Review

FLASH Radiotherapy: How It Works, What We Know, and What's Stopping Us

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Posted Date: 25 December 2025

doi: 10.20944/preprints202512.2314.v1

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FLASH Radiotherapy: How It Works, What We Know, and What's Stopping Us

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Abstract

FLASH radiotherapy (FLASH-RT) sounds cool -- it's a way of blasting tumors with radiation super fast (over 40 Gy/s). Early tests are showing that it might be easier on healthy tissue while still killing cancer cells. Scientists have a few ideas about why this might be the cases, like maybe it drains oxygen quickly, messes with how cells make bad stuff, or protects cell parts. Animal tests on lungs, brains, skin, guts, and blood stuff seem to say FLASH-RT can shield normal tissue. Some early human tests look acceptable with only a few bad side effects. Still, getting it into clinics is tricky. We need better machines, ways to measure doses right, and plans for treatment. It also helps to learn how it works and getting past rules and money stuff. Doctors, scientists, and engineers working together can help find the best methods to do it, figure out how it works and show it is safe and it works in human trials. If we can find a way to make it work, it could be a game-changer for cancer treatment.

Keywords: FLASH radiotherapy; ultra-high dose-rate radiotherapy; radiobiology; normal tissue sparing; tumor control; preclinical models; clinical translation; dosimetry challenges

Introduction

FLASH radiotherapy represents a paradigm shift in the radiation oncology, delivery ultra – high doses rates several orders of magnitude higher than the conventional radiotherapy [1]. While the conventional radiotherapy typically delivers doses at rates of 0.03-0.1 Gy/s over several minutes, FLASH radiotherapy delivers doses at rates ≥40 Gy/s in extremely short timeframes of less than 200 milliseconds [2]. The fundamental promise of FLASH radiotherapy lies in the "FLASH effect" - a phenomenon whereby ultra-high dose rate radiation reduces normal tissue toxicities while maintaining equivalent tumor control compared to conventional radiotherapy [3]. This response has been demonstrated across multiple animal models including mice, rats, zebrafish, pigs, and cats, and in various organs such as lung, skin, gut, and brain [4]. Despite the growing body of preclinical evidence supporting the FLASH effect, the underlying radiobiological mechanisms remain incompletely understood [5]. The most prominent hypothesis involves the oxygen depletion and the altered reactive oxygen species production, though this explanation has its limitations and requires further investigations [6]. The field has progressed from early bacterial and cellular studies to successful treatment of the first human patient with T-cell cutaneous lymphoma, demonstrating clinical feasibility [7]. However, significant barriers to widespread clinical translation remain, including technical challenges in beam delivery, dosimetry accuracy, limited penetration depth of current electron-based systems, and the lack of standardized treatment protocols [8].

Mechanism of FLASH

While the FLASH effect has been consistently demonstrated across multiple preclinical models, the underlying radiobiological mechanisms responsible for this differential tissue response remain incompletely understood and represent one of the most significant barriers to clinical translation [9,10]. The complexity of this challenge is reflected in the contradictory evidence emerging from

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different studies, with some mechanisms showing promise while others face significant limitations [11,12] .

The most prominent hypothesis centers on oxygen depletion and altered reactive oxygen species (ROS) production. This theory proposes that ultra-high dose rate radiation rapidly consumes oxygen through radiolytic processes, creating transient hypoxia that reduces tissue radiosensitivity in normal tissues while having minimal impact on already hypoxic tumors [1,13]. Supporting evidence includes studies showing that increasing oxygen tension through carbogen breathing can reverse the neuroprotective effects of FLASH, and that FLASH produces lower levels of toxic ROS such as hydrogen peroxide [14,15].

However, recent experimental work has challenged the oxygen depletion hypothesis as a complete explanation. Studies measuring oxygen consumption in water phantoms during FLASH irradiation found that while oxygen consumption does occur, it is insufficient to achieve total oxygen depletion even at ultra-high dose rates [16,17]. These findings suggest that complete oxygen depletion is unlikely to occur in well-oxygenated normal tissues and cannot be the sole mechanism responsible for the FLASH effect [18].

As a result, researchers have proposed additional mechanistic hypotheses to explain the FLASH phenomenon. These include radical–radical interactions between adjacent ionizing tracks, differential DNA damage and repair mechanisms between normal and tumor tissues, preservation of mitochondrial function, and modulation of immune and inflammatory responses [19–21]. The immune-mediated hypothesis suggests that FLASH may differentially impact circulating immune cells, the tumor microenvironment, and cytokine signaling pathways, though evidence supporting this mechanism remains preliminary [17,22].

