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ORIGINAL ARTICLE

Towards proton arc therapy: physical and biologically equivalent doses with increasing number of beams in pediatric brain irradiation

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ABSTRACT

Background: Proton arc therapy may improve physical dose conformity and reduce concerns of elevated linear energy transfer (LET) and relative biological effectiveness (RBE) at the end of the proton range, while offering more degrees of freedom for normal tissue sparing. To explore the potential of proton arc therapy, we studied the effect of increasing the number of beams on physical and biologically equivalent dose conformity in the setting of pediatric brain tumors.

Material and methods: A cylindrical phantom (Ø = 150 mm) with central cylindrical targets (Ø = 25 and 30 mm) was planned with increasing number of equiangular coplanar proton beams (from 3 to 36). For four anonymized pediatric brain tumor patients, two 'surrogate' proton arc plans (18 equiangular coplanar or sagittal beams) and a reference plan with 3 non-coplanar beams were constructed. Biologically equivalent doses were calculated using two RBE scenarios: $RBE_{1.1}$; and RBE_{LET}, the physical dose weighted by the LET. For both RBE scenarios, dose gradients were assessed, and doses to cognitive brain structures were reported.

Results: Increasing the number of beams resulted in an improved dose gradient and reduced volume exposed to intermediate LET levels, at the expense of increased low-dose and low-LET volumes. Most of the differences between the two RBE scenarios were seen around the prescription dose level, where the isodose volumes increased with the RBE_{LET} plans, e.g. up to 63% in the 3-beam plan for the smallest phantom target. Overall, the temporal lobes were better spared with the sagittal proton arc surrogate plans, e.g. a mean dose of 3.9 Gy compared to 6 Gy in the reference 3-beam plan (median value, $RBE_{1.1}$).

Conclusion: Proton arc therapy has the potential to improve dose gradients to better spare cognitive brain structures. However, this is at the expense of increased low-dose/low-LET volumes, with possible implications for secondary cancer risks.

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Introduction

The transition from 3D conformal RT (3DCRT) to multifield intensity-modulated RT (IMRT) or volumetric-modulated arc therapy (VMAT) in photon-based RT has improved high-dose conformity and normal tissue sparing, at the expense of a large low-dose 'bath' to the irradiated area [1]. The concept of proton arc therapy is just becoming clinically available, with a recent demonstration of spot-scanning proton arc plan deliverability [2]. The dosimetric benefits of proton arc therapy compared to intensity-modulated proton therapy (IMPT) in terms of normal tissue sparing have already been demonstrated in adults for both extra-cranial tumor sites [3–4] and hippocampus avoidance whole brain irradiation [5]. However, the effects of increasing the number of proton beams on doses to cognitive structures have not been reported in a focal brain irradiation setting for pediatric patients, whose developing brain are particularly sensitive to radiation.

In addition to physical properties that are different from photons, protons also have distinct biological effects due to their detailed pattern of energy deposition. Clinically, the relative biological effectiveness (RBE) of protons is assumed to be 1.1. However, the RBE is known to depend on tissue type and endpoint, and to increase with the microscopic energy deposition, the so-called linear energy transfer (LET) [6]. It is also recognized that the LET is enhanced at the end of the proton range, potentially causing higher than expected biologically equivalent dose deposition in normal tissues distal to the tumor [7].

In clinical practice, the concern for potentially elevated LET/RBE is often addressed by the choice of beam angles, where no more than one beam should stop in a sensitive organ at risk [8]. Other strategies have been explored to include LET-based parameters during plan optimization, showing reduced LET hotspots in the organs at risk with preserved target coverage [9], or increased LET values in the target volume [10]. Another potential solution could be to

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increase the number of incident beams, e.g. with proton arc therapy, in order to smear out the elevated LET regions.

The aim of this study was to investigate the effects of increasing the number of beams on physical and biologically equivalent dose conformity in a simplified geometry. We subsequently explored whether proton arc therapy could better spare cognitive structures compared to conventional IMPT, while mitigating the concerns of elevated LET/RBE at the end of the proton range in the setting of pediatric brain tumors.

