

MINI-REVIEW

FLASH radiotherapy: Separating biological foundations from clinical reality

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Abstract

FLASH radiotherapy (FLASH-RT), with the delivery of ionizing radiation at ultra-high dose rate, typically ≥ 40 Gy/s, has emerged as one of the most debated and potentially transformative developments in modern radiation oncology. Unlike conventional radiotherapy, which optimizes spatial dose distribution, FLASH-RT alters the temporal structure of dose delivery, thereby establishing time as a dominant radiobiological variable. Despite intense global interest, the biological basis of the FLASH effect remains unresolved, reproducibility varies across experimental conditions, and clinical translation remains limited to specialized systems. This review differs from prior summaries by explicitly separating well-established biological effects from speculative mechanistic interpretations and early clinical feasibility. It does not seek to catalog all published FLASH radiotherapy studies, but rather to critically synthesize the literature by highlighting where consensus exists, where interpretations diverge, and where caution is warranted in clinical extrapolation. It aims to prevent overinterpretation of FLASH-RT's current translational readiness. A structured comparison with conventional radiotherapy is presented, along with a discussion of unresolved controversies, practical limitations, and realistic future directions.

Keywords: FLASH radiotherapy, FLASH-RT, Ultra-high-dose radiotherapy

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1. Introduction

Radiotherapy has remained a central pillar of cancer treatment for over a century. Despite major technological advances, such as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, stereotactic techniques, and particle therapy, the fundamental biological limitation of radiotherapy has remained largely unchanged. Tumor control is often constrained by the tolerance of surrounding normal tissues, especially when tumors are located adjacent to critical organs or require dose escalation for durable control. Consequently, most advances in radiotherapy have focused on improving the spatial dose conformity rather than altering the intrinsic biological response to radiation. FLASH radiotherapy (FLASH-RT) represents a conceptual departure from this paradigm. Instead of refining where the dose is delivered, it fundamentally alters how fast the dose is delivered, making time a dominant radiobiological variable.

Though ultra-high dose-rate irradiation has been explored since the mid-20th century,

its biological relevance remained largely underexplored until recently. As discussed in contemporary FLASH-RT reviews, early observations of dose–rate-dependent effects were initially largely regarded as radiobiological curiosities, limited by technological constraints and a lack of translational relevance.^{1,2} The modern resurgence of interest in ultra-high dose-rate irradiation was sparked by the landmark study by Favaudon *et al.*³ in 2014. They demonstrated that ultra-fast electron irradiation delivered at dose rates exceeding 40 Gy/s surprisingly reduced radiation-induced lung fibrosis in mice compared with conventional dose–rate irradiation, while maintaining equivalent tumor control. This profound differential response, characterized by substantial normal tissue sparing with preserved tumor control, underpins the therapeutic promise of FLASH-RT.^{1,3}

Independent validation of the FLASH effect was provided by Vozenin *et al.*⁴, who confirmed normal tissue sparing in lung models and extended these observations to the skin and intestinal tissues. Subsequent work demonstrated striking neurocognitive preservation following whole-brain FLASH irradiation in mice⁵, while Buonanno *et al.*⁶ explored the evidence base to include gastrointestinal and hematopoietic endpoints.

The rapid expansion of FLASH research has been accompanied by growing concern regarding inconsistent definitions, heterogeneity in experimental parameters, and premature extrapolation to clinical practice. Critical analyses have highlighted that many studies labeled as “FLASH” differ substantially in beam characteristics, pulse structure, and irradiation time, raising questions about reproducibility and biological interpretation.^{2,7,8} These concerns underscore the need for a rigorous research framework for FLASH-RT.

Rather than viewing the proposed mechanisms as parallel and competing explanations, recent physicochemical and molecular analyses suggest that FLASH responses may be temporally ordered.^{1,8} Ultra-high dose delivery initiates immediate radical–radical recombination and transient oxygen modulation within microseconds. It is followed by altered DNA damage patterning and mitochondrial responses, and subsequently tissue-level vascular and immune modulation. This time-sequenced cascade model integrates physicochemical events with biological responses, offering a hierarchical framework rather than a set of independent hypotheses.

