REVIEW ARTICLE

Clinical Implementation of Ultra High Dose Rate FLASH Radiotherapy: Potential, Challenges and Future Directions

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ABSTRACT

Ultra-high dose rate FLASH radiotherapy (FLASH-RT) has gained significant attention in the radiotherapy community in recent years. This technique delivers radiation at an exceptionally high dose rate—often thousands of times higher than that of conventional radiotherapy (CONV-RT)—within an extremely brief period.This novel irradiation tech- nique shows a protective effect on normal tissues, also known as the flash effect. At the same time, FLASH-RT is comparable to CONV-RT in terms of tumor- killing efficacy. As basic research dedicates to uncover the mechanisms by which FLASH-RT reduces radiation-induced normal tissue damage, clinical trials of FLASH-RT have been gradually conducted worldwide. This article systematically reviews the evidence of the feasibility and safety of FLASH-RT in clinical practice and offers insights into the future translation of this technology in clinic.

KEYWORDS

Ultra-high dose rate flash radiotherapy; Mechanism; Clinical translation; Ra- diation-induced damage to normal tissues; Prospects

INTRODUCTION

Radiotherapy is a key approach in cancer treatment, aiming to deliver a high radiation dose to tumors while minimizing exposure to surrounding healthy tissues and organs at risk. This strategy maximizes the potential to cure or reduce the tumor while lowering the frequency and severity of radiation-induced side effects. Based on dose rate, conventional radiotherapy (CONV-RT) can be divided into categories such as conventional dose rate radiotherapy (≤ 0.03 Gy/second), high dose rate brachytherapy (approximately 0.3 Gy/second), and stereotactic body radiotherapy (around 1 Gy/second).

In recent years, the development of technology allows linear accelerators provide various radiotherapy strategies including ultra-high dose rate flash radiotherapy (FLASH-RT)(5). FLASH-RT is a cutting-edge treatment modality to deliver the total radiation doses into the target volume by ultra-high dose rate (mean dose rate, 100 Gy/second; and instantaneous dose rate, up to 106 Gy/second) in a very short time (less than 200 millisecond and preferably microse- conds)(2). FLASH effect was observed in normal tissues after FLASH-RT by offering superior tissue protection in comparison to CONV-RT without compromising cancer treatment in various in vivo models(6). FLASH-RT has a unique and revolutionary radiobiological advantage; and become an emerging science-driven advances in radiotherapy. Re- searchers and clinicians are dedicated to promote the clinical translation of this innovative technology.

CLINICAL BASIS OF FLASH-RT

FLASH-RT related basic research

Since the mid-20th century, and especially from 2014, great progress has been achieved for FLASH-RT with the advance- ment of science and technology in radiation oncology. The flash effect has been replicated in zebrafish and various mammal model thereafter. Compared with CONV-RT, FLASH-RT significantly reduces radiation-induced normal tissue damage, including brain, skin, lungs, intestines, mesenchymal tissue, muscle, and hematopoietic stem cells; in the meantime, FLASH-RT maintaining similar tumor-killing effect as CONV-RT(7-11). Generally, the following parameters are needed to implement FLASH-RT: Average dose rate ≥ 40 Gy/second, instantaneous dose rate ≥ 100 Gy/second, irradiation time ≤ 200 ms(2). Currently, oxygen consumption, reactive oxygen species (ROS), and the immune cell sparing has been hypothesized to clarify the biological mechanisms of the flash effect(12-16).

Oxygen consumption: Oxygen content is one of the influencing factors of cell survival fraction(17). With the increase of oxygen content, the survival fraction of normal cells decreases after radiotherapy(18). Based on the plasmid model, flash effect is affected by oxygen content(19). The oxygen depletion hypothesis emphasized the significance of instantaneous dose rate within FLASH-RT(20,21). FLASH-RT can deliver the entire radiation dose to the target area within milliseconds, rapidly depleting a large number of oxygen molecules in normal tissues. However, for hypoxic tumor tissues, the influence is minimal. This instantaneous of hypoxia is beneficial for protecting normal tissues(22). In contrast, Cao *et al* (23) showed that at the cellular level, the oxygen consumption capacity of flash irradiation was inferior to that of conven- tional irradiation; in normal tissues, the continuous oxygen supply during conventional irradiation can offset its inherent oxygen consumption capacity(23). Therefore, FLASH-RT does consume oxygen, but it is not enough to fully explain the flash effect.

