cm uniform VHEE beams at UHDR at CLEAR.
- Next steps… Further studies required on x-ray production and losses for production of larger beams (up to 5-10 cm).

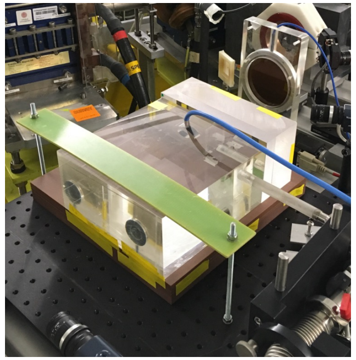
The potential use of very high-energy electron (VHEE) beams (50-250 MeV) for Radio Therapy (RT) recently gained interest, since electrons at these energies can travel deep into the patient.

- Potential advantages of VHEE RT:
  - Depth – dose profile for electrons better than X-rays
  - Charged particles can be focused and steered (not possible with X-rays)
  - Electron beams rather unsensitive to tissue inhomogeneities
  - Electron accelerators comparatively more compact, simpler and cheaper than proton/ion machines
- This last advantage is now especially true given the recent advances on high-gradient acceleration (e.g. X-band CLIC technology)
- Ultra-high dose rate (above 100 Gy/s) radiation delivery, termed FLASH RT, showed normal tissue sparing capabilities, without compromising tumor control. Electron linacs can relatively easily reach the high beam currents needed for FLASH treatment of large fields.

- More and more existing electron linac facilities are now being intensively used to investigate VHEE/FLASH RT

VHEE/FLASH RT studies at the CLEAR facility (CERN)