Material and methods

A cylindrical phantom (Ø = 150 mm, V = 2693 cm^3) with two centrally located cylindrical targets (Ø = 25 mm, V = 12 cm^3 and Ø = 30 mm, V = 22 cm^3) was constructed to investigate the influence of increasing the number of beams on the dose gradients, for photon- vs. proton-based irradiation (i.e. IMRT vs. IMPT). The phantom and targets diameters were estimated to be representative of a pediatric patient with a centrally located brain tumor.

Anonymized data from four pediatric craniopharyngioma patients previously treated with double scattering proton therapy at the University of Florida Health Proton Therapy Institute were included in this study. As the primary target volume (PTV – median volume 49 cm^3 [range 26–66 cm^3]) is centrally located in the brain, close to cognitive structures, we investigated the effects of proton arc surrogate on the doses delivered to cognitive structures.

For each patient, three treatment plans were constructed:

- A reference plan, using the same field configuration as in the clinically delivered plans; i.e. right and left superior anterior oblique fields and a superior posterior oblique field.
- A coplanar proton arc surrogate plan, using 18 equiangular beams with 0° couch rotation. For the proton arc surrogate plans, the minimal spot weighting was set to 0.01 MU [5] instead of 2 MU.
- A sagittal proton arc surrogate plan, using 18 equiangular beams and a 90° couch rotation.

LET and RBE calculations

For all proton plans, two RBE scenarios were investigated:

- $RBE_{1.1}$, physical dose uniformly weighted by the clinical RBE value of 1.1
- RBE_{LET}, physical dose weighted by the LET, defined as $D_{LET} = D_{phys}(1+kLET_D)$, $k = 0.055$ μm/keV [11]. This method allows avoiding uncertainties in the selection of the α/β parameter otherwise needed when applying variable RBE models proposed in the literature while identifying regions with potential elevated biological effects caused by a high LET. The LET distributions were calculated using a script developed by Carabe et al. [12] and available in the Eclipse treatment planning system (version 13.7.16, Varian Medical System, Palo Alto, CA, USA).

Plan comparison

In the phantom plans, different isodose volumes were investigated as a measure of the dose gradient. In the proton plans, these parameters were calculated for both RBE scenarios as a marker of the effect of LET on the dose distribution. In the patient plans, the volume of the isodose 2, 10 and 40 Gy were calculated for all plan configurations and both RBE scenarios, for their association to cognitive impairment [13] and secondary cancer risks [14].

The Hausdorff Distance (HD) between the central plane of the PTV and different isodose levels (2, 10 and 40 Gy) was investigated as a measure of plan conformity. Furthermore, mean doses to cognitive structures were reported.

Results

Phantom plans

For the two treatment modalities, most of the differences were seen in terms of improved dose gradients when increasing the number of fields (Figure 1). In the photon plans, the isodose volumes at 10 Gy and lower increased for increasing number of beams, e.g. from 661 cm^3 in the 3-beam plan to 790 cm^3 in the 36-beam plan (2 Gy dose level). There was a reduction in the volumes receiving 20 and 30 Gy, and no variations in the volumes receiving higher doses. In the proton plans ($RBE_{1.1}$ scenario), the volume receiving 20 to 40 Gy remained overall constant with increasing number of beams, while there was a decrease in the isodose volume 10 to 5 Gy. The volume receiving very low doses (<2 Gy) was increased between the 3-beam and 36-beam plans, e.g. from 420 to 663 cm^3. The 2 and 5 Gy isodose volumes tended to be reduced with the RBE_{LET} scenario compared to $RBE_{1.1}$, whereas a trend toward a reduction of difference in isodose volume between both RBE scenarios was seen for the 10 to 40 Gy dose levels when increasing the number of beams (Figure 2). Notably, for both modalities, a plateau was reached after 12 beams where no further differences in isodose volume were seen when increasing the number of beams. Comparable trends were seen in the phantom with a target Ø = 30 mm (Supplementary Figure S2).