DNA integrity: A group from China focused on the combination of FLASH-RT (photons) and immunotherapy and proposed the "DNA integrity" hypothesis to explain the flash effect(14). The group found that FLASH-RT can alleviate intestinal damage in programmed death ligand 1 knockout mice and significantly improve the survival rate. Although FLASH-RT and CONV-RT

cause similar genomic DNA damage in intestinal epithelial cells, FLASH-RT induces fewer cytoplasmic DNA fragments than CONV-RT, thereby reducing the activation of the cyclic guanosine monophosphate- adenosine monophosphate synthase-stimulator of interferon genes signaling pathway and mitigating intestinal inflam- matory damage. Further investigation revealed that the longer irradiation time of CONV-RT leads to sustained DNA damage in intestinal cells and gradual disruption of DNA integrity, resulting in a large number of DNA fragments. In contrast, FLASH-RT, with a total time of less than 100 milliseconds, allows DNA molecules to maintain relative integrity, thereby reducing the production of DNA fragments and alleviating intestinal tissue inflammatory damage. Overall, the time of radiation dose deposition and the average dose rate are important factors that influencing the flash effect, this is also known as "DNA integrity".

Free radical reaction: ROS has been implied to play an important role in alleviating radiation induced damage to normal tissues(24). In classic radiation biology, both direct effect and indirect effect account for eradicating tumor cells. Previous study indicated the indirect effect of ionizing radiation initiate flash effect rather than the direct effect(25). Water radio- lysis confirmed that the production of free radicals was associated with significant differences between FLASH-RT and CONV-RT in diffusion phase(13). Oxidative stress involved in inducing the flash effect(26). Therefore, ROS generated by the indirect effect of ionizing radiation is essential for the flash effect.

Immune cell sparing: In addition, several groups have attempted to explain the flash effect from the perspective of immune cell sparing(27,28). CONV-RT can lead to lymphopenia, which is related to the dose received by circulating immune cells(29). Compared to CONV-RT, FLASH-RT has a shorter irradiation time, and a single high dose of FLASH- RT is beneficial in reducing the proportion of irradiated lymphocytes and lowering the induction rate of chromosomal aberrations(30). A glioblastoma dose measurement and blood flow model shows that immune cell depletion in FLASH- RT is approximately 4% of that in CONV-RT(27).

Tumor microenvironment remodeling: FLASH-RT has been reported to remodel the tumor microenvironment (TME), which comprises cancer cells, stromal cells, immune cells, vasculature, and extracellular components(15-31). Previous analysis demonstrated FLASH-RT contributed to vascular preservation by sparing endothelial cells and vasculature(31). Alleviated vascular damage prevents hypoxia-driven tumor progression and maintains nutrient delivery, potentially curbing aggressive tumor behavior. By sparing endothelial cells and vasculature, FLASH-RT maintains tumor oxygena- tion better than CONV-RT, which can induce hypoxia through vascular damage(15). The vascular preservation could enhance subsequent therapies reliant on oxygen-dependent mechanisms. Compared to CONV-RT, FLASH-RT may equivalent in promoting acute, pro-inflammatory cytokines (*e.g.*, interferon-γ, tumor necrosis factor-α) without chronic inflammation, balancing immune activation while avoiding tumor-promoting environments(32).

While these theories provide plausible explanations for the flash effect, the flash effect is likely a result of multiple interconnected mechanisms occurring at different spatiotemporal scales. The rapid depletion of oxygen and the altered kinetics of free radical reactions provide immediate protection to normal tissues, while mitochondrial and immunological changes contribute to long-term tissue sparing and repair. Thus, the flash effect should be elucidated from the perspective of physical, chemical, and biological cascades (Figure 1). Future research should focus on integrating these mechanisms into a unified framework and exploring the optimal clinical application of FLASH-RT.

