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FLASH Radiotherapy: Mechanisms, Preclinical Evidence, and Clinical Potential

Abstract

Radiotherapy is a cornerstone of cancer treatment but is limited by damage to healthy tissues. FLASH radiotherapy (FLASH-RT) is an emerging technique that delivers radiation at ultra-high dose rates (typically ≥40 Gy per second in under a second) to widen the therapeutic window. Preclinical studies have demonstrated that FLASH-RT can produce a "FLASH effect," wherein normal tissues suffer significantly less toxicity than with conventional dose-rate radiation, while tumor control is maintained. Mechanistic hypotheses for this remarkable normal-tissue sparing include rapid oxygen depletion, reduced generation of free radicals, and modulation of immune responses, though the exact causes remain under investigation. Initial clinical experience—beginning with the first human FLASH treatment in 2019—has shown feasibility and promising safety in patients. However, translation of FLASH-RT to routine practice faces substantial technical challenges in beam delivery and dosimetry. Further research, including clinical trials, is needed to optimize parameters and confirm the therapeutic benefit in humans. FLASH radiotherapy has the potential to revolutionize radiation oncology by dramatically reducing treatment-related side effects without compromising tumor control.

Introduction

Over half of all cancer patients require radiotherapy during the course of their illness, highlighting the central role of radiation in oncologic care[1]. The efficacy of radiotherapy, however, is constrained by the tolerance of normal tissues. Advanced techniques such as intensity-modulated radiotherapy and stereotactic body radiotherapy have improved dose precision, yet radiation-induced toxicity remains a dose-limiting concern. There is a critical need for approaches that can expand the therapeutic window—maximizing tumor cell kill while minimizing normal tissue injury.

FLASH radiotherapy (FLASH-RT) has emerged as a novel strategy to achieve this goal. FLASH-RT delivers radiation doses in extremely short bursts, often exceeding 40 Gy per second[2]. The concept dates back to 1959, when Dewey and Boag noted reduced radiation sensitivity in bacteria subjected to pulsed exposure., suggesting a dose-rate–dependent sparing effect[3]. However, it was not until 2014 that the term "FLASH radiotherapy" was introduced by Favaudon et al., who reported that mice irradiated at ultrahigh dose rates showed striking normal tissue preservation compared to conventional dose-rate irradiation, without loss of tumor control[4]. This finding ignited widespread interest in FLASH-RT. Subsequent preclinical studies in mammals reinforced the existence of a FLASH effect across various tissues, indicating that delivery of radiation in an ultrafast burst can differentially spare normal tissue while maintaining antitumor efficacy.

Encouragingly, the first-in-human use of FLASH-RT was reported in 2019, when an electron beam FLASH treatment was successfully used to treat a patient with T-cell cutaneous lymphoma[5]. This landmark case demonstrated the feasibility of translating FLASH from bench to bedside, albeit in a carefully controlled setting. Since then, a handful of clinical case reports and a pilot trial have explored FLASH-RT in patients, fueling optimism that the preclinical benefits might be replicated in clinical practice.

The biological mechanisms underlying the FLASH effect are a subject of intensive research and debate. Several hypotheses have been proposed—including rapid oxygen depletion in normal tissues during the high-dose-rate exposure, altered DNA damage signaling, and immune-mediated effects—but no single explanation has been confirmed[6]. It is also unclear whether the effect is universal or varies with factors such as tissue type, radiation modality, or total dose. Given the promise of FLASH-RT and the many open questions, we undertook a comprehensive review of current evidence. In this paper, we summarize the state-of-the-art knowledge on FLASH radiotherapy, including its physical basis, preclinical findings, emerging clinical evidence, and the challenges that must be overcome for broader clinical implementation.

