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Short Communication

Risk of second primary cancer from proton arc therapy of pediatric brain tumors

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A B S T R A C T

Proton arc therapy (PAT) is currently explored for clinical implementation, despite its associated low-dose bath. This study therefore aimed at evaluating the risk of radiation-induced second primary cancer (SPC) for PAT in pediatric brain tumor patients. Two brain-specific models for SPC induction were applied in five cases to compare volumetric modulated arc therapy (VMAT), intensity modulated proton therapy (IMPT) and PAT surrogate plans. The PAT integral dose was reduced by a median of 29% compared to VMAT, and 17% compared to IMPT. For both models, the estimated SPC risks were consistently the lowest for PAT.

1. Introduction

There is growing interest around the developments and potential benefits in dose tailoring that can be achieved with proton arc therapy (PAT) [1]. However, the low-dose bath is higher with PAT compared to intensity modulated proton therapy (IMPT) [2]. Therefore, and in particular for pediatric patients, concerns exist with regards to radiation-induced second primary cancers (SPC) with PAT, as the impact of low doses on SPC risks is still unclear [3–4].

While a few studies investigated SPC risk after passive-scattering PAT [5–6], SPC risk estimates for active-scanning PAT are lacking even though this would be the likely delivery method in a clinical setting. Indeed, passive-scattering PAT necessitates complex beam modifying materials to shape each field during treatment delivery [6], while active-scanning PAT could offer continuous spot delivery during gantry rotation [7]. Brain tumors have been considered good candidates to benefit from PAT [1], but the risk of SPC has not yet been assessed, despite a recent study highlighting that pediatric brain tumor patients are at increased risk of developing a SPC [4].

The aim of this study was therefore to compare the risk of SPC in pediatric patients with centrally located brain tumors treated with IMPT or active-scanning PAT. Photon-based volumetric modulated arc therapy (VMAT) estimates were also included as another established treatment modality presenting a low-dose bath.

2. Materials and methods

Anonymized data from five pediatric craniopharyngioma patients were included in this study, following International Review Board approval from the University of Florida Health Proton Therapy Institute.

VMAT, IMPT and PAT-surrogate plans were optimized using the Eclipse treatment planning system (*version 13.7.16, Varian Medical System, Palo Alto, CA, USA*) with a prescribed dose of 54 Gy(RBE) to the primary target volume (PTV). The PTV median volume was 35.9 cm^3 [18.2 – 66.4 cm^3], centrally located in the suprasellar brain region. The VMAT plans consisted of three arcs of 6 MV beam quality, including one full arc and two non-coplanar arcs at couch angle 45° and 365° [8]. The IMPT plans used three fields (right/left superior anterior oblique fields, and a superior posterior oblique field). Single arc surrogate proton plans (hereafter referred to as PAT plans) were calculated using 18 equiangular coplanar beams with a minimal spot weighting of 0.01 monitor units [2]. For all patients, the three plans were PTV-based and offered equivalent target coverage (Fig. 1). Of note, both arc plans (VMAT and PAT) were optimized for temporal lobe sparing [2]. For the proton plans, a fixed relative biological effectiveness (RBE) of 1.1 was used, as applied clinically.

The integral dose (ID, Joules or Gy.L) [9] to an organ of i voxels was calculated as

$$ID = \sum_i V_i D_i \rho_i$$

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where V is the volume, D the dose and ρ the density in each voxel i of the organ of interest. A density of $\rho = 1$ g/cm^3 was assumed across the whole brain.

Relative risks (RRs) of radiation-induced SPC of the central nervous system (CNS), based on the organ equivalent dose (OED) concept, were analyzed and compared by applying two risk equivalent dose (RED) models: a linear model [10], where SPC risk simply increases linearly with dose, and a CNS-specific mechanistic model [10] taking into account biological processes, such as the effect of fractionation or the repair ability of specific tissues. The full equations are available in Supplementary Material.

The OED was obtained by summing over the whole dose-volume histogram of the normal brain (defined as whole brain – clinical target volume (CTV)), such as:

$$OED = \frac{1}{V_T}\sum_i V(D_i) \times RED(D_i)$$

The relative risk of radiation-induced SPC of the CNS was then expressed as:

$$RR = \frac{OED_A}{OED_B}$$

with A and B representing different treatment modalities. A RR < 1 would imply that treatment modality A has a lower risk of inducing a CNS SPC than modality B.

