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FLASH Radiation Therapy: A Review on the Ultra-high Dose Rate Paradigm of Radiotherapy

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Background: What is FLASH Radiation Therapy

FLASH Radiotherapy (**FLASH-RT**) is a new paradigm of radiation therapy (RT), featuring **ultra-high Dose rate** (UHDR) radiation of tumours, of **Dose rate** ($\dot{D}$) **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 of the anti-tumour effect of the radiation* [1]. The event was originally **observed in 1959** [2] and was brought into the foreground of modern cancer treatment research by **Favaudon *et al*.** [3] in **2014**; ever since FLASH has been an active research field.

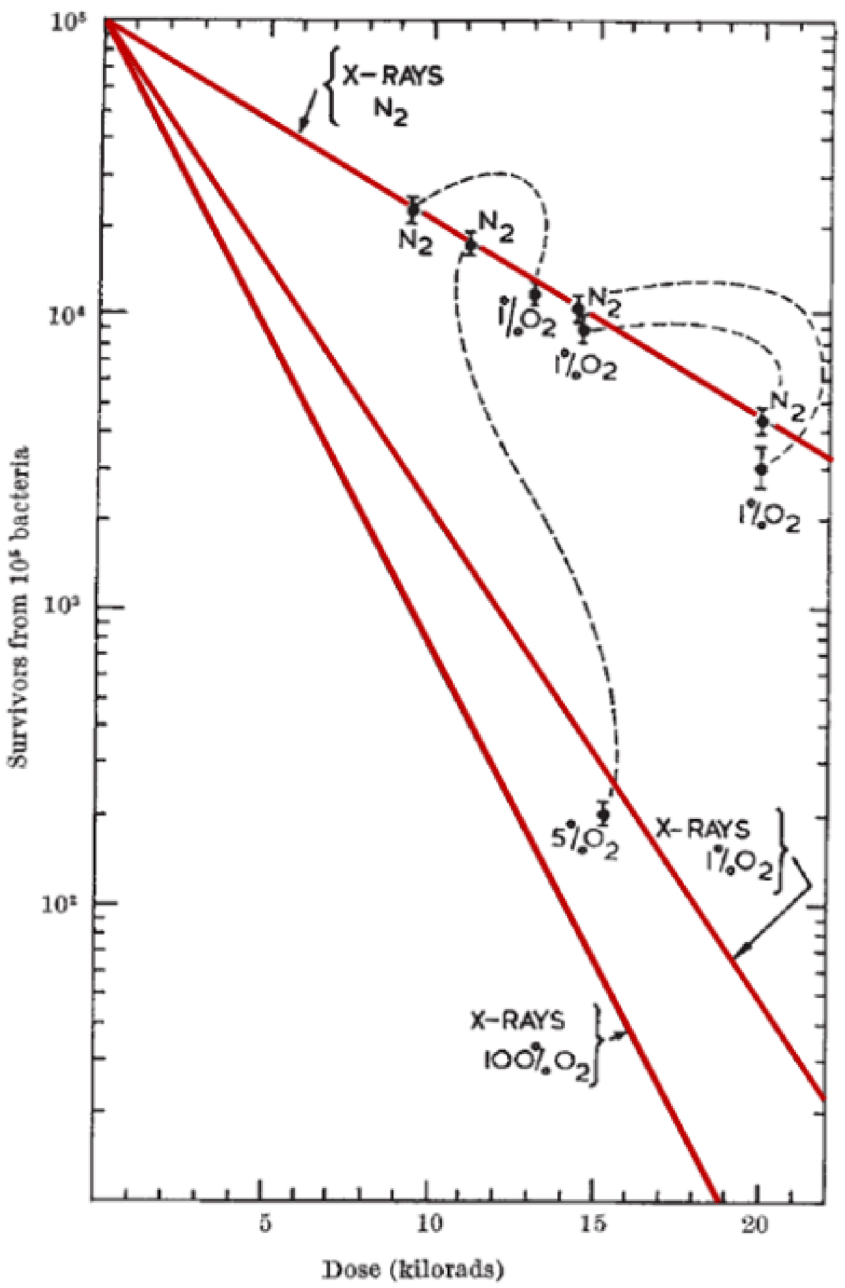


Fig. 1. Survival curves for X-Ray irradiation of *Serratia marcescens* with $\dot{D} \sim 5 - 10$ krad μs^{-1} [2].