Methods

A literature review was conducted to collect and synthesize data on FLASH radiotherapy. We searched PubMed, Google Scholar, and Web of Science for articles published up to October 2025 using keywords such as “FLASH radiotherapy,” “ultra-high dose rate radiation,” “FLASH effect,” and “normal tissue sparing.” Relevant peer-reviewed publications in English, including preclinical studies, clinical trials, and review articles, were selected for analysis. Key findings were extracted concerning the biophysical parameters of FLASH-RT, observed biological effects in experimental models, proposed mechanisms, and any clinical applications to date. Reference lists of pertinent articles were also screened to identify additional reports. No human subjects or confidential patient data were involved in this review; thus, institutional review board approval was not required. The gathered information was organized into thematic sections (preclinical results, clinical studies, etc.) for qualitative synthesis. This narrative review aims to present a comprehensive overview of FLASH radiotherapy and to discuss its potential and challenges based on the current literature.

Results

FLASH Beam Delivery and Dosimetry

Achieving ultra-high dose rates for FLASH-RT in practice requires specialized beam delivery techniques. To date, most FLASH experiments have utilized electron beams, since conventional linear accelerators can be modified to deliver electrons at extremely high dose rates over short distances. Electron FLASH has been technically easier to implement in preclinical and early clinical settings, but its limited penetration depth (only a few centimeters in tissue) confines treatment to superficial targets. In order to treat deep-seated tumors with FLASH, researchers have explored other modalities. Proton beams, with their greater penetrative range, have been adapted for FLASH delivery in both animal studies and first-in-human trials. Proton FLASH involves either using specialized cyclotrons/synchrotrons or modifying clinical proton systems to deliver pulsed high-dose-rate radiation. Early proton FLASH systems have demonstrated the feasibility of delivering dose rates in the order of 100 Gy/s in a research setting. High-energy photon (X-ray) FLASH has also been investigated using modified linear accelerators and synchrotron sources, although it is technically challenging to generate the required dose rate with clinical X-ray beams. Dosimetry for FLASH-RT presents unique challenges: standard ionization chambers and dosimeters can become saturated at extreme dose rates, necessitating new dosimetry protocols and equipment. Despite these hurdles, multiple groups have confirmed that accurate dose delivery and monitoring is achievable for FLASH under controlled conditions, laying the groundwork for safe experimentation in vivo.

Preclinical Evidence of the FLASH Effect

Animal studies have overwhelmingly shown that FLASH irradiation can spare normal tissues from radiation injury, as compared to conventional dose-rate exposure, while still effectively controlling tumors. For example, in a mouse model of thoracic irradiation, ultra-high-dose-rate electron FLASH significantly reduced lung fibrosis and senescent cell burden in normal lung tissue relative to conventional dose-rate radiation[7]. In contrast to mice receiving standard radiation, FLASH-irradiated mice showed preservation of lung progenitor cells and less chronic inflammation, indicating a radioprotective effect on healthy lung parenchyma[7]. Importantly, tumor control in these experiments was not compromised: the growth of orthotopic lung tumors or implanted cancer cells was similar between FLASH and conventional dose-rate groups[7], highlighting that tumoricidal efficacy was maintained even as normal tissue toxicity was reduced.

A similar differential benefit has been observed in the central nervous system. FLASH irradiation of the brain has been shown to preserve neurologic function in preclinical models. In studies by Montay-Gruel et al., high-dose-rate brain irradiation in mice preserved cognitive abilities, an effect attributed to lower oxidative stress and reduced neuroinflammatory responses[8]. Consistent with these findings, histological studies have found that FLASH can prevent the normal tissue damage typically seen in irradiated brains—such as alleviating radiation-induced gliosis and maintaining the integrity of the blood-brain barrier—effects not seen at lower dose rates. Taken together, these results suggest that FLASH-RT could be especially beneficial in limiting late neurocognitive side effects of cranial radiotherapy.

Other normal tissues have shown analogous protection. In skin models, ultra-high dose rate irradiation causes markedly less acute and late skin toxicity compared to conventional radiation. Soto et al. (2020) demonstrated that FLASH irradiation led to reduced skin desquamation and ulceration in mice, with only mild skin reactions observed, whereas standard dose-rate irradiation produced severe dermatitis and chronic wounds[9]. This reduction in skin toxicity with FLASH was achieved without sacrificing tumor control in the irradiated field, underscoring that normal tissue sparing does not come at the expense of anticancer efficacy[9]. Gastrointestinal studies have likewise indicated that FLASH

can spare intestinal crypt cells and reduce gastrointestinal syndrome in mouse models, though the degree of protection appears to depend on the irradiated volume and other parameters.

