Preliminary Experience of Treating Children and Young Adults With Image-Guided Proton Beam Therapy in India

Srinivas Chilukuri, MD, MBBS[1]; Nagarjuna Burela, MD, DNB[1]; Ramya Uppuluri, MD, FNB[1]; D. Indumathi, MD[1]; Sapna Nangia, MD[1]; Pankaj Kumar Panda, BDS, MSc[1]; Dayananda Sharma Shamurailatpam, PhD[1]; Revathi Raj, DCH, MRCP, FRCPath[2]; Thirumalai Raja, MD, DM[1]; and Rakesh Jalali, MD[1]

original reports abstract

PURPOSE Proton beam therapy (PBT) has been a preferred modality in pediatric malignancies requiring radiotherapy. We report our preliminary experience of treating consecutive patients younger than 25 years with image-guided pencil beam scanning PBT from the first and only center on the Indian subcontinent.

METHODS Patients were selected for PBT on the basis of a multidisciplinary tumor board decision. Patient demographic data, as well as tumor and treatment-related characteristics of the cohort, were captured. Patient and treatment-related factors and their association with acute toxicities were analyzed using univariable and multivariable analyses.

RESULTS Forty-seven patients (27 with CNS and 20 with non-CNS tumors) with a median age of 9 years (range, 2-25 years) were evaluated. Most common diagnoses were ependymoma, rhabdomyosarcoma, and glioma. Seventy-seven percent of patients traveled more than 500 km, and 70% of them lived in metropolitan cities. Forty-nine percent of patients had recurrent disease at presentation, and 15% had received a previous course of radiation. The median dose delivered was 54.8 cobalt gray equivalents (range, 40.0-70.4 cobalt gray equivalents) to a median clinical target volume of 175 mL (range, 18.7-3,083.0 mL), with 34% of patients requiring concurrent chemotherapy (CCT). Acute grade 2 and grade 3 dermatitis, mucositis, and hematologic toxicity was noted in 45% and 2%, 34% and 0%, and 38% and 30% of patients, respectively. Grade 2 fatigue was noted in 26% of patients. On multivariable analysis, for CNS tumors, both CCT and craniospinal irradiation were independently associated with $\geq$ 2 grade hematologic toxicity, whereas among non-CNS tumors, a clinical target volume $>$ 150 mL was associated with $\geq$ 2 grade fatigue, head and neck irradiation was associated with $\geq$ 2 grade mucositis, and CCT was associated with grade $\geq$ 2 hematologic toxicity.

CONCLUSION This study demonstrates safe implementation of a PBT program for children and young adults on the Indian subcontinent. Image-guided pencil beam scanning PBT in judiciously selected patients is feasible and can be delivered with acceptable acute toxicities.

JCO Global Oncol 6:1736-1745. © 2020 by American Society of Clinical Oncology

INTRODUCTION

De-intensification of cancer treatment in children and young adults has gathered considerable momentum as long-term childhood cancer survivors are at an increased risk of serious health issues related to treatment.[1,2] Because radiation is one of the major contributors to late effects in children (including growth defects, neurocognitive defects, endocrinopathies, cardiovascular effects, lymphedema, and secondary malignant neoplasms),[3] there has been a widespread evaluation of radiation de-intensification in the last two decades for several hematologic and solid tumors.[4-6] Radiation therapy, however, cannot be completely avoided in many clinical protocols and remains an integral component of management; the best possible conformal techniques of radiation should be used in such situations.[7]

Proton beam therapy (PBT), because of its superior physical properties, results in significantly lower doses of radiation to healthy normal structures. PBT thereby has the potential to mitigate both acute and late radiation-related effects. This is especially impactful in children and young adults as the result of a much larger tumor to body volume ratio (compared with adults) and also because of a higher propensity to develop permanent radiation sequelae. Multiple prospective and retrospective studies have shown that the dosimetric benefit achieved results in favorable clinical outcomes.[8-15] Despite the lack of randomized controlled trials demonstrating superiority of PBT over conformal photon-based techniques, most

ASSOCIATED CONTENT

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on September 15, 2020 and published at ascopubs.org/journal/go on November 12, 2020: DOI https://doi.org/10.1200/GO.20.00319

CONTEXT

Key Objective

Can proton beam therapy, which is emerging as a preferred radiotherapy modality, be safely implemented for pediatric patients with cancer with acceptable acute toxicities on the Indian subcontinent?

