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Proton therapy for pediatric head and neck malignancies

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Abstract

Purpose: Pediatric head and neck malignancies are managed with intensive multimodality therapy. Proton beam therapy (PBT) may reduce toxicity by limiting exposure of normal tissue to radiation. In this study, we report acute toxicities and early outcomes following PBT for pediatric head and neck malignancies.

Materials and methods: Between 2010 and 2016, pediatric patients with nonhematologic malignancies of the head and neck were treated with PBT. Clinical and dosimetric data were abstracted from the medical record and treatment planning system with institutional review board approval.

Results: Sixty-nine consecutive pediatric patients were treated with proton-based radiotherapy for head and neck malignancies. Thirty-five were treated for rhabdomyosarcoma to a median dose of 50.4 Gy relative biological effectiveness [RBE]. Ten patients were treated for Ewing sarcoma to a median dose of 55.8 Gy[RBE]. Twenty-four patients were treated for other histologies to a median dose of 63.0 Gy[RBE]. Grade 3 oral mucositis, anorexia, and dysphagia were reported to be 4, 22, and 7%, respectively. Actuarial 1-year freedom from local recurrence was 92% (95% CI 80–97). Actuarial 1-year overall survival was 93% (95% CI 79–98) in the entire cohort. Oral cavity mucositis was significantly correlated with oral cavity dose (D80 and D50 [$P < 0.05$], where D80 and D50 are dose to 50% of the volume and dose to 80% of the volume, respectively).

Conclusions: In this study, we report low rates of acute toxicity in a cohort of pediatric patients with head and neck malignancies. PBT appears safe for this patient population, with local control rates similar to historical reports. Longer follow-up will be required to evaluate late toxicity and long-term disease control.

KEYWORDS

head and neck malignancies, proton therapy, radiation therapy

1 | INTRODUCTION

Malignancies of the head and neck account for approximately 12% of all pediatric cancers.[1] Nonhematologic malignancies of the head and neck in the pediatric population, most commonly neural tumors including neuroblastoma, thyroid malignancies, and soft tissue sarcomas including rhabdomyosarcoma (RMS), are managed with multimodality therapy that may include chemotherapy, radiation, and surgery.[2] Postoperative or definitive radiation often plays a critical role in management given anatomic constraints, which may limit the ability to achieve a complete surgical resection.

Given the critical structures in the head and neck, patients are at risk for acute and late toxicities that may result in decreased quality of life. Patients may experience mucositis and dermatitis during treatment that may necessitate feeding tube placement, narcotic administration for pain control, hospitalization for symptom management, or treatment breaks. Late toxicities include dental anomalies, xerostomia, craniofacial abnormalities, trismus, endocrine abnormalities, cataracts, and osteoradionecrosis.[3–5] In addition, areas exposed to radiation are at risk for secondary malignancies that may manifest decades after primary radiation therapy.[6]

Proton beam therapy (PBT), using double scattering proton therapy (DS-PT) or pencil beam scanning proton therapy (PBS-PT) techniques,

Abbreviations: CT, computed tomography; CTV, clinical target volume; DS-PT, double scattering proton therapy; GTV, gross tumor volume; IMPT, intensity-modulated proton therapy; IMRT, intensity-modulated radiation therapy; OAR, organs at risk; PBS-PT, pencil beam scanning proton therapy; PBT, proton beam therapy; RBE, relative biological effectiveness; RMS, rhabdomyosarcoma; SFUD, single-field uniform distribution; VMAT, volumetric-modulated arc therapy

has been shown in dosimetric studies of adult head and neck malignancies to reduce the amount of normal tissue exposed to radiation compared to modern photon plans.[7–9] Decreased dose to organs at risk (OARs) and overall volume of normal tissue irradiated may decrease rates of acute and late toxicity including secondary malignancies.[10]

However, because PBT is more sensitive to changes in patient anatomy than X-ray therapy, there is concern for risk of altered dose distribution and decreased local control. There are few clinical reports on toxicity and disease control in pediatric head and neck malignancies using PBT.[11–14] Therefore, in this study, we aim to evaluate acute toxicity and early disease control using PBT for nonhematologic pediatric malignancies of the head and neck.

2 | METHODS

Between 2010 and 2016, pediatric patients with nonhematologic malignancies of the head and neck were enrolled onto an institutional review board approved registry study allowing for prospective collection of demographic and treatment data.

Demographic characteristics including age and sex, tumor characteristics (histology, tumor subsite, and tumor stage), chemotherapy timing and type, surgery, radiation dose, and radiation modality were abstracted from the electronic medical record. Toxicity was prospectively assessed at each weekly on-treatment visit using Common Terminology Criteria for Adverse Events version 4 (CTCAEv4.0).[15] Acute toxicity was defined as toxicity occurring within 90 days of the completion of radiation therapy.

