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FLASH radiotherapy: an emerging approach in radiation therapy

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ABSTRACT

FLASH radiotherapy (RT) is a technique involving the delivery of ultra-high dose rate radiation to the target. FLASH-RT has been shown to reduce radiation-induced toxicity in healthy tissues without compromising the anti-cancer effects of treatment compared to conventional radiation therapy. In the present article, we review the published data on FLASH-RT and discuss the current state of knowledge of this novel approach. We also highlight the technological constraints and complexity of FLASH-RT and describe the physics underlying this modality, particularly how technology supports energy transfer by ionising radiation (e.g., beam on/off sequence, pulse-energy load, intervals). We emphasise that current preclinical experience is mostly based on FLASH electrons and that clinical application of FLASH-RT is very limited. The incorporation of FLASH-RT into routine clinical radiotherapy will require the development of devices capable of producing FLASH photon beams.

Key words: FLASH RT; radiotherapy; ionising radiation; ultra-high dose rate; dosimetric parameters; biological effect; FLASH electrons; FLASH photons

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Introduction

Radiation therapy has long been a cornerstone of cancer treatment and the anti-tumour efficacy of this treatment continues to improve in line with advances in our understanding of tumour biology and in imaging and radiation delivery. Using current technology, highly conformal radiation beams can be delivered precisely to the target, thus minimising damage to surrounding healthy tissues. Nevertheless — despite the availability of sophisticated radiotherapy techniques (IMRT, SBRT, among others) — the probability of completing eliminating the cancerous tissues is dose dependent, which is limited by the risks of severe radiation-induced side effects.

The limitations of conventional radiotherapy could potentially be overcome by an emerging technology known as flash radiotherapy (FLASH-RT), which is defined as the ultrafast delivery of radiation at dose rates that are several orders of magnitude greater than those used in conventional radiotherapy (40 Gy/s *vs.* 0.5–5 Gy/min, respectively) [1]. FLASH-RT has theoretical benefits support-

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ed by preclinical data suggesting that the delivery of doses to the tumour target using significantly higher dose-rates (FLASH) could achieve better disease control with fewer side effects. If the advantages of FLASH-RT — mainly improved safety and efficacy — are confirmed in clinical trials, this novel technique could potentially transform the field of radiation oncology, becoming the dominant radiation therapy modality for certain tumours, and perhaps even replacing conventional radiotherapy in the future. Nonetheless, despite the enormous promise of this new modality, there is still much we do not know and substantially more research is needed.

Overview of protective effect on healthy tissues and clinical evidence

Robust preclinical data show that FLASH-RT causes less damage to healthy tissues than conventional radiotherapy [1, 2]. The theoretical mechanism underlying this protective effect is the ultrafast delivery of radiation doses (measured in milliseconds), which induces oxygen depletion and transient hypoxia, thereby providing a protective effect in normal tissues but not in cancer cells [2, 3]. Research suggests that the rapid dose delivery may increase normal tissue tolerance, thus allowing for higher tolerance of total doses with better cure rates [3–5]. This is important given that the side effects caused by the unavoidable irradiation of critical organs during radiotherapy represent a major concern in radiotherapy, limiting the curative potential of radiotherapy for many cancers, particularly those located near critical organs such as the heart and lungs. Perhaps the most significant advantage of FLASH-RT is its potential capacity to overcome radiation resistance through the delivery of single, high dose fractions ≥ 10 Gy [6], which cannot be achieved with conventional radiotherapy due to tolerance parameters for normal tissues [3].

The body of preclinical data supporting FLASH-RT continues to grow and one clinical report has also been published [1, 7]. In that study, FLASH-RT was used successfully to treat a patient with subcutaneous T-cell lymphoma, who achieved a complete and durable tumour response with minimal toxicity [7]. However, substantially more data — both preclinical and clinical — are needed to better understand the clinical effects of FLASH-RT, especially its effect on immune response. At present, the clinical evaluation of FLASH-RT is limited due to the lack of appropriate radiation delivery systems. While current systems can be modified to deliver FLASH-RT, a new generation of machines will be needed before this technique can become more widely available for clinical use [8, 9].