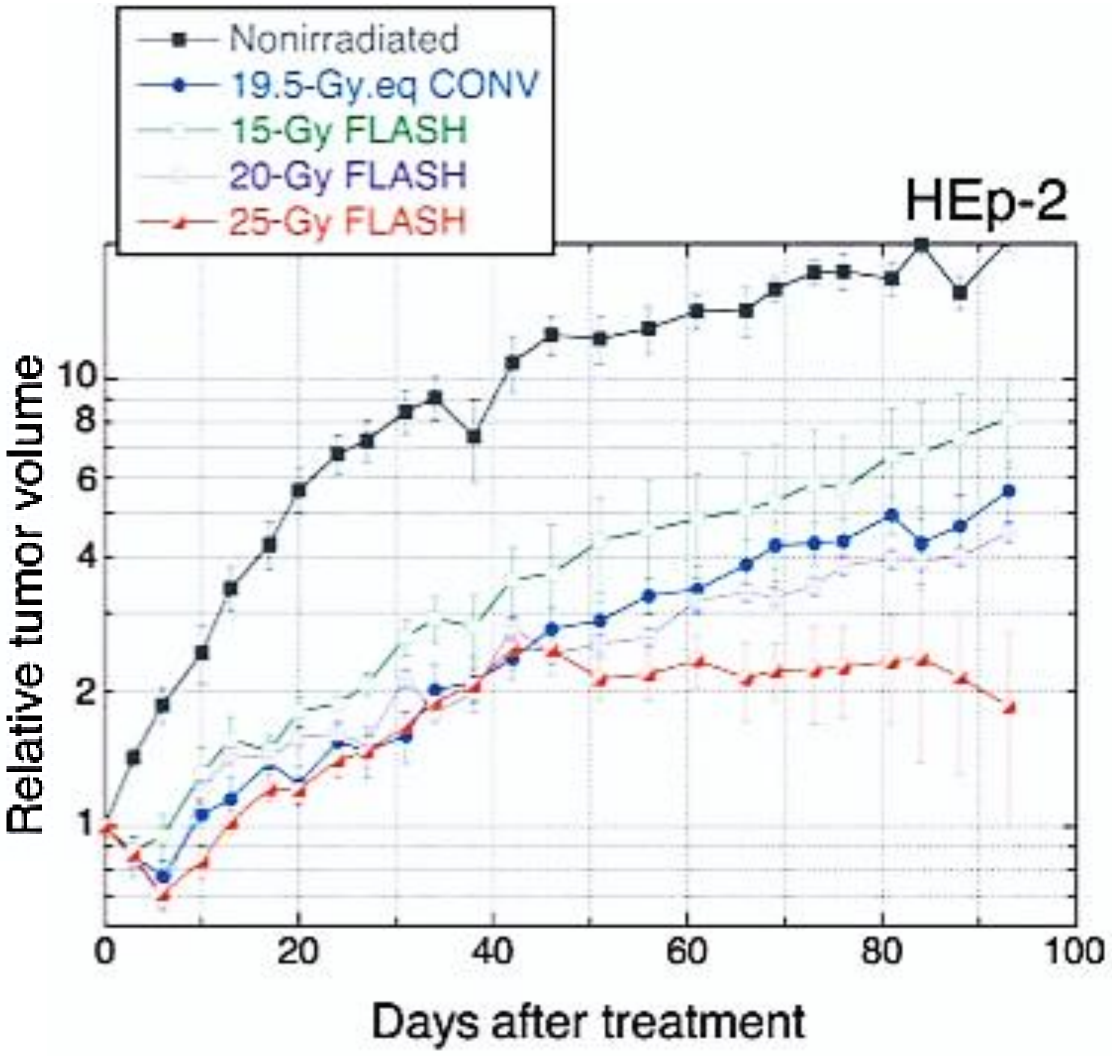


Fig. 2. Relative tumour volume time-evolution of HEp-2 (*n* = 40) tumour xenografts in mouse model of lung fibrosis, after conventional (^{137}Cs γ-Rays, $\dot{D} = 0.03$ Gy s^{-1}) and FLASH (4.5 MeV *e*-, $\dot{D} = 60$ Gy s^{-1}) irradiation [3].

