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Original Article

Clinical translation of FLASH radiotherapy: Why and how?

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ABSTRACT

Over the past decades, technological advances have transformed radiation therapy (RT) into a precise and powerful treatment for cancer patients. Nevertheless, the treatment of radiation-resistant tumors is still restricted by the dose-limiting normal tissue complications. In this context, FLASH-RT is emerging in the field. Consisting of delivering doses within an extremely short irradiation time, FLASH-RT has been identified as a promising new tool to enhance the differential effect between tumors and normal tissues. Indeed, preclinical studies on various animal models and a veterinarian clinical trial have recently shown that compared to conventional dose-rate RT, FLASH-RT could control tumors while minimizing normal tissue toxicity.

In the present review, we summarize the main data supporting the clinical translation of FLASH-RT and explore its feasibility, the key irradiation parameters and the potential technologies needed for a successful clinical translation.

Radiation therapy (RT) is a major actor in cancer management, with more than half of all cancer patients treated with RT, mostly given with curative potential. RT generally exploits the empirical observation that normal tissues can recover from the harmful effects of ionizing radiation to a higher extent than tumors. This differential effect can be exacerbated by two factors that can independently increase the normal tissue tolerance. The first factor is the fractionation of the total dose with a good protection of normal tissues at 2 Gy per fraction and even more pronounced below 2 Gy/fraction [1]. The second factor is related to technologies that improve dose-delivery precision and reduce the volume of normal tissues irradiated at high doses, and subsequently prevents the potential collateral damages of RT. These two factors, i.e. fractionation and precise volume optimization can be combined to some extent and are both extremely powerful in increasing normal tissue tolerance [2]. They contributed to define the standards of care with conventional dose-fractionation. RT is administered today with high precision using Intensity Modulated RT (IMRT), Image Guided RT (IGRT), Stereotactic Body RT (SBRT), and proton therapy [3]. For example, Stereotactic Ablative Radiotherapy (SABR) delivers the dose with millimetric precision, enables maximal sparing of normal tissues and in turn achieves very high curative dose to the tumor [4]. In addition to these geometrical sparing of normal tissues, shortening the overall time for the dose delivery and so called FLASH-radiotherapy (FLASH-RT) [5,6], is emerging as a third potential major factor able to increase normal tissue tolerance, which in turn would make it possible to deliver higher curative doses and opens new avenues for overcoming tumor radiation resistance. The following presents the potential implications and challenges for the clinical translation of FLASH-RT.

What is the FLASH effect?

FLASH-RT involves the ultra-fast delivery of RT at dose-rates generally several thousand times higher than the ones currently used in routine clinical practice (CONV-RT) [5]. While FLASH-RT versus CONV-RT have been characterized initially using their mean dose-rate (>i.e. $\geq$40 Gy/s for FLASH-RT vs $\geq$0.01 Gy/s for CONV-RT), the full definition is more complex and involves several interdependent physical parameters such as repetition rate, pulses (number and width), and total duration of exposure. These parameters described in Table 1 have been essentially generated using the Oriatron eRT6 [7] and were used in our recent experimental studies describing the benefits of FLASH-RT. In these most recent studies, the FLASH-RT effect was found to be reproducible with

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Table 1
Parameters with which the FLASH effect has been observed. Both Kinetron [5] and Oriatron (eRT6) [7] are irradiation devices dedicated to produce FLASH irradiation.

Animal model	Device	Volume (cm^2)	Duration of RT (ms)	Dose delivered (single dose in Gy)	Mean dose-rate (Gy/s)	Dose-rate within the pulse (Gy/s)	Ref.
Mice, Zebrafish	Kinetron Oriatron	< 2	< 200	> 8	> 40	> $1.8.10^5$	[5,11] (Montay-Gruel, in rev.)
Pig/Cats	Kinetron Oriatron	< 12	< 200	up to 41	300–400	> 1.10^6	[12]
Pig	Oriatron	100	< 200	31	160	$0.8,10^6$	[12]

1–10 pulses of 1.8–2 microsecond, an overall time of less than 200 ms and a dose-rate within the pulse above 1.8×10^5 Gy/s (Table 1). In addition, it is important to point out that in all these studies, total RT dose was delivered in one single large fraction.