FLASH-RT in animal trials

The efficacy and safety of FLASH-RT have been investigated in numerous animal experiments. Favaudon *et al*(3) used a mouse lung tumor model to deliver a single dose of 17 Gy FLASH-RT to the bilateral lungs and observed a significantly reduced lung fibrosis compared to CONV-RT 5-7 weeks later. Vozenin *et al*(33) replicated the flash effect in mini-pig models with a single dose reaching 28-34 Gy. 36 weeks post-irradiation, histological analysis showed skin fibrosis, necrosis, and keratinization was much more severe in the CONV-RT site than that in the FLASH-RT lesion, further analysis revealed inflammatory infiltration and epithelial cell remodeling were involved in regulating radiation-induced normal tissue damage; the number of hair follicles preserved in the flash-irradiated skin was significantly higher than that in the CONV-RT site, and immunofluorescence staining showed that epidermal cluster of differentiation 34 + stem cells were effectively preserved in the FLASH-RT group(33). In addition, the team included six cats with primary nasal squamous cell carcinoma (T2/T3N0M0) and administered electron FLASH-RT (single dose, 25-41 Gy), tumor lesions were successfully eradicated, only three cats developed mild to moderate radiation-induced acute dermatitis around the nose (33). Therefore, single high-dose FLASH-RT associated normal tissue damage is controllable.

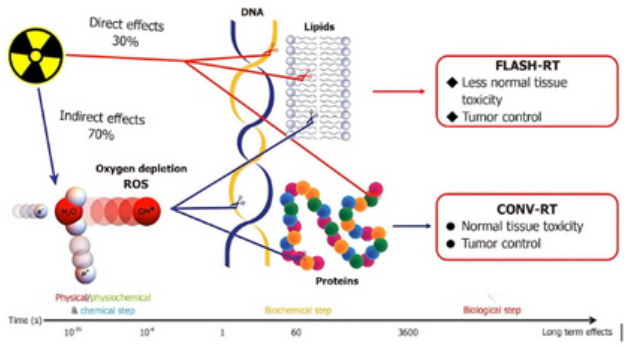
Subsequently, the University of Zurich collaborated with Lausanne University Hospital and conducted a phase III animal trial, cat patients with primary nasal squamous cell carcinoma were treated with either FLASH-RT (seven cases, single dose, 30 Gy) or CONV-RT (nine cases, 4.8 Gy × 10 fractions). Both groups experienced mild radiation-induced acute normal tissue damage, and tumors were well controlled at the first year. However, three cats in the FLASH-RT group developed maxillary bone necrosis 9-15 months post-FLASH-RT(34). This may be attributed to hotspots (42 Gy) in the irradiated area, which exceeded the tolerance of cat patients' maxillary bone and oral mucosa.

CURRENT STATUS OF FLASH-RT FOR CLINICAL TRIALS

Electron FLASH-RT

In 2019, Lausanne University Hospital conducted the first clinical trial of electron-beam FLASH-RT(35). The patient with cutaneous lymphoma had previously received CONV-RT, including fractionation regimens of 20 Gy in 10 fractions and 21 Gy in 6 fractions (average dose rate: 0.08 Gy/second), the patient had experienced Grade 3 radiation-induced acute skin damage. In contrast, a single dose of 15 Gy FLASH-RT (average dose rate: 166 Gy/second) was associated with grade 1 skin toxicity, and the skin injury alleviated in a shorter period. Moreover, tumors were eradicated at the irra- diated site. In the next two years, the tumor control rate of FLASH-RT was comparable to that of CONV-RT, and the late

Figure 1 The tissue response to ultra-high dose rate flash radiotherapy is the result of a series of physical, chemical and biological cascades. FLASH-RT: Ultra-high dose rate flash radiotherapy; CONV-RT: Conventional radiotherapy; ROS: Reactive oxygen species; H2O: Oxidant; OH: Hydroxyl radical.



radiation toxicities were similar between FLASH-RT and CONV-RT(36). This study demonstrated the feasibility of applying electron-beam FLASH-RT in human skin.

In 2021, Lausanne University Hospital registered a phase I dose-escalation clinical trial (22-34 Gy) of FLASH-RT for malignant melanoma of the skin (No. NCT04986696). In 2023, a phase II clinical trial for basal cell carcinoma and squamous cell carcinoma of the skin was registered (No. NCT05724875). Both studies are currently recruiting patients.