3. Results

PAT plans had consistently the smallest ID compared to the two other modalities: the median [range] ID was 0.7 Gy.L [0.5 – 1.1 Gy.L] for PAT, 0.8 Gy.L [0.6 – 1.2 Gy.L] for IMPT and 0.8 Gy.L [0.6 – 1.7 Gy.L] for VMAT (Fig. 2a).

Across all patients, SPC risks from both RED models were consistently the lowest for PAT, followed by IMPT and VMAT. Using the linear model, the median [range] RR was 0.92 [0.81 – 0.95] for PAT vs. IMPT, 0.56 [0.53 – 0.64] for PAT vs. VMAT, and 0.61 [0.61 – 0.68] for IMPT vs. VMAT. From the full-mechanistic model, the median [range] RR was 0.92 [0.83 – 0.97] for PAT vs. IMPT, 0.53 [0.48 – 0.58] for PAT vs. VMAT, and 0.58 [0.52 – 0.6] for IMPT vs. VMAT (Fig. 2b).

For both ID and SPC risks, patient-specific values can be seen in the Supplementary Material (Fig. S1 and Fig. S2).

4. Discussion

Despite more tissue exposed to low doses with PAT compared to IMPT, the integral dose was consistently the lowest in PAT plans. We found a clear tendency towards a reduced risk of SPC with PAT for the two investigated RED models. When comparing both proton modalities to VMAT, the estimated SPC risks were roughly halved.

While a reduced risk of SPC with IMPT compared to VMAT for pediatric brain tumor patients have been reported [11], to date, no studies on SPC risk after active-scanning PAT for pediatric cases have been published. However, our results can be compared to previous work investigating surrogate plans for passively-scattered PAT, i.e. plans obtained from equally spaced proton beams (16 [5] or 48 [6] beams). The first study investigated the risk of bladder and rectum SPC after VMAT vs. PAT for prostate cancer [5], while the latter reported on SPC risk after para-aortic lymph node irradiation with intensity modulated radiotherapy (IMRT) vs. static passively-scattered proton therapy (PSPT) vs. PAT (for stomach, small bowel, kidney, liver and spinal cord) [6]. In both cases, the authors found no difference in SPC risk between the treatment techniques when applying a linear non-threshold model, while both the linear exponential and plateau model predicted a reduction in SPC risk with PAT vs. VMAT/IMRT [5–6]. In general, SPC risks were lower with PAT vs. PSPT when the plateau model was used, and similar for the linear-exponential estimates [6]. Our results from the full-mechanistic model are therefore consistent, as we also reported a reduced SPC risk with PAT vs. VMAT. However, when applying a linear model, we showed a lower risk with PAT vs. VMAT, as opposed to equal risk as in both previous studies.

