Physics in Medicine &
Biology

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To cite this article: Sophie Wuyckens *et al* 2025 *Phys. Med. Biol.* **70** 19NT01

IOP Publishing Phys. Med. Biol. 70 (2025) 19NT01 https://doi.org/10.1088/1361-6560/ae023c

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

RECEIVED
10 September 2024

REVISED
21 August 2025

ACCEPTED FOR PUBLICATION
1 September 2025

PUBLISHED
25 September 2025

NOTE

FLASH-enabled proton SBRT for a challenging case of spine metastasis

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Keywords: conformal FLASH, spine metastasis, proton therapy, SBRT

Supplementary material for this article is available online

Abstract

Objective. The FLASH effect, characterized by potential sparing of organs at risk (OARs) through ultra-high dose rate (DR) irradiation, has garnered significant attention for its capability to address indications previously untreatable at conventional DRs with hypofractionated schemes. While considerable biological research is needed to understand the FLASH effect and determine the FLASH modifying factors (FMF) for individual OARs, treatment planning studies have also emerged. This study evaluates the feasibility of achieving FLASH conditions in proton stereotactic body radiotherapy for spine metastases and establishes the required FMFs under different fractionation regimens. *Approach*. A conformal FLASH Proton SBRT plan was generated for a patient with spine metastasis in a research version of RayStation11B (RaySearch laboratories AB, Stockholm) on an IBA Proteus Plus system. Two oblique posterior beams were used in the plan. The prescribed dose to the CTV was set according to 3 different fractionation regimens: 5 fractions (fx) of 7 Gy, 8 fx of 5 Gy, and 10 fx of 4.2 Gy. Spot filtering and sorting techniques were applied to maximize the 5% pencil beam scanning DR in the spinal cord (SC). The FLASH effect was assumed to be observed within irradiated regions above 40 Gy s^{-1} and 4 Gy per fraction. *Main results*. The generated plans successfully ensure robust target coverage in each fraction. The volume of SC that does not comply with the clinical goal adheres to the FLASH effect conditions in each fraction. Depending on the aforementioned fractionation schemes used, a FMF of approximately 0.6 to 0.8 is necessary to enable such treatment in FLASH conditions. *Significance*. This study indicates that treating challenging spine metastases with protons using FLASH delivery is technically feasible. However, clinical viability depends on optimistic parameters to trigger the FLASH effect and FMF values below 0.8, which are not yet guaranteed given current research.

1. Introduction

Spinal metastases affect up to 70% of terminal cancer patients (Hong *et al* 2022) and can significantly impact their quality of life, primarily due to severe pain, decreased mobility, and potential neurological deficits (Liu *et al* 2022). The management of spinal metastases typically involves a multidisciplinary approach including surgery, radiation therapy (RT), and systemic treatments. RT is predominantly delivered using conventional external beam RT (cEBRT), aimed at pain palliation, prevention of local disease progression, and maintenance or recovery of neurological function (Mizumoto 2011). However, the maximal dose which can be delivered using cEBRT is often limited by the adjacent critical organs, such as the spinal cord (SC), resulting in suboptimal local tumor control.

Specialized radiotherapy techniques, such as stereotactic body radiotherapy (SBRT), bring higher precision by delivering a high dose to the tumor while sparing surrounding healthy tissues (Glicksman 2020). These advancements are particularly promising for patients with longer life expectancies and oligometastatic diseases, leading to potential improvements in local control and pain relief. However, in the case of metastases encompassing the SC, SBRT is contraindicated given that SC tolerance is no longer respected.

The discovery of the FLASH effect represents another significant advancement in RT. FLASH is characterized by the sparing of organs at risk (OARs) through ultra-high dose rate (UHDR) irradiation without compromising tumor control (Vozenin *et al* 2019). *In vivo* studies have confirmed the advantage of FLASH radiotherapy in mouse (Favaudon *et al* 2014, Montay-Gruel 2017), mini-pig and cat cancer models (Vozenin 2019). When combined with proton pencil beam scanning (PBS), the feasibility of conformal FLASH PBS planning has already been demonstrated in several treatment sites (Wei 2022, Lattery *et al* 2023, Kaulfers 2024) through the use of a patient-specific range modulator (Kang *et al* 2022, Deffet *et al* 2023). The high precision of protons, their sharp dose gradient, and the potential OAR-sparing effect of FLASH make this modality a potential candidate for treating indications previously untreatable with conventional DR using hypofractionated schemes.

