FLASH Radiation Therapy

A Review on the Ultra-high Dose Rate Paradigm of Radiotherapy

A. Koutsostathis[1*], A. Adamopoulou[1], V. Rangos[2], C. Koumenis[3], A. G. Georgakilas[1]

[1] Department of Physics, School of Applied Mathematical and Physical Sciences, National Technical University of Athens
[2] School of Medicine, National Kapodistrian University of Athens
[3] Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania

NATIONAL TECHNICAL UNIVERSITY OF ATHENS
School of Applied Mathematical and Physical Sciences
Department of Physics

DNA Damage Lab

Perelman School of Medicine
University of Pennsylvania

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What is FLASH Radiation Therapy?

FLASH Radiotherapy (**FLASH-RT**) is a new paradigm of radiation therapy, featuring **ultra-high Dose rate** (UHDR) irradiation of tumours with **Dose rate** ($\dot{D}$) of **40 Gy s^{-1} or higher**. The so-called **FLASH effect** can be defined as *the in vivo effect in which administration of radiation with UHDR can* ***reduce the radiotoxicity in normal tissue, with little to no impact to the anti-tumour effect of the radiation*** [1].

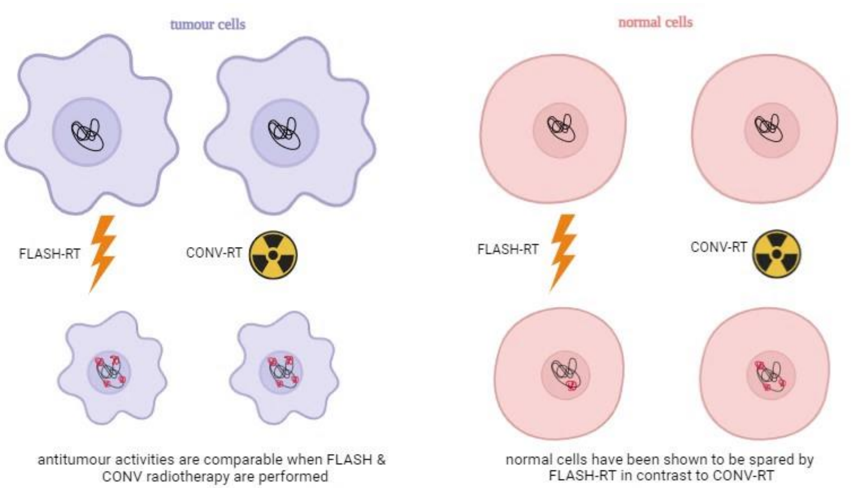


Fig. 1. Schematic of the FLASH-effect; the anti-tumour effect is maintained for both conventional (CONV) and FLASH-RT, whereas healthy tissue is spared with FLASH-RT, when compared to CONV-RT. The red coloured "knots" signify cell radiation damage.

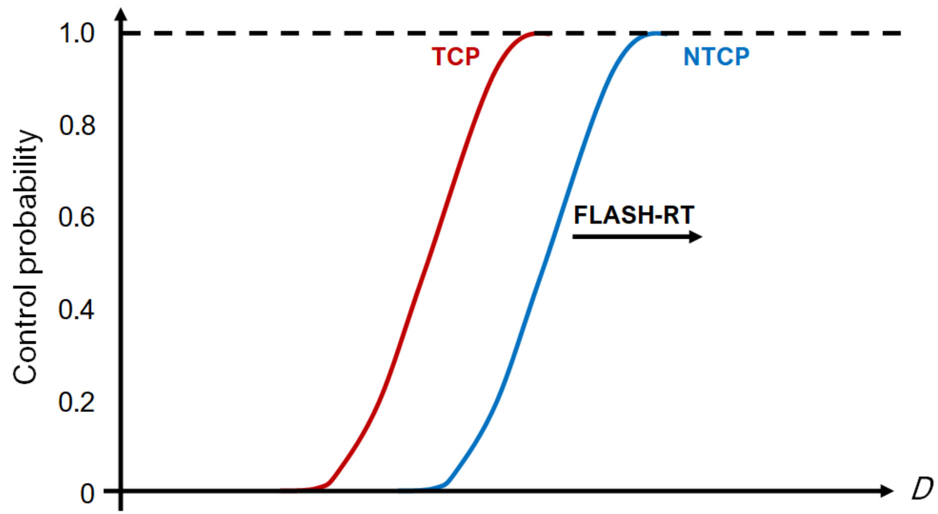
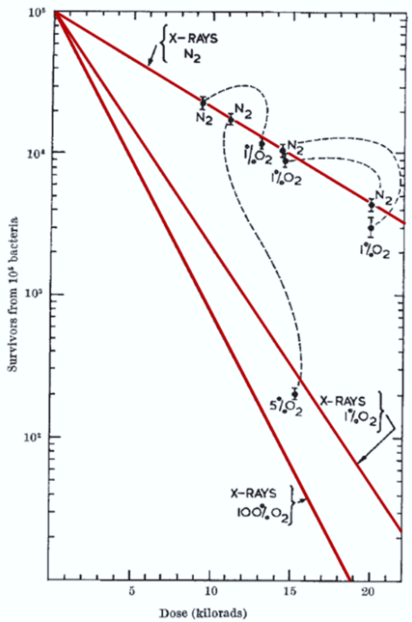


Fig. 2. FLASH-RT significantly improves the potential for cancer treatment, by allowing for a larger therapeutic window, between the Tumour Control and Non-tumour Control Probability curves.

