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# Development of Ultra-High Dose-Rate (FLASH) Particle Therapy

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## Abstract

Research efforts in FLASH radiotherapy have increased at an accelerated pace recently. FLASH radiotherapy involves ultra-high dose rates and has shown to reduce toxicity to normal tissue while maintaining tumor response in pre-clinical studies when compared to conventional dose rate radiotherapy. The goal of this review is to summarize the studies performed to-date with proton, electron, and heavy ion FLASH radiotherapy, with particular emphasis on the physical aspects of each study and the advantages and disadvantages of each modality. Beam delivery parameters, experimental set-up, and the dosimetry tools used are described for each FLASH modality. In addition, modeling efforts and treatment planning for FLASH radiotherapy is discussed along with potential drawbacks when translated into the clinical setting. The final section concludes with

further questions that have yet to be answered before safe clinical implementation of FLASH radiotherapy.

**Keywords**

FLASH radiotherapy; proton radiation; electron radiation; heavy-ion radiation; FLASH effect modeling

## I. Introduction

The goal of radiotherapy is to employ ionizing radiation to eradicate cancerous cells, while minimizing radiation damage to adjacent healthy tissues. In the context of radiotherapy, dose is defined as the amount of ionizing radiation energy absorbed per unit mass of tissue. Particle therapy, i.e. radiotherapy using proton or heavier ion beams, can further reduce the radiation dose to healthy tissues. Their unique physical characteristic, known as the Bragg peak, see Fig. 1 (a), allows for a lower dose to be deposit along the path until the particles reach a well-defined depth (e.g. tumor position), where a peak of energy deposition occurs, followed by a sharp dose fall off at the distal end of the field (within a few millimeters) [1].

Conventional radiotherapy delivers the radiation dose at a rate of 0.02 Gy/s to 0.4 Gy/s. Recent developments using proton pencil beam scanning (PBS) may achieve higher instantaneous dose rates (~1-10 Gy/s) but the total time to deliver the entire treatment field is still like the double-scatter based proton radiotherapy. Recent pre-clinical studies have shown that irradiations at ultra-high (FLASH) dose rates (≥40 Gy/s) have the potential to improve healthy tissue sparing while maintaining the “curative” effects to the cancerous tissues [2]-[8]. Ionizing radiation beams at such high dose rates have been demonstrated for electron, photon, and proton beams (see Table 1). A pre-clinical study with a mini pig and a veterinarian clinical study on cats were also performed by Vozenin et al., confirming the advantages of electron FLASH irradiation. The cats were treated for locally advanced nasal squamous cell carcinoma and had a complete macroscopic response with mild to no acute toxicity [4]. Several groups are working on a path to translate FLASH radiotherapy (FLASH-RT) safely into the clinical setting. Bourhis et al. reported treatment of the first patient with multiresistant T-cell cutaneous lymphoma with FLASH-radiotherapy using a 5.6 MeV electron beam from an Oriatron 6e linear accelerator (linac) [9].

Although photon therapy is most widely used for cancer treatment, the production of Bremsstrahlung x-rays (photons) by high-energy electrons bombarding a target is not an efficient process. FLASH photon beams exceeding 40 Gy/s have not been realized in any commercial clinical systems yet, although several conceptual designs have been published [10,11]. Only research facilities using free-electron laser can achieve such a high dose rate [5]. Recently, a research team successfully achieved 6-8 MeV FLASH photons with dose rate up to 1000 Gy/s using a superconducting linac in a Free Electron Laser facility in China [12]. They successfully demonstrated the FLASH sparing effects in mice for lung and small intestine tissues while maintaining the same tumor control for breast cancers artificially introduced to the mice.

The concept of average and pulse dose rate will be introduced in Section II. Average dose rate for both quasi-continuous and pulsed beam delivery systems involves the total delivered dose and the total beam delivery time. For pulsed delivery systems, pulse dose rate relates to the dose delivered per pulse and the temporal pulse width. Across all FLASH modalities, average and pulse dose rates can be defined to compare temporal aspects of beam delivery systems.

The radiobiological mechanism(s) responsible for the healthy tissue sparing effect of FLASH-RT is still not fully understood. Several hypotheses have been proposed such as a reduction of reactive oxygen species (ROS) [13-17]. Many of these will be discussed in Section IV.

This review aims to summarize the developments to-date for multiple FLASH modalities with a focus on particles heavier than electrons. FLASH technology, dosimetry, and biological studies are reviewed with a discussion on possible radiobiological mechanisms responsible for the FLASH effect.

## II. FLASH Modalities

### A. Electron FLASH

Most FLASH irradiation studies have been carried out with high energy electron beams from dedicated research linacs, e.g. the 4.5 MeV electron beam from the Kinetron at Institute Curie (Orsay, France) and the 6 MeV electron beam from the Oriatron at CHUV (Lausanne, Switzerland) [2,18]. The availability of linacs that can reach these ultra-high dose rates was significantly increased when a paper from a research group at Stanford University (CA, USA) described how a clinical linac could be modified to deliver such beams while still maintaining clinical function. The group converted 9 and 20 MeV electron beams to FLASH beams from a Varian Clinac 21EX (Varian Medical Systems Inc., Palo Alto, CA) [19] by using an external system to control the beam delivery on a pulse-by-pulse basis. Radiobiological studies were performed by placing the mouse inside the linac head to achieve the desired dose rate (Fig 2). This was later also described for an 8 MeV electron beam from an Elekta Precise (Elekta AB, Stockholm, Sweden) linear accelerator by the group at Lund University (Sweden) [20], where ultra-high dose rates were achieved by removing the tungsten target from the beam path for MV photon beam delivery. A group at Dartmouth has recently described a similar method of converting a Varian Clinac 2100 C/D for delivery of 10 MeV electron FLASH beams, which is fast (20 minutes) and reversible (back to clinically acceptable specifications), reaching a dose-per-pulse of 0.86 Gy and an average dose rate of 310 Gy/s at treatment isocenter [21].