Proton FLASH-RT

In 2020, the Cincinnati Children's/UC Health Proton Therapy Center performed the world's first proton FLASH-RT clinical trial (FAST-01, NCT04592887)(37). 10 patients (aged 27-81 years) with painful extremity bone metastases were included. All the patients were previously treated with CONV-RT (8 Gy in a single fraction). A total of 12 metastatic lesions were eligible for proton FLASH-RT. The ProBeam proton radiotherapy therapy system was utilized to conduct FLASH-RT (a single dose of 8 Gy, dose rate of 60 Gy/second). The average treatment time of proton FLASH-RT was 15.7 minutes, the irradiation time was less than 1 second. Three months after FLASH-RT, completely or partially remission was achieved in 7 patients. Among the 12 irradiated lesions, 6 lesions achieved complete remission and 2 lesions achieved partially remission. FLASH-RT was comparable to palliative CONV-RT in relieving pain. Radiation-associated injury was mild, transient and mild skin pigmentation was identified as the most common side effects (Radiation Oncology/Toxicity grading grade 1), and there were no serious adverse effects after FLASH-RT. The results suggested that proton FLASH- RT was safety and clinically feasible.

Key parameters for these FLASH-RT clinical trials were shown in Table 1. With the encouraging results, the Cincinnati Children's/UC Health Proton Therapy Center initiated a prospective, single-arm clinical trial (FAST-02, NCT05524064) in 2022. Patients with painful bone metastases in the thorax were recruited, the study aimed to clarify therapeutic effect of proton FLASH-RT on pain relief, and evaluate radiation-associated injury to organs at risk including lung and heart.

THE CHALLENGES OF FLASH-RT FOR CLINICAL TRIALS

FLASH-RT device for clinical trial

Electron FLASH-RT: FLASH-RT can instantaneously deliver high-energy radiation. Currently, the energy of commonly used medical linear accelerators is limited, and a specific irradiation platform is required, or existing linear accelerators need to be modified to achieve FLASH-RT. The first human trial conducted by Lausanne University Hospital in 2019 used the Oriatron eRT6 electron linear accelerator developed by PMB-ALCEN. The dosimetric parameters used for FLASH-RT including an energy of 5.6 MeV, an average dose rate of 166 Gy/second, an instantaneous dose rate of 1.8 × 105 Gy/second, and can only penetrate tissues to a depth of about 3 cm. thus, the device is mainly designed for superficial tumors (38). The phase I clinical trial of dose escalated FLASH-RT (22-34 Gy) for cutaneous malignant melanoma was carried out by using the Mobetron intraoperative radiotherapy system(39). The Mobetron is a self-shielded electron beam linearccelerator designed by IntraOp Medical company in the United States. The average and instantaneous dose rate of Mobetron were 100 and 1000 Gy/second, this device can penetrate tissues to a depth of about 4 cm(40). Furthermore, there were several groups from European and United States successfully established electron FLASH-RT platforms by modifying the existing linear accelerators(41-44).

Very-high-energy electron (VHEE) beams have been explored recently. VHEE can penetrate deeply into the tissues with energy above 100 MeV(45). Compared with conventional energy electron beams commonly used in clinical practice, VHEE beams with energy of 250 MeV can be utilized to treat deep-seated tumors in the region 5 cm-30 cm(46). Moreover, VHEE has uniform dose distribution, high conformity and low scattering rate, which is superior to X-ray(47,48). It was confirmed that VHEE could effectively cause DNA damage based on the plasmid model, and approximately 99% of the damage was caused by indirect effects of radiation(49). However, whether VHEE beams can induce normal tissue sparing effect remains to be further studied.

Proton FLASH-RT: The penetration depth of low-linear energy transfer irradiation is limited, and electron FLASH-RT applies only to superficial tumors(50). Interestingly, the ProBeam proton system developed by Varian Medical System (United States) was capable of using to treat deep-seated tumors, with an average dose rate of 60 Gy/second and an instantaneous dose rate of 100 Gy/second(37). Protons have the advantages of strong tissue penetration, uniform dose distribution, high conformity, and Bragg peak(51). However, proton device is incredibly expensive and the cost is relatively high, which is not conducive to the large-scale utilization of FLASH-RT.

X - **ray photon FLASH-RT:** For medical linear accelerators that generates high-energy X-ray to prescribe CONV-RT, the X- ray was generated by electron flying through a periodic magnetic field(52). Nevertheless, the energy conversion rate (about 1%) is extremely low and current clinical systems are orders of magnitude too slow for general FLASH-RT(53). To achieve X-ray FLASH-RT, a more powerful accelerator and an electron-to-photon conversion target that can tolerate instantaneous ultra-high dose rate are required(54). The group from Stanford University established the Pluridirectional high-energy agile scanning electronic radiotherapy (PHASER) platform by using the next-generation medical linac technology to achieve image-guided photon FLASH-RT(55). The PHASER could obtain much higher beam currents (500 times) compared to conventional medical linacs to produce FLASH-RT. The group from China Academy of Engineering Physics established a platform for advanced radiotherapy research based on the superconducting electron accelerator, the device can produce FLASH-RT with an average dose rate up to 2000 Gy/second, and the instantaneous dose rate up to 9