After completion of radiation therapy, patients were followed by the pediatric oncology and/or radiation oncology team at 3–6 month intervals either at our institution or at the referring institution for patients living remotely. For the latter group, follow-up data were obtained from the referring institution.

Local recurrence was defined as recurrent disease within the radiation treatment field. Local recurrence was evaluated by a physicist (S.B.) to determine if in-field failures were in regions of concern for proton beam uncertainties. Regional recurrence was defined as recurrent disease within regional lymph nodes outside of the radiation treatment field. Distant recurrence was defined as disease outside of regional lymphatics. Time to recurrence was defined as time from completion of radiation therapy until local, regional, or distant recurrence. Time to death was defined as time from the completion of radiation therapy until death or censorship.

Patients were simulated supine with Aquaplast mask immobilization. Young patients underwent simulation and treatment 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 and fused with the pretreatment MRI and [(18)F]fluorodeoxyglucose positron emission tomography scans.

The gross tumor volume (GTV) was defined as residual disease including the entire prechemotherapy volume accounting for any changes in normal structures and cropping out of normal anatomy. For sarcoma patients, the clinical target volume (CTV) was defined as a 1–2 cm margin from the GTV, cropping out of normal structures. The CTV for patients with nasopharyngeal, salivary, and squamous cell malignancies was defined according to tumor site and nodal status, encompassing the primary tumor volume, involved nodes, and at risk nodal regions. A PTV was defined as a 0.3–0.5 cm geometric margin from the CTV for dose recording and reporting purposes per ICRU78.[16]

The simulation CT was used for plan optimization and dose calculation in all cases. All proton plans were generated from an energy-degraded 230 MeV cyclotron. For shallow targets, a 7.5 cm range shifter was applied in the beam path in order to further reduce the minimum beam energy of 100 MeV available at our institution.

For patients treated with DS-PT, one to three fields were centered on the CTV with beam angles optimized to maximize CTV coverage and minimize exposure to normal structures. The distal and proximal range margins in the direction of each proton beam were designated to account for uncertainty in the conversion of CT images to stopping power (3.5%) and uncertainties in beam calibration and compensator manufacturing (3 mm). Lucite compensators were manufactured for each beam to ensure distal conformality of the beam to the CTV and the multileaf collimator was used to increase lateral beam conformality. A compensator smearing radius of 8 mm was applied to account for any misalignment, inter-, and intrafraction motions.

PBS-PT plans were single-field uniform dose (SFUD) in combination with up to 20% intensity-modulated proton therapy (IMPT). Two to three beams were optimized to cover the CTV and avoid dose to the OARs for DS-PT and PBS-PT. An optimization volume with 3.5% of beam range was used to correct for uncertainties associated with CT imaging and conversion from CT numbers to water-equivalent depth proximally and distally to the CTV and an additional 1 mm to correct for uncertainties in beam calibration. The average range margin applied was 0.5 cm (Fig. 1).

For a subset of patients, combined intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) photon and proton plans were generated. IMRT or VMAT was considered in cases with metal hardware and in cases in which photons resulted in greater sparing of OARs due to higher gradient lateral dose distributions. The number of beams or arcs and their arrangement were chosen based on tumor location and anatomic considerations. IMRT and VMAT plans were created using inverse planning. A 6 megavoltage (MV) linear accelerator was used to deliver computer-controlled multisegment therapy with multileaf collimators to produce intensity-modulated treatments.

Patients with RMS were treated from 36.0 Gy relative biological effectiveness [RBE] to 59.4 Gy[RBE] in 1.8 Gy[RBE] fraction sizes (Table 1). Patients with Ewing sarcoma were treated from 55.8 Gy[RBE] to 65.6 Gy[RBE] in 1.8 Gy[RBE] fraction sizes (Table 2). Patients with other tumor histologies were treated from 36.0 Gy[RBE] for a patient with angiofibroma to 81.0 Gy[RBE] for a patient with osteosarcoma in 1.8–2.0 Gy[RBE] fraction sizes (Table 3).

