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Original Article

Clinical practice in European centres treating paediatric posterior fossa tumours with pencil beam scanning proton therapy

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A B S T R A C T

Background and purpose: As no guidelines for pencil beam scanning (PBS) proton therapy (PT) of paediatric posterior fossa (PF) tumours exist to date, this study investigated planning techniques across European PT centres, with special considerations for brainstem and spinal cord sparing.
Materials and methods: A survey and a treatment planning comparison were initiated across nineteen European PBS-PT centres treating paediatric patients. The survey assessed all aspects of the treatment chain, including but not limited to delineations, dose constraints and treatment planning. Each centre planned two PF tumour cases for focal irradiation, according to their own clinical practice but based on common delineations. The prescription dose was 54 Gy(RBE) for Case 1 and 59.4 Gy (RBE) for Case 2. For both cases, planning strategies and relevant dose metrics were compared.
Results: Seventeen (89 %) centres answered the survey, and sixteen (80 %) participated in the treatment planning comparison. In the survey, thirteen (68 %) centres reported using the European Particle Therapy Network definition for brainstem delineation. In the treatment planning study, while most centres used three beam directions, their configurations varied widely across centres. Large variations were also seen in brainstem doses, with a brainstem near maximum dose (D2%) ranging from 52.7 Gy(RBE) to 55.7 Gy(RBE) (Case 1), and from 56.8 Gy(RBE) to 60.9 Gy(RBE) (Case 2).
Conclusion: This study assessed the European PBS-PT planning of paediatric PF tumours. Agreement was achieved in e.g. delineation-practice, while wider variations were observed in planning approach and consequently dose to organs at risk. Collaboration between centres is still ongoing, striving towards common guidelines.

Introduction

Proton therapy (PT) has been increasingly used in the management of paediatric brain tumour patients [1,2]. Compared to conventional photon-based radiotherapy, the dose deposition properties of protons allow for a reduction in low-to-medium doses to healthy tissues [3], expected to lower the risk of adverse effects. Literature supporting this notion is emerging for, e.g., quality of life, neurocognition and endocrine function [4–6].

The posterior fossa (PF) is the most common location for paediatric brain tumours, with the target volume adjacent to critical organs at risk (OARs) such as the brainstem or the upper cervical spinal cord. In the past, there have been discussions and contradictory data on whether the risk of brainstem injury after PT is higher or comparable to after photon therapy [7–16].

In 2016, the National Cancer Institute (NCI) convened a workshop where PT-specific brainstem dose constraints and recommendations for treatment planning were proposed [17]. As of yet though, there has been no similar initiative to review the different European planning practices for PT of paediatric PF tumours.

The NCI report focused on passive-scattering and uniform-scanning PT, due to the extensive clinical experience gained at the time from those techniques [17]. However, since then, PT delivery methods have evolved considerably from scattering technique to the state-of-the-art pencil beam scanning (PBS) delivery [18] currently used at most European PT centres treating paediatric patients [19].

Compared to passive-scattering, PBS uses less passive elements, offers multi-field optimization and therefore many possibilities in terms of field number or directions and plan optimization. PBS thereby allows for improved target dose conformality and OAR sparing [20], leading to variations with regards to dose constraints [21] and prioritization.

PBS-PT might also result in more modulated linear energy transfer (LET) (and thus relative biological effectiveness (RBE)) distributions compared to passively-scattered PT, potentially affecting OARs such as the brainstem [20,22].

Overall, the experience gained from passive-scattering might not be directly transferable to PBS. However, no PBS-specific guidelines have been published for the treatment of paediatric PF tumours. Combined with the increased flexibility that PBS offers, this lack of consistent guidelines and standardized approaches could lead to a large diversity in PBS-PT clinical practice.

This study therefore aimed at assessing PBS-PT practice across European PT centres treating paediatric PF tumours, with special considerations for brainstem and spinal cord sparing. The current clinical practice was first assessed via an online survey, followed by an inter-institutional treatment planning comparison and a workshop.

Material and methods

In September 2021, a web-based questionnaire was distributed to representative from nineteen European PT centres treating paediatric patients, identified through the Particle Therapy Co-Operative Group (PTCOG) list of facilities in operation [23]. The survey addressed clinician and physicists, as the questions covered clinical and technical aspects of paediatric PF tumour treatment.

The topics investigated were patient positioning and imaging protocols, definitions of OARs, beam arrangements, the treatment planning process, dose constraints applied, RBE/LET considerations and clinical follow-up. The blank survey is available in Supplementary Material.

To offer quantitative insights into the different clinical practices, a multi-institutional treatment planning study was subsequently initiated in April 2022, followed by a hybrid workshop (Aarhus, Denmark, November 2022) where further discussions took place. Anonymized DICOM data (CT-scan, target volume and OAR delineations) from one paediatric patient was used to explore two representative PF cases: an atypical teratoid rhabdoid tumour (ATRT) and an ependymoma (EP). Approval for sharing the patient's anonymized data was received from the treating institution and the patient's guardians.