A brief history of… FLASH



Dewey D, Boag J. (1959) *Nature* **183**(4673):1450-1451

Fig. 3. Survival curves for the X-Ray irradiation of *Serratia marcescens* with $\dot{D} \sim 5 - 10$ krd μs^{-1} under anaerobic (100% N_2), hypoxic (1% O_2, 99% N_2) and oxygenated (100% O_2) conditions [2].

1959

Numerous findings and publications in support of the findings of Dewey and Boag, in the 60’s and 70’s. [3-10]

2014

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

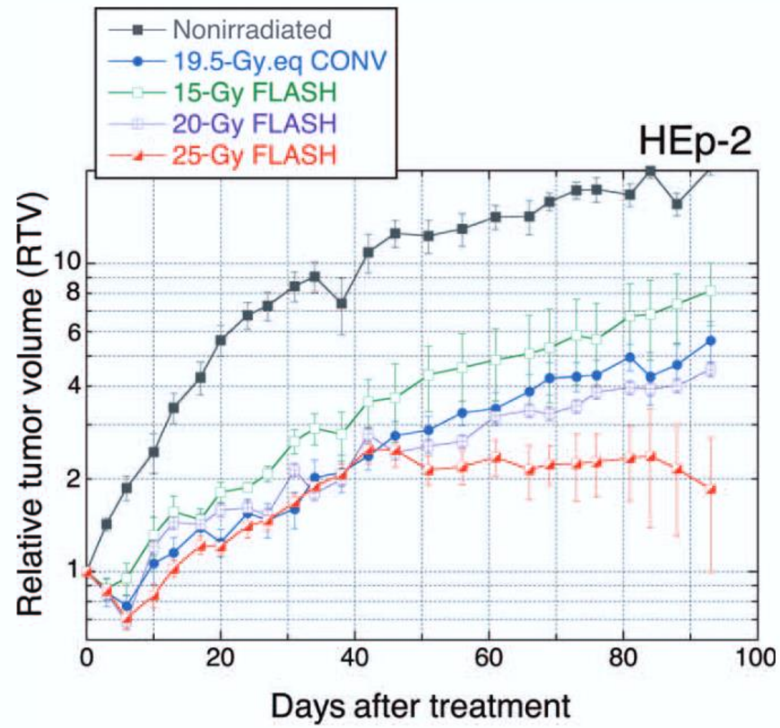


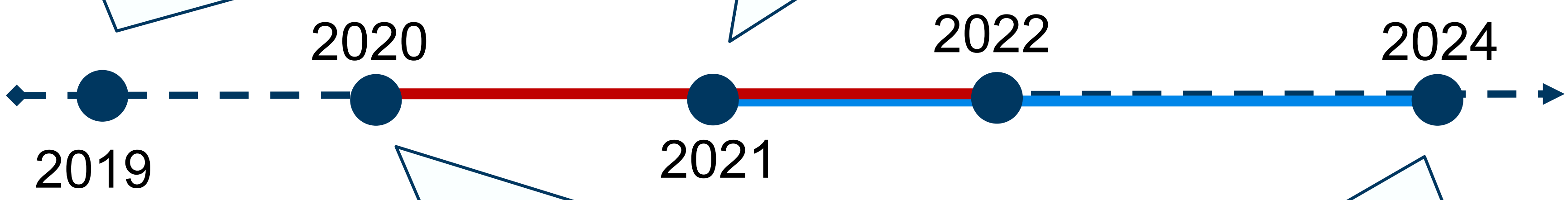
Fig. 4. Relative tumour volume time-evolution of HEp-2 ($n = 40$) tumour xenografts in mouse model of lung fibrosis, after conventional (^{137}Cs γ-Rays, $\dot{D}$ = 0.03 Gy s^{-1}) and FLASH (4.5 MeV *e*-, $\dot{D}$ = 60 Gy s^{-1}) irradiation [11].

A brief history of... FLASH

Bourhis J, *et al*. (2019) *Radiother Oncol* **139**:18-22

First human patient of *electron* FLASH-RT
(CHUV, Switzerland)

Start of the Phase I **IMPulse clinical trial in electron FLASH-RT of advanced melanoma** (CHUV) [14]



Mascia A E, et al. (2023) JAMA Oncol **9**(1):62-69

FAST-01: First human clinical trial for treatment of symptomatic bone metastases
(Cincinnati Children's/UC Health Proton Therapy Center)

Daugherty E C, *et al*. (2024) *Rad Oncol* **19**(34)

FAST-02 clinical trial is announced and begins
(US FDA IDE 2022)

First human patient [12]