Normal structures were contoured by a radiation oncologist following consensus guidelines.[17] Dose–volume constraints were individualized for each patient based on the location of the primary tumor and patient age. In cases where the target volume

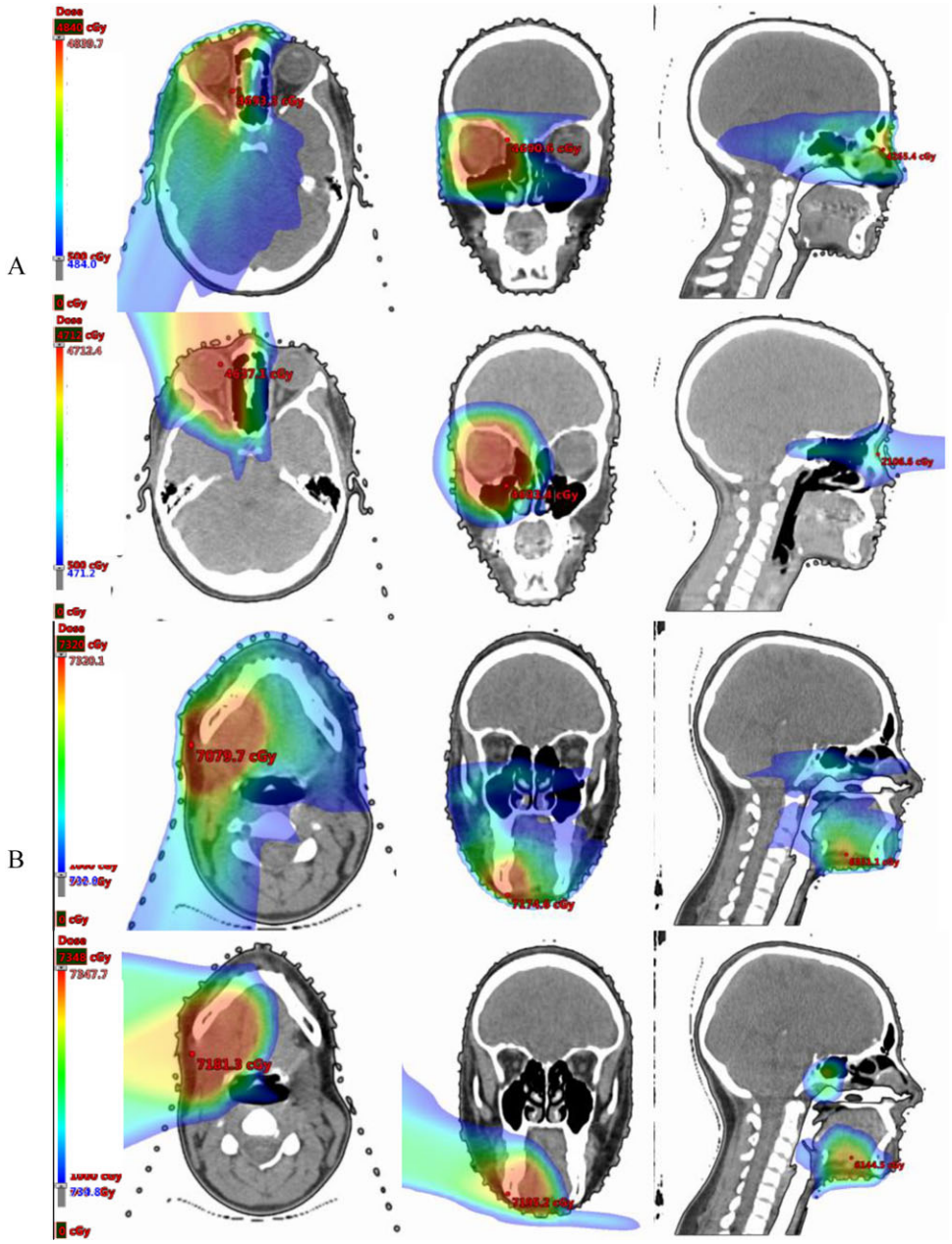

FIGURE 1 Examples of RapidArc clinical backup and PBS-PT plans for RMS of the right orbit (A) and adenoid cystic carcinoma of the right submandibular gland including CN XII and V3 (B)

encompassed or was adjacent to a noncritical OAR, target coverage was prioritized. Cone down boost volumes were occasionally used when target coverage resulted in excess dose to critical structures including the brainstem, spinal cord, and optic structures. Institutional planning constraints were as follows: cord maximal dose 50.0 Gy[RBE], volume receiving 45.0 Gy[RBE] (V45) ≤ 90%; brainstem maximal dose 60.0 Gy[RBE], V54 ≤ 95%; optic chiasm maximal dose 54.0 Gy[RBE]; optic nerve maximal dose 54.0 Gy[RBE]; eye maximal dose 45.0 Gy[RBE]; cochlea maximal dose 35.0 Gy[RBE], mean 30.0 Gy[RBE]; temporal lobe maximal dose 54.0 Gy[RBE], mean dose 25.0 Gy[RBE]; parotid gland maximal dose 40.0 Gy[RBE], mean dose 26.0 Gy[RBE]; lacrimal gland mean 30.0 Gy[RBE]; and lens maximal dose 7.0 Gy[RBE].