In the context of spinal metastases, conformal FLASH PBS could therefore may offer clinical advantages by enabling radical intervention for cases currently deemed non-treatable, thus preventing SC compression, VCF, and paralysis. This study thus aims to evaluate the feasibility of FLASH-enabled Proton SBRT plans for spinal metastases from a treatment planning point-of-view and to establish the clinical conditions required to achieve this, in terms of both biological effectiveness and treatment delivery.

2. Materials and methods

2.1. Patient cohort and target delineation

A single patient with spine metastasis was selected for this case study. The anonymized patient data was retrieved from a retrospective database from Cliniques Universitaires Saint-Luc (Brussels, Belgium), for which ethical approval was granted. The clinical target volume (CTV) included the entire vertebra, encompassing the SC. The SC, as an OAR, was identified as the only critical structure that necessitated careful sparing (see figure 1).

2.2. Treatment planning strategy

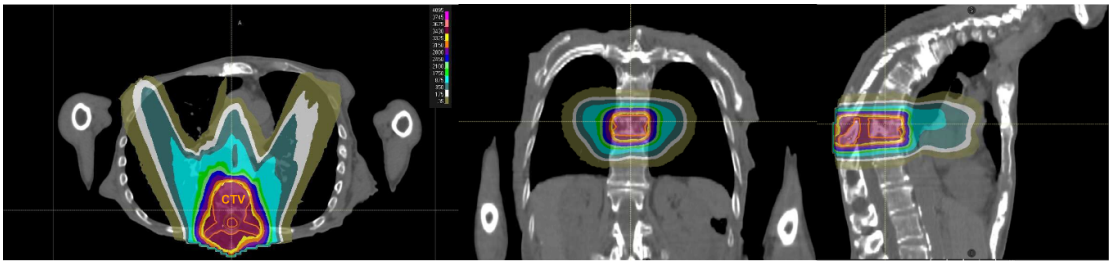
The conformal FLASH PBS proton plans were robustly optimized using a research version of RayStation 11B that includes the FLASH module as part of a research collaboration agreement between RaySearch Laboratories and our institute.

The beam configuration consisted of two lateral posterior obliques beams positioned at 160° and 200°. This configuration was chosen to ensure adequate target coverage. For each beam, a 6.5 slab aluminum range shifter was used, along with a 6 cm brass block. This guaranteed that the highest machine energy and thus maximum possible beam current could be reached. The brass block was conformed to provide a 1 cm margin around the CTV. The proton treatment machine used for the simulation is an IBA Proteus Plus (see SM1 for modeling details).

The robust optimization process included two stages: initial standard dose robust optimization followed by DR optimization. During robust optimization, single field optimization (SFO) was applied, meaning each beam was optimized separately according to the fractionation scheme (see section 2.3). Moreover, the plan was designed with only one beam delivered per fraction, thus a certain number of fractions were assigned to each beam to deliver the total dose. Robust objective functions focused on ensuring minimum total coverage for the CTV only. The optimization included a total of 21 scenarios: 7 setup scenarios (1.5 mm shifts in the 6 different Cartesian directions, and the nominal case) times 3 range scenarios ($\pm 3\%$ range error, and the nominal case). The DR optimization occurs in two steps: one based on dose optimization, namely, spot filtering, and the other based on the delivery pattern, namely, spot sorting. For spot filtering, low-weight spots below a certain threshold were filtered out (based on monitor units, MU). The threshold chosen for the minimum MU per spot in the plan, was case-specific (see next section). Spot sorting was optimized with a method that finds the path across spots that maximizes the volume that receives FLASH, which in this case was the SC (Wase *et al* 2025).