× 106 Gy/second(56). Another group in Tsinghua University developed a compact linear accelerator to produce ultra-high dose rate X-ray, the average dose rates at source-surface distances of 50 cm and 70 cm were 80 Gy/second and 43 Gy/second, respectively(57). The results confirmed the feasibility of X-ray FLASH-RT with a room temperature radio- frequency linear accelerator system can perform FLASH-RT at a clinical source-surface distance, and is expected to provide a problem-solving technique for future X-ray FLASH-RT equipment development.

While FLASH-RT holds transformative potential, its broader application for deep tumors hinges on overcoming device-related dose rate and penetration barriers (Table 2). Innovations in accelerator technology, beam delivery, and radiobiology will be critical to unlock its full clinical utility. Moreover, it is worth noting that the cost of FLASH-RT platform is one of the important limiting factors for the promotion of clinical trials. To reduce the cost, designed for compactness, economy, intelligent, and clinical efficiency are required for FLASH-RT devices. Devices that was compa- tible with existing radiotherapy facilities can be considered. Compared with proton FLASH-RT platform, the VHEE linear accelerator has a cost advantage and may proposed for clinical application.

The implementation of FLASH-RT

Despite the advantage of FLASH-RT in reducing radiation damage to normal tissues, relevant clinical studies are still in their infancy. As an emerging technology, both clinicians and patients may be unfamiliar with FLASH-RT's benefits and risks, leading to hesitancy in trial participation. In addition, early-phase trials involve experimental protocols with uncertain long-term outcomes, complicating informed consent and recruitment efforts. Therefore, detailed implementa- tion guidelines should be established, and strict control over the indications is necessary(35-37). The clinical trial should be performed under the framework of International Ethical Guidelines for Health-related Research Involving Humans organized by World Health Organization, the project should be reviewed and approved by the ethics committee of the local institution. The eligible patients are associated with disease progression that may lead to life-threatening compli- cations, and FLASH-RT is expected to bring benefits. A FLASH-RT group that consists of at least two senior radiation oncologists, two radiation physicists and one radiologic technician should be established.

Dose and fractionation schedules in FLASH-RT

In CONV-RT, single-dose irradiation is often positively correlated with radiation-induced normal tissue damage(58). Fractionated radiotherapy is applied to maximize the eradication of cancer cells while minimizing adverse effects to normal tissues(59). Current evidence regarding the impact of dose rate on radiation-associated normal tissue damage is encouraging. Numerous of studies have validated that a single high-dose FLASH-RT can effectively reduce normal tissues damages(60). However, it is unclear whether the fractionation schemes and treatment modalities used in CONV- RT are equally applicable to FLASH-RT. Böhlen *et al*(61) suggested that the FLASH effect is tissue-specific and negatively correlated with the dose delivered. In the first patient treated with FLASH-RT at Lausanne University Hospital, the FLASH effect was not obvious(35). Furthermore, in a Phase III animal trial of feline primary squamous cell carcinoma, late radiation-induced normal tissue damage was observed(34).

This highlights the limitations of single high-dose FLASH-RT. Maity and Koumenis(62) suggested that the late radiation toxicities observed after FLASH-RT might be correlated with large irradiated field size. Vozenin *et al*(2) demon-

Table 1 Key parameters from ultra-high dose rate flash radiotherapy clinical trials

Trial phase	Tumor type	Dose rate (Gy/s)	Total dose (Gy)	Normal tissue toxicity	Tumor control	Follow-up
I	Cutaneous	166	15-35	Reduced skin fibrosis	Comparable	24 months
I	Bone metastases	200	8	Minimal myelopathy	Partial	9 months

Table 2 Summary of clinical trials and application scenarios for ultra-high dose rate flash radiotherapy with

