



# Flash Radiotherapy – Window of Opportunity at an Embryonic Stage

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## SUMMARY

No tumor group can be irresponsive to chemotherapy, especially radiotherapy, when applied in sufficient doses. However, in most cases, it is not possible to give effective doses that can destroy the tumor due to side effects and damage that may occur in healthy, normal tissues. Although current technological possibilities transmit the rays to the target area and protect the surrounding healthy tissues and organs much more effectively than before, there is a need for more studies and scientific content on this subject. FLASH-RT has theoretical advantages over conventional radiotherapy. Giving radiation in small, daily doses helps protect healthy cells by giving more time to repair. However, new research shows that there may be a way to deliver radiation at record speeds while sparing healthy tissue. FLASH (ultra-high dose rate radiotherapy), an innovative technique, uses electrons to target tumors while minimizing damage to healthy tissue. More importantly, FLASH is claimed to achieve these effects in less than a second, which can exponentially shorten the duration of radiation sessions. Recent studies indicated how using proton radiation instead of electrons or photons and other technical tweaks could turn FLASH into a powerful tool that can deliver radiation in milliseconds. Significant technological advances are needed to generate FLASH photons, potentially protons, very high energy electrons, and heavy ions. Such radiation sources will allow the required dose distribution to be obtained at more immense depths inside the human body, where most tumors occur.

**Keywords:** Conventional radiotherapy; FLASH radiotherapy; pulse radiation; tumor tissue; ultra-high dose rate radiotherapy.

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## INTRODUCTION

More than half of people diagnosed with cancer receive radiation therapy. Radiation damages the DNA of cancer cells, slowing their progression or killing them. However, this is a slow process; radiation does not destroy cancer cells immediately; sometimes, it takes weeks of treatment to damage the cells' DNA enough to destroy them.[1] Another reason why radiation therapy may take several weeks is because the treatment is

most likely successful when the cancer cells grow and divide into new cells. Therefore, extending treatment over a longer period increases the chance that radiation will target cancer cells while they are growing. Radiotherapy treatment is applied to individuals over days or weeks. The main reason for such an application is to minimize possible side effects.[2]

No tumor group can be irresponsive to chemotherapy, especially radiotherapy, when applied in sufficient doses. However, in most cases, it is not possible

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to give effective doses that can destroy the tumor due to side effects and damage that may occur in healthy, normal tissues. Although current technological possibilities transmit the rays to the target area and protect the surrounding healthy tissues and organs much more effectively than before, there is a need for more studies and scientific content on this subject.[3] It is essential to divide radiotherapy treatment into session-by-session doses and allow time between sessions for healthy, normal tissues to renew. This process is intense for patients, the radiotherapy team, and doctors. At this point, it would be an appropriate step, considering the psychological pressure, for the patient individual to complete his ongoing intensive treatment and return to his life comfortably. The possibility of flash radiotherapy within seconds is exciting for science.[4]

In radiation therapy, a treatment method specifically targeted to a specific area, radiation energy neutralizes cancer cells. Radiotherapy ionizes atoms. It is planned to damage the DNA structures of tumor cells to kill them. This damage occurs by breaking the double helix structure in DNA. However, both normal and cancerous cells in the area where the treatment is given are affected by this situation. However, the damage sustained by healthy normal cells is repaired much more quickly. Cancer cells, on the other hand, are targeted at proliferation and grow much faster. Therefore, it lags behind healthy cells in detecting and repairing DNA damage. There is a specific limit for healthy cells to be exposed to radiation. In this process, attention should be paid to the balance of the amount of radiation given to the individual, which should be adjusted carefully. The process of dividing the total dose to be delivered in treatment by certain levels daily, that is, the fraction, allows healthy cells to repair themselves.[5,6]

Side effects shown may vary from person to person. However, it also depends on the area being treated and the characteristics of the tumor. There are also many factors, such as total dose, dose in each application, and the person's sensitivity to radiation therapy. In addition, other treatment methods the person receives, if any, may also be effective. During the process, swelling may occur in the tissues.[7] Edema may occur. If applied to the abdominal area, nausea and vomiting may occur. Depending on the application area, wounds and inflammation may occur. When applied to the lower abdomen, it may cause problems in the urinary tract and intestines. Edema decreases after treatment, and side effects disappear.[5–7]