Methods: Modifications of p^+ CONV-RT settings for FLASH

Modifications for p^+ FLASH-RT aim at:
- **higher** proton fluence (F_p) and
- **higher** beam current (I_{beam}),

while maintaining:
- the sparing of the healthy tissue of the **Bragg peak**
- accurately controlled **dose distribution to the tumour and surrounding healthy tissue** (Pencil Beam Scanning and positioning of the Bragg peak/formation of the SOBP) [4 - 7]

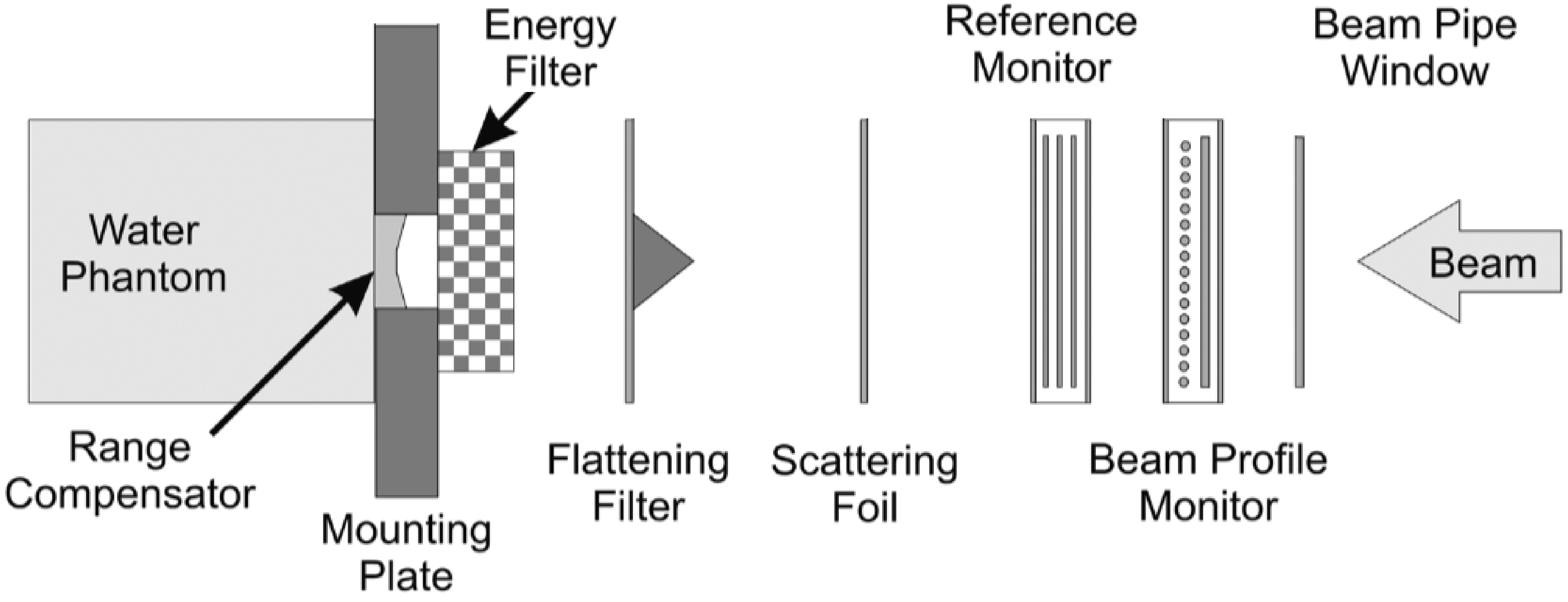


Fig. 3. Schematic of the beamline modifications to enable FLASH conditions, for the HITACHI synchrotron of the Texas MD Anderson Cancer Center [4].