Knowledge Generated

Image-guided pencil beam scanning proton beam therapy was found to be safe in a variety of pediatric intracranial and extracranial malignancies in the Indian context.

Relevance

This study demonstrated that proton beam therapy was associated with acceptable acute toxicities in this cohort of carefully selected patients treated with a multidisciplinary approach. Proton beam therapy seems to be a promising radiation therapy modality for pediatric and young adult malignancies on the Indian subcontinent. We hope that this study will lead to increased acceptability and encourage the public and the private health care sector to adopt advanced radiation therapy technologies in this region, which is home to one-fifth of the world's population.

collaborative group trials conducted in North America (Children's Oncology Group) and Europe allow patients to be treated with PBT.[16,17] In fact, it is the treatment modality preferred by a majority of the world's leading pediatric oncologists for most solid tumors requiring radiation therapy.[18] The concerns related to safety of the older-generation passive scattering proton therapy, such as neutron contamination and higher rates of treatment-related necrosis, have been addressed sufficiently with the advent of contemporary pencil beam scanning (PBS) PBT with on-board volumetric imaging, modern planning algorithms, and better understanding of biologic uncertainties of PBT.

Our three-room PBT facility (Proteus Plus, with two fully rotating gantries and one fixed beam [manufactured by Ion Beam Applications, Louvain-La-Neuve, Belgium]), capable of delivering contemporary image-guided PBS PBT, is the first proton therapy center on the Indian subcontinent. The proton facility is attached to a 150-bed comprehensive cancer facility, which is funded by a private sector enterprise. The patient treatments began in January 2019[19,20] and, since then, our center has been the only referral center for PBT in this region. The patients and physicians of this region, which is home to nearly one-quarter of the world's population, have diverse socioeconomic, cultural, and educational backgrounds. Little is known regarding their preference and adoption of this relatively new and cost-intensive technology. We hereby report our preliminary experience with respect to the demographic profile and acute toxicities in children and young adults with image-guided PBS PBT.

METHODS

Patients were identified from a prospectively maintained database at our center. The present work is a retrospective audit of baseline characteristics, diagnosis, treatment delivery parameters, treatment-related acute toxicity, and follow-up information of all children and young adults (< 25 years of age) who were consecutively treated at our center between January 2019 and March 2020. This study was approved by the institutional ethics committee.

Initial Work-Up and Selection

The decision to offer PBT for each of the patients was made after a thorough evaluation and discussion by the multidisciplinary tumor board. Patients were referred from all over the country, as well as from adjoining regions. Our criteria included patients eligible for only radical intent treatment requiring relatively high doses of radiation or with tumors located adjacent to radiosensitive structures (making them prone to late radiation sequelae) or who had required large field irradiation and were recommended for PBT. Patients requiring whole organ irradiation were not chosen for PBT except in those receiving craniospinal irradiation (CSI). In certain cases, a dosimetric plan was generated before a decision to treat with PBT was made.

A few days before the day of simulation, children (< 10 years of age) were encouraged to visit the treatment facility to view treatments of other children to familiarize themselves with the procedure and reduce anxiety. All patients underwent a simulation procedure (with or without sedation) consisting of immobilization and multimodality imaging (computed tomography [CT] and magnetic resonance imaging of the site to be treated) nearly 1 week before the decided day of starting treatment.