The striking observation made after the exposure of biological tissues to FLASH-RT, is a relative protection of normal tissues, as compared to conventional dose-rate RT. This reduction in normal tissue toxicity was first described in the seventies using mouse models of gut and skin toxicity [8,9]. Later, Hendry et al. confirmed the reduction in normal tissue toxicity [10], using 10 MeV electron beam at 50 pulses per second and dose-rates within the pulse above 10^5 Gy/s which remarkably reduced mice tail necrosis, compared to similar doses delivered at much lower dose-rates (10^3 Gy/s). It took more than three decades for this phenomenon to be "re-discovered" in 2014 by our group with Vincent Favaudon and Marie Catherine Vozenin [5]. Indeed, in addition to showing a unique protection of normal tissues with FLASH-RT, a major differential effect between tumors and normal tissues was reported, as FLASH-RT triggered a similar anti-tumor effect as compared with conventional RT at isodose, in lung, breast and head and neck tumor models [5]. Moreover, the possibility of increasing the dose to the tumor using FLASH-RT was shown without induction of normal-lung toxicity [5]. Recently, this marked improvement of the differential effect between tumor and normal tissues triggered by FLASH-RT was investigated and confirmed in various normal tissue and tumor models tested in Lausanne [11,12], Orsay [5], Grenoble [13] and Stanford [14]. More biological results are now available and reported in this special issue of *Radiotherapy & Oncology*.

The first obvious difference between FLASH-RT and CONV-RT is the time required to deliver the dose which ranged from microsecond to hundreds of milliseconds for FLASH-RT but raised up to minutes for CONV-RT. This extremely short time of exposure made possible by FLASH-RT suggests an early modulation of the radiochemical events that depend upon oxygen concentration in the irradiated volume. FLASH-RT could cause a rapid consumption of local oxygen and elicit a transient radiation-induced hypoxia, as already described in several past publications in bacteria and eukaryotic cellular models [15–19] as well as in mouse models in relatively old reports [8,10]. The oxygen dependency of the FLASH effect was confirmed recently by our team showing that hyper-oxygenation could abolish the FLASH effect in mouse (Montay-Gruel et al., in revision). Additional mechanistic studies are ongoing to further characterize the mechanisms involved in the differential effect of FLASH-RT and are not under the scope of this present review.

Do the pre-clinical data support the clinical translation of FLASH-RT?

The consistency of the normal tissue protection among species, the magnitude of this benefit, and the excellent anti-tumor effects observed so far, all suggest that the FLASH effect could also be reproduced in human patients and encourage the testing of this hypothesis in clinical trials.

A first significant observation motivating clinical translation is the consistency of the pre-clinical data across four animal species, i.e., zebrafish, mice, mini-pig and cat, showing that FLASH-RT remarkably reduces normal-tissue side effects compared to conventional dose-rate RT (Table 2), while providing an efficient anti-tumor effect. In zebrafish embryos, the magnitude of the normal tissue protection obtained by FLASH-RT was significantly superior to the one obtained by amifostine exposure [20] (Fig. 1). Concerning mouse models, all types of normal tissues, including skin, lung, gut and brain, appeared to be spared by FLASH-RT compared to conventional dose-rate RT [5,8–14].

A second observation supporting the clinical translation is the magnitude of the normal tissue protection allowed by FLASH-RT, compared to conventional RT. The most relevant result comes from the dose escalation experiment comparisons between conventional dose-rate and FLASH on the skin of a mini-pig [12]. Single irradiation doses ranging from 22 Gy to 34 Gy were delivered, with an applicator of 2.6 cm diameter to the same animal and at the same time. With an absence of late skin necrosis at 9 months as endpoint, 25 Gy delivered at conventional dose-rate brought a similar outcome to 34 Gy delivered with FLASH-RT. This result suggests that the dose modifying factor for FLASH-RT is at least 1.36 compared with dose delivered at conventional dose-rate [12] (Table 2). Interestingly, as the follow-up period is still ongoing, no late alteration was observed in the FLASH-irradiated zones where the skin appears macroscopically normal 28 months post-irradiation. More recently, and as suggested in the editorial by Harrington [6], the impact of FLASH-RT on a large irradiation field needed to be investigated. Therefore, the delivery of 31 Gy with FLASH-RT was realized with an 8×8 cm^2 irradiation field on the skin of the mini-pig. This dose and volume led to transient

Table 2
Summary of the FLASH effect across species.

