Original Article

Trade-off in healthy tissue sparing of FLASH and fractionation in stereotactic proton therapy of lung lesions with transmission beams

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Article info

Article history:
Received 25 February 2022
Received in revised form 12 August 2022
Accepted 14 August 2022
Available online 18 August 2022

Keywords:
Stereotactic lung treatment
Proton therapy
Flash radiotherapy
Radiobiological modeling
Treatment planning

A R T I C L E   I N F O

Purpose and objective: Besides a dose-rate threshold of 40–100 Gy/s, the FLASH effect may require a dose > 3.5–7 Gy. Even in hypofractioned treatments, with all beams delivered in each fraction (ABEF), most healthy tissue is irradiated to a lower fraction dose. This can be circumvented by single-beam-per-fraction (SBPF) delivery, with a loss of healthy tissue sparing by fractionation. We investigated the trade-off between FLASH and loss of fractionation in SBPF stereotactic proton therapy of lung cancer and determined break-even FLASH-enhancement ratios (FERs).

Materials and Methods: Treatment plans for 12 patients were generated. GTV delineations were available and a 5 mm GTV-PTV margin was applied. Equiangular arrangements of 3, 5, 7, and 9 244 MeV proton transmission beams were used. To facilitate SBPF, the number of fractions was equal to the number of beams. Iso-effective fractionation schedules with a single field uniform dose prescription were used: D95%PTV = 100%Dpres per beam. All plans were evaluated in terms of dose to lung and conformity of dose to target of FLASH-enhanced biologically equivalent dose (EQD2).

Results: Compared to ABEF, SBPF resulted in a median increase of EQD2mean to healthy lung of 56%, 58%, 55% and 54% in plans with 3, 5, 7 and 9 fractions respectively and of 236%, 78%, 50% and 41% in V100%EQD2, quantifying conformity. This can be compensated for by FERs of at least 1.28, 1.32, 1.30 and 1.23 respectively for EQD2 mean and 1.29, 1.18, 1.28 and 1.15 for V100%EQD2.

Conclusion: A FLASH effect outweighing the loss of fractionation in SBPF may be achieved in stereotactic lung treatments. The trade-off with fractionation depends on the conditions under which the FLASH effect occurs. Better understanding of the underlying biology and the impact of delivery conditions is needed.

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Since its discovery in 2014 [1], FLASH as a differential effect between tumors and healthy tissue has attracted a lot attention in radiotherapy [2–4]. It has been consistently observed in radiobiological experiments in animals and amounts to a reduction of the radiosensitivity of healthy tissue in ultra-high dose rate (>40–100 Gy/s) high dose (>3.5–7 Gy) [4] irradiation, relative to that of the tumor. While the dependence of radiosensitivity on dose rate and oxygenation has been known since the 1960s [5], FLASH as a differential effect provides a novel and fundamentally different way to further increase the therapeutic bandwidth of radiotherapy - in addition to fractionation and high-precision irradiation techniques with image guidance.

Most animal experiments have been performed with high-dose rate electron beams, focusing e.g., on neurocognitive function [6], lung fibrosis [1], skin [7] and abdominal toxicities [8] as healthy tissue end points. FLASH has also been demonstrated in a first patient treatment [9]. Ultra-high dose rates are readily available in cyclotron-accelerated therapeutic proton beams [10] and evidence is gathering that the FLASH effect exists in such beams [11–15]. FLASH proton therapy (FLASH-PT) holds the promise of combining the FLASH effect with the physical advantages of proton beams. It is particularly well-suited for deep-seated targets. Recently, accrual for a first clinical trials on FLASH-PT with pencil beam scanning (PBS) has been completed [16].

https://doi.org/10.1016/j.radonc.2022.08.015
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With protons, the overall highest dose rate is achieved at the maximum cyclotron energy of 250 MeV. Such beams have a 38 cm range in water and shoot through the patient in the first foreseen clinical applications, e.g. bone metastases and thoracic lesions [17–20]. Their use may come at the expense of conformity of dose to the target. Moreover, as the FLASH effect threshold comes with a fraction dose threshold of 3.5–7 Gy [4], clinically, it is limited to hypofractionated treatments.