Crucially, the FLASH effect has been replicated using proton beams, showing that it is not exclusive to electron radiation. Velalopoulou et al. reported an experiment using proton FLASH in a mouse sarcoma model, where normal tissue (such as skin and muscle) was significantly less damaged by the radiation, while the implanted sarcoma responded to treatment as effectively as under conventional dose-rate exposure[10]. In that study, normal epithelial and connective tissues within the irradiation field showed minimal fibrosis and toxicity after high-dose-rate proton therapy, whereas conventional-rate proton irradiation caused the expected tissue injury[10]. Yet the tumor outcomes (tumor growth delay and cell kill) were equivalent between FLASH and conventional groups, confirming preservation of therapeutic effect[10]. This finding is particularly important as it extends the FLASH paradigm to deeper tissues and clinical particle therapy modalities. Taken together, numerous preclinical studies across different animal models and organ systems consistently support that ultra-high dose rate FLASH can dramatically reduce normal tissue side effects for a given radiation dose, without compromising tumor control.

It should be noted, however, that the magnitude of the FLASH effect can vary, and not all experiments have yielded positive results. A few studies have reported *no significant normal tissue sparing* with FLASH under certain conditions. For instance, Venkatesulu et al. found that ultra-high dose rate irradiation (~35 Gy/s) did not spare normal tissues in their models of cardiac irradiation and abdominal irradiation in mice, as measured by markers of cardiac injury and intestinal damage[11]. These negative findings suggest that FLASH might not confer benefits in all scenarios, possibly due to factors like the specific organ system or the endpoints measured. Similarly, a recent study by Zhang and colleagues examined partial-volume proton FLASH irradiation of the mouse intestine and observed no reduction in intestinal toxicity compared to conventional dose rates[12]. In that experiment, only a segment of the intestine was irradiated with FLASH, and the expected sparing of intestinal crypt cells was not evident[12]. Such results highlight that the FLASH effect may depend on achieving certain dose-rate thresholds or irradiated volume conditions, and that it may not manifest if the FLASH parameters are suboptimal. Overall, while the preclinical evidence for FLASH-RT is largely encouraging, these inconsistencies underscore the need for further research to delineate the boundaries of the effect.

Early Clinical Studies

Translating FLASH radiotherapy to human patients has begun on a cautious, experimental basis. The first reported human treatment with FLASH-RT was conducted in Lausanne, Switzerland, in 2018 and published in 2019 by Bourhis et al.[5]. In this case study, a 75-year-old patient with refractory cutaneous T-cell lymphoma received a single fraction of 15 Gy using an electron FLASH beam (delivered in well under one second) to lesions on the skin[5]. The treatment was completed successfully with no acute skin toxicity beyond mild erythema, and the lymphoma lesions showed a complete clinical response[5]. Notably, the patient's normal skin in the FLASH-treated area experienced far less reaction than would be expected from a 15 Gy dose delivered conventionally, aligning with the sparing seen in animal models. This pioneering treatment provided a first indication that the FLASH effect could translate to humans.

Following that proof of concept, additional individual cases have been explored. In 2022, Gaide et al. reported a comparative treatment in a patient with cutaneous lymphoma, where some lesions were

treated with FLASH-RT and others with conventional dose-rate radiation for intra-patient comparison[13]. The ultra-high dose rate was again achieved with electrons on a modified linear accelerator. Their observations suggested that the FLASH-treated lesions had similar tumor control to the conventional treatment but with noticeably reduced acute skin toxicity[13]. The patient's FLASH-irradiated skin maintained integrity with only faint dermatitis, whereas the areas treated with standard dose rates developed more pronounced inflammation[13]. Although this was a single-patient experience, it reinforced the feasibility of FLASH in a clinical setting and provided direct side-by-side evidence hinting at a therapeutic advantage.