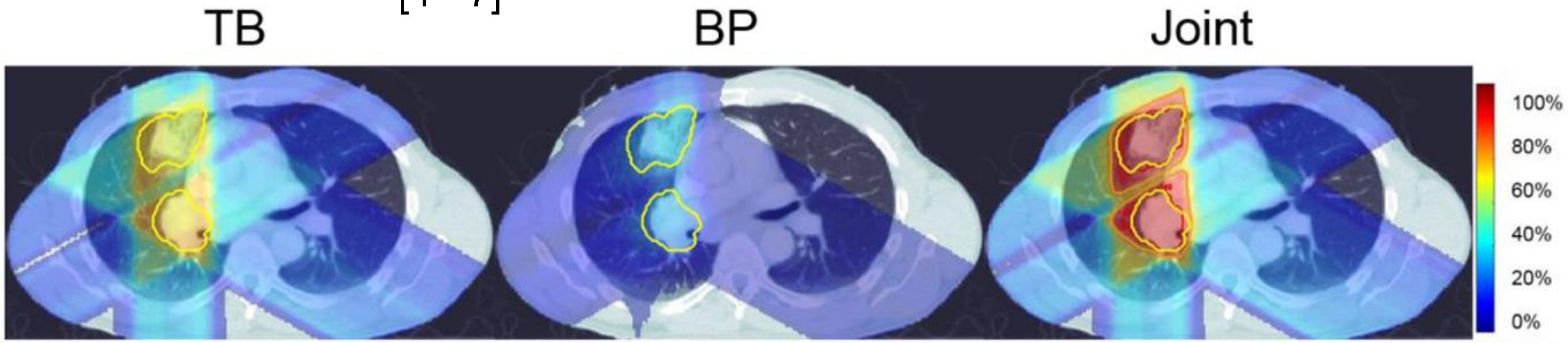


Fig 4. The **Simultaneous Dose and Dose Rate Optimisation** method, employs **UHDR transmission beams** (TB) of p^+ (Bragg peak outside of the body) to irradiate the **tumour boundary**, and **non-UHDR p^+ to form Bragg Peaks** (BP) **inside the tumours** [7].

Methods: Novel systems for FLASH-RT

Pluridirectional High-energy Agile Scanning Electronic Radiotherapy

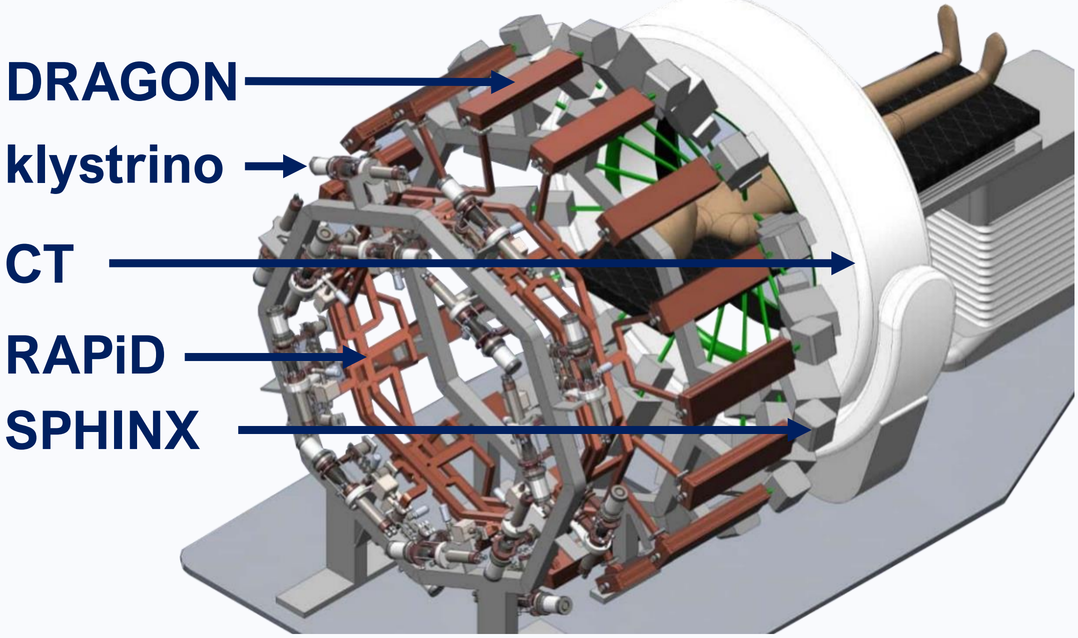


Fig. 5. PHASER is a **compact** system for Bremsstrahlung-produced X-Rays; a network of 16 **klystrinos** is connected to 16 **LINACs** (DRAGONs), of cell-independent RF power distribution, followed by a system (SPHINX) of **scanning magnets**, Bremsstrahlung **targets** and **collimators**. The geometry shares the same isocentre with a **CT scanner** ring [8 - 9].

Very High-Energy Electron (**VHEE**) beams [10 - 12]

- **$T_{\mathrm{VHEE}} \sim$ 50 - 250 MeV**
- **increased depth** penetration and **indifference to medium inhomogeneities**
- economical modifications of existing *e*- LINACs
- 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