Skin tumour (**CD30+ T-cell cutaneous lymphoma**) with $d = 3.5$ cm
Irradiation with **5.6 MeV electron beam** with the **Oriatron eRT6 LINAC** [16] at **CHUV** (Lausanne University Hospital)
$\mathbf{D_{PVT} = 15\,Gy}$ ($D_{healthy} = 10$ Gy), $\mathbf{t = 90\,ms}$, $n = 10$ fractions ($\mathbf{T_{pulse} = 1\,\mu s}$, $f_{rep} = 100$ Hz),
Dose rates: $\langle \dot{D}_p \rangle = \mathbf{15\,MGy\,s^{-1}}$, but $\langle \dot{D} \rangle = \mathbf{166\,Gy\,s^{-1}}$ (90% isodose at 1.3 cm depth)
Pre- and post-irradiation **Dose distribution measurements with GafChromic films**

Fig. 5. Temporal evolution of the irradiated area before the treatment, at 3 weeks' time after the irradiation (peak of skin reaction) and at 5 months' time after the irradiation. The study appeared to have favourable results for the patient [12].

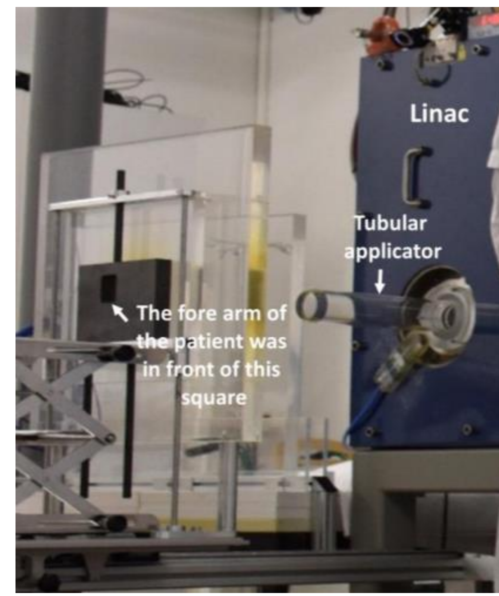


Fig. 6. Experimental setup of at the Oriatron eRT6 LINAC at CHUV [12, 16].

FAST-01: First human trial [13]

Objectives:

- assessment of the **clinical workflow feasibility** of FLASH-RT for the palliative treatment of **painful bone metastases**
- evaluation of treatment related toxicities and **adverse events** (AEs)
- assessment of **pain response** at the treated sites

Technical implementation characteristics:

- treatment at **Cincinati Children's/UC Health Proton Therapy Centre Varian ProBeam system** with **open-field transmission** and **PBS** with **250 MeV protons**.
- $D = 8$ Gy, $n = 1$ fx, $\dot{D} = 51 - 61$ **Gy s^{-1}**

Patient characteristics: **10 patients** (> 18 y old) with **1-3 painful metastases in the extremities**, **2 or more months of life expectancy** and with **no prior RT to the intended lesion(s)**

Fig. 7. Coronal CT through a lesion in the right distal femur. The radiation dose (blue line) as a function of depth of penetration into the body for FLASH delivery with a 250 MeV proton beam [13].

FAST-01: First human trial [13]

FLASH treatment workflow feasibility

- no FLASH-related technical issues/delays
- average time on the treatment bed was **18.9 min per patient**

Adverse effects:

- **mostly skin-related** (e.g. edema, erythema, skin hyperpigmentation, pruritus, etc.)
- **mild and consistent with CONV-RT**

Pain relief and post-treatment response:

- **33%** had **transient pain flares**
- **67%** reported **pain relief**
- **50%** reported **complete response** (no pain)

confirmation of the workflow **feasibility** of **proton FLASH-RT** in **clinical settings**

Fig. 8. AEs attributed to FLASH treatment (up). Photographs of a single patient illustrating transient, mild hyperpigmentation the day of the treatment & at 3 different time points during follow-up (down) [13].

Delivering Hadron FLASH-RT [17-23]

FLASH Hadron Therapy

- **Transmission field**
- **Passive scattering of the beam and RT-field-control with ridge filters**
- **Pencil Beam Scanning**

Simultaneous Dose and Dose Rate Optimisation

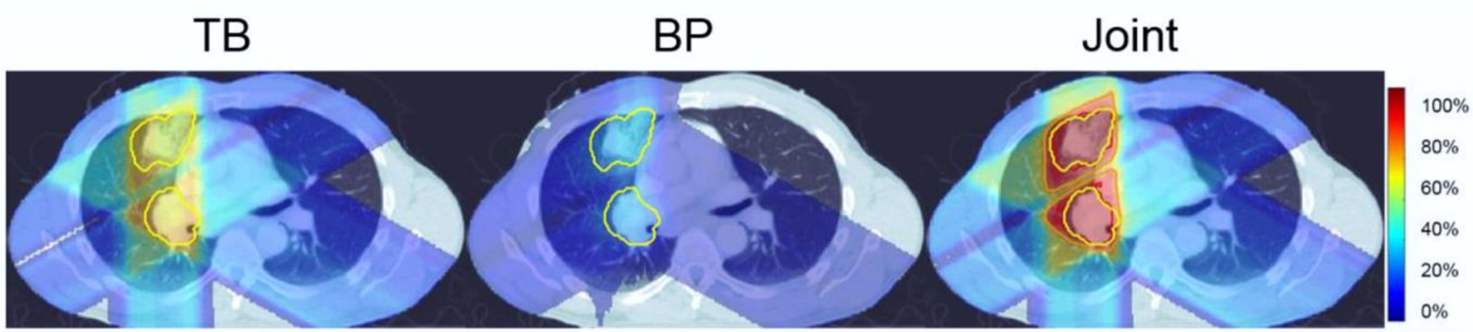


Fig 9. The **SDDRO** method, employs **UHDR transmission beams** (TB) of protons (Bragg peak outside of the body) to irradiate the **tumour boundary**, and **non-UHDR proton beams to form Bragg Peaks** (BP) **inside the tumours** [18].