With delivery of all beams in each fraction (ABEF) of, e.g., 54 Gy with 3 beams in 3 fractions, the beam doses of 6 Gy may fall below the FLASH threshold, compromising FLASH in healthy tissue irradiated by one beam only. In the volume with overlapping beams from different angles, the average dose rate is compromised by gantry and couch shifting times to values far below the FLASH dose-rate threshold of 40–100 Gy/s. It is not clear yet to what extend the FLASH effect exists in revisits of the same OAR voxels in one fraction. This can be circumvented by single beam per fraction (SBPF) delivery with single-field uniform dose (SFUD) treatment planning to ensure adequate target dose in each fraction. SFUD, however, limits conformity of physical dose, and SBPF comes with a loss of healthy tissue sparing by fractionation, further compromising conformity of biologically equivalent dose.

To assess (i) the clinical feasibility of stereotactic FLASH-PT in clinically realistic hypofractionated treatments and (ii) which biological aspects/unknowns are important for clinical translatability, we investigated the trade-off between the FLASH effect and loss of fractionation in FLASH-enhanced SBPF vs ABEF delivery of the same treatment plans in stereotactic proton therapy of small lung lesions. As 18 Gy per fraction with a single beam may not be clinically acceptable in all patients, we focused on different isoeffective fractionation regimens derived from 54 Gy in 3 fractions and a radiobiological equivalent dose (SFUD) treatment planning to ensure adequate target dose in each fraction. SFUD, however, limits conformity of physical dose, and SBPF comes with a loss of healthy tissue sparing by fractionation, further compromising conformity of biologically equivalent dose.

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Method and materials

Patient data

Anonymized planning-CT scans and delineations of 12 patients with primary lung cancer and lung metastasis, clinically treated with photons in prone (5) or supine (7) position, were used. GTV delineations were available and an isotropic 5 mm GTV-PTV margin was applied. Only small PTVs (median 6.4 cc, range 4.4–10.1 cc) and only one lesion per patient, 3 right-sided and 12 left-sided, were included. The median GTV volume was 1.2 cc (range 0.5–2.6 cc).

Treatment planning

Treatment plans with 244 MeV proton transmission (shoot-through) beams, the highest energy currently commissioned, were implemented in Erasmus-iCycle, our in-house developed software for automated prioritized optimization of radiotherapy treatment plans [21], using the HollandPTC clinical proton beam model and the Astroid dose engine [22,23].

For this study the common fractionation schedule of 54 Gy in 3 fractions [24] was used. To evaluate the impact of fractionation with more moderate yet FLASH-compatible fraction doses, we also considered 63.5 Gy in 5, 73.7 Gy in 7 and 80.0 Gy in 9 fractions, see supplementary material [SM]. These are isoeffective fractionation regimens based on 54 Gy in 3 fractions assuming a radiobiological α/β ratio of 10 Gy for the target. The number of beams was kept equal to the number of treatment fractions, to facilitate FLASH-enhanced SBPF delivery, allowing for a direct comparison to delivery of all beams in each fraction (ABEF).

An SFUD approach with transmission beams was used with: D_{\text{SFUD,PTV}} = 100\% D_{\text{pres}} per beam. Dosimetric constraints were put on (i) minimum dose to GTV and PTV (ii) maximum dose to critical serial OARs and (iii) dose to contralateral lung and to ipsilateral lung minus a 20 mm expansion of the PTV. Prioritized objectives were used on (i) maximum dose to PTV, (ii) maximum dose to GTV, (iii) 3 mm and 6 mm shells around the PTV and (iv) dose to all OARs and other non-specified tissue, see also Table 1. The initial set of pencil beams was chosen on a 5 mm lateral grid. Pencil-beam selection [25] was used to reduce the number of transmission pencil beams and, hence, delivery time. Co-planar equiangular arrangements of beams were used to mimic beam overlap and improve conformity of dose to the target. The overall orientation was chosen so as to maximally avoid serial OARs, i.e., esophagus and spinal cord.