The ATRT case was located in the caudal part of the PF, with full overlap of the clinical target volume (CTV) with the brainstem at the medulla oblongata level. The EP tumour was wrapped around the brainstem, with the CTV overlapping the brainstem from the pons to the craniocervical junction. The ATRT target was symmetrical around the midline, while the EP target was lateralized (Fig. 1).

For both cases, the prescription dose (for RBE = 1.1) was 54 Gy(RBE) in 30 fractions to the CTV, with an additional boost (CTVboost) to a total dose of 59.4 Gy(RBE) in 33 fractions for the EP case. The EP CTV was the original CTV used for the clinical case in the distributed CT-scan. For the purpose of this study, CTVboost was defined as CTV minus brainstem, in order to prescribe a higher dose than the tolerance of e.g. the brainstem or spinal cord, as is often the case clinically. The ATRT CTV was copied from a different clinical case. The OARs and target volumes provided in the structure set were common to all centres and to facilitate fair comparison, no further modifications were allowed.

The centres were asked to plan on that common structure set, but based on their own clinical practice, i.e. no instructions were given on the treatment planning process. All planning centres shared their DICOM files for both plans, that were then imported into RayStation (v11B, RaySearch Laboratories AB, Stockholm, Sweden) treatment planning system (TPS) for further analysis.

For all plans, general planning parameters as well as dose-volume

[1] Shared authorship.

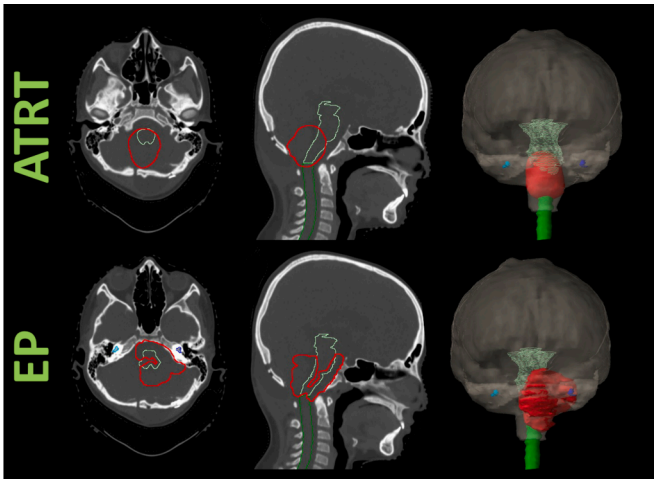

Fig. 1. Transversal, sagittal and 3D view of the ATRT (upper row) and EP (lower row) cases used in the treatment planning comparison. The CTV is shown in red, the brainstem in light green, the spinal cord in dark green, and the right/left cochlea in light/dark blue respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

histograms (DVHs) were retrieved and relevant metrics compared. The hinge angle, defined as the maximum angle between field directions in 3D, was calculated.

Results

Seventeen (89 %) of the nineteen contacted PT centres responded to the survey (Fig. 2). Fourteen (82 %) of the responding centres followed the European Particle Therapy Network (EPTN) definition for both the cranial and caudal extent of the brainstem. Twelve (71 %) further distinguished between the brainstem and the brainstem core/centre, usually cropping the brainstem volume by 2 to 5 mm for generating the core or generating a new structure from the centre of the brainstem. When asked if they permitted the distal end of a beam to be directed towards the brainstem, four (23 %) of the responding centres indicated 'yes' and three (18 %) 'no'. Of the remaining ten centres, eight (47 %) allowed at most one beam to range out into the brainstem, one (6 %) did not allow for an overlap from several beam directions in the same region, and one (6 %) applied target coverage concessions in the overlap region.

When surveyed about the dose constraints used for target coverage, brainstem (including the core/surface when applicable) and upper cervical spine (including individual cervical spine levels when applicable), large variations were seen between the responding centres, as reported in Table 1.

Complete results of the survey are reported in Supplementary Material.

Of the sixteen ATRT plans received (Fig. 2), ten (62.5 %) were optimized with three beams, three (19 %) with two beams, and two (12.5 %) with four beams. One centre proposed a two-plan approach, with three and two beams. Ten (62.5 %) of the received plans used a coplanar field configuration, and large variations were seen in beam angles, with hinge angles ranging from 20° to 180° (Supp. Table. 1, Supp. Vid. 1,2).

Thirteen (81 %) centres used CTV-based robust optimization with different sets of range and set-up uncertainty parameters (Table 2), while the remaining three (19 %) centres used PTV-based optimization. Fourteen (87.5 %) centres performed robustness evaluation, with institution-specific parameters (Table 2).

All plans achieved a similar target coverage in the nominal scenario (Supp. Fig. 1). The median volume receiving 95 % of the prescription dose (V95%) was 99.9 % [range 97.1 %–100 %].