The present review adopts an integrative and critical framework that explicitly addresses foundational discoveries, organ-specific biological evidence, mechanistic uncertainties, and clinical limitations of FLASH-RT. Rather than reiterating established observations, the

review emphasizes points of convergence and divergence across studies, providing a balanced appraisal of where FLASH-RT is biologically robust versus where evidence remains sparse. It is intended to guide clinicians and researchers toward a realistic understanding of FLASH-RT and its potential role in future clinical practice.

2. FLASH radiotherapy: The mean dose rate alone is insufficient

FLASH radiotherapy is generally defined as irradiation delivered at a mean dose rate of ≥ 40 Gy/s.^{1,3,4} While this definition provides a convenient benchmark, recent analyses have convincingly demonstrated that mean dose rate alone fails to capture the critical features of ultra-high dose-rate irradiation. Modern radiation delivery systems mostly operate in a pulsed mode, but the dose delivered per pulse is extremely small, typically on the order of 10^{-4} Gy. In contrast, FLASH-RT delivers a substantially higher dose per pulse, often ranging from 0.1 to 1 Gy, within pulse durations measured in microseconds. As a result, the instantaneous (intrapulse) dose rate during FLASH delivery can reach 10^5 – 10^6 Gy/s.^{1,9,10}

Matuszak *et al.*¹⁰ demonstrated that conventional linacs may transiently achieve relatively high intrapulse dose rates but deliver insufficient dose per pulse to elicit FLASH-associated biological effects. FLASH systems, in contrast, combine high intrapulse dose rates with high dose per pulse and extremely short total irradiation times (less than 200 ms). These parameters collectively define the unique temporal structure of FLASH irradiation. Scarmelotto *et al.*⁸ demonstrated that the FLASH effect was not observed when dose delivery was prolonged beyond a critical temporal window, even if the nominal mean dose rate remained within the FLASH range. These findings strongly suggest that FLASH-RT should be defined not by a single scalar parameter but by a multidimensional temporal signature.^{1,8,10}

Several physical parameters emerge as central to FLASH radiobiology, based on cumulative evidence from physics and biology-driven studies.^{1,2,7,9,10} These include:

- (i) Dose per pulse, which determines the local density of ionization events.¹
- (ii) Instantaneous dose rate, governing radical formation and recombination kinetics.^{1,9}
- (iii) Pulse duration and repetition frequency, influencing oxygen consumption and replenishment.^{1,8}
- (iv) Total irradiation time, which appears to define a critical window for biological sparing.^{4,10}

Based on cumulative modeling and preclinical evidence, an operational FLASH definition could incorporate not only a mean dose rate ≥ 40 Gy/s but also a dose per

pulse ≥ 0.1 Gy, instantaneous dose rate $\geq 10^5$ Gy/s, and total irradiation time within a sub-second window (<200 ms).^{1,8,9} These thresholds reflect the temporal constraints necessary for radical recombination and transient oxygen modulation, providing a testable framework for experimental reproducibility.

3. The importance of the *in vivo* context

Another critical theme emerging from early FLASH research is the divergence between *in vitro* and *in vivo* findings. While many *in vivo* studies have robustly demonstrated normal tissue sparing, several *in vitro* experiments have failed to reproduce the FLASH effect under normoxic conditions. This discrepancy, highlighted by Scarmelotto *et al.*⁸ and Wilson *et al.*², suggests that FLASH biology is strongly influenced by tissue-level factors, such as vascular architecture, oxygen diffusion, immune interactions, and microenvironmental heterogeneity—features that are absent or poorly modeled in cell culture systems.

This observation reinforces the notion that FLASH-RT cannot be fully understood through simplified experimental systems alone and underscores the need for integrated biological and physical modeling that reduces neuroinflammation, decreases microglial activation, and preserves functions.

4. Organ-specific preclinical evidence under FLASH conditions

4.1. Lung

The lung is the most extensively studied organ in FLASH research. In the earliest observation by Favaudon *et al.*³, it was demonstrated that mice receiving ultra-fast electron irradiation to the thorax exhibited less radiation-induced pulmonary fibrosis compared with those treated at conventional dose rates, despite receiving equivalent total doses. These findings were independently reproduced by Vozenin *et al.*⁴, who demonstrated that lung sparing (lung function and structure) persisted months after FLASH irradiation, indicating protection against late toxicity rather than merely delayed injury.