FLASH and fractionation modeling

Treatment delivery and fractionation regimens were evaluated in terms of the total equivalent dose in 2 Gy fractions (EQD2), defined as EQD2(d,D) = (α/β + d)D/(α/β + 2 Gy), with the fraction dose d, the total dose D = n × d, n the number of fractions and α/β the ratio of radiobiological α and β parameters. We assumed α/β = 3 Gy for all healthy tissues. Since FLASH is a fraction dose effect [4], the FLASH enhancement ratio (FER, \( \geq 1 \)) was applied to all physical fraction voxel doses, i.e., \( d_j \rightarrow d_j/FER \) to all OAR voxels j, with no threshold within a beam.

Table 1

| Target/OAR | Constraints | Objectives |
|------------|-------------|------------|
| CVT \( \rightarrow \) GTV | \( D_{\text{max}} \geq D_{\text{pres}} \) | \( D_{\text{max}} \leq 124\% D_{\text{pres}} \) |
| PTV minus GTV | \( D_{\text{min}} = 98\% D_{\text{pres}} \) | \( D_{\text{max}} \leq 124\% D_{\text{pres}} \) |
| Ipsilateral lung minus PTV + 20 mm | \( D_{\text{max}} \leq 32\% D_{\text{pres}} \) | \( D_{\text{max}} = 0 \) |
| Ipsilateral bronchus | \( D_{\text{mean}} \leq 38.1 \) | Avoid |
| Liver, stomach, bowel | | |

Evaluation

FLASH-enhanced EQD2 distributions for ABEF and SBPF delivery were calculated for FERs from 1.0 (no FLASH effect) to 2.0 in steps of 0.05. Voxel fraction EQD2s for FLASH-enhanced single-beam per fraction delivery were summed up for all fractions. The total EQD2 distributions were evaluated in terms of mean dose to ipsilateral lung (EQD2mean). As both SFUD planning with transmission beams and SBPF delivery come at the expense of conformity of EQD2 to
the target, also the volume receiving 100% of the prescribed dose (\(V_{100\%\, EQD2_{pres}}\)) was evaluated. Since the target is included, for maximum OAR sparing this is equal to the GTV. To evaluate the \(V_{100\%\, EQD2_{pres}}\), prescribed doses of 54 Gy in 3, 65.5 Gy in 5, 73.7 Gy in 7 and 80.0 Gy in 9 fractions were converted to EQD2 with \(\frac{\alpha}{\beta} = 3\) Gy, i.e., 226.8 Gy, 210.9 Gy, 199.4 Gy and 190.2 Gy for 3, 5, 7 and 9 fraction plans respectively. FLASH-enhanced values of EQD2 mean and \(V_{100\%\, EQD2_{pres}}\) were normalized to non-FLASH-enhanced values for the ABEF results for each patient, and population median and full ranges (minimum to maximum) were calculated. Break-even FERs, i.e., the FER at which the FLASH effect compensates for the loss of healthy tissue sparing through fractionation in SBPF delivery, were calculated by linear interpolation between the data points. Linear interpolation of the data points to FER intervals of 0.01 was used to calculate cumulative population break-even histograms. These quantify the fraction of patients benefiting from FLASH as a function of FER.

**Delivery times**

Treatment planning was based on integral dose-depth profiles, normalized to \(D_{max}\) in water. Delivery times were calculated based on 0.3 Gprotons per unit beam weight, a proton beam current of 220nA at the nozzle and a switching time of 0.2 ms between pencil beams. Beam dose rates are calculated as the nominal dose per beam, divided by the delivery time.

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**Fig. 1.** (a) Absorbed dose distribution for a treatment plan with five equiangular 244 MeV transmission beams. Depending on delivery and the FLASH effect, this leads to the EQD2 distributions in panel (b)-(d). Panel (b) shows the EQD2 distribution for conventional delivery of all beams in each fraction (ABEF), while panel (c) shows that of non-FLASH-enhanced single-beam per fraction (SBPF) delivery. The difference between (b) and (c) shows the effect of the loss of fractionation. Panel (d) shows the EQD2 distribution for FLASH-enhanced SBPF delivery with FER = 1.8. At this FER, the FLASH effect more than compensates the loss of healthy tissue sparing through fractionation. The EQD2 is calculated in healthy tissue outside the GTV only, with \(\frac{\alpha}{\beta} = 3\) Gy. From blue to red, the isodose levels correspond to 10% — 120% of 65.5 Gy for the absorbed dose in panel (a) and the corresponding EQD2 of 210.9 Gy in panels (b)-(d) respectively. The GTV and PTV contours are displayed in green and red respectively.