Pulsed energy delivery by ionising radiation to the target

Before discussing the technical limitations of currently available linear accelerators (linacs), it is important to understand how radiation is delivered to the target in terms of time and dose rate as this is crucial to the discussion of the structural changes produced by radiation at both the molecular and tissue levels. Linear accelerators produce beams in pulses, which can be emitted regularly at certain intervals, a process that differs significantly from older radiotherapy delivery techniques (Cobalt-90 units), which emitted gamma radiation through radioactive decay.

The time-intensity structure of energy transportation is complex. The radiation leaves the output of linac in pulses. The pulse parameters — that is, the duration and the value of energy transported in a pulse (ultimately expressed by the average dose rate) — depends on the properties of the source of electrons and on the properties of the accelerating device, generating high frequency microwaves (magnetron or klystron, if this is used to amplify microwave power). Example sources of high frequency sinusoidal microwaves work on inner frequencies of around 3 GHz. Pulses (typically of rectangular shape) of duration usually from 1 to a few microseconds are sequenced with frequencies of 50–300 Hz, depending on the purpose for which radiation is to be used, thus making intervals between pulses respectively from 20 to 3.3 ms. The dose absorbed in human body depends on both electrons' energies (related to their acceleration) and their quantity (number). In radiotherapy the electrons energy is predefined by a depth of tumours in the body, which must correlate with electrons range in tissues. The number of electrons depends on the properties of the source. The accelerators built-up dosimetry system controls "output dose" and adjusts either the number of electrons emitted by source or pulse frequency. In clinical radiation accelerators, the source delivers much fewer electrons per pulse compared to industrial accelerators, where much higher beam intensities are needed.

Consequently, the number of electrons per pulse, number of the pulses produced in a period of time and pulses duration along the quality of accelerating device describe capacity to carry and deliver energy to the accelerator output and correspond to the output dose-rate.

To show the difference between time-dose delivery structure between conventional and FLASH radiotherapy we will discuss the following example.

In conventional radiotherapy pulses can be sequenced with 100 Hz (at 10 ms intervals) and can be 4 μs long. If we assume example dose-rate measured at standard condition in a phantom of 0.02 Gy/s (1.2 Gy/min) then during a session of 2 minutes a fraction dose of 2.4 Gy is delivered in 12000 pulses. Thus, 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 duration of treatment and average dose rate are assumed to be less than 200 ms and bigger than 40 Gy/s. Assuming the literature reported pulses sequencing scheme 100 Hz [6], we can calculate the number of pulses per entire treatment from a few to 20 (for 200 ms). Data from various studies tell us about dose-rate within the pulse from 10^5–10^6 Gy/s. If we assume the elsewhere reported duration of the pulse of 1.8-2.0 μs, then we come to a dose delivered during one pulse of 0.2 Gy, respectively (for 10^5 Gy/s and 2.0 μs).

We can notice a significant difference 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 vs 40 Gy/s; dose-rate within pulse 50 Gy/s *vs.* 10^5 Gy/s; the dose delivered during one pulse 2×10^{-4} Gy *vs.* 0.2 Gy. The sequencing of pulses can be, however, similar in both modes 50–300 Hz as well as duration of the pulses 1–4 μs. The treatment duration required to deliver 8 Gy in these two modes is consequence of the energy load per time unit and can be around 8 minutes *vs.* 0.2s.

Thus, the time-dose relationship between conventional radiotherapy and FLASH-RT has many differences, which poses a significant technological challenge in terms of accurate dose measurements, as well as our understanding of the biological response. 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 eg. 300 *vs.* 50 Hz) or prolonging the pulse duration. Because FLASH technology must transport significantly more energy within a pulse, we need sources emitting thousands more electrons per pulse.

Petersson et al. [10] described the potential to convert conventional linacs into FLASH devices. To better control the delivered dose and to estimate pulse-to-pulse deviations, the FLASH beam must be controlled at the dose level rather than at the pulse level by lowering the gun current or utilising a dose monitoring system for each pulse [11]. However, accomplishing this would require modifying the linac. High, stable yields can be achieved by implementing a warm-up procedure before administering FLASH-RT, although — as the preliminary results reported by Lempart et al. demonstrate [11] — fine-tuning the resonance frequency of the accelerator could be an alternative to warm-up. Nevertheless, to ensure that the expected treatment outcome is safely achieved, the machine will require further refinement. Built-in dosimetric devices must be developed to support the high degree of accuracy required in clinical applications. The inner dosimetry systems must be capable of monitoring transport of energy at the accelerator output and provoke adjustment of number of electrons emitted or pulse frequency if a dose at the output is not equal to the value predefined by the operator for the current treatment. Despite the technological hurdles, current studies show that this can be done [1, 3, 7]. The technology underlying these processes is extremely complex and beyond the scope of the present article. However, the key takeaway is that it can impact biological findings.

