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Review Article

Treatment planning considerations for the development of FLASH proton therapy

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ABSTRACT

With increasing focus on the translation of the observed FLASH effect into clinical practice, this paper presents treatment planning considerations for its development using proton therapy.

Potential requirements to induce a FLASH effect are discussed along with the properties of existing proton therapy delivery systems and the changes in planning and delivery approaches required to satisfy these prerequisites. For the exploration of treatment planning approaches for FLASH, developments in treatment planning systems are needed. Flexibility in adapting to new information will be important in such an evolving area.

Variations in definitions, threshold values and assumptions can make it difficult to compare different published studies and to interpret previous studies in the context of new information. Together with the fact that much is left to be understood about the underlying mechanism behind the FLASH effect, a systematic and comprehensive approach to information storage is encouraged.

Collecting and retaining more detailed information on planned and realised dose delivery as well as reporting the assumptions made in planning studies creates the potential for research to be revisited and re-evaluated in the light of future improvements in understanding. Forward thinking at the time of study development can help facilitate retrospective analysis. This, we hope, will increase the available evidence and accelerate the translation of the FLASH effect into clinical benefit.

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Since the emergence of FLASH radiotherapy, and its promise of normal tissue protection with no, or limited, compromise on tumour control [1], plans for its route into the clinic have been widely considered [2–5]. Pre-clinical studies have shown that FLASH radiotherapy can cause a dose modification factor of 1.2–1.6 in various systems [6], thereby inducing a sparing effect in healthy tissue of about 20–40% compared to conventional dose rates. Although many of these initial FLASH studies were done using electrons [1,7,8], the ability of protons to reach deep-seated tumours, the reduced entrance dose compared to conventional X-ray radiotherapy, and the clinical availability of ‘FLASH-near-ready’ technology, make protons a promising modality for clinical translation of the FLASH effect.

To further advance protons as a choice for FLASH therapy, the FLASH effect has also been demonstrated in various pre-clinical studies using protons. For example, Diffenderfer et al. showed reduced fibrosis and loss of proliferating intestinal crypt cells in

mice after abdominal irradiation using FLASH compared to conventional radiation, with no observed difference in tumour growth delay [9]. Studies using whole thorax irradiation of mice using clinical proton systems have demonstrated reduced lung fibrosis, reduced skin dermatitis, improved breathing function and greater overall survival with FLASH compared to conventional irradiation [10,11]. Improved tumour control for FLASH has also been observed using proton irradiation of lung tumours in mice [12]. Other studies found that the FLASH effect also holds for photon irradiations [13]. Thus, the FLASH effect may be a modality-independent phenomenon, with protons currently considered a more direct route towards wider patient treatment.

A number of machine vendors are investigating the suitability of their existing proton systems for FLASH treatments. New technology, advanced dosimetry and safety systems will be required to produce and properly monitor ultra-high dose rate deliveries. In addition to the hardware, FLASH-capable treatment planning systems are being developed, but are currently restricted to research use and not clinically released.

The translation of the observed pre-clinical effect into clinically relevant tools for patient treatment planning and FLASH

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treatments comes with many obstacles which need to be understood and solved. One major hindrance of clinical translation is the ongoing search for the biological mechanisms responsible for the FLASH effect [14]. Some of the proposed mechanisms currently under consideration include:

- Radiation-induced transient depletion of oxygen [15,16]
- Differential ability of normal and tumour cells to detoxify reactive oxygen species [17]
- Differential production of radicals [18,19]
- Reduced killing of circulating lymphocytes [20]

Each of these mechanisms could have different implications for treatment planning.

In this article, we first suggest the key requirements for proton FLASH therapy to be translated from pre-clinical studies into the clinic. Next, we discuss how these requirements could be met clinically and look at additional considerations for a clinical setup. Lastly, we will state some recommendations for the future development of FLASH-compatible treatment planning systems.

