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FLASH-RT: the future of cancer therapy?

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Abstract

FLASH radiotherapy (FLASH-RT) is an emerging technique that delivers radiation at ultra-high dose rates, offering the potential to achieve equal or superior tumour control compared to conventional radiotherapy, while significantly reducing toxicity to surrounding healthy tissues. Experimental studies have consistently demonstrated tissue-sparing effects, and early clinical experiences suggest potential benefits in sensitive patient groups, such as children or those requiring re-irradiation. Although the precise biological mechanisms are not yet fully understood, the observed protective effects suggest a complex interplay of physicochemical and cellular processes. The translation of FLASH-RT into clinical practice was still limited by significant technological challenges, particularly in dosimetry, beam generation, and treatment delivery. Nevertheless, the rapid pace of research and the promising balance between safety and efficacy highlight FLASH-RT as a potential breakthrough in the future of cancer therapy.

Keywords: FLASH radiotherapy; ultra-high dose rate; normal tissue sparing; cancer treatment.

Introduction

Radiation therapy is a standard clinical method that uses ionizing radiation to treat malignant tumours, and sometimes benign conditions. From the beginning, its main goal has been to destroy cancer cells at the targeted site while avoiding serious side effects [1]. Although the primary aim is to target the tumour site, the effects of ionizing radiation are not limited to cancer cells, which means that healthy surrounding tissues and organs can also be affected, sometimes resulting in treatment-related toxicity. Advancements in technology over the past decades have helped lower the side effects of radiotherapy by improving its accuracy, enabling higher doses to be concentrated on the tumour while reducing exposure to nearby healthy organs [2].

An innovative approach known as FLASH radiotherapy (FLASH RT) has emerged as potential solution to some of the limitations seen with standard radiotherapy techniques. It involves delivering radiation at extremely high dose rates, exceeding those used in conventional treatment by several magnitudes (e.g., 40 Gy per second compared to 0.1–5 Gy per minute) [3]. By delivering radiation at an exceptionally high dose in a single, ultra-fast session, this method may reduce the overall treatment duration, enhance the ability of healthy tissues to withstand radiation, and enable the use of curative dose levels [4]. If ongoing clinical research confirms the superior safety and therapeutic effectiveness of FLASH RT, this innovative technique could significantly reshape the practice of radiation oncology. It holds the potential to become the preferred treatment option for selected tumour types and might eventually supersede conventional radiotherapy in specific clinical settings [3]. This article aims to provide an overview of the current understanding of FLASH radiotherapy, highlighting its underlying biological mechanisms and exploring its potential clinical applications and future role in cancer treatment.

Fundamentals of FLASH RT

The concept of FLASH was initially introduced by Favaudon and colleagues in 2014. Their research demonstrated that FLASH radiotherapy can effectively damage tumour tissue while minimizing harm to surrounding healthy tissues, providing a clear advantage over conventional radiotherapy techniques [5]. In support of these observations, their preclinical study revealed that a conventional 15 Gy dose used to treat lung tumours consistently resulted in pulmonary fibrosis—a significant late adverse effect occurring between 2 and 6 months after treatment. In contrast, fibrosis was not observed at doses below 20 Gy when FLASH RT was delivered. Furthermore, FLASH demonstrated protective effects on healthy tissues by reducing apoptosis, preserving microvascular integrity, and minimizing skin damage [6].

FLASH radiotherapy introduces several fundamental differences compared to conventional radiotherapy, particularly in terms of dose rate, treatment time, and biological response. Compared to conventional clinical dose