Magnitude of the FLASH dose rate. What is the optimal rate?

Recent studies in mouse models have shown that the protective effect of FLASH-RT for healthy tissue depends on the dose rate, with rates of 100 Gy/s providing significantly greater protection that lower rates (e.g., 33 Gy/s). However, as discussed above, the dose rate by itself is insufficient to describe the expected biological response. Other variables, including the dose per pulse, dose rate during the pulse, pulse duration, interval, and overall irradiation time, must be considered [3, 4].

In their review of the literature, Bourhis and colleagues noted that increasing the dose rate improved

the effectiveness of FLASH-RT in a mouse model [3]. In another study (mouse model), Montay-Gruel et al. showed that increasing the mean dose delivery rate from 33 to 100 Gy/s reduced brain toxicity and preserved spatial memory in irradiated mice [12].

Biological effect of FLASH dose rate delivery

Administration of a single, high dose of radiation with FLASH-RT provides better normal tissue protection than can be achieved with conventional radiotherapy [2–5]. The mechanism by which FLASH-RT reduces normal tissue toxicity is believed to be due to differences in biological response of normal and cancer cells, mainly in terms of radiation-induced rates of removal and decay of free radicals, which explains the beneficial therapeutic index of FLASH-RT. However, volume effects can limit some of the biological benefits of ultra-high dose rates, leading to scattering of scanned beams, which reduces oxygen consumption [13].

Oxygen tension between normal and cancerous tissues is one of the keys to better understanding FLASH-RT. Ultra-high dose rates contribute to oxygen depletion in normal tissues, thereby inducing radioresistance, which means that healthy tissues surrounding the target are able to better tolerate radiation. Studies performed to assess intestinal and skin toxicity in mouse models [14, 15] and bacteria and eukaryotic cellular models [16–18] suggest that FLASH-RT induces instant oxygen depletion, leading to transient, radiation-induced hypoxia. This is relevant because tumours are comprised of oxic, hypoxic and anoxic cell populations whereas normal tissues are usually well supplied with oxygen and have a system to maintain their proper oxic state. 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 [12]. However, this effect is dependent on the specific brain region or measurement technique used to determine oxygen tension.

Vozenin et al. evaluated FLASH doses at 50 pulses per second (10 MeV electrons) to mouse tail skin using variable pulse sizes and pulse repetition frequencies [4]. Two other studies assessed the effects of 1–10 pulses (1.8–2 μs) of FLASH-RT on lung and brain tissues in a mouse model, demonstrating that higher dose rates reduce treatment-related toxicity [2, 12]. These dependencies suggest that response is primarily determined by total dose exposure time. Previous studies have shown the presence of the FLASH effect when the irradiation time is less than 4.5 s, with the intrapulse dose rate having only a small effect [4]. By contrast, more recent studies suggest that the FLASH effect can be achieved with shorter radiation times (< 200 ms) and higher intrapulse rates [4]. At present, it is not clear whether the immune response following FLASH-RT contributes to the FLASH effect and other biological responses, such as DNA damage and inflammation, could also contribute to this effect. More studies are needed to clarify these questions.

Dosimetric parameters describing FLASH-RT — physics underlying biological effects observed

In conventional radiotherapy, the dose is considered to be the primary parameter determining biological effects. The time-dose relationship expressed by the fractionation scheme (rather than by the dose rate) is well-understood and is widely supported in clinical practice by radiobiological models [19–22]. Indeed, this approach fits well with real clinical practice as most radiation techniques use only a few types of linacs, all of which generate radiation using similar technology with similar dose rate schemes. However, FLASH-RT has changed this scenario, requiring significant magnification of energy transfer in a short period of time.

The characteristics of the aforementioned effects in biological tissue and in vivo are described by dose, which must be measured. However, accurate measurement is challenging due to the aforementioned time-intensity structure of pulsed energy transport. The physical and chemical processes used for dose measurements are dependent on time. An accurate 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.