PBT Planning

The planning process consisted of target identification, organ at risk delineation, treatment prescription with required dose volume constraints, and treatment optimization to achieve desired dose constraints. Suitable plans were generated either with single-field or multifield optimization techniques or a combination of both (referred to as hybrid plans), which were robust to range and setup uncertainties up to acceptable thresholds. A pretreatment

patient-specific quality assurance was performed to verify the approved plan before the treatment was implemented. Each day, pretreatment imaging with kV x-rays and/or cone beam CT (CBCT) was done to verify the patient position and to ensure the precision of treatment on a daily basis. The decision of imaging modality for verification and its frequency was individualized on the basis of the patient, tumor site, and treatment plan characteristics. Patients were followed up with at least weekly to assess the treatment toxicities (National Cancer Institute Common Toxicity Criteria version 4.0). Repeat check scans (CT or magnetic resonance imaging) were done periodically (once every 1 to 2 weeks, as decided by the treating team) or if required during the treatment (on the basis of clinical or CBCT information). Patients received concurrent chemotherapy (CCT) per the treatment plan. All patients underwent response assessment imaging 4 to 12 weeks after treatment and were followed up with regularly. Data were analyzed using SPSS version 22. Relevant treatment and tumor-related factors and their association with acute toxicities were analyzed using the χ^2 test and multivariable analysis of variance. When multiple clinical target volumes (CTV) were irradiated to different doses, the CTV that was prescribed a lower dose was considered for analysis.

RESULTS

Forty-seven patients with a median age of 9 years (range, 2-25 years) were treated at our institution with image-guided PBS PBT until the cutoff point. During this period, this cohort constituted 28% of the total number of patients treated with PBT at our center. Table 1 describes the baseline characteristics of the patients. Twenty-seven patients were diagnosed with a CNS tumor and the rest with a non-CNS tumor (Figs 1A and 1B). The most common diagnosis was ependymoma, followed by rhabdomyosarcoma (RMS) and glioma. Twenty-three patients had recurrent disease, of whom seven patients were presented for reirradiation. Thirteen children (80% were children $>$ 6 years of age and two children were between the ages of 6 and 8 years) required at least one procedure of sedation during either simulation and/or treatment (Figs 2A and 2B). Of these, only seven children required sedation during the entire treatment (all of them were $<$ 4 years, except one autistic child who was 8 years old).

Treatment-related characteristics are listed in Table 2. Among patients who received CSI, 10 patients were $<$ 15 years and the remainder were $>$ 15 years. Indications for CSI were ependymoma (for recurrent [n = 3] and upfront [n = 1]), medulloblastoma (n = 4), germ cell tumors (n = 2), pinealoblastoma (n = 2), and neuroblastoma (n= 1). A 15-year-old girl with an intracranial germinoma received whole ventricular irradiation. On analysis of the technique of PBT planning, multifield optimization was used in 21 patients (of whom 17 had non-CNS tumors), single-field optimization was used in 11 patients (all of whom had CNS tumors), and hybrid plans were used in 15 patients (including all 13 patients who had CSI). The median number of fractions received was 30 (range, 23-33 fractions) for patients with CNS tumors to a median dose of 54 cobalt gray equivalents (CGE; range, 40.0-55.8 Gy) and 32 fractions (range, 17-35 fractions) for patients with non-CNS tumors to a median dose of 59.4 CGE (range, 30.6-70.4 Gy). One patient with recurrent parameningeal RMS received hyperfractionation with 52.8 CGE in 40 fractions with a twice-daily fractionation.

The median number of CBCT scans per patient for CNS tumors was 16 (range, 4-29 scans), whereas for patients with non-CNS tumors it was 20 (range, 7-33 scans). Six patients underwent an adaptive replanning based on the check CT scans and/or CBCT imaging. Sixteen patients (34%) also received CCT per the original treatment plan.

