

ORIGINAL ARTICLE



Risk of brainstem necrosis in pediatric patients with central nervous system malignancies after pencil beam scanning proton therapy

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ABSTRACT

Background: Radiation therapy (RT) plays an important role in management of pediatric central nervous system (CNS) malignancies. Centers are increasingly utilizing pencil beam scanning proton therapy (PBS-PT). However, the risk of brainstem necrosis has not yet been reported. In this study, we evaluate the rate of brainstem necrosis in pediatric patients with CNS malignancies treated with PBS-PT.

Material and methods: Pediatric patients with non-hematologic CNS malignancies treated with PBS-PT who received dose to the brainstem were included. All procedures were approved by the institutional review board. Brainstem necrosis was defined as symptomatic toxicity. The actuarial rate was analyzed by the Kaplan Meier method.

Results: One hundred and sixty-six consecutive patients were reviewed. Median age was 10 years (range 0.5–21 years). Four patients (2.4%) had prior radiation. Median maximum brainstem dose in the treated course was 55.4 Gy[RBE] (range 0.15–61.4 Gy[RBE]). In patients with prior RT, cumulative median maximum brainstem dose was 98.0 Gy [RBE] (range 17.0–111.0 Gy [RBE]). Median follow up was 19.6 months (range, 2.0–63.0). One patient who had previously been treated with twice-daily radiation therapy and intrathecal (IT) methotrexate experienced brainstem necrosis. The actuarial incidence of brainstem necrosis was 0.7% at 24 months (95% CI 0.1–5.1%).

Conclusion: The rate of symptomatic brainstem necrosis was extremely low after treatment with PBS-PT in this study. Further work to clarify clinical and dosimetric parameters associated with risk of brainstem necrosis after PBS-PT is needed.

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Introduction

Primary malignancies of the central nervous system (CNS) are the most common solid tumors in pediatric patients, comprising approximately 18% of all cancer diagnoses [1]. Radiation therapy plays a central role in the management of these patients but is associated with a wide range of late toxicities including secondary malignancy, neurocognitive deficits, damage to neuroendocrine and sensory organs, and psychosocial impairments [2–4]. Many dosimetric series have demonstrated decreased doses to critical normal structures using proton therapy (PT) and early clinical data suggest excellent clinical outcomes in patients treated with PT [5–17].

The relative biological effectiveness (RBE) of proton as compared to photon radiation is on average 1.1 for conventional fractionation. However, the RBE may differ by location within the Bragg peak, and increase to 1.2 or 1.3 at the distal end of the spread-out Bragg peak (SOBP) when using passive scatter proton therapy [18]. Using stringent dosimetric constraints and planning techniques, more recent series using passive scatter proton therapy have demonstrated rates of

grade 2 and higher brainstem necrosis from 2.4–6.7% at 2.8–3.0 years [12,19–21].

Many centers are now utilizing pencil beam scanning proton therapy (PBS-PT). PBS-PT offers significant dosimetric advantages compared to passive scatter proton therapy. In particular, PBS-PT allows for sparing of normal tissues proximal to the target and use of intensity modulation to increase dose conformality [22]. Use of PBS-PT may further alter the RBE [23,24]. Currently, there is no literature on clinical rates of brainstem necrosis after treatment with PBS-PT. In this study, we evaluate the rate of symptomatic brainstem necrosis after PBS-PT for pediatric patients with CNS malignancies.

Material and methods

Between 2012 and 2018, pediatric patients ≤ 21 years with non-hematologic CNS malignancies treated at the Roberts Proton Center at the University of Pennsylvania and Children's Hospital of Philadelphia with PBS-PT were enrolled

onto an institutional-review board approved registry allowing for prospective collection of demographic and treatment data.

Patients who received no radiation dose to the brainstem were excluded, as were patients with follow-up <6 weeks. Brainstem necrosis was defined according to standards described by Indelicato and colleagues, including (1) new or progressive symptoms and/or signs after irradiation involving motor weakness or palsies of cranial nerves V–VII or IX–XII with (2) corresponding radiographic abnormalities within the brainstem and (3) absence of local disease progression [20].