Experimental studies are still limited by the lack of suitable detectors capable of measuring the beam fluence of the FLASH effect online. Suitable detectors must fulfil three main requirements: 1) compliance with the requirements of both preclinical and clinical studies, 2) 100% reliability, and 3) suitable for use in existing linear accelerator facilities [23].

Accurate and reproducible dosimetry can be ensured by using passive dosimetric detectors [10, 24]. Vignati et al. evaluated a silicon sensor application used as a sensing device for FLASH-RT and its readout electronics, finding that this technology could monitor photon beams over the entire FLASH dose range. However, for electrons, this device was limited to the lower end of the dose range [23]. Chemical dosimeters are a promising approach to measuring high-dose rates; however, due to dose rate dependence at low dose rates or few doses per pulse, chemical dosimeters are unable to quantify an inhomogeneous dose rate distribution. The Cherenkov detector presents the highest theoretical time resolution (on the order of ~ps), making this detector the leader for online monitoring of machine productivity, regardless of dose rate dependence. Ashraf et al. [22] compared dosimetric tools at high dose-rates and concluded that luminescent detectors including Cherenkov and scintillation-based detectors are promising for real-time dosimetry at FLASH dose-rates due to their remarkable dose-rate independence. The thermoluminescent detectors (TLD) and optically-stimulated luminescence detectors (OSLD), which are used to passively measure doses, can also be considered in FLASH-RT due to their dose rate independence.

FLASH-RT: improved target accuracy due to the short delivery time

Crucially, ultrafast dose delivery obviates the need to compensate for tissue and tumour motion during radiation delivery [4]. FLASH-RT allows for the delivery of 8 Gy in only 0.2 s; by comparison, it would take approximately 20 minutes to deliver the same dose with CyberKnife. If FLASH-RT can eliminate the risks associated with intratreatment organ and tumour motion, this would further support the use of higher doses for the treatment of certain cancers in which dose elevation is likely to yield better clinical results. Undoubtedly, for the treatment of deep-located tumours, highly adapted image-guidance techniques are required as well.

Technology needed to treat tumours lying deeper than several centimetres

Majority of tumours are located at depths that are non-reachable by electrons generated by medical linear accelerators (up to 25 MeV). Therefore, the radiation must be able to produce therapeutic dose at depths greater than 15 cm in the body. For this reason, electron beam FLASH-RT is unlikely to revolutionise radiotherapy due to the simple fact that the benefits of this technique are only applicable to skin cancers or tumours located within a few centimetres of the body surface. Possible solutions are photon or proton beam-based FLASH-RT or use of very high energy electrons (VHEE).

Very high energy electrons (VHEE)

The use of very high energy electrons, range of 50–250 MeV (VHEE), which can penetrate to greater depths, is limited due to technical issues related to electron acceleration in a conveniently-sized medical device (i.e., a device that is neither too big nor too complicated). However, works are carried out to build suitable accelerators [24, 25]. Additional advantage is that dose-distributions produced by VHEE electrons seem to be less dependent on body inhomogeneities than those obtained using protons [26].

Photon beam-based FLASH-RT

In general, conventional radiotherapy is based on 15 MV photon beams, which is sufficient to obtain good dose coverage for all tumours due to the properties of interaction between photons and tissues. However, in order to obtain ultra-high dose-rates for photons, we must first solve technical challenges related to the low efficiency in how electron beams are converted to photon beam. Only a small fraction of the energy fluence of electrons is transferred to photons, with the majority of the energy fluence 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 acceleration of such quantity of electrons and their energy transfer to photons have to be solved [3, 27].

Proton beam-based FLASH-RT

Protons of energies around 200 MeV or carbon ions of energies 300 MeV/n can have sufficient range in the body (15–20 cm) to be able to deliver energy on therapeutic depth for majority of the tumours. Buonanno et al. [28] and Beyreuther et al. [29] both evaluated the use of proton beams to deliver

FLASH-RT. Previous studies have shown that proton radiation involves higher dose rates delivered in nanoseconds than those prescribed to achieve FLASH effects [30, 31]. Irradiation times of 100 ms for conventional radiotherapy is still too short to induce the FLASH effect. Girdhani et al. [32] 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. As discussed by Hughes et al. [1] further study is needed on the impact of growing LET at the Bragg peak on the FLASH effect and on physiological oxygen concentrations.