In addition to case reports, the first clinical trial of FLASH radiotherapy in humans has recently been completed. FAST-01, a Phase I trial evaluating FLASH-RT for painful bone metastases, showed that treatment was feasible within standard clinical workflows, achieving FLASH dose delivery without procedural complications.. In terms of outcomes, the pain relief achieved in these patients was comparable to historical results with conventional palliative radiotherapy, and importantly there were no unexpected acute toxicities observed[14]. Treated normal tissues (skin, subcutaneous tissue, bone) did not exhibit any severe adverse effects in the short-term follow-up, supporting the safety of the approach[14]. While longer-term data and larger studies are needed, this trial provides the first prospective evidence in a cohort of patients that FLASH-RT is technically feasible and can be delivered without acute harm. Additional clinical studies are now in development or underway, including trials exploring FLASH for other indications (such as intraoperative radiotherapy or select tumor sites) using both electron and proton beams. These early clinical experiences, though limited, are a crucial step toward determining whether the FLASH effect can significantly benefit patients by reducing treatment-related toxicity.

Discussion

The development of FLASH radiotherapy represents a paradigm shift in radiation oncology, with the potential to substantially reduce normal tissue complications and improve the therapeutic index of radiotherapy. Preclinical studies in animals have provided compelling proof that delivering radiation at ultra-high dose rates can fundamentally alter the biological response of tissues to radiation, sparing healthy cells while still eradicating cancer cells[4]. If this dichotomous effect translates reliably to humans, FLASH-RT could allow oncologists to deliver higher radiation doses to tumors (for better tumor control) or to treat cancers that are currently deemed untreatable with radiation due to proximity to sensitive organs. In essence, FLASH radiotherapy aims to "have our cake and eat it too" in radiation treatment: maximizing tumor kill and minimizing collateral damage. A recent comprehensive review noted that FLASH-RT might revolutionize radiotherapy by dramatically widening the therapeutic window, but it also emphasized that significant research is still needed to realize this potential[15]. The enthusiasm is tempered by the fact that we are only beginning to understand how and under what conditions FLASH achieves its protective effect.

Biologically, the mechanistic underpinnings of the FLASH effect remain an open question. Current evidence suggests that no single mechanism can fully explain the spectrum of observations, and multiple factors likely contribute in concert[6]. The leading hypothesis centers on oxygen dynamics. At conventional dose rates, radiation damage to cells is amplified in the presence of oxygen (the oxygen effect), because oxygen reacts with radiation-induced free radicals to cause permanent DNA damage. In FLASH irradiation, the dose is delivered so rapidly that there is a sudden, intense burst of radical formation that can acutely consume available oxygen in the tissue microenvironment. This is thought

to induce a state of transient hypoxia in normal tissues, thereby reducing oxygen-dependent radiation damage in those tissues during the exposure[16]. Essentially, well-oxygenated normal cells experience a momentary lack of oxygen due to FLASH, protecting them from the full brunt of radiation injury. By contrast, many tumors are already hypoxic or less well oxygenated; thus, further oxygen depletion may not confer as much protection to tumor cells, allowing radiation to remain lethal to the cancer. Some experimental studies support this oxygen depletion model—for instance, measurements have shown a drop in tissue oxygen tension during FLASH irradiation, and one study by Jansen et al. demonstrated that the sparing effect correlates with the degree of oxygen consumption at high dose rates[16]. However, other experiments have questioned whether oxygen is truly exhausted enough in the relevant time frames to account for the FLASH effect. It is possible that only certain tissues or conditions achieve the critical level of oxygen depletion.