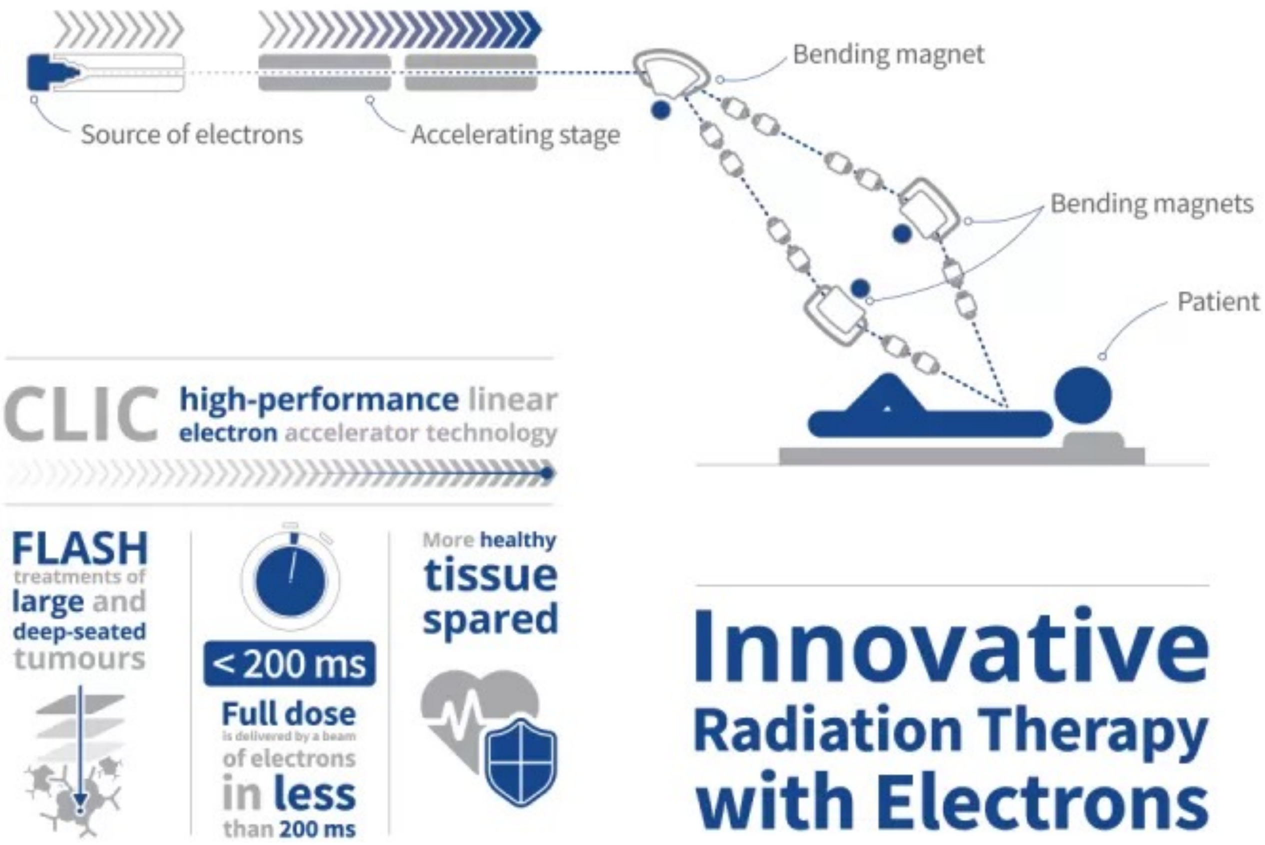


Facility	Applications
ARES	Accel. components, Diagnostics R&D Medical: VHEE RT, Electron CT Acceleration: ACHIP [29]
CLARA	Accel. components, Diagnostics R&D Medical: VHEE RT Acceleration: DWA, (P/L)WFA, THz
CLEAR	High gradient acceleration, plasma lens Radiation damage, Diagnostics R&D Medical: VHEE & FLASH RT
