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RESEARCH ARTICLE

Clinical outcomes and quality of life in children and adolescents with primary brain tumors treated with pencil beam scanning proton therapy

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Abstract

Background: Long-term treatment-related toxicity may substantially impact well-being, quality of life (QoL), and health of children/adolescents with brain tumors (CBTs). Strategies to reduce toxicity include pencil beam scanning (PBS) proton therapy (PT). This study aims to report clinical outcomes and QoL in PBS-treated CBTs.

Procedure: We retrospectively reviewed 221 PBS-treated CBTs aged <18 years. Overall-free (OS), disease-free (DFS), and late-toxicity–free survivals (TFS), local control (LC) and distant (DC) brain/spinal control were calculated using Kaplan-Meier estimates. Prospective QoL reports from 206 patients (proxies only ≤4 years old [yo], proxies and patients ≥5 yo) were descriptively analyzed. Median follow-up was 51 months (range, 4-222).

Results: Median age at diagnosis was 3.1 years (range, 0.3-17.7). The main histologies were ependymoma ($n = 88$; 39.8%), glioma ($n = 37$; 16.7%), craniopharyngioma ($n = 22$; 10.0%), atypical teratoid/rhabdoid tumor (ATRT) ($n = 21$; 9.5%) and medulloblastoma ($n = 15$; 6.8%). One hundred sixty (72.4%) patients received chemotherapy. Median PT dose was 54 Gy(relative biological effectiveness) (range, 18.0-64.8). The 5-year OS, DFS, LC, and DC (95% CI) were 79.9% (74-85.8), 65.2% (59.8-70.6), 72.1% (65.4-78.8), and 81.8% (76.3-87.3), respectively. Late PT-related ≥G3 toxicity occurred in 19 (8.6%) patients. The 5-year ≥G3 TFS was 91.0% (86.3-95.7). Three (1.4%) secondary malignancies were observed. Patients aged ≤3 years at PT ($P = .044$) or receiving chemotherapy ($P = .043$) experienced more ≥G3 toxicity. ATRT histology independently predicted distant brain failure ($P = .046$) and death ($P = .01$). Patients aged ≥5 years self-rated QoL higher than their parents (proxy assessment). Both reported lower social functioning and cognition after PT than at baseline, but near-normal long-term global well-being. QoL was well below normal before and after PT in children ≤4 years.

Abbreviations: ATRT, atypical teratoid/rhabdoid tumor; CBTs, children with brain tumors; CCS, childhood cancer survivors; CCSS, Childhood Cancer Survivor Study; CRT, conventional radiotherapy; CSI, craniospinal irradiation; DC, distant control; DFS, disease-free survival; FU, follow-up; KM, Kaplan-Meier; LC, local control; LGG, low-grade glioma; OS, overall survival; PBS, pencil beam scanning; PT, proton therapy; QoL, quality of life; RBE, relative biological effectiveness; RION, radiation-induced optic neuropathy; RN, radiation necrosis; SM, secondary malignancy; TFS, toxicity-free survival; yo, years old

Conclusions: The outcome of CBTs was excellent after PBS. Few patients had late ≥G3 toxicity. Patients aged <5 years showed worse QoL and toxicity outcomes.

KEYWORDS
children, late effects, pediatric brain tumors, pencil beam scanning, proton therapy, secondary malignancy, toxicity

1 | INTRODUCTION

Five-year childhood cancer survivorship currently stands around 80% and is increasing in high-income countries.[1] However, long-term childhood cancer survivors (CCS) incur high rates of treatment-related adverse events, inflicting them with chronic health conditions and deteriorating their quality of life (QoL).[2,3] Brain CCS face neuromotor, neurosensory, neurocognitive, and psychosocial late effects,[4,5] which are more common in patients who receive radiotherapy.[6] As such, the health providers' main concern is to decrease treatment-related toxicity and increase the therapeutic ratio.[7] One such strategy is the administration of proton therapy (PT) to children and adolescents with primary brain tumors.[8] The dosimetric advantages of protons over conventional radiotherapy (CRT) are due to their sharp distal dose falloff and reduced entry dose.[9,10] Favorable neuropsychological outcomes after PT have been demonstrated over CRT.[11,12] Regrettably, due to logistical and financial challenges, PT is not widely available for routine cancer care of children with brain tumors (CBTs). Long-term follow-up (FU) data thus only exist for small cohorts of CBTs treated with protons. This lack of data is most problematic for PT delivered with pencil beam scanning (PBS), the most advanced PT delivery technique, which allows for higher dose conformation and reduces neutron contamination.[13] The aim of this study is to report long-term clinical outcomes and QoL in a large cohort of CBTs treated with PBS PT and to assess prognostic factors related to these clinical outcomes.

2 | METHODS

2.1 | Patients

A query of our institutional database identified 231 children <18 years with primary brain tumors and treated with PBS between 1999 and 2017 as part of the first irradiation course. We excluded 10 (4.3%) patients treated for reirradiation, or with clinical FU <12 months.