	Mouse	Cat	Pig	Zebrafish embryo
FLASH-RT is better than conventional dose-rate RT for normal tissue protection	Yes	Yes (when compared with published studies)	Yes	Yes
Dose modifying factor in normal tissue	≥1.8 (lung) ≥1.4 (brain)	Not evaluated	≥1.36	≥1.4
Improvement of the differential effect (tumor/normal tissues) with FLASH-RT	Yes	Yes	Not tested	Not tested
References	[5] (Montay-Gruel, in rev.)	[12]	[12]	Vozenin, (pers. com.)

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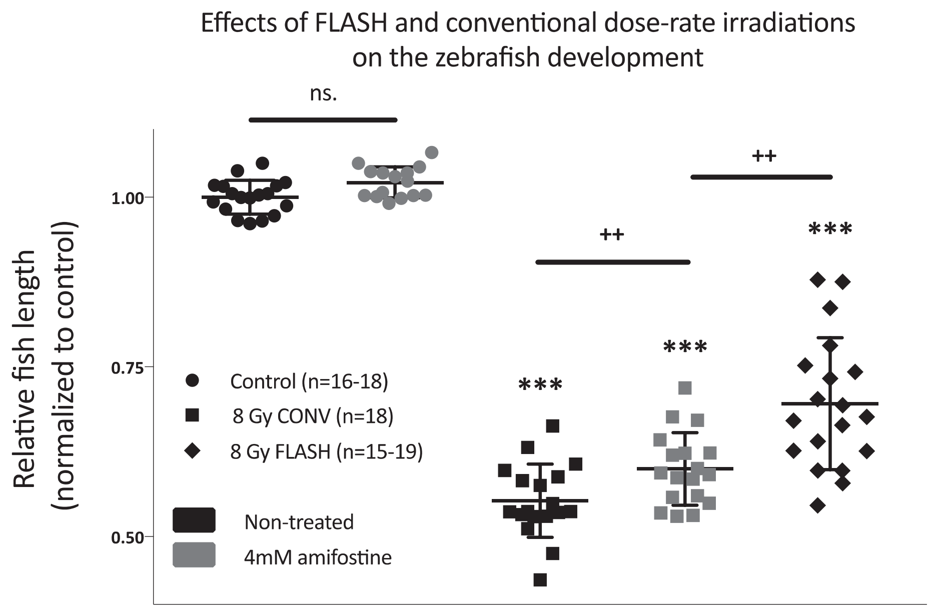

Fig. 1. FLASH-RT is more efficient at protecting normal tissues than Amifostine. Amifostine (4 mM; Sigma) was added to the zebrafish embryos water 1 h before irradiation. Irradiation was performed 4 hours post-fertilization (hpf). Embryos were given 8 Gy delivered with FLASH-RT (1 pulse of 1.8×10^{-6} s) or conventional dose-rate irradiation (0.1 Gy/s) with the eRT6 LINAC [7]. Radiation-induced alteration of zebrafish morphology was assessed 5 days post-fertilization (dpf) by body length measurement. FLASH-RT induced fewer morphological alterations than all other irradiated groups, an effect that was not impacted by antioxidants. Mean ± SD and Mann–Whitney's-test: $^{*}P < 0.05$; $^{**/++}P < 0.01$; $^{***}P < 0.001$ (N = 9–19 embryos/group).