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**Results**

All target planning constraints were met in all treatment plans. A typical example of the total absorbed dose, the EQD2 for conventional ABEF delivery, SBPF without FLASH enhancement and SBPF delivery with a FER of 1.8 are shown in Fig. 1. Also, all OAR constraints were met in all treatment plans. Non-FLASH-enhanced values for the EQD2 mean and \(V_{100\%\, EQD2_{pres}}\) were normalized to healthy ipsilateral lung and the EQD2 mean of 210.9 Gy for ABEF and SBPF delivery are shown in Fig. 2. The loss of fractionation is substantial, leading to a median increase of EQD2 mean to healthy lung of 56%, 58%, 55% and 54% in plans with 3, 5, 7 and 9 fractions respectively and a median increase of 236%, 78%, 50% and 41% in \(V_{100\%\, EQD2_{pres}}\). Patient population ranges of these percentage losses are listed in Table 2. As can also be seen in Fig. 2, a median reduction of 54% (full range: 44%-69%) of the \(V_{100\%\, EQD2_{pres}}\) in SBPF delivery can be achieved by using 5 instead of 3 beams. Median reductions of 67% (55%-79%) and 73% (65%-82%) can be achieved with 7 and 9 beams respectively (relative to 3 beams).

The dependence on FER of EQD2 mean and \(V_{100\%\, EQD2_{pres}}\) for all patients and plans is shown in the panels of Fig. 3. The graphs display patient population median values while the error bars indicate the full population range, i.e., the overall minimum and maximum values. Break-even FERs for EQD2 mean and \(V_{100\%\, EQD2_{pres}}\), i.e., the values of the FER at which the fractionation disadvantage is outweighed by the FLASH effect, are listed in Table 2, where, for reference, also the EQD2 mean and \(V_{100\%\, EQD2_{pres}}\) obtained for ABEF delivery are listed. The break-even FER for the EQD2 mean lies around 1.3 and hardly depends on the number of beams and fractions. Break-even FERs for the \(V_{100\%\, EQD2_{pres}}\)
depend on the beam and fraction number and decrease from 1.3 for 3 to 1.1 for 9 beams. FLASH-enhancement has the most impact on plans with a smaller number of beams, where also the $V_{100\%\text{ EQD}2\text{pres}}$ without FLASH enhancement is larger (see Table 2). For sufficiently large FERs, the FLASH enhanced dose in all healthy tissue falls below 100% EQD2 pres and the $V_{100\%\text{ EQD}2\text{pres}}$ is equal to the GTV.

The panels in Fig. 4 show population break-even FER histograms for $EQD2_{\text{mean}}$ and the $V_{100\%\text{ EQD}2\text{pres}}$ to the ipsilateral lung. These results confirm that break-even FER for $EQD2_{\text{mean}}$ hardly depends on the number of beams and fractions. The transition from FERs for which no patients benefit from FLASH to values for which all patients in this homogeneous group benefit is quite steep, both for $EQD2_{\text{mean}}$ and for $V_{100\%\text{ EQD}2\text{pres}}$.
The number of pencil beams per beam, the total beam weights in Gps, the estimated treatment delivery times and the beam dose rates are listed in Table 3. All beam delivery times are below 100 ms. The beam dose rates show a slight decrease with an increasing number of beams and fraction but are all well above the FLASH threshold of 40–100 Gy/s. This confirms that FLASH-compatible delivery of these treatment plans is technologically feasible in principle.

Experimental data on the FLASH effect on lung fibrosis in mice is consistent with a FER larger than 1.8 [1]. This would enable a...
population-median healthy tissue sparing of 37%, 30%, 29% and 28% in terms of the EQD2\textsubscript{mean} and 54%, 66%, 78%, 95% in terms of the V\textsubscript{100%EQD2} for plans with 3, 5, 7 and 9 beams respectively.