Clinical experience

The first clinical use of FLASH-RT in a real-world setting to treat humans was described by Bourhis et al. who performed this treatment at the Lausanne University Hospital [7] using the Oriatron eRT6 5.6-MeV linac, a prototype specifically constructed to accelerate electrons in FLASH mode. In that study, a patient with a T-cell cutaneous lymphoma tumour (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 oedema (CTCAE, v5.0) in the soft tissues surrounding the tumour. Moreover, the tumour response was rapid, complete, and durable (5-month follow-up), leading the authors to conclude that FLASH-RT appears to be both feasible and safe, thus warranting further clinical evaluation. Those findings, considered together with the growing body of preclinical data, support continued research into this promising new approach to radiotherapy.

FLASH-RT may be indicated in two main clinical scenarios 1) the treatment of radioresistant tumours and 2) minimisation 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 achieving a reasonable degree of local control. This potential benefit of FLASH-RT is important 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.

Despite the significant technological advances in radiotherapy in the last decade, further improvement would be welcome to reduce treatment times and increase efficacy. In addition, a better understanding of radioresistance is needed. Improvements in these areas would help ensure the quality of treatment and patient safety by minimising treatment-related adverse effects and preserving quality of life, ideally, allowing the patient to recover their previous health status and to return to their usual life and work activities. In short, new approaches and technological developments in radiation oncology are needed, similar to the major achievements of targeted therapies and immunomodulatory agents in recent years [8, 9].

Finally, another factor that needs to be considered in FLASH-RT is the biological diversity present in most cancers. Given that all effects occur on a cellular level, tumours of different origin located in a different environment may respond differently to the dose rate used in FLASH-RT. Summary FLASH-RT challenges is presented in Table 1.

Conclusions

FLASH-RT has theoretical advantages over conventional radiotherapy. Preclinical experiments support the use of FLASH-RT, but they were carried out at depths up to several centimetres limited by the range of megavoltage electrons accelerated by linear accelerators.

Major technological advances are needed to enable the generation of FLASH photons, and potentially of protons, VHEE and heavy ions. Such sources of radiation will allow required dose distribution to be obtained at bigger depths inside human body, where most tumours occur.

If use of FLASH-RT is clinically confirmed, this approach might be rapidly incorporated into routine clinical practice, thus modernising currently available radiotherapy solutions.

Conflicts of interest

None declared.

Table 1. FLASH radiotherapy (FLASH-RT) challenges

General
Accurate dose monitoring and delivery at ultra-high dose rates
Technologies, which can provide FLASH dose-rate radiation that can reach majority of tumours lying at depth of 10–20 cm in the body, eg. very high-energy electron (VHEE) beams [33], laser particle accelerators [34], pluri-directional high-energy agile scanning electronic radiotherapy (PHASER) [25]
Dosimetry
Detectors able to measure online the beam fluence at FLASH dose-rate
Detailed simulations and modeling of the detector behavior in environment proper for FLASH-RT
Recombination effect, saturation, and sensor linearity with dose-rate
Calibration and quality assurance tools
Precise beam characteristic tools: verification of machine output, dose delivered per pulse, and dose-rate in real-time, pulse duration, interval, and overall irradiation time
Full pencil beam scanning for proton beam-based FLASH-RT
Radiobiology and clinical practice
Detail relationship on how FLASH effect varies with LET and oxygen concentration
Experimental proofs for distinction of oxygen level between normal and malignant tissue allowing its quantification
Treatment planning systems utilising FLASH radiotherapy planning
Immune factors in both normal and tumor tissues exposed to FLASH-RT
Mechanisms of DNA damage response and immune response after FLASH-RT
Clinical study when beams able to reach 10–20 cm in a body are available

LET — linear energy transfer

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Ethical permission

Ethical approval was not necessary for the preparation of this article.

