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STATUS OF VHEE RADIOTHERAPY RELATED STUDIES AT THE CLEAR USER FACILITY AT CERN

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Abstract

Despite the increase in interest in using Very High Energy Electron (VHEE) beams for cancer radiotherapy many unanswered questions in its development remain. The use of test facilities will be an essential tool used to solve these issues. The 200 MeV electron beam from the CERN Linear Accelerator for Research (CLEAR) has been used extensively, in collaboration with several research institutes, to perform dosimetry studies and explore potential applications of VHEE beams to radiotherapy, including the exploitation of the so called FLASH effect. In this paper, we present an overview of past studies with emphasis on the more recent results. We describe methods, techniques and equipment developed at CERN in this framework, and give an outlook on future activities.

INTRODUCTION

Establishing innovative treatment modalities for cancer is a major 21st century health challenge. Although electrons are widely used to generate X-rays for radiotherapy, in general they are not directly used for irradiation. The small medical electron linacs used in hospitals for X-ray production have a limited energy reach, and low energy electrons have limited penetration range. They can then only be used directly for the treatment of superficial tumors and had so far limited clinical applicability.

Recently, studies involving ultra-high dose rate delivery of ionizing radiation (mean dose rate above 100 Gy/s), termed FLASH radiotherapy (FLASH-RT), have uncovered some unexpected potential therapeutic benefits, causing tremendous excitement in the radio-oncology field. Data show that FLASH-RT provides significant normal tissue sparing with respect to conventional radiotherapy, without compromising tumor control. The FLASH effect seems to be present for various kinds of ionizing radiation, but the use of electrons looks particularly promising given the high current that can be delivered by electron linacs and the very high dose rates thus achievable, also for relatively large irradiation fields. In parallel, since electrons with higher energies can travel deep into the patient, the idea of investigating the use of very high-energy (50-250 MeV) electron (VHEE) beams for radiotherapy has gained interest, even for non - FLASH dose rates. The advantages of VHEE therapy are that the depth – dose profile from the electrons is flatter than the quasi exponential dose given by X-rays, less sensitive than X-rays and proton beams to tissue inhomogeneities, and in addition the delivered electrons (as well as protons and other charged particles) may be focused and steered in ways that are not possible for X-rays. VHEE linacs are of course longer and more costly than medical electron linacs, but compare favorably to proton or ion accelerators. The recent progress in high-gradient acceleration, and the future perspectives of novel plasma based accelerating schemes, have been a game changer, making possible the realization of very compact machines. Indeed, the field can dramatically profit from CERN expertise in accelerators, in particular the one on high-gradient electron acceleration developed within the CLIC study. The CLEAR user facility has also offered a unique opportunity for experimental VHEE and FLASH studies with its high-current 200 MeV e-beam.

THE CLEAR FACILITY

CLEAR is a versatile 200 MeV electron linac, followed by a 20 m experimental beamline, which is operated at CERN as a multi-purpose user facility [1, 2].

The primary focus for CLEAR is general accelerator R&D and component studies for existing and possible future machines at CERN, based on a broad internal and external user community [3, 4]. The program covers two of the top priorities identified by the European Strategy for Particle Physics, namely the prototyping and validation of accelerator components for the upgrade of the Large Hadron Collider and its injector chain, and studies of high-gradient acceleration methods. The latter includes X-band studies for linear accelerators and also novel concepts as plasma based technology [5,6] and THz sources [7]. CLEAR also provides beams for irradiation tests, an activity started in the framework of a collaboration with the European Space Agency (ESA) [8], but rapidly extended to medical application studies.

INITIAL EXPERIMENTS

The first experimental campaign on the potential use of VHEE for radiotherapy (RT) in CLEAR, in collaboration with the University of Manchester group, started already in 2017, a few weeks after the first beam in the then newly approved facility and continued in 2018 and 2019 [9]. The initial focus was on the experimental verification of the dose deposition profiles in water phantoms, comparing measurements with theoretical models, and the study of the effect of inhomogeneities [10].

A water phantom was irradiated by a 156 MeV beam, and transverse dose profiles were recorded at various depths us-

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ing radiosensitive EBT-XD Gafchromic films. The results of the dosimetry experiments were compared with simulation results from the TOPAS/GEANT4 Monte Carlo codes, showing very good agreement and thus giving a first validation of the model. The tests were repeated inserting blocks of different materials and geometry in the phantom. These experiments confirmed the prediction from simulations, showing a relatively small VHEE dose distribution variation for heterogeneous intervening media (less than 5–8% dose variation in the central plane for 2 cm thick cuboid inserts with densities of 0.01-2.2 g/cm^3), especially when compared to the prediction for other radiotherapy modalities (dose change in the central plane up to 100% and 74% of the dose maximum for proton and photon beams, respectively). These findings indicated that VHEE beams have a potential to be a reliable mode of radiotherapy for treating tumors in highly inhomogeneous and mobile regions such as the lung, bowel or cervix.

