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**Titolo**

Advanced Planning and Evaluation Methods for Electron FLASH Radiotherapy: Application to Uveal Melanoma

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**Riassunto**

Radiotherapy (RT) remains a cornerstone of modern oncology, with approximately 50% of cancer patients in developed countries receiving it as part of their treatment, either with curative intent or for palliation. However, in clinical practice the maximum radiation dose deliverable to the tumor is constrained by the tolerance of surrounding healthy tissues and organs at risk (OARs). While this limitation is essential to reduce normal tissue toxicity, it can compromise treatment efficacy and prevent complete tumor eradication.

Over the past decades, significant technological advances have improved the precision of radiation delivery. Techniques such as Intensity-Modulated Radiation Therapy (IMRT), Stereotactic Radiotherapy (SRT), and particle therapy with protons or heavy ions have enabled superior dose conformity, better sparing adjacent normal tissues. Nevertheless, certain malignancies, such as melanoma, remain particularly challenging, often considered incurable or only treatable at the cost of severe side effects.

In recent years, a novel radiobiological phenomenon known as the FLASH effect has generated increasing interest in the scientific community. This effect is characterized by a remarkable reduction in normal tissue toxicity without sacrificing tumor control, provided that radiation is delivered at ultra-high dose rates (UHDR), typically exceeding 40Gy/s. A growing body of preclinical evidence from in vitro and in vivo studies supports this observation, although the underlying biological mechanisms remain poorly understood.

Empirical studies have identified several beam parameters that appear critical to eliciting the FLASH effect. These include a dose-per-pulse (DPP) greater than 1Gy and a total irradiation time shorter than 200 ms. However, advancing our understanding of FLASH-RT requires not only radiobiological investigation but also robust and reproducible experimental platforms. A key limitation of earlier studies has been the lack of systems capable of delivering both FLASH and conventional dose rates under comparable beam conditions, such as energy spectrum, field size, and geometry. This inconsistency has introduced variability, further complicating efforts to isolate the mechanisms responsible for the FLASH effect.

Recently, progress in accelerator technology specifically designed for FLASH research has begun to address this gap. New-generation platforms are now capable of providing precise control over key parameters, enabling side-by-side comparisons between FLASH and conventional irradiation modalities under consistent experimental conditions.

In This thesis aims to investigate the feasibility of treating uveal melanoma with low-energy

electron FLASH-RT using the ElectronFLASH (EF) linac as a model system, both with low-energy electron beams of 7 and 9MeV, and with virtual energy spectra up to 30MeV. To carry out this work, we performed a quantitative comparison between the SRT treatment and the Monte Carlo simulated FLASH-RT plans for each patient treated in the Radiation Oncology Department of Santa Chiara Hospital, Pisa (Italy), focusing on medium and large tumors.

In doing so, a custom quantitative metric was developed to enable an objective comparison between treatment modalities, integrating multiple dosimetric and radiobiological parameters extracted from dose–volume histograms (DVHs). This new index allows a consistent assessment of plan quality both between different plans proposed for the same patient, and across different radiotherapy techniques, providing a robust framework for evaluating the potential benefits of FLASH-RT in ocular applications, and potentially other fields.

To correctly address the FLASH sparing effect, we introduced a dose modifying factor (DMF), allowing us for a relative biological effectiveness (RBE) dose comparison. To overcome the current lack of experimental data about DMFs, we identified a range of optimal values, necessary to FLASH-RT to be comparable or to be better than SRT.

Exploiting both real and Monte Carlo simulated data, this study allows to identify new possible paths to future technological developments of UHDR/UHDP machines for treatment of deep tumors.