The technique, called flash radiotherapy, where shots are fired for up to seconds, and the dose rate is between 30 and 106 Gy/s, offers a procedure several hundred

times faster than conventional radiotherapy. Scientific studies show that the lethal effect on the mass is similar to regular radiotherapy, but the side effects on healthy tissues are minimal. Radiotherapy aims to destroy cancer cells and minimize damage and any side effects to the rest of the body.[8] "FLASH" Therapy, an innovative technique in radiation therapy, claims short-term pulses of electrons at very high dose rates are less harmful to healthy tissues but are as effective as radiation at classical dose rates in inhibiting tumor growth. It has been tested with low-energy electrons in small animals at a high dose rate (>40–100 Gy/h), 2000 times faster and 1000 times more intense than conventional radiotherapy. The "Flash Effect" is the improvement of the tolerance of healthy tissue to the given radiation dose.[8,9]

## UNDERSTANDING TARGET PULSE RADIATION

It is important to get acquainted with the mechanism of radiation delivery to the target in terms of time, dose, and structural changes produced by radiation at both the molecular and tissue levels. The commercially available linear accelerators generate beams in pulses at regularly specific intervals. This process differs significantly from older radiotherapy delivery techniques (Cobalt-90 units), which emit gamma radiation through radioactive decay.[10]

The radiation leaves the output of linac in pulses. The duration and energy transported in a pulse (average dose) depends on the properties of the source of electrons and the properties of the accelerating device generating high-frequency (50–300) Hz. The dose absorbed in the tissue depends on both electrons' energies (related to their acceleration) and their quantity (number). The clinical radiation accelerators deliver much fewer electrons per pulse than industrial accelerators, where much higher beam intensities are needed. The conventional radiotherapy pulses can be sequenced with 100 Hz (at 10 ms intervals).[10,11]

In the case of an example, the dose rate at a standard condition in a phantom is 0.02 Gy/s (1.2 Gy/min), then during a session of 2 min, a fraction dose of 2.4 Gy is delivered in 12000 pulses. The dose delivered during one pulse is 0.0002 Gy, and the dose rate within a pulse is around 50 Gy/s. In FLASH radiotherapy, the duration of treatment and average dose rate are assumed to be <200 ms and bigger than 40 Gy/s. Assuming the literature reported a pulse sequencing scheme of 100 Hz,[12] we can calculate the number of pulses per treatment from a few to 20 (for 200 ms). Data from various studies tell us that the dose rate within the pulse

ranges from 105 to 106 Gy/s. If the pulse duration is 1.8–2.0  $\mu$ s, the dose delivered during one pulse of 0.2 Gy, respectively (for 105 Gy/s and 2.0  $\mu$ s). A significant difference can be achieved in the magnitude of both time and energy load per pulse between conventional radiotherapy and FLASH RT: Average overall dose rate 0.02 Gy/s versus 40 Gy/s; dose rate within pulse 50 Gy/s versus 105 Gy/s; the dose delivered during one pulse  $2 \times 10^{-4}$  Gy versus 0.2 Gy. However, the sequencing of pulses can be similar in both modes, 50–300 Hz, as well as the duration of the pulses 1–4  $\mu$ s. The treatment duration required to deliver 8 Gy in these two modes is the consequence of the energy load per time unit and can be around 8 min versus 0.2 s.

Although the aforementioned innovation poses a window of opportunity, it also escalates challenges on accurate dose adjustment and dose-response relationship. To obtain a dose of 8 Gy in 200 ms requires an increase in the energy transported per time unit, which requires strengthening the energy transported per pulse and perhaps also by producing more pulses per time unit (higher frequencies such as 300 vs. 50 Hz) or prolonging the pulse duration. As FLASH technology must transport significantly more energy within a pulse, we need sources emitting thousands more electrons per pulse.[10,13]