Increasing the number of beams resulted in a reduction of the volume receiving LET above 3.5 keV/μm, at the expense of an increased low-LET volume. This did not translate into large differences in terms of mean LET values, i.e. 2.1 keV/μm with 3 beams vs. 2.3 keV/μm with 36 beams. While the volume receiving intermediate LET was reduced when increasing the number of beams, the LET 'hot-spots' were not necessarily eliminated by adding more beams, as seen for example in the 9-beam plans where the maximum LET value was 7.2 keV/μm (Supplementary Figure S1).

Patient plans

In terms of isodose volume, almost no differences were seen between the three plans for the 40 Gy dose level, while the isodose volume increased with the RBE_{LET} scenario compared to $RBE_{1.1}$. For the 10 Gy dose level, the reference plan had

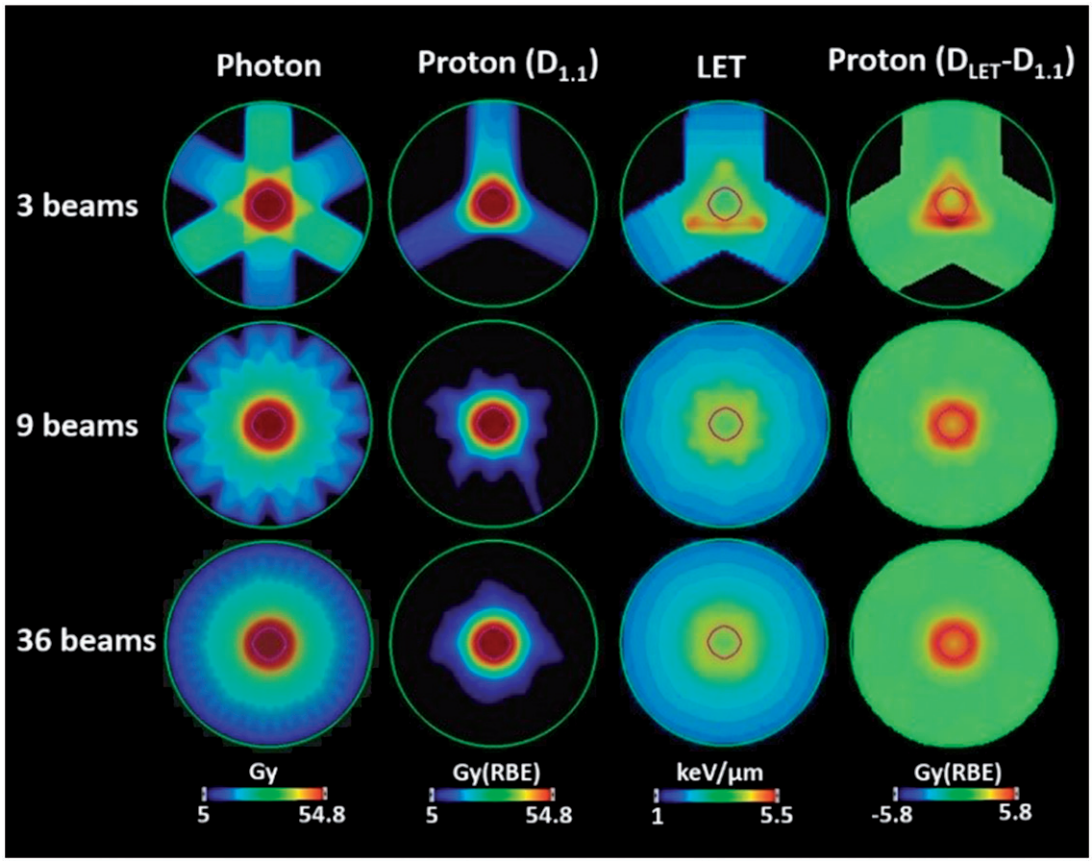


Figure 1. Distributions of photon dose (column 1), proton RBE = 1.1 dose (column 2), proton LET distribution (column 3) and proton dose difference RBE_{LET}-$RBE_{1.1}$ (column 4) for the three, nine and thirty-six beams plans in a transverse slice of the phantom with target Ø = 25 mm.