The brainstem near maximum dose (D2%) varied between 52.7 Gy (RBE) and 55.7 Gy(RBE) across all centres, with a median of 54.2 Gy (RBE). Considerable variation was also observed in the volume of brainstem receiving intermediate doses (Fig. 3a). D2% to the brainstem core was typically only slightly lower than the D2% to the entire brainstem (Fig. 4a). For the spinal cord C1, a larger variation in the volume receiving intermediate doses was observed in the group-DVH (Fig. 3b). The median D2% across all centres was 52.8 Gy(RBE) [47 Gy(RBE)–54.3 Gy(RBE)] for the spinal cord C1, overall lower than D2% to the brainstem for all but two centres (Fig. 4b).

The median of the mean doses (Dmean) to the brain-minus-CTV was 2.6 Gy(RBE) [2.1 Gy(RBE)–5 Gy(RBE)] across all centres, while Dmean to all other OARs was in most cases close to zero (Supp. Table 2).

Of the sixteen EP plans received (Fig. 2), thirteen (81 %) were sequential boost plans, two (12.5 %) were simultaneously integrated boost (SIB) plans (both with three coplanar fields) and one was an hybrid plan (45 Gy(RBE) with three non-coplanar proton fields, and two sequential VMAT plans 45–54 Gy(RBE) and 54–59.4 Gy(RBE)). For the initial phase of the thirteen sequential plans, eleven institutions used three beams, one institution used two beams, and one institution used four beams. For the sequential boost, nine plans consisted of three beams, two of two beams, and two of four beams. For both phases of the plans, eight used a coplanar field configuration, and large variations were seen in beam angles, with hinge angles ranging from 70° to 178° (Supp. Table 1, Supp. Vid. 1, 3). All centres consistently used the same optimization and robustness evaluation methods as for the ATRT case (Table 2).

In all sixteen composite plans (59.4 Gy(RBE)), the median CTVboost V95% was 98.8 % [95 %–100 %] across all nominal plans. The 20–80 percentile bands were wider for the EP case than for the ATRT case, reflecting more variability in the target coverage for the EP case (Supp. Fig. 1). Across the fourteen non-SIB plans, the median CTV V95% was 97.6 % [92.9 %–100 %] (initial plan) and the median CTVboost V95% was 96 % [53 %–99.7 %] (boost plan). Target coverage concessions were applied by some centres, especially in the boost plan (Supp. Fig. 2).

For the brainstem, the median D2% across all centres was 58.3 Gy (RBE) [56.8 Gy(RBE)–60.9 Gy(RBE)] (Fig. 3c). D2% to the brainstem core was 57.7 Gy(RBE) [55.1 Gy(RBE)–60.7 Gy(RBE)], with centres presenting the lowest D2% to the brainstem also choosing to selectively reduce the dose to the brainstem core at the expense of CTVboost D95% (Fig. 4c). For the spinal cord C1, large variations in DVH shape were seen across centres with large min–max width for all dose levels and a median D2% of 53.7 Gy(RBE) [47.6 Gy(RBE)–56.9 Gy(RBE)] (Fig. 3d). Comparing D2% to the brainstem vs. spinal cord C1, some of the largest concessions in CTVboost D95% were driven by sparing the spinal cord C1 (Fig. 4d).

The median Dmean to the brain-minus-CTV was 5.2 Gy(RBE) [3.9 Gy (RBE)–12.5 Gy(RBE)] across all centres. The contralateral cochlea and hippocampus were mostly spared, with a median Dmean of 4.6 Gy(RBE) [1.1 Gy(RBE)–20.5 Gy(RBE)] for the right cochlea and 6.6 Gy(RBE) [2.6 Gy(RBE)–21.4 Gy(RBE)] for the right hippocampus. The median Dmean was 58.6 Gy(RBE) [38 Gy(RBE)–61.7 Gy(RBE)] for the left cochlea, and 32.5 Gy(RBE) [21.8 Gy(RBE)–48.4 Gy(RBE)] for the pituitary. Doses to all other OARs are reported in Supplementary Table 2.

Discussion

This study explored the European landscape in PBS treatment of paediatric PF tumours. The high participation rate for both the survey and treatment planning study, respectively 89 % and 80 %, underlines the strong interest of the community in this topic. Similarities were seen in the delineations and number of fields used, while wider variations were reported in beam arrangement, target and brainstem/spinal cord dose constraints, as well as plan optimization and robustness practices.