In the 221 patients included in the analysis, median age at diagnosis and at PT start were 3.1 (range, 0.3-17.7) and 4.1 years (range, 0.8-18.2), respectively. The most common histologies were ependymoma (n = 88; 39.8%), glioma (n = 37; 16.7%), craniopharyngioma (n = 22; 10.0%), atypical teratoid/rhabdoid tumor (ATRT) (n = 21; 9.5%), and medulloblastoma (n = 15; 6.8%). Most patients with glioma had low-grade histology (n = 30, 81% of gliomas). Eighty-nine percent of ependymoma cases were WHO grade III. Median age at PT was 2.1 years (range = 1.1-4.9), 2.8 years (0.8-15.2), 4.9 years (2.5-10.2), 9.9 years (2.5-18.2), and 11.1 years (2.2-17.9) in patients with ATRT, ependymoma, medulloblastoma, craniopharyngioma, and low-grade glioma (LGG), respectively. Overall, 59% patients were males. A 60% female predominance was however found in patients with LGG. One hundred sixty patients (72.4%) received chemotherapy; in 38 (17.2%) cases concomitantly with PT. Patient baseline characteristics are detailed in Tables 1, S1, and S2. This analysis was approved by the North-West and Central Switzerland Ethics Committee (EKNZ2019-00346) and has been conducted according to institutional guidelines.

2.2 | Proton therapy

All CBTs were treated with PBS on a scanning gantry. High-resolution planning-computed tomographies were registered with relevant MRI sequences for target delineation. Irradiation plans were generated using the three-dimensional dose-calculation software PSI-Plan. Proton doses were expressed in Gy(relative biological effectiveness, RBE) [Gy(RBE) = proton Gy x 1.1].[14]

The median total PT dose, fraction number, and dose per fraction were 54 Gy(RBE) (range, 18-64.8), 30 (range, 10-36), and 1.8 Gy(RBE) (range, 1.5-2), respectively. Craniospinal irradiation (CSI) was given to 21 (10.0%) patients; in 4 cases with photons, followed by a PT boost. Three other patients received partial photon irradiation to avoid delaying treatment start (2 cases, 18 and 36 Gy), or due to technical issues during PT (1 case, 10 Gy).

2.3 | Monitoring and follow-up

Treatment- and tumor-related baseline morbidity was captured before PT. Acute toxicities were documented weekly during PT. Long-term clinical and radiological FU was performed by the referring physicians. The Study and Research Office retrospectively obtained FU documentation according to quality checklists. Questionnaires focused on investigating capacity to perform daily personal and educational activities were prospectively sent to patients (File S7). FU data were reviewed at weekly mortality/morbidity meetings, where disease status and late toxicity (occurring 90 days after PT completion) were captured. Toxicity was graded with the Common Terminology Criteria for Adverse Events v4.0.[15]

TABLE 1 Patient, tumor and treatment characteristics

Characteristics	*n*	%
Patients total	221	100
Gender		
Male	129	58.4
Female	92	41.6
Age at Dg (years)[a]	3.1 (0.3-17.7)	
Age at PT (years)[a]	4.1 (0.8-18.2)	
Histology		
Ependymoma	88	39.8
Glioma	37	16.7
Craniopharyngioma	22	10.0
ATRT	21	9.5
Medulloblastoma/PNET	20	9.1
Germ cell tumor	14	6.3
Choroid plexus tumor	6	2.7
Meningioma	4	1.8
Other	9	4.1
Disease at PT		
Initial diagnosis	144	65.2
Recurrence/progression	77	34.8
Metastasis at PT	12	5.4
Tumor site		
Supratentorial	108	48.9
Infratentorial[b]	100	45.2
Brainstem	13	5.9
WHO grade		
I	37	16.7
II	29	13.1
III	88	39.8
IV	45	20.4
NA[c]	22	10.0
Number of surgeries[d]		
0	11	5.0
1	133	60.2
2	46	20.8
>2	31	14.0
Extent of surgical resection		
Gross total	79	35.7
Subtotal	111	50.2
Biopsy only	20	9.1
No surgery/biopsy	11	5.0
Chemotherapy		
Any	160	72.4
None	61	27.6
Concomitant chemotherapy	38	17.2
Proton therapy		
Dose[a] Gy(RBE)	54.0 (18-64.8)	
N fractions[a]	30 (10-36)	
Dose per fraction[a]	1.8 (1.5-2)	
Craniospinal irradiation	21	10.0

[a]Median value (range).
[b]Nonbrainstem.
[c]Tumor not graded on the WHO scale.
[d]Including nondiagnostic procedures such as ventricular derivations.
Abbreviations: ATRT, atypical teratoid/rhabdoid tumor; Dg, diagnosis; *n*, number; NA, not applicable; PNET, primitive neuroectodermal tumor.

2.4 | Quality of life

From 2005 onward, in collaboration with the University of Münster/Bonn, patients were offered to enroll in a health-related QoL study. After giving their informed consent, the parents filled a proxy version of the PedsQL for children aged 1 to 4[16] or a proxy PEDQOL questionnaire for children ≥5 years.[17] Children ≥5 years were also offered the self-rating PEDQOL questionnaire. Patients who started assessment with the PedsQL surveys were offered to switch to the PEDQOL questionnaires at the age of 5. Surveys took place before PT start (E1), 2 months after PT (E2), then yearly after PT (E3+). QoL data were available and used for 206 patients. This ongoing pediatric QoL study received a separate approval from the EKNZ Committee (EKNZ2014-244).