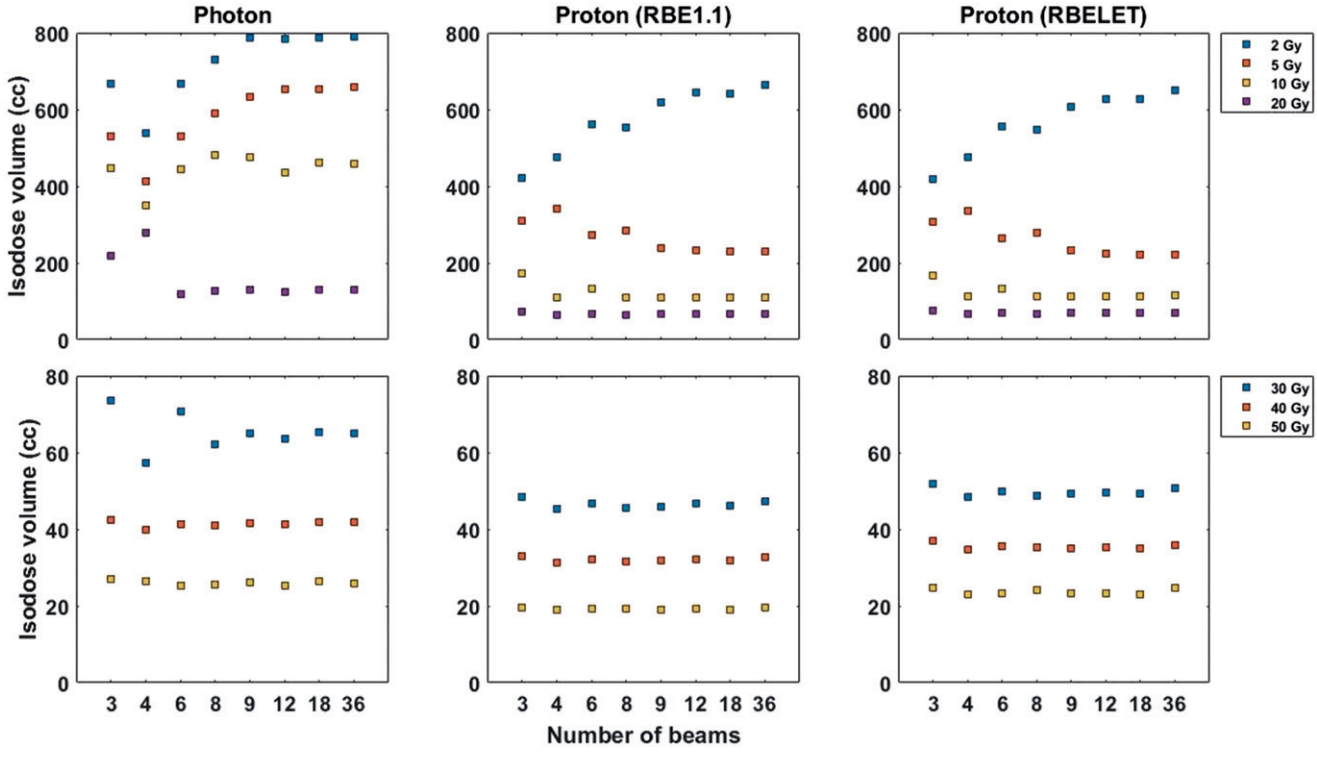


Figure 2. Isodose volume from different dose levels in the photon (left column), proton $RBE_{1.1}$ (middle column) and proton RBE_{LET} plans (right column) presented for an increasing number of beams in the phantom with target Ø = 25 mm.

overall the largest isodose volume while the coplanar proton arc surrogate plan had consistently the smallest in all four patients (median volume of 447 cm^3 compared to 349 cm^3; $RBE_{1.1}$ scenario). The opposite was seen for the 2 Gy dose level, where the reference plan had consistently the smallest volume in all four patients (median volume of 802 cm^3 in the reference plan compared to 1137 cm^3 in the coplanar arc surrogate plan; RBE_{LET} scenario). The isodose volume at 10 and 2 Gy was reduced compared to $RBE_{1.1}$ values in both proton arc surrogate plans, whereas there was a slight increase in the 10 Gy isodose volume with the RBE_{LET} scenario in three out of four patients (Supplementary Table 1).