2.3. Fractionation regimens and clinical goals

To study the effect of different fractionation regimens on the FMF values, three regimes were tested: 42 Gy in 10 fractions (fx) of 4.2 Gy, 40 Gy in 8 fx of 5 Gy, and 35 Gy in 5 fx of 7 Gy. The clinical goals for the target and SC for each regimen are detailed in table 1 in SM2 (Timmerman 2022).



(a) Axial (b) Coronal (c) Sagittal

Figure 1. Isodoses for the 7 × 5 Gy fractionation scheme. The priority was on achieving the FLASH effect in the spinal cord.

SFO optimization was performed by assigning an even number of fractions per beam for the first two schemes. The third scheme was designed with 3 fractions for beam 1 and 2 fractions for beam 2. The minimum threshold for spot filtering was set to 22 MU per spot for the first two fractionation regimens and 34 MU per spot for the third one.

2.4. Plan evaluation

The FLASH effect is assumed to be observed when the delivered dose exceeds 4 Gy and the DR surpasses 40 Gy s^{-1} (Rothwell *et al* 2022).

2.4.1. Dose evaluation

Target coverage and SC clinical goals were evaluated using dose-volume histogram (DVH) metrics as standard. The nominal and robust CTV coverages were assessed both in total and per beam to ensure clinical goal compliance in each fraction.

2.4.2. DR evaluation

DR distribution per fraction and per beam was assessed for the SC voxels receiving at least 4 Gy, by means of the DR-volume histogram (DRVH). The DVRH is based on the same concept as DVH, but using DR instead of dose. For evaluation, the 5% percentile DR definition (Deffet *et al* 2023) was used.

2.4.3. The FLASH-modifying factor (FMF)

We used the FMF to quantify the difference in biological effectiveness between the dose delivered at UHDR (D_{UHDR}) and at conventional DRs (D_{CONV}). It is defined by the ratio of the dose required to achieve the same biological effect under conventional conditions to the dose required under FLASH conditions (Böhlen *et al* 2022), that is,

$$\mathrm{FMF} = \left.\frac{D_{\mathrm{CONV}}}{D_{\mathrm{UHDR}}}\right|_{\mathrm{isoeffect}} . \tag{1}$$

A FMF < 1 indicates greater normal tissue sparing for an equivalent level of tumor control. In practice, this means that the dose tolerance for OARs can be increased using the FLASH effect, allowing for a higher dose to be delivered to the tumor. This results in a higher probability of tumor control while preventing complications in normal tissues. The lower the FMF, the stronger this effect becomes.

In this study, as FLASH plans are simulated, the dose distributions are converted into FMF-weighted doses with

$$D_{\mathrm{UHDR}} = \mathrm{FMF} \cdot D_{\mathrm{CONV}} . \tag{2}$$

3. Results

DVHs for the CTV for all regimens can be found in SM3 for each beam separately and a single fraction. Robust DVH bands are also computed for both the CTV and SC. The clinical goal (D95>95%Dp) is achieved for both beams in the nominal and worst-case scenarios (see table 1). This clinical goal is also achieved for the total dose in every case (34.5 Gy, 41.65 Gy and 39.63 Gy, respectively).

Next, the DRVH for the SC is presented in figure 2 for each beam separately within a single fraction. The plotted volume of the SC corresponds to the region irradiated above 4 Gy, which is more likely for benefiting

Table 1. CTV coverage results per beam, for all fractionation schemes, in both nominal and worst-case scenarios.