in-field superficial ulcerations (5 to 7 months post-RT), followed by a complete resolution of the lesions (7.5 months post-RT), and no further reactivation 11 months post-irradiation. As pig and human skins are known to be physiologically very close, these results suggest that the FLASH effect could be maintained after exposure to a very high single-dose of irradiation, even on a large volume. This improved tolerance of normal tissues, compared to conventional RT suggests that higher curative doses with FLASH-RT could be used, thus offering a potential to overcome some of the clinical radio-resistant tumor situations. Further studies assessing the concomitant impact of volume and dose-rate are ongoing. In addition, a veterinarian clinical trial in cat-patients with spontaneous squamous-cell carcinomas of the nasal planum was performed to evaluate the curative effect of FLASH-RT in a dose escalation study using single doses of irradiation ranging from 25 to 41 Gy. No dose-limiting toxicity was observed, and the Maximal Tolerated Dose (MTD) was not reached. Only minimal or mild mucosal and skin reactions were observed, without major disturbance of food intake and without subsequent late side effects. The tumor control rate was high, compared to the literature with a rate of 84% at 1 year. When comparing the outcome after FLASH-RT with previous studies having used fractionated RT, the tolerance/efficacy ratio appeared markedly superior with a single dose of FLASH-RT. This is consistent with an improvement of the differential effect between normal tissues and tumors, despite the use of extremely high FLASH-RT dose per fraction [12] and will be validated in an ongoing phase III veterinarian clinical trial performed at our institution.

A third observation supporting the clinical translation is the intact capacity of FLASH-RT to eradicate tumors, despite its normal tissue sparing effect. Indeed, all the currently available data indicate that FLASH-RT is iso-effective compared to conventional dose-rate RT for the tumors, as illustrated using U87 human glioblastoma implanted subcutaneously (Fig. 2). The anti-tumor efficacy of FLASH vs CONV-RT has been reproduced in various mouse tumor models (including xenografts, orthotopic and transgenic models) of breast, lung, head and neck, ovarian and brain cancers, and suggest a major increase in the differential effect between normal tissues and tumors [5,11,15] (Montay-Gruel et al., in revision). Furthermore, we recently investigated the effect of fractionated FLASH-RT on tumor growth delay and the iso-efficacy of conventional dose-rate RT and FLASH-RT, which was again confirmed (Fig. 3). The impact of fractionated FLASH-RT on normal tissue is currently being studied.

What are the beam characteristics needed for clinical translation?

In order to reproduce the FLASH effect in human normal tissues, it is important to control and define the parameters used in pre-clinical *in vivo* studies [5,11–14,21]. First, a strict and reliable monitoring of the dose has been designed and implemented [7,22,23]. Second, the dose-rate expressed as the mean dose-rate in gray per second was first proposed as a surrogate to describe the FLASH beam characteristics [5]. In our first report, the FLASH effect (normal tissue sparing) involved the delivery of single doses given in pulses of one microsecond with a mean dose-rate defined above 40 Gy/s. In subsequent studies, we further narrowed the physical parameters required to obtain the FLASH effect using a cognitive assay in mice. We showed that mean dose-rates above 33 Gy/s protected half of irradiated mice whereas 100 Gy/s protected all irradiated mice from radiation-induced cognitive defects [11]. However, additional parameters can markedly impact the outcome of FLASH-RT such as the dose per pulse, the number of pulses delivered, and the dose-rate within the pulse. Our current knowledge defining the parameters required to obtain the FLASH effect is summarized Table 1. These data along with the analysis of the published literature (Fig. 4) support the idea that the most relevant parameters for the FLASH effect are the combination of dose, dose-rate within the pulse, and overall time of irradiation (<200 milliseconds), and not only the mean dose-rate as we initially thought. The role of each of these parameters is currently being explored in more details, and might be critical for optimizing the clinical use of FLASH-RT. Considering the conditions derived