FOCUSED VHEE BEAMS

The depth dose distribution of a single, wide, collimated VHEE beam is quasi-uniform, which can lead to healthy tissue being overexposed. However, a potential way to control the depth dose distribution in a patient is to use a magnetic device to focus the beam and concentrate the dose in the area of the tumor, while spreading out the dose in the surrounding healthy tissue. Focused radiation beams could also be used to precisely target hypoxic regions of a tumour, which would enhance the efficacy of radiotherapy. In October 2019, two groups, from University of Strathclyde and University of Manchester, performed independent experiments in CLEAR aimed at a proof-of-principle demonstration of the proposed method [9, 11] The CLEAR beamline was modified on purpose, in order to allow the placement of water phantoms in a position of the beam line where strong focusing with some reasonable tunability could be achieved by a quadrupole triplet. A temporary dump was installed behind the water phantom (see Fig. 1). Unfortunately, due to limitations of the beam line optics, it was not possible to obtain a strong focusing effect in both horizontal and vertical axis. In spite of that, both groups obtained a confirmation of the depth dose profile shaping, in very good agreement with simulations, in different focusing and beam energy conditions. In particular, the University of Strathclyde group measured the depth–dose profile of 158 MeV and 201 MeV electron beams focused into the water phantom, and demonstrated on-axis dose enhancement at a depth of 5–6 cm, validating theoretical predictions that focused VHEE beams would concentrate dose into a well-defined volume deep in tissue, distributing over a larger volume the dose delivered to surrounding tissue.

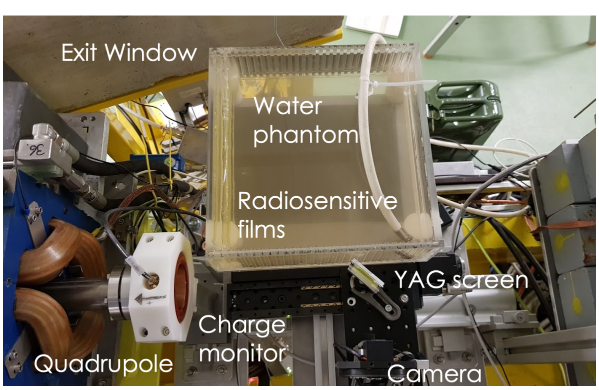

Figure 1: The experimental setup for the focusing VHEE experiments in CLEAR. The water phantom is mounted on a movable stage, to allow for several irradiations between accesses and in-air beam size measurements by the YAG screen.

HIGH DOSE RATE DOSIMETRY

Development of standard dosimetry protocols and characterization of suitable detectors is essential in order to make VHEE, FLASH and other high dose-rate RT modalities directly applicable in a clinical setting. In particular, dosimetric measurements in FLASH studies have been obtained so far using passive methods like radiochromic films and alanine, which need post-irradiation processing, while clinical practice requires real - time dosimetry. The standard for real - time RT dosimetry is nowadays based on the use of secondary standard ionisation chambers. However, it has been shown that ionization chambers exhibit significant recombination effects with increased dose-rate [12, 13], although no systematic studies were yet carried out in the case of VHEE beams. Two independent collaborations carried out such studies in CLEAR, using different types of ionization chambers and comparing them with other detectors, both active and passive. The first study [14] showed that the absolute recombination factor in a Roos ionisation chamber is strongly dependent on the dose-per-pulse, and leads to significant correction factors with the subsequent uncertainty issues. A possible solution proposed was the use of ionisation chamber geometries with smaller electrode spacing or cylindrical cavity shape in which an increased electric field strength at lower voltages should result in more effective charge collection efficiency and lower recombination effects. The second study [15] used an Advanced Markus ionization chamber positioned in a water phantom, and radiochromic films as control. It also showed an important collection efficiency loss of the chamber (down to about 30% efficiency, in good agreement with expectations), as well as polarity effects. The result indicated that it might be possible to perform reliable ionization chamber dosimetry in high dose rate beam conditions if additional procedures, including characterization and correction of saturation effects, are introduced. Both studies provides a groundwork for a wide variety of further dosimetric studies, in view of developing reliable procedures and equipment for high dose rate VHEE/FLASH RT dosimetry.