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References

1. Hughes JR, Parsons JL. FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. Int J Mol Sci. 2020; 21(18), doi: 10.3390/ijms21186492, indexed in Pubmed: 32899466.
2. Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med. 2014; 6(245): 245ra93, doi: 10.1126/scitranslmed.3008973, indexed in Pubmed: 25031268.
3. Bourhis J, Montay-Gruel P, Gonçalves Jorge P, et al. Clinical translation of FLASH radiotherapy: Why and how? Radiother Oncol. 2019; 139: 11–17, doi: 10.1016/j.radonc.2019.04.008, indexed in Pubmed: 31253466.
4. Vozenin MC, Hendry JH, Limoli CL. Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken. Clin Oncol (R Coll Radiol). 2019; 31(7): 407–415, doi: 10.1016/j.clon.2019.04.001, indexed in Pubmed: 31010708.
5. Vozenin MC, Baumann M, Coppes RP, et al. FLASH radiotherapy International Workshop. Radiother Oncol. 2019; 139: 1–3, doi: 10.1016/j.radonc.2019.07.020, indexed in Pubmed: 31445836.
6. Wilson JD, Hammond EM, Higgins GS, et al. Ultra-High Dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool's Gold? Front Oncol. 2019; 9: 1563, doi: 10.3389/fonc.2019.01563, indexed in Pubmed: 32010633.
7. Bourhis J, Sozzi WJ, Jorge PG, et al. Treatment of a first patient with FLASH-radiotherapy. Radiother Oncol. 2019; 139: 18–22, doi: 10.1016/j.radonc.2019.06.019, indexed in Pubmed: 31303340.
8. Herrera FG, Bourhis J, Coukos G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. CA Cancer J Clin. 2017; 67(1): 65–85, doi: 10.3322/caac.21358, indexed in Pubmed: 27570942.
9. Bristow RG, Alexander B, Baumann M, et al. Combining precision radiotherapy with molecular targeting and immunomodulatory agents: a guideline by the American Society for Radiation Oncology. Lancet Oncol. 2018; 19(5): e240–e251, doi: 10.1016/S1470-2045(18)30096-2, indexed in Pubmed: 29726389.
10. Petersson K, Jaccard M, Germond JF, et al. High dose-per-pulse electron beam dosimetry - A model to correct for the ion recombination in the Advanced Markus ionization chamber. Med Phys. 2017; 44(3): 1157–1167, doi: 10.1002/mp.12111, indexed in Pubmed: 28094853.
11. Lempart M, Blad B, Adrian G, et al. Modifying a clinical linear accelerator for delivery of ultra-high dose rate irradiation. Radiother Oncol. 2019; 139: 40–45, doi: 10.1016/j.radonc.2019.01.031, indexed in Pubmed: 30755324.
12. Montay-Gruel P, Petersson K, Jaccard M, et al. Irradiation in a flash: Unique sparing of memory in mice after

