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External beam radiotherapy with electrons of low (IOeRT) and high (VHEE) energies: Status and prospects for conventional and FLASH irradiations

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Summary. — The field of cancer treatment is continuously evolving with the goal of enhancing tumor control probability, minimizing complications in normal tissues, and improving the life expectancy and quality of life for patients. Currently, there is a renewed focus on both low (Intra Operative electron Radio Therapy applications) and Very-High Energy Electron (VHEE) beams, particularly due to their potential to be delivered at FLASH intensities. The unique characteristics of electron interactions with matter can be leveraged to offer effective alternatives to standard Radiotherapy (RT) and Proton Therapy (PT) treatments, with electron technology being the most adaptable for FLASH treatment deliveries among the three. In this study, we explore the achievable efficiency in IOeRT and VHEE treatments at both conventional and FLASH regimes using a GPU-based fast Monte Carlo (MC) simulation as a tool for dose calculation and treatment optimization. The results obtained for partial breast irradiations and the treatment of pancreatic cancer will be compared with the latest technologies in RT and PT.

1. – Introduction

For a few years, experimental evidence has been growing, supporting that normal tissues complications can be reduced if the dose is delivered at rates that are much higher (hundreds of times or more) with respect to the current clinical practice. If confirmed, this so-called FLASH effect has the potential to re-shape the future of radiation treatments especially with charged particles, with a significant impact on many oncology patients [1]. In this context, today, there is a renewed interest on both low (Intra Operative electron Radio Therapy - IOeRT applications) and Very-High Energy Electron (VHEE) beams, particularly due to their potential to be delivered at FLASH intensities. The unique characteristics of electron interactions with matter can be leveraged to offer effective alternatives to standard Radiotherapy (RT) and Proton Therapy (PT) treatments, with electron technology being the most adaptable for FLASH treatment deliveries among the three.

Despite the IOeRT high efficacy, the planning technology has not evolved since its conception, being outdated in comparison to the current state of the art in other RT techniques and therefore diminishing the IOeRT clinical potential. The absence of proper imaging, treatment planning and applicator docking or position checking is directly related to the underdosage or geographical miss of the Clinical Target Volume (CTV) as reported by the ELIOT trial [2]. The TPS, up to now, was not foreseen in the clinical workflow for two main fundamental reasons: the lack of "post-surgery" imaging, needed to allow for the dose calculation, and the time needed for an optimisation process. Such planning tool becomes additionally interesting in view of the FLASH clinical implementation.

Electrons of "very" high energy (above 50 MeV), on the other hand, have been already explored in the past for the treatment of deep-seated tumors but they never reached the clinical implantation. Recent advancements in compact, high-gradient electron acceleration and experimental evidence of Organs at Risk (OARs) sparing in Ultra High Dose Rate (UHDR) irradiation modalities have the potential to reshape this landscape.

In this contribution the possibility to use a fast GPU-based Monte Carlo (MC) software, FRED (Fast paRticle thErapy Dose evaluator) [3] was explored to develop a TPS for IOeRT and VHEE applications and to perform a feasibility study on the potential of the FLASH effect into the clinic. The case of Partial Breast Irradiation (PBI) and the treatment of a pancreatic lesion were considered for IOeRT and VHEE therapy application respectively.

2. – IOeRT application

The IOeRT planning involves rapid intra-operative imaging and fast MC simulations for the computation of absorbed dose maps when exploring various irradiation configurations. The S.I.T. Sordina IORT Technologies S.p.A. company, will exploit an intra-operative imaging acquired using 3D real-time ultrasound system. This system will be able to provide the position, post-tumor resection, of the protective disk whenever implanted and allow for the Regions of Interest (ROIs) definition. The acquired imaging is the starting block for the exploration of different treatment configurations, such as beam energies, applicator positions, dimensions, and bevel angles. MC simulations are then used to evaluate the Planning Target Volume (PTV) coverage and optimal OARs sparing through dose maps and Dose Volume Histograms (DVHs) analysis. The imaging relative to an anthropomorphic RANDO male phantom with a silicone breast prosthetic application was used as input for the study. According to the standard PBI procedure, ROIs were defined with a depth of no more than 7 cm, equal to the optimal viewing depth of the ultrasound (see fig. 1, panel (A)) and a dose prescription of 20 Gy was assumed. The best plan selection involved computing DVHs, as well as maximum and mean dose values absorbed by each ROI. The goal is to maximize the proper PTV coverage, defined as the fraction of the PTV volume that receives 95% of the goal dose (D95) while ensuring the OARs sparing. According to the PTV transversal dimension and thickness, the scan was performed exploring electrons of 8, 10 and 12 MeV, applicator diameters ranging from 40 to 70 mm to account for a small or large safety margins, and 9 different applicator positions around the PTV. Once the scan was performed and all dose maps computed, the best irradiation strategy was chosen. Thanks to the excellent time performance of FRED the overall planning optimization took only few minutes, a time window completely compatible with the few minutes available during the surgery. Figure 1, panel (B), shows the optimized dose map, *i.e.*, the one obtained with 10 MeV