Requirements for FLASH

The key parameter determining whether or not a FLASH effect can be observed is the dose rate. Studies have shown the dose rate must be sufficiently high to induce a protective effect. A threshold in the range 40–100 Gy/s is often assumed [e.g. [21–24]], based on initial FLASH results using 40 Gy/s dose rates [1]. However it is unclear whether this requirement can be treated as a step-like threshold at a particular value or if it acts more like a gradient. Work by the Lausanne group has suggested the latter, showing a FLASH effect at 30 Gy/s and a more pronounced effect at 100 Gy/s [7]. This gives an indication of where a minimum value may lie, however an exact parameterisation of this gradient-like threshold and its dependence on other parameters, for example the involved tissue, is yet to be clarified. A number of studies based on various mechanisms have modelled the multi-parameter dependence of the FLASH dose rate, and suggested a minimum dose rate of the order of 10–100 Gy/s [15,18,20,25]. Elucidation of the mechanism would be invaluable in determining this threshold more precisely. Moreover, even with a firm knowledge of the dose rate value required for normal tissue sparing from the FLASH effect (FLASH sparing), translating this parameter to a clinical setup with spatial and temporal delivery characteristics is not straightforward; difficulties arise in terms of how the dose rate is defined and the time-scale over which this threshold should be met (see Section “Translation of FLASH parameters into clinical treatment planning” below).

In addition to a high dose rate, it remains likely that the FLASH effect also requires a sufficiently high dose. A number of early studies looking at survival of bacterial or mammalian cells under high-dose-rate irradiation have shown evidence for an oxygen-dependent dose threshold, in the form of a breakpoint in survival curves [e.g. [26–29]]. This ‘breaking’ behaviour, in which cellular sensitivity starts to follow an anoxic-like response after a certain dose is reached, provides evidence for radiolytic oxygen depletion being responsible for the protective effects of ultra-high-dose-rate radiation. More recent *in vitro* studies have also demonstrated a dose-dependent sparing effect which, for low oxygen conditions (<2% O₂), becomes significant at 18–20 Gy, thus corroborating this theory [30–32]. Following the radiolytic oxygen depletion hypothesis, a dose threshold governed by initial levels of oxygen to deplete for an observable shift in radiosensitivity, becomes an integral requirement for FLASH. However, a possible dose threshold is

less easily explained by other mechanisms currently being explored [33].

Evidence for a dose threshold has so far generally been limited to *in vitro* studies [30–32,34]. *In vivo*, the requirement for a sufficiently high dose to generate normal tissue toxicity limits the range of doses that can be used in investigations. Most *in vivo* FLASH studies to date have used doses of around 10 Gy or higher [6,14,34]. Some conflicting dose dependence has been studied in mouse models; Abel et al. saw an onset of a protective effect between 15–17.5 Gy [11], Chabi et al. showed a differential effect for FLASH radiation at 4 Gy in a leukaemia mouse model [35], and Montay-Gruel et al. showed FLASH sparing of cognitive functions for hypofractionated doses of 2×7 Gy, but with no benefit from a FLASH effect shown for 4×3.5 Gy [36]. Therefore it is unclear whether a high dose is required to drive the effects of FLASH or simply differentiate them from conventional irradiation.

While the full characterisation of the basic pre-clinical parameters required to produce a FLASH effect remain under investigation, any work in trying to meet these requirements in a more complex clinical scenario could be considered futile. However, given the flexibility and research capability of modern treatment planning systems and radiobiological models, a number of groups have set out to explore different treatment options for FLASH, and identify the most promising scenarios given both our current understanding and emerging pre-clinical data [4,23,24,37–39]. Due to the ability of commercial proton systems to deliver treatment fields at ultra-high dose rates, the vast majority of FLASH treatment planning investigations have focused on FLASH delivery using proton beams. Based on preclinical evidence, the requirement to trigger the FLASH effect in these treatment planning studies to date are generally assumed to be a minimum dose rate of 40 Gy/s [4,23,24], with some studies also considering a minimum dose of 4–10 Gy [37–39].