2.5 | Statistical analysis

Overall survival (OS), disease-free survival (DFS), local (LC) and distant (DC) CNS control, as well as late PT-related ≥G3 toxicity-free survival (TFS) were calculated using the Kaplan-Meier (KM) method. A neurological late-PT–related ≥G3 TFS function was generated. Survival was calculated from PT start. The log-rank test was used to assess differences between variables for univariate analysis of predefined clinical and treatment characteristics. Cox regression model was used to perform multivariate analysis. Selection of factors introduced into the model was based on the significance of univariate analysis, taking *P*-value ≤.05. Analyses were performed on the Statistical Package for Social Sciences software suite (IBM SPSS Statistics_v24.0, IBM Corp., Armonk, NY).

Completed PedsQL questionnaires until 3 years after treatment were considered for QoL data analysis. PEDQOL questionnaires until 5 years after PT (E7) were considered due to the small sample sizes available after this time point. A numeric score (0-100 points) was calculated for each domain at each time point, a higher score means a better QoL. Without full individual patient overlap between time points, mean scores were descriptively compared with two independent, age-similar norm groups at each time point.[18] The

TABLE 2 Patterns of first failures

Event	Cause/location/type	*N* (%)
Failure	Any	74 (100)
First failure	Local only	47 (63.5)
	Distant brain only	8 (10.8)
	Spine only	3 (4.1)
	Non-CNS only	1 (1.3)
	Local and brain	3 (4.1)
	Local and spine	2 (2.7)
	Local, brain, and spine	4 (5.4)
	Brain and spine	6 (8.1)

Abbreviations: CNS, central nervous system; *N*, number.

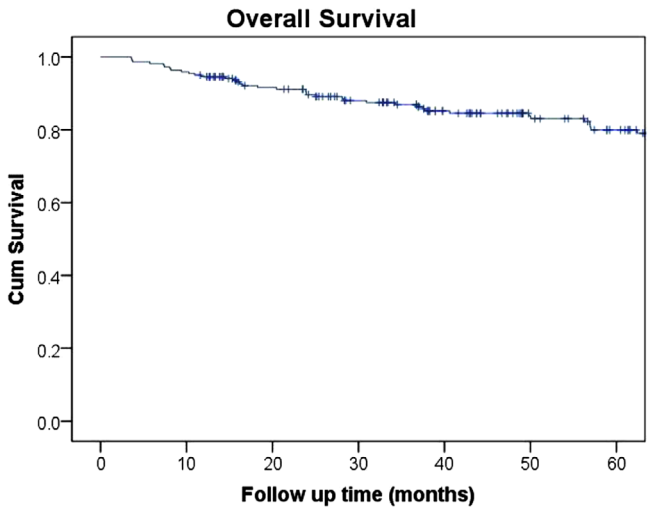

FIGURE 1 Kaplan-Meier curve for overall survival

self-assessment PEDQOL norm group was derived from two different subsamples including 795 participants from the German Rhein-Ruhr metropolitan area in 1999 (n = 552 children 8-18 years old (yo), including 293 females) and from a 2006 school-based assessment in Berlin, Germany (n = 243 children 5-18 yo, including 136 females). The proxy-assessment PEDQOL norm group data were obtained in the same Berlin assessment (n = 232 parents).

3 | RESULTS

3.1 | Survival and tumor control

Median FU time was 51.1 months (range, 4.0-222.0). Treatment failure was observed in 74 of 221 (33.5%) patients. Isolated local failure was the most common pattern (n = 47; 63.5%) (Table 2). The estimated (95% CI) 5-year DFS, LC, and DC were 65.2% (59.8-70.6), 72.1% (65.4-78.8), and 81.8% (76.3-87.3), respectively (Figure S1). During the FU period, 43 (19.5%) patients died. The estimated 5-year OS was 79.9% (95% CI: 74-85.8) (Figure 1). Most deaths (n = 36; 83.7%) were caused by tumor progression. Three patients died of undocumented causes; two patients thereof had documented tumor progression. Treatment-related adverse events led to four deaths: two patients died due to secondary malignancies (SMs), another during an attempted SM resection, and one patient died from brainstem radiation necrosis (RN). Of note, 5 years after PT, 53.3% of patients with metastasis at PT were distantly controlled and 65.6% were alive. Five-year OS was 100%, 94.7% (95% CI: 84.7-100), 80.8% (95% CI: 71.4-90.2), 64% (95% CI: 38.4-89.6), and 45.2% (95% CI: 21.1-69.3) in patients with craniopharyngioma, LGG, ependymoma, medulloblastoma, and ATRT, respectively. In the same order, 5-year DC was 100%, 95.5% (95% CI: 86.9-100), 80.3% (95% CI: 71.7-88.9), 50% (95% CI: 23.1-76.9), and 60.6% (95% CI: 36-82.2). Table S3 details survival outcomes for the main histologies.

On univariate analysis, no tested factor was the predictor of local failure. Age at PT ≤5 years, metastasis at PT, WHO grades 3 to 4, and ATRT histology were significant predictors of distant CNS failure. Age at PT ≤5 years and WHO grades 3 to 4 were significant predictors of disease failure. Age at PT ≤5 years, WHO grades 3 to 4, metastasis, and ATRT histology were significant predictors of death. After multivariate analysis, ATRT histology was an independent predictor for distant CNS failure (P = .046) and for death (P = .01). Age at PT ≤5 years, was close to being an independent predictor for distant CNS failure (P = .068) (Table 3).