The main limitations for these beams are the large lateral penumbra and the limited depth of penetration of the electrons, which is limited to a few cm in tissue at these energies (Fig. 1 (a) and Fig. 3). While the finite range did not limit pre-clinical work in mice, relying on electrons at these beam energies would only allow superficial lesions to be clinically treated with electron FLASH-RT. Recently, intra-operative radiotherapy treatment (IORT) equipment, working at similar electron beam energies (5-12 MeV), have been upgraded to allow for ultra-high dose rate delivery, e.g. the Mobetron (IntraOP Medical Corporation,

Sunnyvale, CA), FLASHKNIFE (PMB-Alcen, Peynier, France), and the ElectronFLASH (Sordina IORT Technologies, Vicenza, Italy). Besides being able to be used for pre-clinical studies, IORT-systems could potentially be used for clinical trials of FLASH-IORT as well as for superficial tumors. However, in order to reach deep-seated tumors with external beam FLASH-RT, the energy of the electron beams must be substantially increased to very-high energy electron (VHEE) beams (hundreds of MeV) [22].

## B. Proton FLASH

Compared to electron radiotherapy, clinically used proton facilities offer an increased range (~4-32 cm for 70-230 MeV protons compared to ~1-7 cm for 4-20 MeV electrons) allowing to treat deep-seated tumors. Proton FLASH-RT has the potential to combine FLASH tissue sparing with the spatial advantages in shaping the dose (Bragg peak). Recent technological developments have allowed for the investigation of FLASH-RT using charged particles. As mentioned above, multiple studies have demonstrated possibilities for proton beam modulations to achieve FLASH dose rates [23-26].

Proton FLASH irradiations have recently been demonstrated using isochronous cyclotrons [23,25,27], and a synchrocyclotron [7]. In a cyclotron, a magnetic field guides the protons in circular paths while an electric field applied between the “dees” accelerates them. One of the main design considerations in a cyclotron is to compensate for the relativistic mass increase as the particles are accelerated. Two categories of cyclotrons exist to overcome that issue: 1) isochronous cyclotron in which the magnetic field is spatially modulated and 2) synchrocyclotron in which the frequency of the applied electric field is changed to assure that the protons are accelerated after each time they pass the dee. As schematically illustrated in Fig. 4, the output radiation from an isochronous cyclotron is quasi-continuous (nanosecond pulse structure), whereas radiation from a synchrocyclotron is pulsed (microsecond pulse structure). Protons – directed by the magnetic field – orbit many times in the vacuum chamber of the cyclotron before reaching their final energy at the exit window of the cyclotron. The energy of the exiting protons in a cyclotron is fixed to avoid extra complexity in the design. In proton therapy cyclotrons, an energy selection system (ESS), or range degraders are used to reduce the energy (range) of the protons in order to cover the whole treatment target with the radiation field. In that case a dose pattern known as “spread-out Bragg peak” (SOBP) is formed as a result of superposition of multiple pristine Bragg peaks with different ranges (Fig 1 (b)). In order to spread the beam laterally, either passive scattering systems or pencil beam scanning systems (PBS) are employed. Most modern proton therapy facilities use the latter mechanism.

Synchrocyclotron systems can better modulate the pulse dose and in comparison to cyclotron systems provide a platform to further investigate whether pulse dose rate or average dose rate is the main driver of the FLASH effect in proton therapy [7,28].

The average dose rate, $\dot{D}$, for a quasi-continuous beam can be calculated according to Eq. (1)

$$\dot{D} = \frac{D}{t} \tag{1}$$

in which $D$ is the total measured dose using the International Atomic Energy Agency (IAEA) Code of Practice TRS-398 protocol [29] and $t$ is the total beam delivery time.

The average dose rate for a pulsed output shown in Fig. 4 (b,c) can be calculated according to Eq. (2)

$$\dot{D} = \frac{Df}{N} \tag{2}$$

in which $N$ is the number of macropulses and $f$ is the pulse repetition rate.

The pulse dose rate, $\dot{D}_p$, for a pulsed output is calculated using Eq. (3)

$$\dot{D}_p = \frac{D}{N\tau} = \frac{\dot{D}}{f\tau} \tag{3}$$

in which $\tau$ is the temporal pulse width.

A proton FLASH implementation (Fig. 5 (a)) using a synchrocyclotron was recently demonstrated using a gantry-mounted clinical proton therapy machine (Mevion Medical Systems, Littleton, MA) [7]. The Mevion system employs a compact 8 Tesla superconducting synchrocyclotron to accelerate protons to 230 MeV (range ~32.0 g/cm$^2$). In order to deliver protons at FLASH dose rates, the alignment of the superconducting coil and several configurable parameters including the amplitude of the radiofrequency system, the emission voltage applied to the ion source and the pulse repetition rate were optimized. A boron carbide absorber block was placed in the beam path for range modulation. In this way a pristine Bragg peak with 4.1 cm range corresponding to 70 MeV proton energy over a ~1 cm$^2$ area was obtained. Average dose rates of 100 Gy/s and 200 Gy/s were measured at the entrance and at the Bragg peak, respectively, using a plane-parallel chamber (PPC05, IBA Dosimetry GmbH, Germany). More recently, the feasibility of creating SOBP beams at FLASH dose rates using the same system was demonstrated [34]. In order to create a SOBP, the authors used a “ridge” filter containing circular holes on a PMMA block placed upstream of the boron carbide absorber. An average dose rate of ~150 Gy/s was achieved over an ~1 cm$^3$ volume. The pulse dose rate was ~2 orders of magnitude higher than the average dose rate (see Table I).

Most studies to-date have been performed using the entrance plateau region of the proton depth dose curve, referred to as the shoot-through mode [7,23,27,32,35]. The benefit with this delivery technique is that only a single beam energy is used, which makes the delivery time much shorter and removes any issues related to range uncertainty. To fully take advantage of the physical characteristics of protons, the use of the Bragg peak in the form of an SOBP will be critical for conformal dose delivery. Since energy switching (that involves magnetic field changes) is a rather slow process, currently not well-suited for FLASH dose rate beam delivery, beam-modifying devices, such as ridge filters, may need to be used to create a usable SOBP. Limitations of these beam modifying devices include reduction of dose rate and the need for target/patient-specific devices, created for each beam to be delivered. The groups from Washington University and the University of Pennsylvania are

both investigating the potential for the use of SOBP for proton FLASH pre-clinical studies [34].