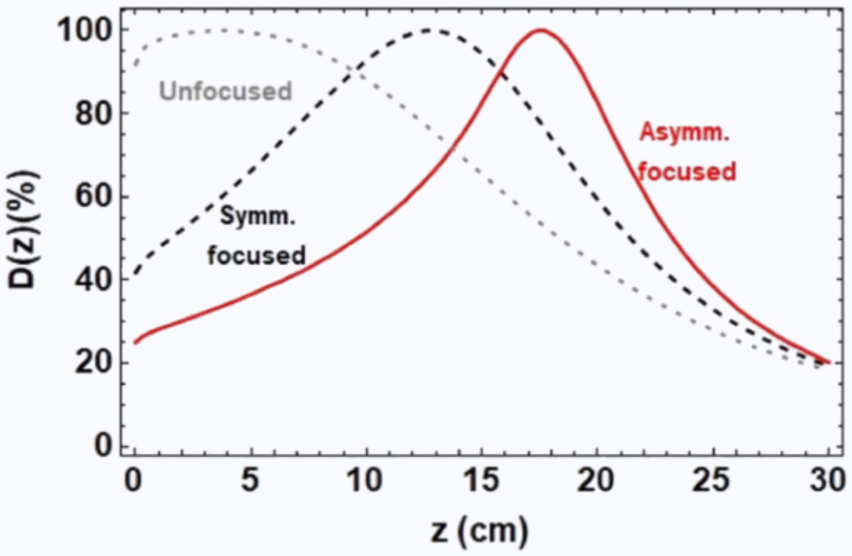


Fig. 6. Monte-Carlo simulations for the normalised Bragg curves of 250 MeV *e*- of different types of beam focusing. [10].

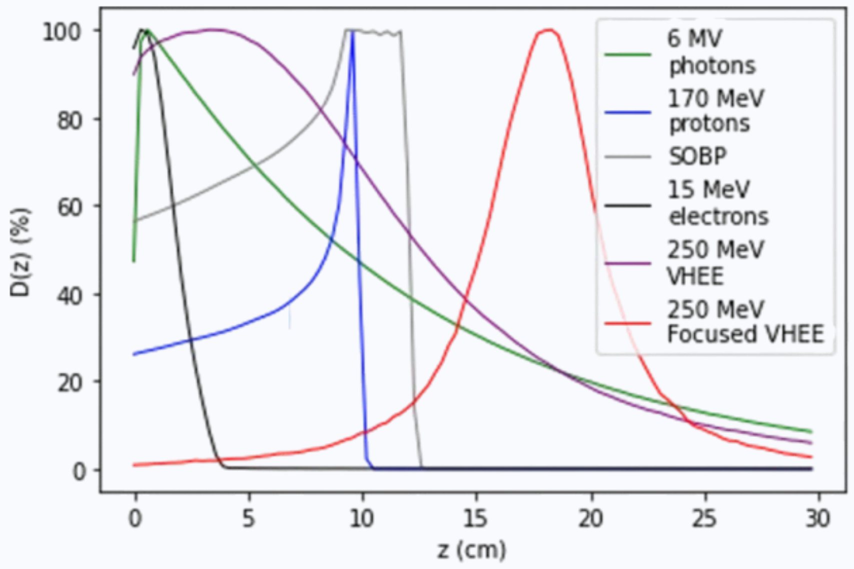


Fig. 7. Monte-Carlo simulations for the normalised Bragg curves of various RT modalities (σ = 6.7 mm, $n \sim 10^6$, $n_\gamma \sim 5 \times 10^5$) [11].

Results: Widely supported theories on the FLASH effect

FLASH effect: complex and unclear → importance of exploring the specific mechanism behind it
(physicochemical and biological)