The multifactorial nature of the FLASH effect is increasingly recognized, with researchers proposing that multiple interconnected mechanisms may work together in a chronological sequence following radiation exposure [23,24]. This complexity is further compounded by the recognition that specific beam parameters—including instantaneous dose rate, pulse size, pulse repetition frequency, and total exposure duration—must be carefully optimized simultaneously to achieve the FLASH effect [25].

The incomplete understanding of these mechanisms represents a critical knowledge gap that must be addressed for optimal clinical translation of FLASH radiotherapy [26,27]. Without a clear mechanistic framework, it remains challenging to optimize treatment parameters, predict which patients will benefit most, or ensure consistent therapeutic outcomes across different clinical contexts [28].

Preclinical and Early Clinical Evidence for FLASH Radiotherapy

The preclinical evidence supporting FLASH radiotherapy has grown substantially since its introduction, with studies demonstrating the FLASH effect across diverse animal models and organ systems. The robustness of this phenomenon is highlighted by its reproduction in mice, rats, zebrafish, pigs, and cats, as well as in organs including lung, skin, gut, and brain [27,28]. Most of these studies utilized electron beams in the 4–6 MeV range, delivered at dose rates exceeding 40 Gy/s for irradiation durations shorter than 200 milliseconds [27].

Among the most compelling data are neurological studies, where ultra-high dose rate irradiation (≥100 Gy/s) in mouse models prevented radiation-induced neurocognitive deficits, persistent neuroinflammation, and neuronal structural degradation typically seen with conventional dose-rate exposures [28]. These protective effects were maintained over a 6-month follow-up period and were associated with reduced reactive oxygen species production and preserved neuronal architecture [28].

Beyond the central nervous system, FLASH radiotherapy has demonstrated normal tissue sparing in lung, skin, intestine, and cardiac models, without compromising antitumor efficacy [29]. Additional studies have extended this evidence to gastrointestinal and hematopoietic systems, supporting the broad applicability of FLASH across organ systems [30]. Nevertheless, some organs

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such as the liver and pancreas still lack comprehensive preclinical validation, underscoring the need for targeted investigation in these tissues [31].

Clinical translation began in 2019 with the first reported human treatment: a patient with multi-resistant CD30+ T-cell cutaneous lymphoma was successfully treated with FLASH radiotherapy, achieving complete and durable tumor response with minimal toxicity [32]. This landmark case was followed by the initiation of the first clinical trial investigating proton FLASH for symptomatic bone metastases [32].

Despite these advances, researchers caution that further preclinical studies are needed to refine dose–response relationships and confirm tissue-specific effects. While promising data exist in models of lung cancer, glioblastoma, breast cancer, and head and neck squamous cell carcinoma, comprehensive tumor coverage remains incomplete [33]. Importantly, evidence suggests that FLASH may allow delivery of single-fraction high doses (≥10 Gy) that would be intolerable with conventional radiotherapy due to normal tissue toxicity [32,34].

The reproducibility of findings across independent groups has strengthened confidence in the FLASH effect, with protective outcomes observed at instantaneous dose rates ranging from 10^5 Gy/s to 10^9 Gy/s [35]. Nonetheless, translation to clinical practice requires well-designed prospective trials to establish optimal treatment parameters, long-term safety, and efficacy [36,37].

Clinical Challenges in Translating FLASH Radiotherapy

While FLASH radiotherapy has shown robust preclinical promise, major obstacles remain before widespread clinical adoption is achievable. A technological gap between preclinical and clinical systems persists, as current radiotherapy delivery systems cannot yet achieve the intensity and coverage necessary for comprehensive treatment [38]. Generating beams with sufficient intensity to elicit the FLASH effect using X-rays, protons, or heavy ions remains technically challenging despite significant engineering efforts [39,40].

Equipment and delivery limitations present immediate barriers to translation. Unlike conventional radiotherapy, which typically employs five to seven treatment beams, current FLASH platforms cannot deliver multiple irradiation beams simultaneously [41,42]. Further progress requires sources capable of delivering FLASH at greater depths and across larger radiation fields to accommodate tumors in diverse anatomical sites [43]. At present, most available devices are restricted to animal experiments with limited irradiation fields, underscoring the need for extensive system modifications before human application [44].

Dosimetry and treatment planning also represent critical challenges. The ultra-high dose rates of FLASH complicate accurate dosimetry, reproducibility of beam parameters, and the integration of FLASH into existing treatment planning and quality assurance workflows [45]. Translation into clinical use requires reliable dosimetry methodologies and equipment that can consistently measure doses and dose rates under ultra-rapid conditions [46]. Additionally, improvements in real-time adaptive systems are required to ensure accurate beam delivery and target alignment during FLASH irradiation [41].

