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FLASH Radiotherapy: Biological Mechanisms and Potential for Reducing Radiation-Induced Organ Toxicity

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Abstract

Radiotherapy (RT) remains a cornerstone of oncological management, indicated for over half of all cancer patients. Although technological iterations — intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) — have refined spatial precision relative to conventional two-dimensional approaches, radiation-induced normal tissue toxicity persists as a critical dose-limiting constraint.

The radiobiological mechanisms of ionising radiation encompass direct macromolecular DNA damage and indirect oxidative stress propagated by reactive oxygen species, with cellular outcomes heavily modulated by the dose delivery rate. Consequently, ultra-high dose-rate FLASH-RT has emerged as a novel paradigm, executing therapeutic delivery within millisecond intervals at dose rates exceeding 40 Gy/s.

Preclinical and nascent clinical data demonstrate that FLASH irradiation maintains robust tumouricidal efficacy while substantially attenuating normal tissue sequelae. This differential response is hypothesised to arise from transient microenvironmental oxygen depletion, altered reactive oxygen species kinetics, differential DNA damage repair pathways, and distinct immunomodulatory interactions. While the precise molecular orchestration requires further elucidation, FLASH-RT possesses the potential to optimise the therapeutic index. Systematic experimental and clinical validation remains imperative to standardise delivery parameters and integrate this modality into routine clinical oncology.

Keywords: FLASH radiotherapy, ultra-high dose rate, organ toxicity.

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Introduction

Cancer remains one of the most significant health challenges faced by modern societies and it is among the leading causes of mortality worldwide. According to the data from the International Agency for Research on Cancer (IARC) reported in the GLOBOCAN database, over 19 million new cancer cases and nearly 10 million deaths have been recorded annually in recent years, with projections indicating a further increase in these figures over the coming decades [1]. As a result of the growing patient population and prolonged survival times, increasing clinical attention is being directed not only toward the efficacy of oncological treatment but also toward its safety profile and patients' post-therapeutic quality of life (QoL). Given the rising incidence rates and the dynamic evolution of medicine, highly effective and precise diagnostic and therapeutic modalities are becoming crucial [2].

Radiotherapy (RT) remains one of the pivotal therapeutic modalities in oncological management, utilising ionising radiation to eradicate cancer cells or to inhibit their ability to proliferate [3]. In clinical practice, RT is implemented in both radical and palliative settings [4]. According to the World Health Organization (WHO), over 50% of oncological patients require RT as a primary component of their treatment. It plays a critical role particularly in prostate cancer management, serving as one of the most frequently utilised radical treatment modalities [5]. Furthermore, it constitutes a standard therapeutic approach in non-small cell lung cancer (NSCLC) — applied in both radical and multi-modal treatment strategies, particularly for patients who are not candidates for surgical resection [6]. RT techniques can be categorised into two major groups based on the position of the radiation source. The most prevalent method is external beam radiation therapy (EBRT), where the radiation source — typically a linear accelerator — is positioned outside the patient's body, allowing the tumour site to be irradiated from a specified distance [4]. An alternative to this approach is internal radiation therapy (brachytherapy), which involves the precise placement of a radioactive source directly within the tumour volume or in its immediate vicinity [7].

Over the past decades, advancements in RT have primarily driven a transition from simple two-dimensional techniques to highly precise planning methods. Historical 2D techniques, introduced in the 1960s, relied on defining radiation fields based on planar X-ray images. Bony structures visualised on these radiographs served as anatomical reference points to estimate the tumour's position within the patient's body [8].A major clinical breakthrough occurred with the implementation of three-dimensional (3D) RT. By incorporating computed tomography (CT) and magnetic resonance imaging (MRI), 3D planning enabled spatial, three-dimensional visualisation of the tumour. Consequently, it became possible to conform the radiation beams to the actual geometry of the tumour, significantly improving the precision of dose distribution [9]. The introduction of 3D planning established the foundation for further technological evolution in RT. Concurrently, it initiated the intensive development of advanced computerised treatment planning systems and optimisation algorithms, which allowed therapy to be more precisely tailored to individual patient clinical characteristics [9].

