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MEDICAL ACTIVITIES IN CLEAR: STUDIES TOWARDS RADIOTHERAPY USING VERY HIGH ENERGY ELECTRONS (VHEE) IN THE FLASH REGIME

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Abstract

Given the present availability of high-gradient accelerator technology for compact and cost-effective electron linacs in the 100-200 MeV energy range, the interest for Very High Energy Electron (VHEE) radiotherapy (RT) for cancer treatment recently reached an all-time high. Particular significance is assumed by the Ultra-High Dose Rate (UHDR) regime where the so-called FLASH biological effect takes place, in which cancer cells are damaged while healthy tissue is largely spared. VHEE beams from linacs are especially well adapted for FLASH RT, given their penetration depth and the high beam current needed to treat large deep-seated tumours. In recent years, several multidisciplinary user groups carried out a number of studies on VHEE and FLASH RT issues using the CERN Linear Accelerator for Research (CLEAR) user facility, in close collaboration with the local operation team. In this paper, we give an overview of such activities and describe the main results of chemical and biological tests aimed at clarifying the damage mechanisms at the root of the FLASH effect and the relevant beam parameters needed to achieve it. We also describe the dedicated systems and methods developed and used in CLEAR for these activities, focusing on recent advances in the crucial aspects of uniform beam delivery and high dose rate real-time dosimetry.

INTRODUCTION

The CERN Linear Electron Accelerator for Research (CLEAR) is a 200 MeV electron linac followed by an experimental beam line, operated at CERN as a user facility [1]. It serves a wide and diverse scientific community covering many activities, including development of instruments and components for existing and future accelerators and tests of novel concepts as plasma and THz acceleration. In recent years, the investigation of medical applications of electron beams with energies above 100 MeV has become one of its main activities. Over the past years, the question of whether ultra-high-dose rate (UHDR) beams might offer a new modality for cancer treatment is one of the most discussed subjects in modern radiotherapy (RT). The so-called FLASH RT mode, in which the total therapeutic dose is delivered at UHDR in a fraction of a second, has been shown in several experiments to significantly increase the differential response between healthy and tumour tissue [2–4]. Very-high-energy electron (VHEE) beams with energies above 100 MeV are promising candidates for FLASH RT due to their favorable dose distributions and accessibility of ultrahigh dose rates. Linear electron accelerators can easily provide the high intensity beams needed for UHDR, and have the additional advantage, thanks to recent advances in high-gradient technology, of being rather compact and relatively cheap. The CLEAR electron beam has a wide parameter range, offering great flexibility for experiments [5–8]. In particular, CLEAR beam energy range (30-220 MeV) and high charge per pulse (up to 75 nC) have made it so far the only facility widely available to users for complete VHEE/UHDR studies. Beam parameters are shown in Table 1. A diagram of the beamline is shown in Fig. 1.

Table 1: Updated List of CLEAR Beam Parameters

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 – 3 nC
Norm. emittance	1 – 20 μm
Bunches per pulse	1 – 150
Max. pulse charge	75 nC
Repetition rate	0.8333 – 10 Hz

METHODS, DOSIMETRY AND BEAM DELIVERY TECHNIQUES

The CLEAR team has developed in the last years methods and data analysis techniques dedicated to VHEE and FLASH studies, including detailed procedures for passive dosimetry techniques, sample handling, and beam delivery. It also explored new methods for real-time dosimetry in UHDR conditions.

Radiochromic films (RCFs) change colour macroscopically due to polymerisation caused by ionising radiation. The colour change is related to the accumulated dose. After irradiation, the films are optically scanned and the resulting image is processed to determine the dose received, using an experimentally measured calibration curve. They are

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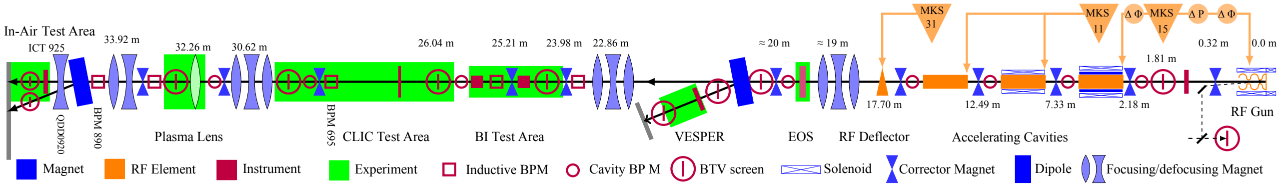

Figure 1: CLEAR beam line in 2022. Notice that the electron beam travels from right to left [6].