FLUTE	Diagnostics R&D, THz Experiments Medical: FLASH RT, Detectors Machine Learning
PITZ	Min. beam emittance developments THz source development Medical: FLASH RT & dosimetry
SPARC_LAB	Acceleration: PWFA, LWFA Radiation sources: FEL, THz, betatron

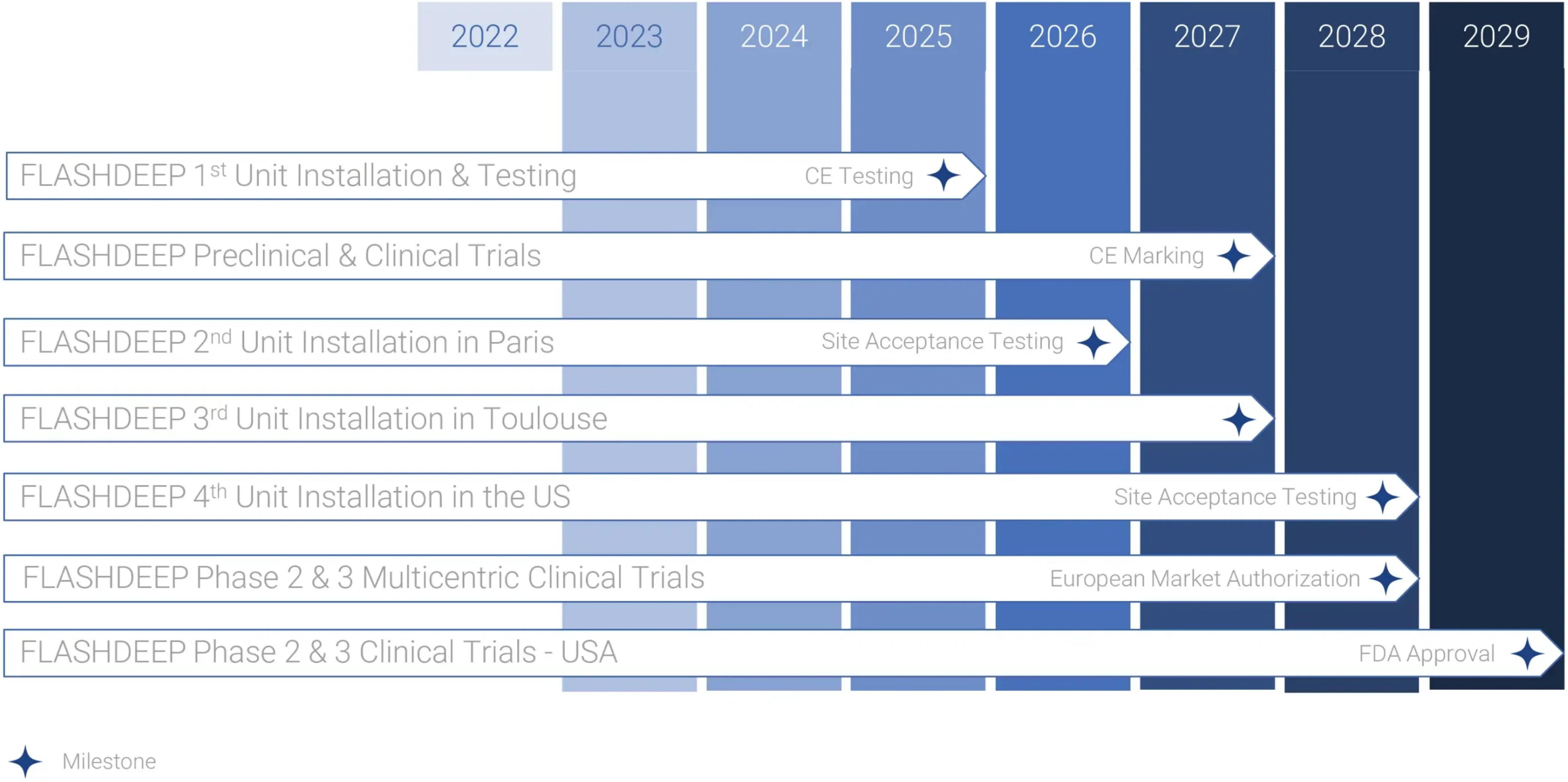
From: D. Angal-Kalinin et al., Electron beam test facilities for novel applications, Proc. IPAC '23