Proton FLASH implementation using an isochronous cyclotron with a transmission technique (Fig. 5 (b)) was recently demonstrated using an IBA proton therapy machine [23]. An X-ray small animal radiation research platform (SARRP) was placed in the proton research beam room [36]. The imaging capabilities of the SARRP was used to aid initial alignment and set-up for proton FLASH irradiation of mouse whole abdomen using the entrance plateau region of a 230 MeV (range ~32 g/cm$^2$) proton beam. A uniform 2 × 2 cm$^2$ field was created by using a double scattered system and collimation. A first scatterer was made of lead and placed in front of the beam exit pipe to spread the Gaussian beam shape. A metal ball-bearing was placed downstream to create the uniform field shape at the location of the target. FLASH dose rates (78±9 Gy/s) and standard dose rates (0.9±0.1 Gy/s) were used with the same beam energy and set-up geometry, differing only in cyclotron beam current, to irradiate mice [23]. FLASH dose rates significantly reduced the loss of proliferating cells in intestinal crypts compared with standard dose rates. Relative dosimetry was performed with radiochromic (GafChromic™ EBT3, Ashland Inc., KY, USA) film and absolute dosimetry was performed with a National Institute of Standards and Technology (NIST) traceable Advanced Markus® chamber (PTW Freiburg GmbH, Germany) with the IAEA TRS-398 protocol. A similar setup was achieved in [27] using a smaller treatment field (1.6 × 1.1 cm) with dose rates ~130 Gy/s.

In collaboration with Cincinnati Children's Hospital, Varian Medical Systems (Palo Alto, CA) demonstrated that a pencil beam scanning system could be used to deliver proton FLASH radiation for rectangular open fields, such as 5cm × 5cm up to 5cm × 12cm, in shoot-through mode using a 250 MeV scanning proton beam [37]. Dosimetry of FLASH delivery was validated to within 3% of ion chamber measurement using a calorimeter at approximately 65 Gy/s averaged dose rates for various rectangular fields. Varian and the Cincinnati Children's/UC Health Proton Therapy Center recently announced that they had started the first clinical trial of FLASH therapy, the FAST-01 study (FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases), using this beam and treatment technique [38].

### C. Heavy Ion FLASH

Ion-beam radiotherapy offers a highly conformal irradiation of tumors while sparing normal tissues. Ion beams feature a sharper lateral penumbra and Bragg peak compared to proton beams, but suffer from a fragmentation tail depositing a small amount (a few %) of the dose beyond the distal falloff, which will need to be accounted for in the treatment planning stage so that unnecessary dose is not deposited to sensitive structures beyond the target (Fig. 1 (a)). In comparison to conventional modalities (i.e. photons), ion beams may provide beneficial effects to the patients bearing radioresistant and inoperable tumors, in terms of both precision and effectiveness [39-41] due to their high linear energy transfer (LET) and RBE (relative biological effectiveness), partially overcoming radioresistance in hypoxic regions of tumors.

Biological effectiveness, depth and lateral dose distributions can differ between different particle beams [42,43]. Based on these differences and tumor characteristics, the optimal beam therapy could potentially be individualized for each cancer patient. For example, lower LET particles, such as protons, have a narrow range of RBE, which consequently has a reduced uncertainty in biological response and reduced risk of late tissue effects. Due to their lighter mass, proton beams exhibit larger lateral penumbra and range scattering that may affect treatment efficacy when precision is critical. On the other hand, heavier ions, such as carbon or oxygen ions, ensure a higher level of dose conformity, which improves tumor control while sparing normal tissues and organs at risk. Differently than protons, heavier ions exhibit significant RBE variations due to the higher LET, which must be explicitly considered in therapy planning [44-47]. Further optimization of particle radiotherapy could be achieved by combining heavy and light ions in a single treatment field [48] enabling uniform effective dose, RBE, and physical dose distributions within the target volume.

Considering higher LET particles, such as carbon ion beams, there is not yet much published FLASH data available [49]. This is mostly due to the limited number of carbon facilities for patient care (12 facilities world-wide as of March 2021 https://www.ptcog.ch/index.php/facilities-in-operation) and technical limitations of synchrotron accelerators to reach both higher dose and higher rates with multiple spills of accelerated particles [50]. Compared to clinically available photon, electron, or proton facilities, carbon ion centers tend to be larger in scale, additionally limiting their availability (Fig. 6). However, comparative investigations on low and high LET FLASH beams could shed a light on the oxygen depletion hypothesis formulated to explain FLASH sparing effect on healthy tissues [51]. The oxygen enhancement ratio (OER) is generally estimated to be 3 for low LET photons and protons, meaning that cell killing is roughly 3-fold greater in normoxic vs. anoxic conditions. In contrast, the estimated OER for carbon and other heavy ions varies with LET and is estimated to range from 2.5 (at low LET) to 1.0 (at high LET) [52]. Therefore, at depth of high LET, i.e. in the Bragg peak, heavy ions are more effective at killing cells in the hypoxic cores of tumors compared to low LET particles. Furthermore, assuming that oxygen depletion is the main driver of the FLASH effect, heavy ion FLASH-RT could be doubly effective. Ion FLASH-RT could spare healthy tissue in the entrance plateau region because of lower LET in this part promoting the FLASH effect, while sensitizing tumors by generating molecular oxygen at the Bragg peak [50].

In 2020 at the Heidelberg Ion Therapy Center (HIT) [53,54], accelerator settings were developed to realize FLASH dose rates). This was achieved by increasing the available number of particles per spill while decreasing extraction time resulting in an increase of average dose rate (from tenths to 100+ Gy/s). However, due to the limited number of particles per spill, a reasonable compromise between dose-level and irradiation field size must still be considered before performing biological experiments. Current projects at the HIT facility aim to increase the number of particles available per spill to achieve larger irradiation fields or at higher dose levels (> 8Gy).