Subsequent progress in RT led to the development of dynamic delivery techniques, such as Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). IMRT is an advanced cancer treatment modality that utilises ionising radiation to eliminate cancer cells. Unlike conventional methods, it allows for the modulation of beam parameters during irradiation, enabling highly precise adjustment of the beam shape and dose distribution to the targeted area. As a result, the entire tumour volume can be effectively covered while minimising the dose delivered to adjacent healthy tissues and sensitive structures. This approach translates into enhanced treatment safety, a reduced risk of complications, and ultimately, improved therapeutic outcomes [10].

The next evolutionary stage of this technology is VMAT. This technique involves continuous patient irradiation during the rotation of the accelerator head around the body, while simultaneously modulating the radiation intensity, rotation speed, and the shape of the radiation field. This approach enables a more efficient dose distribution, reduces treatment delivery time, and enhances patient comfort [8, 9]. Both IMRT and VMAT currently constitute the standard of care in RT, significantly optimising the ratio between therapeutic efficacy and the risk of adverse effects [11].

The evolution of dynamic methods has also prompted a renaissance of a concept known since the 1950s: FLASH ultra-high dose-rate RT[11]. This technique relies on delivering the therapeutic dose within a fraction of a second, which potentially yields a significant reduction in healthy tissue toxicity while maintaining full efficacy in tumour destruction. Although the specific phenomenon of healthy tissue sparing at extremely high dose rates was observed decades ago, it was only the modern technology that allowed its precise, clinical utilisation. It is precisely this potential that makes the mechanisms of ultra-high dose rates a pivotal reference point for future

considerations regarding the evolution of RT [12].

Radiobiological effects of RT

The radiobiological effects of therapy are the result of both direct and indirect interactions of ionising radiation with cellular structures [13].

Direct effects involve the transfer of energy from quanta or particles directly to critical intracellular macromolecules. The interaction of radiation with macromolecules leads to physical and chemical changes in their structure. The key therapeutic target in this process is DNA. Ionising DNA may result in the formation of single- and double-strand breaks, the substitution or loss of nucleotides, as well as the formation of DNA-DNA and DNA-protein cross-links [14]. The cellular response to radiation-induced DNA damage begins with its detection by a sensor system consisting of various protein complexes, including DNA-dependent protein kinase (DNA-PK) and ataxia telangiectasia mutated (ATM). Subsequently, the information about the damage is transmitted to downstream protein complexes, which, depending on the type and scale of the damage, can arrest the cell cycle, activate repair mechanisms, or direct the cell toward programmed death [15].

The indirect effect of ionising radiation stems from the radiolysis of water present in the cell. The process of water radiolysis is a series of reactions leading to the dissociation of the H_2O molecule. The mechanism is based on the ejection of electrons from water molecules by ionising radiation, which causes the formation of radical cations that further react to form hydrated electrons (e^-_{aq}) and hydroxyl radicals (OH•). Free radicals react with each other to form a stable compound — hydrogen peroxide (H_2O_2) — which, due to its strong oxidising properties, leads to numerous damages to organic compounds [15]. Radicals present in the cell also attack polyunsaturated fatty acids, leading to the formation of lipid peroxides. This process significantly reduces the integrity of the cell membrane, increasing its permeability and thus disrupting the controlled influx of components into the cell [16]. Equally critical is the modification of proteins, where the oxidation of amino acid side chains by free radicals leads to an irreversible loss of enzymatic and transport activity. At the genetic level, radicals induce non-specific damage to DNA and RNA, which can lead to the induction of mutations or neoplastic transformations. The cumulative effect of these processes leads to cellular dysfunctions, which form the molecular basis for the pathogenesis of many diseases. The ultimate fate of the cell after irradiation depends on the efficiency of DNA repair pathways and the tissue type. Differences in the damage response between healthy and tumour cells determine which of the cell death mechanisms (apoptosis, necrosis, autophagy, mitotic catastrophe, cellular senescence) will be initiated [14].