Very High Energy Electron (VHEE) Radiotherapy

- CERN and CHUV Hospital collaboration to build the first clinical VHEE machine – DEFT (Deep Electron FLASH Therapy).
- Construction and commissioning scheduled for 2025 and clinical trials planned to start in 2027.
- Other VHEE FLASH facilities planned: Stanford (PHASER) and Sapienza, Rome (SAFEST), add Lumitron/UC Irvine and ongoing developments in UK.



Centre hospitalier universitaire vaudois


2022
2023
2024
2025
2026
2027
2028
2029
FLASHDEEP 1st Unit Installation & Testing
CE Testing
FLASHDEEP Preclinical & Clinical Trials
CE Marking
FLASHDEEP 2nd Unit Installation in Paris
Site Acceptance Testing
FLASHDEEP 3rd Unit Installation in Toulouse
FLASHDEEP 4th Unit Installation in the US
Site Acceptance Testing
FLASHDEEP Phase 2 & 3 Multicentric Clinical Trials
European Market Authorization
FLASHDEEP Phase 2 & 3 Clinical Trials - USA
FDA Approval
Milestone

What do we need to know before clinical translation

RRP’s editorial on FLASH:


ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

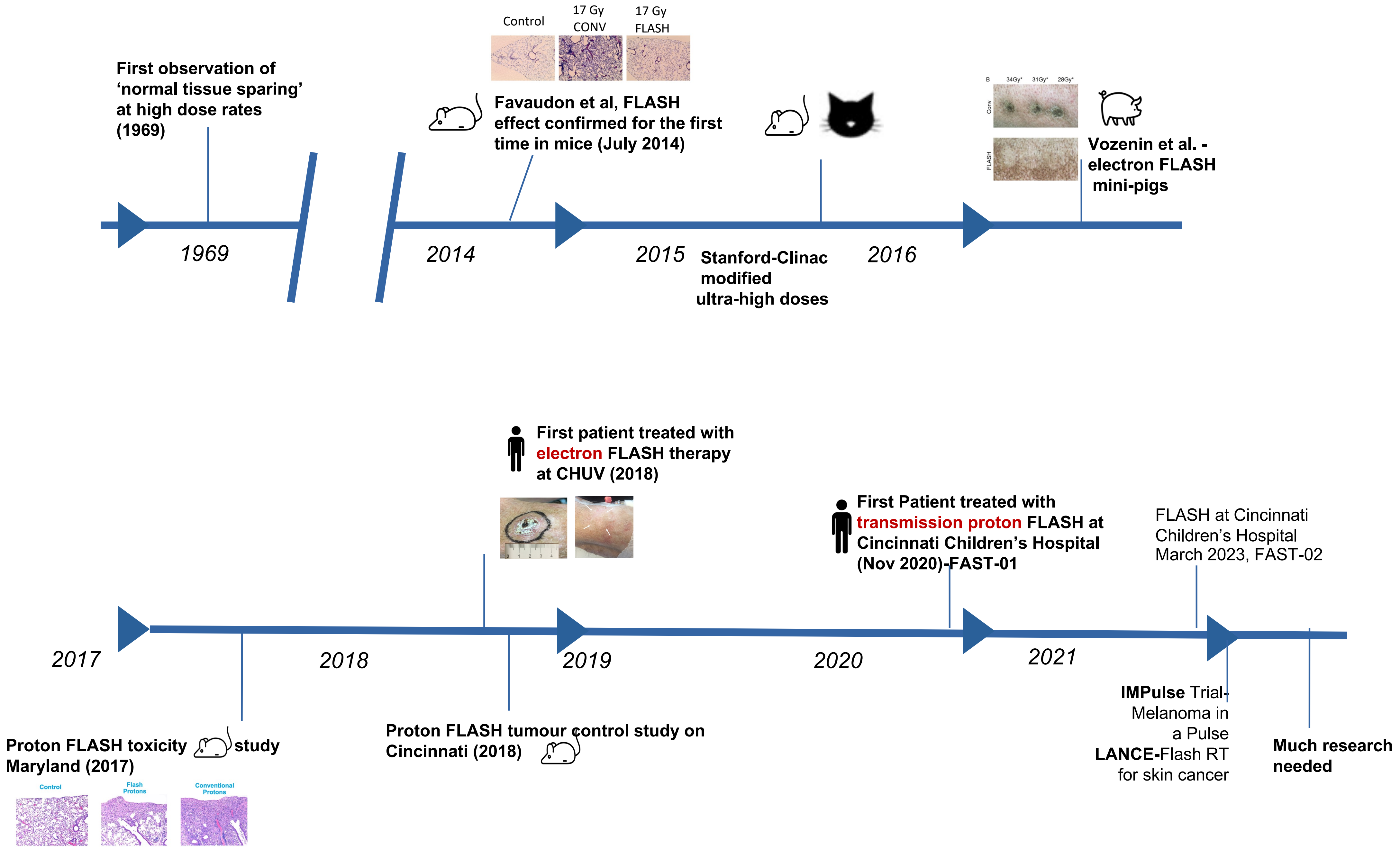
Available online 3 February 2021

In Press, Journal Pre-proof

FLASH Radiotherapy: New Technology Plus Biology Required

While FLASH-capable technology is rapidly emerging, radiation oncology needs to **remember to be cautious, methodical**, and **data-driven** as we Target Safely. The FLASH effect requires both **new technology and preclinical studies to understand its biological basis**. Implementation of this intriguing treatment modality requires particular diligence and robust trials that assure the Journal Pre-proof technology performs and especially demonstrates effective tumor cell killing as we move into the transformational domain of exploiting both the extraordinary technology and biology of the radiation beam.

Mazal et al state:	As usual in the field, there are at least three issues limiting the development of these new approaches: (a) the understanding of the **mechanisms** involved, (b) **technical limitations**, and (c) the **safe implementation of clinical protocols with significant follow-up**. (Mazal, et al, doi.org/10.1259/bjr.20190807)


First observation of 'normal tissue sparing' at high dose rates (1969)
1969
Control
17 Gy CONV
17 Gy FLASH
Favaudon et al, FLASH effect confirmed for the first time in mice (July 2014)
2014
2015
Stanford-Clinac modified ultra-high doses
2016
34Gy*
31Gy*
28Gy*
Conv
FLASH
Vozenin et al. - electron FLASH mini-pigs
First patient treated with electron FLASH therapy at CHUV (2018)
First Patient treated with transmission proton FLASH at Cincinnati Children's Hospital (Nov 2020)-FAST-01
FLASH at Cincinnati Children's Hospital March 2023, FAST-02
2017
2018
2019
2020
2021
Proton FLASH toxicity study Maryland (2017)
Control
Flash Protons
Conventional Protons
Proton FLASH tumour control study on Cincinnati (2018)
IMPulse Trial-Melanoma in a Pulse
LANCE-Flash RT for skin cancer
Much research needed

FLASH RT – so many questions remain

The exact mechanisms underlying FLASH and the relative sparing of normal tissue remain unclear. In general, FLASH is considered to be a result of a number of biological, radiochemical and delivery parameters.

It is unclear which of parameters of UHDR RT are required or optimal to produce FLASH effects. In early publications, 40 Gy/s was suggested as a dose-rate threshold. Subsequent studies have demonstrated that the dose, intra-pulse dose rate, and number of pulses play important roles in electron FLASH effects.

Although in vivo animal FLASH studies have been performed with single scattered and collimated beams, clinical particle-beam UHDR treatment delivery used and likely will use pencil beam scanning (PBS) that employs lateral scanning of a series of pencil beams located at various depths to cover the tumour volume.

Many things to consider and do: Dose rate, Energy range, which particle(s) - electrons vs. protons vs. photons vs carbon vs helium, Scanning, Focusing, Dosimetry, Treatment planning tools, New real time-imaging , Tests in vivo, in vitro, Animal studies, Clinical trials

Our recent data from Marie Catherine Vozenin's group with zebra fish embryos suggest that:

the overall time of irradiation does not matter
however, the dose delivered in the pulse does matter

Publication under review

Thank you for your attention

Acknowledgement: many thanks to all colleagues and the CLEAR team who provided material used in the talk, specially Joseph Bateman, Cameron Robertson and Marie Catherine Vozenin