3.2 | Acute toxicity and treatment interruptions

PT was well tolerated and there were no acute-toxicity–driven PT interruptions. The only ≥G3 event was an acute G4 optic neuropathy that responded to corticosteroids. Treatment was stopped early (43.2 Gy of the planned 54 Gy) in a child, where tumor progression was diagnosed under therapy, in order to perform emergency surgery.

3.3 | Late toxicity

Late G2 endocrinopathy was found in 60 (27.1%) patients; 37 (16.7%) radiation-induced, 13 (5.9%) tumor-related, 8 (3.6%) postoperative, and 2 (0.9%) chemo-related events. In PT-related cases, median pituitary Dmean was 50.5 Gy(RBE) (range, 0-57.9). In five patients where pituitary Dmean was <30 Gy(RBE) (range, 0-11.7), median hypothalamus Dmean was 22.1 Gy(RBE) (range, 12.5-45.8). Cognitive disturbance ≥G2 was reported in 31 (14%) patients, in 26 (11.8%) cases after PT. Hearing impairment ≥G2 was found in 24 (10.8%) cases, in 19 (8.6%) cases due to PT. Optic neuropathy ≥G2 was present in 37 (16.7%) patients, overwhelmingly (78.3% of cases) due to tumor compression. Radiation-induced optic neuropathy (RION) occurred in three patients (1.4%). Seizures were described in 12 (5.4%) cases, 5 (2.3%) cases likely caused by PT. Brain RN ≥G2 occurred in 10 (4.5%) patients. Other ≥G2 neurological disorders (mainly hemisyndromes, cranial nerve disorders, and ataxia) were identified in 72 (32.6%) patients; 14 cases (6.3%) were PT-related, including 4 (1.8%) occurrences of moyamoya syndrome.

TABLE 3 Univariate and multivariate analysis on local control, distant CNS failure, any failure, death, and late CNS ≥G3 toxicity events

Characteristic		5 y LC[a] [%]	P[b]	5 y DC[a] [%]	P[b]	5 y DFS[a] [%]	P[b]	5 y OS[a] [%]	P[b]	5-y ≥G3 TFS[a] [%]	P[b]
All patients		72.1 ± 6.7	–	81.8 ± 5.5	–	65.2 ± 5.4	–	79.9 ± 5.9	–	91.0 ± 4.7	–
Age at PT	≤3 y	65.5 ± 13.5	.947	78.6 ± 9.4	.258	62.7 ± 11.3	.452	72.4 ± 11.4	**.047**[c]	84.9 ± 10	**.044**/.659
	>3 y	72.1 ± 8.2		83.6 ± 6.7		66.5 ± 8.4		84.2 ± 6.7		94.8 ± 4.2	
	≤5 y	68.9 ± 8.8	.101	75.2 ± 7.8	**.002**/.068	59.2 ± 9.0	**.009**/.769	81.6 ± 7.1	**.02**/.822	87.2 ± 7.3	.103
	>5 y	76.2 ± 10		91.1 ± 6.3		73.1 ± 10.2		86.8 ± 7.8		95.9 ± 4.5	
Metastasis	M+	74.1 ± 25.3	.656	53.3 ± 31.6	**.004**/.373	53.3 ± 3.2	.279	65.6 ± 2.7	**.049**/.1	100	.417
	M0	72.2 ± 6.9		83.4 ± 5.5		65.8 ± 7.1		80.9 ± 6.1		91.7 ± 4.5	
WHO grade	1-2 or ungraded	74.9 ± 10.4	.325	91.5 ± 6.5	**.001**/.277	72.9 ± 10.4	**.034**/.698	90.1 ± 7.1	**.002**/.211	97.2 ± 3.7	**.03**/.430
	3-4	70.5 ± 8.6		75.8 ± 7.6		60.3 ± 8.8		73.2 ± 8.6		86.2 ± 7.5	
Histology	ATRT	76.1 ± 21.4	.848	60.6 ± 21.6	**.001/.046**	54.5 ± 22.3	.151	45.2 ± 24.1	**.000/.01**	81.3 ± 24.3	.077
	Others	71.8 ± 7.1		84.1 ± 5.5		66.3 ± 7.1		83.7 ± 5.9	91.7 ± 4.7		
Chemotherapy	None	77.1 ± 1.2	.081	88.0 ± 9.0	.068	72.1 ± 12.7	**.043**/.440	95.3 ± 6.5	**.000/.024**	98.3 ± 3.3	**.043**/333
	Any	70.2 ± 7.8		79.5 ± 6.7		62.6 ± 8.0		74.3 ± 7.6	87.7 ± 6.5		
	PT without chemotherapy	70.8 ± 7.4	.631	82.7 ± 5.9	.543	64.0 ± 7.6	.660	82.5 ± 6.1	.336	93.0 ± 4.5	.112
	Concurrent chemotherapy	77.1 ± 14.1		77.6 ± 14.1		69.8 ± 15.1		69.2 ± 16.3	81.5 ± 14.9		
CSI	No	71.7 ± 7.1	.656	83.8 ± 5.5	**.001**	65.4 ± 7.1	.412	81.2 ± 6.1	.062	90.4 ± 4.9	.756
	Yes	78.6 ± 1.9		63.5 ± 22.1		63.9 ± 21.8		68.9 ± 21	100		

[a] ±2 standard error.