**Discussion**

We have investigated the trade-off between fractionation and the FLASH in SBPF delivery of stereotactic treatments for small lung lesions, enabling beam doses above the FLASH dose threshold of about 7 Gy and FLASH-compatible dose rates. Our main finding is that the break-even FER for the mean EQD2 to healthy lung tissue is about 1.3 and hardly depends on the number of beams. For the volume irradiated to 100% of prescribed dose, expressed as an EQD2, we found break-even FERs ranging from 1.3–1.1 for plans with 3 to 9 beams. Since data on lung fibrosis in mice is consistent with a FER larger than 1.8 [1], FLASH enhancement may be within reach in stereotactic proton therapy of lung lesions.

In modeling the FLASH effect, we have made three assumptions: (i) FLASH is a linear local healthy tissue effect, i.e. the FER ratio is applied to non-target voxel doses, (ii) the FER is applied to physical fraction doses and, hence, independent of $\alpha/\beta$ and (iii) an entire treatment beam is either FLASH or not and FLASH is homogeneous, i.e., possible variations of the FLASH effect within a beam, for instance in the penumbrae, where fraction doses are lower, are neglected. As a result of assumption (i), the trade-off between FLASH and fractionation and, therefore, the break-even point, varies between voxels in a patient. To convert this local variation into a more global, potentially clinically meaningful dosimetric endpoint, we evaluated the $V_{100% EQD2}$ and the EQD2\textsubscript{mean} to healthy ipsilateral lung. The $V_{100% EQD2}$ is quasi-local in that it depends on the small and relatively homogeneous high-dose volume, while the EQD2\textsubscript{mean} is a more global metric. The EQD2\textsubscript{mean} depends linearly on dose and volume, as opposed to a near-min/max ($D_{\text{max}}/D_{\text{min}}$) or an equivalent uniform dose [26] and involves equal weighting of wide range of dose levels. In contrast, the $V_{100% EQD2}$ is evaluated at one dose level only. Therefore, assumption (i) has limited impact on our results. Based on assumption (ii), the EQD2 was calculated for FLASH-enhanced fraction doses and summed for all fractions. Depending on the FLASH dose threshold, assumption (iii) may be more critical. For a dose threshold of 3.5–7 Gy, the beam doses considered here are well into the FLASH regime, but if it were comparable to the beam dose, higher break-even FERs would have been found [SM]. A better understanding of the dose dependence of the FLASH effect within a beam is essential for its clinical translatable. For a strictly uniform beam doses and fully overlapping beams, the break-even FER increases with dose and with the number of beams [SM].

In the clinical treatment plans the FLASH effect may also be attained in voxels where not all beams overlap. Moreover, in optimized treatment plans the break-even FER involves weighted averaging of all voxel doses, including the intermediate and lower (penumbra) doses. This results in lower break-even FERs. Also, as a result of this averaging, the break-even FER for EQD2\textsubscript{mean} does not significantly depend on the number of beams [SM], as can be seen in Fig. 3a and Fig. 4a.

In modeling fractionation effects, we have assumed a fixed $\alpha/\beta = 3$ Gy for all healthy tissue; a lower value would lead to higher break-even FERs and vice versa [SM].

Although a patient’s lung function post-treatment depends on dose to both lungs, we focused on dose to the ipsilateral lung as a proxy of healthy tissue damage. The biggest impact of FLASH is expected in the intermediate and high-dose volume surrounding the target. Moreover, dose to contralateral lung may also be reduced by the choice of beam directions. Other dose volume parameters, e.g. $V_{15Gy EQD2}$, $V_{10Gy EQD2}$ and $V_{20Gy EQD2}$ are clinically relevant. But since the corresponding beam dose levels may fall below the FLASH dose threshold when delivered with two or more overlapping beams, these were not included in the analysis presented here.

We have used equiangular arrangements of proton transmission beams maximally avoiding critical serial OARs and minimizing beam overlap in the high-dose volume. Further per-patient fine tuning of beam directions, non-coplanar beams or automated beam selection may be desirable in clinical practice.