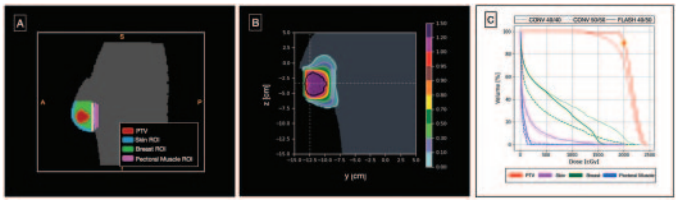

Fig. 1. – Panel (A): visualisation of anthropomorphic phantom CT. The ROIs are highlighted: the PTV, approximated as a spherical region with a mean radius of 2.5 cm, positioned at a depth of 1.3 cm from the skin, in red, the Radio-Protection Disk (RPD) defined as a cylinder (radius of 3.9 cm) with a 3 mm thick layer of PTFE, followed by 3 mm of stainless steel, in white. The skin, in blue, was defined with a thickness of 5 mm. The pectoral muscle, in green, was structured as a cylindrical-shaped region (1.2 cm thick, mean radius of 3.9 cm) positioned just after the RPD, while the breast region, in purple, encompassed all tissues between the Skin and the RPD surrounding the PTV. Panel (B): isodose map of the optimized PBI treatment. Panel (C): biological effective DVH for the IOeRT FLASH treatment.

electrons collimated by the 50 mm applicator diameter and positioned on the centered position with respect to the PTV. For this configuration the obtained D95 was 96%. PBI treatment aligns well with FLASH effect requirements, being compatible with the high-dose rates used to deliver 20 Gy in a single fraction. In this study the FLASH-modifying factor (FMF) modeled according to Bohlen *et al.* in [4] was implemented with values of FMF^{min} and D_{Th} equal to 0.65 and 6 Gy, respectively. According to the dose absorbed by each voxel in the full treatment, an FMF re-weighed dose was calculated to evaluate the FLASH potential. In IOeRT the FLASH effect can be exploited to combine a minimally invasive surgery technique, which avoids postoperative complications, with the very precise delivery of IOeRT irradiation, thus reducing the probability of tumor local recurrence. Figure 1, panel (C), shows the comparison of 3 different DVHs: the dashed line represents the "current clinical workflow", *i.e.*, a small applicator exactly matching the surgical breach of 40 mm (CONV 40/40), the dotted line represents the correct PTV treatment, *i.e.*, large surgical breach and thus applicator dimension equal to 50 mm (CONV 50/50), while the solid line describes the FLASH IOeRT minimally invasive treatment, *i.e.*, small surgical breach (40 mm) and a larger applicator dimension equal to 50 mm (FLASH 40/50). As can be seen, all the OARs, in FLASH configuration, have reduced effective doses, when compared to the conventional one, with the additional advantages of minimizing the surgical impact while ensuring the correct PTV coverage.

3. – VHEE treatments

To assess the potential of VHEE treatments in both conventional and FLASH regimes, an optimized treatment plan with electrons with energies below 130 MeV was evaluated against Volumetric Modulated Arc Therapy (VMAT) with photons. The case of a pancreatic cancer was chosen as an example. The patient underwent Stereotactic Body Radiation Therapy with a high dose per fraction (6 Gy) at Campus Biomedico Hospital. For simulating VHEE treatment, FRED was employed, requiring CT information, the field geometry, and beam specifications to calculate absorbed dose maps. An Intensity-Modulated Radiation Therapy (IMRT)-like configuration was used. Simulated electron pencil beams had a transverse size of ∼ mm, and a divergence of ∼ mrad. The analysis was focused on the 70 to 130 MeV energy range, assuming an active scanning-like beam delivery technology.

After obtaining absorbed dose maps, the fluence of each pencil beam (PB) was optimized to cover the PTV while sparing OARs as much as possible. Dosimetric constraints on OARs and PTV were verified for clinical acceptability. The main dosimetric constraint was related to the duodenum for which a dose lower than 33 Gy was targeted. In the case of VMAT and VHEE delivered at conventional and FLASH rates, a satisfactory PTV coverage was obtained. The duodenum absorbed a dose equal to 30 Gy both for VMAT and VHEE. The biological dose became as low as 28 Gy in the case of FLASH irradiations. From these preliminary studies, it was observed that VHEEs are competitive compared to advanced techniques such as VMAT, demonstrating good target coverage even in complicated OARs geometries like in the case of pancreas and duodenum. Evaluation of the FLASH effect potential was performed after the treatment optimization using the FMF model reported in [4] with D_{th} equal to 22.5 Gy and an FMF_{min} of 0.8. The observed increase in OARs sparing has the clear potential of enhancing the treatment's efficacy leading to a dose escalation in the PTV.

4. – Conclusion

The availability of accurate and fast dose calculation algorithms for clinical applications and the recent advancements in electron acceleration technology coupled with the FLASH effect potential have renewed interest in IOeRT and paved the way for the clinical implementation of external beam radiotherapy with VHEE. These developments mark a significant breakthrough in the use of electron-based therapies, which today represent a valid alternative to RT and PT.

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