For the 2 Gy dose level, the reference 3-beam plans had overall the smallest HD with increasing values toward the three beam directions. Large reductions in HD were seen around the temporal lobes and hippocampus in the two proton arc surrogate plans compared to the reference plan, for the three dose levels explored. In the example patient, the lowest HD values in these regions were seen in the coplanar proton arc surrogate plan, i.e. from 23 mm in the reference plan to 10 mm in the coplanar proton arc surrogate plan in the vicinity of the left temporal lobe (10 Gy dose level, $RBE_{1.1}$). For the three plans, an increase in HD values was observed toward the cerebellum for the 40 Gy dose level, and at all dose levels for the coplanar proton arc surrogate plan (Supplementary Figure S3).

When comparing the two RBE scenarios, the largest differences were seen at the 10 Gy dose level, with up to 10 mm decrease in HD for the reference plan with the RBE_{LET}, while almost no differences (<1 mm) were seen for the sagittal proton arc surrogate. For the 40 Gy dose level, there was around 2 mm increase in HD with RBE_{LET} doses compared to $RBE_{1.1}$ for the coplanar proton arc surrogate plan and 1 mm for the two other plan configurations. This increase was mostly seen toward the cerebellum. Overall, for all patients, the largest HD differences in the transversal plan between the two RBE scenarios were seen in the coplanar proton arc surrogate plans, inherently to the beams being distributed in the transversal plan only (Supplementary Figure S3).

The mean dose in the cognitive structures located cranially of the target volume (i.e. subventricular zones and corpus callosum) was consistently reduced in the coplanar proton arc surrogate plans for all patients. For example, the median corpus callosum mean dose was 24 Gy in the sagittal proton arc surrogate plans, 16 Gy in the reference 3-beam plans and 10 Gy in the coplanar proton arc surrogate plans ($RBE_{1.1}$). This was at the expense of the cerebellum, where the median of the mean dose increased to 5.8 Gy with the coplanar arc surrogate compared to 0.1 Gy in the reference 3-beam plan (RBE_{LET}). The mean dose to the temporal lobes was consistently the lowest in the sagittal proton arc surrogate plans compared to the reference 3-beams plans (Supplementary Table 2).

The volume of normal brain tissues (i.e. brain-PTV) receiving intermediate- to high-LET (from around 3 keV/μm) was reduced in the coplanar proton arc surrogate compared to the reference plan. The volume of normal brain tissues and brainstem exposed to low-LET was the lowest in the reference 3-beam plans. In all patients, the maximum LET in the brainstem was the lowest in the coplanar proton arc surrogate plans (Figure 3).