[b] *P*-value for univariate/multivariate analysis (multivariate was performed for variables where univariate *P*-value was ≤.05). Bold values indicate significance.

[c] Only the most significant age threshold on univariate (5 years) was used for multivariate analysis.

Late PT-related ≥G3 toxicity occurred in 19 (8.6%) patients (Table 4). All three G4-5 events were brainstem RN. KM estimate gave a 91.0% (86.3-95.7) late radiation-induced ≥G3 TFS. Univariate analysis showed that age at PT ≤3 years, WHO grade 3 to 4 and chemotherapy were significant predictors for late ≥G3 toxicity (Table 3), whereas CSI was not ($P = .756$).

3.4 | Secondary malignancies

Three SM cases were confirmed (Table 4). Two children diagnosed with posterior fossa ependymoma at <3 years of age developed glioblastoma within the high-dose region, 8 and 10 years after PT, respectively. A third patient was diagnosed with acute myeloid leukemia 51 months after PT.

3.5 | Quality of life

PEDQOL proxy-assessment scores (mean ± SD) for Family Functioning and Global Well-Being were mostly below norm at E1, at 68.63 ± 22.28 (norm = 81.96 ± 17.42) and 65.70 ± 23.55 (norm = 81.02 ± 17.84), respectively. At E7, those scores were close to norm levels, at 78.80 ± 16.22 and 75.67 ± 22.13, respectively. Inversely, Cognition and Social Functioning with Peers scored 73.40 ± 19.08 (norm = 76.57 ± 17.30) and 75.84 ± 16.52 (norm = 79.78 ± 13.83) at E1, but 65.83 ± 21.93 and 65.55 ± 19.97 at E7, respectively. All other parameters were within 6 points of the norm at E1 and at least at similar levels at E7 (Figures 2 and S2).

PEDQOL self-assessment scores were consistently higher than proxy-assessment scores and mostly above norm. Likewise in proxy-assessment, Family Functioning and Global Well-Being scored 69.18 ± 25.13 (norm = 74.94 ± 19.08) and 67.47 ± 28.54 (norm = 74.67 ± 23.74) at E1, but 78.19 ± 19.71 and 76.56 ± 21.94 at E7, respectively. Cognition and Social Functioning with Peers scored 75.94 ± 19.29 (norm = 68.79 ± 17.66) and 75.00 ± 18.81 (norm = 74.34 ± 17.88) at E1, but 67.06 ± 19.81 and 69.73 ± 20.32 at E7, respectively. The domains of autonomy, emotional functioning, body image, and physical functioning are mostly at or up to 12 points above norm at all time points (Figures 2 and S2).

PedsQL data show QoL scores well below norm in all surveyed domains, without clear differences between time points. The total score was 43.9 ± 18.0 (norm = 87.8 ± 8.7) at E1 and 47.3 ± 14.9 at E7 (Figure S3).

4 | DISCUSSION

The SEER registry reports a 73.6% 5-year OS in 11 200 CBTs.[19] A similar 70% to 74% survival rate is found in the Swedish Childhood Cancer registry.[20] The estimated 5-year OS of 79.9% in our study compares well to these data. Mizumoto et al reported a 81.7% 5-year OS in a multicentric cohort of 79 CBTs treated with PT,[21] further demonstrating PT's noninferiority to CRT in terms of tumor control.

In univariate analysis, patients aged ≤5 years showed worse OS and DC (Table 3). This may derive from a higher prevalence of aggressive tumors in this group, as age loses statistical significance for these endpoints after correction for grade, metastasis, chemotherapy use, or CSI, which are proxies for disease aggressiveness. Gender, PT at initial treatment versus at salvage, time from diagnosis to radiation, tumor site, surgical resection extent, number of surgeries, and PT dose ≤54 Gy versus >54 Gy were not found to be significant predictors for any of the selected endpoints, probably due to the histological heterogeneity of the cohort.

Although metastatic patients had significantly worse outcomes (Table 3), the encouraging 53.3% 5-year DFS correlates with findings in extracranial pediatric tumors.[22] Similarly, ATRT histology was an independent adverse risk factor in this study (Table 3), but with a significant proportion of long survivors (5-year OS 45.2%), in line with previous publications.[23,24] This finding further warrants curative approaches in patients with ATRT and select metastatic CBTs. Long-term toxicity concerns justify considering PT. Of note, our patients who received CSI did not show increased ≥G3 toxicity incidence (Table 3).

In all ≥G3 toxicity cases, relevant organs at risk (OARs) were directly adjacent to or within treatment target (Table 4).[25] This illustrates the evident lack of sparing benefit of protons for such located OARs. Hua et al report 14% of hearing loss after photon irradiation in CBTs.[26] Our somewhat lower 10.8% prevalence indicates that PBS-PT may allow better hearing structures sparing, provided they are not abutting/included in the target volume. Of note, chemotherapy was received by all but two patients who presented with ≥G3 toxicity (Table 4) and was a statistically significant risk factor for this endpoint (Table 3).