Demographic characteristics including age and sex, tumor histology and subsite, use and type of chemotherapy, surgery, and radiation dose were abstracted from the electronic medical record. After completion of radiation therapy, patients were followed by the pediatric oncology and/or radiation oncology team at 3 to 6-month intervals either at our institution or the referring institution for patients living remotely. For the latter group, follow-up data were obtained from the referring institution.

Patients were simulated supine with Aquaplast mask immobilization. Patients were individually evaluated for ability to tolerate treatment without sedation by the physician and child life specialists and those unable to comply were simulated and treated with general anesthesia. Computed tomography (CT) scans were obtained at 1.5 mm interval slices (Siemens Sensation and/or Philips GEMINI TF). All images were transferred into Eclipse planning system version 11.0 (Varian Medical Systems, Palo Alto, CA).

The simulation CT was used for plan optimization and dose calculation in all cases. All proton plans were delivered from an energy-degraded 230 MeV cyclotron (IBA Systems, Leuven, Belgium). For shallow targets, a 7.5 cm range shifter or U-shaped bolus of 6.2 cm water equivalent thickness was applied in the beam path in order to further reduce the minimum beam energy of 100 MeV available at our institution.

For focal and craniospinal (CSI) boost treatments PBS-PT plans were single-field uniform dose (SFUD) in combination with up to 20% intensity-modulated proton therapy (IMPT) [25,26]. Single field optimization (SFO) was used for the SFUD plans and multi-field optimization (MFO) for the IMPT plans. For both SFUD and IMPT plans, a PBS target volume (PBSTV) was created from the CTV. In order to create the PBSTV, a 3 mm uniform expansion from CTV was created in all dimensions except for the beam direction, where 3.5% of each beam range was used to correct for uncertainties associated with CT imaging and an additional 1 mm was added to correct for uncertainties in beam calibration. The average range margin applied was 5 mm. Two to 3 fields per plan were optimized to cover the PBSTV and avoid dose to the organs at risk (OARs). Beams with the range ending in the same location and heavily weighted spots next to OARs were not used. A PTV was defined as a 3 mm geometric margin from the CTV for dose recording and reporting purposes per ICRU78 [27]. Daily imaging guidance was performed with kilovoltage (KV) imaging, allowing for a setup uncertainty of less than 3 mm.

Table 1. Institutional dose constraints.

OAR	Dose Constraint
Brainstem	Maximal dose 60.0 Gy[RBE] V54.0 Gy[RBE] ≤ 95%
Cochlea	Maximal dose 35.0 Gy[RBE] Mean 30.0 Gy[RBE]
Eye	Maximal dose 45.0 Gy[RBE]
Lacrimal Gland	Mean 30.0 Gy[RBE]
Lens	Maximal dose 7.0 Gy[RBE]
Optic Chiasm	Maximal dose 54.0 Gy[RBE]
Optic Nerve	Maximal dose 54.0 Gy[RBE]
Parotid gland	Maximal dose 40.0 Gy[RBE] Mean dose 26.0 Gy[RBE]
Spinal Cord	Maximal dose 50.0 Gy[RBE] V45.0 Gy[RBE] ≤ 90%
Temporal Lobe	Maximal dose 54.0 Gy[RBE] Mean dose 25.0 Gy[RBE]

OAR: organ at risk; V54.0 Gy[RBE]: volume receiving 54.0 Gy[RBE]; V45.0 Gy[RBE]: volume receiving 45.0 Gy[RBE].

CSI was planned as previously described [28]. Briefly, plans consisted of opposed lateral cranial fields, and 1 to 3 orthogonal posterior spine fields based on length of target volume. The physician-defined CTV contained the entire brain and thecal sac, extending anteriorly at the level of the eye to cover the optic nerves and cribriform plate. For patients less than 15 years of age, the CTV included the entire vertebral body. A PBSTV was created from the CTV with a 3 mm expansion in all directions except for the beam direction for which the expansion was calculated based on distal range uncertainties as above. A volumetric gradient dose optimization method was used in planning the prescribed dose to the PBSTV. A planning target volume (PTV) was created as a 3 mm uniform expansion from the CTV and used for plan evaluation and dose reporting only. Daily KV images of each field were obtained prior to treatment.