The ultimate mechanism of cell elimination after irradiation constitutes one of the key determinants of RT efficacy. Factors affecting the balance between cell survival and death, such as oxygen availability or irradiation parameters, can significantly modify the biological response of tissues. For this reason, they are the subject of intense research into new treatment methods, including FLASH-RT [17].

Another important factor determining the biological effects of ionising radiation is the linear energy transfer (LET), which describes the amount of energy deposited by radiation per unit length of tissue [18]. Low-LET radiation, such as X-rays, gamma rays, and high-energy electrons, deposits energy relatively sparsely along its path and induces DNA damage predominantly through indirect effects mediated by reactive oxygen species. In contrast, high-LET radiation, including alpha particles, carbon ions, and other heavy charged particles, produces densely ionising tracks and causes more complex and clustered DNA damage, including closely spaced single- and double-strand breaks and DNA cross-links. The distinction between low- and high-LET radiation is particularly relevant in RT, as LET influences the type and complexity of DNA damage, cellular repair capacity, and ultimately the response of both tumour and healthy tissues to irradiation [18].

Dose rate and its biological significance

The dose rate of ionising radiation is one of the fundamental concepts utilised in dosimetry and radiobiology. It defines the change in the absorbed or delivered radiation dose per unit of time. Dose rate is mostly expressed in grays per minute (Gy/min), sieverts per minute (Sv/min), or their respective submultiples. In contrast to the total absorbed dose, which quantifies the cumulative amount of energy deposited in tissues, the dose rate accounts for the duration of exposure, a factor of paramount importance for evaluating the biological effects of radiation [19]. Both parameters directly determine the progression of processes occurring at the cellular and molecular levels, including the induction of chromosomal and DNA damage, activation of repair mechanisms, protein modification, gene expression, and the induction of cell death. Consequently, the manner in which the

same total dose is delivered, as characterised by varying dose rates, can modulate the therapeutic response and result in disparate levels of toxicity [19].

Organ toxicity in RT

Organ toxicity represents one of the primary constraints of RT, resulting from the interaction of ionising radiation with healthy tissues localised within the irradiated field [20]. Despite substantial advances in treatment-planning precision, the complete prevention of healthy tissue damage remains unattainable. The mechanism underlying the development of organ toxicity is primarily associated with cellular DNA damage, the generation of free radicals, and the disruption of regenerative processes within tissues. These processes can induce structural and functional alterations in organs, which, depending on the radiation dose and individual patient sensitivity, may be transient or permanent. Based on the onset of symptoms relative to the completion or course of treatment, organ toxicity in RT is classified as either early or late [21].

Early toxicity typically manifests during treatment or within 90 days following its completion, predominantly affecting tissues with high proliferative activity, such as the cutaneous epithelium, mucous membranes, and bone marrow cells. Clinical symptoms include, among others, desquamation, mucositis, and dysphagia. In the majority of cases, these acute reactions are reversible and resolve within a few weeks post-therapy. However, they can significantly compromise treatment tolerance and the patient's QoL [21].

Late toxicity develops months or years after the cessation of RT and is primarily linked to damage in tissues with low proliferative activity, such as connective tissue, blood vessels, and parenchymal organ structures. The pathomechanism of these changes involves chronic inflammation, tissue fibrosis, vascular endothelial damage, and microcirculatory disturbances. Consequently, this can lead to a progressive loss of organ function and, in certain instances, tissue necrosis [21]. Examples of late radiation-induced complications include pulmonary fibrosis following thoracic irradiation, cardiotoxicity following mediastinal RT, radiation nephropathy, and salivary gland dysfunction following head and neck irradiation [22].