The 1.4% (three cases, Table 4) rate of ≥G3 brainstem RN from this study matches the 1.3% found by three major pediatric cancer centers using protons,[27] and compares well to photon cohorts where incidence ranged from 1.6-2.5%[28] to 3.7%.[29] Strategies to prevent brainstem RN include the use of volumetric dose constraints.[27] The lower 5.4% rate of late seizures in this cohort compared to Childhood Cancer Survivor Study (CCSS) data[30] may derive from the low RN rate. The 1.8% prevalence of moyamoya disease at the last FU in this series is half the 3.5% reported by Ulrich et al.[31] This as well as the low 1.4% prevalence of RION in this cohort suggest that protons may reach superior toxicity profiles over CRT. Factors influencing RN incidence were investigated by Bojaxhiu et al[32] on a mostly overlapping cohort of children who received cranial PBS-PT.

Late-G3–cognitive impairment was reported in five (2.3%) cases in this study. This very low rate of cognitive decline may be due to the inconsistent reporting of this metric during FU. Olsson et al objectively found mental retardation and/or generally reduced cognitive capacity in 14% of CBTs treated with CRT.[33] Prospective data were warranted to confirm PT's potential improved cognitive outcomes as described by Gross et al[12] and Kahalley et al[34]

The long-term prevalence of pituitary deficiency in CBTs who received cranial CRT was 51.4% in the St. Jude Lifetime Cohort Study[35]

TABLE 4 Characteristics of patients with PT-related late grades 3 to 5 CTCAE_v4 toxicity or secondary tumors

Event	Case[a]	Initial tumor	Sex	Age at PT[b]	Preexisting condition[c]	Chemo	No. of surg.	CSI	RT (Gy)	Type SM/toxicity	Time to event[d]	Dose to area/OAR (Gy)	Overlap with PTV[e]	Status at last FU
G 3-5 Tox	1	Ependymoma IT G3	F	3.0 y	Postop stroke	Yes	2	No	59.4	G5 RN BS	5	RN/BS/BSC Dmax 60/60/59	Full	D (toxicity)
	2	Ependymoma IT G3	F	3.7 y	Tumor ataxia	No	1	No	59.4	G4 RN BS	5	RN/BS/BSC Dmax 60/61/60	Full	NED
	3	ATRT IT G4	F	2.3 y	Postop ataxia	Yes conc.	1	No	54.0	G4 RN BS	12	RN/BS/BSC Dmax 55/56/54	Full	D (unkn.)
	4	Craniopharyngioma ST G1	M	5.6 y	–	No	1	No	54.0	G3 moyamoya	86	Willis Dmean 54, Dmax 56	Full	NED
	5	Ependymoma IT G3	M	2.3 y	–	Yes	2	No	59.4	G3 moyamoya	37	Willis Dmean 40, Dmax 60	Partial	NED
	6	Choroidal plexus Pa ST G3	M	5.2 y	–	Yes	1	No	54.0	G3 moyamoya, G3 cognitive impairment[f]	15	Willis Dmean 44, Dmax 56	Partial	D (disease)
	7	Astrocytoma pilocytic ST G1	F	8.2 y	NF-1	Yes	1	No	46.0	G3 cavernoma	20	MRI images unavailable	–	NED
	8	ATRT ST G4	F	1.4 y	–	Yes conc.	2	No	54.0	G3 epilepsy	44	Temp. lobe L/R Dmax 7/57 [Gy]	No/part.	NED
	9	Ependymoma IT G3	M	3.1 y	–	Yes conc.	2	No	60.0	G3 hearing impairment	10	Cochlea L/R Dmean 7/50	No/part.	NED
	10	Medulloblastoma IT G4	M	2.7 y	–	Yes	2	No	55.8	G3 hearing impairment	67	Cochlea L/R Dmean 36/30	Full/full	NED
	11	Ependymoma IT G3	M	1.1 y	–	Yes	1	No	54.0	G3 hearing impairment	58	Cochlea L/R Dmean 19/47	adj./part.	NED
	12	ATRT IT G4	F	2.7 y	–	Yes conc.	7	No	54.0	G3 hearing impairment	65	Cochlea L/R Dmean 14/53	adj./full	NED

(Continues)

TABLE 4 (Continued)

Event	Case[a]	Initial tumor	Sex	Age at PT[b]	Preexisting condition[c]	Chemo	No. of surg.	CSI	RT (Gy)	Type SM/toxicity	Time to event[d]	Dose to area/OAR (Gy)	Overlap with PTV[e]	Status at last FU
	13	Ependymoma IT G3	M	1.5 y	G1 hearing	Yes	1	No	59.4	G3 hearing impairment	45	Cochlea L/R Dmean 31/53	adj./part.	NED
	14	Ependymoma IT G3	M	8.9 y	–	Yes conc.	1	No	59.4	G3 hearing impairment	38	Cochlea L/R Dmean 6/38	No/adj.	NED
	15	Ependymoma IT G3	M	2.0 y	–	Yes	1	No	59.4	G3 hearing impairment	36	Cochlea L/R Dmean 24/58	adj./full	NED
	16	Choroidal plexus Pa IT G2	F	4.3 y	–	Yes	2	No	54.0	G3 cognitive impairment	24	Hipp. L/R Dmean 18/13	adj./adj.	LF
	17	PNET ST G4	F	2.8 y	–	Yes conc.	1	No	54.6	G3 cognitive impairment	49	Hipp. dose not assessable[g]	-	NED
	18	Choroidal plexus Ca IT G3	M	1.5 y	–	Yes	2	No	54.0	G3 cognitive impairment	72	Hipp. L/R Dmean 53/6	Full/adj.	NED
	19	GCT NS ST	M	9.0 y	–	Yes	1	Yes	54.0	G3 cognitive impairment	89	Hipp. L/R Dmean 51/48	part./part.	NED
2nd tumor	20	Choroid plexus Ca ST G3	F	2.4	–	Yes	2	No	54.0[h]	Acute myeloid leukemia[i]	51	–	NA	D (SM)
	21	Ependymoma IT G2	M	2.4	–	Yes	1	No	59.4	Glioblastoma	126	–	Full	D (SM)
	22	Ependymoma IT G3	M	1.2	–	Yes	1	No	59.4	Glioblastoma	100	–	Partial	D (SM) (surgery)