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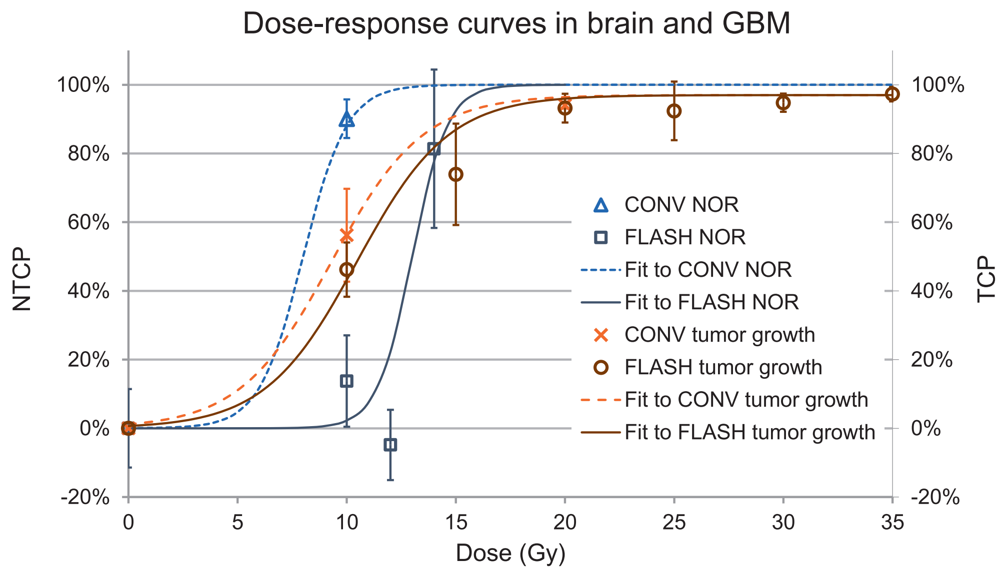

Fig. 2. NTCP/TCP after FLASH and CONV-RT in normal brain and GBM. To investigate tumor response, subcutaneous glioblastoma models, 10 M U87 human GBM cells were engrafted in the flank of female nude mice ($N = 5$–6 mice/group) under isoflurane anesthesia. Tumors were irradiated with the eRT6 LINAC using a 1.7 cm round collimator at FLASH (circles; between 125 Gy/s and 1 pulse of 1.8×10^{-6} s) or conventional dose-rates (crosses; 0.1 Gy/s) when tumor volume reached 60 mm3 (57 ± 17 mm3). Iso-efficacy of FLASH-RT and conventional dose-rate irradiation was observed by tumor-growth delay assessment of U87 human GBM xenografted tumors irradiated at 0, 10, 15, 20, 25, 30 and 35 Gy with FLASH-RT (FLASH) and 0, 10 and 20 Gy with conventional dose-rate irradiation (CONV). The time evolution of the tumor volume after irradiation was found in good agreement with the predictions of the two-compartment kinetic model of Looney et al. [25]. The plots of the tumor control probability (right scale) was calculated using the relation $TCP = (V_{Ctrl} - V_{RT})/V_{Ctrl}$ where the volumes are measured 15 days after irradiation. Data error bars correspond to standard deviation and solid brown line to a logistic fit to the FLASH data. Due to the reduced number of points, the fit to the CONV data (dashed line) was estimated as a shift of the FLASH curve. To investigate normal tissue toxicity, C57Bl6/J WT mice ($N = 5$–13 mice/group) were tested using the novel object recognition (NOR) task 2 months post-FLASH and CONV-RT. Calculation of the discrimination index was obtained as DI = 2*Recognition Index −1. Control animal show a maximal $DI_{max} = 60\%$ and maximal loss of cognition is given by a $DI_{min} = 0\%$. In these conditions, conventional dose-rate irradiation at 10 Gy caused significant reduction in DI (6%) whereas 10 and 12 Gy doses administered by FLASH prevented radiation-induced cognitive deficits (DI = 52 and 63%). Interestingly, at the higher dose of 14 Gy, the benefits of FLASH were lost, as DI values (=11.2%) were similar to that found after conventional dose-rate irradiation. These value are plotted as normal tissue control probability calculated by $NTCP = (DI_{max} - DI)/(DI_{max} - DI_{min})$. Data error bars correspond to standard deviation, solid blue line to a logistic fit to the FLASH data. The CONV curve shown (dashed line) was estimated as a shift of the FLASH curve.