1. Oxygen Depletion hypothesis

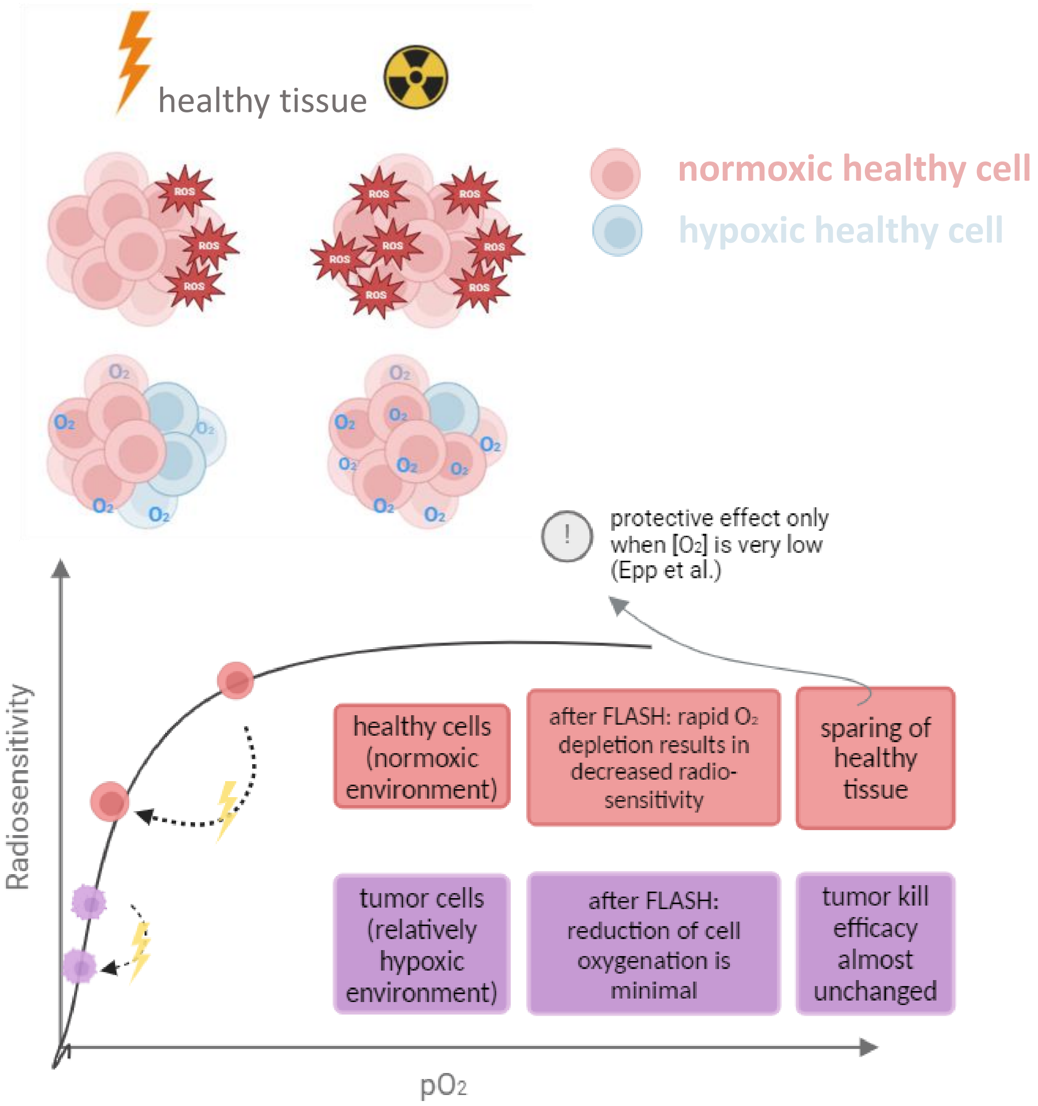


Fig. 8. O_2 depletion's and reduced ROS levels' possible contribution to the sparing effect of FLASH in healthy cells [13,14,16]

2. Metabolism of peroxidised compounds & Fenton chemistry

FLASH effect attributed to the **different metabolism** of **peroxidised compounds** and labile **iron** content between tumor & normal cells [22]

maintain the metabolic process → lower peroxidised compounds & iron content } **less susceptible** to **damage** from Fenton chemistry

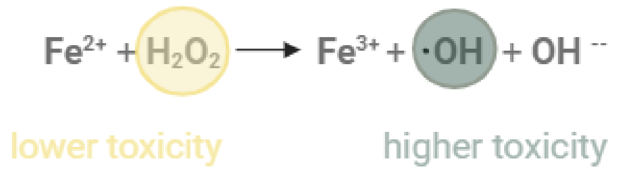


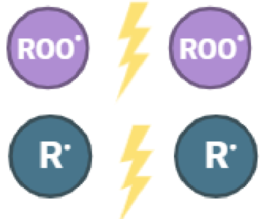
Fig. 9. Model of peroxidised compound metabolism and Fenton chemistry in FLASH [15, 22].

3. Free radical recombination

Labarbe *et al*. [23]: theoretical model based on the formation & decay dynamics of ROS (**ROO·** & **R·**)

for **ROO·** & **R·** is known that:

- ✓ **interaction** with **DNA** & induction of chromosomal breaks, aneuploidy, mutation → **cell death**
- ✓ **reaction** with unsaturated **lipids** to generate **ROOH**