[a]Arbitrary numbering
[b]Patient age at PT start in years
[c]Relevant to the late event
[d]In months
[e]From area involved by SM/OAR
[f]Cognitive impairment potentially a result of the moyamoya syndrome
[g]Most of R hippocampus resected along with tumor, left hippocampus not individualized due to massive hydrocephalus
[h]36 Gy photon therapy (CRT) before 18 Gy PT
[i]More typically chemoinduced
Abbreviations: adj., adjacent (within 5 mm of PTV); BS , brainstem; BSC, brainstem center; Ca, carcinoma; Chemo, chemotherapy; conc., concomitant; D, dead (cause); F, female; G, grade; Gy(RBE), gray (relative biological effectiveness); Hipp., hippocampus; IT, infratentorial; LF, local failure; M, male; *N*, number; NED, no evidence of disease; NF-1, neurofibromatosis type 1; OAR, organ at risk; Pa, papilloma; part., partially; PTV, planning target volume; RN, radiation necrosis; ST, supratentorial; surg., surgeries; unkn., unknown; y, years

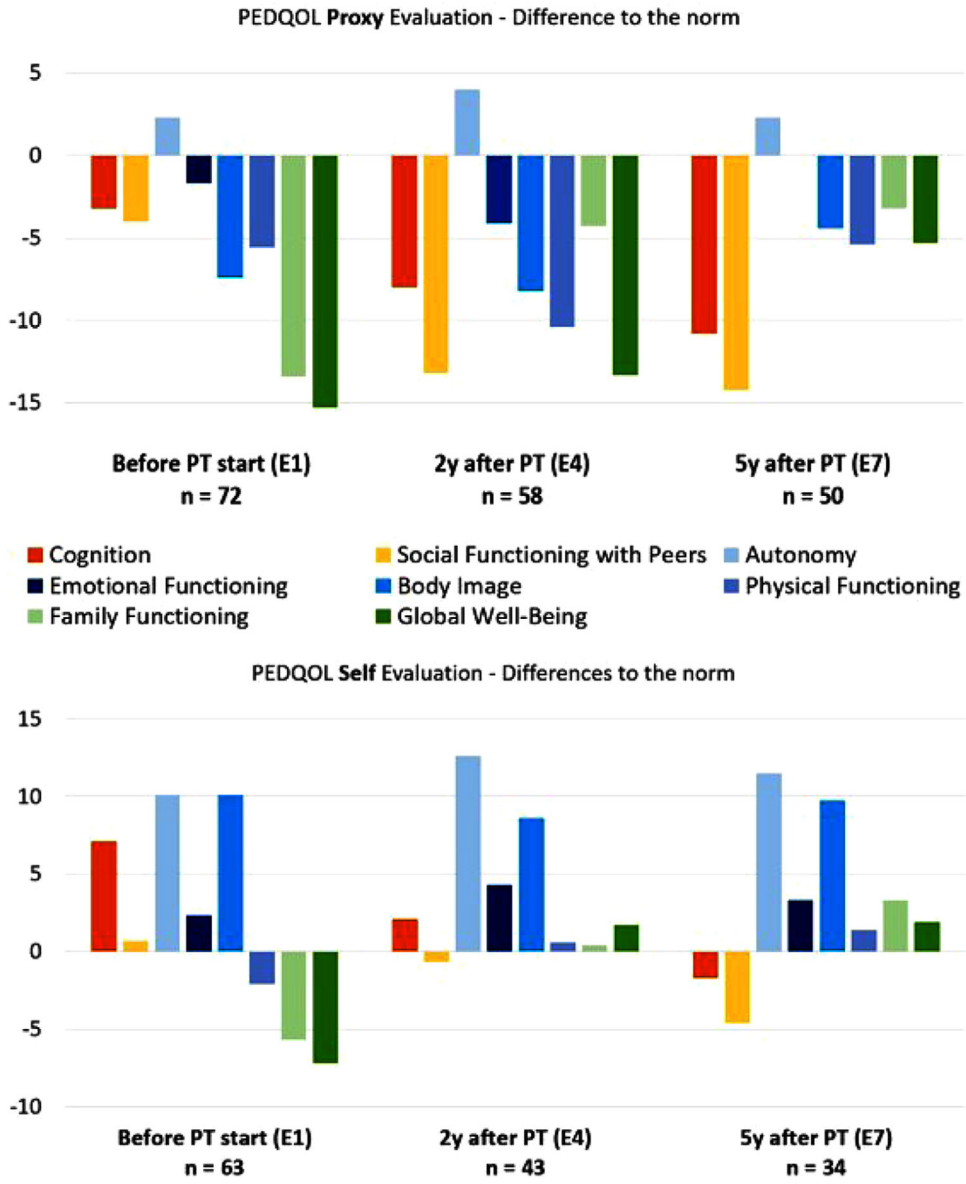

FIGURE 2 Mean score deviations from the norm in PEDQOL Proxy evaluations

Note. A positive value means a higher mean score than in the norm group. Self-evaluation (top) and proxy evaluation (bottom). Baseline (E1) corresponds to proton therapy start. E4 and E7 correspond to 2 and 5 years after proton therapy, respectively. Data for other time points are provided in Figure S2. Abbreviations: *n*, number of patients with available data at this time point (note that not all subscales were completed by all patients/proxies); y, years

and 50% as reported by Shalitin et al.[36] Vatner et al found a 5-year hormone deficiency rate (55.5%) in young patients treated with protons.[37] Overall, our 27.1% prevalence of endocrine deficiency at the last FU stands low in the spectrum of previously reported data, but still represents a significant morbidity burden that may increase with longer FU. Noteworthy, the five cases where irradiation in the hypothalamus region likely caused endocrinopathy illustrate the need for strict sparing of this organ whenever feasible.[37]

Other neurological disorders (typically motor problems, ataxia, and cranial nerve disorders) were frequently reported, similar to CCSS results.[30] Most (4/5) disorders were caused by local tumor invasion or surgical resection procedures; hence the irradiation modality likely has little potential to improve those endpoints. Protocols not only aimed at delaying or deescalating irradiation,[38] but also at optimizing the therapeutic ratio of all treatment modalities are strongly warranted.[39,40]

The 1.4% SM rate is promising, but more FU time is needed to capture this event, which typically occurs decades after treatment.[41] The young age at treatment and the glial nature of the SMs align with previous findings.[42,43]

PEDQOL data showed different rating patterns between proxy and self-assessments. Inversely to parents/caregivers, patients scored QoL

mostly above norm (Figure 2). This is a well-known trend in QoL publications.[44-46]

Cognition and Social Functioning scores were reported more below norm at later time points than before PT (Figure 2), reflecting typical late intellectual impairments and deficits in social adaptation in this diagnosis group.[7] This suggests that PT, although potentially impacting patients less than photons, does not nullify the risk of late cognitive impairment, which has a multifactorial etiology (tumor localization, surgery, irradiation, chemotherapy, patient-specific conditions). Additional strategies are needed to prevent cognitive decline, not limited to but including hippocampal sparing.[47,48]

