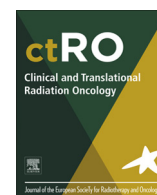


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Original Research Article

Outcomes for pediatric patients with central nervous system germ cell tumors treated with proton therapy

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ABSTRACT

Purpose: We assessed outcomes after proton therapy (PT) for central nervous system germinomas or non-germinomatous germ cell tumors (NGGCTs) in children.

Patients and methods: We identified children with germ cell tumors of the central nervous system who received proton therapy in 2006–2009 and extracted information on tumor response, treatment failures, and toxicity.

Results: Of the 20 identified patients (median age 12 years [range 3–16]), 9 had germinoma and 11 NGGCTs; 19 patients received three-dimensional conformal PT and 1 scanning-beam PT. Fourteen patients had craniospinal irradiation (CSI), 4 had ventricular irradiation that excluded the 4th ventricle, and 2 had whole-ventricle irradiation. All received involved-field boosts. At a median follow-up interval of 5.6 years (range, 0.3–8.2 years), 1 patient with germinoma had an out-of-field failure in the 4th ventricle and 2 with NGGCT died from disease progression after CSI. Rates of local control, progression-free survival, and overall survival at 5 years were 89%, 89%, and 100% for patients with germinoma; corresponding rates for NGGCTs were 82%, 82%, and 82%. The most common late toxicity (9 patients [45%]) was endocrinopathy.

Conclusions: PT for CNS germ cell tumors is associated with acceptable disease control rates and toxicity profiles.

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Introduction

Central nervous system (CNS) germ cell tumors (GCTs) include two general types—germinomatous and nongerminomatous germ cell tumors (NGGCTs). Although treatment has evolved for these tumors over the past 3 decades, significant controversy remains. Radiation therapy, whether photons or protons, is a key component of treatment for either tumor type. Historically, germinomas were treated with craniospinal irradiation (CSI); however, concern for late effects has resulted in CSI being gradually replaced with

whole-ventricular radiation therapy (WVRT). The addition of chemotherapy may allow further reductions in radiation field size and dose [1,2]. Given the relatively unfavorable treatment outcomes for NGGCTs, irradiation of the craniospinal axis is considered standard by many practitioners. However, new studies are exploring more limited radiation fields for this type of tumor as well [3].

Relative to photon-based radiation, particle therapy such as proton beam therapy (PBT) can improve sparing of normal tissues [4–6]. Dosimetric comparisons suggest that PBT should reduce adverse effects for both germinomas and NGGCTs. However, clinical experience with PBT for such tumors is limited. We sought to assess tumor response, treatment failures, and toxicity among children treated for CNS GCTs at The University of Texas MD Anderson Cancer Center Proton Therapy Center (Houston, TX).

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Patients and methods

Patient eligibility

Inclusion criteria were (1) a diagnosis of isolated CNS GCT based on imaging findings, tumor markers, or histologic confirmation; (2) age ≤ 18 years at time of PBT; and (3) receipt of definitive PBT at the Proton Therapy Center from 2006 through 2009. All patients were enrolled in a prospective study of proton therapy for pediatric malignancies approved by the institutional review board. Of the 24 patients initially identified, 4 were excluded who were treated for recurrent disease after previous photon therapy at other facilities. The remaining 20 patients comprise the subject of this report.

Tumor classification and staging

CNS GCTs were classified according to the World Health Organization system [7,8]. Briefly, elevated levels of tumor markers in serum or cerebrospinal fluid (CSF; alpha-fetoprotein [AFP] level >10 ng/dL or institutional norm, or beta-human chorionic gonadotropin [β -HCG] level >100 mIU/mL) indicated NGGCTs. Extent of disease was evaluated with brain and spine magnetic resonance imaging [MRI] and CSF cytology. When more than 1 lesion, only the diameter of the single largest primary lesion was recorded as the baseline target lesion size. Primary lesion location was recorded as pineal, suprasellar, bifocal, or disseminated. Disseminated disease was defined by imaging or surgical evaluation (or both) as the presence of: more than 1 intracranial tumor focus (excluding bifocal disease alone); leptomeningeal spread; spinal metastases; or tumor cells in the CSF. Surgical interventions were assessed by reviewing operative and radiology reports and categorized as gross total resection (GTR; complete excision without residual disease); subtotal resection (STR; residual disease evident after resection attempt); or biopsy/shunt placement (resection not attempted).