4.2. Central nervous system

One of the most striking findings in FLASH irradiation research is the preservation of neurocognitive function following whole-brain irradiation. An *in vivo* study has demonstrated that FLASH-RT preserves spatial memory and learning capacity at doses that caused profound neurocognitive impairment when delivered at conventional dose rates.⁵ These functional benefits correlate with reduced neuroinflammation, preservation of vascular integrity, and limited microglial activation.⁴

4.3. Gastrointestinal tract

Buonanno *et al.*⁶ explored FLASH effects in the gastrointestinal tract, demonstrating improved crypt survival, reduced epithelial apoptosis, and preservation of intestinal stem-cell compartments following abdominal FLASH irradiation in mice. Compared with conventional radiotherapy, FLASH-treated animals exhibited improved weight maintenance and reduced signs of acute gastrointestinal distress.

4.4. Cutaneous tissues and vasculature

In skin models, FLASH irradiation resulted in reduced dermatitis severity, faster epithelial recovery, and preservation of dermal architecture compared with conventional dose-rate exposure.¹¹ Vascular analyses revealed reduced endothelial damage and preserved microvascular integrity.⁴

5. Tumor response under FLASH conditions

In contrast to its effects on normal tissues, FLASH-RT does not intrinsically enhance tumor radiosensitivity.^{2,8,11} Tumor control achieved with FLASH irradiation across multiple tumor models is generally comparable to that achieved with conventional dose-rate radiotherapy when equivalent doses are delivered.^{2,3,6,12}

The preservation of tumor control despite proposed oxygen depletion presents a conceptual problem. If transient hypoxia were the dominant mechanism, tumor tissues already hypoxic would be expected to exhibit partial protection. However, multiple preclinical reports have failed to demonstrate tumor sparing under FLASH conditions. This inconsistency reinforces the notion that tumor-normal tissue differentials likely arise from differences in vascular dynamics, redox buffering capacity, and DNA repair competency rather than oxygen depletion alone.¹¹⁻¹³

Tumor hypoxia, microenvironmental heterogeneity, and fractionation appear to modulate tumor response. Notably, the majority of FLASH studies employ single-fraction or hypofractionated regimens, and the interaction between FLASH delivery and conventional fractionation biology remains poorly understood.^{2,7,11-15} Importantly, normal tissue sparing rather than increased tumor kill constitutes the primary therapeutic advantage of FLASH-RT.¹³⁻¹⁵

6. Biological mechanisms underlying the FLASH effect

No single mechanism fully explains the FLASH effect. Mechanistic analyses converge on the idea that extreme temporal compression of dose delivery alters

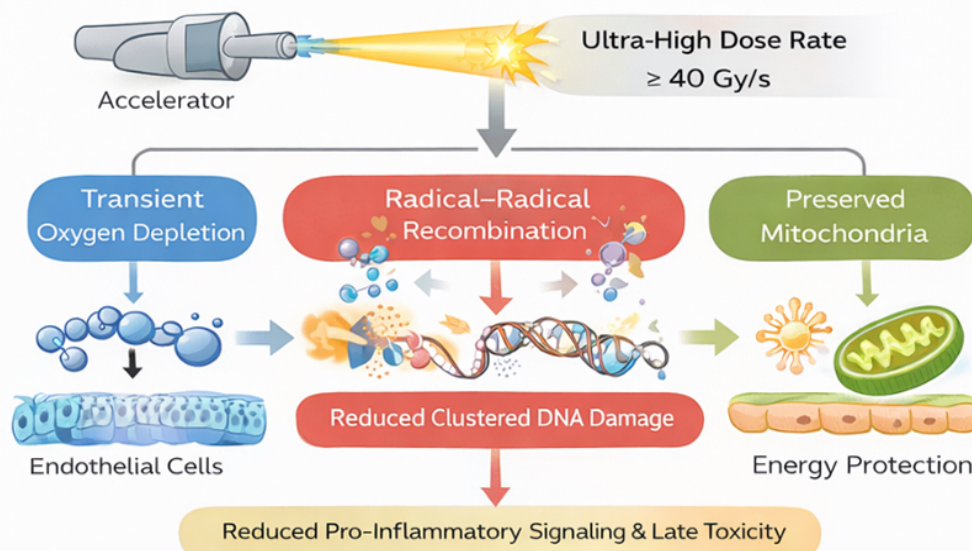


Figure 1. Temporal cascade model of the FLASH effect illustrating hierarchical layering of physicochemical, molecular, and tissue-level processes. Image created by the authors with ChatGPT.

physicochemical and biological processes during irradiation^{1,8,11,16} (Figure 1, Table 1).