Beyond oxygen, several other radiobiological factors are being explored. Ultrafast dose delivery might alter the chemistry of radiation damage: when dose is given in a microsecond pulse, the initial burst of ionization events could saturate the capacity for radical-mediated damage, resulting in fewer DNA double-strand breaks in normal cells[6]. In effect, critical cellular targets in normal cells might be hit by a high dose so quickly that the usual damage signaling and apoptotic pathways are not fully activated, or early repair mechanisms are triggered differently. There is evidence that FLASH irradiation leads to a distinct pattern of DNA damage and repair kinetics compared to conventional dose rates[6]. Furthermore, FLASH may spare normal tissue by differentially affecting the immune system and stromal environment. One hypothesis is that ultra-high dose radiation causes less activation of endothelial cells and inflammatory cascades in normal tissue, thereby reducing subsequent inflammation and fibrosis[15]. Additionally, studies have observed that FLASH causes less depletion of circulating lymphocytes and blood cells than conventional radiation[17]. Jin et al. reported that mice irradiated to high doses at FLASH dose rates had a more preserved peripheral leukocyte count and immune profile relative to those given the same dose slowly[17]. This relative preservation of the immune system could not only reduce normal tissue toxicity (since radiation-induced immune cell depletion can contribute to toxicity and impaired healing) but might also impact tumor control in complex ways. It is worth noting that immune activation can assist tumor kill (especially with the combination of radiotherapy and immunotherapy), so the net effect of FLASH on anti-tumor immunity is another topic of active research. Other proposed contributors to the FLASH effect include reduced activation of certain cell death pathways (e.g., apoptosis or pyroptosis in normal cells may be mitigated) and differences in vascular responses (ultra-rapid irradiation may avoid the wave of vascular damage that conventional radiation can inflict on normal tissue blood vessels)[6].

Critically, none of these hypotheses fully explains all observations, and some may act together. The mechanism likely differs by tissue type; for example, the brain's FLASH sparing might be heavily influenced by reduced neuroinflammation and glial activation, whereas the lung's FLASH effect might hinge more on oxygen dynamics and stem cell preservation. The ongoing mechanistic studies are not merely academic—understanding the basis of the FLASH effect will guide how to best harness it clinically, such as which dose rates and fractionation schedules are optimal.

Parameter optimization is another important aspect under investigation. FLASH-RT involves an interplay of parameters: dose rate, total dose, pulse structure (if the beam is pulsed), and the time interval of delivery. Preclinical studies suggest that a threshold dose-rate (around 40–100 Gy/s) and a sufficiently large dose per pulse are needed to observe the FLASH effect[2]. If the dose is protracted even slightly (for instance, delivered over several seconds instead of milliseconds), the sparing effect may diminish or disappear. Some experiments have also examined *fractionated* FLASH (delivering

multiple FLASH fractions over days or weeks, similar to standard fractionation). Early results indicate that the benefits of FLASH can persist in fractionated regimens, but only if each fraction is delivered with FLASH characteristics. A study by Dai et al., for example, found a FLASH effect in a split-dose scenario with two 2 Gy pulses given in quick succession, though the effect was not as pronounced as single-pulse FLASH[15]. On the other hand, if fractions are given too far apart or at lower dose rates, normal tissue does not seem to gain the same level of protection. These findings imply that to maximize clinical benefit, FLASH might be best utilized in hypofractionated treatments or even single high-dose treatments (radiosurgery-like), where the full dose can be packed into one brief burst. This is a significant departure from conventional radiotherapy practice and will require careful clinical testing.

From a technical and logistical perspective, numerous challenges must be addressed before FLASH-RT can be widely adopted. First, very few clinical radiotherapy machines at present are capable of delivering the required dose rates. The modifications made for research (such as repurposing linear accelerators to deliver high-dose-rate electrons, or using experimental high-current proton beams) are not yet standard in hospitals. There is active work by equipment manufacturers and academic centers to develop dedicated FLASH delivery systems—for instance, prototype linacs that can toggle between conventional and FLASH modes, or upgrades to proton therapy units to enable FLASH dose rates. As this technology evolves, it must maintain precise dose control; delivering large doses in an instant leaves little room for error in dose calculation and beam targeting. Ensuring dosimetric accuracy at ultra-high dose rates is non-trivial: traditional radiation detectors can under-respond or fail at these dose rates, so institutions have developed new dosimetry methods (such as chemical dosimeters, ultrafast diodes, or specialized ion chambers) to calibrate FLASH beams[15]. Treatment planning for FLASH also raises new considerations. Dose distribution in the patient remains paramount, but if FLASH confers a differential biological effect, planning systems may need to incorporate radiobiological models specific to FLASH. Moreover, current planning algorithms assume dose is delivered quasi-continuously; with FLASH, delivering a homogeneous dose in a single pulse might be complicated by limitations like beam current, instantaneous dose rate changes, and field size constraints.