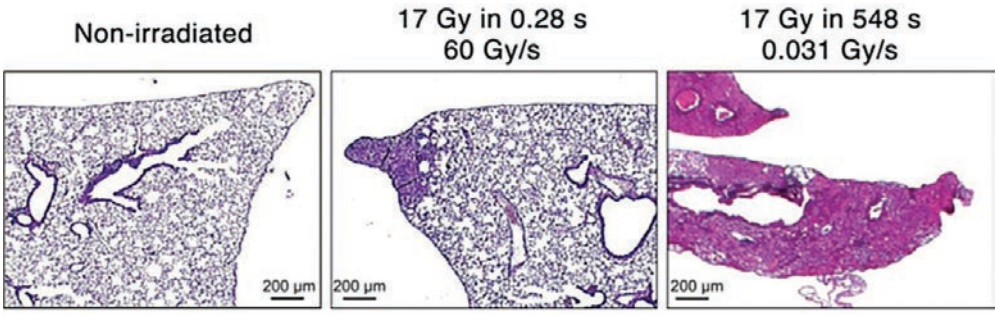

Figure 1. Effect on healthy lung tissue of a 17 Gy irradiation delivered in 0.28 s, i.e. a dose rate of 60 Gy/s (center image) and in 548 s, i.e. a dose rate of 0.031 Gy/s (right image). Tissue irradiated at a very high dose rate has the same appearance as unirradiated tissue, whereas tissue irradiated at a low dose rate is totally altered.
Source: https://institut-curie.org/flash-radiotherapy-story-revolutionary-discovery-institut-curie

rates, which range from 0.01 to 0.40 Gy/s, ultra-high dose rate radiotherapy (UHDR-RT) was initially developed using microsecond pulses of 5 MeV electrons. These pulses have an intrapulse dose rate ranging from 10^6 to 10^7 Gy/s, with a time-averaged dose rate exceeding 40 Gy/s and a duty cycle of less than 0,5 sec. This approach has shown to significantly reduce normal tissue toxicity across various organs while maintaining at least the same level of tumour control, a phenomenon known as the FLASH effect [7]. FLASH-RT is generally described as a non-invasive external radiotherapy method that delivers ultra-high dose rates (UHDRs) to the target area, significantly exceeding the dose rates used in conventional radiotherapy (≥40 Gy/s compared to 1–4 Gy/min), all within an extremely brief exposure time [8].

Biological Effects and Mechanism of Action

While several studies have reported the presence of the FLASH effect, the exact biological mechanisms driving this phenomenon remain unclear [5]. The mechanisms through which FLASH radiotherapy induces its effects are complex and can generally be divide into physicochemical and biological components [9]. To explain the potential benefits of FLASH-RT at both the biological and physicochemical levels, four interconnected hypotheses have been proposed: 1) radical-radical interactions, 2) DNA damage, 3) mitochondrial damage, and 4) oxygen depletion. Among these, the hypothesis of oxygen depletion caused by ionizing radiation has received significant attention and is the most widely discussed in recent studies [8].

Table 1. Comparison of FLASH-RT and CONV-RT.
Source: James C.L.Chowand Harry E. Ruda, Mechanisms of Action in FLASH Radiotherapy: A Comprehensive Review of Physicochemical and Biological Processes on Cancerous and Normal Cells[9]

Aspect	FLASH-RT	CONV-RT
Treatment Time	Ultra-fast (milliseconds)	Typically seconds to minutes
Dose Rate	Extremely high (>40 Gy/s)	Moderate to high (0.001–0.4 Gy/s)
Normal Cell Sparing	Enhanced due to UHDR	Limited, increased risk to normal cells
Oxygen Effect	Reduced due to ultra-short exposure	Present, potential impact on tumour response
Radiobiological Effect	Increased therapeutic index	Standard radiobiological principles
Fractionation	Single or few fractions possible	Multiple fractions common
Patient Comfort	Reduced overall treatment time	Longer treatment sessions
Machine Wear and Tear	Potentially reduced	Standard wear and tear
Integration with Imaging	Compatibility with advanced imaging	Standard imaging requirements
Organ Motion during Treatment	Reduced impact due to faster delivery if the tumour position is known immediately prior to treatment	Continuous monitoring and adaptation
Patient Throughput	Potentially increased	Treatment duration may impact throughput
Clinical Trial Status	Investigational, ongoing research	Established, widely practiced
Cost and Accessibility	Potential for higher costs	Generally more accessible

1) The free radical interaction hypothesis suggests that the extremely high dose rates used in FLASH radiotherapy result in a sudden increase in free radicals, which quickly react with one another. Through the formation of more stable molecular compounds, these reactions limit further chain activity of free radicals, resulting in less cellular damage – such as reduced DNA damage, lower protein oxidation, and decreased lipid peroxidation. At the same time, some free radicals interact with oxygen to produce reactive oxygen species (ROS), which can spread throughout the cell and damage essential structures, such as lipids and DNA [10].