It is worth mentioning that passively-scattered PAT would be subject

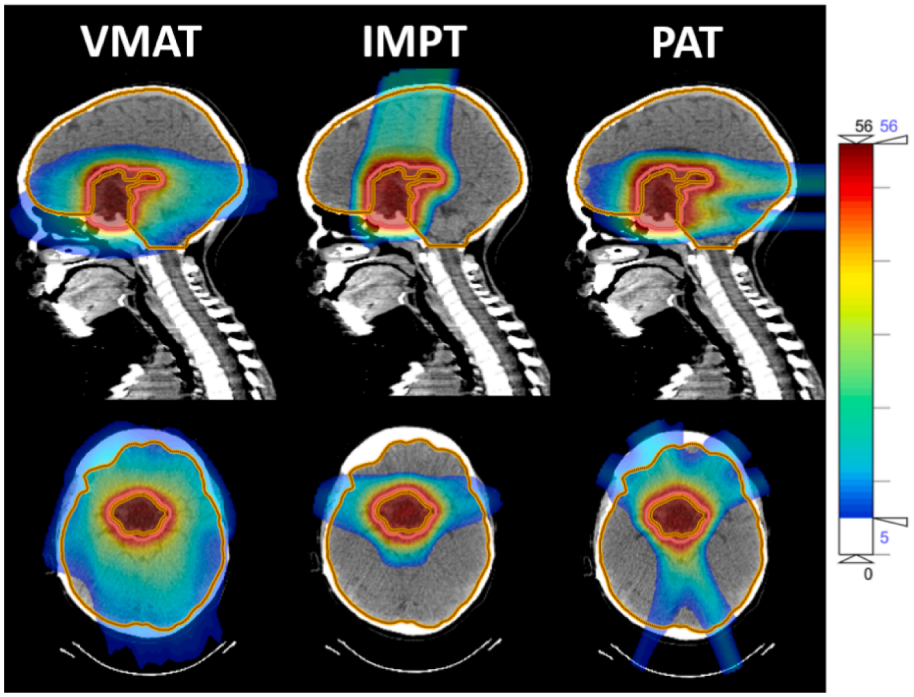

Fig. 1. Dose distribution (RBE = 1.1) for an example patient for the three treatment modalities (dose range: 5 – 56 Gy(RBE)). The PTV is delineated in red, and the CNS (defined as whole brain – CTV) in brown. The top row shows the sagittal view, and the bottom row the transversal view. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

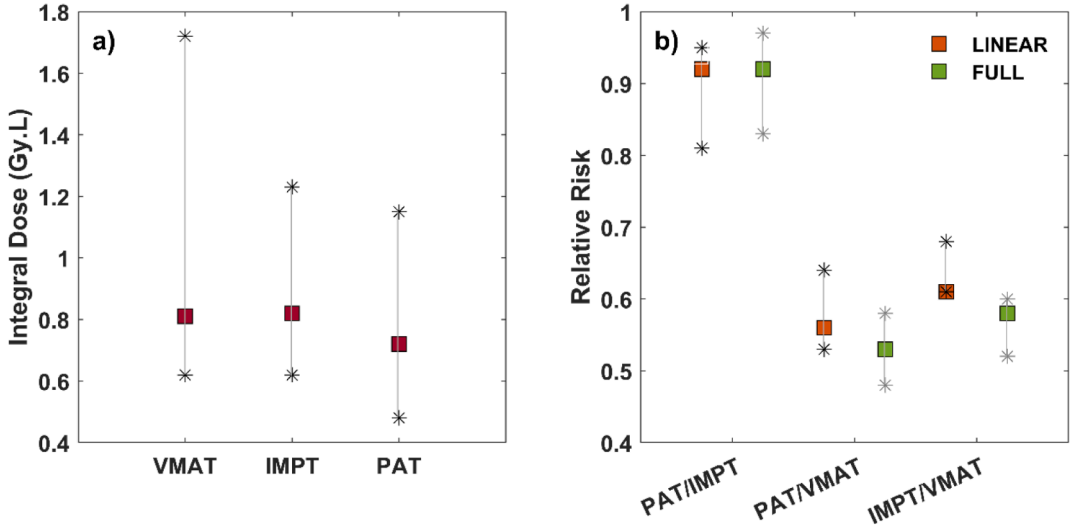

Fig. 2. Median [range] over the five cases of a) ID (Gy.L) to the CNS (defined as whole brain – CTV) and b) RR of SPC the CNS. A RR of 1 represents equal risk between the modalities, while a RR < 1 is in favor of the modality in the numerator of the ratio. Orange colors are results from the linear risk model (LIN), and green colors are from the full-mechanistic model (FULL). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to high-energy secondary neutron production due to the interaction between the protons and the beam-modifying materials (e.g. scatterers and collimators), as opposed to active-scanning PAT [12]. As neutrons have a relatively high radiogenic risk, Rechner et al. [5] included the effect of stray radiation in their SPC risk calculations. Because the secondary neutron production is considerably lower in active-scanning proton therapy, their contribution to SPC risks was not included in our calculations. Our SPC risk estimates from the proton therapy modalities could therefore be slightly underestimated if this hypothesis is not valid.