## ADVANTAGES OF UTILIZING PROTONS

The main physical property of the proton is that it is superior to photons due to its “Bragg peak.” Until the desired depth is reached, it leaves less of its energy than the photon in normal tissues, while at the desired depth, that is, in the tumor tissue, it discharges all of its remaining energy and resets. Since it releases its energy into the tumor after this depth, there is no unnecessary exit dose and no irradiation in normal tissues. Therefore, the damage to healthy tissues remains minimal.[14] On the other hand, the photon proceeds by discharging its energy from the moment it penetrates the body; there is no extra energy transfer at the desired depth, and it leaves the body, continuing to release a dose after the tumor. Therefore, the integral dose of particle therapy compared to photon is 3 times less. The relative biological effect of protons is 10–15% more effective than that of photons. Depending on the depth, the relative biological effect varies between 1 for photons, 1.1 for protons, and 1.2–3.2 for carbon. Although it is not an ideal ray with these features, it is preferable to the photon. In some treatments performed with photons, the desired dose cannot be delivered to the tumor

due to the limited doses of critical organs. In particle treatment, higher doses can be given to the tumor.[15]

Uveal melanoma is one of the cancers most commonly treated with proton. Other areas of use are the treatment of pediatric cancers, cranially located tumors (chondroblastoma, chordoma), head-and-neck cancers, brain and spinal cord, pelvis, para-aortic tumors (seminoma), spine tumors, lymphomas, prostate cancer, digestive system cancers, breast cancer, eye, and second series irradiations.[16] Especially in patients with a very high probability of definitive cure, such as lymphoma, the probability of secondary cancer due to radiotherapy increases up to 30%. It may be recommended that proton be preferred first in treating such cancers seen at a young age. The lower radiation dose delivered to normal tissue by the proton compared to the photon reduces the risk of secondary cancer and the acute and chronic side effects of radiotherapy.[17]

Although the majority of cancer types for which radiotherapy is applied are included in the field of use of proton therapy, primarily pediatric tumors are a priority. To minimize secondary cancers that may occur as a result of radiotherapy in children, the basic principle is to keep the integral dose received by the whole body to a minimum, and proton therapy provides this best. The most critical success of proton therapy in pediatric tumors is that it improves treatment-related morbidity by delivering a significant reduction in the permanent harmful effects that may occur due to long-term radiotherapy in children and a reduction in the development of secondary tumors.[18] Thus, the role of particle radiotherapy in the treatment of pediatric tumors is gradually increasing as the possible long-term side effects of radiation and radiation-related morbidity in children will decrease. This significant increase in the treatment success rate is very promising and may result in photon therapies being replaced by proton therapies in childhood tumors in the future.[19]

Briefly, the advantages of particle radiotherapy can be elaborated as being more biologically effective than photons and, therefore, may increase the chance of response to treatment. In addition, resistant tumors that do not respond to conventional radiotherapy can be effectively treated. It can easily reach tumors deep in the body. Charged particles are accelerated to more than a quarter of the speed of light and targeted at the tumor tissue.[20] Depending on speed and energy, charged particles can reach up to 30 cm within tissue. However, as photons travel to a deeper tumor, they release most of their energy to the surrounding tissues and are more effective up to 3 cm deep into the tissue.[21] Destruc-

tive effects are powerful with heavy ions. This effect allows for treating some cancers, such as chordomas and chondrosarcomas. Ions reach the tumor more precisely, releasing their destructive energy more accurately – surrounding healthy tissue is protected, and fewer side effects develop. This is especially important for tumors close to vital tissues such as the skull base, optic nerve, or intestine. Proton therapy is especially preferred in children because it protects more surrounding healthy tissue than traditional treatments, and fewer late side effects are expected. Thus, growth-developmental plates in children are more protected and reduce the development of secondary cancer.[20–22]

### **MECHANISM OF ACTION IN FLASH RADIOTHERAPY**

The main logic that lies beneath high-dose radiation with FLASH-RT is healthy tissue protection compared to conventional radiotherapy. The biological mechanism of FLASH radiotherapy is not fully elucidated but is mainly based on two hypotheses. The first one is believed to be the “oxygen effect,” which scavenges free oxygen species and removes and decays free radicals. The second mechanism is explained through the distinct immune and inflammatory response compared to conventional radiotherapy, leading to enhanced anti-tumor effects.[23]