PBT treatment planning

Treatment plans were based on computed tomography (CT) simulation with subsequent registration to volumetric MRI scans to facilitate target volume delineation. Two patients received WVRT to the entire ventricular system (right and left lateral, third, and fourth ventricles, with or without prepontine cistern); 4 received WVRT excluding the fourth ventricle (WVRT– [minus] 4th); and 14 patients received CSI encompassing the entire cranium, treated by right posterior oblique and left posterior oblique beams, and multiple spinal fields defined by posterior–anterior beams [9]. Proton beam energies ranged from 160 MeV to 200 MeV. CSI field junctions were shifted to minimize the risk of potential overlap. All patients received sequential involved-field boosts. Gross tumor volume (GTV) was defined as the tumor bed and residual disease, contoured from the pre-chemotherapy images with adjustment for shifts after surgery or chemotherapy. A 0.5–1.0-cm margin for microscopic disease was added, as determined by the treating physician or per protocol, to form the clinical tumor volume (CTV), with adjustment for anatomic boundaries. The total prescribed dose was in Gy(RBE), using a relative biologic effectiveness (RBE) value of 1.1 [10].

Diagnosis and response to treatment

Date of diagnosis was defined as the date of definitive biopsy or, if no biopsy performed, the date of the first diagnostic MRI and tumor marker measurement. Follow-up interval was calculated from date of PBT completion until last known contact. Measurable

target lesions (≥ 10 mm) at baseline and their subsequent response to treatment were assessed with the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1 [11].

Toxicity

Information on tumor- and treatment-related morbidity was extracted from multidisciplinary clinical evaluations, laboratory values, and imaging. Treatment-induced toxicity was evaluated prospectively with the Common Toxicity Criteria for Adverse Events, version 4.0. Acute toxicity was that appearing <90 days from the initiation of treatment; ≥ 90 days was considered late. Endocrinopathies were defined as deficiencies confirmed by laboratory screening and requiring supplementary medication. Panhypopituitarism was diagnosed by the primary clinician as a deficiency of >3 anterior pituitary hormones. Visual field and visual acuity deficits were recorded if physical or ophthalmologic exams showed declines from baseline. Vascular toxicity was reported if symptoms correlated with vasculopathy on cranial imaging. Hypothalamic dysfunction was diagnosed by the primary clinician on the basis of several related comorbidities, such as thermoregulation dysfunction, behavior disorders, emotional lability, hyperphagia, morbid obesity, sleep disturbances, autonomic instability, and metabolic syndrome.

Statistical analysis

Patient, tumor, and treatment characteristics were evaluated with descriptive statistics. Categorical data were analyzed for non-random associations with Pearson's χ^2 test (Fisher's exact test used if <5 values per cell). Wilcoxon's rank-sum tests were used to compare outcomes between two independent groups with continuous data. Overall survival (OS) was calculated from date of diagnosis until date of last known contact or death. Progression-free survival (PFS) was calculated from date of completion of PBT until date of tumor progression or recurrence, last known contact, or death. The Kaplan–Meier method was used to calculate OS and PFS times. Two-sided P values of <0.05 were considered statistically significant. Analyses were performed with JMP software (version 10.0.2; SAS Institute Inc.).

Results

Patient and treatment characteristics

Twenty patients met criteria for this analysis; patient, disease, and treatment characteristics are summarized in Table 1. Median age at initial diagnosis was 12.0 years (range, 3.4–16.1 years). Seven patients (35%) initially had evidence of disseminated disease (4 with gross intracranial seeding, 4 with positive CSF cytologic findings, and 1 with infiltrating intra-axial extension >1 cm beyond tumor). No patients had initial gross seeding of the spinal canal.