		CTV D95% Beam 1 [Gy]		CTV D95% Beam 2 [Gy]	
Fractionation regimen	Goal per fx [Gy]	Nominal	Worst Case	Nominal	Worst Case
7 Gy × 5 fx	6.65	6.82	6.77	6.81	6.75
5 Gy × 8 fx	4.75	4.84	4.82	4.94	4.89
4.2 Gy × 10 fx	3.99	4.1	4.03	4.02	3.97

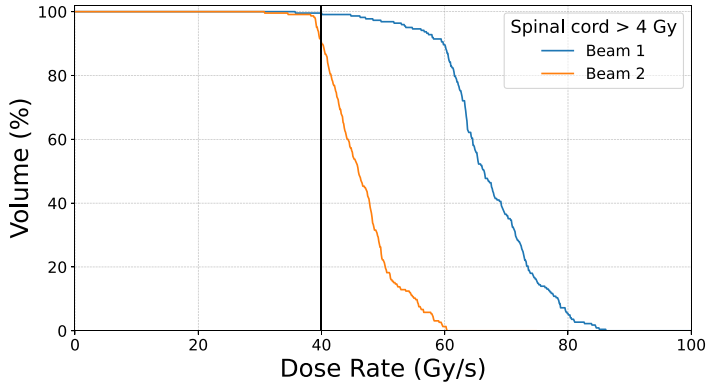


Figure 2. DRVH of spinal cord for each beam and per fraction (7 Gy × 5 fx regimen). UHDR (i.e. $> 40\,\mathrm{Gy\,s^{-1}}$) is achieved for both beams in the high dose spinal cord region (i.e. > 4 Gy).

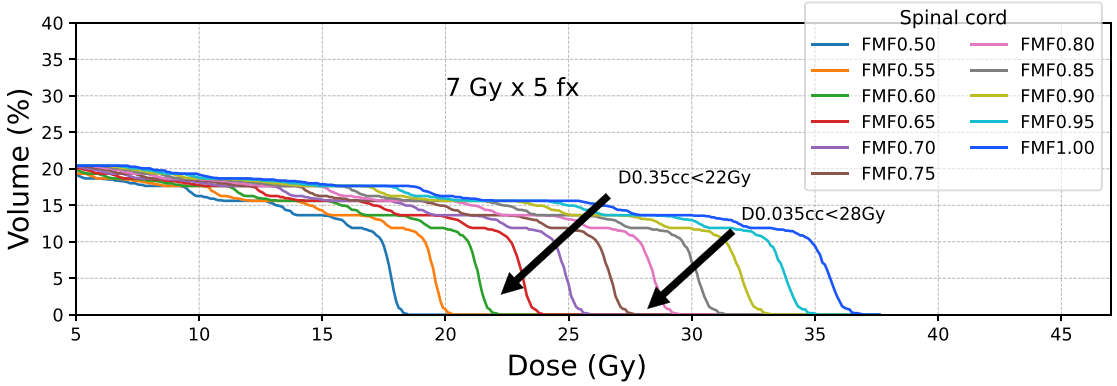


Figure 3. DVH of spinal cord re-weighted by FLASH modifying factor (FMF) values for the 5 fx of 7 Gy scheme.

from a FLASH effect. The DRVH indicates that both beams achieve an UHDR in this SC region, covering 98.60% and 99.33% of the volume with DR $> 40\,\mathrm{Gy\,s^{-1}}$ for beam 1 and beam 2, respectively.

To determine the necessary FMF value in the SC to enable such treatment (i.e. meet the clinical goals) in FLASH conditions, the SC DVH was re-weighted using a range of realistic values. Figure 3 illustrates the result alongside the clinical goals associated with the 5 fx of 7 Gy fractionation regimen. The other two regimens can be found in SM4 & SM5. The analysis shows that the FMF increases as the number of fractions increases (and the dose per fraction decreases), with values ranging from 0.6 to 0.8. using both an optimistic FMF value (i.e.,FMF< 1) and a non-triggering FLASH effect scenario (i.e. FMF $= 1$). The narrow width of these bands indicates that setup and range errors have limited impact on the physical dose distribution.

4. Discussion

In this study, proton SBRT plans were designed for a challenging spine metastasis case and subsequently converted to conformal FLASH plans within the RayStation TPS. The aim was to assess whether, under the given assumptions for the occurrence of the FLASH effect and its magnitude, a FLASH-enabled proton SBRT plan could provide a feasible treatment option for cases that would otherwise be unsuitable for conventional RT. This is particularly critical in cases such as the one presented in this study, where the metastasis

encompasses the whole SC, which has limited radiation tolerance and high toxicity risk. The SC could therefore be spared by means of the FLASH effect, while ensuring proper tumor control.