reliable, easy to procure and use, and allow for excellent two-dimensional spatial resolution. Even more importantly, their dose-rate independent response is fundamental to assess delivered dose in High Dose Rate (HDR) experiments. Radiochromic films have therefore been chosen as the main dosimetry tool in CLEAR and have been used routinely since a few years for most medical irradiation studies. Detailed procedures for handling and exploiting the films were developed and validated in CLEAR in order to ensure a reliable dosimetry, and are described in more detailed in [9]. However, the fact that RCFs require a delay of about 24 hours for reliable reading introduces a limitation on the number of measurements which can be reasonably managed. The development of a robotic system,the CLEAR-Robot (or C-Robot) [10], by the CLEAR operation team allowed for remote handling of a relatively large number of samples and has been fundamental to avoid frequent access to retrieve exposed films and exchange samples. This made possible to perform experiments needing good statistics or involving several control parameters to be changed over a large range. The robot is made of 3 linear stages for the 3 spacial axes and uses a 3D printed grabber and plastic holders which can be specifically designed to be adapted to each experiment, to hold samples and films. The sample positioning in the beam can be controlled with a 50 µm accuracy. A screen-camera system can monitor directly the electron beam position and size at any transverse and longitudinal positions in the irradiation area. Two tanks (one storage tank and one ”water phantom” tank) can be used with the robot. The C-Robot is controlled using two custom Arduino circuits, is fully interfaced to the local computing network and is fully open-source. All informations can be retreived from the C-Robot website [10] and the C-Robot Gitlab Repository [11].

One of the challenges to be addressed to allow the transition of FLASH radiotherapy into the clinical stage is the development of accurate fast dosimetry adapted to UHDR conditions. Such reliable dosimetry systems are an integral part of existing radiotherapy machines. Plane-parallel ionisation chambers are the recommended standard for clinical reference dosimetry of electrons. However, the response of conventional ionisation chambers to UHDR is nonlinear and tends to saturate due to a significant reduction in collection efficiency at high dose-per-pulse [12, 13]. Alternative approaches to active dose monitoring at UHDR have therefore become an important field of research. One such approach explored at CLEAR is to exploit the beam instrumentation normally used in electron accelerators in order to establish a calibrated dosimetry method. In particular, an active dosimetry method based on a YAG scintillating screen and an integrating current transformer has been developed in CLEAR [14]. Such method provides a simultaneous measurement of the absolute dose delivery as well as of the 2D dose distribution. The measurements have been correlated with corresponding readings from RCFs, and procedures for image processing were established. This method, employed on the flat beam delivered by the CLEAR double-scatterer system (see below) have demonstrated a precision of a few percent. Alternative schemes were also pursued: in collaboration with the universities of Oxford and Groningen, initial results were obtained using Cherenkov radiation produced by an optical fiber array and collected by a CCD camera [15], showing a remarkable response linearity for a large range of dose rates. Promising results were also obtained by Victoria University employing plastic scintillator detectors (PSD). Dose rates up to 1.2 10^9 Gy/s were investigated, showing again an excellent linearity [16].

Beam delivery is paramount both for irradiation experiments and for clinical translation. Most applications require a large uniform field, with dimensions ranging from one to several centimeters. In collaboration with Oxford University, a scheme to produce and deliver a uniform beam to CLEAR users was developed. The scheme is based on the use of a flat scattering foil to magnify the initially Gaussian beam, followed by a shaped scatterer to obtain the uniformity in most of the beam area. A circular collimator is finally used to get a sharp cut of the remaining beam tails. Such system was tested in CLEAR with excellent results [17, 18]. A schematics of the setup and the flat beam profiles measured with a 200 MeV electron beam are shown in Fig. 2. The system is now routinely used in CLEAR.

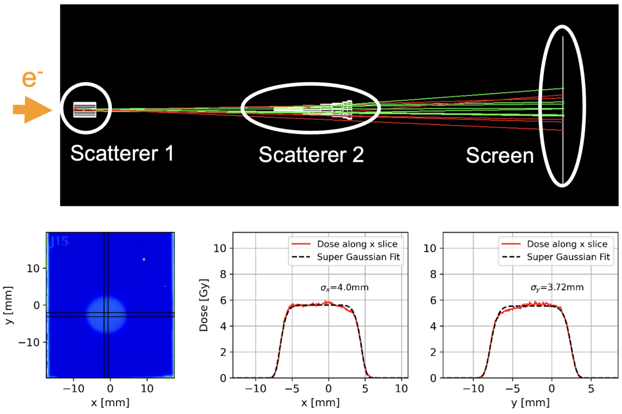

Figure 2: Schematics of the double scatterer system (top) and the flat transverse dose profiles obtained with a YAG screen (bottom).

Preliminary experiments were also performed at CLEAR to validate a method, predicted by beam dynamics simulations, in which a proper balance between space-charge repulsive forces and solenoid focusing in a photoinjector eventually leads to a transversely uniform electron beam. The initial tests shown that the process to obtain such uniform distribution is correctly understood [19, 20]. In collaboration with Manchester University, the use of quadrupoles to focus tightly the electron beam to concentrate the dose at depths of the order of 5–10 cm into a water phantom was successfully explored, showing the possibility to treat a tumor in a patient, while spreading out the dose in the surrounding healthy tissues [21, 22]. In collaboration with Victoria University, the potential for Spatially-Fractionated radiotherapy (SFRT) with VHEE/UHDR beams was tested, using both a grid collimator [16] and scanning pencil beams.