Meeting these requirements in treatment planning

Proton treatment options for FLASH therapy

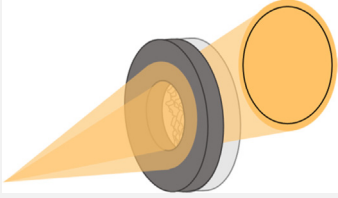
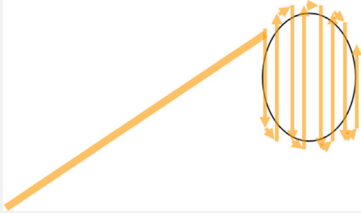
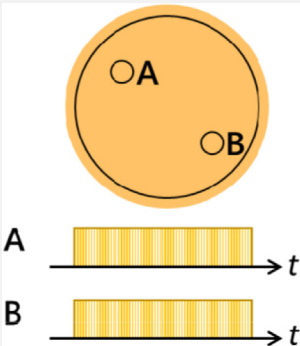
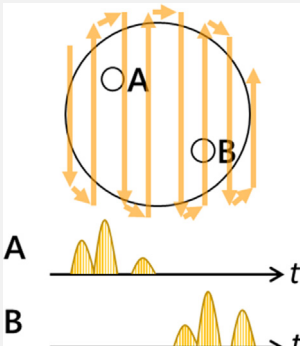
Over the past decade proton therapy has evolved from using mostly passive scattering delivery approaches to the use of pencil beam scanning (PBS). With passive scattering, the proton beam is scattered to spread it out laterally with compensators and collimators used to conform to the shape of the target volume. Energy modulation to create a spread out Bragg peak (SOBP) is achieved by passing the beam through a spinning range modulator wheel or a ridge filter, a stationary device with a fine structure of varying thickness that results in a polyenergetic beam exiting the device. Using this technique, the dose rate delivered decreases with increasing field size due to the limited integral dose.

With PBS, a thin proton pencil beam is scanned over the target volume in successively delivered energy layers. Both approaches are currently used clinically, though the most recent proton therapy centres have been installed with PBS systems. The advantage of the achievable dose distributions was one of the main reasons for the shift towards PBS treatments.

Table 1 shows a comparison of these two methods and how these delivery options vary with respect to parameters important for FLASH therapy [40].

PBS is considered the standard of modern proton therapy. Significant effort has gone into trying to maintain advantages of scanned proton delivery while meeting requirements for FLASH therapy. These efforts consisted both of hardware improvements, e.g. trying to reduce the time required for scanning a treatment field, but also innovative ideas in treatment planning methods, often sacrificing one or more of the benefits of standard PBS deliveries. Some of the proposed ideas include “Transmission FLASH”

Table 1
Comparison of passive scattering and pencil beam scanning delivery.

	Passive scattering	Pencil beam scanning
		
Conformality	Reduction in proximal conformality with fixed width SOBP. Lateral conformality may be improved due to the use of collimators.	Improved conformality. Enables multi-field optimisation techniques which can further improve conformality.
Patient-specific hardware requirements	Requires beam-specific collimators (to shape the beam) and compensators (to achieve distal conformality to the target volume).	No patient specific devices required (or potentially used with a collimator which can improve conformality).
Treatment limitations	Maximum field sizes typically up to 25 cm diameter at the isocentre plane.	Maximum field sizes typically up to 40 cm × 30 cm at the isocentre plane.
Time structure of dose delivery	 <p>There may be a fine time structure to dose delivery arising from the pulse repetition rate of the particle accelerator, the use of range modulating wheels or other passive techniques (e.g. wobbling or uniform scanning). For energy modulated fields the use of a rotating range modulator wheel (with a rotation time of ~0.1 s) may not be appropriate for FLASH delivery. Alternatively, static energy modulation devices may be used which deliver all energies simultaneously. Dose is delivered to the entire volume at the same time i.e. each voxel sees the same energy deposition time structure.</p>	 <p>The pencil beam is scanned across the volume resulting in spatially varying time characteristics on a longer time frame than the pulse repetition frequency of the cyclotron. Dose is delivered to different parts of the volume at different times with contributions from spots in close proximity as well as from the low dose penumbra from other neighbouring spots. With multiple energy layers the dose to a given point may have contributions from the entrance region of multiple different energy layers. Energy layer switching may be of the order of 1 s.</p>
Delivery system requirements	Static beam line.	Active beam line – needs steering.
Existing evidence with FLASH	Preclinical: [9,41]	Preclinical: Clinical study: FAST-01 trial [42]

and “Conformal/Bragg peak FLASH”. The former sacrifices on conformality for higher dose rates by shooting proton beams through the patient, while the latter may apply static energy modulation devices to stop the beam within the patient providing distal conformality. One of the challenges in achieving ultra-high dose rates for FLASH delivery is the efficiency of current systems in delivering sufficient current to the target, which is greatest for high cyclotron energies. Both transmission and conformal/Bragg peak FLASH are used to address this, with pros and cons for each modality – see summary in Table 2.