The overall aim of this work stemmed from previous discussions on

Fig. 2. Map of the European centres participating in the survey (brown star), the treatment planning comparison (green star), or both (blue star). Of note, Sweden is following a distributed PT concept [33], i.e. the Skandion Clinic (Uppsala) is delivering PT but the planning is done at the referring regional clinics (there is therefore a single PT centre in Sweden, not three as this figure could suggest). For Spain, two different centres are located in Madrid and both participated in this study, thereby the two overlapping stars. A single Swedish centre was invited to answer the survey as 'Skandion Clinic representatives', while for the multi-institutional treatment planning comparison, two additional Swedish centres were included. In total, 17 of the 19 invited centres (89%) answered the survey and 16 out of 21 (76%) institutions participated in the planning comparison. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the risk of brainstem injury after PF irradiation in paediatric patients [17]. However, beside radiotherapy dose, brainstem injury risk factors are multiple and include young age at treatment, number and extent of surgeries, post-surgical clinical status, chemotherapy [10,24] or tumour histology [17].

Results from the survey showed good agreement between centres for brainstem delineation, with 82 % of the institutions following the EPTN guidelines [25]. The three remaining institutions all used the border of foramen magnum as a caudal limit, while for the cranial extent slightly more variations were seen. This is in agreement with a previously published inter-observer delineation study, where most variations were occurring at the cranial part of the brainstem but also at the middle cerebellar peduncles levels (lateral extent), with surface distances of up to 1.5–2 mm[26]. However, questions on the lateral extent of the brainstem were not part of this survey.

Twelve centres distinguished between the brainstem and its core/centre, with most institutions using different definitions for delineation, as only 33 % were following the EPTN guidelines [25]. In addition, eleven institutions also applied different dose constraints for the brainstem core vs. surface, with the constraints differing across institutions. For the ATRT case, small variations were seen in the brainstem vs. brainstem core D2% while for the EP case, where the prescription dose was higher, a specific sparing of the brainstem core was seen in some plans.

While consistency was seen for delineation, the survey and treatment planning comparison showed wide variations in dose constraints for the brainstem, brainstem core, and spinal cord. These reported variations also translated in large spread of dose to those OARs. Compared to the EP case in this study, a Nordic study reported similar variations in the D2% range across four PBS plans for an EP case (prescription dose 59.4 Gy(RBE)) for the brainstem, brainstem core and spinal cord C1 [27]. Specifically, the largest spread was seen for the spinal cord C1 D2% with 9.3 Gy(RBE) across European PT centers vs. 11.1 Gy(RBE) in the Nordic study while the spread in brainstem D2% was more moderate (4.1 Gy (RBE) vs. 2.2 Gy(RBE)).

Overall, and especially for the EP case, doses to most OARs varied substantially across centres. While PBS-technique was consistently used, these dose variations can be attributed to the unique optimization and prioritization process in each centre [27,28], as well as the choice of beam configuration. By not providing a list of OAR constraints or guidance in clinical trade-offs, we captured the actual clinical practice across European PBS-PT centres. As already concluded in a European treatment planning study of paediatric cranio-spinal irradiation [29], large variations in OAR doses will persist across centres as long as common dose-constraints guidelines are not adopted. While they reported up to 16 Gy(RBE) spread for Dmean to the larynx/proximal

Table 1
Dose constraints used in European PT centres reported by the survey responders for target coverage, brainstem (including the core/surface when applicable) and spinal cord (including individual upper cervical spine levels when applicable). N/A: Not Applicable.