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BIOLOGICAL EFFECTS OF HIGH DOSE RATES

Although evidence of both healthy tissue sparing and tumor control aspects of the FLASH effect is now abundant for low energy electrons and other ionizing beams [16, 17], to the point that a pre-clinical successful skin-cancer patient treatment has been performed at CHUV-Lausanne [18] and clinical trials are about to start [19], there is still no direct FLASH experimental demonstration in the case of high-energy electrons. Experimental tests have been carried out in CLEAR in collaboration with CHUV-Lausanne in order to verify the differential effect of high-dose rate VHEE irradiation with respect to conventional slow dose delivery on zebra fish eggs. Batches of fertilized eggs were irradiated with different doses in the 10 Gy range, in two different modes (fast and slow dose delivery) and their development in the following weeks compared between them and with control non-irradiated samples. Unfortunately, the delivered dose stability and the statistical properties of the samples were not good enough to draw a firm conclusion, beyond the point that the evidence was compatible with a FLASH sparing effect [20]. Further tests are planned, after improvements done to the dose delivery set-up and experimental procedures, and should be carried out later this year. More recently, the first plasmid DNA irradiation with VHEE was performed at CLEAR in collaboration with the University of Manchester. DNA damage yields were measured in dry and aqueous environments to determine that ~ 99% of total DNA breaks were caused by indirect effects, consistent with other published measurements for protons and photons. No significant variation in damage yield was observed as a function of dose-rate, indicating that a FLASH effect was not present at the nanoscale within the plasmid irradiations [21]. This is considered to be a key initial pre-clinical step on the way to clinical implementation of VHEE radiotherapy.

EXPERIMENTAL IMPROVEMENTS

During the last years we made several improvements [22] critical also for medical irradiation studies, like higher and more stable beam charges, larger beams by scatterers, additional diagnostics, and lately started a project to develop new manipulation techniques to allow much faster and systematic sample irradiation in different conditions.

The state-of-the-art dosimetry test procedure in CLEAR follows the steps: 1) Manual positioning and alignment (using a linear stage). A few samples are positioned on the stage and moved in the beam axis for irradiation as needed. 2) Accelerator setup for the irradiation. 3) Irradiation. 4) Access to the experimental hall, needing the intervention of Radiation Protection (RP) experts and at least 30 minutes wait from the beam shutdown. 5) Retrieval of the irradiated samples. 6) Post-processing of the samples. Such a procedure is long and tedious. Only a small set of samples at a time can be irradiated, and for each access a complete beam shutdown procedure is needed. Shutting down and re-establishing beam conditions may also cause a non-negligible perturbation of the conditions for the consecutive irradiation, possibly needing a new beam set-up. In order to perform more tests without accessing the hall, a remote positioning system is under development. Different versions of the system were installed and tested.

A first system, holding many Gafchromic films and allowing several irradiations at a time was developed. However, such a system is only adapted to hold film and not samples of other kind. Therefore, using a grant from the Italian Association GMEE [23], a new robotic system with four degrees of freedom was designed and is now under development. A picture of the system under commissioning is shown in Fig. 2. The robotic system is based on three linear translation stages and a 3D printed grabber piloted by a servo motor, and it will be shortly tested in the beamline.

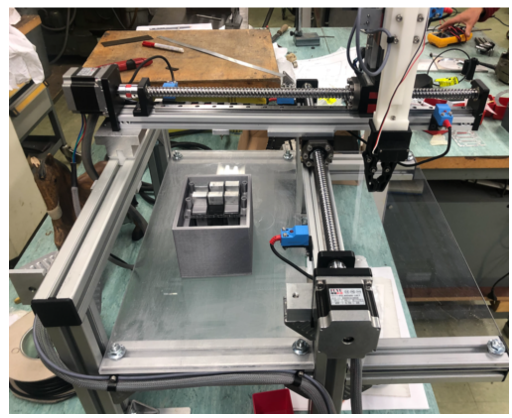

Figure 2: Robotic system to pick and place the samples.

CONCLUSION

The CLEAR user facility at CERN, with its high-charge electron beams in the 60 - 230 MeV range, provides a so far unique opportunity for experimental studies on VHEE/FLASH radiotherapy. Since its start a series of experiments were performed in collaboration with many research groups, obtaining cutting edge results on measurements of dose deposition profiles in water phantoms and the impact of inhomogeneities, on the effect of beam focusing on dose deposition profiles, on high dose rate dosimetry, and biological effects of high dose rates. Several improvements of the experimental conditions have been carried out or are ongoing, and further experiments are being planned. VHEE/FLASH activities are firmly established as a major part of the CLEAR experimental program of the next few years.

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