Translation of FLASH parameters into clinical treatment planning

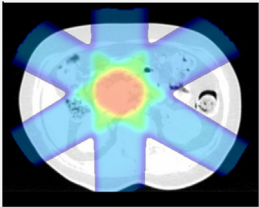
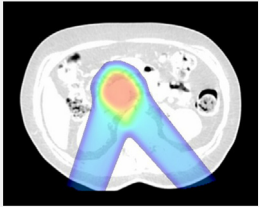
Pre-clinical work has established that the FLASH effect requires a high dose rate and possibly a high dose. For most pre-clinical studies, particularly using electrons, the generation of high dose rates is based on the pulse structure of the beam, and is generally calculated assuming spatiotemporal uniformity (such that each point in the target receives dose with the same time structure). For clinical protons, determining the most effective delivery techniques and treatment planning tools to meet

these dose and dose rate requirements requires a number of additional considerations.

Given the spatially and temporally highly variable dose deposition for scanned proton therapy, the calculation of the local dose rate is non-trivial. The microsecond scale is dictated by the used accelerator and can typically not be varied by the user. While cyclotrons provide a quasi-continuous beam with a repetition rate in the order of 100 MHz [46], a synchrotron beam is inherently pulsed with a fine structure of the order of 10–100 MHz [47]. On a larger scale, in the order of milliseconds, the time structure is dominated by the spot-wise delivery of the treatment field. Through adjustments of the scan path, this time pattern can be influenced by the user. For synchrotrons, an additional consideration is the timing of the spill repetition rate in the order of a few Hz and may impact FLASH delivery [48]. For a multi-field treatment plan, there is an even larger time scale on the order of minutes, induced by the gantry rotation. Lastly, fractionated treatments are spread over multiple days, adding another scale to the delivery time structure.

This multitude of time scales raises the question, over which time frame the delivered dose rate should be averaged in order

Table 2
Properties of pencil beam scanning FLASH delivery techniques.

	Transmission	Conformal/Bragg peak	
		With energy modulation device	Without energy modulation device
			
Beam energy	High energy, high current monoenergetic field.	High current monoenergetic field which passes through a static energy modulation device to produce a polyenergetic beam.	Multiple energies – dose built up sequentially in 3D.
Conformality	Lack of distal sparing. Lateral conformality can be improved by the use of high energies and by multiple beams.	Conformal dose. If necessary conformality can be enhanced by use of additional beam-specific apertures.	
Number of beams	Multiple beams may be required to produce a conformal dose. distribution – consequently there may be a lower dose per beam.	Fewer beams, down to a single beam, are required to produce a conformal plan. With fewer beams there is more choice in planning approach regarding avoidance regions.	
Robustness	Less sensitive to setup and range uncertainties. Intra-beam motion minimised by short delivery time.	Can be sensitive to setup range uncertainties. Intra-beam motion minimised by short delivery time. Inaccuracies associated with production of 3D range modulators could lead to additional range uncertainties. Generation of these devices should be done robustly to consider various perturbation scenarios.	Can be sensitive to setup range uncertainties.
Flexibility	Easily adaptable via beam currents. No need for additional devices.	Plan adaptation may require the manufacture of new field-specific collimators and compensators. Use of hypofractionation for FLASH may increase importance of plan adaptation due to reduction of the 'averaging' effect from fractionation.	Easily adaptable via beam currents. No need for additional devices.
Radiobiology	Less sensitive to variations in RBE as dose is delivered from the entrance region of the beam. RBE may be lower than conventional proton therapy in both the tumour and normal tissue.	End of range RBE uncertainties. For hypofractionated treatments, there are additional considerations with regard to RBE [43]. For low dose rate delivery, the RBE factor decreases with increasing dose which may mitigate some RBE uncertainty.	
Patient-specific hardware requirements	No patient-specific devices required.	Requires beam-specific static energy modulation devices. 3D printed devices have been proposed [44].	No patient-specific devices required.
Treatment limitations	Limits on maximum patient size in beam direction. Beam is required to exit the patient.	As per conventional proton therapy.	
Time structure of dose delivery	Time structure of delivery depends on the delivery time of neighbouring spots on a fine time scale. On a larger time scale there is also a time structure extending across beams.	Time structure of delivery depends on the delivery time of neighbouring spots.	Time structure is more complex with spatially varying time characteristics depending on contribution from neighbouring spots and more distal spots in other energy layers. [45]
Delivery system requirements	Current isochronous cyclotron systems can operate in transmission with high beam currents. Fast lateral scanning may be required.	Fast lateral scanning may be required.	Fast lateral scanning may be required. Faster energy layer switching may be required.
Treatment planning infrastructure	Requires the ability to optimise transmission beams. Approaches for planning with transmission beams established in photon IMRT.	Requires the ability to derive the required beam-specific hardware.	Can use existing treatment planning approaches.
Existing evidence	Approach of FAST-01 trial.	No clinical application yet using such beam specific hardware for conventional or FLASH therapy.	No clinical evidence with FLASH but this is the basis of modern conventional proton therapy.