Survey Responders	CTV coverage	Brainstem	Brainstem Core	Brainstem Surface	Spinal Cord	Spinal Cord C1	Spinal Cord C2	Spinal Cord C3
A	V98% > 95 %	D1% < 54 Gy(RBE)	D1% < 54 Gy (RBE)	D1% < 60 Gy (RBE)	*Tumour above foramen magnum:* *Tumour below foramen magnum:*	D2% < 50 Gy(RBE) D2% < 54 Gy(RBE)	D2% < 45 Gy(RBE) D2% < 50 Gy(RBE)	D2% < 45 Gy(RBE)
B	V98% > 98 %	N/A	D0.03 cc ≤ 55.8 Gy(RBE)	D0.03 cc ≤ 60 Gy(RBE)	N/A	D0.03 cc ≤ 54 Gy(RBE)	D0.03 cc ≤ 54 Gy(RBE)	D0.03 cc ≤ 50 Gy(RBE)
C	V95% > 95 %	Dmax < 60 Gy(RBE)	Dmax < 54 Gy (RBE)	N/A	Dmax < 54 Gy (RBE)	Dmax < 54 Gy(RBE)	Dmax < 50.4 Gy (RBE)	Dmax < 45 Gy(RBE)
D	D98% > 95 %	V59.4 Gy(RBE) < 66 %	N/A	N/A	N/A	D2% < 56 Gy(RBE)	D2% < 54 Gy(RBE)	D2% < 54 Gy(RBE)
E	V95% = 100 %	D50% < 52.4 Gy(RBE); D10% < 55.4 Gy(RBE); D0.1 cc < 56.6 Gy(RBE)	D0.1 cc < 56.1 Gy(RBE)	N/A	30 fx: Dmax < 54 Gy(RBE) 33 fx: Dmax < 55 Gy(RBE)	N/A	N/A	N/A
F	V95% > 98 %	D50% < 52.4 Gy(RBE); D2% < 56.6 Gy(RBE)	N/A	N/A	D2% < 54 Gy (RBE)	D2% < 54 Gy(RBE)	D2% < 50.4 Gy(RBE)	D2% < 50.4 Gy(RBE)
G	D95% > 95 %	N/A	D0.03 cc < 54 Gy(RBE)	D0.03 cc < 60 Gy(RBE)	D0.03 cc < 50 Gy(RBE)	D2% < 50 Gy(RBE)	D2% < 45 Gy(RBE)	D2% < 45 Gy(RBE)
H	D95% > 98 %	D1% < 54 Gy(RBE)	N/A	N/A	D1% < 54 Gy (RBE)	*Spinal Cord core: D1% < 52.2 Gy(RBE)*		
I	D95% = 100 %	Dmax < 54 Gy(RBE)	N/A	N/A	Dmax < 45 Gy (RBE)	N/A	N/A	N/A
J	V95% > 98 %	D50% < 52.4 Gy(RBE); D10% < 55.4 Gy(RBE); D0.1 cc < 56.6 Gy(RBE)	Dmax < 54 Gy (RBE)	Dmax < 62.4 Gy(RBE)	Dmax < 45 Gy (RBE)	Dmax < 54 Gy(RBE)	Dmax < 50.4 Gy (RBE)	Dmax < 45 Gy(RBE)
K	V98% > 98 %	D2% < 56 Gy(RBE)	N/A	N/A	D2% < 45 Gy (RBE)	Dmax < 50 Gy(RBE)	Dmax < 45 Gy(RBE)	Dmax < 45 Gy(RBE)
L	D99% = 100 %	N/A	D2% < 54 Gy (RBE)	D2% < 60 Gy (RBE)	D2% < 54 Gy (RBE)	N/A	N/A	N/A
M	V98% > 95 %	D2% < 60 Gy(RBE)	Dmax < 54 Gy (RBE)	Dmax < 64 Gy (RBE)	D2% < 56 Gy (RBE)	N/A	N/A	N/A
N	D98% > 95 %	V59.4 Gy(RBE) < 66 %; D2% < 110 %	N/A	N/A	*Tumour above foramen magnum:* *Tumour below foramen magnum:*	D2% < 50 Gy(RBE) D2% < 54 Gy(RBE)	D2% < 45 Gy(RBE) D2% < 50 Gy(RBE)	D2% < 45 Gy(RBE)
O	V95% > 99.9 %	D2% < 62.5 Gy(RBE); V59.4 Gy(RBE) < 66 %; D0.1 cc < 58 Gy(RBE); D50% < 54 Gy(RBE)	N/A	N/A	N/A	D2% < 50 Gy(RBE)	D2% < 45 Gy(RBE)	D2% < 45 Gy(RBE)
P	V95% > 95 %	D1% < 55 Gy(RBE)	D1% < 54 Gy (RBE)	D1% < 63 Gy (RBE)	D1% < 55 Gy (RBE)	N/A	N/A	N/A
Q	V95% > 98 %	D0.05 % < 56 Gy(RBE)	N/A	N/A	D0.05 % < 56 Gy(RBE)	N/A	N/A	N/A

oesophagus, our study showed even largest spread in Dmean especially for the hypothalamus – pituitary axis (28.1 Gy(RBE) and 26.6 Gy(RBE) respectively in the EP case). Those differences in dose can be considered clinically relevant. This emphasizes the need to share practices and attempt to harmonize, to reduce the risk of toxicity. One should keep in mind that doses to OARs is a trade-off between coverage and prioritizing the different OARs.

After the NCI workshop, PT-specific brainstem dose constraints derived to account for RBE differences between photon and proton were introduced in US centres [17]. Furthermore, it has also been reported that the US protocols typically ask for tighter dose constraints to the brainstem compared to European guidelines [21]. Based on our analysis, none of the EP plans would fulfil the current NCI $D_{0.1cc}$ goal constraint (<56.6 Gy(RBE)), with $D_{0.1cc}$ ranging from 57.2 Gy(RBE) to 61.4 Gy (RBE). As of yet though, there was no European consensus to accept those dose constraints and guidelines have not been implemented in European PT protocols. However, the large range in brainstem dose constraints currently seen across European PT centres could call for a review, aiming for a potential harmonization.

Differences in clinical choices were mostly observed in the EP plans, where the prescription dose was higher and therefore challenging OAR dose constraints with a potential need for target coverage concessions. Interestingly, some of the largest concessions in target coverage were driven by sparing of the spinal cord C1, resulting in a D2% spread of 9.3 Gy(RBE). Overall, opinions differed on the needed compromises between target coverage and OAR sparing, pointing in the direction of ongoing discussions on the potential need to re-evaluate prescription dose for e.g. EP tumours [30].