6.1. Oxygen depletion hypothesis

The oxygen depletion hypothesis is one of the earliest and most frequently cited explanations for the FLASH effect. It proposes that ultra-high dose-rate irradiation rapidly consumes molecular oxygen faster than it can be replenished by diffusion.^{2,4} This leads to transient hypoxia in well-oxygenated normal tissues and reduced oxygen-mediated DNA damage. Experimental observations showing attenuation of normal tissue sparing under hyperoxic conditions support a contributory role for this mechanism.^{8,11,16}

However, several limitations have been identified. Quantitative modeling suggests that complete oxygen depletion would require very high doses delivered within extremely short timeframes, whereas FLASH effects have been observed at doses insufficient to fully deplete tissue oxygen. Additionally, tumor control is often preserved under FLASH conditions despite baseline tumor hypoxia, which is difficult to reconcile with a purely oxygen-centric explanation.⁸ Collectively, these findings indicate that oxygen depletion is potentially an important but insufficient contributor to the FLASH effect.

Though oxygen depletion remains central, evidence suggests it functions as an upstream modulator rather than a sufficient explanation in itself. Radical recombination and reactive oxygen species (ROS) kinetics appear temporally dominant during irradiation, whereas DNA damage quality modulation and endothelial preservation

represent downstream biological manifestations. Several studies have demonstrated that complete oxygen depletion is not consistently required for normal tissue sparing, indicating that oxygen modulation is contributory but not exclusive.^{8,11,12} This suggests a layered hierarchy in which physicochemical dynamics precede and condition cellular and tissue-level responses.

In summary:

- (i) Consensus: Transient oxygen modulation is biologically plausible and is supported by several experimental observations under defined dose-per-pulse and time constraints.
- (ii) Key uncertainty: Magnitude, spatial distribution, and duration of oxygen depletion within tissues during FLASH irradiation remain insufficiently quantified.
- (iii) Critical experiment needed: Real-time, high-resolution oxygen mapping during ultra-high dose-rate irradiation.

6.2. Reactive oxygen species kinetics and radical chemistry

Reactive oxygen species kinetics have emerged as a central mechanistic theme, as proposed by Borghini *et al.*¹ Ma *et al.*¹¹ demonstrated that FLASH irradiation modifies early oxidative stress signaling and reduces persistent ROS generation in normal tissues. These effects appear highly sensitive to both the dose per pulse and the total irradiation time. Borghini *et al.*¹ emphasized that radical recombination processes occur on microsecond timescales, aligning closely with FLASH pulse durations. Prolongation of dose delivery beyond this temporal window diminishes

these physicochemical advantages, explaining the loss of FLASH protection observed under suboptimal delivery conditions.

In summary:

- (i) Consensus: Radical recombination and altered ROS kinetics occurring on microsecond timescales are consistent with the temporal structure of FLASH irradiation.
- (ii) Key uncertainty: The extent to which these physicochemical processes translate into biologically meaningful tissue protection remains incompletely established.
- (iii) Critical experiment needed: Integrated experimental systems linking radical chemistry measurements with downstream biological endpoints under standardized FLASH parameters.

6.3. DNA damage quality and response

FLASH radiotherapy may alter the quality of DNA damage, with some studies suggesting reduced clustering of complex lesions. If confirmed, such qualitative changes could reduce late normal-tissue toxicity while preserving antitumor efficacy. Normal tissues, which retain intact DNA damage response pathways, are better able to repair these simpler lesions and recover. Tumor cells, despite experiencing a similar qualitative shift, remain vulnerable due to pre-existing defects in DNA repair and checkpoint control, resulting in preserved tumor control rather than tumor protection. This mechanism therefore contributes to an improved therapeutic ratio by selectively sparing normal tissues without compromising antitumor efficacy.^{5,11,16}

In summary:

- (i) Consensus: Potential qualitative modulation of DNA damage is consistent with some experimental findings.
- (ii) Key uncertainty: Direct evidence for lesion simplification across modalities is limited.
- (iii) Critical experiment needed: Cross-platform lesion complexity quantification using standardized assays.