Seventeen patients (85%) had surgical intervention at diagnosis. Of these, 3 had initial STR to relieve compressive symptoms before definitive chemoradiotherapy; 1 with a solitary pineal mixed NGGCT (patient 10) developed asymptomatic cyst growth during chemotherapy and underwent cyst decompression to reduce the boost volume before PBT was begun; and 1 had growing teratoma syndrome (patient 18), once during chemotherapy and once during radiation therapy, both requiring emergent debulking procedures. Second emergent surgery was a GTR followed by completion of the planned chemoradiotherapy regimen, with no evidence of recurrence at 5.2 years follow-up.

Four patients with germinoma received definitive PBT, and the other 5 received induction chemotherapy followed by PBT. Two patients (10%) were ≤ 5 years old at the time of PBT. PBT was

Table 1
Patient, disease, and treatment characteristics.

Characteristics	Value or no. of patients (%)			P Value
	All patients [n = 20]	Patients with germinoma [n = 9]	Patients with NGGCT [n = 11]	
Follow-up, time, months				
Median (range)	58.2 (3.7–89.9)	62.0 (49.9–89.9)	55.3 (3.7–77.6)	0.184
Age at RT, years				
Median (range)	12.5 (4.0–16.4)	12.5 (7.9–16.4)	12.4 (4.0–14.1)	0.648
Tumor size, cm				
Median (range)	3.0 (0.9–6.0)	2.9 (0.9–5.5)	3.2 (2.0–6.0)	0.323
Sex				
Male	11 (55)	5 (56)	6 (55)	1.000
Female	9 (45)	4 (44)	5 (45)	
Race/ethnicity				
Asian	2 (10)	0 (0)	2 (18)	0.303
African American	2 (10)	2 (22)	0 (0)	
Hispanic	4 (20)	1 (11)	3 (27)	
Caucasian	12 (60)	6 (67)	6 (55)	
Tumor location				
Suprasellar	5 (25)	2 (22)	3 (27)	0.240
Pineal	8 (40)	3 (33)	5 (45)	
Bifocal	1 (5)	1 (11)	0 (0)	
Disseminated	6 (30)	3 (33)	3 (27)	
Presenting symptoms				
Hydrocephalus	13 (65)	5 (56)	8 (73)	0.642
Visual symptoms	16 (80)	8 (89)	8 (73)	0.591
Endocrinopathy	10 (50)	5 (56)	5 (45)	1.000
Initial surgical intervention				
None	3 (15)	0 (0)	3 (27)	0.248
Biopsy and/or shunt	14 (70)	8 (89)	6 (55)	
STR	2 (10)	1 (11)	1 (9)	
GTR	1 (5)	0 (0)	1 (9)	
Induction chemotherapy				
Yes	16 (80)	5 (56)	11 (100)	0.026
No	4 (20)	4 (44)	0 (0)	
Primary radiation field				
WVRT ± 4th Ventricle	6 (30)	5 (56)	1 (9)	0.050
CSI	14 (70)	4 (44)	10 (91)	
Radiation dose, Gy(RBE)				
Median (range)	52.2 (30.0–54.0)	45.0 (30.0–45.0)	54.0 (54.0–54.0)	<0.001

Abbreviations: NGGCT, nongerminomatous germ cell tumor; RT, radiation therapy; STR, subtotal resection; WVRT (–4th), whole-ventricular radiotherapy (excluding the fourth ventricle); CSI, craniospinal irradiation.

delivered with passive scatter techniques to 19 patients and with scanning-beam techniques to 1 patient (patient 9). The dose per fraction was 1.5 Gy(RBE) or 1.8 Gy(RBE).