The development of advanced RT techniques has significantly contributed to mitigating the risk of organ toxicity. Techniques such as VMAT and IMRT enable a highly precise conformation of the radiation dose distribution to the geometry of the tumour, while maximising the preservation of surrounding healthy tissues [23]. Furthermore, the integration of advanced imaging modalities into treatment planning facilitates more accurate localisation of both the neoplastic lesion and organs at risk (OARs). Nonetheless, organ toxicity remains a key limitation of RT and a critical factor influencing the safety and QoL of patients undergoing oncological treatment. Thorough risk assessment of complications, meticulous treatment planning, and the deployment of modern irradiation techniques are of utmost importance to minimise adverse effects while maintaining high therapeutic efficacy [24].

Ultra-High Dose Rate RT (FLASH)

In recent years, the concept of irradiation using ultra-high dose rates, termed FLASH radiotherapy (FLASH-RT), has garnered renewed interest within the field of radiation oncology [25].

FLASH-RT represents an approach developed on the basis of observations indicating that the dose rate significantly influences the biological response of irradiated tissues [25]. Although pioneering studies on the effects of ultra-high dose rates were conducted in the 1950s, the evolution of contemporary radiotherapeutic technologies has driven a resurgence of interest in this methodology [11]. In contrast to conventional irradiation regimens, where the dose rate typically ranges from 0.01 to 0.1 Gy/s, the FLASH technique utilises dose rates exceeding 40 Gy/s, with the total exposure duration restricted to milliseconds. Such an ultra-short delivery time leads to distinct radiobiological outcomes compared to conventional irradiation [25]. Concurrently, it substantially shortens the delivery time of a single fraction, thereby mitigating the impact of patient and organ motion (e.g., respiratory movement), enhancing targeting precision, and improving patient comfort as well as the throughput efficiency of the procedure [17].

Accumulating evidence indicates that the application of FLASH irradiation is correlated with a reduction in healthy tissue damage compared to conventional RT. One of the leading hypotheses explaining this phenomenon highlights the role of tissue oxygenation and the availability of molecular oxygen within the cellular microenvironment, which can modulate radiochemical reactions and the subsequent biological response. In radiobiology, oxygen acts as a natural radiosensitising agent. Its presence at the time of radiation interaction enables the chemical fixation of DNA damage, rendering it irreversible and leading to cell death [17].

While healthy tissues are typically characterised by stable physiological oxygenation states, tumour regions frequently exhibit areas of hypoxia, arising as a consequence of aberrant vascular architecture and deficient oxygen supply [26]. As a result, neoplastic cells located within hypoxic niches display increased radioresistance compared to well-oxygenated healthy tissues. In this context, it is suggested that FLASH-RT may partially abrogate the differences in radiation response stemming from oxygen availability [17].

The molecular foundations of the FLASH effect have not yet been fully characterised and remain the subject of numerous experimental investigations and modelling analyses. One of the leading hypotheses accountings for the selective sparing of normal tissues is the concept of transient depletion of cellular oxygen [27]. This model posits that the delivery of an ultra-high radiation dose within an ultra-short timeframe (on the order of 100 ms) initiates intense radiochemical reactions that prompt the rapid consumption of dissolved oxygen and the generation of free radicals. In conventional RT, which spans several minutes, the oxygen consumed during radical generation is continuously replenished by the circulatory system. In the FLASH technique, where the dose is delivered within a fraction of a second, a precipitous drop in molecular oxygen concentration occurs before new oxygen molecules can be transported from the blood vessels into the cells [28]. This process induces a state of transient hypoxia within healthy, well-oxygenated tissue, which prevents the fixation of DNA lesions by free radicals, thereby rendering the tissue naturally more radioresistant. Conversely, tumour masses, which feature regions where hypoxia is already established prior to irradiation, exhibit no significant modification in their radiosensitivity [29].