### **REACTIVE OXYGEN SPECIES-MEDIATED CELL DAMAGE-THE OXYGEN EFFECT**

The ultra-high dose radiation rates contribute to oxygen depletion in normal tissues, thereby inducing radioresistance, which means that healthy tissues surrounding the target can tolerate radiation better. Evidence is based on animal studies (Mouse model).[24,25] and bacteria and eukaryotic cellular models suggest that FLASH-RT induces instant oxygen depletion, leading to transient, radiation-induced hypoxia.[26,27]

The tumor cells are composed of oxic, hypoxic, and anoxic populations, whereas normal tissues depend on oxygen supply. One study showed that a 10 Gy radiation dose delivered to the brain by FLASH-RT resulted in lower primary oxygen tension in the target tissue than in the skin, providing a neuroprotective effect.[28] Vozenin et al.[29] evaluated FLASH doses at 50 pulses per second (10 MeV electrons) to mouse tail skin using variable pulse sizes and pulse repetition frequencies. In a mouse model, two other studies assessed the effects of 1–10 pulses (1.8–2  $\mu$ s) of FLASH-RT on lung and

brain tissues, demonstrating that higher dose rates reduce treatment-related toxicity.[28,30] These findings suggest that response is primarily determined by total dose exposure time. Recent studies indicated that the FLASH effect can be achieved with shorter radiation times (<200 ms) and higher intrapulse rates.[29]

### **IMMUNE AND INFLAMMATORY RESPONSE**

The data on immune and inflammatory responses are controversial. In animal studies, it was elaborated that DNA damage and inflammation indicated the signaling pathway of TGF was downregulated in mice.[31,32] TGF has been identified as a critical factor in the radiation resistance of tumor-infiltrating T cells, and additionally, it was stated that TGF- signaling inhibits the immune system and promotes cancer progression, leading to the conclusion that inhibitors targeting the TGF pathway may enhance the treatment of malignant tumors.[33] Flash irradiation, characterized by reduced treatment time, allows more circulating immune cells to survive than conventional radiotherapy. Rama et al.[34] found that Flash proton beams improved the control of lung tumors, possibly due to the recruitment of CD3+ T lymphocytes into the tumor. Compared to conventional dose rates, the ultra-high dose radiation (UHDR) induced a 1.8-fold increase in TGF-levels 24 h after irradiation, while conventional dose rates led to a 6.5-fold increase.[35] This suggests that flash radiation has the potential to reduce radiation-induced chronic inflammation. The absence of an inflammatory response may contribute to the modulation of immune and inflammatory processes within the tumor microenvironment. Chromosomal aberrations might occur after radiotherapy and are related to the duration of exposure and volume; however, to date, Flash therapy has not been associated.[36] At 10-week post-irradiation in mice, conventional dose rates led to a statistically significant increase in five out of ten tested cytokines, while flash radiation only increased three cytokines. These results showed that flash-RT induced fewer pro-inflammatory cytokines compared to conventional radiotherapy.

### **DOSING CHALLENGE IN FLASH RADIOTHERAPY**

The dosing adjustment in conventional radiotherapy depends on achieving biological response. A well-established fractionation scheme exists rather than a dose rate by clinicians. A majority of the radiotherapy

techniques utilize only a few linacs, all of which generate radiation using similar technology with similar dose rate schemes. On the contrary, FLASH-RT requires significant magnification of energy transfer in a short period. Measurement accuracy is challenging due to the time intensity of pulsed energy transport. A precise description of the physical parameters is essential to ensure proper induction of the FLASH effect in biological tissue and to select the optimal pulse size and repetition frequency of the FLASH dose.[36,37]

## VERY HIGH ENERGY ELECTRONS (VHEE)

The use of VHEE, in the range of 50–250 MeV, can penetrate greater depths. However, their use is limited due to technical issues related to electron acceleration in a conveniently sized medical device, neither too big nor too complicated. The additional advantage is that the dose distributions of VHEE electrons seem less dependent on body inhomogeneities than those obtained using protons.[38]

## DISCUSSION

FLASH-RT allows for the delivery of 8 Gy in only 0.2 s; by comparison, it would take approximately 20 min to deliver the same dose with CyberKnife. The treatment of deep-located tumors requires highly adapted image-guidance techniques. As a matter of fact, ultrafast dose delivery obviates the need to compensate for tissue and tumor motion during radiation delivery.[29] Deeply located tumors are non-reachable by electrons generated by medical linear accelerators (up to 25 MeV).