Outcomes

Median follow-up time for entire cohort was 5.6 years (range, 0.3–8.2 years) with a 5-year local control, PFS, and OS rates of 85%, 85%, and 90%. Germinoma patients had a median follow-up time of 5.5 years (range, 4.2–8.2 years) with 5-year PFS and OS rates of 89% and 100%. NGGCTs patients had a median follow-up time of 5.8 years (range, 0.3–7.9 years; 2 patients died within 6 months follow-up), with 5-year PFS and OS rates of 82% and 82%. Two patients were lost to follow-up at 5.1 years and 4.3 years; after their care was transferred to other facilities. Details of treatment characteristics and outcomes are given in Table 2.

At last follow-up, no evidence of active disease was present in all 9 germinoma patients and in 8 (73%) of the NGGCT patients. All patients without tumor progression had normalization of tumor markers after chemotherapy, including 2 patients with stable radiographic disease.

Four patients had disease progression, 3 within 13 months of PBT; 2 of these events directly contributed to the 2 deaths reported (patients 15 and 19). The first failure (patient 8) had localized

suprasellar germinoma (pure germinoma histology with CSF β -HCG [77 mIU/mL]), initially treated with chemotherapy followed by WVRT excluding the 4th ventricle. Disease progression occurred 12.7 months after PBT, with a “drop” metastasis in the 4th ventricle (at the inferior end of previously treated 30 Gy isodose line). Salvage therapy was 36 Gy CSI, given with intensity modulated photon-based RT, which resulted in remission throughout remaining 4.9 years follow-up.

The second failure (patient 15) had a localized pineal NGGCT (initial serum AFP >3000 ng/dL) with refractory disease (tumor growth) after initial chemotherapy and CSI. Salvage treatment included GTR followed by high-dose chemotherapy with autologous stem-cell transplant then 13 cis-retinoic acids. Despite stable minimal residual disease throughout follow-up, biochemical failure (increased AFP) occurred at 2.1 months follow-up. Patient died at 3.7 months follow-up.

The third failure (patient 19) had a localized pineal NGGCT (initial serum AFP 551 ng/dL) with no residual tumor evident on imaging after initial chemotherapy and CSI. At 1-month follow-up, MRI revealed several new brain and spine lesions. High-dose chemotherapy was begun, but a severe infection developed before the planned transplant. Patient died at 6 months follow-up.

The fourth failure (patient 10) had a pineal NGGCT (pure germinoma on biopsy, but with elevated serum and CSF AFP

Table 2
Treatment characteristics and outcomes for 20 patients with central nervous system germ cell tumors.

Presentation				Surgery		Chemotherapy		Radiation therapy			Outcomes			
Pt #	Sex	Age (yrs)	Tumor Type	Location	Initial resection	Type (cycles)	Response	Initial volume	Dose [Gy(RBE)]			Response (3 mo f/u)	Progression (Salvage)	At last follow-up
								Initial	Boost	Total				
1	F	11	Germinoma	Suprasellar	Biopsy	—	—	WVRT–4th	25.2	16.2	41.4	CR	No	NED
2	M	13	Germinoma	Pineal	Biopsy*	—	—	WVRT–4th	25.2	19.8	45.0	CR	No	NED
3	M	16	Germinoma	Pineal	Biopsy*	CE(2) + PC(2)	PR	WVRT–4th	21.6	18.0	39.6	CR	No	NED
4	M	12	Germinoma	DD	Biopsy	CE(2) + PC(2)	PR	CSI	21.0	9.0	30.0	CR	No	NED
5	F	8	Germinoma	DD	STR	CE(1)**	PR	CSI	21.6	18.0	39.6	CR	No	NED
6	M	15	Germinoma	Bifocal	Biopsy	—	—	CSI	21.6	23.4	45.0	CR	No	NED
7	F	16	Germinoma	DD	Biopsy	CE(2)	CR	CSI	21.6	23.4	45.0	NED	No	NED
8	F	8	Germinoma	Suprasellar	Biopsy*	ICE(6)	PR	WVRT–4th	23.4	21.6	45.0	CR	Yes (IMRT)	NED
9	M	9	Germinoma	Pineal	Biopsy	—	—	WVRT†	23.4	21.6	45.0	CR	No	NED
10	M	12	NGGCT	Pineal	Biopsy*	ICE (6)	SD	CSI	36.0	18.0	54.0	PR	Yes (chemo)	Alive w/ disease
11	M	12	NGGCT	Pineal	Shunt	ICE (6)	SD	CSI	30.6	23.4	54.0	SD	No‡	NED
12	F	13	NGGCT	Suprasellar	Shunt*	ICE (6)	CR	CSI	30.6	23.4	54.0	NED	No	NED
13	M	14	NGGCT	DD	Biopsy	ICE (6)	PR	CSI	36.0	18.0	54.0	CR	No	NED
14	M	14	NGGCT	Pineal	Shunt	ICE (6)	PD	CSI	30.6	23.4	54.0	SD	No	NED
15	M	12	NGGCT	Pineal	Biopsy*	ICE (3)**	SD	CSI	36.0	18.0	54.0	SD	Yes§	Deceased
16	F	14	NGGCT	DD	—	ICE (6)	PR	CSI	30.6	23.4	54.0	CR	No	NED
17	F	4	NGGCT	Suprasellar	STR	PEI (4)**	CR	WVRT	21.6	32.4	54.0	NED	No	NED
18	F	5	NGGCT	Suprasellar	STR/GTR*	ICE (6)	NED	CSI	36.0	14.4	50.4	NED	No	NED
19	M	13	NGGCT	Pineal	—	ICE (6)	CR	CSI	30.6	23.4	54.0	NED	Yes (none)	Deceased
20	F	9	NGGCT	DD	—	ICE (6)	PR	CSI	36.0	18.0	54.0	CR	No	NED