Similar considerations and results on FLASH and fractionation may apply to other treatment planning and delivery approaches. In Refs. [17,19], proton transmission beams have been demonstrated to be non-inferior to conventional radiotherapy with photons (VMAT) for stereotactic treatment of small lung lesions. Proton Bragg-peak beams have the disadvantage of increased lateral scattering around the Bragg-peak. Also, placing the Bragg peak in small lung lesions, surrounded by dilute lung tissue, is technologically challenging and comes with substantial range uncertainty. Full IMPT with proton transmission beams may lead to more conformal plans but comes with the challenge of patching fields and a target that moves with respiration between beams and fractions.

The proton energy of 244 MeV used here is the highest energy available in our current beam model. The overall highest dose rate will be achieved at the maximum cyclotron energy of 250 MeV. Although the difference in instantaneous dose rate is substantial, the difference between the lateral profiles and the dose-depth curve in the entrance part of the beam is expected to be small and have little impact on the treatment plans (the Bragg-peak is not inside the patient).

A PTV-based approach was used with transmission beams because the basic assumption underlying the PTV-concept in conventional radiotherapy, i.e., the invariance of dose under (small) shifts and deformations, applies to such beams with and SFUD approach, where proton range uncertainty and intensity modulation have been eliminated. The 5 mm GTV-PTV margin used, would be compatible only with state-of-the-art breathing motion management, i.e., tracking or gating. Depending on the clinical implementation of stereotactic treatment with proton transmission beams, larger margins, or an internal target volume (ITV) may be needed. This would increase the irradiated volume and, hence, the overall delivery times.

The optimization used here was solely done on physical (beam) dose and dose rates were calculated for each beam as the ratio of the nominal beam doses and estimated delivery times. Depending on the delivery setup used, spot delivery times may fall below the monitor chamber detection times, typically on the order 1–3 ms in which case a lower nozzle current could be used, still leading to FLASH compatible dose rates $>$ 40–100 Gy/s. Alternatively, further pencil-beam reduction [25] may be used in treatment planning. With FLASH models [27] and more advanced FLASH-based dose-rate metrics [26,19] gradually becoming available, a simultaneous optimization of dose rate and dose and/or FLASH-enhanced dose [29], possibly combined with scanning-pattern optimization [30], may become feasible. The question which (dose-rate) metric is most predictive of FLASH in IMPT with PBS is not resolved yet.
The SBPF approach used here may be extended to treatments with two or more beams per fraction, one above the FLASH dose threshold and one or more below it. In this way an optimal combination of healthy tissue sparing during fractionation and FLASH may be achieved. Overlap between FLASH and non-FLASH beams and the order of irradiation may become important. Further radiobiological research to investigate and optimize such treatments is crucial for the further clinical development of FLASH-PT.

Conclusion

The loss of fractionation in SBPF delivery is substantial, but a FLASH effect outweighing this and resulting in more healthy tissue sparing may be feasible in stereotactic proton therapy of lung lesions. The biggest relative gain in conformity of dose is already achieved with five beams (as compared to three beams), in which case the beam dose of 13.1 Gy is well above the FLASH dose threshold of 7 Gy.

Better understanding of the underlying biology and physiology, and hence of the actual FER, both in radiobiological experiments and in a clinical setting, is crucial for the further development of FLASH radiotherapy. Our results could be used to guide these experiments and serve as a starting point for the design of clinical trials on stereotactic FLASH-PT of small lung lesions.

Conflict of Interest

The department of radiotherapy of the Erasmus MC Cancer Institute received a research grant from the Dutch cancer society and has research collaborations with Elekta AB, Stockholm, Sweden and Accuray Inc., Sunnyvale, USA. HollandPTC has a research collaboration with Varian, Palo Alto, USA.

Acknowledgement

We thank Thyrza Jagt for discussions, Pepik Cruissjen for initial treatment planning, Jasper Kouwenberg for help with commissioning the 244 MeV HollandPTC beam model in Erasmus-iCycle [21] and Marta Rovituso and Kees Spruijt for discussions on delivery parameters.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.08.015.

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