Actuarial local, regional, and distant recurrences and overall survival were analyzed by the Kaplan–Meier method. Correlation between oral mucositis was performed using Pearson correlation coefficient with toxicity considered as a continuous variable. Dose was evaluated as mean dose to the oral cavity, D80% (dose to 80% of the oral cavity), D50 (dose to 50% of the volume), and D20 (dose to 20% of the volume). Linear regression was performed adjusting for receipt of chemotherapy. $P < 0.05$ was considered statistically significant.

3 | RESULTS

Sixty-nine consecutive patients were treated with proton-based radiation therapy for head and neck malignancies during the specified study period.

TABLE 1 Characteristics of patients with RMS of the head and neck

Characteristic	Number (%)
Age at initiation of PBT	
1–5 years	16 (46)
6–10 years	8 (23)
11–15 years	5 (14)
16–22 years	6 (17)
Gender	
Male	22 (63)
Female	13 (37)
IRS stage	
I	16 (46)
II	7 (20)
III	10 (29)
IV	2 (5)
Tumor subsite	
Parameningeal	
Infratemporal fossa	1 (3)
Nasopharynx	5 (14)
Paranasal sinus	3 (8)
Cervical lymph nodes	1 (3)
Facial	2 (6)
Hypopharynx	1 (3)
Mandible/ maxilla	6 (17)
Orbit	10 (29)
Oropharynx	1 (3)
Oral cavity	4 (11)
Salivary gland	1 (3)
Histology	
Embryonal/botryoid	22 (63)
Alveolar/undifferentiated	13 (37)
Chemotherapy	
Alkalytors	35 (100)
Anthracyclines	2 (6)
Surgery	
Biopsy only	32 (92)
Resection	3 (8)
Radiation dose (Gy[RBE])	
Median (range)	50.4 (36.0–59.4)
Radiation modality[a]	
DS-PT	18 (51)
PBS-PT	13 (37)
Mixed IMRT/PBT	4 (11)

[a]Does not sum to 100% due to rounding.

TABLE 2 Characteristics of patients with Ewing sarcoma of the head and neck

Characteristic	Number (%)
Age at initiation of PBT	
1–5 years	1 (10)
6–10 years	4 (40)
11–15 years	2 (20)
16–23 years	3 (30)
Gender	
Male	6 (60)
Female	4 (40)
Stage	
I	9 (90)
IV	1 (10)
Tumor location	
Ethmoid sinus	2 (20)
Mandible	1 (10)
Mastoid	1 (10)
Maxillary sinus	4 (40)
Orbit	2 (20)
Chemotherapy	
Alkalytors	10 (100)
Anthracyclines	10 (100)
Surgery	
Biopsy only	8 (80)
Resection	2 (20)
Radiation dose (Gy[RBE])	
Median (range)	55.8 (55.2–65.6)
Radiation modality	
DS-PT	2 (20)
PBS-PT	6 (60)
Mixed IMRT/PBT	2 (20)

Of these, 35 patients were treated for RMS. Median age in this group was 6 years (range, 1–22). Nine patients presented with parameningeal disease and 13 patients had translocation positive disease. The majority of patients (32/35) underwent biopsy only as their only surgical procedure and all received multiagent chemotherapy, which included an alkylating agent. Median radiation dose was 50.4 Gy[RBE]. Patients were treated with DS-PT (51%), PBS-PT (37%), or mixed proton/IMRT plans (11%) (Table 1).

Ten patients were treated for Ewing sarcoma of the head and neck. Median age was 13 years (range, 2–23). Common tumor subsites included the maxillary sinus (40%), orbit (20%), and ethmoid sinus (20%). Patients most often had undergone biopsy only (8/10) and all received multiagent alkylator- and anthracycline-based chemotherapy. Median radiation dose in this group was 55.8 Gy[RBE]. Patients were treated with DS-PT (20%), PBS-PT (60%), or mixed proton/IMRT plans (20%) (Table 2).