Abbreviations: NGGCT, nongerminomatous germ cell tumor; DD, disseminated disease; STR, subtotal resection; GTR, gross total resection; CE, carboplatin, etoposide; PC, cisplatin, cyclophosphamide; ICE, ifosfamide, carboplatin, etoposide; PEI, cisplatin, etoposide, ifosfamide; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; NED, no evidence of active disease; WVRT–4th, whole-ventricular radiotherapy (excluding the fourth ventricle); CSI, craniospinal irradiation; IMRT, intensity-modulated (photon) radiation therapy.

* Additional surgical interventions before radiation therapy included shunt placement, additional biopsy, or both.

** Chemotherapy-related toxicity prevented completion of additional planned cycles.

*** Last two of four cycles consisted of high-dose PEI followed by autologous stem cell rescue.

† Patient received intensity-modulated proton therapy (IMPT); all others received 3D-conformal proton therapy.

‡ Cyst growth requiring shunt placement for symptomatic hydrocephalus at 5.5 years follow-up; no change in solid tumor and tumor markers remained normal throughout follow-up.

§ Refractory to chemoradiotherapy; salvaged with gross total resection, high dose chemotherapy (temozolomide, thiopeta, carboplatin), and autologous stem cell rescue followed by 13 cis-retinoic acid.

levels), treated with initial chemotherapy and CSI. Local tumor recurrence with abnormal serum and CSF AFP levels occurred at 7.6 years follow-up. At time of this report, patient was receiving additional chemotherapy, with planned consolidative myeloablative chemotherapy and autologous stem-cell transplant.

Toxicity analyses

Acute-onset radiotherapy-related toxicity requiring medical intervention included brain edema ($n = 4$) and somnolence syndrome ($n = 1$), all of which resolved with steroids. One patient treated with CSI reported odynophagia during PBT that required pain medication. No grade 3 or 4 acute toxicities were recorded.

At initial presentation, 5 patients had hypothalamic dysfunction, with panhypopituitarism and primary suprasellar tumors that extensively involved the hypothalamus. No other patients developed documented hypothalamic dysfunction throughout treatment or follow-up.

At initial presentation, only patients with suprasellar tumor involvement ($n = 10$) had ≥ 1 endocrinopathies ($P < 0.001$), including hypothyroidism ($n = 10$), hypogonadism ($n = 7$), diabetes insipidus ($n = 8$), adrenal insufficiency ($n = 6$), and growth hormone (GH) deficiency ($n = 5$). PBT dose–volume review revealed a median hypothalamic–pituitary mean dose of 43.8 Gy(RBE) (range, 18.0–53.7 Gy(RBE)) and a median thyroid mean dose of 0.0 Gy (range, 0.0–0.2 Gy).