GSI Helmholtz Center for Heavy Ion Research in Darmstadt, Germany has a heavy ion synchrotron accelerator that has undergone upgrades to be capable of delivering carbon ion

FLASH [55]. For FLASH dose rates, the theoretical carbon ion particle fluence needed was found to be $10^{10}$ $s^{-1}$ using the GSI system.

## III. Dosimetry

Accurate dose measurement is an integral part of radiation therapy quality assurance for pre-clinical and clinical studies. Various types of dosimeters including, ionization chambers, semiconductor-based instruments, and radiochromic films, each with their own advantages and limitations are routinely used for radiotherapy dosimetry. Ionization chambers are considered as “gold standard” dosimeters for radiotherapy machines calibration and absolute dosimetry [56-58]. However, at FLASH dose rate they can suffer from significant ion recombination effects resulting in a dose rate dependency [59,60]. Semiconductor-based dosimeters can provide high spatial resolution measurements, however, in addition to exhibiting dose rate dependency they suffer from angular dependency, long-term radiation damage, and non-“tissue equivalence” due to the relatively higher atomic number of silicon ($Z = 14$) compared to that of tissue ($Z \sim 7.5$) [61]. Recently, the technological efforts needed to develop a silicon-based device and its readout electronics for FLASH dose-rate monitoring was investigated and summarized by Patera et al. [62]. Radiochromic films with high spatial resolution and tissue-equivalent dosimetric properties cannot provide real-time measurement, they also suffer from LET dependency at particle therapy fields [63,64].

Absolute dosimetry is one of the challenges in FLASH irradiation due to the uncertainty in the dosimeter’s response to the ultra-high dose rates. Most dosimeters, even ionization chambers, which are subject to ion collection efficiency issues, manifest variant degrees of dependence on dose rate. These dosimeters should be used with extreme caution in the range of FLASH dose rates. When an ionization chamber is calibrated against a dose rate independent dosimeter, it can be used for absolute dosimetry of FLASH radiation fields as demonstrated in various studies. Although, with increased measurement uncertainty and limited to the specific characteristics of the calibration beam and dose rate. Other dosimeters for FLASH irradiation include calorimeter, Faraday cup, and thermoluminescent dosimeter (TLD), as recommended by ICRU report 78 [65] and other studies [66]. Of the three recommended dosimeters, calorimeter is bulky and time-consuming equipment that is not suitable for routine clinical and research use. TLDs are not real-time dosimeters and need to be traceable to NIST calibrations if used for absolute dosimetry. A sophisticated but viable option in a standard clinical and research setting is a Faraday cup, which collects the net charge in a beam. Unlike other dosimeters for which a correlation between the collected signals and physical dose can be established by either calibration or signal conversion, a Faraday cup collects the charge from particles regardless of energy, directions, and positions. The number of particles in a beamlet, together with the spatial distribution and energy spectrum, are used as input parameters for the calculation of absolute dosimetry with Monte Carlo simulation. However, this technique relies on meticulous benchmarking and validation.

A Faraday cup used for measuring the number of protons in a beam has to be placed upstream in the beamline immediately after the protons are retracted from a cyclotron in order to minimize the contamination with secondary protons, electrons, and other nuclei

from the interactions of protons with the components in the beamline. The measurements should be repeated until a solid correlation between the number of protons and the monitor unit (MU) chamber reading is established. This correlation converts MU to the number of protons in all the subsequent measurements and Monte Carlo simulations. An initial guess of energy spread in the proton energy is acceptable and further tweaked in the Monte Carlo simulation to match the measured integral depth dose. The beam divergence and spatial distribution of protons should be captured on films placed upstream in the beamline. Absolute dosimetry can be calculated with all the parameters and beamline components properly modeled in the Monte Carlo simulation.

When dealing with unexpected biological results, such as the FLASH effect, and when many research groups are now venturing into this new research field, accurate and comparable dosimetry of the delivered radiation is essential [3]. However, dosimetry in pulsed beams of ultra-high dose rates and similarly high dose-per-pulse values is non-trivial; as current radiotherapy dosimetry protocols are not designed for such conditions [57,67], and as online dosimeters (i.e. ionization chambers, diodes, and diamond detectors) experience significant drops in response when the dose rate/dose-per-pulse is increased beyond what is used in conventional radiotherapy [59-61]. Therefore, pre-clinical FLASH studies have mainly relied on passive dosimeters, validated to function accurately in such extreme irradiation conditions, e.g. radiochromic film (GafChromic™ EBT3 and EBT-XD), TLD chips, Alanine pellets, or Methyl Viologen [2,3,61,68,69]. The main limitation of relying on passive dosimeters is the time delay before readout of the delivered dose, which can be minutes to days. This complicates fine-tuning of the dose delivery, while real-time monitoring and control of the delivery require other tools, e.g. an induction torus or coils [18], charge collector plates [70] or simply relying on dosimeters for counting the number of pulses being delivered [18,71,72]. However, in recent publications some other types of on-line dosimeters, based on Cherenkov light dosimetry and calorimetry, have been presented as interesting options for real-time FLASH dosimetry [73,74]. Radiation-induced acoustic signals have also been demonstrated to be useful for FLASH dosimetry. Oraiqat et al. showed that ionizing radiation acoustic imaging using a phased array transducer could be used to take two-dimensional signal amplitude images that had a linear correspondence with pulse dose rate from a modified Varian linac producing electron FLASH beams [75]. Real-time imaging was achieved as well as for deep-tissue dosimetry in phantoms. However, there needs to be significant advancements in reconstruction algorithms for use in potential clinical settings and inhomogeneous materials.

The European Metrology Programme for Innovation and Research (EMPIR) is currently running a project called “UHD-pulse”, which is focused on “Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates” [76,77]. Furthermore, the American Association of Physicists in Medicine (AAPM), the European Society for Radiotherapy & Oncology (ESTRO), and the European Federation of Organisations for Medical Physics (EFOMP) have recently formed a joint Task Group (Task Group 359) with the aim to identify and address beam quality specifications and beam calibration issues that are related to FLASH-RT, in photon, electron, proton and heavier-ion beams. These ventures will surely result in several publications on dosimeters for FLASH radiation and a report with recommendations and guidelines for FLASH dosimetry.