Adapting RT systems for FLASH [17-23]

Requirements for proton FLASH-RT [19-22]

- **higher** proton-beam fluence (F_p)
- **higher** beam current (I_{beam})
- **minimal beam losses** and **position misalignments**
- **D and $\dot{D}$-independent** (passive) **detectors** for **online dosimetry**

Cyclotrons for FLASH-RT [20-21,23]

- **quasicontinuous cyclotron beams** are suitable for **sub-second *D*-delivery**
- **Pencil Beam Scanning** can be employed, being I_{beam}-independent
- **passive double-scattering** can also be employed; it requires very **accurate adjustment of the scatterers** and **monitoring of activation-induced neutrons**
- **very fast range modulators**

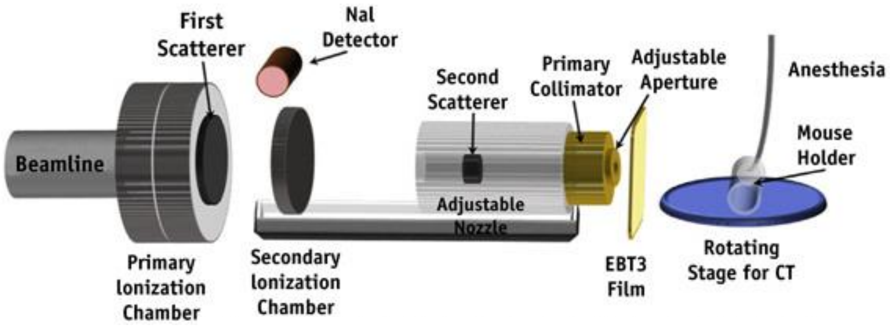


Fig. 10. Schematic of the proton FLASH-RT experimental setup at UPenn. An IBA Proteus Plus cyclotron produces a proton beam, which is then scattered by two Pb scatterers and collimated by a a custom brass collimator. The irradiation is guided by CT-defined geometry [20].

Adapting RT systems for FLASH [17-23]

Synchrotrons for FLASH-RT [17,19,22]

- **single-spill delivery** of the therapeutic Dose
- **custom beam-shaping elements**
- **patient-specific range modulators** to allow for optimised irradiation of the tumour volume
- **reduced distance of irradiated volumes** from the beam extraction, to limit beam current losses

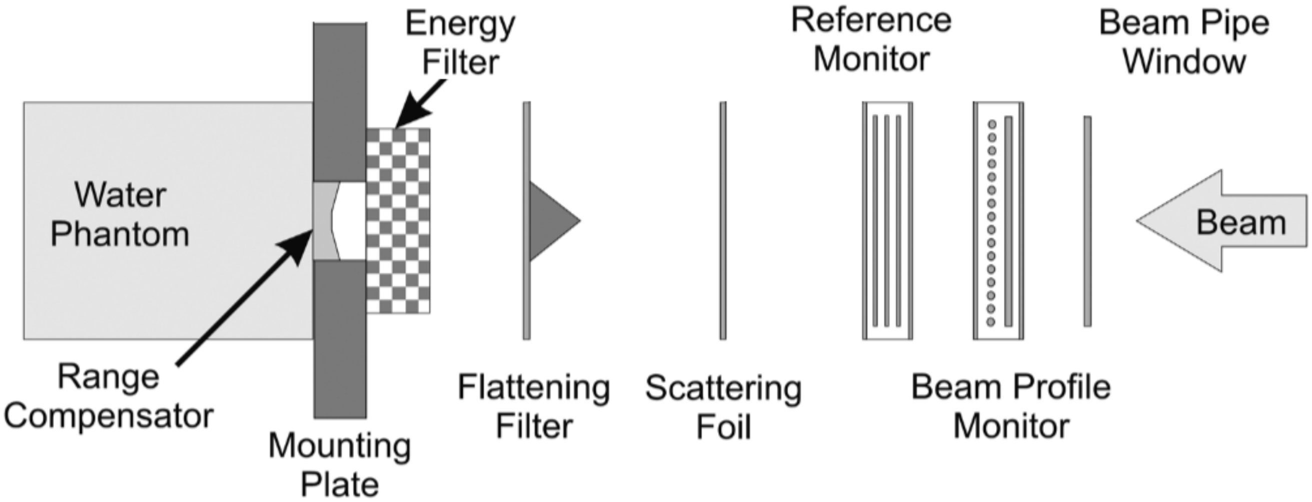


Fig. 11. Schematic of the beamline modifications to enable FLASH conditions, for the HITACHI synchrotron of the Texas MD Anderson Cancer Center [22].