All 10 patients with panhypopituitarism at last follow-up also had panhypopituitarism before PBT; 7 at initial presentation and

3 shortly after the initial surgical intervention. All 11 patients with diabetes insipidus at last follow-up were diagnosed prior to PBT.

Nine patients were diagnosed with new-onset post-treatment endocrinopathies; 7 with GH deficiency alone, 1 with GH deficiency and hypothyroidism (hypothalamic–pituitary mean dose of 38 Gy), and 1 with primary/secondary hypogonadism attributable to both chemotherapy and PBT (hypothalamic–pituitary mean dose of 48 Gy). GH deficiency at last follow-up was associated only with suprasellar tumor involvement ($P = 0.004$); no association was found with total dose ($P = 0.685$) or hypothalamic–pituitary mean dose ($P = 0.808$).

Sixteen patients (80%) had documented visual symptoms or signs at initial presentation, including 10 with dorsal midbrain syndrome, 5 with visual field or visual acuity deficits (all had primary suprasellar tumor involvement of the optic apparatus), and 7 with diplopia secondary to cranial nerve VI palsy. Only 1 patient experienced improvement of visual field and acuity deficits which occurred after initial STR.

Two patients developed new-onset visual symptoms with acuity deficits within 1–3 years after PBT; both presented with pineal tumors, dorsal midbrain syndrome, diplopia secondary to cranial nerve VI palsy, and hydrocephalus requiring shunt placement. Both patients initially had 20/20 visual acuity bilaterally with subsequent worsening in visual acuity ($\sim 20/70$) during follow-up. One patient developed bilateral optic neuritis, most likely secondary to a yet-undefined autoimmune disease, and the other developed unilateral optic atrophy. Neither patient had additional surgery, chemotherapy, or radiation after PBT. Treatment plan review of

both patients revealed bilateral optic nerve maximum doses were <39 Gy, and optic chiasm maximum doses of 31.4 Gy and 51.2 Gy (corresponding mean doses 26.8 Gy and 40.6 Gy). For comparison, the 13 patients without visual deficits during the course of disease had a median optic chiasm maximum dose of 51.2 Gy (range, 22.1–54.2 Gy) and a median optic nerve maximum dose of 37.5 Gy (range, 7.5–53.8 Gy).

Although formal neurocognitive testing was not done consistently, 14 patients were reported to be doing well in school or to have active careers at last follow-up. One patient was diagnosed with a late-onset seizure disorder at 4 years follow-up, but this patient had also experienced multiple falls with head injuries, attributed to gait ataxia caused by chemotherapy-induced neuropathy.

Patient 18, who had a large (5.2-cm) 3rd ventricle suprasellar NGGCT (mature and immature teratoma involving bilateral thalamic and basal ganglia) was diagnosed with Moyamoya disease after the sudden appearance of choreoathetoid movement of the right arm at 3 years after multiple surgical interventions (STR, GTR, and two shunts) followed by chemoradiotherapy (at 5 years of age). This patient's choreoathetoid movement resolved without intervention, and the vasculopathy has been stable without requiring intervention other than prophylactic daily aspirin.

Discussion

Our findings demonstrate that PBT can provide favorable clinical outcomes for germinomas and NGGCTs, with favorable late toxicity profiles. For germinomas, our 5-year OS rate of 100% and PFS rate of 89% were consistent with recent photon-based studies, with reported 5-year OS rates of >90% and PFS ~90% [12–15]. Corresponding rates for NGGCT (OS 82% and PFS 82%) were also consistent with recent photon-based studies, with 5-year OS rates of 70–93% and PFS 40–84% [3,16–18]. These results suggest that the high dose conformality profile of PBT does not compromise long-term local control or OS relative to photon-based RT to similar treatment volumes. Our results are similar to those of a 22-patient experience at Massachusetts General Hospital [5] in which OS and PFS rates were 100% and 95% at a median follow-up time of 28 months.