Twenty-four patients were treated for other tumors of the head and neck including salivary gland malignancies (42%), nasopharyngeal carcinoma (21%), and sarcomas (24%). Median patient age was 14 years (range, 1–21). Patients most often had an attempted complete resection and many received platinum-based (33%) or anthracycline-based (17%) chemotherapy. Median radiation dose in this group was

TABLE 3 Characteristics of patients with non-RMS, non-Ewing sarcoma of the head and neck

Characteristic	Number (%)
Age at initiation of PBT	
1–5 years	2 (8)
6–10 years	3 (12.5)
11–15 years	16 (67)
16–20 years	3 (12.5)
Gender	
Male	15 (63)
Female	9 (38)
Stage	
I	4 (17)
II	7 (29)
III	3 (13)
IV	8 (33)
X	1 (4)
Kadish C	1 (4)
Tumor location	
Cervical lymph nodes	1 (4)
Infratemporal fossa	1 (4)
Nasal cavity	1 (4)
Nasopharynx	7 (29)
Oral cavity	1 (4)
Orbit	2 (8)
Parapharyngeal space	1 (4)
Salivary gland	10 (42)
Tumor histology	
Nasopharyngeal carcinoma	5 (7%)
Adenoid cystic carcinoma	3 (4%)
Adenocarcionma	2 (3%)
Mucoepidermoid	2 (3%)
Acinic cell carcinoma	1 (1%)
Alevolar soft part sarcoma	1 (1%)
Angiofibroma	1 (1%)
Esthesioneurobastoma	1 (1%)
High grade sarcoma	1 (1%)
Myoepithelioma	1 (1%)
NUT	1 (1%)
Osteosarcoma	1 (1%)
Poorly differentiated sarcoma	1 (1%)
Rhabdoid tumor	1 (1%)
Squamous cell carcinoma	1 (1%)
Synovial sarcoma	1 (1%)
Chemotherapy	
Platinum	8 (33)
Alkalytors	2 (8)
Anthracyclines	4 (17)
Surgery	
Biopsy only	7 (29)
Resection	17 (71)
Radiation dose (Gy[RBE])	
Median (range)	63.0 (36.0–81.0)
Radiation modality	
DS-PT	3 (12)
PBS-PT	11 (46)
Mixed IMRT/PBT	10 (42)

63.0 Gy[RBE]. Patients were treated with DS-PT (12%), PBS-PT (46%), or mixed proton/IMRT plans (42%).

No patient experienced greater than grade 3 toxicity. Common grade 2 toxicities included fatigue (22%), anorexia (12%), oral mucositis (20%), dysphagia (13%), and radiation dermatitis (26%). Grade 3 oral mucositis, anorexia, dysphagia, dehydration, and radiation dermatitis were reported to be 4, 22, 7, 1, and 1%, respectively (Table 4). Twenty-one patients had a feeding tube prior to beginning radiotherapy. Nine patients who had not required a feeding tube at baseline had placement of a feeding tube or initiation of tube feeds during radiation therapy (13%). Twenty patients initiated or increased opiate use during radiation therapy (29%). Thirteen patients initiated gabapentin while receiving radiation therapy (19%). One patient was hospitalized for dehydration and pain control. No patient required a break in treatment due to toxicity.

Eight patients were lost to follow up after completion of radiation therapy. Median clinical follow up was 13.9 months (range, 1.71–58.3) for the remaining patients. Local recurrence alone occurred in one patient with RMS. Three patients with RMS developed regional recurrence alone. Distant disease alone developed in three patients with nasopharyngeal carcinoma, synovial sarcoma, and RMS. Local and distant recurrence occurred in two patients with Ewing sarcoma and esthesioneuroblastoma. One patient with RMS developed local and regional recurrence. Combined local, regional, and distant recurrence occurred in two patients with RMS and midline NUT carcinoma of the parotid.

Actuarial 1- and 3-year freedom from local recurrence was 92% (95% CI 80–97) and 85% (95% CI 68–93), from regional recurrence was 94% (95% CI 83–98) and 86% (36% 95% CI 67–94), and from distant recurrence was 86% (95% CI 70–93) and 78% (95% CI 54–90) (Fig. 2). In RMS, 1-year freedom from local recurrence was 84% (95% CI 58–95), from regional recurrence was 85% (95% CI 61–95), and from distant recurrence 95% (95% CI 69–99). In Ewing sarcoma, 1-year freedom from local recurrence was 86% (95% CI 33–98), from regional recurrence was 100% (95% CI 100), and from distant recurrence was 86% (95% CI 33–98).

The recalculated dose distributions based on the verification CTs acquired for this patient cohort during the course of treatment suggested that the failures were not related to proton beam uncertainties. Patients were treated with salvage surgery ($n = 2$), radiation therapy ($n = 8$), and chemotherapy ($n = 10$).