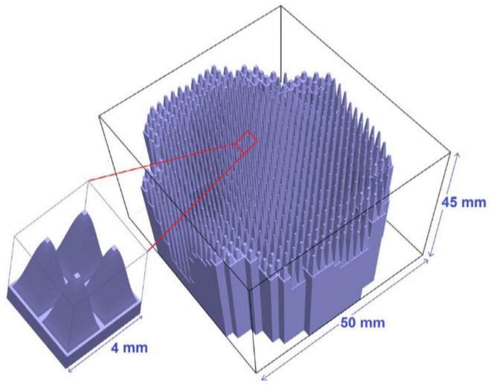


Fig 12. Design of a 3DRM for FLASH-irradiation of a 25 cm^3 lung carcinoma with a 240 MeV amu^{-1} $^{12}C^{4+}$ beam [17].

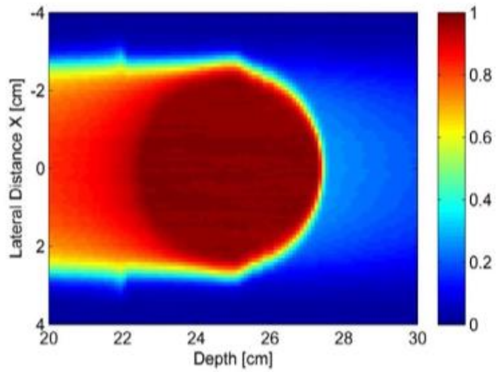


Fig 13. *D* application to a 3DRM for a spherical target volume (*r* = 25 mm) with a 400 MeV amu^{-1} $^{12}C^{4+}$ beam [17].

VHEE: A novel technology for FLASH-RT [24-26]

- T_{VHEE} ~ **50 - 250 MeV**
- **increased depth** penetration and **indifference to medium inhomogeneities**
- quadrupole-magnet focusing allows for **spread-out *e-* peak** over the target region
- proposed VHEE LINACs to bunch at **C- and X-band** frequency (**4 - 12 GHz**) and gradient (**50 - 100 MeV m^{-1}**) ranges

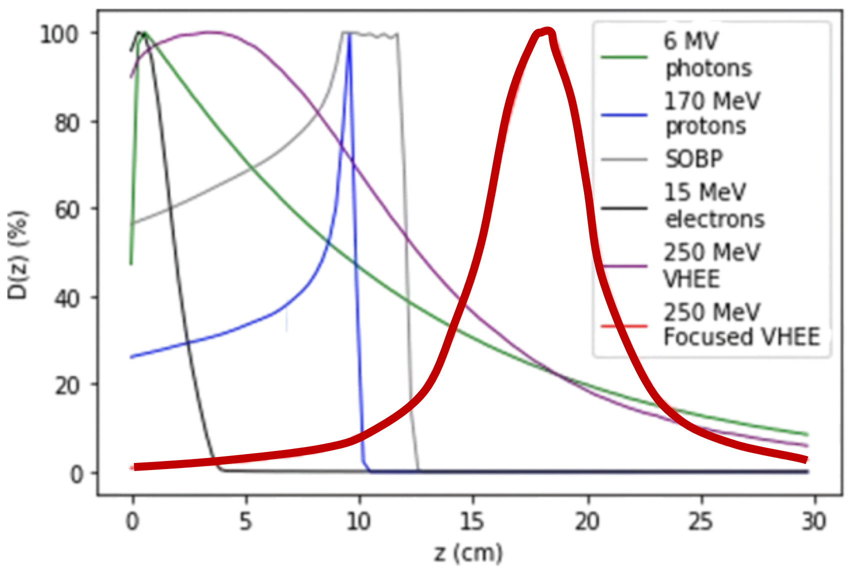


Fig 14. Monte-Carlo simulations for the normalised Bragg curves of various RT modalities ($\sigma = 6.7$ mm, $n \sim 10^6$, $n_\gamma \sim 5 \times 10^5$) [24].

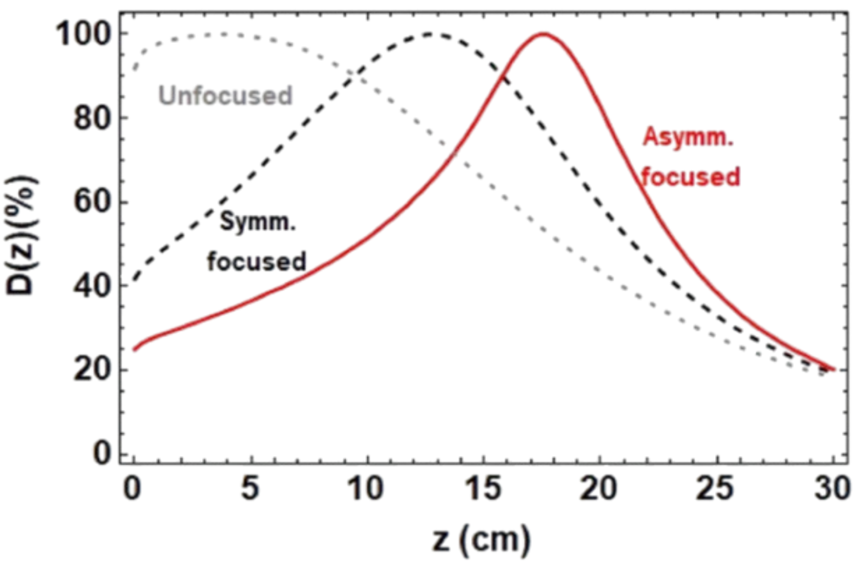


Fig 15. Monte-Carlo simulations for the normalised Bragg curves of 250 MeV *e-* of different types of beam focusing. [25].