The choice between different particle sources creates distinct differences in oxygen consumption during FLASH-RT, which are broadly categorised by their LET [30]. Low-LET radiation sources such as electrons and very high energy electrons (VHEE) produce a uniform distribution of sparse ionisation events across the tissue. Because of this diffuse track structure, low-LET beams are exceptionally efficient at driving widespread, bulk radiolytic oxygen consumption uniformly throughout the cellular microenvironment, maximising the transient hypoxia needed for the FLASH protective effect. Conversely, high-LET radiation sources – such as protons and heavy ions produce much denser ionisation tracks. This high ionisation density alters radical recombination kinetics, leading to localised oxygen consumption patterns that differ significantly from uniform low-LET fields. Regarding their practical options and limitations, low-LET electrons offer straightforward production via modified linear accelerators for superficial or shallow targets, but struggle with deep penetration unless scaled to complex very high energy setups. On the other hand, high-LET options like protons excel at travelling deep into the body to target hidden tumours, but face technical hurdles in maintaining uniform ultra-high dose rates across extended paths, while heavy ions offer immense biological potency against hypoxic tumours but are severely restricted by extreme facility costs and complex nuclear interactions [17, 31].

A direct consequence of these abrupt shifts in local oxygen concentration is the modification of the generation and scavenging kinetics of reactive oxygen species, which constitutes the second pivotal hypothesis explaining the FLASH phenomenon. In conventionalRT, ionising radiation leads to the production of free radicals, including hydroxyl radicals, which permanently damage cellular structures in the presence of oxygen. In FLASH-RT, the extreme brevity of exposure alters redox reaction dynamics. It is suggested that in healthy tissues, owing to the diminished oxygen availability induced by the

FLASH effect, fewer free radicals are generated, or they are more rapidly neutralised by endogenous antioxidant systems [17, 32].

Beyond its direct impact on oxygen metabolism and radical production, the FLASH effect plays a role in modulating the host immune response. In contrast to conventional RT, which can cause substantial depletion of circulating lymphocytes due to prolonged exposure times, FLASH-RT damages only a small fraction of immune cells within the vasculature inside the treatment field, owing to the highly compressed exposure duration [12].

At the same time, it is emphasised that no single hypothesis comprehensively accounts for all observed biological discrepancies between conventional and FLASH irradiation. Alternative mechanisms currently under investigation include differential regulation of the oxidative stress response, variations in the activation of intracellular antioxidant systems, modulation of DNA damage repair pathways, and the impact of radiation on inflammatory cascades. It is highly probable that the FLASH effect is multifactorial in nature, emerging from the simultaneous interplay of several coexisting biological processes [17].

Revelation of the FLASH sparing effect

One of the earliest reports regarding FLASH-RT involved an experiment conducted using a murine lung

model (C57BL/6), where FLASH-RT significantly reduced the risk of radiation-induced pneumonitis compared to conventional irradiation, while preserving tumour growth control. It was demonstrated that mice irradiated with FLASH exhibited a lower accumulation of inflammatory cells and interstitial lung damage than those treated with conventional RT, suggesting its potential advantage in mitigating thoracic organ toxicity [25].

A subsequent critical milestone in the development of this technology was the confirmation of the FLASH-sparing effect in higher mammals. Studies were performed using a minipig model and cats with naturally occurring tumours. The minipig skin experiment demonstrated that FLASH-RT induces substantially less toxicity than conventional irradiation. While doses delivered via conventional techniques led to severe fibrous necrosis, FLASH exposure limited damage merely to transient hair loss. Concurrently, a phase I clinical study on cats with advanced nasal squamous cell carcinoma confirmed the tolerance of healthy tissues when high single doses were applied, while achieving full clinical remission in all subjects within 6 months. These results allowed the healthy tissue protection factor to be estimated at a minimum of 20% in favour of the FLASH method, providing strong foundations for initiating clinical trials in humans [33].