The brainstem was defined as the midbrain, pons, and medulla extending cranially from the inferior edge of the third ventricle and optic tracts and inferiorly to the foramen magnum. Target coverage was prioritized in cases where the target volume encompassed or was adjacent to a non-critical OAR. Cone down volumes were used when target coverage resulted in excess dose to critical structures including the brainstem, spinal cord, and optic structures (Table 1). Dose to the brainstem was extracted from the dose-volume histogram (DVH).

Calculation of cumulative doses from prior radiotherapy courses was performed with absolute dose from the combination of all plans delivered to the patient in the treatment planning software. For one patient whose initial plan could not be re-created, doses were estimated from the DVH of prior treatment fields. In order to determine the lowest possible doses delivered to the brainstem that may have resulted in toxicity, in this case, the minimum dose to the brainstem from the first course was added to the dosimetric parameter of interest from the second course. No modifications of dose were made in order to account for normal tissue repair over time or altered fractionation. Actuarial rate of brainstem necrosis was analyzed by the

Kaplan Meier method. Patients were censored at the time of death or last follow-up.

Results

One hundred and sixty-six consecutive patients were treated with PBS-PT for primary CNS malignancies during the study period specified (Table 2). Median follow-up was 19.6 months (range, 2.0–63.0). Median patient age was 10 years (range 0.5–21.0 years). The most common histologies were astrocytoma (26%), medulloblastoma (23%), and ependymoma (16%). Tumors were generally equally distributed between the supratentorium and infratentorium. Four patients (2.4%) had a prior course of photon ($n=2$) or proton ($n=2$) radiation. Of the entire population studied, 135 (81%) had >50.4 Gy[RBE] cumulative dose to the brainstem (Table 3).

Table 2. Patient characteristics.

Characteristic	Number (%)
Patient age, y, median (range)	10 (0.5–21)
<5 y at time of radiotherapy	30 (18)
Gender	
Male	107 (64)
Female	59 (36)
Histology	
Astrocytoma	44 (26)
Medulloblastoma	39 (23)
Ependymoma	26 (16)
Germinoma	14 (8)
Other	15 (9)
ATRT	11 (7)
Craniopharyngioma	6 (4)
Embryonal tumor	6 (4)
NGGCT	3 (2)
Parameningeal RMS	2 (1)
Location	
Supratentorial	84 (51)
Infratentorial	82 (49)
Operations prior to RT	
1	149 (90)
>1	17 (10)
Extent of resection	
Complete resection	100 (60)
Gross residual/ biopsy only	60 (36)
Treated by imaging	6 (4)
Chemotherapy	
Neoadjuvant chemotherapy	64 (38)
Concurrent chemotherapy	43 (26)
Adjuvant chemotherapy	99 (60)
Intrathecal methotrexate	13 (8)
Radiation Dose (Gy[RBE])	
Median, Boost (range)	54.0 (30.0–63.0)
Median, CSI (range)	36.0 (15.0–41.4)
Radiation Volume	
Craniospinal	63 (38)
Focal	103 (62)

ATRT: atypical teratoid rhabdoid tumor; NGGCT: non germinomatous germ cell tumor; RMS: rhabdomyosarcoma.

Median treatment dose delivered was 54.0 Gy[RBE] (range 30.0–63.0 Gy[RBE]) and 38% of patients received CSI to a median dose 36.0 Gy[RBE] (range 15.0–41.4 Gy[RBE]), average 29.3 Gy[RBE]). Median dose per fraction was 1.8 Gy[RBE] (range, 1.8–2.0 Gy[RBE]).

Median maximum brainstem dose in the treated course was 55.4 Gy[RBE] (range 0.15–61.4 Gy[RBE]). Median dose to 2% of the brainstem (D2) was 54.3 Gy[RBE] (range, 0.08–60.2 Gy[RBE]), to 5% of the brainstem (D5) was 53.8 Gy[RBE] (range 0.03–59.7 Gy[RBE]), to 10% (D10) was 53.3 Gy[RBE] (range 0.01–59.4 Gy[RBE]), to 20% (D20) was 52.1 Gy[RBE] (range 0.00–59.1 Gy[RBE]), and to 50% (D50) was 45.0 Gy[RBE] (range 0.00–57.6 Gy[RBE]) (Table 3).