6.4. Endothelial and vascular protection

FLASH-RT acts not only on parenchymal cells but also on the tissue microenvironment as a whole. Early endothelial protection contributes to normal tissue sparing following FLASH-RT. FLASH irradiation preserves microvascular integrity, with reduced endothelial cell injury and vascular leakage compared with conventional dose rates.^{11,16} By maintaining vascular function, FLASH may limit secondary hypoxia, inflammation, and fibrotic remodeling, thereby reducing late tissue toxicity.^{4,8,11,16}

In summary:

- (i) Consensus: Vascular preservation has been observed in select *in vivo* models.
- (ii) Key uncertainty: Platform dependence and dose-structure thresholds remain undefined.
- (iii) Critical experiment needed: Comparative cross-modality vascular injury studies.

6.5. Mitochondrial and metabolic effects

FLASH-RT may preserve mitochondrial function in normal tissues during the early post-irradiation period. Maintenance of mitochondrial integrity and redox balance could reduce oxidative stress and help stabilize cellular energy metabolism.^{11,17} Though these observations remain preliminary, they provide a plausible link between early physicochemical effects of FLASH and longer-term protection against tissue injury.^{11,16,17}

In summary:

- (i) Consensus: Early experimental observations suggest that FLASH irradiation may better preserve mitochondrial integrity and cellular redox balance in normal tissues compared with conventional dose-rate irradiation.
- (ii) Key Uncertainty: The causal relationship between mitochondrial preservation and normal tissue sparing remains unclear.
- (iii) Critical experiment needed: Mechanistic studies integrating mitochondrial functional assays, metabolic profiling, and oxidative stress measurements under controlled FLASH versus conventional irradiation conditions.

6.6. Immune modulation and inflammatory signalling

Ultra-high dose-rate irradiation may reduce radiation-induced lymphopenia and dampen pro-inflammatory signalling, potentially by shortening irradiation time and preserving vascular integrity.^{2,11,18} While these effects could contribute to reduced late toxicity, current evidence does not support a direct role for immune modulation in enhancing tumor control.^{11,18,19} Accordingly, immune effects are best viewed as modulatory rather than primary drivers of the FLASH effect.^{18,19}

In summary:

- (i) Consensus: Immune modulation is observed in some preclinical models.
- (ii) Key uncertainty: Whether immune effects are primary drivers or secondary consequences remains unresolved.
- (iii) Critical experiment needed: Immune-deficient model validation under standardized FLASH conditions.

7. Radiation modalities and clinical systems in FLASH radiotherapy

The biological promise of FLASH-RT has been established primarily through electron-based preclinical studies. Accordingly, recent work has focused on modality-specific capabilities, constraints, and early clinical implementation^{1,9,19,20} (Figure 2).

7.1. Electron FLASH

Electron beams represent the most mature FLASH modality, with the majority of foundational preclinical studies, including those by Favaudon *et al.*³, Vozenin *et al.*⁴, Montay-Gruel *et al.*⁵, and Buonanno *et al.*⁶ Electron FLASH enables high dose per pulse with relatively easy beam generation and dosimetry. However, Matuszak *et al.*¹⁰ emphasized that the limited penetration depth restricts its clinical applicability to superficial targets, posing a major barrier for treating deep-seated tumors in humans.

7.2. Proton FLASH

Proton FLASH has emerged as a promising approach for extending FLASH benefits to deeper tissues. As reported in the FAST-01 trial by Mascia *et al.*²⁰, modified clinical proton systems were used to deliver ultra-high dose-rate beams for palliation of painful bone metastases. Ongoing challenges related to beam control, dose uniformity, and dosimetric verification have been highlighted by Buonanno *et al.*⁶ and Wilson *et al.*²

7.3. Photon FLASH

As discussed by Matuszak *et al.*¹⁰ and Borghini *et al.*¹, achieving FLASH-relevant dose rates with photons requires extremely high beam currents and specialized accelerator designs. Although proof-of-concept studies exist, real-time dosimetry and beam monitoring remain major unresolved obstacles, and no clinically deployable photon FLASH systems are currently available.^{9,21, 22}