2) The rapid dose delivery of FLASH-RT leads to transient oxygen depletion, reducing oxygen fixation of DNA lesions in normal tissue [11]. Tumours, often chronically hypoxic, derive less benefit from this protective mechanism. In addition, the compressed burst of ROS may limit diffusion and secondary reactions, leading to reduced oxidative base damage in normal cells [12]. At the same time, clustered DNA damage in tumour cells may persist as complex lesions that are more difficult to repair [13].

3) Beyond ROS reduction, FLASH-RT appears to regulate key molecular factors involved in the mitochondrial network. Specifically, proton FLASH irradiation has been shown to prevent mitochondrial dysfunction in normal lung fibroblasts through a mechanism linked to the maintenance of the phosphorylated form of the protein *Dynamin-1-like protein (Drp1)* [14]. Drp1 is essential for *mitochondrial fission* (fragmentation), which is often associated with cellular dysfunction and the induction of apoptosis. The preservation of Drp1 phosphorylation by FLASH-RT suggests that maintaining mitochondrial homeostasis by preventing pathological fragmentation is critical for normal cell survival [14]. A pivotal finding is that the mitochondrial sparing primarily occurs in non-tumorigenic (normal) cells, while tumour cells remain effectively targeted. Experiments using pancreatic cancer (PDAC) cell lines demonstrated that FLASH-RT spared mitochondrial function in non-tumorigenic pancreatic cells but not in PDAC tumour cells [15]. This supports the differential damage hypothesis, suggesting that the FLASH effect is achieved due to the distinct metabolic differences between healthy and malignant tissue.

4) The therapeutic benefit of FLASH-RT relies on the differential response between normal and tumour tissue, a feature the oxygen depletion hypothesis explains through metabolic differences [16]. Tumour tissue, which often contains large volumes of pre-existing chronic hypoxia (due to chaotic vascularization and rapid growth),

Flow diagram of the preclinical validation of the FLASH effect

1. Definition of Objectives & Experimental Design

- Formulating key hypotheses (e.g., normal tissue sparing with preserved tumor control)
- Selection of models (e.g., mice, pigs, rabbits)
- Selection of tissues/organs for evaluation (normal and tumor)

2. Selection of Radiation Parameters (Physical Parameters)

- Dose per pulse
- Number of pulses
- Intervals between pulses
- Mean dose rate
- Total dose
- Type of beam/particles (electrons, protons, X-rays)
- Rollimation, field shape, and irradiation geometry
- Monitoring and verification of actual delivery (dosimetry)

Assessment parameters:

- Assessment of normal tissue toxicity
  - Acute effects (histology, cellular stress, inflammation, edema)
  - Late effects (fibrosis, function loss)
- Assessment of tumor efficacy:
  - Tumor growth/regression
  - Survival
- Biological/molecular markers:
  - Oxidative stress, ROS (reactive oxygen species)
  - DNA damage/repair (e.g., hypoxia/oxygenation, immune response, and inflammatory markers)

3. Comparative Analysis: FLASH vs Conventional

- Comparison of normal tissue toxicity
- Calculation of tumor control
- Biological significance
- Statistical significance
- Comparison of normal tissue toxicity (comparison tumor)
- Calculation of therapeutic index (benefit-to-risk ratio)
- Statistical significance

4. Reproduction and Optimization

- Repeating experiments with parameter variations
- Testing in different models/tissue types
- Scaling to larger volumes/complex systems
- Correlation of physical parameters with biological effects