For patients who had prior RT, median time to re-irradiation was 25.8 months (range, 23.5–81.5). Median maximum brainstem dose for both treated courses was 98.0 Gy[RBE] (range 17.0–111.0 Gy[RBE]). Median D2 was 91.0 Gy[RBE] (range, 16.0–110.2 Gy[RBE]), median D5 was 87.4 Gy[RBE] (range 15.5–110.0 Gy[RBE]), median D10 was 85.8 Gy[RBE] (range 15.0–109.8 Gy[RBE]), median D20 was 83.4 Gy[RBE] (range 14.3–106.6 Gy[RBE]), and median D50 was 74.0 Gy[RBE] (range 9.1–89.4 Gy[RBE]) (Table 4).

Overall, one patient (0.6%) experienced brainstem necrosis. This patient had undergone a previous course of radiotherapy, with further details described below. No patient being radiated for the first time experienced brainstem necrosis. In the entire population (including de novo and reirradiation patients), the actuarial incidence of brainstem necrosis was 0.7% at 12 and 24 months (95% CI 0.10–5.1%). Of patients who received ≥ 50.4 Gy[RBE] cumulative dose to the brainstem, the absolute rate of necrosis was 0.7% and actuarial incidence was 0.9% at 12 and 24 months (95% CI 0.13–6.3%).

The patient noted above who developed brainstem toxicity was a 12-year-old with medulloblastoma. The patient had been previously treated at another institution; initially, she was treated with chemotherapy alone and experienced progression requiring re-resection. This had been followed by sequential intrathecal (IT) methotrexate and twice-daily craniospinal photon radiation therapy to 39.0 Gy with a boost to the tumor bed to 60.0 Gy. The maximum dose to the brainstem in the first course was 61.2 Gy. Her care was transferred to our institution at the time of second relapse. A second course of 54.0 Gy[RBE] was delivered to the region of recurrent disease 23.5 months following the first radiation course. The maximum cumulative dose to the brainstem was 96.3 Gy[RBE]. After development of clinical symptoms of brainstem necrosis, the patient was treated with steroids and hyperbaric oxygen. There were no deaths related to brainstem necrosis.

Table 3. Brainstem Dose in the treated plan, entire cohort.

Dose parameter	Brainstem dose
Maximal dose	55.4 Gy[RBE] (range, 0.15–61.4)
D2	54.3 Gy[RBE] (range, 0.08–60.2)
D5	53.8 Gy[RBE] (range, 0.03–59.7)
D10	53.3 Gy[RBE] (range, 0.01–59.4)
D20	52.1 Gy[RBE] (range, 0.00–59.1)
D50	45.0 Gy[RBE] (range, 0.00–57.6)

Table 4. Cumulative brainstem dose, re-irradiation.

Dose parameter	Brainstem dose
Maximal dose	98.0 Gy[RBE] (range 17.0–111.0)
D2	91.0 Gy[RBE] (range 16.0–110.2)
D5	87.4 Gy[RBE] (range, 15.5–110.0)
D10	85.8 Gy[RBE] (range, 15.0–109.8)
D20	83.4 Gy[RBE] (range, 14.3–106.6)
D50	74.0 Gy[RBE] (range 9.1–89.4)

Evaluation of prognostic clinical and dosimetric factors predictive of radiation necrosis was not performed due to the limited number of events.

Discussion

In this study, we report clinical outcomes for pediatric patients treated with PBS-PT for CNS malignancies. In patients undergoing their first course of radiation, we observed no cases of clinical brainstem necrosis, with a median follow-up of 19.6 months. In our entire population, including 4 patients who had received previous radiotherapy, we observed an absolute incidence of brainstem necrosis of 0.6% overall and 0.7% estimated incidence of necrosis at 12 and 24 months. Within the high-risk group who received ≥ 50.4 Gy[RBE] cumulative dose to the brainstem, the rate of necrosis was 0.7% and 0.9% estimated incidence of necrosis at 12 and 24 months, with no necrosis in patients undergoing their first radiation course. There were no treatment-related deaths. These early results suggest that use of PBS-PT in pediatric patients with primary CNS malignancies is without excessive risk of brainstem necrosis and may potentially maximize safety in the re-irradiation setting.