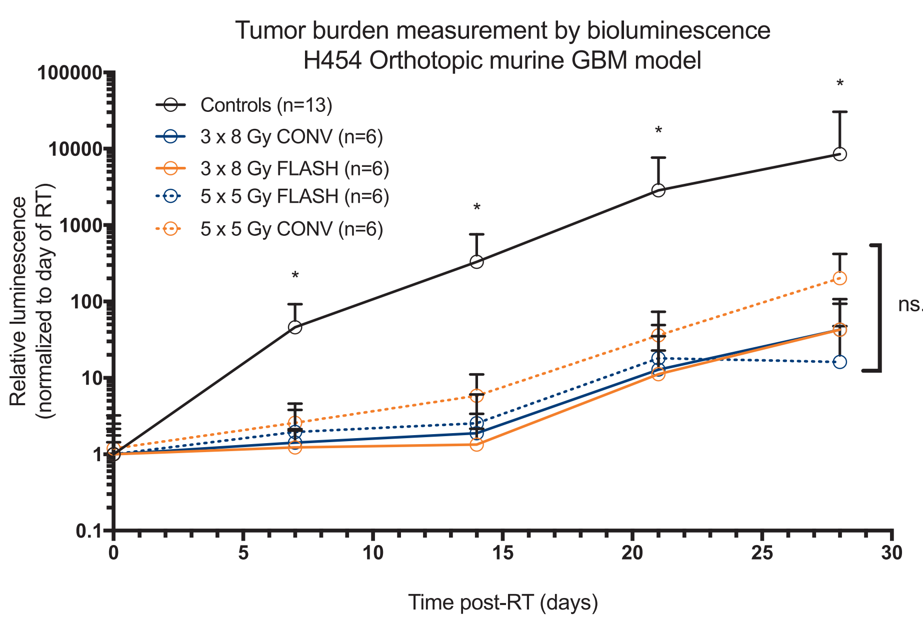

Fig. 3. Effect of fractionation on tumor growth delay. 500’000 H454-luc+ murine GBM cells were implanted orthotopically in the striatum of Nude mice and irradiated 3 days post-injection (J-3) after tumor establishment. Animals were given whole brain FLASH (1 pulse of 1.8×10^{-6} s) or conventional dose-rate RT (0.1 Gy/s) at 10 Gy single dose, 3×8 Gy or 5×5 Gy fractionated regimens (24 h inter fraction). All irradiations were performed with the eRT6 LINAC (Jaccard, 2018). Tumor burden was measured weekly for individual mice by bioluminescence (Illumina IVIS), and normalized against the signal measured the day of irradiation. All regimens induced a significantly better tumor delay compared to non-irradiated control animals. In all treatment regimens, no statistical difference was observed between CONV and FLASH-RT irradiation modality. Results are given as mean relative radiance (normalized against J-3 values) ± SEM. P values are derived from Mann–Whitney’s tests: $^{*}P < 0.05$ ($N = 6$ mice/group).

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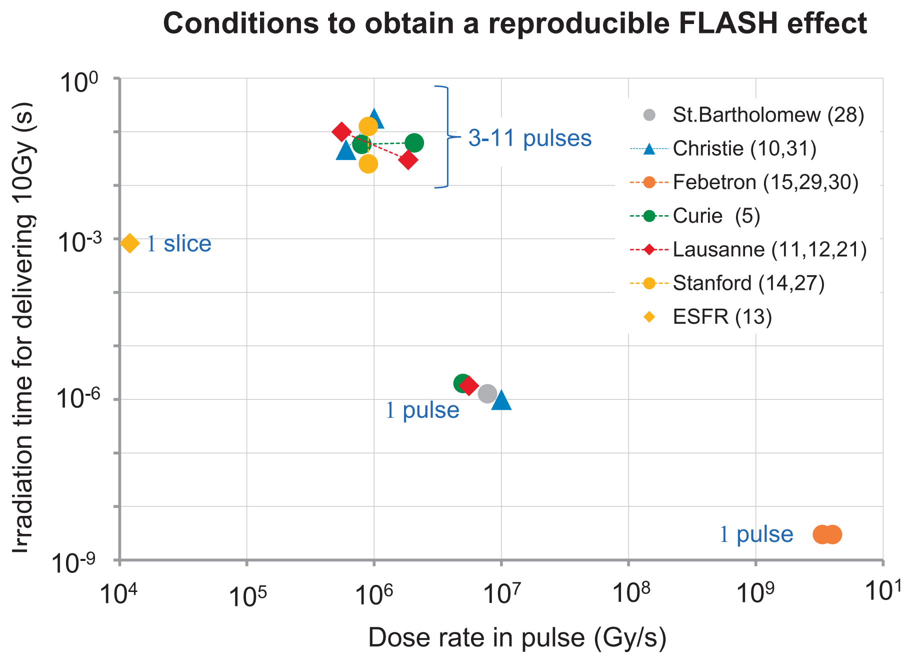