5. Transition to Clinical Translation

- Standardization of terminology, reporting, and protocols
- Planning of clinical study protocols based on preclinical data
- Development of QA/QC procedures for FLASH delivery
- Planning of clinical study protocols based on preclinical data

operates close to the O2 threshold where the Oxygen Enhancement Ratio is already low [17]. Therefore, the radiolytic consumption of oxygen in tumour tissue is less consequential than in well-oxygenated normal tissue, allowing the dose to remain cytotoxic to the tumour. Although the radiolytic oxygen depletion hypothesis provides a plausible physicochemical basis for the FLASH effect, explaining how ultra-high doses selectively reduce the biological efficacy of radiation in well-perfused normal tissues, it may not be the sole biological factor; consequences such as preservation of mitochondrial integrity and reduced immune activation are likely secondary effects resulting from reduced initial oxidative damage [18].

Preclinical Validation of the FLASH Effect

Preclinical studies have demonstrated a consistent pattern: tumours respond to FLASH-RT similarly to conventional irradiation, but surrounding normal tissues exhibit significantly less toxicity. This phenomenon, termed the FLASH effect, has been reported in rodents, mini-pigs, and companion animals, thereby establishing a foundation for clinical translation [19,20].

The first evidence of the FLASH effect came from Favaudon et al. (2014), who demonstrated reduced pulmonary fibrosis in mice following thoracic irradiation with UHDR electron beams. Subsequent studies confirmed protection of the brain, skin, and gastrointestinal tract from radiation-induced injury [21,22].

Moving beyond rodents, studies in mini-pigs and dogs have reinforced the translational potential of FLASH-RT. Vozenin et al. [19] reported that single-dose UHDR irradiation of pig skin caused markedly less ulceration compared to conventional dose rates. Similarly, in spontaneous canine cancers, FLASH treatment achieved tumour control with improved normal tissue tolerance [20].

Across diverse models, tumour growth delay and tumour control probability (TCP) appear equivalent between FLASH and conventional dose-rate irradiation [19,23]. This consistency strengthens the therapeutic index by uncoupling tumoricidal efficacy from normal tissue damage.

Technological Challenges and Limitations

Despite its promising biological advantages, the clinical implementation of FLASH radiotherapy is constrained by several technical challenges. Delivering ultra-high dose rates requires significant modifications of existing treatment equipment and the development of specialized delivery systems. In addition, accurate dosimetry and rigorous quality assurance are essential to ensure treatment precision, yet they remain particularly challenging to achieve at such high dose rates. Current investigations have primarily relied on electron beams, while proton and photon-based approaches are still in experimental stages, each presenting unique limitations and engineering requirements. Addressing these technological barriers is a critical step before FLASH-RT can be widely adopted in routine clinical practice.

FLASH RT relies on a specific combination of dose, dose rate, and irradiation time that exceeds the capabilities of current clinical linear accelerators. Standard accelerators deliver radiation using X-ray photon beams with a broad energy spectrum, created through *bremsstrahlung* of primary electrons, usually in the energy range of 6–20 MeV. To achieve the dose rates required for FLASH RT, current clinical linear accelerators would need a power output that is several thousand times higher than their standard capacity [24].

Accurate measurement of dose and consistent quality assurance are major obstacles in translating FLASH-RT into clinical practice. Ultra-high dose rate beams dramatically alter the time structure and intensity compared to conventional radiotherapy, which conventional detectors cannot reliably quantify. Common ionization chambers, for example, struggle with saturation and recombination effects under such extreme conditions. Therefore, there is a growing exploration of alternatives, such as solid-state detectors, current transformers, and scintillation-based or luminescent dosimeters, that better handle the rapid, high-output pulses characteristic of FLASH RT. Additionally, the unique beam parameters, such as instantaneous dose rate and pulse duration, require entirely new measurement protocols. Current standards simply do not accommodate these conditions [25].

Most of the experimental work in FLASH radiotherapy has been performed so far with electron beams, primarily because they can be generated with existing linear accelerators after relatively simple modifications. Electrons enable the achievement of ultra-high dose rates necessary for the FLASH effect. However, their limited penetration depth restricts their clinical use to superficial or shallow-seated tumours [26].