The biological effect of protons is yet another possible cause for variability in the PBS treatment of PF tumours, as e.g. field direction and

Table 2
Summary of the optimization and evaluation type and parameters used by all sixteen centres taking part in the treatment planning comparison. For the optimization parameters, the range/set-up uncertainties parameters used for robust optimization or the CTV-to-PTV margin used for PTV optimization are reported. For the evaluation methods, the range/set-up uncertainties parameters are reported.

	Optimization		Evaluation	
	Type	Parameters	Type	Parameters
1	Robust	3 %/3mm	Worst-case	3 %/2mm
2	Robust	3 %/3mm	Worst-case	3 %/1.5 mm
3	Robust	3.5 %/2mm	Worst-case	3.5 %/2mm
4	Robust	3.5 %/2mm	Worst-case	3.5 %/2mm
5	Robust	3 %/3mm	Voxel-wise	3 %/3mm
6	Robust	3.5 %/3mm	Worst-case	3.3 %/2.8 mm
7	Robust	3.5 %/3mm	Worst-case	3.5 %/3mm
8	Robust	3 %/3mm	Worst-case	3 %/3mm
9	Robust	3.5 %/3mm	Worst-case	3.5 %/3mm
10	Robust	3.5 %/3mm	Worst-case	3.5 %/3mm
11	PTV	3 mm	Worst-case	3 %/2mm
12	Robust	3.5 %/2mm	Worst-case	3.5 %/4mm
13	Robust	3.5 %/2mm	Worst-case	3.5 %/2mm
14	Robust	3.5 %/1–2 mm	Worst-case	3.5 %/1–2 mm
15	PTV	3 mm	None	
16	PTV	5 mm	None	

optimization process can influence the LET/RBE distributions [31]. However, this study focused on the current clinical practice in European PT centres, and none of the centres reported actively using LET-optimization or systematically assessing LET distributions for paediatric PF tumour patients.

A way to limit the effect of a potential increased proton RBE is to carefully place the distal-edge of the beam, where the LET is the highest. In our survey, three centres didn't allow distal-edges to be directed towards the brainstem (likely commenting for brain tumour in general, rather than PF tumours specifically), but overall, most centres aimed for at most one beam stopping in the brainstem, or avoiding overlap of several distal-edges. These results are in line with a recent European survey, where all participating PT centres reported avoiding beams stopping in OARs when possible to counteract a potential variable proton RBE [32].

One important limitation of this study is the difficulty in comparing target coverage between centres, due to the large range of coverage criteria used by the centres, the differences in optimization technique and parameters, and the differences in robustness evaluation methods. To illustrate target coverage and concessions across institutions, we reported CTV V95% and D95% of the nominal plans, as these metrics were the most cited in the survey. However, this doesn't imply that these should be preferred clinically.

Target coverage was only semi-quantitatively assessed, as neither set-up nor range uncertainties were included in the reported metrics. Indeed, different uncertainty parameters were used across centres, challenging a fair comparison, and, to date, perturbed doses cannot be