The Oxygen Depletion Hypothesis [27-29]

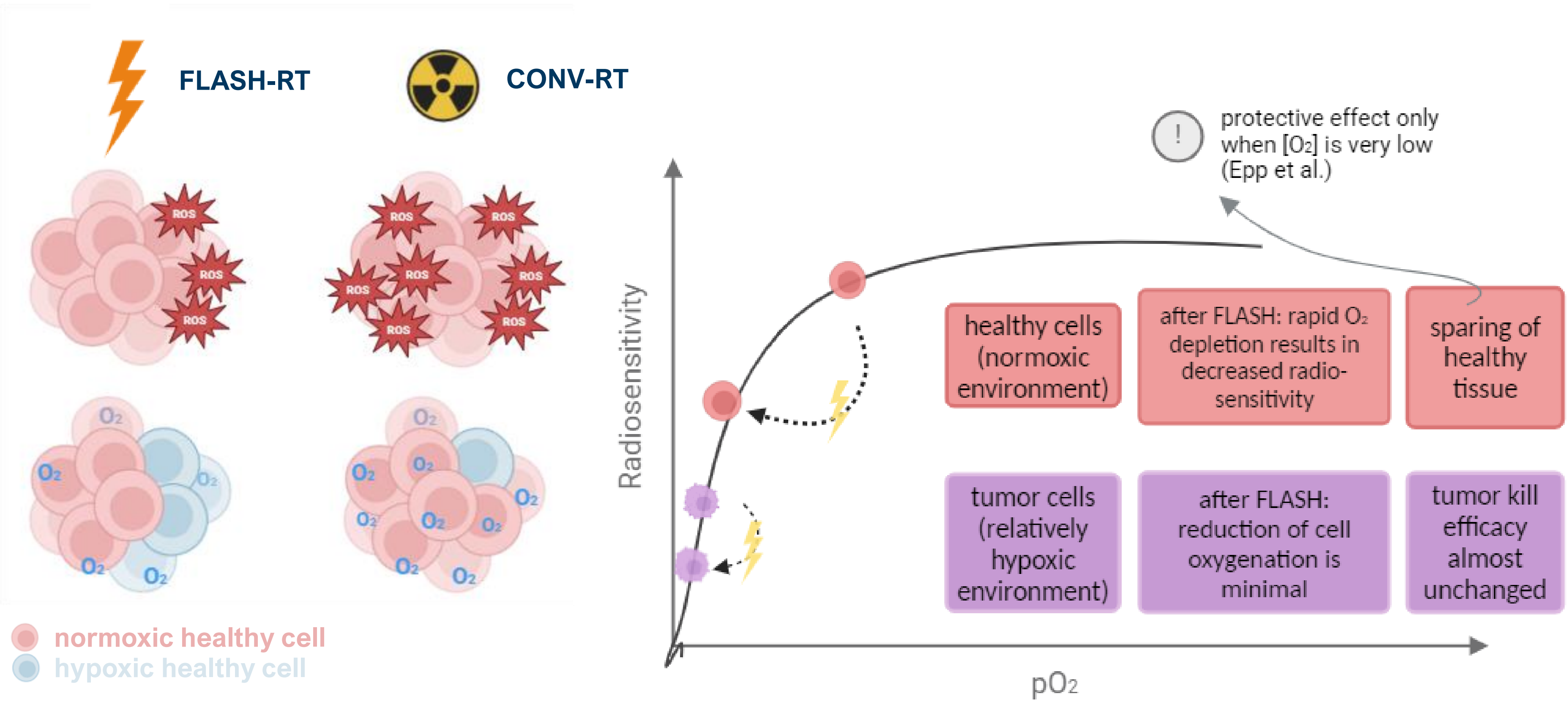


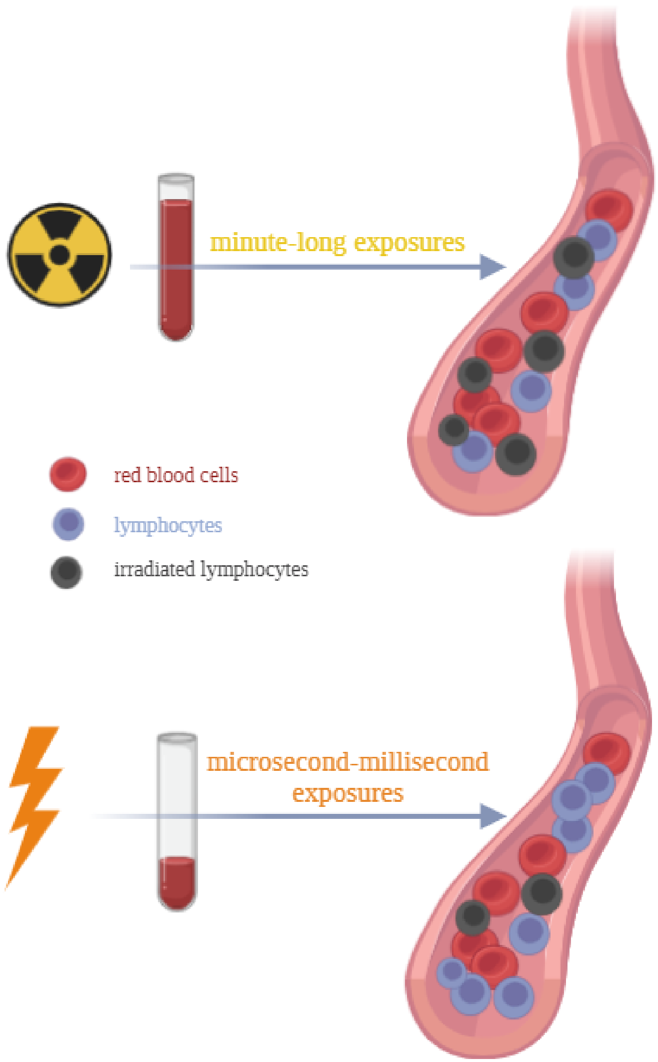
Fig. 16. Potential contributions to the sparing effect of FLASH in healthy cells, from the depletion of O_2 and reduction in ROS levels.

Potential mechanisms for the FLASH effect

Circulation immune cell protection hypothesis [1, 27, 30-31]

larger volume of irradiated blood