TABLE 4 Acute toxicities after PBT in pediatric patients with sarcomas of the head and neck

Acute toxicity	No. of patients (%)
Anorexia	
Grade 1	12 (17)
Grade 2	8 (12)
Grade 3	15 (22)
Dehydration	
Grade 1	1 (1)
Grade 2	4 (6)
Grade 3	1 (1)
Dry mouth	
Grade 1	22 (32)
Grade 2	2 (3)
Grade 3	2 (3)
Dysgeusia	
Grade 1	14 (20)
Grade 2	7 (10)
Dysphagia	
Grade 1	13 (19)
Grade 2	9 (13)
Grade 3	5 (7)
Fatigue	
Grade 1	28 (41)
Grade 2	15 (22)
Headache	
Grade 1	4 (6)
Grade 2	1 (1)
Mucosal infection	
Grade 1	2 (3)
Grade 2	1 (1)
Grade 3	1 (1)
Nausea	
Grade 1	9 (13)
Grade 2	2 (3)
Grade 3	1 (1)
Neck edema	
Grade 1	6 (9)
Grade 2	1 (1)
Oral mucositis	
Grade 1	10 (14)
Grade 2	14 (20)
Grade 3	3 (4)
Radiation dermatitis	
Grade 1	42 (61)
Grade 2	18 (26)
Grade 3	1 (1)
Salivary inflammation	
Grade 1	14 (20)
Grade 2	3 (4)
Taste change	
Grade 1	1 (1)
Grade 2	3 (4)

There were four patient deaths in patients with RMS ($n = 2$), Ewing sarcoma ($n = 1$), and midline NUT carcinoma of the parotid ($n = 1$). Actuarial 1- and 3-year overall survival was 93% (95% CI 79–98) and 90% (95% CI 74–96) in the entire cohort. Median overall survival was not reached (Fig. 2). In RMS, 1-year overall survival was 96% (95% CI 73–99). In Ewing sarcoma, 1-year overall survival was 83% (95% CI 27–98).

Correlation between dose and grade of toxicity was significant for D80 and D50 ($P = 0.003$, $P < 0.0001$). D80 and D50 remained statistically significant after adjustment for receipt of chemotherapy ($P = 0.002$, $P < 0.0001$).

4 | DISCUSSION

In this study, we find low rates of acute toxicity in patients with pediatric head and neck malignancies. No patient experienced greater than grade 3 toxicity and rates of grade 3 oral mucositis and radiation dermatitis were reported in 4% and 1%, respectively. Local control and survival were high in the cohort overall and in the two largest histologic subgroups at early follow-up and review of in-field failures does not suggest that recurrences were due to proton beam uncertainties. On dosimetric analysis, we find that higher grade oral mucositis is significantly correlated with D80 and D50 after adjustment for receipt of chemotherapy.

Rates of acute toxicity were generally lower than those reported historically. Reports using 2D fields in RMS reported 46% grade 3 or 4 mucositis and 7% grade 3 or 4 radiation dermatitis, while a study of pediatric patients with nasopharyngeal carcinoma reported 12% grade 3 mucous membrane toxicity.[4,18]

In a study of IMRT for pediatric head and neck RMS, authors report comparable rates of toxicity to the previous IRS-IV study, in which 46% of patients had grade 3 or 4 mucositis.[4,19] An IMRT series from 2000 to 2007 utilizing a cone-down boost reported 15% grade 3 acute mucosal toxicity.[20] While grade 3 mucositis were reduced by using a cone-down boost, the rate remains higher than that seen on this study. Similarly, a phase II study of pediatric patients treated with proton therapy for head and neck malignancies reported 3% grade 3 mucositis.[14] Decreased rates of acute toxicity may improve the ability to deliver full dose chemotherapy and avoid of treatment breaks, which have been suggested to decrease local control in pediatric and adult head and neck malignancies.[21–23] In addition, our analysis suggests that grade of oral cavity mucositis may be correlated with doses to large volumes of the oral cavity, D80 and D50, which would be reduced using proton therapy as compared to photon-based techniques.