to correlate with the observed FLASH effect? Whereas Van de Water and colleagues suggested the use of spot-wise dose rate calculations, weighted and averaged by the respectively delivered dose [24], a definition closer to the field-average dose rate was proposed by Folkerts et al., ignoring any distant spots that do not contribute substantial dose (using a user-defined lower dose threshold) to the voxel in question [49]. Another approach is the sliding window dose rate calculation, where an evaluation window is moved over the dose delivery time trace per voxel for each field, and the combination of FLASH dose rate and dose thresholds deter-

mines the time window width (e.g. 40 Gy/s and 4 Gy thresholds imply a 100 ms time window) [39].

The relevant time scale of the dose rate will depend on the memory of the tissue. It is yet to be determined, e.g., whether a cell irradiated by the second treatment field still 'remembers' having received dose from the previous field, or whether the cell registers each treatment field as an entirely new irradiation, in particular, when considering FLASH time scales. Because of this unknown, it is imaginable that within a single treatment field, a part of the dose will cause the FLASH effect and another may not meet thresholds

needed to induce the FLASH effect. In addition, it is unclear whether the FLASH effect will persist for a certain time, even if some dose is delivered at a lower dose rate.

Assuming that the FLASH effect can occur at multiple times and multiple locations during a treatment, it would be helpful to have a biological dose calculation that considers the fact that any dose delivered as FLASH to an organ at risk will have a smaller biological effect. Every dose contribution could be weighted by a factor, depending on whether said contribution is FLASH or not. Such a biologically-weighted dose distribution could give the physician an idea of how much damage a given treatment plan will cause to a patient. Multiple groups have presented such a FLASH-weighted dose calculation [37,38,50,51]. The main caveat of these FLASH relative biological effectiveness (FLASH-RBE) calculations is that they strongly depend on the underlying assumptions of the time structures, dose limits and mechanisms of the FLASH effect.

The potential requirement of lower limits on dose to induce FLASH tissue sparing could impact the calculated FLASH-RBE. Changing the lower dose threshold can mean that regions of normal tissue are moved in or out of FLASH sparing. Dose thresholds will therefore have a profound limitation on treatment options, potentially pushing FLASH therapy into a hypofractionated regime. Thus, FLASH-TPSs should be able to optimise the minimal dose at a location, delivered in a short time period in organs at risk. Furthermore, it may be likely that the FLASH-RBE is dependent on the organ of interest and the endpoint for normal tissue sparing. FLASH-TPSs should therefore include the FLASH-RBE as a variable parameter, such that different values can be applied to different tissue types within the same plan, and plans can be designed using different sparing endpoints.

Further considerations for FLASH treatment planning

Suggested treatment planning approaches to achieve a high dose rate in organs at risk have typically involved some compromise to plan quality. With such compromises, it is essential to evaluate whether the benefits of a FLASH effect outweigh the dosimetric and biological costs of inducing it.

Transmission beams will contribute dose to tissues that would have otherwise received no dose at all. In such cases no magnitude of FLASH sparing can be expected to benefit these tissues. There is also a potential reduction of conformality in regions that would normally receive dose. Planning studies should be used to compare the quality of transmission beam plans with the most appropriate clinical standard to ensure no such compromises are made [4,23,52]. While the FLASH-RBE remains uncertain, care should be taken in assuming any levels of FLASH sparing within treatment plans to ensure dose to OARs does not look more favourable than in reality. The physical dose should also be specified in these studies along with the sparing factor assumed.

For treatment with single, alternating fields, each fraction has radiobiological implications that may be much larger than an anticipated FLASH effect can mitigate (see Fig. 1). Another option is the proposed use of 'disjoint field optimisation', where each field is used to deliver the full prescribed dose to one part of the tumour, without overlap with other fields [39]. The radiobiological implications of such techniques should be weighed up against any potential FLASH sparing. Similarly, the potential use of fewer fractions to achieve sufficient dose may be disadvantageous in some tissues. Starting from a disadvantaged dose distribution, the required FLASH effect to both overcome these limitations and then to provide a further clinical advantage may require careful consideration of possible treatment indications.