Radiotherapy is required to produce a therapeutic dose at depths >15 cm in the body. For this reason, electron beam FLASH-RT is unlikely to revolutionize radiotherapy due to the simple fact that the benefits of this technique are only applicable to skin cancers or tumors located within a few centimeters of the body surface. Possible solutions are photon or proton beam-based FLASH-RT or VHEE.[39]

Conventional radiotherapy is based on 15 MV photon beams, which is sufficient to obtain good dose coverage for all tumors due to the properties of the interaction between photons and tissues. However, to get ultra-high dose rates for photons, we must first solve technical challenges related to the low efficiency of converting electron beams to photon beams. Only a tiny fraction of the energy fluence of electrons is transferred to photons, with most of the energy dissipated through various

phenomena, including heat. This means that a FLASH photon accelerator must have a source capable of producing many more electrons (by a factor of 1000) than is achievable with currently available devices, and further on, the problems with the acceleration of such quantity of electrons and their energy transfer to photons have to be solved.[40,41] Protons of energies around 200 MeV or carbon ions of 300 MeV/n can have a sufficient range in the body (15–20 cm) to deliver energy on therapeutic depth for most tumors. Girdhani et al.[42] compared conventional radiotherapy to FLASH-RT with proton beams to assess possible lung-sparing effects and the impact on normal tissues, finding that proton-based FLASH-RT may spare normal tissues (both acute and late) due to a superior immune response.

Bourhis et al.[43] have utilized FLASH-RT in a real-world setting to treat humans for the first time at the Lausanne University Hospital using the Oriatron eRT6 5.6-MeV linac, a prototype specifically constructed to accelerate electrons in FLASH mode. A patient with T-cell cutaneous lymphoma (diameter: 3.5 cm) received 15 Gy delivered in 90 ms. At 3 weeks, treatment-related toxicity was limited to Grade 1 epitheliitis and transient Grade 1 edema in the soft tissues surrounding the tumor. The tumor response was rapid, complete, and durable (5-month follow-up). FLASH-RT was found feasible and safe, thus warranting further clinical evaluation.[43]

FLASH-RT may be indicated in two main clinical scenarios: (i) The treatment of radioresistant tumors and (ii) the minimization of radiation-induced toxicity when the high doses needed for local control would result in unacceptable toxicity if delivered with conventional radiotherapy. In the first scenario, dose escalation could be achieved without inducing additional radiation-related side effects, potentially improving the therapeutic index. In the second scenario, FLASH-RT could reduce treatment-related toxicity while still earning a reasonable degree of local control. This potential benefit of FLASH-RT is essential given that many patients are not candidates for radiotherapy because they cannot tolerate the high doses needed for local disease control. In this regard, it is worth noting that it may be possible to generate the FLASH effect at lower doses, which would further expand the clinical potential of FLASH-RT; however, more research is needed in this area.[44,45]

Last but not least, another factor that must be considered in FLASH-RT is the biological diversity in most cancers. Given that all effects occur on a cellular level, tumors of different origins located in different environments may respond differently to the dose rate used in FLASH-RT.[44]

## CONCLUSION

FLASH-RT has theoretical advantages over conventional radiotherapy. Giving radiation in small, daily doses helps protect healthy cells by giving more time to repair. However, new research shows there may be a way to deliver radiation at record speeds while sparing healthy tissue. FLASH (ultra-high dose rate radiotherapy), an innovative technique, uses electrons to target tumors while minimizing damage to healthy tissue. More importantly, FLASH is claimed to achieve these effects in less than a second, which can exponentially shorten the duration of radiation sessions. The new study shows how using proton radiation instead of electrons or photons and other technical tweaks could turn FLASH into a powerful tool that can deliver radiation in milliseconds. Significant technological advances are needed to generate FLASH photons and potentially protons, VHEE, and heavy ions. Such radiation sources will allow the required dose distribution to be obtained at more immense depths inside the human body, where most tumors occur.

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