CHEMISTRY AND BIOLOGICAL STUDIES

Several irradiation experiments were performed in the last two years in collaboration with external institutes, with the aim to clarify the mechanisms at the root of the FLASH effect, comparing the effects of UHDR with conventional dose rates on controlled samples. Some details of the working procedures are given in [23] and Fig. 3 shows the typical experimental set-up. Chemistry experiments were carried out in collaboration with the Lausanne and Geneva University hospitals (CHUV and HUG). Water radiolysis at different oxygen levels and temperatures indicated a reduced production of H_2O_2 and free radicals following UHDR exposure with respect to low dose rate irradiation, a difference further enhanced at physiological temperature [24]. This result is consistent with measurements carried out at CHUV with low energy electrons (5.5 MeV). Plasmids' irradiation was also performed, showing that Plasmid DNA damage is dose rate insensitive at doses of about 10 Gy for both low energy and high energy electrons [24]. In previous experiments at CLEAR in collaboration with Manchester University [25, 26], pBR322 plasmids were also irradiated using beam parameters comparable to those applied in CHUV/HUG studies. Variation of the bunch dose rate and intensity induced measurable difference in single strand breaks at doses above 90 Gy. Those results are compatible with the findings of [24] and suggest that DNA damage might be dose rate independent at lower doses (below 10 Gy) and dose-rate dependent at high doses (above 20 Gy). Collectively, however, the sum of experimental data obtained so far suggest that DNA damage is unlikely to explain the FLASH effect. The more relevant tests, however, are being carried out in vivo on biological dosimeters, i.e. on Zebra Fish Eggs, ZFE, or drosophila (D. melanogaster) larvae, or on live human cells. In collaboration with Victoria University and the École Polytechnique Fédérale de Lausanne (EPFL), drosophila larvae were irradiated to doses of 15 to 45 Gy with 200 MeV electrons at CLEAR. Post irradiation, the larvae were tracked through development to adulthood, and eclosion of adult flies was used to assess the possibility of normal tissue sparing at UHDR, as well as the RBE of VHEE beams [27]. Results were compared to the ones of a similar experiment done using 9-20 MeV electrons produced by a conventional radiotherapy linac. Finally, ZFE irradiations performed with CHUV and HUG have shown the first evidence of FLASH effect for a VHEE beam, and hinted at a strong dependence of this effect from the fast time structure of the beam [24]. Further studies are ongoing for confirming and extending such results, as well as exploring the response to VHEE/UHDR beams of human cells, both healthy and cancerous.

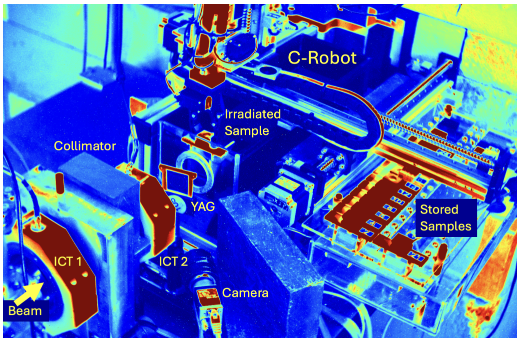

Figure 3: Experimental set-up used for ZFE irradiations. Most chemistry and biological experiments used a similar set-up.

CONCLUSION

The CLEAR user facility at CERN has been intensively used to investigate the potential of VHEE beams in cancer radiotherapy. In particular, irradiation tests were performed in the UHDR regime, which has arisen a lot of interest for the so called FLASH biological effect, in which cancer cells are damaged while healthy tissue is largely spared. CLEAR is a unique facility for addressing the FLASH effect with VHEE beams, providing a range of beam parameters well covering the requirements. The experiments in 2023–2024 were strategically chosen to help progress VHEE/FLASH RT studies towards clinical use, and new tools were developed to improve the efficiency of the facility and better serve the medical community. The focus was on a better understanding of the mechanisms of the FLASH effect and on developing its enabling technologies and methods, including beam delivery and dosimetry. Relevant results were achieved and published (or are in course of publication) in several areas: a) dosimetry studies with various methods, including novel real-time dosimetry methods; b) irradiation methods and beam delivery modalities, c) FLASH effect studies via chemical, plasmid and in vivo radiobiology experiments. The next years are crucial for fully establishing VHEE/FLASH RT techniques, including fundamental studies, time structure dependence and optimization of parameters, as well as its supporting technologies, including beam delivery, dosimetry, and beam control. CLEAR has the potential to serve the VHEE/FLASH community, playing a pivotal role in the field, including facilitating knowledge transfer to other laboratories.

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