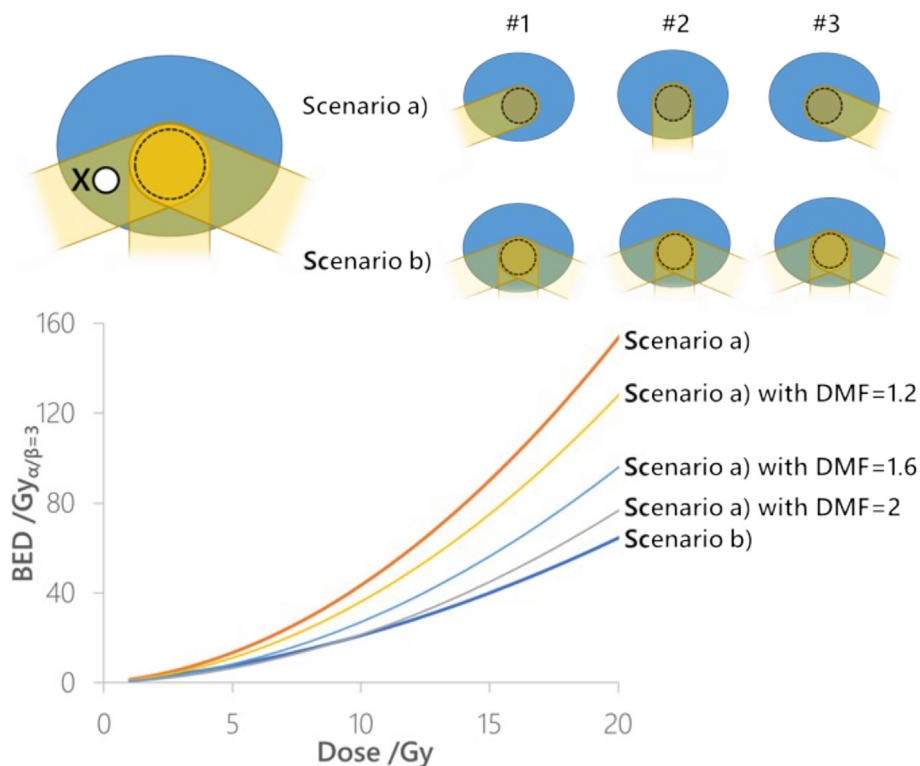


Fig. 1. Consider the dose to point X which is delivered as part of a 3 fraction treatment course in 2 scenarios. In scenario (a) the dose is delivered using a single beam each fraction. The dose contributing to point X is delivered in a single fraction. In scenario (b) all 3 beams are delivered each fraction and the dose to point X is delivered over 3 fractions. The same total dose is delivered but one third of the dose is delivered in each fraction. Biologically effective dose (BED) is shown for a range of doses in the graph along with consideration of possible dose modification factors (DMF) for FLASH. BED is calculated using the linear quadratic model though it should be noted that the radiobiological basis of this may need modification for extreme hypofractionation.

A further point to consider is how FLASH dose rates should be optimised for both tumour and normal tissue regions in a treatment plan. Pre-clinical studies have shown iso-effective tumour control between FLASH and conventional radiation [1,53]. Although the mechanism behind the differential response between normal tissue and tumour is not known, it is evident that this is based on inherent biological differences between the tissue types [17]. Most treatment planning studies to date aimed to achieve FLASH dose rates at all points in a treatment plan, under the assumption that only the normal tissue will be spared [23,38,39,49]. However the ways in which this differential response could be exploited for clinical outcome are yet to be seen. A protective effect only in the healthy tissue could either mean reduced side effects for patients for the same dose to the tumour, or a greater dose to the tumour for the same effect in the normal tissue. Constraints in treatment planning could therefore be shifted to accommodate higher dose thresholds in OARs for FLASH delivery. However, without sufficient clinical evidence and understanding of the biology, treatment planning remains to be difficult as we need accurate estimates of the differential response. In this regard, treatment plan optimisation based on inducing a FLASH effect in the healthy tissue (particularly in OARs) but not in the tumour could be considered. Although this may require a greater understanding of the parameters involved, it would avoid the issue of possible tumour sensitivity to FLASH irradiations [54].