Another challenge is verifying that the FLASH effect occurs in humans as it does in mice. While early patient outcomes are reassuring, comprehensive clinical data on normal tissue toxicity—especially late-arising effects—will be needed. Late fibrosis, neurologic deficits, or other organ damage can take months or years to manifest after radiation. Thus, long-term follow-up of patients treated with FLASH-RT is essential to ensure that sparing observed acutely is sustained over time and that no unexpected complications emerge. Additionally, different human tissues might have different sensitivities to FLASH; for example, it remains to be seen if highly proliferative tissues (like intestinal epithelium or bone marrow) derive as much benefit from FLASH as was seen in some animal models. Early-phase clinical trials will help answer these questions. It is encouraging that the FAST-01 trial and case reports so far have not reported any undue toxicity, but those involved relatively small volumes and single fractions. Future trials may explore FLASH for larger treatment volumes or in combination with conventional fractions (e.g., a FLASH boost alongside standard radiotherapy), which could reveal new insights or challenges.

Finally, practical considerations such as cost and workflow need to be mentioned. Specialized FLASH-capable machines could be expensive and require new infrastructure. If FLASH-RT is proven effective, there will be a question of how to integrate it into busy radiation oncology clinics—potentially as a one-time treatment or as part of a hybrid regimen. The treatment itself is very

fast (microseconds), but setup, verification, and machine tuning for FLASH might introduce new time considerations. Training staff to operate FLASH equipment and handle the unique quality assurance will also be necessary. Despite these obstacles, the radiotherapy community is highly motivated by the prospect of improving patient outcomes. Collaborative consortia have formed internationally to share data on FLASH, and regulatory agencies are beginning to develop frameworks to evaluate FLASH treatments in clinical trials.

In summary, the discussion around FLASH radiotherapy reflects both excitement and caution. FLASH-RT holds great promise: it could enable higher doses per fraction with fewer side effects, potentially shortening treatment courses and enhancing patient quality of life. It might also expand the use of radiotherapy to tumors near sensitive organs that today might be managed with less effective therapies due to fear of toxicity. However, FLASH is not yet a proven clinical modality; it is in the experimental stage, and important questions remain about why it works, how broadly it applies, and how to implement it safely. The next few years are likely to bring a surge of research, from laboratory studies refining our understanding of mechanisms to clinical trials assessing safety and efficacy in specific cancers. If those studies are successful, FLASH radiotherapy could indeed become a transformative advance in cancer treatment, changing the paradigm of how radiation is delivered.

Conclusion

The preclinical promise of FLASH-RT lies in its capacity to limit normal tissue injury through rapid dose delivery, offering a potential shift in the paradigm of radiotherapy. By compressing radiation delivery into an instantaneous flash, this technique has demonstrated the ability to minimize damage to healthy tissues while preserving anti-tumor activity. Early evidence from animal studies and initial human trials suggests that FLASH-RT could significantly widen the therapeutic window of radiotherapy, potentially allowing more aggressive and effective cancer treatments with fewer side effects. The clinical translation of FLASH-RT is still in its infancy, and many challenges — including understanding its mechanisms, optimizing delivery parameters, and developing suitable technology — must be overcome. At present, FLASH radiotherapy should be considered experimental, but its initial successes provide a strong rationale for continued investigation. In the coming years, ongoing research and clinical trials will clarify the true impact of FLASH in patient care. If its promise is realized, FLASH radiotherapy may become a game-changing modality that enhances the efficacy of radiation treatment and improves the quality of life for cancer patients by drastically reducing the collateral damage of radiation therapy.

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