

VHEE FLASH RADIOTHERAPY: CUTTING-EDGE RESEARCH AT CLEAR, THE CERN LINEAR ELECTRON ACCELERATOR FOR RESEARCH

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Abstract

With the availability of cost-effective and compact electron LINACs operating in the 100-200 MeV energy range, there has been a growing interest in using Very High Energy Electron (VHEE) radiotherapy (RT) for cancer treatment. A particularly intriguing aspect is the Ultra High Dose Rate (UHDR) or FLASH dose regime, where healthy tissues are spared while tumor control is maintained, compared to Conventional Dose Rate (CDR). VHEE beams are well-suited for FLASH RT, given their deep penetration and high beam current, making them effective for treating large, deep-seated tumors. The CLEAR (CERN Linear Electron Accelerator for Research) facility has been at the forefront of exploring VHEE and FLASH RT, conducting numerous unique experiments in collaboration with multidisciplinary user groups. These groups cover dosimetric, chemical, and biological studies. This paper introduces recent measurements, techniques, and methods used to observe the FLASH effect at CLEAR.

INTRODUCTION

Radiotherapy at Ultra-High Dose Rate (UHDR), also known as FLASH radiotherapy, is currently seen as one of the most promising innovations in radiation oncology. This “FLASH effect” reduces inflammation and protects various healthy cell tissues without compromising tumor control [1]. Surprisingly, the effect is intensified in hypoxic radioresistant tumors, further broadening radiotherapy’s therapeutic window and offering new opportunities for cancer cure.

The effect appears beam-agnostic and has been seen with low energy electrons (4-10 MeV) [2], photons [3] and protons [4]. Research now focuses on how ultra-short radiation delivery influences early molecular events, such as water radiolysis and radical formation. These early changes may shape the biological outcomes of irradiation.

Recent studies explored these early effects leveraging three different radiation sources: the Lausanne Hospital electron machine eRT6/Oriatron with Intermediate Energy Electrons (IEE), standard X-rays, and the CERN Linear Electron Accelerator for Research (CLEAR) with Very High Energy Electrons (VHEE). The studies consist of irradiation of water, plasmid DNA, and Zebrafish Embryos (ZFE). Findings suggest that the timing of radiation delivery, particularly picosecond and microsecond-scale pulses, is key to preserving biological integrity. Understanding these tem-

poral dynamics may unlock the full therapeutic potential of FLASH. This paper summarises the results obtained at CLEAR with ZFE.

SETUP & METHODS

The CLEAR test facility [5, 6] offers a large range of electron beams with customisable parameters, as detailed in Table 1. An overview of the time structure and charge parameters achievable at CLEAR is shown in Fig. 1, along with a schematic layout of the beamline in Fig. 2.

Table 1: CLEAR Beam Parameters in 2025

Parameter	Value
Beam Energy	30 – 220 MeV
Beam Energy Spread	< 0.2% rms (< 1 MeV FWHM)
Bunch length RMS	0.1 – 10 ps
Bunch frequency	1.5 or 3.0 GHz
Bunch charge	0.005 – 1.6 nC
Norm. emittance	1 – 20 μm
Bunches per pulse	1 – 150
Max. pulse charge	87 nC
Repetition rate	0.8333 – 10 Hz

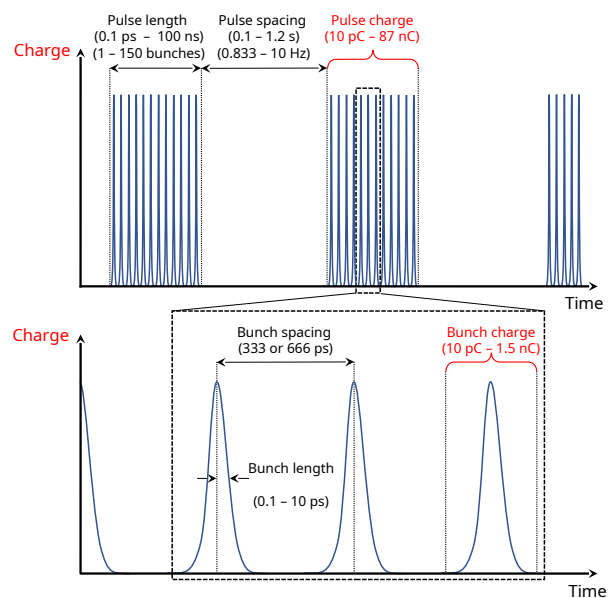


Figure 1: CLEAR beam time structure and charge parameters at the end of the beam line in 2025.