As outlined above, there may be some risk to incorporating FLASH sparing into treatment plans given the uncertainty surrounding the parameters involved. Ensuring that the relevant dose rate is optimised, that there is no unnecessary compromise to plan quality, or that any possible tumour sparing is accounted for, may require greater knowledge of the underlying biology. However, a complete understanding of the mechanisms behind the sparing effect may not be crucial for the development and clinical translation of FLASH, as clinical effects can be empirically derived. Nevertheless, it would help clarify the requirements to produce the FLASH sparing effect using various delivery scenarios, provide more clearly-defined parameters for treatment, and allow for optimisation of the effect.

For example, a mechanism based on radiolytic oxygen depletion [15,16] would require a threshold in instantaneous dose rate such that oxygen is depleted in a timeframe shorter than the replenishment of oxygen from the blood. It would also require either a dose threshold characterised by normal tissue oxygenation levels, or a threshold in oxygenation levels based on the prescribed fractional dose. It is proposed that the lack of tumour effect for this mechanism is governed by tumours being too hypoxic to undergo a significant change in radiosensitivity [6]; a threshold in tumour oxygen levels may therefore also be required for treatment to be effective.

For a mechanism based on circulating lymphocytes [20,55], a more relevant parameter may be the overall time for which dose is applied. This, as well as the size of the irradiated volume, should be minimised to ensure a significant reduction in the number of lymphocytes killed as they circulate through the dose target volume. For mechanisms based on differential biochemical response [17], the dose rate of interest would depend on the timeframe of the relevant chemical reaction pathways. There may also exist a threshold in dose to activate an initial radiolytic response, as well as limitations in the cell/tissue types that may exhibit a significant sparing effect.

It is clear then that many of the unknowns that hinder the development of FLASH treatment planning could be resolved through a better understanding of the FLASH mechanism. Nevertheless, many aspects of this work can still go ahead while investigation into the mechanism is underway. With this in mind, it is important to consider optimal ways to synergise these

research tracks for future FLASH investigation and implementation.

Looking to the future

TPS development

With all the above-described unknowns and the ongoing research in mind, it is evident that any TPS for FLASH treatment research needs to be flexible enough to incorporate new findings. In this respect, the approach of assigning a flexible FLASH-weighted dose distribution ("FLASH-RBE") is promising. However, such efforts need to be able to adjust to new data. On the one hand, it needs to be possible to add new functionality to an existing TPS – for instance, if data suggest the use of a new dose rate definition, the TPS should be extended by such a dose rate calculation. As discussed in previous sections, there is a wide variety of potential additions to a TPS. On the other hand, all such extensions comprise a certain set of parameters that may need to be tuned according to emerging biological data. For example, a module that calculates a FLASH-RBE would likely require dose and dose rate thresholds to determine where and when the FLASH effect would occur. All such parameters may not be universal, but instead may be organ-, tissue- or region specific.

Furthermore, any addition to a TPS needs to be properly validated and tested before it can be used clinically, which, depending on the number of involved new parameters, may be time-consuming. Thus, it is strongly advised to not only develop flexible TPS modules, but also keep sufficient information to allow future studies to determine FLASH-RBE values for a TPS with any new set of determined requirements to induce a FLASH effect.

An additional point of concern for FLASH planning is the dynamics and capabilities of the delivery machine. The current lack of interface between treatment planning and machine delivery means that essential information for dose rate estimation, such as the scanning deadtimes and beam intensities, may not be available at the treatment planning level. As this may be sensitive, complex and machine-specific information, obtaining this from the manufacturer may not always be trivial. Any links between the TPS and delivery system, as well as the models used for dose rate estimates, also need to be validated and commissioned before clinical use.

While there are still considerable uncertainties in the requirements to realise a FLASH effect, and similarly the magnitude of the benefit expected from a given treatment plan, some form of sensitivity analysis may be valuable. The evaluation of plans given anticipated uncertainties in proton range and patient setup are commonplace in proton therapy. A similar approach to the uncertainties associated with the FLASH effect may be useful to ensure safety and efficacy where there is still much to be understood.