Beam type	Energy/characteristics	Clinical application scenarios	Current trial phase	Key advantages	Limitations
Low-energy electrons	≤ 10 MeV	Superficial tumors (*e.g.*, skin cancers, cutaneous lesions)	Phase I trials ongoing	Mimics pre-clinical conditions for safety validation. Minimal normal tissue damage	Limited penetration depth (approximately 3 cm-5 cm). Restricted to accessible tumors
FLASH-VHEE	50-250 MeV	Deep-seated tumors (*e.g.*, lung, brain, abdominal)	Pre-clinical development	Higher penetration depth (up to 20 cm-30 cm). Potential for homogeneous dose distribution	Requires specialized accelerators. Technical challenges in beam control
Protons	70-250 MeV	Deep-seated tumors with critical organ proximity	Prototype development	Combines flash dose rates with Bragg peak precision. Enhanced normal tissue sparing	High infrastructure costs. Limited availability of flash-enabled systems
X-rays (linac-based)	6-20 MV	Broad applications (superficial and deep tumors)	Early feasibility studies	Utilizes existing linear accelerators with modifications. Flexible energy adjustments	Requires beam parameter optimization (dose rate ≥ 40 Gy/second). Limited clinical data

VHEE: Very high-energy electrons.

strated that FLASH-RT reduces radiation-associated normal tissue damages by approximately one-third compared to CONV-RT, and a single high-dose irradiation may concealed the potential normal tissue-sparing effect. Meanwhile, previous studies of FLASH-RT have indicated that a single irradiation dose of less than 5 Gy is insufficient to trigger the FLASH effect(25). Therefore, in daily clinical practice, the implementation of single high-dose or low-dose (single dose < 5 Gy) fractionated FLASH-RT should be approached with great caution. To achieve optimal normal tissue sparing effect without attenuating tumor control rates, hypo-fractionated radiotherapy may appropriate for FLASH-RT. Due to the unique radiobiological effects of FLASH-RT, whether biological effective dose or equivalent dose in 2-Gy fractions can be used to evaluate the therapeutic effects of hypo-fractionated FLASH-RT remains to be explored. Moreover, current studies typically focus only on the acute toxicities that occur after FLASH-RT, lacking long-term follow-up observations and in-depth mechanistic investigations of late complications.

Quality control and quality assurance of FLASH-RT

FLASH-RT is a novel technique for tumor treatment with an ultra-high does rate of more than 40 Gy/second, the irradiation time is extremely short compared to CONV-RT. The integrated process of FLASH-RT is complex and involves understanding of the principles of radiochemistry, medical physics, radiation biology, treatment planning, radiation dosimetry, simulation, radiation safety and protection to ensure accurate and safe delivery of treatment(35-37). The safety of FLASH-RT is of paramount importance, quality control and quality assurance are essential in before and during the application of FLASH-RT.

For CONV-RT, the American Association of Physicists in Medicine Task Group 142 report (TG 142) is itself regarded as a comprehensive guideline covering quality control recommendations for linear accelerators (linacs), while the Task Group 198 report (TG 198) provides the implementation details to ensure standardized operation in routine clinical applications(63). Based on these reports, it is essential to closely monitor dosimetric parameters related to ultra-high dose rates to minimize errors and maintain treatment accuracy. It is recommended that the quality control and quality assurance for FLASH-RT include the following parameters: Beam energy; Pulse repetition frequency; Duty cycle;

Temporal pulse structure; Beam intensity; Cumulative dose *per* irradiation; Dose *per* pulse; Instantaneous dose rate; Average dose rate *per* beam; Average dose rate *per* fraction; Dose distribution *per* beam; Dose distribution *per* fraction(64). Because the instantaneous dose rate of FLASH-

-RT is significantly higher than that of CONV-RT, ionization chambers and
semiconductors will achieve saturation during FLASH-RT(65,66). Alanine dosimeter, thermoluminescence dosimeter, GafchromicTM EBT films, and photoluminescence dosimeter has been utilized to measure the does rate of FLASH-RT(67, 68). The diamond detector exhibits a considerable linearity of does response to both electron and photon FLASH-RT, and could provide a relatively rapid and accurate dosimetry(69). The group from Tsinghua University designing a large dynamic range current measurement circuit based on the pre-integration method, and developed a diamond detector system prototype with real-time current output using a diamond sensor (B1-HV, CIVIDECTM Instrumentation, Austria) (70). The device is expected to be applied in the quality assurance of FLASH-RT. In addition, image-guided FLASH-RT can be considered to ensure real-time tracking of tumors and improve dose delivery. Overall, when implementing
FLASH-RT, optimal quality control and quality assurance is the cornerstone of giving correct and accurate dose to tumor, and reducing radiation damage to normal tissues.