Discussion

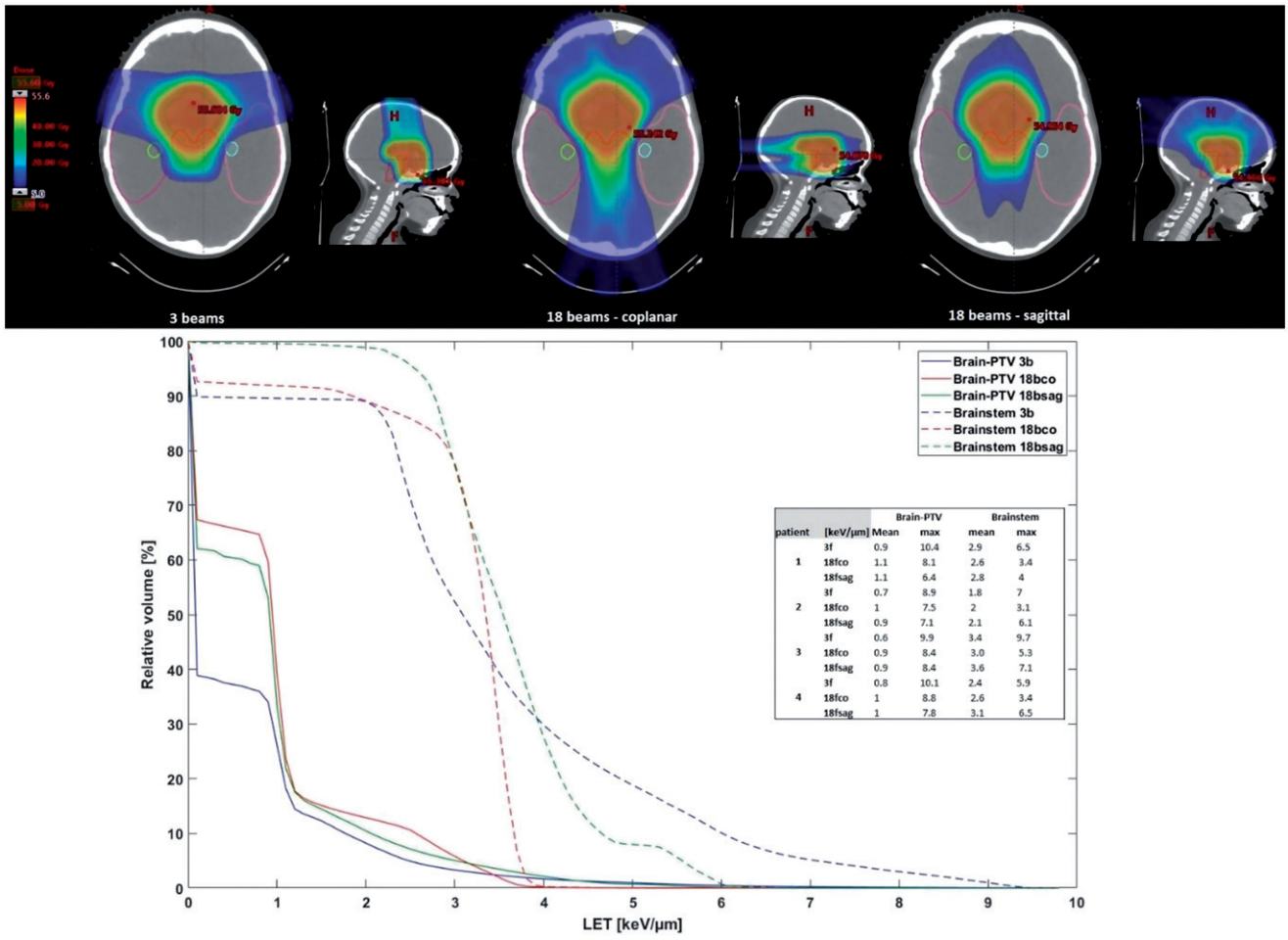
In this study, we investigated the effect of increasing the number of proton beams on the physical and biologically equivalent dose conformity in the setting of pediatric brain tumor patients. We found that increasing the number of beams resulted in an improved dose gradient at the expense of increased low-dose/low-LET volumes.

The reduction in intermediate-LET volume seen with the coplanar proton arc surrogate compared to the reference 3-beams IMPT plans was inherent to the increased number of beams, as no LET parameters were included in the cost function. However, the LET distribution is influenced by the optimization process and the resulting weight of some of the fields for sparing of normal tissues. Including some LET parameters in the optimization of proton arc plans could therefore result in even more smearing of the intermediate-LET values within the normal tissues, or redistribution to the target volume as demonstrated for IMPT optimization [9–10].

While adding more proton beams resulted in reduced isodose volumes for most dose levels, the low-dose bath (<2 Gy) was increased in the proton arc surrogate plans. There might therefore be implications for the risk of secondary cancer, especially when treating pediatric patients [14]. However, even though the volume receiving low doses was larger than in the conventional IMPT plans, the proton low-dose bath was still smaller than observed in IMRT plans, as demonstrated in the phantom. In addition, large uncertainties exist regarding the RBE of protons for the endpoint of carcinogenesis, limiting discussions on dose–response relationship of secondary cancer risk [15]. The enhanced risk of secondary cancer with proton arc therapy should therefore be investigated through more specific studies.