Proton beam radiation therapy is characterized by Bragg peak dose deposition which results in normal tissue sparing distal to the proton beam. Data suggest that the average proton RBE can be considered between 1.1 and 1.15 from the entrance of a SOBP, increasing to 1.35 at the distal edge and as high as 1.7 in the distal fall-off at 2.0 Gy[RBE] per fraction. These values are variable based on physical parameters including linear energy transfer (LET). However, values are also modified by biological parameters including cell cycle phase, oxygenation level, and tissue type. In addition, higher LET at the end of the range results in a higher RBE continuing beyond the distal fall-off of the Bragg peak [18].

These variations in RBE are not currently routinely accounted for in radiation treatment planning. Early reports using passive scatter proton therapy for treatment of pediatric CNS malignancies demonstrated imaging findings of necrosis in 31–47% of cases and symptomatic necrosis in 25% [29–31]. In order to reduce these risks, especially to the brainstem, recent series advocate for standardized planning approaches minimizing the number of beams which range out into the brainstem and using stringent constraints for dose to the brainstem [19]. Using these parameters for treatment planning, a large multi-institutional series of 617 pediatric patients demonstrated 2.4% grade 2 or higher brainstem toxicity, 1.3% grade 3 or higher brainstem toxicity, and 0.4% fatal brainstem toxicity after a median follow up of 3 years [19]. These compared favorably to modern photon series, in which the rates of grade 3 and higher brainstem necrosis range from 2.5–3.4% at a median follow up of 2.8–4.3 years [21,32].

In contrast to passive scatter proton therapy, which relies on custom apertures and compensators to create a spread-out Bragg peak (SOBP), PBS-PT utilizes magnetic scanning to paint dose across a volume of interest. This results in a modulation of the Bragg peak from the accumulation of

different spots from single or multiple fields. In addition to optimizing dose distribution, algorithms to calculate dose averaged LET and optimize LET distribution for clinical treatment planning are being evaluated [33,34]. Although LET was not taken into consideration for treatment planning in this study, the results suggest that there is not increased risk of brainstem necrosis across standard radiation doses and fields including patients at high risk with a dose of ≥ 50.4 Gy[RBE] to the brainstem.

Previously reported clinical characteristics associated with brainstem necrosis include age < 5 years old, posterior fossa location, more extensive resection, hydrocephalus and CSF shunt placement, receipt of any chemotherapy and IT or HD methotrexate based chemotherapy, and need for anesthesia during radiotherapy [20]. In our series, radiation necrosis occurred solely in one patient who had received prior radiotherapy, treated with a hyperfractionated protocol including IT methotrexate. While proton radiation is often used in the setting of re-treatment, our study suggests that these patients remain at the highest risk of treatment-related toxicity.

Limitations of this study include a cohort with short-term follow up from a single institution. While other series have included only high-risk patients who received > 50.4 Gy[RBE], given the lack of data regarding the effects of PBS-PT on brainstem necrosis we elected to study a larger population. We attempted to control for dose by separately evaluating patients at highest risk who received > 50.4 Gy[RBE]. However, continued long-term study of this high-risk population after treatment with PBS-PT is indicated. In addition, we included patients previously treated with radiation therapy, in whom absolute cumulative brainstem dose may not accurately reflect biologic differences in normal tissue repair and fractionation.

Conclusion

Use of PBS-PT does not appear to result in increased risk of brainstem necrosis in pediatric patients treated for CNS malignancies compared to other radiation modalities. Further study in high-risk patients alone and patients receiving re-irradiation with longer follow up may provide additional dosimetric and clinical data associated with brainstem toxicity after PBS-PT.

Disclosure statement

No potential conflict of interest was reported by the authors.

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