FLASH-RT sensitivity

FLASH-RT is different from CONV-RT by sparing normal tissues, whether FLASH-RT has similar radiation sensitivity compared with CONV-RT is unclear. Sensitive to FLASH irradiation facilitate to further screening eligible patients for FLASH-RT. In the phase 3 animal trial of primary nasal squamous cell carcinoma in cats, one cat in the FLASH-RT group experienced disease progression 1-year post irradiation, while there was no tumor progression observed in the CONV-RT group(34). The results suggested that individual sensitivity to radiation may lead to different results. Previous bioinfor- matics analysis of human acute lymphoblastic leukemia showed that genotype may involve in regulating the sensitivity of FLASH-RT(11). However, the sample size for studies estimated the sensitivity of FLASH-RT is small, and further exploration is necessary.

Combined FLASH-RT with other anticancer treatment

FLASH-RT is emerging as a transformative modality in cancer treatment, particularly due to its unique ability to combine with other therapies to enhance efficacy and reduce toxicity.

Combination with immunotherapy: FLASH-RT has shown significant potential when combined with immunotherapy (14). This combination leverages the unique ability of FLASH-RT to modulate the TME by reducing immunosuppressive factors and enhancing immune cell infiltration(15). For example, FLASH-RT has been shown to decrease the expression of programmed death ligand 1 on tumor cells, thereby enhancing the efficacy of anti-programmed death-1 antibodies(14). Additionally, FLASH-RT reduces the levels of transforming growth factor-beta (TGF-β), a cytokine associated with tumor metastasis and immune evasion(3). This reduction in TGF-β can further augment the antitumor effects of immuno- therapy.

Combination with chemotherapy: Combining FLASH-RT with chemotherapy can potentially enhance the overall therapeutic efficacy by leveraging the complementary mechanisms of both modalities. CONV-RT often induces DNA damage, which can be synergistically enhanced by chemotherapy agents(71). FLASH-RT, with its unique ability to spare normal tissues while maintaining tumor control, may allow for higher doses of chemotherapy without exacerbating toxicity. However, further research is needed to optimize the sequencing and dosing of FLASH-RT and chemotherapy.

Combination with surgery: FLASH-RT can also be integrated with surgical interventions to improve outcomes. For instance, FLASH-RT can be used preoperatively to reduce tumor size and enhance surgical resectability, or postoperatively to eliminate residual cancer cells and reduce the risk of recurrence. The reduced toxicity of FLASH-RT compared to CONV-RT makes it an attractive option for patients undergoing surgical procedures, as it minimizes damage to surrounding healthy tissues.

Combination with CONV-RT: FLASH-RT can be combined with CONV-RT to optimize treatment outcomes. This combination can leverage the benefits of both modalities, such as the rapid delivery of high doses by FLASH-RT and the more prolonged, fractionated approach of CONV-RT. Studies have shown that FLASH-RT can reduce inflammation and vascular damage within the TME, which are common side effects of CONV-RT(15-32). This synergistic approach may enhance tumor control while minimizing adverse effects. The IMPULSE trial (NCT04986696) is exploring the use of FLASH-RT in treating skin metastases from melanoma, with initial findings indicating no dose-limiting toxicities at lower dose levels.

CONCLUSION

In summary, FLASH-RT is a milestone in cancer treatment. Preliminary clinical trial data indicate that FLASH-RT is feasible and safe. The extremely short treatment time per fraction significantly enhances work efficiency and offers the advantage of reducing radiation-induced normal tissues damage. Molecular and genetic studies are critical to decode FLASH-RT's unique radiobiology. By dissecting DNA repair dynamics, redox signaling, immune modulation, and epigenetic regulation, researchers can identify actionable targets to optimize FLASH-RT and expand its clinical utility. Collaborative efforts across radiobiology, genomics, and bioinformatics will accelerate translation from bench to bedside. In the near future, FLASH-RT is expected to undergo further clinical validation through ongoing Phase II trials in the United States and Switzerland. These studies will confirm its efficacy and safety across various cancer types. Technological advancements in proton and electron beam delivery will also enhance the applicability of FLASH-RT, allowing deeper tissue penetration and more precise targeting of tumors. This could enable higher radiation doses to be delivered, potentially improving cure rates for radioresistant tumors without increasing toxicity to surrounding healthy tissues. We look forward to more clinical trials to facilitate the clinical translation of FLASH-RT, so that cancer patients can benefit to a great extent.

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