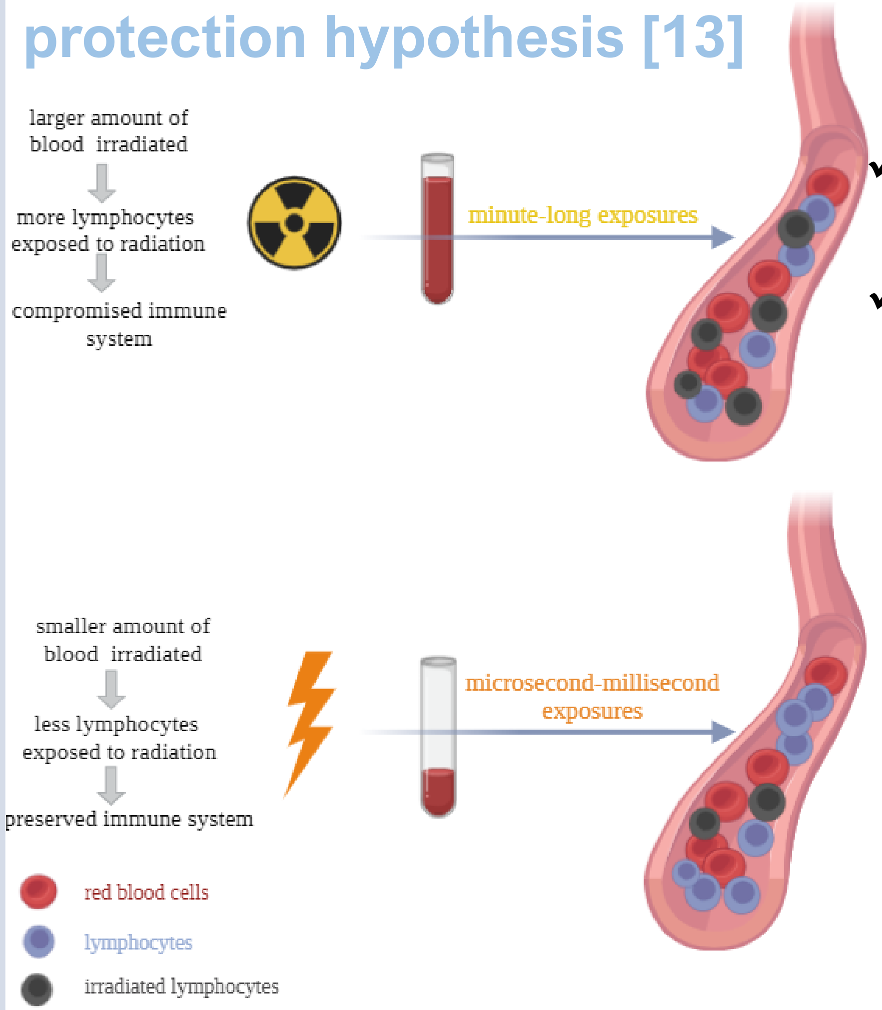
in the framework of Labarbe: rapidly elevated [ROO·] & [R·] due to UHDR

! **ROO·** & **R·** can undergo **self-recombination**

→ increased proportion of recombination reactions & subsequently cell damage is reduced

Results: Widely supported theories on the FLASH effect

4. Circulating immune cell protection hypothesis [13]



Partial irradiation of blood volume

- ✓ found through modeling & computation
- ✓ studies on heart and abdomen of mice exhibited unexpected results [17,18]

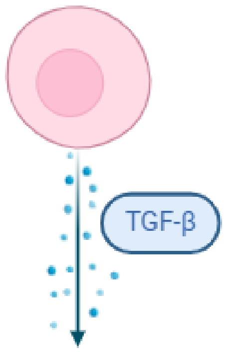
↓

further exploration and validation

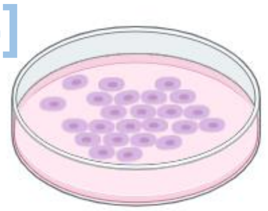
Fig. 10. Effect of FLASH-RT on immune function (left) & alteration in the expression of certain cytokines as a possible contributor to the sparing effect (down)

Cytokines & FLASH [19]

- ✓ FLASH-RT seems to **reduce** the **expression of TGF-β** in normal tissues (important role in regulating immune system and tumor growth)
- ✓ possible explanation of protective effect in healthy cells



5. Stem cell niche preservation [14]



reduced stem cell senescence

- ✓ preserved regenerative capacity
- ✓ reduced inflammatory cytokines which lead to tissue damage

lung protection

- ✓ decreased lung injury by reducing stem cells by 50% compared to CONV-RT [21]

maintanance of anti-tumor effect

6. DNA integrity hypothesis

Shi et al. (intestinal crypts of mice) [22]

- ✓ **minimization** of the probability of **DNA breakage**
- ✓ **maintenance** of **genomic stability**
- ✓ reduction of cGAS-STING pathway signalling activation