↓
exposure of lymphocytes to radiation
↓
compromised immune system

reduced volume of irradiated blood
↓
minimal exposure of lymphocytes to radiation
↓
preserved immune system



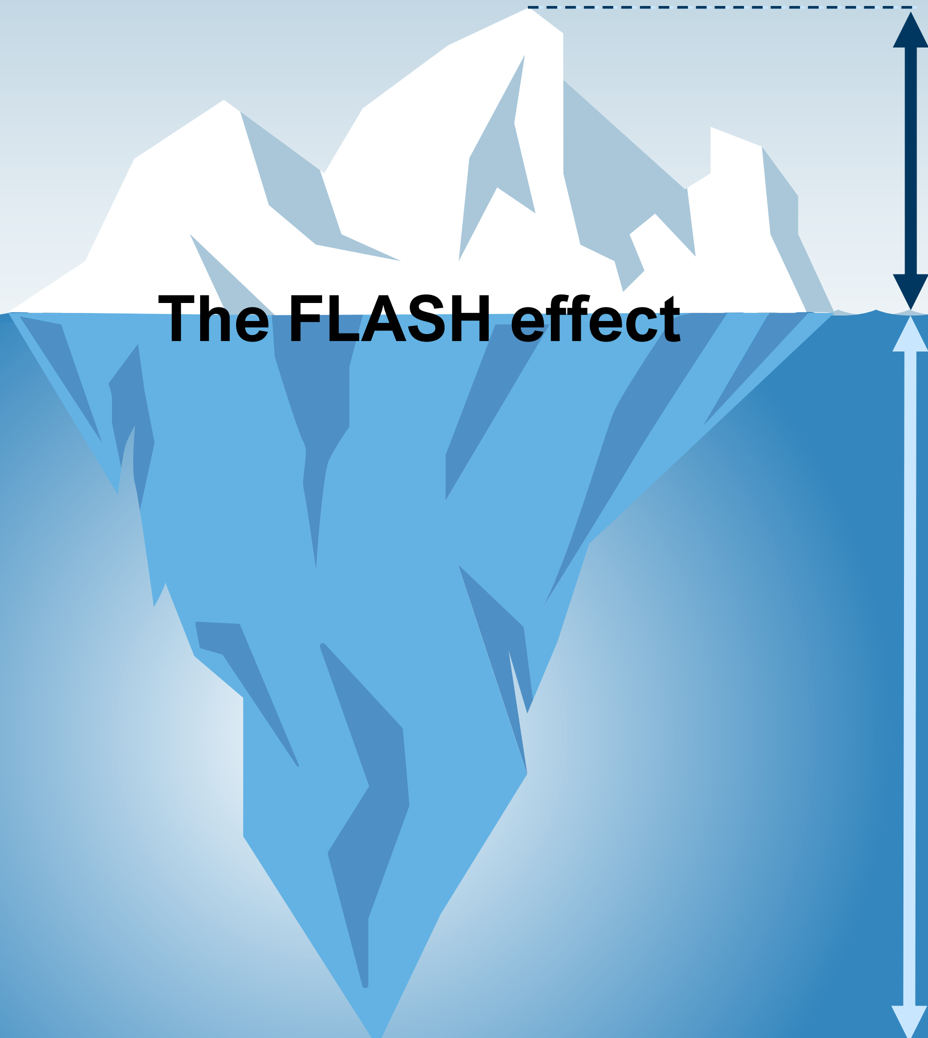
However… studies on heart and abdomen of mice exhibited unexpected results [30-31], and therefore **further exploration and validation** of this theory is necessary.