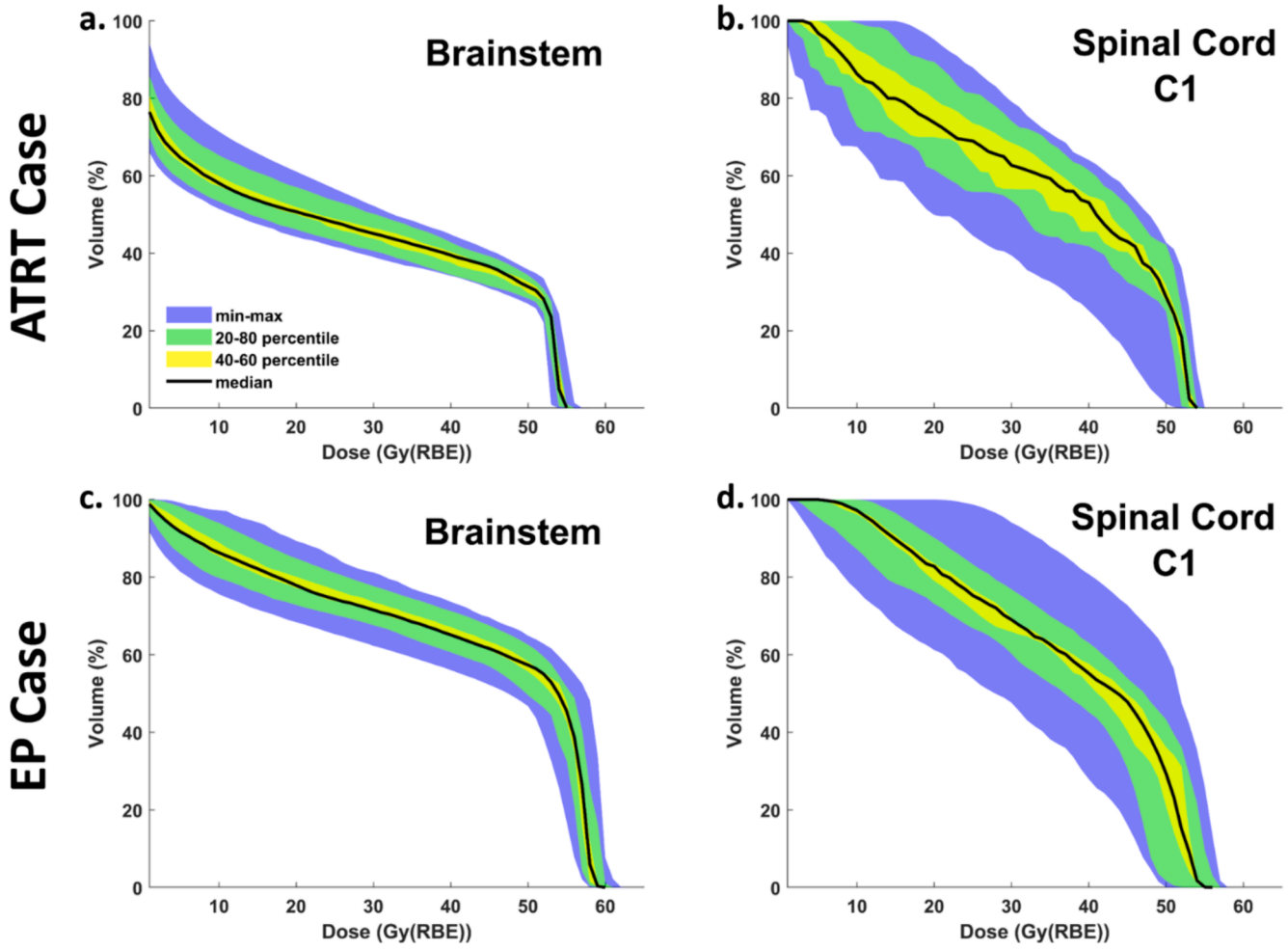

Fig. 3. Brainstem and spinal cord C1 group-wise DVHs for the ATRT case (upper panel) and the EP case (lower panel) depicting the variations in terms of dose distributions across all sixteen plans.