## IV. Modeling of the FLASH effect

Despite an increasing number of experiments demonstrating FLASH tissue sparing, the underlying effects are still elusive. The most prominent potential mechanisms hypothesized are related to oxygen or effects on chemical reactions due to the involved time scales. FLASH irradiations are delivered within micro- to milliseconds, while conventional radiation therapy takes in the order of seconds to minutes. Therefore, the underlying mechanisms are likely related to processes that happen within the time lapse of FLASH pulses, suggesting chemical reactions. The fast delivery time could lead to a change in the pattern of DNA damage by low LET particles when delivered at ultra-high dose rates leading to intertrack reactions. other mechanisms have also been proposed, for example, related to the immune response [78,79]. The effect on immune response could be mitigated by a smaller fraction of the circulating blood volume being irradiated, potentially sparing circulating lymphocytes [80]. However, most modeling efforts focus on oxygen effects.

Spitz et al [15] suggested FLASH-RT normal tissue sparing while preserving tumor efficacy is due to three key aspects: instantaneous oxygen depletion and the ability of healthy cells to a) better regulate labile iron ions (Fenton chemistry) and b) more effectively remove organic hydroperoxides. In their qualitative analysis, a chain of reactions resulted in a possibly sufficient oxygen consumption to generate a FLASH effect. Similarly, Petersson et al. [81] modeled oxygen depletion for FLASH irradiations and concluded that oxygen depletion and a consideration of the oxygen effect can potentially explain the FLASH effect for tissue of intermediate oxygen tension, however, not for high or very low oxygen tensions. The analytical model from Praxt and Kapp suggested that the FLASH effect should be observed only in hypoxic cells [82]. These models state that with 0% oxygen or with very high concentrations of oxygen, there is no FLASH effect. Going a different direction, using a set of differential equations, Labarbe et al. [83] suggest the reduction in organic peroxyl radical (ROO.) lifetime via radical recombinations as an explanation for the FLASH effect.

However, in a response to Spitz et al., Koch [84] suggested that several of their assumptions needed refinement and that radiochemical oxygen consumption (ROC) could not explain the FLASH effect. Wardman [85] similarly cautioned against using reaction rates from pure water to model chemistry in a cell. His conclusion suggests that, while most of the modeling efforts so far do not consider the correct cell environments, there is a potential for chemical reactions to be the driving force behind the FLASH effect. However, many reaction chains in actual cell environments are not yet understood sufficiently to obtain accurate models.

Several Monte Carlo track structure codes tried to estimate the potential impact on chemical reactions. Ramos et al. [86] showed that inter-track reactions may affect G-values of solvated electrons and hydroxyl radicals at short time scales (<1ms). The inter-track effects are further LET-dependent showing a larger effect for low-LET protons. At high LET, reactive species are more concentrated in the track core, resulting both in recombinations and, on average, a larger distance between the adjacent tracks. Boscolo et al. [87] quantified higher oxygen consumption for irradiations of lower LET. The authors estimate doses over 150 Gy, instantaneously delivered, would be necessary for complete depletion of oxygen. Lai et al. [88] reported that doses of 30 Gy at dose rates of 107 Gy/s for 4.5 keV electrons

are not sufficient to fully deplete oxygen for a large range of initial oxygen concentrations. Interestingly, Zakaria et al. [49] suggest that high LET carbon FLASH-RT can be used to further increase the therapeutic ratio. Carbon ions produce molecular oxygen along their tracks but predominantly in the Bragg peak region. According to their calculations, the generated oxygen can potentially even overcome tumor hypoxia, thereby creating a more sensitive tumor tissue in the target region, while not producing sufficient oxygen to void the FLASH effect in the plateau region.

All these track structure simulations studies, however, are based on pure water simulations and did not include the full cell environment. Effects are likely smaller due to the presence of multiple scavengers. However, as pointed out by Wardman, it may not be necessary to deplete all oxygen to achieve a FLASH effect. While oxygen effects have been studied for decades, much work is still to be done to understand the processes within a cell at these short time scales.

Another focus in FLASH related modeling is understanding the possibilities and limitations for patient FLASH irradiations. Several groups have tried to determine clinical parameters for FLASH-RT, modeling clinical treatment facilities to estimate the (potentially) available dose rate phase space. Van deWaters et al. [89] compared dose rates for proton scanning patients using a conventional treatment plan, a standard spot reduced treatment plan, an arc-spot reduced plan (i.e. assuming up to 120 field angles rotating around the patient), and arc-spot reduced plan with a shoot-through delivery where higher energy protons are shot through the entire patient. For a 6 Gy fraction dose, they achieved dose rates well above 40 Gy/s in nearly the entire brain for a head and neck patient with the shoot-through method, albeit at the cost of increased integral dose in healthy tissue. The authors, however, used averaged dose rates, not spot specific dose rates or pulse dose rates. They also did not take into account any beam off time while rotating the gantry, showing a very idealized delivery situation. Zou et al. [90] discussed the current limitations of FLASH proton scanning therapy and conclude that, not considering energy switching times and magnet slew times, treatment fields of up to $4 \times 4\ cm^2$ can be delivered with dose rates above 40 Gy/s. Larger fields could be achieved using patched fields, depending on the radiobiological mechanism of FLASH therapy. Gao et al. [91] developed an optimizer to simultaneously optimize dose and dose rate, however, the appropriate weighting would still have to be determined by experiments.

Modeling efforts are of great interest to help understand the underlying mechanisms of the FLASH effect. At the same time, they are used to estimate the feasibility of translating FLASH-RT into the clinic, assuming certain dose and time constraints to induce FLASH tissue sparing. However, many open questions remain as the radiobiological data to constrain the models is still very limited. Thus, additional modeling work and radiobiological studies are undoubtedly in the work that will continue to try and find answers or guide the next experiments.