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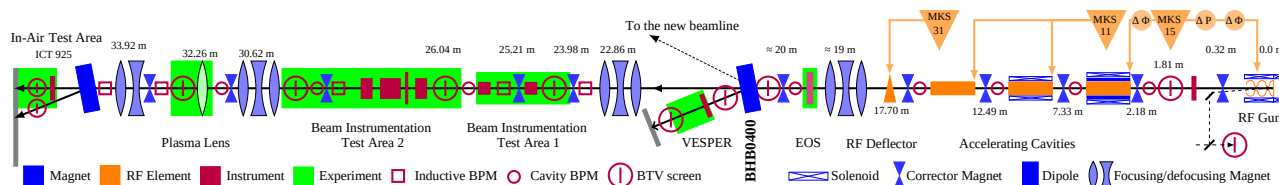


Figure 2: CLEAR beam line in 2025. Note that the electron beam travels from right to left.

For these studies, the irradiation of samples were done at CLEAR in the In-Air Test Area with the C-Robot [7–9]. Developed by the CLEAR team, this robotic system was engineered to allow the fast irradiation of a wide array of samples for medical purposes. It consists of a grabber and three linear stages for precise displacement along the X, Y, and Z axes. It carries two tanks: one for the storage of the samples and one for the irradiation of the samples. The water temperature in both tanks can be set to $(28 \pm 0.1)^\circ\text{C}$, with temperature maintained by dedicated heating probes and pumps. This robotic system enables the manipulation and irradiation of up to 32 distinct 3D-printed holders with an accuracy in position of $50\ \mu\text{m}$, with each holder able to accommodate a PCR (polymerase chain reaction) tube containing samples. A picture of a 3D printed holder with the PCR used for irradiation is shown in Fig. 3.



Figure 3: Picture of the 3D printed holder with a PCR tube and a radiochromic film. Note that the ZFE are kept in the cap of the tube for the irradiation.

To accurately predict the target dose, two YAG scintillating screens were used: a $50\ \mu\text{m}$ thick screen installed in air before the irradiation water tank (the in-air YAG) and a $200\ \mu\text{m}$ thick screen that can be moved by the C-Robot in water at the location of the sample irradiation (the in-water YAG). A dedicated tool was used to compute the predicted delivered dose from the charge density at the location of the samples. The in-air YAG was used for online dosimetry and remains in place during the irradiation of the samples. A picture of the setup is shown in Fig. 4.

Additionally, two EBT-XD radiochromic films were installed on each sample holder (one in front of the sample

and one behind) to measure the absolute delivered dose. In order to ensure the required precision, the films are scanned and analysed 24 hours after the irradiation [10]. These radiochromic films were calibrated using conventional treatment machines at the University Hospital of Lausanne (CHUV) and at the University Hospitals of Geneva (HUG).

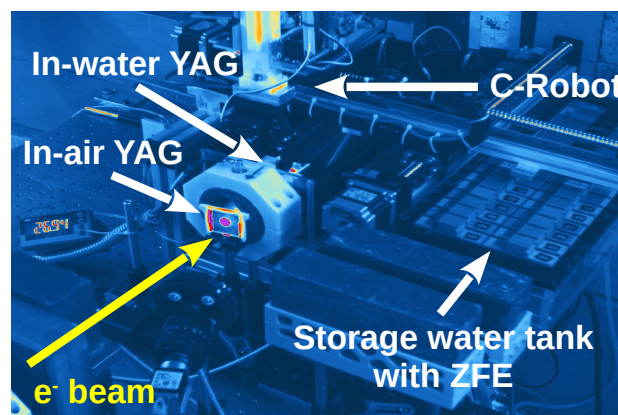


Figure 4: Picture of the CLEAR setup for the irradiation.

Two distinct dose rates were used for this study: a Conventional Dose Rate (CDR) of $0.125 - 0.2\ \text{Gy/s}$ and an Ultra High Dose Rate (UHDR) of $10^8 - 10^{11}\ \text{Gy/s}$. For CDR irradiation the target dose was accumulated using several pulses of a single, $3.0\ \text{ps}$ bunch with a repetition rate of $10\ \text{Hz}$. This corresponded to an irradiation of $20\ \text{mGy}$ in $3\ \text{ps}$ sent every $0.1\ \text{s}$. The UHDR irradiations were performed with a single pulse of 6 to 40, $3.0\ \text{ps}$ bunches with a bunch separation of $666\ \text{ps}$, corresponding to an irradiation of $333\ \text{mGy}$ in $3\ \text{ps}$ sent every $666\ \text{ps}$.

For both dose rates, total doses of 8 to 12 Gy were delivered to the samples. The detailed beam parameters used for the irradiation are listed in Table 2.

ZEBRAFISH EMBRYO IRRADIATION

Zebrafish were bred to produce embryos at the Fish Facility PTZ (Plateau Technique pour Zebrafish, CHUV/UNIL, Lausanne, Switzerland) or at the University of Geneva (CMU, UNIGE, Switzerland).