The analysis shows that UHDR can be achieved within this sensitive OAR, which creates favorable conditions for the FLASH effect to occur. It also shows that the SC FMF necessary to enable such treatment under FLASH conditions is highly dependent on the fractionation scheme. This dependence is expected, as decreasing the dose per fraction typically increases the tolerance of healthy tissues to radiation, a relationship that is well documented in a recent review study (Böhlen *et al* 2022). The referenced study also provides average FMF values and their standard deviations, reporting 0.95 ± 0.11 for all data below a single fraction dose of 10 Gy, with values decreasing to as low as 0.7 for mammalian skin-reaction data, but only above 25 Gy. Consequently, for a SC irradiated with less than 10 Gy per fraction, as in our study, the FMF of 0.95 suggests that none of the fractionation regimens we presented could meet clinical goals. Only when the FMF drops below 0.8, using the scheme with the lowest dose per fraction, is the SC sufficiently spared. However, achieving UHDR while exceeding the hypothetical dose threshold to enable FLASH conditions becomes even more challenging with lower doses per fraction. Nevertheless, more preclinical data is still needed to determine precise FMF values that may relate to specific toxicity endpoints for a certain OAR. These values may fall within a clinically achievable range for dose delivery, offering better treatment options for patients. Once experimental studies converge on FMF values for different organs *in vivo*, they will guide the selection of appropriate fractionation schemes to deliver FLASH plans and help predict the sparing effects associated with FLASH treatment.

Plan robustness is key to achieve good quality dose delivery, handle uncertainties, and ensure proper target coverage. However, achieving fully robust treatments is challenging when planning with the FLASH delivery. The requirement for multi-field plans to be delivered on a one-beam-per-fraction scheme necessitates not only overall plan robustness but also individual beam robustness for each fraction. Additionally, robustness in dose distribution may not necessarily imply robustness in dose-rate metrics, which are dependent on the temporal and spatial structure of the beam delivery. Small spatial shifts (from setup errors) or changes in range could for instance move the high-dose-rate region away from the intended voxels or bring low-dose-rate regions into critical areas. On top of that, the less conformal dose distributions obtained with planning in FLASH mode can deteriorate target coverage due to setup and range errors, which in turn reduces both V4 Gy and V40 Gy s^{-1} in the surrounding OARs. In our study, the robustness results for the patient showed narrow DVH band widths, suggesting that the physical dose to both the target volume and the SC is relatively insensitive to these uncertainties. We did not evaluate dose-rate robustness, as its definition and clinical relevance in FLASH planning remain unclear, but this certainly warrants further investigation.

The observation of the FLASH effect in the SC in our study was predicated for a delivered dose above 4 Gy and the DR surpassing 40 Gy s^{-1} in each fraction, which are values the most commonly found in the literature (Montay-Gruel 2017, Vozenin *et al* 2019, Kacem *et al* 2022). The DRVH analysis for the SC confirmed that these thresholds were met, with over 98% of the SC volume receiving a DR greater than 40 Gy s^{-1}. Importantly, though, the thresholds for the FLASH effect are not universally agreed upon as they may actually vary depending on irradiation conditions and biology (e.g. tissues and oxygenation states). Preclinical studies have shown varying thresholds for the onset and saturation of the FLASH effect, with reported values for DR ranging from less than 10 Gy s^{-1} up to over 280 Gy s^{-1} (Montay-Gruel 2017, Cunningham 2021, Ruan 2021, Kacem *et al* 2022). In practice, it means that achieving such high DRs and doses within the SC may not be feasible. Given the uncertainty about the FLASH effect thresholds and DRs, we did consider exploring more conservative FLASH criteria (e.g. 80 Gy s^{-1}, 8 Gy minimum). Nevertheless, increasing the dose and dose-rate threshold would require larger doses per fraction, which, as shown in our study, reduce the required FMF and make FLASH a highly challenging goal rather than a practical treatment option. Additionally, even if higher doses were prescribed to achieve the FLASH effect, it remains uncertain whether a physician would be willing to prescribe such high doses, particularly given the potential risks.