## V. Future Work and Ongoing Challenges

There are a number of questions to be answered before safe and effective clinical translation of FLASH-RT. All pre-clinical and clinical studies to date have been with small field sizes. While this is adequate for smaller pre-clinical models such as mice and small lesions, this is impractical for most of the tumors targeted in the clinic.

With proton and carbon ion particle therapy, there still remain many questions with regards to the shoot-through technique versus using the Bragg peak. With the shoot-through technique, a uniform dose and dose rate can be delivered easily; however, this technique results in deposition of a great deal of exit dose distal to the target and may require multiple treatment fields to achieve a reasonable dose conformality to the target. On the other hand, if FLASH-RT is delivered with the Bragg peak or an SOBP, the areas proximal to the target will be exposed to doses that are potentially delivered with lower dose rates than necessary to induce FLASH tissue sparing. Further biological studies need to be done to investigate these challenges, which include the effects of FLASH delivery using multiple fields and/or over multiple fractions. Results from these studies may lead to new treatment planning techniques and optimization based on dose rates and different target structures.

As more pre-clinical studies are performed, it is important to accurately report all dosimetric parameters used for all published studies. Average dose rate and the definition of dose rate with regards to the pulse structure, if any, should be reported. Any ion recombination correction effects should be investigated and stated to provide adequate data for comparing results across different modalities and institutions.

An additional complication with FLASH-RT is the delivery of conformal treatment doses via multiple fields. Conventional radiotherapy involves multiple fields to deliver an optimal dose distribution that is conformed to the target. With FLASH-RT, the time between treatment fields may become a significant concern. Mechanical limitations will hinder the delivery of the entire dose at a single FLASH dose rate. Effects of delivery of multiple fields with high dose rates with varying times between the fields will need to be studied. Treatment planning studies must be performed with incorporation of the realistic beam delivery times. Delivery of a SOBP requires stacked monoenergetic Bragg peaks, the energy switching time needs to be incorporated in the models. Additionally, multiple beams will require gantry rotation time that will affect the overall treatment delivery time structure. Fractionation effects and accuracy of FLASH with low dose delivery is still unknown.

Other challenges include questions regarding quality assurance and validation of FLASH-RT treatment plans in real-time. And last, while FLASH-RT may be delivered in time scales fast enough to counteract internal organ motion, there are still challenges with synchronizing the pre-treatment imaging with the timing of the FLASH beam delivery.

Despite these challenges, the potential to spare healthy tissue selectively in radiation therapy has prompted a large amount of research projects in multiple fields including dosimetry, delivery, treatment planning, mechanistic modeling and radiobiology. As long as the observed benefit can be translated into clinical scenarios and maintain improved

treatment outcome, FLASH-RT will become another option to treat patients in the near future.

## VI. Conclusion

FLASH radiation therapy shows to be a promising treatment modality for cancer and has created great interest in the radiation oncology community. This review summarizes the different FLASH modalities using electrons, protons, and heavy ions along with their dosimetry techniques, challenges, and findings so far with regards to radiobiological studies. With different beam generating devices, there are different pulse structures and there is a need for standardization in order to compare beams, effects and mechanisms across modalities. Future radiobiological studies, clarifying the mechanism behind the FLASH effect, will be essential to deduce what the optimal particle, pulse structure, and beam delivery technique is for the safe and effective clinical implementation of FLASH-RT.

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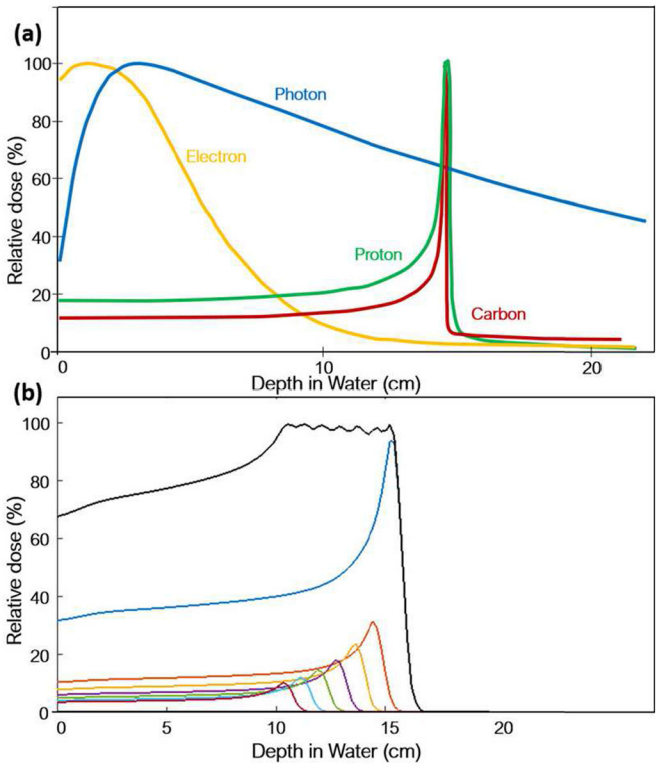


**Fig. 1.**

(a) Representative percent depth dose curves for photon (blue, ~6 MV), electron (yellow, ~18 MeV), proton (green, ~145 MeV), and carbon ion (red, ~300 MeV/u) beams in water. (b) Representative depth dose curve for a proton spread out Bragg peak (black) with the weighted monoenergetic Bragg peaks (multicolored) used to generate the spread out Bragg peak.