Tolerance and Acute Toxicity

Overall, weight loss was noted in 30 patients during the treatment, with a median weight loss of 0.95 kg (range, 0.1-10.5 kg, corresponding to 0.15%-10.9% of body weight). Seventeen patients gained weight during the treatment, with a median of 0.9 kg gained (range, 0.1-5.3 kg or 0.5%-21.7% of body weight). Table 3 depicts acute toxicities noted in CNS and non-CNS tumors. The most common acute toxicity noted, irrespective of the site of irradiation, was radiation dermatitis. Twenty-one patients (45%) had grade 2 dermatitis, and only one patient (2%) had grade 3 dermatitis (a 13-year-old child with nasopharyngeal carcinoma who received 70 Gy to bilateral neck). Eighteen patients (38%) had grade $\geq$ 2 and 14 patients (30%) had grade $\geq$ 3 hematologic toxicities, of whom 12 patients (26%) had grade $\geq$ 3 neutropenia. None of the patients developed grade 3 mucositis or dysphagia that would have mandated a need for a feeding tube during treatment. None of the patients had treatment interruption beyond 2 consecutive days. Three patients (6%) had cumulative treatment interruption for 4 days either because of toxicity or logistics.

On univariable analysis (χ^2 test) of patients with CNS tumors showed that CCT ($P = .009$), CSI ($P < .001$), and volume of CTV were associated with $\geq$ 2 grade hematologic toxicity (Table 4). On multivariable analysis, both CCT ($P = .03$) and CSI ($P < .001$) were independently associated with $\geq$ 2 grade hematologic toxicity.

Among non-CNS tumors, on univariable analysis, CTV $>$ 150 mL was significantly associated with $\geq$ 2 grade fatigue ($P = .017$), head and neck irradiation ($P = .01$) was associated with $\geq$ 2 grade mucositis, and CCT ($P = .02$) was associated with grade $\geq$ 2 hematologic toxicity. The same variables were found to be significant on multivariable analysis. ($P = .05$, $P = .03$, and $P = .01$, respectively).

Follow-Up and Early Outcomes

With a median follow-up of 6 months (range, 2-14 months), four patients had progressed (after a median time of

TABLE 1. Baseline Characteristics

Parameter	CNS	Non-CNS	Total
Age, years			
> 1-3	3	2	5
> 3-6	3	6	9
> 6-12	13	6	19
> 12-18	3	2	5
> 18-25	5	4	9
Sex			
Male	22	12	34
Female	5	8	13
Origin			
India	26	13	39
Middle East	0	5	5
South East Asian	1	1	2
Others	0	1	1
Distance from residence to proton center, km			
≤ 500	5	6	11
> 500	22	14	36
Area of residence			
Metropolitan cities	14	19	33
Nonmetropolitan cities	13	1	14
Prearrival diagnosis			
Present	26	20	46
Not present	1	0	1
Pretreatment surgical procedure			
Radical excision with negative margins	9	2	11
Radical excision with positive margins	6	8	14
Partial excision	11	4	15
Biopsy only	1	6	7
Pretreatment chemotherapy			
Yes	6	14	20
No	21	6	27
Concurrent chemotherapy			
Yes	8	8	16
No	19	12	31
Presentation			
Upfront	14	10	24
Recurrent/salvage	13	10	23
Sedation during treatment			
For complete proton therapy	5	2	7
For simulation only	2	0	2
For simulation and initial fractions	2	2	4
No sedation	18	16	34
Reirradiation	4	3	7
Funding[a]			
Private insurance	3	3	6
Partial institutional support	13	15	28
Crowdfunding (full/partial)	3	6	9
Self-paid (with or without support from other sources)	22	15	37

[a]Data presented may not add up to 100%.

3 months), of whom three patients (one each with pelvic RMS, metastatic neuroblastoma, and recurrent ependymoma) progressed in the irradiated volume whereas one child with refractory yolk sac tumor progressed with lung metastases. Three of these patients are undergoing salvage treatment, whereas one patient remains controlled after salvage surgery and chemotherapy. All other patients continue to be followed up and have no clinical or radiologic signs of progression.