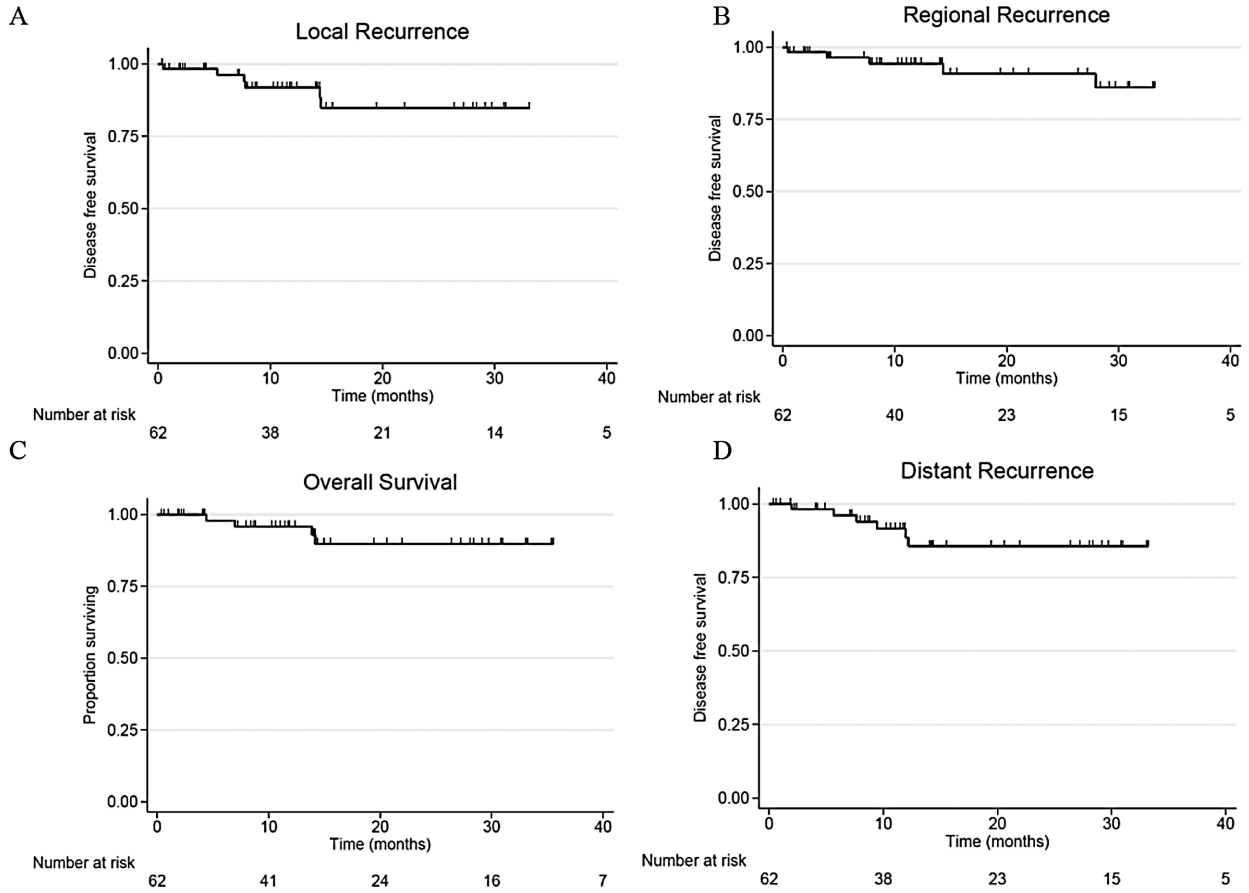

FIGURE 2 Local (A), regional (B), and distant (C) disease-free survival and overall survival (D) in pediatric patients with head and neck malignancies

PBT may significantly reduce late toxicities in this patient population. At a median of 7.7 years after IMRT for RMS of the head and neck, 76.7% of patients had facial disfigurement, 36.7% of patients demonstrated growth hormone deficiency, 33.3% demonstrated dental problems, 20% had hearing loss, 20% had visual disturbance, and 6.7% had a secondary malignancy.[5] These rates appear to be reduced in studies of RMS patients using PBT, with 0–30% rates of decreased growth velocity, 20–70% facial hypoplasia, 0–8% visual complications, 3–30% dentition issues, 0–3% auditory complications, and no reported secondary malignancies.[11,13] If late toxicities are reduced, PBT may allow for dose escalation in refractory histologies. In one series of patients treated with escalated doses using PBT for chordoma and chondrosarcoma, 7% experienced severe late effects including radiation necrosis and 60% local control was achieved in the chordoma group.[12] This is in concordance with a systematic review of all major chordoma series, demonstrating 5-year local control and overall survival of 36% and 54% for photons versus 64% and 80% for protons.[24] While rates of local control are high, follow-up of patients in this cohort will be required to determine the rates of late toxicity following escalated doses of radiation.