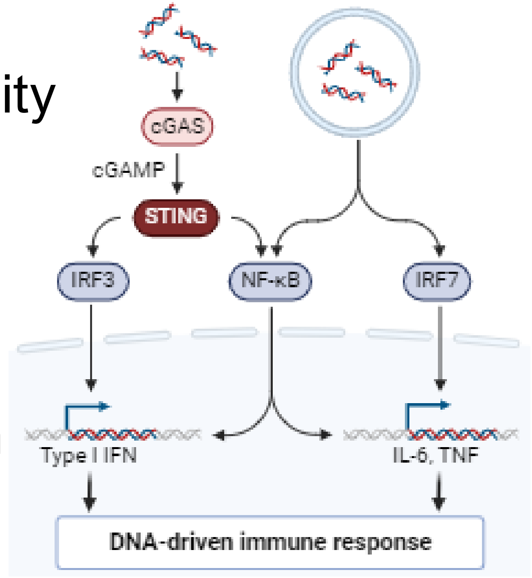


Fig. 11. DNA integrity hypothesis: minimising DNA breaks and limiting pathway signalling activation

Results: Noteworthy Clinical Trials

Proton trials

Mascia *et al*. (2023) - FAST-01 human trial [24]

- Varian ProBeam, 51 - 61 Gy s^{-1}
- 8/12 reported **partial or total pain relief**

Kyle Kim *et al*. (2024) – Mice [26]

- Proteus Plus Cyclotron, 230 MeV, 122 Gy s^{-1}
- **Better preservation** of cardiac function and **reduced inflammatory response**

Zhang *et al*. (2023) – Mice [18]

- 224MeV proton beam,112 - 128 Gy s^{-1}
- **Decreased survival** for irradiation in abdominal region

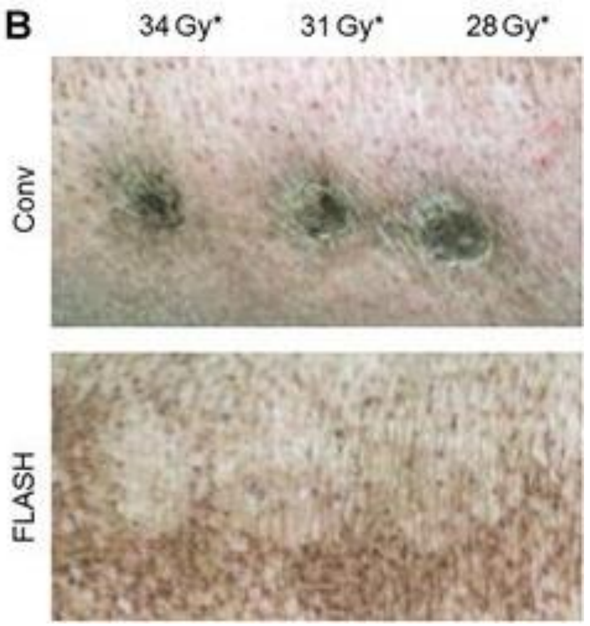


Fig. 13. Comparison between CONV-RT and FLASH-RT on mini pig skin [27].

Fig. 12. FLASH-RT on cutaneous lymphoma - First human trial [25].

Electron trials

Bourhis *et al*. (2019) – First human trial [25]

- 5.6 MeV LINAC 166 Gy s^{-1}
- **Complete tumour response**, minimal side effects

Vozenin *et al*. (2019) - Mini-pig and Cats [27]

- 4.5 MeV Kinetron & 6 MeV Oriatron, 300 Gy s^{-1}
- Minimal skin damage at high doses, durable **tumour control** (84% survival rate in cats).

Conclusions: Challenges in the Technical and Clinical sectors

[28 – 33]

Challenges for Clinical Practice

- **lack of clinical data and long-term effect observations**, which prevent regulatory approval for FLASH-RT,
- **incomplete understanding of the underlying mechanisms** of the FLASH effect,
- **lack of models for** accurate **Dosimetry calculation and delivery of UHDR radiation** to patients,
- **unmapped variation of response** of UHDR radiation in different types of tissue and cancer, depending on the total absorbed Dose, $\dot{D}$ and characteristics of radiation (eg. density of ionisations),
- **high cost of specialised UHDR irradiation facilities**.

Technological Challenges

- UHDR beams require an **increase in the mean beam current of $\sim 10^2$**, compared to CONV-RT,
- modification of p^+ systems for **sub-second SOBP-building energy changing of the beam** is quite technologically challenging,
- production of **UHDR kVp** and **High-Energy X-Rays** from interaction of e^- beams with **Bremsstrahlung conversion targets** requires **significantly larger beam current** than currently available in compact, room-temperature LINACs,
- increased requirements for **clinical dosimetry** systems in terms of **$\dot{D}$-dependency**, **spatial and time resolution** and **dynamic range**.

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