Because of the computational limitations, the proton arc surrogate plans were limited to 18 beams. However, this approximation appeared valid based on the phantom results, showing that the isodose volumes for both the $RBE_{1.1}$ and RBE_{LET} scenarios were comparable between the 18 and 36 beams plans, with no differences in target coverage. For the same reason, we only investigated coplanar plans. However, the implementation of non-coplanar proton arc plans could potentially better spare normal brain structures, as this has been demonstrated for the hippocampi in VMAT plans of craniopharyngioma patients [16].

Similarly, extending the study to more irregular tumor shapes could allow for a better demonstration of the potential of proton arc therapy on the sparing of organs at risk. Indeed, craniopharyngioma targets are usually of regular shape and may therefore underestimate some of the advantages of proton arc therapy. As the biggest benefits of IMRT/IMPT are often apparent in shaping dose around irregular and concave target volumes, one might expect proportional advantages using proton arc therapy. In our study, the patient benefiting the most from the proton arc surrogate



patient	[keV/µm]	Brain-PTV Mean	Brain-PTV max	Brainstem mean	Brainstem max
	3f	0.9	10.4	2.9	6.5
1	18fco	1.1	8.1	2.6	3.4
	18fsag	1.1	6.4	2.8	4
	3f	0.7	8.9	1.8	7
2	18fco	1	7.5	2	3.1
	18fsag	0.9	7.1	2.1	6.1
	3f	0.6	9.9	3.4	9.7
3	18fco	0.9	8.4	3.0	5.3
	18fsag	0.9	8.4	3.6	7.1
	3f	0.8	10.1	2.4	5.9
4	18fco	1	8.8	2.6	3.4
	18fsag	1	7.8	3.1	6.5

Figure 3. Upper panel: Dose distribution (RBE = 1.1) for the three reference plan (3 beams) and the proton arc surrogate (18 beams coplanar, 18 beams sagittal) in transversal and sagittal planes. The PTV is delineated in green, the brainstem in red, the temporal lobes in pink/purple and the hippocampi in green/blue. Lower panel: LET volume histogram for the three, eighteen coplanar and eighteen sagittal beam plans for the brain-PTV and brainstem in one of the patient. 3f: reference 3-beam plan, 18fco: coplanar proton arc surrogate plan and 18fsag: sagittal proton arc surrogate plan. The table in insert presents the mean LET and maximum LET values of the three plans, for the four different patients.

plans in terms of temporal lobe and hippocampi sparing had a large target volume and an irregular PTV shape compared to the others.

In the patients arc surrogate plans, range shifters were required for some of the beams (4/5 out of the 18) in order to cover the proximal margin of the target, but the range shifters were not supported by the LET script. We therefore relied on the other beams to achieve adequate coverage of the target volume, possibly leading to suboptimal proton arc plans with discrepancies in the weighting of the fields. However, the phantom plans did not necessitate range shifters and a similar improvement in dose gradient and reduction in the volume receiving intermediate-LET was seen when adding more beams.

As this study was an exploration of the concept of proton arcs for focal RT of pediatric brain tumors, we did not focus on the delivery efficiency of the plans. While the minimum spot weighting was reduced to 0.01 MU to mimic proton arc delivery settings [5], other parameters reported for the proton arc optimization algorithm were not taken into account. For example, we did not include thresholds on the number of energy layers per beams depending on their weighting [17]. These parameters would in part influence the plan deliverability and the delivery time, which were not the primary focus of this study but could be of concern for the treatment of pediatric patients, especially when anesthesia is required.

In conclusion, increasing the number of proton beams resulted in an improved dose gradient at the expense of increased low-dose/low-LET volumes. A better sparing of the temporal lobes could be achieved with proton arc configurations compared to conventional IMPT. Overall, the implications of proton arc therapy on the risk of secondary cancer require further studies.

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Disclosure statement

All authors have no conflicts of interest to declare.

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