According to Swiss and European ethics regulations, ZFE before 5 days of development can be used as biodosimeters, with no ethical approval required for experiments. The irradiation performed at CLEAR took place 4 hours post fertilization (4 hpf). Each PCR tubes of $200\ \mu\text{L}$, containing 8 ZFE were stored and irradiated in 28°C egg water. The

Table 2: Beam parameters used for ZFE irradiation

Modality	CDR		UHDR	
Dose [Gy]	8	10	8	10
Beam Charge [nC]	8	10	8	10
Beam Energy [MeV]	200	200	200	200
Bunch per Pulse	1	1	24	30
Number of Pulses	400	500	1	1
Pulse Duration [ns]	0.003	0.003	7.66	9.66
Repetition Rate [Hz]	10	10	0.833	0.833
Pulse Duration [ns]	0.003	0.003	7.66	9.66
Total Duration of Irradiation [s]	40	50	7.66×10^{-9}	9.66×10^{-9}
Mean Dose Rate [Gy/s]	0.200	0.200	1.04×10^9	1.04×10^9
Instantaneous Dose Rate [Gy/s]	6.67×10^9	6.67×10^9	1.09×10^{11}	1.12×10^{11}

irradiation of all the samples of one batch were performed in less than 40 minutes to ensure the ZFE were all in the same developmental stage.

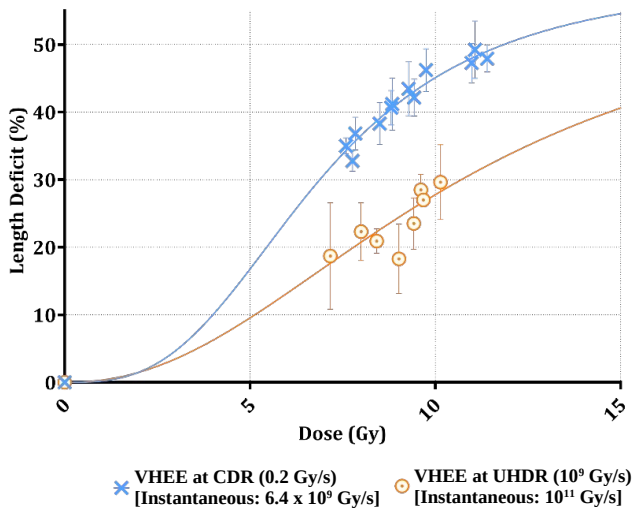


Figure 5: The Length Deficit of ZFE irradiated at CLEAR with VHEE at CDR and UHDR.

Radiation-induced alterations in ZFE length were measured with microscopic imaging 5 days post-fertilization following embryo fixation. The ZFE length deficit is defined as:

$$\%ZFELengthDeficit = (1 - \frac{l_{RT}}{\langle l_{CTRL} \rangle}) * 100$$

with l_{RT} the length of the irradiated embryo and $\langle l_{CTRL} \rangle$ the average length of the non-irradiated control embryos. The length deficits for these studies are shown in Fig. 5.

A clear difference in the length deficit is observed between the ZFE irradiations undertaken at CDR and at UHDR. The ZFE irradiated at UHDR are on average around 20 % longer than the ZFE irradiated at CDR, showing a dose-rate dependent sparing of ZFE development with VHEE irradiations.

These results show that living organisms are sensitive to variations in the electron beam intensity. At CLEAR, high

intensity bunches of electrons (333 mGy/bunch) at UHDR (10^9 Gy/s average dose rate and 10^{11} Gy/s instantaneous dose rate) spares ZFE morphogenesis while lower intensity bunches (20 mGy/bunch) at CDR (0.2 Gy/s average dose rate and 6.7×10^9 Gy/s instantaneous dose rate) are more toxic to ZFE. Recent observations also show that the sparing of ZFE is not likely to be enhanced any further at higher intensity and dose rate, suggesting that the benefits of normal tissue protection reach a plateau above 10^6 Gy/s.

CONCLUSIONS

This study provides the first direct evidence that living organisms show sensitivity to changes in beam intensity with VHEE, specifically demonstrating that compressing the beam delivery time can significantly influence the biological response. These findings offer a solid, evidence-based foundation for guiding the development of next-generation FLASH radiotherapy systems. Importantly, the study highlights that the high intensities and dose rates achievable with FLASH could allow for increased total radiation doses, enhancing the therapeutic window by sparing normal tissues while maintaining tumoricidal efficacy. This positions VHEE beams as particularly promising candidates for the clinical implementation of FLASH radiotherapy, offering a potent combination of precision, biological selectivity, and technological compatibility for future cancer treatment advancements.

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