7.4. Very-high-energy electrons and heavy ions

Very-high-energy electrons and heavy ions represent experimental FLASH modalities. They may, in theory, combine deep penetration with ultra-high dose rates, while heavy ions offer high linear energy transfer and favorable depth-dose characteristics. However, these approaches remain confined to research settings, with no current clinical implementation.^{1,2,23}

8. Clinical systems and early human experience

Clinical FLASH-RT has thus far been limited to a small number of specialized systems. The first human FLASH

treatment was reported by Bourhis *et al.*²⁴ They used the Oriatron eRT6, a dedicated 5.6 MeV electron linear accelerator, to treat a patient with cutaneous T-cell lymphoma (Table 2).

Proton FLASH clinical experience remains limited to early-phase trials. The FAST-01 trial, reported by Mascia *et al.*²⁰, represents the first prospective human evaluation of proton FLASH, focusing on palliative bone metastases. Although safety and workflow feasibility were demonstrated, these results should not be extrapolated to curative settings that exist.^{6,20,25,26}

It is important to note that no randomized clinical trials, fractionated curative regimens, or deep-organ FLASH treatments using photons have yet been reported.

9. FLASH radiotherapy comparison with conventional radiotherapy

As rightly emphasized by Wilson *et al.*² and Li *et al.*⁷, FLASH-RT should not be viewed as a superior tumoricidal modality, but rather as a potential means of improving the therapeutic ratio through selective normal tissue sparing (Table 3 and Figure 3).

9.1. Limitations and barriers to clinical translation

Across critical evaluations, several recurring barriers to FLASH-RT translation are consistently identified.^{2,7,21} These include the lack of standardized physical definitions, incomplete mechanistic understanding, unresolved dosimetry, quality-assurance, limited penetration depth of electron FLASH, and the absence of robust clinical efficacy data.^{1,2,20}

Additionally, the interaction between FLASH delivery and fractionation biology remains poorly understood, as FLASH studies typically employ single-fraction or hypofractionated regimens, limiting their applicability to tumors requiring conventional fractionation.

Progress in FLASH-RT depends on several parallel developments. Radiobiological studies must continue to refine the understanding of oxygen kinetics, radical chemistry, and tissue-level responses. Innovation in technical systems is required to develop reliable photon and proton FLASH systems with validated dosimetry and treatment planning.

Disciplined, hypothesis-driven clinical trials are essential to avoid over-enthusiasm and ensure patient safety. FLASH-RT should be evaluated initially in carefully selected indications where normal tissue sparing offers clear benefits, such as pediatric oncology, re-irradiation, and oligometastatic disease near critical organs.

Table 1. Evidence grading of proposed biological mechanisms underlying the FLASH effect

Observed phenomenon/ proposed mechanism	Evidence strength	Study context (model & type)	Cross-platform reproducibility	Key uncertainty	Critical experiment needed
Normal tissue sparing (lung, CNS, GI)	Strong	Multiple <i>in vivo</i> models (mouse lung, brain, GI; large animal models)	Electron reproducible; proton emerging	Fractionation dependency	Standardized multi-fraction cross-platform studies
Oxygen depletion	Moderate	<i>In vivo</i> murine models + physicochemical modeling	Parameter-dependent (DPP & time sensitive)	Quantitative depletion thresholds	Real-time intratissue pO ₂ measurement during UHDR
Radical recombination/ROS kinetics	Moderate	Physicochemical modeling + biological correlation studies	Strong DPP dependence	Translation from chemistry to the tissue scale	Coupled radical kinetics–biological validation
DNA damage quality modulation	Limited–Moderate	<i>In vivo</i> murine + <i>in vitro</i> cellular studies	Inconsistent across platforms	Direct clustered lesion quantification	High-resolution lesion complexity assays
Endothelial preservation	Moderate	<i>In vivo</i> vascular injury models (lung, CNS)	Organ-dependent; limited cross-modality data	Dose–structure thresholds	Cross-platform vascular comparison studies
Immune modulation	Limited	Preclinical immune-competent models	Variable	Primary vs. secondary mechanism	Immune-depleted model validation

Abbreviations: CNS: Central nervous system; DPP: Dose per pulse; GI: Gastrointestinal; ROS: Reactive oxygen species; UHDR: Ultra-high dose rate.