DISCUSSION

We have demonstrated that image-guided PBS PBT in our setting was safely implemented. Treatments were delivered with acceptable acute toxicities in patient cohorts that were carefully selected based on a multidisciplinary tumor board decision.

Challenges in implementing a PBT program in a country such as India are multipronged. They include:

1. Technical challenges in safe implementation of PBT by ensuring the availability of trained physicians, physicists, therapists, nurses, support staff, administrative staff, and engineers and by ensuring the availability of engineering parts, adequate maintenance/upkeep of the machines, and prompt redressal of technical issues.

2. Creating awareness about the optimal use, benefits, and harms of a relatively new cost- and labor-intensive technology among the general public and physicians in the region.

3. Financial challenges with respect to ensuring that most of the deserving patients receive the optimal treatment.

To a large extent, we overcame some of these challenges to safely implement a PBT program in the country. Because PBT is most established in the pediatric population, it was relatively easy to implement the program for this group of patients, which constituted 28% of the total number of patients treated so far. Most of the staff were recruited several months to a few years before treatments began at the center. This allowed for adequate training of the personnel in all aspects of PBT implementation at established proton centers across the United States and Europe and by means of frequent onsite training for the therapists by the vendor. Continuous engagement with the machine vendor, regulatory authorities, and local and central government

ensured the availability of machine-related equipment and personnel to minimize machine downtime and maximize patient safety. Extensive educational initiatives for the general public and physicians were undertaken by the clinical team much before the initiation of treatments to ensure appropriate patient referral by means of dedicated seminars and lecture series across the region. These educational initiatives continue to date. Our center also successfully underwent accreditation and certification for quality and patient safety by the Joint Commission International.

Because of the potential benefits of PBT in children, its use in this patient population has increased significantly. In the United States, there was nearly a 10-fold increase in the last 15 years.[21] A study done on the basis of a US national cancer database showed that patients treated with PBT are more likely to be from higher socioeconomic strata, have a residence located more than 200 miles from the treating center, be younger than 10 years of age, and have a diagnosis of bone or soft-tissue sarcoma, ependymoma, or medulloblastoma.[21] Despite a wide variation in sociopolitical and cultural backgrounds of patients and a significant variation in knowledge and perception regarding PBT among oncologists,[22] the demographic profile of patients treated at our center was comparable to other established PBT centers and that of the Pediatric Proton Consortium Registry.[23] The common sites for use of PBT at our center were CNS, head and neck, and skull base, as was noted in the Pediatric Proton Consortium Registry. The most common histologies treated at our center were pediatric sarcoma (including RMS, Ewing sarcoma, and non-RMS sarcomas), ependymoma, glioma, and medulloblastoma. Seventy-seven percent of our patients traveled $>$ 500 km, and 70% of them lived in metropolitan cities.

Our study demonstrated a low incidence of grade 3 acute toxicities despite a median dose of 54 CGE for CNS tumors and 59.4 CGE for non-CNS tumors. Twenty-eight percent of our patients received CSI, and nearly 70% of patients had non-CNS tumors that were in the head and neck region. Acute toxicities noted in our study were comparable to those in other reported studies.[24-27] Our study showed that overall, 62%, 26%, and 0% of patients had grade 1, grade 2, and grade 3 fatigue, respectively. Among patients with non-CNS tumors, a CTV $>$ 150 mL was associated with grade $\geq$ 2 fatigue. Treatment-related fatigue, which is multifactorial, has been under-reported across several studies, especially in children. In a study of 57 patients with RMS treated with PBT, although grade 1 fatigue was not reported, 14% of children had grade 2 fatigue,[24] whereas in another study wherein 48 children were treated with PBT for CNS tumors, 77% of children had grade 1 to 2 fatigue.[25] Expectedly, our study also showed that CSI and CCT were associated with grade $\geq$ 2 hematologic toxicity. Although PBT can potentially spare the vertebral bone marrow, 77% of our patients who underwent CSI were $<$ 15 years and hence the entire vertebral body was irradiated to the prescription dose to avoid spinal deformities. Among the three adolescents who received CSI where major portions of vertebral bodies were spared, two of them did not have any significant hematologic toxicity.