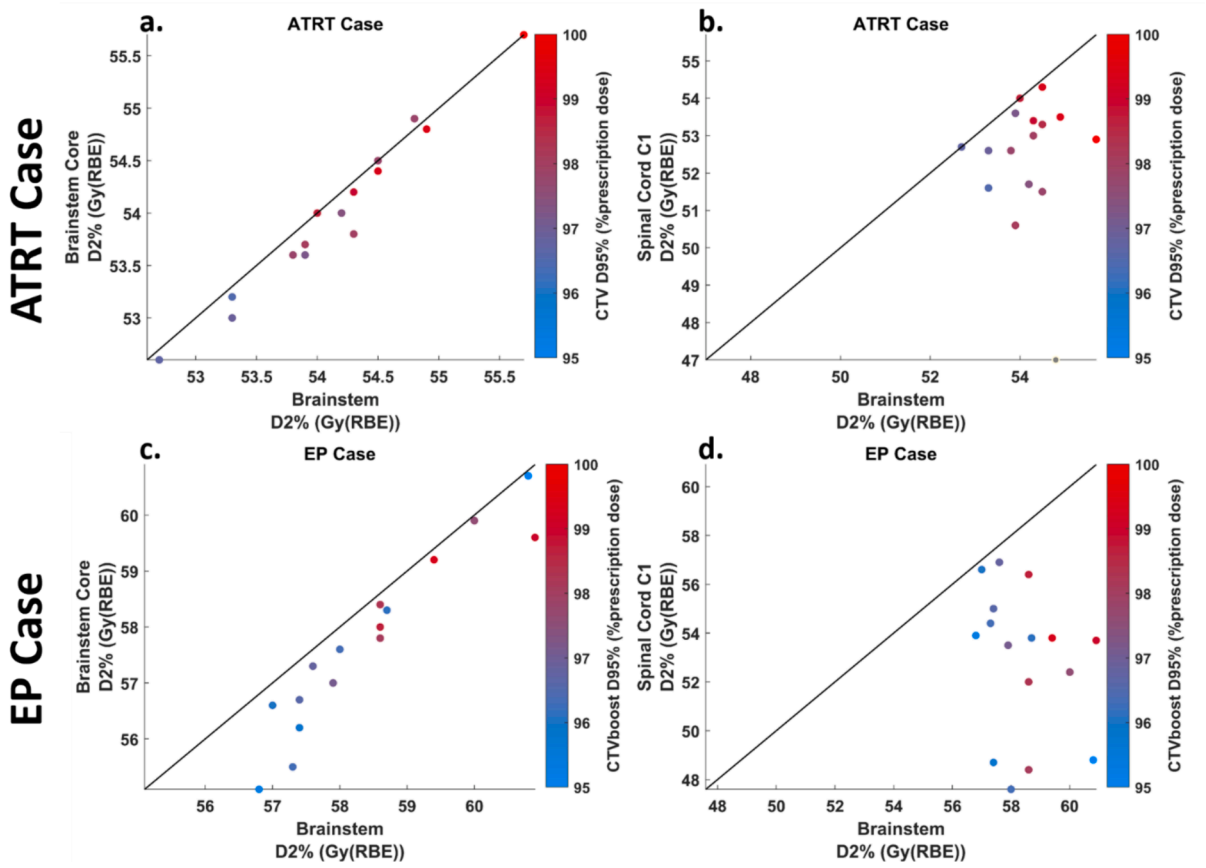

Fig. 4. Dose burden to OARs with regard to D2% to the brainstem vs. brainstem core (left panels)/spinal cord C1 (right panels) for the ATRT case (upper panels) and the EP case (lower panels). Each dot represents a centre, with dot colour indicating CTV D95% (the warmer the colour, the higher the D95%). The unity line represents equal dose between the brainstem and the brainstem core/spinal cord C1. Note that the brainstem core dose metrics are reported for a common brainstem core delineation, based on the EPTN guidelines [25].

exported from TPSs. Discussions should be started to align the way target dose is reported, including the robustness aspects. Of note, those uncertainties would also influence the dose delivered to OARs and its interpretation.

In conclusion, this study described the pattern of practice in European PBS-PT centres for the treatment of paediatric PF tumours, showing consensus in e.g. delineation-practice, and wider variations for e.g. brainstem doses. The collaboration between all involved European PT centres is still ongoing, and further work will include a DELPHI-like process for developing common guidelines. Ultimately, the overarching goal of this collaboration is to improve clinical practice for PBS treatment of paediatric PF tumour patients.

CRediT authorship contribution statement

Laura Toussaint: Conceptualization, Formal analysis, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Witold Matysiak:** Conceptualization, Formal analysis, Investigation, Visualization, Writing – review & editing. **Claire Alapetite:** Investigation, Writing – review & editing. **Javier Aristu:** Investigation, Writing – review & editing. **Agata Bannink-Gawryszuk:** Investigation, Writing – review & editing. **Stephanie Bolle:** Investigation, Writing – review & editing. **Alessandra Bolsi:** Investigation, Writing – review & editing. **Felipe Calvo:** Investigation, Writing – review & editing. **Fernando Cerron Campoo:** Investigation, Writing – review & editing. **Frances Charlwood:** Investigation, Writing – review & editing. **Charlotte Demoor-Goldschmidt:** Investigation, Writing – review & editing. **Jérôme Doyen:** Investigation, Writing – review & editing. **Katarzyna Drosik-Rutowicz:** Investigation, Writing – review & editing. **Pauline Dutheil:** Investigation, Writing – review & editing. **Anna Embring:** Investigation, Writing – review & editing. **Jacob Engellau:** Investigation, Writing – review & editing. **Anneleen Goedgebeur:** Investigation, Writing – review & editing. **Farid Goudjil:** Investigation, Writing – review & editing. **Semi Harrabi:** Investigation, Writing – review & editing. **Renata Kopec:** Investigation, Writing – review & editing. **Ingrid Kristensen:** Investigation, Writing – review & editing. **Peter Lægsdmand:** Investigation, Writing – review & editing. **Carola Lütgendorf-Caucig:** Investigation, Writing – review & editing. **Arturs Meijers:** Investigation, Writing – review & editing. **Alfredo Mirandola:** Investigation, Writing – review & editing. **Fernand Missohou:** Investigation, Writing – review & editing. **Marta Montero Feijoo:** Investigation, Writing – review & editing. **Ludvig P. Muren:** Investigation, Writing – review & editing. **Barbora Ondrova:** Investigation, Writing – review & editing. **Ester Orlandi:** Investigation, Writing – review & editing. **Erik Pettersson:** Investigation, Writing – review & editing. **Alessia Pica:** Investigation, Writing – review & editing. **Sandija Plaude:** Investigation, Writing – review & editing. **Roberto Righetto:** Investigation, Writing – review & editing. **Barbara Rombi:** Investigation, Writing – review & editing. **Beate Timmermann:** Investigation, Writing – review & editing. **Karen Van Beek:** Investigation, Writing – review & editing. **Anthony Vela:** Investigation, Writing – review & editing. **Sabina Vennarini:** Investigation, Writing – review & editing. **Anne Vestergaard:** Investigation, Writing – review & editing. **Marie Vidal:** Investigation, Writing – review & editing. **Vladimir Vondracek:** Investigation, Writing – review & editing. **Damien C. Weber:** . **Gillian Whitfield:** Investigation, Writing – review & editing. **Jens Zimmerman:** Investigation, Writing – review & editing. **John H. Maduro:** Conceptualization, Resources, Writing – review & editing.

Yasmin Lassen-Ramshad: Conceptualization, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110414.

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