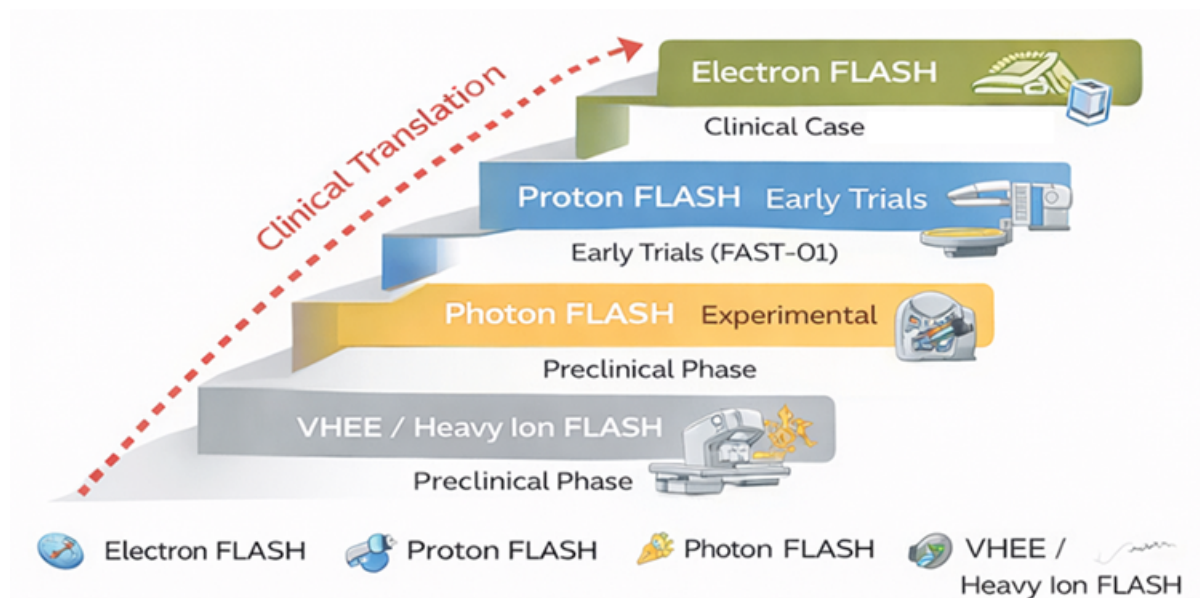


Figure 2. Current translational status of FLASH radiotherapy modalities, ranging from clinical electron FLASH to early proton FLASH trials and experimental photon and very-high-energy electron (VHEE)/heavy-ion FLASH approaches, including modality-specific penetration depth, dose-per-pulse capability, and translational readiness. Image created by the authors with ChatGPT.

Table 2. Summary of published human studies and early-phase clinical trials in FLASH radiotherapy

Study	Modality	Indication	Fractionation	Depth	Endpoint	Evidence level
Bourhis <i>et al.</i> ²⁴	Electron	Cutaneous lymphoma	Single	Superficial	Feasibility	Case feasibility
FAST-01	Proton	Bone metastases	Single	Moderate	Safety, pain relief	Phase I
Ongoing trials	Proton/Electron	Palliative	Hypofractionated	Limited	Feasibility	Early phase