Cytokines' suppression

FLASH-RT has been observed to **reduce** the expression of **TGF-β**, which is a possible explanation of protective effect in healthy cells [32].

Fig. 17. FLASH-RT short irradiation time allows for less blood volume to be irradiated, thus resulting in increased sparing of immune cells when compared to CONV-RT.

Potential mechanisms for the FLASH effect



- **O_2 depletion hypothesis**
- **circulation immune cell protection hypothesis**

- metabolism of peroxidised compounds & Fenton chemistry [33]
- recombination of free radicals [34]
- DNA integrity hypothesis [34]
- mitochondrial changes & irradiation of structural targets (lipids, proteins) [1,27-28]
- preservation of the stem-cell niche [28]

Some Big Questions… [35-37]

- What are the underlying mechanisms for the FLASH effect?
- What are the conditions to induce FLASH upon tissue irradiation?
- Can the FLASH effect be induced in combined modality therapy?
- How can we generalise the results for clinical and pre-clinical studies?

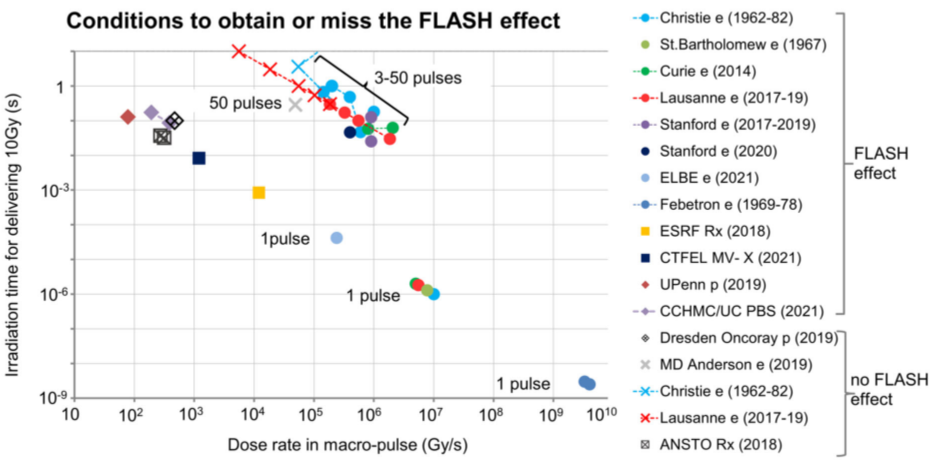


Fig. 18. A summary of the temporal dosimetric characteristics of various published experimental data on in-vivo FLASH experiments [36].

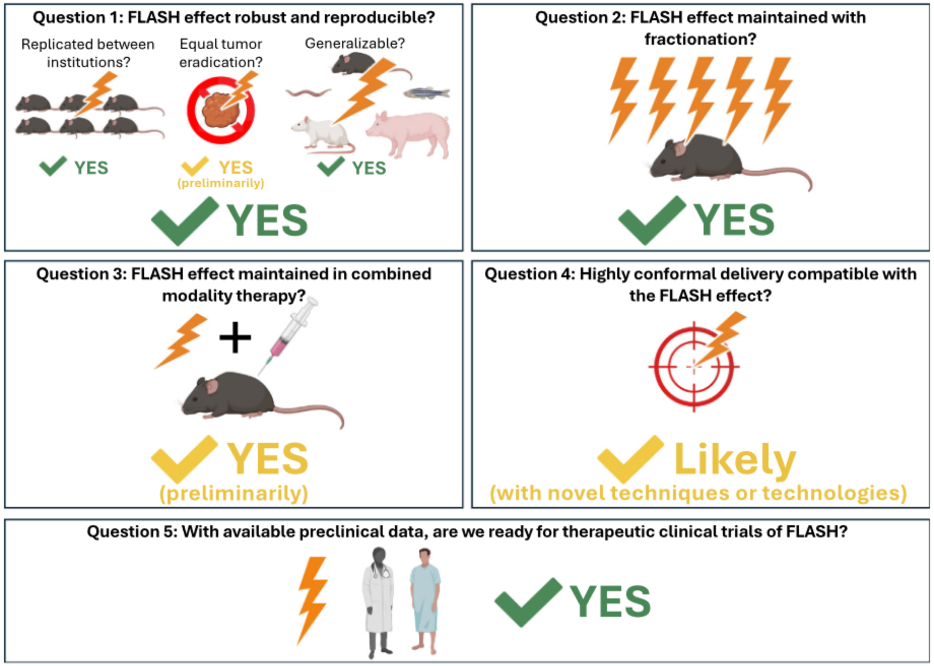


Fig. 19. Answers to critical translational questions, posed at Loo B W, *et al.* (2024) *Semin Radiat Oncol* **34**:351-364, based on existing preclinical data [37].

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Thank you for your attention!

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https://cerncourier.com/a/how-to-democratise-radiation-therapy/ (19.10.24.)