In contrast, proton beams offer a more suitable option for treating deep-seated malignancies, owing to their favourable depth–dose distribution characterized by the Bragg peak. Preclinical studies have demonstrated that proton FLASH maintains tumour control while reducing damage to surrounding healthy tissues. Early data also suggest potential immunological benefits, making proton FLASH one of the most promising modalities for future clinical application [27].

The use of photon beams at ultra-high dose rates remains less developed. Conventional radiotherapy primarily relies on photons, yet producing UHDR photon beams presents significant technical challenges. Although still in early stages, ongoing research is exploring novel approaches to generate photon beams capable of delivering FLASH-level dose rates. Initial preclinical findings indicate feasibility; however, further technical improvements are necessary before photon-based FLASH can be integrated into routine clinical use [28].

Clinical Potential and Future Perspectives

FLASH radiotherapy stands at the threshold of reshaping cancer treatment, offering a compelling balance between effectiveness and safety. Preclinical models have consistently demonstrated that FLASH-RT can preserve normal tissues while maintaining tumour control that is similar to or even exceeds that of conventional radiotherapy [29]. These promising findings are beginning to fuel early-phase clinical efforts that aim to translate this novel modality into standard practice.

One particularly exciting avenue lies in sensitive patient populations, such as paediatric cases or re-irradiation scenarios, where reduced long-term toxicity is paramount [30]. For instance, preclinical evidence suggests that FLASH-RT may offer potential benefits in safeguarding neurocognitive function, reducing skin toxicity, and limiting lung fibrosis [31].

Looking ahead, FLASH-RT has the potential to redefine the standards of radiotherapy. Through ultra-high dose rate delivery, FLASH may enable dose escalation for radioresistant tumours or allow safer delivery in challenging anatomic sites. Integration with systemic treatments, such as immunotherapy, could further enhance therapeutic synergy, leading to better outcomes with less collateral damage [32].

Ultimately, while FLASH-RT remains in exploratory phases, its trajectory suggests a paradigm shift in radiotherapy. As technology matures and clinical validation accumulates, this modality may evolve from a promising innovation to a transformative standard in cancer treatment.

Conclusion

FLASH radiotherapy is steadily moving from experimental promise toward clinical reality. By combining effective tumour control with significant protection of normal tissue, it has the potential to reshape the future of radiation oncology. Before it becomes part of everyday practice, must overcome technological barriers and its safety confirmed through well-designed clinical trials. If these requirements are met, FLASH-RT could enable safer dose escalation, expand treatment options for sensitive patient groups, and set a new standard in radiotherapy – bringing patients not only longer survival but also better quality of life. ■

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FLASH-RT: budućnost terapije raka?

Sažetak

FLASH radioterapija (FLASH-RT) je nova tehnika koja isporučuje zračenje ultra visokim brzinama doze, nudeći potencijal za postizanje jednake ili superiorne kontrole tumora u usporedbi s konvencionalnom radioterapijom, uz značajno smanjenje toksičnosti za okolna zdrava tkiva. Eksperimentalne studije su dosljedno pokazale učinke očuvanja tkiva, a rana klinička iskustva sugeriraju potencijalne koristi kod osjetljivih skupina pacijenata, poput djece ili onih kojima je potrebno ponovno zračenje. Iako precizni biološki mehanizmi još nisu u potpunosti shvaćeni, uočeni zaštitni učinci sugeriraju složenu interakciju fizikalno-kemijskih i staničnih procesa. Primjena FLASH-RT-a u kliničku praksu još je uvijek bila ograničena značajnim tehnološkim izazovima, posebno u dozimetriji, generiranju snopa i isporuci zračenja. Ipak, brzi tempo istraživanja i obećavajuća ravnoteža između sigurnosti i učinkovitosti ističu FLASH-RT kao potencijalni proboj u budućnosti terapije raka.

Ključne riječi: FLASH radioterapija; ultra visoka brzina doze; očuvanje zdravog tkiva; liječenje raka.