Despite efforts to minimize the use of RT, several groups have shown that chemotherapy alone has poorer local control outcomes [21,22] and that smaller RT target volumes are associated with marginal failures in many subsets of patients [12,15–21,23,24]. In our study, 4 germinoma patients received PBT to the whole-ventricle system excluding the 4th ventricle; of these, 1 patient with an initial mild elevation in β -HCG (77 mIU/mL) had a recurrence within the 4th ventricle at 1.1 years follow-up. These results support the routine use of comprehensive ventricular irradiation.

The dose distribution of proton therapy has been shown in many dosimetric comparisons to be superior to that obtained with conformal photon-based RT techniques [4–6]. Macdonald et al. recently demonstrated this benefit for pediatric patients with CNS GCT, reporting sparing of the brain and temporal lobes with PBT in comparison to photon-based therapy [5]. Although patients who receive PBT radiation therapy likely benefit from reductions in radiation dose and volume, currently no study has comprehensively and prospectively described neurocognitive outcomes for patients who receive proton therapy for GCTs [19,25,26]. However, initial studies do suggest the potential for improved quality of life following proton therapy in comparison to photon treatment [27].

Hypothalamic dysfunction, endocrinopathy and visual deficits in children with CNS GCTs are commonly linked to initial tumor involvement, surgical manipulation, or both [19,20]. Indeed, all hypothalamic dysfunction and most endocrinopathies in our study

were diagnosed before the PBT was begun. GH deficiency is the most common RT-related hormone deficiency, but can also result from surgical manipulation, location of intracranial tumors, and the hypothalamic-pituitary RT dose [20,28–30]. In our study, GH deficiency was the most common new-onset endocrinopathy after PBT, and most patients had suprasellar tumor involvement and therefore received the total planned RT dose to the hypothalamic-pituitary axis. GH deficiency has been reported after doses as low as 18 Gy; therefore, GH deficiency was not unexpected.

A quarter of patients in the current study presented with visual field or acuity deficits at initial presentation, which were related to suprasellar tumor involvement of the optic apparatus. For photon therapy, few radiation-induced optic neuropathies have been found at treatment doses of \leq 54 Gy in 1.8-Gy fractions [31]. In our study, two patients developed new-onset visual deficits within 1–3 years of completing PBT. These patients had no additional trauma or therapies to explain the visual deficits. However, one of the patients was diagnosed with an unidentified autoimmune disorder that may have accounted for several episodes of bilateral neuroretinitis. Neither of these patients had received >52 Gy to the optic apparatus according to their treatment plans, nor did any beams have distal edges placed within the chiasm or nerve. Further, several other patients with similar or greater doses to the optic apparatus did not have any visual deficits throughout the entire course of disease or follow-up.

One patient who was 5 years old at the time of PBT was later diagnosed with Moyamoya syndrome 3 years after PBT. A rare complication of childhood intracranial cancers, Moyamoya syndrome has been linked with RT, especially when children are younger than 5 at time of treatment [32]. Young children are thought to be more susceptible to surgical or radiation injury because their vasculature is in its greatest phase of growth [33].

No secondary malignancies were found in this study, although further follow-up would be needed to elicit long-term risks relative to those from photon-based RT [18,33,34].

This study did have limitations common to single-institution reports of rare pediatric diseases, including small sample size. Treatment factors including chemotherapy use, target volume delineation and dose prescription also varied considerably. Lastly, objective standardized neurocognitive measures at scheduled intervals would be needed to further clarify the absolute benefit of PBT with regard to sparing the normal brain tissue and, correspondingly, improving neurocognitive outcomes.

Conclusion

Using PBT to treat pediatric GCTs resulted in acceptable long-term local control, OS, and toxicity outcomes compared with photon-based RT.

Conflict of interest

The authors declare no conflicts of interest.

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