Additionally, all the presented results rely on the 5% PBS DR. However, no consensus currently states which DR definition should be used. Various definitions exist (Deffet *et al* 2023), with some averaging the DR and others taking into account the time structure of spot delivery. It remains unclear which definition best correlates with the FLASH effect. This uncertainty complicates the design and interpretation of FLASH treatment plans and also influenced our decision to limit the analysis to a single patient case. Total irradiation time has also been cited as a potential critical parameter for triggering the FLASH effect ($<$100 ms) (Montay-Gruel 2017, Cunningham 2021). Accordingly, we provide the irradiation time data in SM1. Nonetheless, broader validation will be essential once clearer biological and dosimetric criteria are established.

Only one patient case has been considered in this study. This limits its generalizability in practical settings, particularly regarding the feasibility of delivering doses at sufficient high DRs to trigger the FLASH

effect in the SC across diverse patient anatomies. Nevertheless, our central argument about the required minimum FMF for safe irradiation remains valid regardless of the number of patients considered. Assuming the FLASH effect can be established in the spine, the required FMF is influenced more by the fractionation scheme than by anatomical variability. We hope that this single case study encourages further research to determine an appropriate FMF value. If this value is sufficiently low, it would justify the need of conducting similar studies with improved statistical power to establish optimal treatment planning strategies.

Finally, proton therapy, particularly with advanced delivery techniques like conformal FLASH PBS, involves significant financial costs (Yan *et al* 2023). Achieving the required high DRs raises many technical challenges (Schulte 2023). However, the development of novel compact accelerators, such as gantry-less systems (Yan *et al* 2016, Moreau 2024), may improve both access to and the technical feasibility of such treatments. Moreover, since FLASH treatments are typically hypofractionated, the overall cost of care could be reduced once the technology is fully developed. In any case, the potential benefits may be considerable for patients with spinal metastases who are not treatable with conventional RT. In this setting, the high precision and favorable dosimetry of protons, combined with the potential tissue-sparing effects of FLASH, may offer enhanced pain relief, better neurological function preservation, and reduced treatment-related morbidity. Therefore, the cost of such an advanced treatment modality must be balanced with the clinical endpoint for patients.

5. Conclusion

Our study evaluates the technical feasibility of FLASH proton therapy for a challenging case of spine metastasis. However, it shows that the necessary FMF is substantially lower than reported in the literature, making clinical application unlikely considering the requirements on the magnitude of the FLASH effect and the uncertainties associated to its occurrence.

Data availability statement

The data cannot be made publicly available upon publication because they contain sensitive personal information. The data that support the findings of this study are available upon reasonable request from the authors.

Acknowledgments

Sophie Wuyckens and Macarena Chocan Vera benefited from a financial support of Wallonia in the frame of a MecaTech's and BioWin's Clusters program. John A Lee is a Research Director with the Belgian F.R.S.-FNRS.

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References

Böhlen T T, Germond J-F, Bourhis J, Vozenin M-C, Ozsahin E M, Bochud F, Bailat C and Moeckli R 2022 Normal tissue sparing by FLASH as a function of single-fraction dose: a quantitative analysis *Int. J. Radiat. Oncol. Biol. Phys.* **114** 1032–44

Cunningham S *et al* 2021 FLASH proton pencil beam scanning irradiation minimizes radiation-induced leg contracture and skin toxicity in mice *Cancers* **13** 1012

Deffet S, Hamaide V and Sterpin E 2023 Definition of dose rate for FLASH pencil-beam scanning proton therapy: a comparative study *Med. Phys.* **50** 5784–92

Deffet S, Souris K and Sterpin E 2023 Optimization of patient-specific range modulators for conformal FLASH proton therapy Version Number: 1 (arXiv:2303.08649)