Fig. 4. Conditions to obtain a reproducible FLASH effect. Summary of the temporal dosimetry characteristics of the reported experiments' data having observed the FLASH effect *in vivo* [5,10–14,21,27] or oxygen depletion *in vitro* [15,28–31]. The horizontal axis denotes the dose-rate in pulse for electrons and in slice for synchrotron radiation, the vertical axis the total irradiation time for delivering 10 Gy. Parameters for other dose values must be changed accordingly. In mono-pulse mode, the irradiation time is governed by the pulse width, in multi-pulses mode by the pulse repetition rate (10–200 Hz).

from all the available pre-clinical data, a first patient with a skin cancer is planned to be treated at Lausanne University hospital using FLASH-RT.

How to approach the clinical translation of FLASH-RT?

Feasibility with low energy electrons and early clinical evaluation

A logical first step toward clinical translation would be to assess the feasibility of using low-energy electrons under conditions as close as possible to those previously used in the pre-clinical setting. This would allow obtaining a first evaluation and a proof of concept of the FLASH effect in human patients.

Although the technology to produce low-energy electron beams able to deliver FLASH-RT is affordable, very few systems are currently available worldwide. Conventional clinical linacs can be tuned in order to produce electron beams with dose-rates exceeding 200 Gy/s, but their dosimetry and geometric properties are only suitable for small animal experiments (RT field size of a few cm^2 at a distance of a few cm from the source). This configuration was successfully used for biological experiments at Stanford University (CA) with a modified Varian linac [14] and a modified Elekta linac is currently used at Lund University, Sweden and described in this issue [24]. At Lausanne University Hospital, the eRT6 Oriatron (5.6 MeV, electron linac, PMB, Peynier France) can deliver FLASH-RT with an open field size of 20 cm diameter (at 100 cm from the source) and possible secondary collimations down to 1.6 cm diameter (distances from the source ranging from 10 cm up to 400 cm) [7]. Adequate dosimetric validations and traceability have been extensively described using this linac [7,11,22,23] (see also Gonçalves Jorge et al. in this issue). These characteristics are all compatible with the clinical treatment of superficial skin cancers and the feasibility of using FLASH-RT in patients is currently being tested. A second electron linac prototype designed to deliver FLASH-RT in the context of intra-operative radiation therapy (IORT) is under construction and will be able to operate at a higher energy of 10 MeV. This device should be appropriate to further test the FLASH concept in patients with incomplete resection of non-curable cancers (i.e. for example pancreatic tumors). The main advantage of this approach is to use similar conditions to the ones generally used so far to demonstrate the FLASH effect, i.e., high single dose of RT with low-energy electrons delivered in an overall time of less than 200 milliseconds.

For treating deep tumors: very high energy electrons (VHEE), X-rays or protons?

In order to treat deeply located cancers in patients, the development of either FLASH-VHEE or, alternatively, FLASH-X-ray or FLASH-proton devices are needed. Importantly, the FLASH effect could be reproduced with an experimental X-ray beam line at the European Synchrotron Radiation Facility (ESRF) [13] and reviewed in Serduc et al. in this issue of *Radiotherapy & Oncology*. These experiments were performed with comparable parameters and dose-rates with the ones performed using low-energy electrons [11] and compared to conventional dose-rate X-ray irradiations. However, building a clinical device able to deliver FLASH-X-rays implies solving significant technical challenges. Among them, the power of the accelerator should be at least 100 times higher than the one used to produce FLASH electrons and the conversion target to generate photons should have specific characteristics to resist an enormous instantaneous power. Among the ongoing projects, the Pluridirectional High-energy Agile Scanning Electronic Radiotherapy (PHASER) is a promising program (see Loo et al. in this issue).