In contrast, Family Functioning and Global Well-Being were below norm before PT and near-norm values 5 years after PT (Figure 2). This indicates in the broadest sense that limitations (if present) do not negatively influence the patient's emotional experience and coping with everyday life. Kuhlthau et al performed a prospective evaluation of health-related QoL in CBTs treated with protons. They found the different self- and proxy-reported scores still significantly correlated with objective testing and showed a positive global trend.[49] In contrast, CCSS patients reported worse physical function, global distress, and life satisfaction than their siblings.[50] The good overall long-term QoL reported in proton series, including the present, compared to photon-era data suggests a benefit of PT in QoL preservation.

The severe QoL restriction shown by PedsQL questionnaires in patients aged 1 to 4 years (Figure S3) likely stems in these youngest patients' well-known susceptibility for tumor and treatment-related adverse events.[51,52] Although an influence of disease aggressiveness, and therefore treatment intensity, cannot be ruled out here, those results are in line with our finding that patients aged ≤3 years at PT are more vulnerable to high-grade late toxicity (Table 3). This underlines the relevance of multidisciplinary long-term care including psychosocial and/or (neuro)psychological services.

Future perspectives promising more personalized treatments for CBTs undoubtedly include molecular diagnostics. Molecular tumor subgrouping allows for enhanced prognostication and adapted treatment intensity, as demonstrated for patients with medulloblastoma.[53] Similarly, investigating tumor- and constitutive genetic or molecular markers to refine tumor- and patient-specific survival and toxicity outcomes after PT entails great potential and is therefore warranted.

The limitations of this study primarily lie in its retrospective and single-center nature. Its histological heterogeneity limits our capacity to identify specific significant risk factors and to compare tumor-related outcomes with single-histology series. Detailed data on surgical margins, pathologic response to pre-PT chemotherapy, and the level of experience of treating physicians were not consistently available and thus were not included in the analysis. QoL findings go with clinical results in our cohort and correspond to the literature. More data with statistical testing are needed to confirm the observed trends and correlations. Finally, a longer FU time is necessary to assess some of the late toxicity endpoints (SMs, endocrine disorders).

In summary, outcomes of CBTs treated with PBS compare favorably to photon series data. ATRT histology was an independent predictor for distant brain failure and for death, but long-term survivors diagnosed with this brain tumor were also observed. High-grade TFS was excellent (90%). Patients aged <5 years showed worse QoL and toxicity outcomes. Three (1.4%) SMs were observed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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