Image guidance has been shown to improve outcomes for several[28] tumor sites and is practiced widely across all age groups, including the pediatric population.[29] Incorporation of on-board CBCT imaging on PBT equipment has significantly improved the treatment precision. Because PBS is extremely depth-sensitive, small deformations of tissues in the beam path could lead to significant dose perturbations; therefore, frequent volumetric imaging is crucial. At our center, the on-treatment imaging protocol included one to two weekly check CT scans to quantify the dose perturbations apart from the routine use of on-board CBCT. In our study, six patients required adaptive replanning during the treatment. Three patients had significant weight loss leading to loss of tissue in the beam path. An increase in postoperative collection, significant deformation of the bowel as the result of gaseous distension, and frequent setup errors because of nonreproducibility of spinal curvature led to adaptive replanning in the others (one patient each). All these deformations, which triggered a replan, were detected during the on-board CBCT. Based on these results, our on-treatment imaging protocol was amended for most tumor sites to include check CT scans only if the CBCT image showed significant deformations. A detailed imaging audit of the first 150 patients will be published elsewhere.

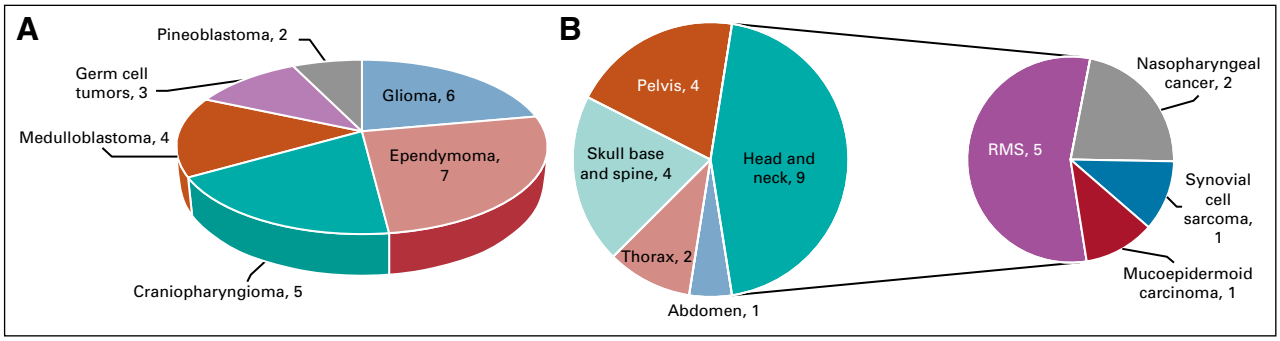

FIG 1. Pie diagram of site-wise diagnosis. (A) CNS and (B) non-CNS. RMS, rhabdomyosarcoma.