Favaudon V *et al* 2014 Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice *Sci. Trans. Med.* **6** 245ra93

Glicksman R M *et al* 2020 Stereotactic ablative radiotherapy for the management of spinal metastases: a review *JAMA Oncol.* **6** 567

Hong S H, Chang B-S, Kim H, Kang D-H and Chang S Y 2022 An updated review on the treatment strategy for spinal metastasis from the spine surgeon's perspective *Asian Spine J.* **16** 799–811

Kacem H, Almeida A, Cherbuin N and Vozenin M-C 2022 Understanding the FLASH effect to unravel the potential of ultra-high dose rate irradiation *Int. J. Radiat. Biol.* **98** 506–16

Kang M, Wei S, Choi J I, Lin H and Simone C B 2022 A universal range shifter and range compensator can enable proton pencil beam scanning single-energy bragg peak FLASH-RT treatment using current commercially available proton systems *Int. J. Radiat. Oncol. Biol. Phys.* **113** 203–13

Kaulfers T et al 2024 Pencil beam scanning proton bragg peak conformal FLASH in prostate cancer stereotactic body radiotherapy *Cancers* **16** 798
Lattery G, Kaulfers T, Cheng C, Zhao X, Selvaraj B, Lin H, Simone C B, Choi J I, Chang J and Kang M 2023 Pencil beam scanning bragg peak FLASH technique for ultra-high dose rate intensity-modulated proton therapy in early-stage breast cancer treatment *Cancers* **15** 4560
Liu Y, Cao X, Zhao X, Shi X, Lei M and Qin H 2022 Quality of life and mental health status among cancer patients with metastatic spinal disease *Front. Public Health* **10** 916004
Mizumoto M et al 2011 Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at shizuoka cancer center hospital *Int. J. Radiat. Oncol. Biol. Phys.* **79** 208–13
Montay-Gruel P et al 2017 Irradiation in a flash: unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s *Radiother. Oncol.* **124** 365–9
Moreau M et al 2024 Democratizing flash radiotherapy *Semin. Radiat. Oncol.* **34** 344–50
Rothwell B, Lowe M, Traneus E, Krieger M and Schuemann J 2022 Treatment planning considerations for the development of flash proton therapy *Radiother. Oncol.* **175** 222–30
Ruan J-L et al 2021 Irradiation at ultra-high (FLASH) dose rates reduces acute normal tissue toxicity in the mouse gastrointestinal system *Int. J. Radiat. Oncol. Biol. Phys.* **111** 1250–61
Schulte R et al 2023 Transformative technology for flash radiation therapy *Appl. Sci.* **13** 5021
Timmerman R 2022 A story of hypofractionation and the table on the Wall *Int. J. Radiat. Oncol. Biol. Phys.* **112** 4–21
Vozenin M-C et al 2019 The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients *Clin. Cancer Res.* **25** 35–42
Vozenin M-C, Hendry J and Limoli C 2019 Biological benefits of ultra-high dose rate FLASH radiotherapy: sleeping beauty awoken *Clin. Oncol.* **31** 407–15
Wase V, Widenfalk O, Nilsson R, Fälth C and Fredriksson A 2025 Fast spot order optimization to increase dose rates in scanned particle therapy flash treatments *Phys. Med. Biol.* **70** 025017
Wei S et al 2022 Use of single-energy proton pencil beam scanning Bragg peak for intensity-modulated proton therapy FLASH treatment planning in liver-hypofractionated radiation therapy *Med. Phys.* **49** 6560–74
Yan S, Lu H-M, Flanz J, Adams J, Trofimov A and Bortfeld T 2016 Reassessment of the necessity of the proton gantry: analysis of beam orientations from 4332 treatments at the Massachusetts general hospital proton center over the past 10 years *Int. J. Radiat. Oncol. Biol. Phys.* **95** 224–33
Yan S, Ngoma T A, Ngwa W and Bortfeld T R 2023 Global democratisation of proton radiotherapy *Lancet Oncol.* **24** e245–54