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Review

Understanding of FLASH radiotherapy through physical to biological interpretation*

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ABSTRACT

This study presents a unified framework, systematically shows a detailed visual representation and emphasizes the understanding via various key factors throughout physical-chemical-biological stages underlying the irradiation process in FLASH radiotherapy (FLASH-RT) from the review of previous published studies. To develop this framework, we pay close attention to the time scale of irradiation process, to incorporated methodologies from current hypotheses documented by in *vitro* and *vivo* studies. Concurrently, the framework illustrates the potential differences in tumor and normal cells induced by FLASH-RT. This synthesis of the literature reveals the potential research points in existing hypotheses which lack of consideration on the entire responses and interactions of each stage from initial physical to biological process. Our interpretation provides both a structured overview and a conceptual explanation, facilitating current understanding and further investigation that could be validated in future experimental settings in FLASH-RT research.

1. Introduction

Radiotherapy is a powerful treatment, employed in about 50% of cancer patients worldwide.[1,2] Conventional radiotherapy (CONV-RT)—refers to clinically standard treatment delivered at dose rates typically around 0.01–1 Gy/s[3]—is widely used in fractionated regimens over several weeks to effectively targets malignant tissues by inducing cell damage through ionizing radiation. However, unexpected collateral damage to healthy tissues limits treatment efficacy and patient outcomes.[4] Over the years, major advancements in radiotherapy techniques, such as proton therapy, image guided radiation therapy (IGRT), intensity-modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT) have been widely used.[2,5,6] Among these advancements, FLASH-radiotherapy (FLASH-RT), characterized by mean dose rates exceeding 40 Gy/s with the total irradiation time less than 500 ms, is the innovative technology that has the potential to minimize the normal tissue toxicity.[4,7,8] It reduces organ motion effects and widens the therapeutic window compared to CONV-RT.[9–14]

Many studies have demonstrated that FLASH-RT exhibits similar tumor control as CONV-RT while minimizing damage to surrounding healthy tissue.[14–19] For example, electron beam-based FLASH-RT demonstrated protection of lung from radiation-induced fibrosis and promising results in targeting breast, head and neck tumors, with an enhanced differential response between normal and tumor tissue in mice.[7] In addition, studies in mice have shown a survival benefit and improved neurocognitive development following electron FLASH irradiation to various anatomical sites, including the brain, skin and guts.[20–24] Also, a decrease in radiation-induced endocrine toxicity was observed in mice after electron FLASH irradiation of the brain.[15] Similarly, cats suffering from nasal squamous cell carcinoma and mini-pigs under skin toxicity experienced beneficial effects from electron FLASH-RT.[14] Furthermore, the pre-clinical application across various radiation modalities, including low energy electron (LEE) FLASH-RT for superficial tumor, very high energy electron (VHEE) FLASH-RT for deep tumors, photon FLASH-RT for majority tumors and proton FLASH-RT for deep tumors with limited dose dispersion, have opened new avenues for improving patient outcomes.[12,25–33]

Numerous hypotheses have been explored by many researchers to explain the mechanism of FLASH-RT. Current studies mainly focus on isolated process, such as oxygen depletion, reactive oxygen species (ROS) suppression, radical-radical recombination (RRR), and immune modulations.[9,11,34,35] These models often lack of the systematic

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