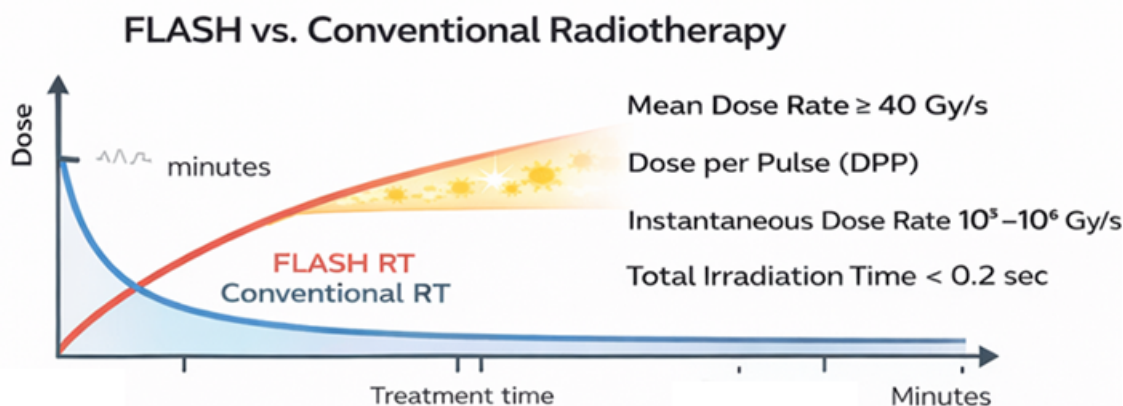


Figure 3. Comparison of dose delivery in conventional radiotherapy (RT) and FLASH-RT. FLASH-RT delivers the prescribed dose within milliseconds at ultra-high mean dose rates (typically ≥ 40 Gy/s), with high dose per pulse, extremely high instantaneous dose rates (10^5 – 10^6 Gy/s), and short total irradiation times (< 0.2 s), in contrast to conventional dose delivery over minutes. Image created by the authors with ChatGPT.

Table 3. Comparative features of FLASH radiotherapy and conventional radiotherapy

Domain	Conventional radiotherapy	FLASH radiotherapy
Mean dose rate (Gy/s)	~ 0.01 – 0.1	≥ 40
Dose per pulse (Gy)	$\sim 10^{-4}$	0.1 – 1
Total irradiation time	Seconds to minutes	Milliseconds
Instantaneous dose rate (Gy/s)	10 – 5	10^5 – 10^6
Normal tissue toxicity	Dose-limiting	Markedly reduced (preclinical)
Tumor control	Effective	Comparable, not superior
Mechanistic basis	Classical radiobiology	Multifactorial (oxygen, reactive oxygen species, DNA quality)
<i>In vitro</i> reproducibility	High	Inconsistent
<i>In vivo</i> reproducibility	Predictable	Robust but conditional
Clinical evidence	Extensive randomized trials	Case reports and feasibility trials
Current status	Standard of care	Investigational

Given the heterogeneity of preclinical findings and the technical constraints associated with ultra-high dose-rate delivery, clinical translation of FLASH-RT should proceed according to clearly defined gating criteria. First, reproducible and independently validated dosimetry at ultra-high dose rates is essential, including real-time monitoring systems capable of resolving microsecond-scale beam characteristics. Second, normal tissue sparing must be confirmed in clinically relevant fractionation models rather than limited single-dose preclinical experiments. Third, robust evidence demonstrating the absence of tumor radioprotection across multiple histologies and oxygenation states is required to maintain confidence in the therapeutic ratio. Fourth, infrastructure feasibility must be demonstrated, including beam stability, treatment planning system compatibility, quality assurance standardization, and workflow integration. Fifth, economic scalability and regulatory readiness must be addressed to ensure equitable implementation beyond specialized research centers.

Early-phase human studies, such as FAST-01, have established workflow feasibility and acute safety but do not yet demonstrate therapeutic superiority over conventional dose-rate radiotherapy. Accordingly, initial clinical prioritization may be most appropriate in scenarios where toxicity reduction would substantially alter management paradigms, including re-irradiation settings, pediatric indications, or anatomically constrained targets adjacent to radiosensitive organs.

10. Conclusion

FLASH radiotherapy highlights that *how fast* radiation is delivered can be just as important as *how much* is delivered, introducing dose-delivery time as a critical variable in radiation oncology. Although the FLASH effect is robust *in vivo* and reproducible across multiple normal tissues, its mechanism is complex, and its clinical translation remains limited. The main promise of FLASH-RT lies not in improving tumor kill, but in reducing radiation-related toxicity and widening the therapeutic window. Determining whether this approach will become part of broader clinical implementation will require rigorous, evidence-based development of standardized delivery systems and well-designed clinical trials.

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Conflict of interest

The authors declare they have no competing interests.

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Writing-original draft: Tanshi Daljit

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

Further disclosure

AI-assisted tools (ChatGPT) were used to generate conceptual schematic figures. All figures were reviewed, edited, and finalized by the authors.

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