Clinical trial outcome analysis

As stated above, since the mechanism of FLASH tissue sparing is currently still elusive, it is important to allow for comprehensive retrospective studies for all clinical trials that may be conducted. A first trial has been conducted looking purely at toxicity and feasibility of delivering FLASH (FAST-01[42]). Additional trials (human and large animal) are actively being planned or have already started. While all trials will be conducted with average dose rates of >40 Gy/s, the averaging methodology and even the total delivery time is not necessarily comparable. Thus, all trials should record log files of actual deliveries, including timing and dose of each beam spot. Alternatively, to avoid the use of machine vendor specific log file data, the TPS used in the trial should report energy deposition time traces per voxel. In addition, while the intra spot time

Table 3

Template for summarising the major assumptions and parameters of any FLASH-related planning study.

Parameters	Values
Dose threshold (binary or gradient + parameters)	E.g. 5 Gy (Define 100% for relative dose thresholds)
Dose rate threshold (binary or gradient + parameters)	Min Gy/s
Dose rate definition (+parameters)	E.g. Dose-Averaged dose rate, PBS dose rate using 0.1 Gy threshold, ...
Delivery time	Time per spot, scanning speed, total time per beam, ...
Assumed dose modifying factor (DMF) for FLASH	Max DMF
Reference modality + fractionation	E.g. IMRT, VMAT, IMPT, ...; 30×2 Gy
Studied modality + fractionation	E.g. Proton transmission, 1×15 Gy
Relative biological effectiveness	E.g. An RBE of 1.1 is assumed
Energy deposition time trace per voxel/Influence matrix and timing characteristics*	Resolution in sufficiently small time bins per voxel (e.g. 1 ms). *Though this may not be reported in a paper this data should be stored and available.

structure is often not recorded, their standard time structure should be noted. All possible data related to trial treatments should be kept. Only such rigorous recording of time structures will allow for adequate comparisons of FLASH trial results, and only such clinical data can really answer the question of which parameters are important for clinical use of FLASH RT.

Recommendations for future planning studies

As stated in previous sections, many questions remain unanswered when it comes to treatment planning for FLASH deliveries. Once more mysteries around the FLASH effect are resolved, it may be sensible to revisit already published planning studies and compare their conclusions with the updated understanding of the FLASH effect. To facilitate such endeavours, we recommend every future FLASH-related planning study paper include a table summarising the major assumptions and parameters. A template table comprising the minimally required items is shown in Table 3. Condensing the most important parameters can substantially simplify the comparison of various planning studies with newly available data.

One critical piece of information clearly is the dose rate definition used throughout a planning study. It needs to be ensured that the reader receives all information required for the used dose rate definition, i.e., inherent parameters.

Moreover, to help the reader contextualise the presented results and conclusion, some considerations of the feasibility of the assumptions made in a study is recommended. Such considerations may include the type of machine, particularly whether it already exists or if the assumptions and parameters are idealised.

Conclusion

As FLASH radiotherapy is advancing towards clinical translation, incorporation of FLASH effect modelling into treatment planning systems is a necessary prerequisite. Control of the FLASH effect by optimisation methods is desirable but not necessary to have initially. The uncertainty surrounding the biological mechanism of FLASH sparing and the parameter requirements to produce the effect provide a barrier for its use in treatment planning. However, this type of investigation can still progress in parallel with more underlying biological research, provided that we proceed with flexibility and caution.

While the causes of the FLASH effect are still under investigation, the incorporation of FLASH into treatment planning should remain empirical and independent of the mechanism. As the major parameter involved, focus should remain on optimising the dose rate, however planning systems should include various options for defining this, and make clear how each definition is calculated. TPSs should also allow flexibility for the user to optimise other parameters that may be involved in FLASH sparing, such as dose

thresholds per fraction and for each organ at risk. TPSs should further be able to test different assumptions regarding FLASH sparing (such as the dose modification factor or dose-rate threshold), as new data emerge.

As FLASH clinical trials are underway, our key recommendation for navigating uncertainty in this new field is to record and provide all treatment data that may be relevant for possible future analysis. As a minimum all studies should report all the parameters in Table 3 to ensure clarity and consensus. Through these means, clinical data may be able to shed light on possible correlations of certain parameters to aid our understanding of the FLASH effect, or validate any prospective developments in the research on the underlying biology (e.g. regarding the relevance of a particular parameter or dose rate definition) so that future treatments can be optimised to improve outcome.

Disclosures

MK is an employee of Varian Medical Systems.
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