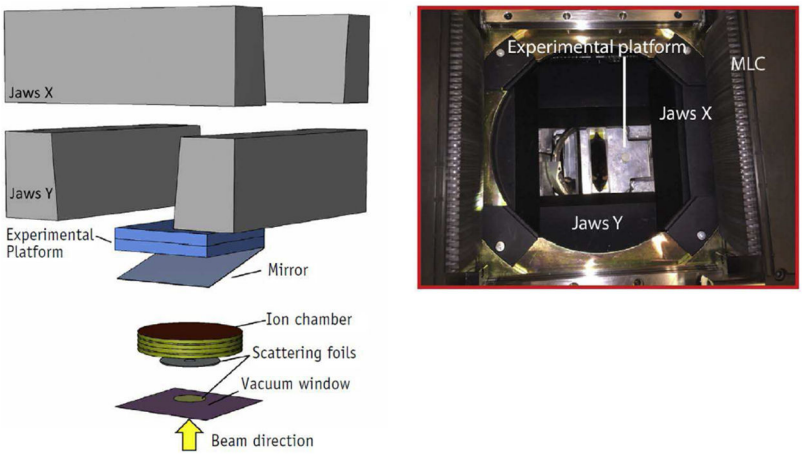


**Fig. 2.**

Setup geometry of radiobiological studies with electron FLASH. The mouse was placed inside the linac head to achieve the desired dose rate (adapted from [19])

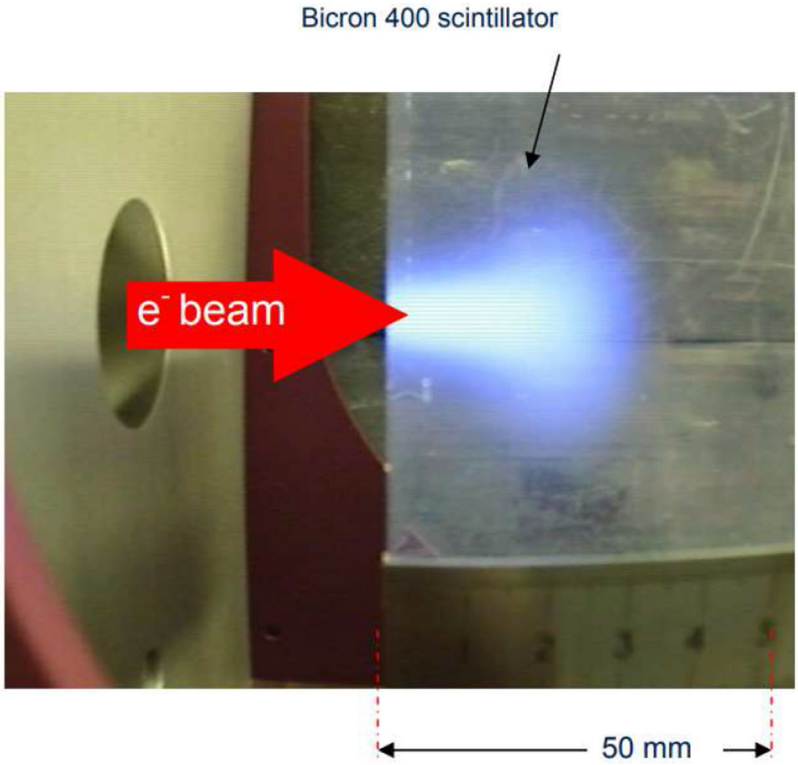


**Fig. 3.**

Dose distribution visualized in a water/tissue equivalent material (plastic scintillator BC-400, Saint-Gobain Crystals, with optical emission at 423 nm) from a 6 MeV electron beam at ultra-high dose rates at the linear accelerator at the University of Oxford (courtesy of Prof Borivoj Vojnovic).

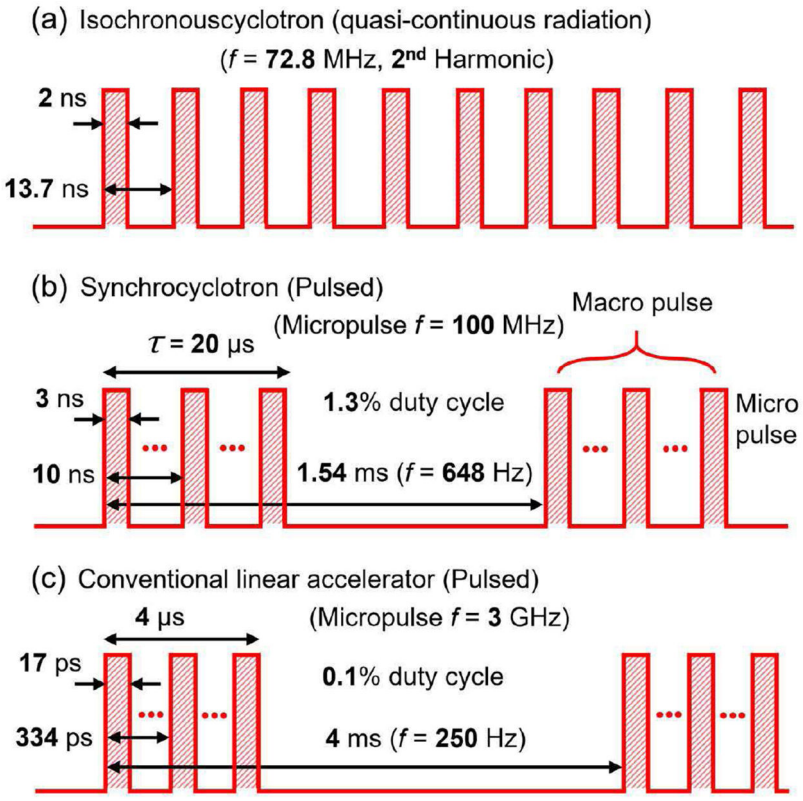


**Fig. 4.**

Schematic of typical macropulse and micropulse structure of (a) an isochronous cyclotron with quasi-continuous beam, (b) a synchrocyclotron with pulsed output, and (c) a medical linear accelerator with pulsed output (drawn not to scale). In (b) and (c), each macro pulse consists a number of micro pulses (adapted from [7]).