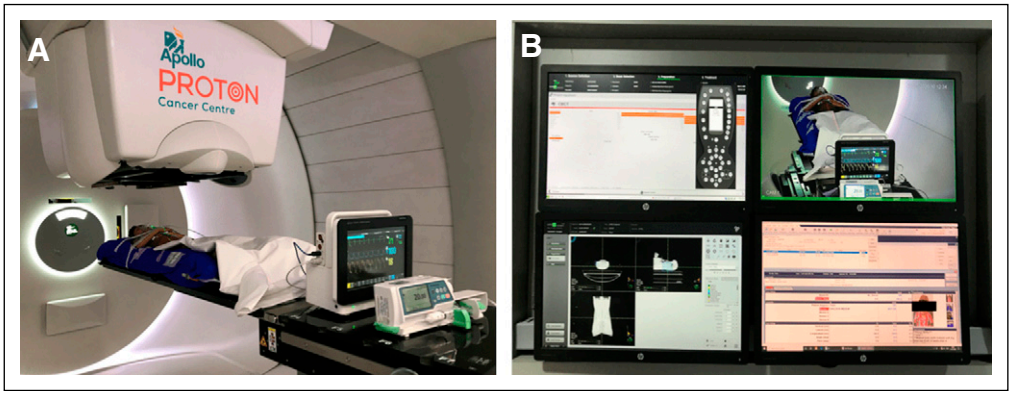

FIG 2. (A) Child being treated under sedation and (B) console with image guidance picture.

Despite the increased adoption of PBT in Europe and North America, the cost and access to PBT are the biggest hurdles to its widespread dissemination. In India, where up to 4.4% of all cancers are seen in children younger than 15 years,[30] there would be a significant demand for this modality. Unfortunately, because approximately 70% of health care is delivered by the private sector in India and the penetration of health insurance is limited, most patients must pay for health care services out of pocket. Only 13% of children in this study had the treatment funded through

TABLE 2. Treatment Characteristics

Variable	CNS Tumors	Non-CNS Tumors	All Patients
Site of treatment			
CSI	12	1	13
Whole ventricular	1	0	1
Focal supratentorial	8	0	8
Focal infratentorial	6	0	6
Skull base	0	3	3
Cervical spine	0	1	1
Face and ipsilateral neck	0	2	2
Face and bilateral neck	0	3	3
Thorax	0	2	2
Abdomen	0	0	0
Pelvis	0	4	4
Median CTV, mL (range)	253.0 (18.7-3,083.0)	148.5 (30.0-2,155.0)	175.0 (18.7-3,083.0)
Median dose prescribed, CGE (range)	54.0 (40.0-55.8)	59.4 (30.6-70.4)	54.8 (40.0-70.4)
Median no. of fractions (range)	30 (23-33)	32 (17-35)	31 (17-35)
Proton technique			
SFO	11	0	11
MFO	4	17	21
Hybrid	12	3	15
Median no. of fields (range)	3 (2-4)	3 (2-4)	3 (2-4)
Median no. of QA CT/MRI sessions per patient (range)	2 (1-4)	2 (1-5)	2 (1-5)
Median no. of CBCT sessions per patient (range)	16 (4-29)	20 (7-34)	19 (4-34)
Treatment with proton plus photon combination	8	1	9
Replanning (adaptive)	2	4	6

NOTE. Data presented as No. unless otherwise indicated.

Abbreviations: CBCT, cone beam computed tomography; CGE, cobalt gray equivalent; CSI, craniospinal irradiation; CT, computed tomography; CTV, clinical target volume; MFO, multifield optimization; MRI, magnetic resonance imaging; QA, quality assurance; SFO, single-field optimization.

TABLE 3. Acute Toxicities: CNS Versus Non-CNS

Toxicity	CNS (%)	Non-CNS (%)
Fatigue (grade)		
0	1	5
1	18	11
2	8	4
Alopecia (grade)		
0	0	10
1	0	6
2	27	4
Dermatitis (grade)		
0	1	1
1	17	3
2	9	15
3	0	1
Nausea (grade)		
0	6	6
1	16	9
2	5	5
Vomiting (grade)		
0	8	8
1	9	8
2	10	4
3	0	0
Mucositis (grade)		
0	20	7
1	2	1
2	5	11
3	0	0
Dysphagia (grade)		
0	20	9
1	2	1
2	5	10
3	0	0
Bowel (grade)		
0	26	18
1	1	1
2	0	1
Anemia (grade)		
0	13	11
1	11	5
2	3	2
3	0	2
4	0	0
Leucopenia (grade)		
0	14	7
1	3	2
2	2	5
3	7	3
4	1	3
Neutropenia (grade)		
0	15	11
1	2	2
2	2	3
3	7	3
4	1	1
Thrombocytopenia (grade)		
0	20	12
1	7	8
2	0	0
3	0	0
4	0	0

private insurance either paid by the families or employer. Sixty percent received partial financial support from our institution, and 20% received additional crowdfunding support toward the treatment.