A limited mechanistic understanding of the FLASH effect further hampers clinical translation. The biological underpinnings of FLASH remain incompletely defined, making it difficult to optimize treatment parameters, establish patient selection criteria, or ensure predictable therapeutic outcomes [47,48]. Current studies primarily focus on early radiation responses, while the long-term and late effects of FLASH remain poorly characterized [41,47].

Clinical validation requirements represent another major hurdle. To date, there is no definitive clinical data confirming the FLASH effect in cancer patients. Uncertainties remain regarding tumor control, the impact on metastatic spread, and long-term safety profiles [42,49]. Early-phase clinical trials are needed to evaluate tumor response, monitor acute and late toxicities across different organ systems, and assess treatment quality and safety [49]. Translational challenges are compounded by fundamental anatomical and physiological differences between preclinical animal models and human patients, raising concerns about direct applicability of experimental findings [50,51].

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Finally, economic and regulatory barriers complicate implementation. FLASH requires specialized, high-cost accelerator systems and personnel with advanced technical expertise, presenting substantial infrastructural challenges [44]. The use of high-energy radiation also raises ethical and regulatory considerations that must be resolved for clinical approval [50]. Successful translation will therefore necessitate not only technological innovation in accelerator systems but also integration of advanced dosimetry, treatment planning tools, and supportive regulatory frameworks [50].

Despite these barriers, continued preclinical work and carefully designed early-phase clinical trials are essential next steps. Researchers emphasize that safe and effective clinical translation will likely take several years, requiring refinement of technological platforms, validation of FLASH fractionation protocols, and long-term toxicity monitoring in human studies [47,48].

Discussion

FLASH radiotherapy represents a promising paradigm shift in radiation oncology, with preclinical studies consistently demonstrating significant normal tissue sparing while maintaining tumoricidal effects. Mechanistically, multiple hypotheses have been proposed to explain the FLASH effect, including transient oxygen depletion, reduced reactive oxygen species production, differential DNA damage responses, mitochondrial preservation, and modulation of immune signaling. Current evidence suggests that no single mechanism fully accounts for the observed effects; rather, a multifactorial interplay likely underlies the phenomenon. This complexity emphasizes the need for more integrative radiobiological studies to delineate the sequence and hierarchy of underlying mechanisms, which is critical for optimizing treatment parameters and patient selection.

Preclinical validation across diverse animal models and organ systems reinforces the robustness of the FLASH effect. Neurological, pulmonary, gastrointestinal, and hematopoietic tissues have demonstrated significant protection, supporting the broad applicability of this approach. Early human experiences, including case reports and ongoing clinical trials, provide proof-of-concept for safe translation, though systematic clinical validation remains limited. These findings highlight FLASH radiotherapy's potential to overcome conventional dose-limiting toxicities, enabling delivery of high single-fraction doses that may improve local control and therapeutic outcomes.

Despite these promising findings, substantial barriers impede clinical translation. Technological limitations, including the generation of ultra-high dose-rate beams across clinically relevant field sizes and depths, remain critical. Accurate dosimetry, treatment planning, and real-time beam delivery systems require further refinement. Moreover, the incomplete understanding of the FLASH effect's mechanistic basis complicates prediction of patient responses and long-term outcomes. Economic and regulatory considerations further constrain rapid adoption, underscoring the need for coordinated multidisciplinary efforts involving physicists, biologists, clinicians, and regulatory agencies.

The evidence collectively suggests that while FLASH radiotherapy holds transformative potential, cautious and methodical clinical development is required. Optimizing beam parameters, validating fractionated protocols, and conducting early-phase clinical trials with careful toxicity monitoring will be essential to ensure both efficacy and safety.

Conclusion

FLASH radiotherapy has emerged as a novel approach with the potential to redefine radiotherapy by minimizing normal tissue toxicity while maintaining tumor control. Preclinical data provide strong evidence for the FLASH effect across multiple organs and animal models, and initial human applications demonstrate feasibility and safety. However, substantial challenges remain, including technological constraints, dosimetric limitations, incomplete mechanistic understanding, and the need for rigorous clinical validation.

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Future research should focus on elucidating the underlying biological mechanisms, optimizing beam delivery and treatment planning, and expanding early-phase clinical trials to establish safety, efficacy, and long-term outcomes. With continued multidisciplinary collaboration, FLASH radiotherapy could become a clinically viable modality that significantly enhances therapeutic ratios in cancer treatmen

Ethical Permission

Ethical permission was not necessary in the preparation of the article.

Funding: This publication was prepared without any external source of funding.

Conflicts of Interest: Author 1 NH has no conflict of interest. Author 2 NA has no conflict of interest. Author 3 NZ has no conflict of interest.

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