Radiation necrosis and neurocognitive dysfunction are concerns with central nervous system radiation. In a report in 2012, 6% of patients treated with proton therapy had symptomatic necrosis, much higher than rates of 2.5–3.7% previously reported in patients treated with photon therapy.[25] This may be due to the higher linear energy transfer at the end of the spread out Bragg peak. Studies have demonstrated the importance of the volume of brain receiving high doses in proton treatment, in particular the volume of infratentorial brain receiving ≥54 Gy, of brainstem receiving 55 Gy, and of the maximal brainstem dose.[26] In addition to adherence to dose constraints, limiting beam arrangements such that no more than one-third of proton beams ends in brainstem tissue outside the PTV and overlap in the distal edge of multiple beams is minimized may reduce this potential risk. Treatment with cranial irradiation is also associated with neurocognitive decline that has been shown to be dose and volume dependent in some series.[27,28] Studies of conformal photon therapy for patients with ependymoma have shown stable neurocognitive function and no increased local failures.[29] Greater normal tissue sparing with proton therapy is anticipated to further minimize risk of neurocognitive decline, although long-term follow up is required to determine the true clinical benefit.

The local control rates in this series appear similar to those previously reported using photon therapy. In this study, local failure occurred in 17% of patients with an actuarial local control of 85% at 2 years overall. Previous reports using photon therapy for head and neck RMS demonstrated 3-year actuarial local control rates of 100% for orbital and nonparameningeal head and neck tumors and 95% for parameningeal tumors, with worse disease-free survival in patients with alveolar histologies.[19] For patients with unresectable

Ewing sarcoma, actuarial 3-year local control was 77% in a modern series.[30] Recent reports of multimodality therapy for patients with esthesioneuroblastoma demonstrate 74% 5-year disease-free survival and 26% 5-year progression-free survival for patients with midline NUT carcinoma.[31,32] Given that proton therapy is a more precise modality with increased sensitivity to changes in tumor size during treatment and adjacent normal tissue density, concern exists regarding risk of decreased local control. However, the rates and patterns of failure reported in this cohort are similar to prior studies and reflect locally aggressive histologies that do not respond well to current treatment paradigms. These results suggest that increased local failure is not occurring specifically from use of proton therapy.

In this study, multiple PBT delivery methods were utilized including DS-PT and PBS-PT. DS-PT relies on physical scattering foils to spread the beam laterally. Custom apertures and compensators shape the field and spread the beam so that the range covers the full distal edge of the target. PBS-PT utilizes magnets to paint dose layer by layer into the target. Compared to DS-PT, PBS-PT is easier to plan and has shorter treatment times, lower integral dose, and spares more normal tissue, especially proximal to the target. However, PBS can result in larger lateral dose fall-off due to the width of the incoming beam.[33] This may be reduced with the use of smaller spot sizes and patient-specific apertures or collimation at the nozzle.[34–36] Dosimetric studies have demonstrated improved sparing of OARs using PBS-PT as compared to DS-PT using these modifications.[37,38]

In addition, with PBS-PT, fields can be optimized separately to cover the entire target (SFUD), or the beams can be optimized to cover the target with the sum of the fields (IMPT). IMPT allows for greater reduction in dose to optimize dose distribution, but is the most sensitive to daily setup variability and anatomic changes over the course of treatment. Therefore, while rates of local control on this study are reassuring, the majority of patients on this study were treated with robust DS-PT plans. Other institutions have reported good local control using PBS-PT plans for pediatric parameningeal RMS but these studies will require confirmation with larger patient numbers and longer follow-up.[11] IMPT has been safely used in treatment of adult patients with head and neck cancer including adenoid cystic carcinoma and oropharyngeal squamous cell carcinoma with 93.3–100% local control, and has been shown to reduce rates of feeding tube dependency in case-matched analysis.[39,40] These studies have led to an ongoing phase III randomized study to determine toxicity of IMRT versus IMPT for HPV-positive oropharyngeal cancer in the adult population.[41]

This study is limited by a small and heterogeneous patient population. Patients had a variety of histologies treated with multiple chemotherapy regimens with differing toxicity profiles. In addition, radiation therapy was delivered using a combination of proton and photon therapy techniques to a range of doses and treatment volumes. While results of acute toxicity are promising compared to historical controls, longer follow up is required to determine the magnitude of benefit in late toxicity. In addition, as the field moves toward IMPT-based proton planning, careful review of rates of local control compared to historical controls will be required to ensure adequate target coverage with highly conformal proton radiation techniques.

In this study, we show low rates of acute grade 2–3 toxicity and no grade 4–5 toxicity in a cohort of pediatric patients with head and neck malignancies treated with intensive multimodality therapy. Although the study is limited by a heterogeneous patient population, results of treatment are promising in this rare disease site. Proton therapy appears well tolerated and safe, with local control rates similar to historical reports in spite of more conformal therapy. Longer follow-up of these patients will be required to evaluate for late toxicity and long-term disease control.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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