Another possible option to translate FLASH irradiation into the clinics might be to use proton beams. FLASH-proton devices (mean dose-rate of 40 Gy/s; field size of 1.2×1.2 cm^2) have been recently developed for experimental purposes [25] and the first biological experiments are reported in this special issue of *Radiotherapy & Oncology* by Bayreuther et al. and [26]. In addition, fast-scanning proton beams can display even higher instantaneous dose-rates within each individual spot (above 200 Gy/s) but the overall time for treating a whole tumor is at best several seconds, generating a mean dose-rate that could be far too low to trigger a FLASH effect.

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Additional challenges for clinical translation

The clinical translation of FLASH-RT is sustained by the outstanding improvement of the differential effect between tumors and normal tissues, as compared to conventional dose-rate RT. It is important to envisage the clinical development of FLASH-RT in a global perspective toward the improvement of radiation treatments and integrating other important factors like fractionation and volume optimizations. Nearly all the pre-clinical studies available so far have been performed using single dose irradiations. Interestingly, we provide here the first evidence showing the isoefficacy of hypo-fractionated FLASH regimen compared to CONV-RT in the control of orthotopic GBM tumors (Fig. 3). In our clinical study treating cat-patients, the highest dose of 41 Gy gave equivalent toxicity as compared to 25 Gy, and the MTD was not reached. This strongly suggests that the clinical use of FLASH would allow the use of high doses per fraction, but it does not mean that the whole treatment should be delivered in a single fraction. The clinical use of FLASH-RT could be performed as a "boost" in the range of 20–25 Gy given at the beginning of the treatment and being followed by high precision conventional RT. Many solid tumors are initially intrinsically hypoxic and will therefore not be protected by FLASH-induced transient hypoxia whereas the surrounding normal tissue will, thus enhancing the differential effect.

Another major challenge in translating FLASH-RT in the clinic is to develop optimal technologies in terms of high precision delivery similar to the technology currently used for conventional RT. Indeed the biological normal tissue sparing offered by FLASH-RT should be seen as complementary to the powerful normal tissue sparing effect offered by high precision delivery, but could not and should not replace it.

Potential risks associated with the ultra-fast delivery of FLASH-RT need to be considered before its clinical use. FLASH-RT consists in delivering a limited number of pulses (<=10 pulses). A safe delivery can be achieved using a dose monitoring and stopping system, able to monitor the dose pulse by pulse. The required high speed detectors, fast signal acquisition and processing electronic technologies are routinely used in high energy physics laboratories to control large particle accelerators and are adaptable to FLASH-RT systems. As an example our FLASH linac in Lausanne is now equipped with such systems and received the agreement of the radioprotection authorities for treating a patient.

Potential clinical advantages beyond the biological effect of FLASH-RT

Additional advantages could increase the potential clinical interest of FLASH-RT, especially since the very short "beam-on time" would make the intra-fraction motion management irrelevant. In addition, FLASH-RT best operates at high or very high dose per fraction and would also make it possible to decrease the number of fractions needed, as compared to conventional dose-rate RT. Ultimately, using FLASH-RT, radiation-oncology departments could benefit from economical and logistical assets, with a potential improvement of both workload and waiting lists. Altogether, these advantages could undeniably make FLASH-RT into a powerful additional tool in cancer treatment management, providing a better tumor treatment and a better quality of life for the patients.

Conclusion

Delivering high curative radiation doses to tumors depends on our ability to spare the normal tissues from the harmful effects of ionizing radiation. Over the last 100 years, both fractionation and precise-volume optimization emerged as powerful tools to increase the differential effect between tumors and normal tissues. FLASH-RT appears as a third potential major player able to markedly improve this differential effect. The consistency of the phenomenon across tissues and species along with the magnitude of the benefit observed in various pre-clinical studies justify its clinical translation, offering a new opportunity to improve radiation treatments especially for resistant tumors. A proof of concept could be done first with low-energy electrons, but technical challenges need to be rapidly solved for allowing VHEE, X-rays, or protons to operate at FLASH dose-rates.

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Conflict of interest statement

None of the authors have any conflicts of interest.

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