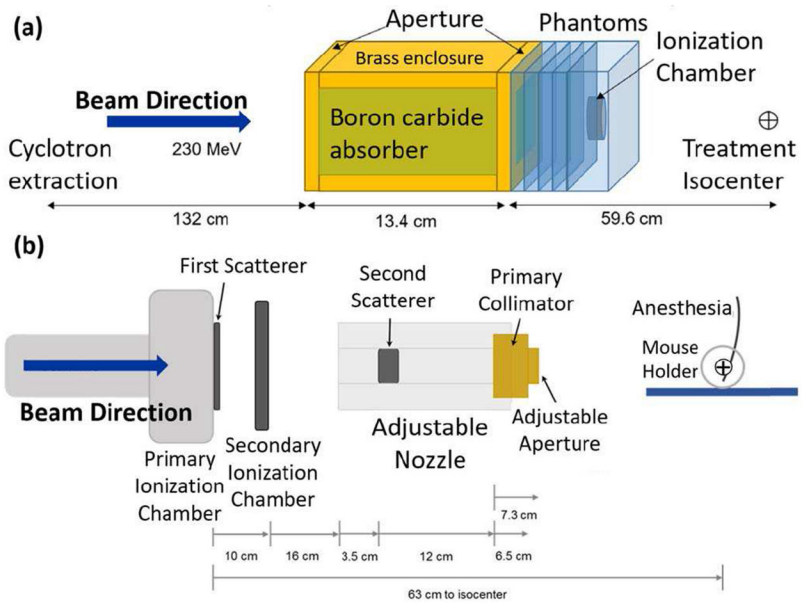


**Fig. 5.**

Proton FLASH study setup geometry for (a) synchrocyclotron and (b) isochronous cyclotron implementations (adapted from [7,23]).

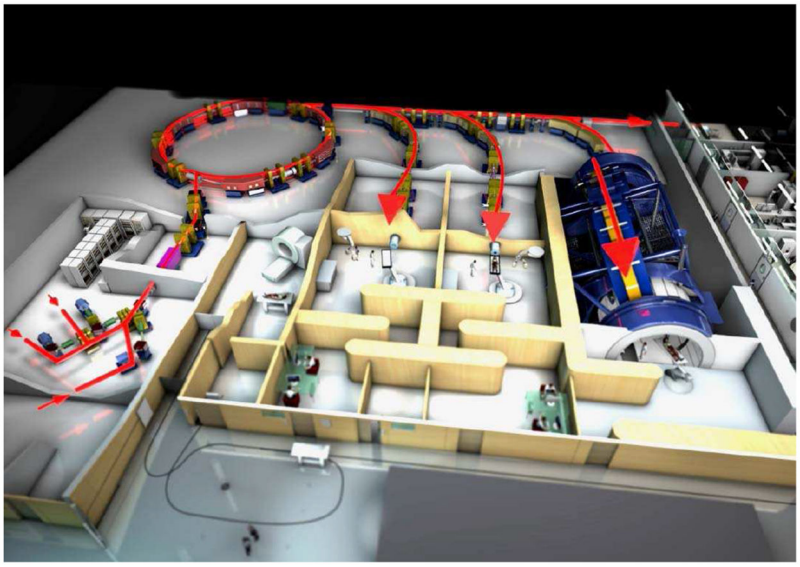

**Fig. 6.**

A 3D model of Heidelberg Ion Therapy Center (HIT) showing the magnitude of a carbon ion facility (with permission from University Hospital Heidelberg).

**TABLE I**

Summary of FLASH radiation beams reported in recent literature (adapted from [7]).

| Year | Radiation Type | Machine | Energy (MeV) | Average Dose Rate (Gy/s) | Pulse Dose Rate (Gy/s) | Pulse Repetition Rate (Hz) | Purpose |
|---|---|---|---|---|---|---|---|
| 2014 | Electron [2] | Kinetron linac [30] | 4.5 | 60 | $5\times10^6$ | 19 | Mouse (Bilateral thorax irradiation) |
| 2017 | Electron [3] | Oriatron 6e linac | 6 | 100 | $5\times10^6$ | 100 | Mouse (Brain irradiation) |
| 2017 | Electron [19] | Varian 21EX | 9 & 20 | 35-210 | $1.7\times10^6$ | 182 | Dosimetry |
| 2018 | Photon [5] | European Synchrotron Radiation Facility [31] | 0.102 mean | 37 | $1.2\times10^4$, in the scanned 50 μm beam slice | Continuous | Mouse (Brain irradiation) |
| 2018 | Proton [25] | IBA isochronous cyclotron | 138-198 | 40 | N/A | 106.14 MHz (quasi-continuous) | Dosimetry |
| 2019 | Electron [20] | ELEKTA Precise linac | 8 | 30-300 | $4\times10^4$-$4\times10^5$ | 200 | Dosimetry |
| 2019 | Electron [4] | Kinetron linac and Oriatron 6e | 4.5 & 6 | 300 | $5\times10^6$ | Not provided | Mini-pig (skin) and cat (nasal tumor) |
| 2019 | Electron [9] | Oriatron 6e linac | 5.6 | 150 | $1\times10^6$ | 100 | Human patient (skin) |
| 2019 | Proton [32] | Varian isochronous cyclotron | 245 | 40 | N/A | 72.8 MHz (quasi-continuous) | Mouse study (whole thorax irradiation) |
| 2020 | Proton [23] | IBA isochronous cyclotron | 230 | 80 | N/A | 106.14 MHz (quasi-continuous) | Mouse (abdomen irradiation) |
| 2020 | Proton [7] | Mevion synchrocyclotron | 70 | 100-200 | $8\text{-}16\times10^3$ | 648 | Feasibility study for a synchrocyclotron |
| 2020 | Proton [27] | IBA isochronous cyclotron | 228.9 | 130 | N/A | 106 MHz (quasi-continuous) | Mouse (partial abdomen irradiation) |
| 2020 | Photon[12] | Superconducting linac | 6, 8 | 800 | N/A | Quasi-continuous | Mouse (lung, intestine, tumor) |
| 2020 | Electron[33] | Intraoperative linear accelerator | 3, 5, 7, 9 | 3 | 0.03-18 | 5-30 MHz | Dosimetry |
| 2021 | Proton [34] | Mevion synchrocyclotron | 60 | 120-160 | $9.3\times10^3$ | 750 | Feasibility of SOBP beam using a synchrocyclotron |
| 2021 | Proton[35] | Varian superconducting cyclotron | 250, 244 | 57, 115 | N/A | 72 MHz | Mouse (leg contracture) with pencil beam scanning |