whole brain irradiation with dose rates above 100 Gy/s. Radiother Oncol. 2017; 124(3): 365–369, doi: 10.1016/j.radonc.2017.05.003, indexed in Pubmed: 28545957.
13. Symonds P, Jones GDD. FLASH Radiotherapy: The Next Technological Advance in Radiation Therapy? Clin Oncol (R Coll Radiol). 2019; 31(7): 405–406, doi: 10.1016/j.clon.2019.05.011, indexed in Pubmed: 31178010.
14. Hornsey S, Bewley DK. Hypoxia in mouse intestine induced by electron irradiation at high dose-rates. Int J Radiat Biol Relat Stud Phys Chem Med. 1971; 19(5): 479–483, doi: 10.1080/09553007114550611, indexed in Pubmed: 5314348.
15. Field SB, Bewley DK. Effects of dose-rate on the radiation response of rat skin. Int J Radiat Biol Relat Stud Phys Chem Med. 1974; 26(3): 259–267, doi: 10.1080/09553007414551221, indexed in Pubmed: 4547756.
16. Epp ER, Weiss H, Djordjevic B, et al. The radiosensitivity of cultured mammalian cells exposed to single high intensity pulses of electrons in various concentrations of oxygen. Radiat Res. 1972; 52(2): 324–332, indexed in Pubmed: 4566064.
17. Weiss H, Epp ER, Heslin JM, et al. Oxygen depletion in cells irradiated at ultra-high dose-rates and at conventional dose-rates. Int J Radiat Biol Relat Stud Phys Chem Med. 1974; 26(1): 17–29, doi: 10.1080/09553007414550901, indexed in Pubmed: 4607987.
18. DEWEY DL, BOAG JW. Modification of the oxygen effect when bacteria are given large pulses of radiation. Nature. 1959; 183(4673): 1450–1451, doi: 10.1038/1831450a0, indexed in Pubmed: 13657161.
19. Thames HD, Withers HR, Peters LJ, et al. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. Int J Radiat Oncol Biol Phys. 1982; 8(2): 219–226, doi: 10.1016/0360-3016(82)90517-x, indexed in Pubmed: 7085377.
20. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. Int J Radiat Oncol Biol Phys. 1982; 8(11): 1981–1997, doi: 10.1016/0360-3016(82)90459-x, indexed in Pubmed: 6759484.
21. Jones B, Dale RG, Deehan C, et al. The role of biologically effective dose (BED) in clinical oncology. Clin Oncol (R Coll Radiol). 2001; 13(2): 71–81, doi: 10.1053/clon.2001.9221, indexed in Pubmed: 11373882.
22. Jones B, Morgan D. Radiotherapy fractionation in radiobiological modelling in radiation oncology. The British Institute of Radiology, London 2007: 70–71.
23. Vignati A, Giordanengo S, Fausti F, et al. Beam Monitors for Tomorrow: The Challenges of Electron and Photon FLASH RT. Front Phys. 2020; 8, doi: 10.3389/fphy.2020.00375.
24. Bourhis J, Stapnes S, Weunsch W. Adapting CLIC Tech for FLASH Therapy. https://cerncourier.com/a/adapting-clic-tech-for-flash-therapy/ (2020).
25. Maxim PG, Tantawi SG, Loo BW. PHASER: A platform for clinical translation of FLASH cancer radiotherapy. Radiother Oncol. 2019; 139: 28–33, doi: 10.1016/j.radonc.2019.05.005, indexed in Pubmed: 31178058.
26. Lagzda A, Angal-Kalinin D, Jones J, et al. Influence of heterogeneous media on Very High Energy Electron (VHEE) dose penetration and a Monte Carlo-based comparison with existing radiotherapy modalities. Nucl Instrum Methods Phys Res. 2020; 482: 70–81, doi: 10.1016/j.nimb.2020.09.008.
27. Esplen N, Mendonca MS, Bazalova-Carter M. Physics and biology of ultrahigh dose-rate (FLASH) radiotherapy: a topical review. Phys Med Biol. 2020; 65(23): 23TR03, doi: 10.1088/1361-6560/abaa28, indexed in Pubmed: 32721941.
28. Buonanno M, Grilj V, Brenner DJ. Biological effects in normal cells exposed to FLASH dose rate protons. Radiother Oncol. 2019; 139: 51–55, doi: 10.1016/j.radonc.2019.02.009, indexed in Pubmed: 30850209.
29. Beyreuther E, Brand M, Hans S, et al. Feasibility of proton FLASH effect tested by zebrafish embryo irradiation. Radiother Oncol. 2019; 139: 46–50, doi: 10.1016/j.radonc.2019.06.024, indexed in Pubmed: 31266652.
30. Schmid TE, Dollinger G, Hable V, et al. Relative biological effectiveness of pulsed and continuous 20 MeV protons for micronucleus induction in 3D human reconstructed skin tissue. Radiother Oncol. 2010; 95(1): 66–72, doi: 10.1016/j.radonc.2010.03.010, indexed in Pubmed: 20347168.
31. Auer S, Hable V, Greubel C, et al. Survival of tumor cells after proton irradiation with ultra-high dose rates. Radiat Oncol. 2011; 6: 139, doi: 10.1186/1748-717X-6-139, indexed in Pubmed: 22008289.
32. Girdhani S, Abel E, Katsis A, et al. Abstract LB-280: FLASH: A novel paradigm changing tumor irradiation platform that enhances therapeutic ratio by reducing normal tissue toxicity and activating immune pathways. Cancer Res. 2019; 79.
33. Small KL, Henthorn NT, Angal-Kalinin D, et al. Evaluating very high energy electron RBE from nanodosimetric pBR322 plasmid DNA damage. Sci Rep. 2021; 11(1): 3341, doi: 10.1038/s41598-021-82772-6, indexed in Pubmed: 33558553.
34. Karsch L, Beyreuther E, Enghardt W, et al. Towards ion beam therapy based on laser plasma accelerators. Acta Oncol. 2017; 56(11): 1359–1366, doi: 10.1080/0284186X.2017.1355111, indexed in Pubmed: 28828925.