In the pediatric population, efforts are made to reduce the risk of radiation-induced long-term effects by reducing the ID, which is also of concern for SPC induction [12]. In our study, the ID was slightly lower for PAT compared to IMPT despite the increased low-dose volume [2]. When compared to VMAT, a large reduction in ID was seen with PAT in the five cases. We reported a median reduction in ID of 17% for PAT vs. IMPT, and 29% for PAT vs. VMAT. These results are in line with previous studies on other tumor sites, where the reduction in ID ranged from 4% to 17% with PAT vs. IMPT [13–16], and ID was more than halved for PAT vs. VMAT [12,14]. For prostate cancer, Engwall et al. reported a reduction in ID ranging from 15% to 19% for PAT vs. IMPT, depending on the number of arcs and specific optimization choices such as energy layers sequencing [17]. This ID reduction with PAT vs. IMPT therefore reflect a shift in dose-volume distribution, where the low-doses are increased whereas intermediate-doses are reduced in the normal tissues surrounding the target volume. This feature of PAT could be of interest for limiting the risk of normal tissue complications, also of high relevance when treating pediatric patients.

Of note, a recent study reported a 10-year cumulative incidence of solid SPC of 1.8% after intensity modulated radiotherapy for pediatric cancer [4], in line with estimates from conventional radiotherapy despite a larger low-dose volume. Therefore, more clinical evidence is required to understand the effect of low-doses on SPC risks [18], when available clinical data are so far not indicating an increased risk.

Our results are based on the assumption that the proton RBE for cell inactivation and cell mutation/cancer induction are equivalent, which remains to be clarified [19]. Carabe et al. presented experimental data showing increased RBE of monoenergetic PAT (PMAT) compared to IMPT for different cell cultures, where PMAT induced larger and more complex DNA damage than IMPT, resulting in difference in cell-survival [20]. Further work is therefore needed to investigate if that could also translate into an increased SPC risk when using PAT, or rather a risk reduction if PAT was to be more effective in cell killing (i.e. reducing potential for cell mutation).

Knowledge of the SPC dose–response is restricted by limited follow-up time in clinical cohorts and available information of the dose exposure and combined therapies [18], thus our risk estimates were based on both a linear and full-mechanistic model proposed by Schneider [10]. The latter took into account the effects of treatment fractionation on cell-repopulation and cell-killing, and derived based on data from the atomic bomb survivors and Hodgkin disease patients. These populations are fundamentally different from pediatric craniopharyngioma patients in their radiation exposure (e.g. dose rate, type of radiation field, fractionation scheme etc.). However, by using models for relative risk assessment rather than absolute measures, some of the uncertainties on the dose–response function or model parameters cancel out in the mathematical equation. While uncertainties still exist for the equations themselves, focusing on relative risk can minimize their impact on the estimated values. For all cases, we consistently obtained identical ranking of the plans from both RED models, with the highest SPC risks estimated for VMAT plans compared to both proton modalities, indicating that the use of PAT would not imply increased SPC risks. Given this consistency in the ranking of modalities, the fact that only five cases were included in this study could be less limiting for the present purpose.

In this study, surrogate PAT plans were used, where we disregarded technical aspects of PAT optimization and delivery [2] and simply used 18 equally-spaced beams with PTV-based optimization. PTV-optimization was chosen rather than robust-optimization due to computational limitations, but also for ensuring a one-to-one comparison with VMAT target coverage. However, one could assume PTV-based optimization to result in higher dose to normal tissues, and therefore our SPC risk estimates would be slightly overestimated compared to what the future clinically deliverable PAT plans could offer [13–16]. Similarly, the shortcomings regarding PAT optimization in terms of e.g. energy layer sequencing will also have an influence on the presented results, as previously shown for the ID [17].

Another obvious limitation of this study is the number of patients. Because only five patients were included, no statistical analysis could be performed to compare SPC risks from the three techniques. Overall, our results should be interpreted with caution and further studies are warranted.

In conclusion, PAT resulted in comparable SPC risks to the IMPT

plans, and lower risks compared to the VMAT plans. The integral dose was also the lowest for the PAT plans while the additional degrees of freedom offered selective dose sparing of substructures, therefore indicating the potential of this delivery technique to reduce a broad range of outcomes beyond SPC. However, the currently existing SPC models lack clinical validation. Long-term follow-up and collection of the delivered dose-volume distributions will be pivotal as we move forward with PAT.

CRediT authorship contribution statement

Laura Toussaint: Conceptualization, Formal analysis, Visualization, Writing – original draft. **Daniel J Indelicato:** Resources, Writing – review & editing. **Ludvig P Muren:** Conceptualization, Writing – review & editing. **Camilla H Stokkevåg:** Conceptualization, 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.phro.2023.100480.

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