A breakthrough in FLASH technology research was the first-in-human clinical application, performed in 2018 at the Lausanne University Hospital. The therapy was administered to a 75-year-old patient with treatment-resistant cutaneous T-cell lymphoma, for whom conventional RT methods were no longer safe due to the risk of severe healthy tissue damage. The treatment outcomes proved exceptionally favourable: only a mild, transient skin inflammation occurred at the irradiation site, and complete tumour regression was noted in less than three months. This success confirmed that the selectivity previously observed in animals, consisting of tumour destruction alongside the protection of surrounding healthy tissues also occurs in humans [34].

A pivotal step toward introducing ultra-high dose rate technology into routine clinical oncology was the publication of the FAST-01 trial results in 2023. This pioneering clinical study provided the first evidence of the feasibility and safety of FLASH-RT in humans, demonstrating high efficacy coupled with minimal tissue toxicity. However, the authors emphasised that the success of FAST-01, conducted on a model of extremity bone metastases, serves merely as a starting point for further clinical investigations. Verifying the FLASH effect in structures exhibiting higher radiosensitivity and physiological complexity remains an ongoing challenge. This is particularly vital in the context of lung cancer RT, where the primary objective is to maximise the tumouricidal dose while simultaneously minimising the risk of radiation-induced pulmonary fibrosis and critical mediastinal structure damage. Consequently, initiating further studies is essential to enable an objective evaluation of FLASH-RT y in thoracic malignancies. A detailed analysis of ultra-high dose rate interactions with the internal organ microenvironment will allow for a comprehensive understanding of the biological mechanisms underlying normal tissue-sparing and the safe implementation of this modality as a standard in lung cancer treatment [35]. As a natural and crucial continuation of the pioneering FAST-01 trial, which established the initial clinical safety and feasibility of proton FLASH-RT for painful bone metastases in the extremities, the subsequent FAST-02 trial expanded this translational momentum into a more clinically complex anatomical region. While FAST-01 demonstrated that single-fraction proton FLASH could be safely delivered to peripheral skeletal sites with minimal toxicity, FAST-02 advanced the field by prospectively evaluating single-fraction proton FLASH for symptomatic thoracic bone metastases. This progression represented a significant test of the technology's capability to protect critical OARs, such as the lungs and heart, while maintaining effective pain palliation and high safety profiles in regions with heightened physiological sensitivity [36]. Building upon these bone metastasis trials, early-phase investigations like the IMPulse trial have simultaneously expanded the clinical horizon into superficial malignancies, exploring the dose-escalation potential of FLASH-RT in patients with cutaneous melanoma metastases. While trials like FAST-01 and FAST-02 tested deep-seated and thoracic structures using protons, the IMPulse trial focused on the distinct clinical challenges of superficial lesions, providing critical human data on skin tolerance, acute cutaneous reaction profiles, and the therapeutic ratio in cutaneous tissue. Together, these clinical milestones transitioning from peripheral bones to complex thoracic targets and superficial melanoma lesions mark a comprehensive, multi-modal evolution toward establishing the safety, versatility, and broader applicability of ultra-high dose rates in modern oncology [37].

Conclusions

In conclusion, as the global burden of cancer continues to rise, the dual imperative of maximising therapeutic efficacy and preserving patient QoL has intensified. RT remains a cornerstone of oncological care, offering critical definitive and palliative interventions across a broad spectrum of malignancies. The discipline's ongoing evolution transitioning from historical, structurally rigid two-dimensional planning to highly precise

modern modalities underscores a continuous technological shift. Ultimately, these historical and technical advancements reflect a broader paradigm shift in radiation oncology, wherein the primary objective is to optimise the therapeutic ratio by delivering highly conformal, lethal doses to neoplastic targets while systematically mitigating toxicity in adjacent healthy tissues. Crucial to this transition is the re-emergence of ultra-high dose rate (FLASH) RT, which holds potential to decouple tumour control from normal tissue toxicity by inducing a unique sparing effect in healthy structures. However, while early preclinical and clinical observations are promising, further comprehensive research remains imperative to fully understand the underlying molecular mechanisms, standardise technical parameters, and validate the safety and efficacy of the FLASH-RT phenomenon prior to its widespread clinical translation.

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