Although the upfront cost of PBT is higher, studies have shown that it is more cost-effective than other conventional radiation techniques for certain pediatric tumors.[31-35] A study evaluating the cost-effectiveness of PBT in medulloblastoma revealed a 52% reduction in risk of secondary malignant neoplasms, 33% reduction in cardiovascular and noncardiovascular mortality, 88% reduction in risk of hearing loss, endocrinopathies, osteoporosis, and intelligence quotient decline with a gain of 0.68 quality-adjusted life-year per child.[31] Most of these cost-effectiveness studies were performed in North America and Europe and hence may not be relevant in the context of low- and middle-income countries. There is a need to generate relevant evidence based on local factors. Unfortunately, there are several challenges in evidence generation for PBT across the world. Active engagement by professional organizations, innovative clinical trial designs, and a collaborative approach between various stakeholders have been proposed as possible solutions.[36]

Although data were collected in consecutive patients, there were a few limitations to this study. The median follow-up was only 6 months and hence we were only able to report acute toxicities. We intend to report detailed dosimetric and clinical outcomes of relatively homogenous groups of patients after a sufficiently long follow-up period. Also, so far,

TABLE 4. Univariable Analyses (χ^2 test)

Variable	Hematologic Toxicity < Grade 2	Hematologic Toxicity ≥ Grade 2	*P*	Fatigue < Grade 2	Fatigue ≥ Grade 2	*P*	Mucositis[a] < Grade 2	Mucositis[a] ≥ Grade 2	*P*
Non-CNS tumors (n = 20)									
CTV, mL									
< 150	6	2	.264	8	0	.03	4	4	.456
> 150	6	6		6	6		4	8	
Location									
Head and neck	9	5	.55	10	4	.831	3	11	.01
Non-head and neck	3	3		4	2		5	1	
PBT dose, CGE									
< 59.4	3	5	.094	6	2	.69	3	5	.852
> 59.4	9	3		8	4		5	7	
CCT									
No	11	2	.02	9	4	.919	5	8	.848
Yes	1	6		5	2		3	4	
CNS tumors (n = 27)									
CCT									
No	15	3	.009	13	5	.386			
Yes	3	6		5	4				
CSI									
No	15	0	.001	11	4	.411			
Yes	3	9		7	5				
PBT dose, CGE									
< 54	11	4	.21	11	4	.71			
> 54	6	6		8	4				
Volume of least risk CTV, mL									
< 150	9	0	.05	6	3	.76			
> 150	8	10		13	5				

NOTE. Data presented as No. unless otherwise indicated.

Abbreviations: CCT, concurrent chemotherapy; CGE, cobalt gray equivalent; CSI, craniospinal irradiation; CTV, clinical target volume; PBT, proton beam therapy.

[a]Any mucositis, bowel, or esophageal toxicity.

we have been unable to collect quality of life data or perform detailed neurocognitive assessments; however, we will be doing so prospectively for the next cohort of patients. In conclusion, this study demonstrated the safe implementation of PBT for children and young adults on the Indian subcontinent. It also reported demographic features of the consecutive 47 patients treated at a new PBT facility and demonstrated that PBT leads to acceptable acute toxicities in judiciously selected children and young adults with CNS and non-CNS tumors. Longer follow-up is needed to evaluate its efficacy with respect to disease outcomes and late toxicities.

AFFILIATIONS

[1]Apollo Proton Cancer Centre, Chennai, India
[2]Apollo Specialty Hospital, Chennai, India

CORRESPONDING AUTHOR

Srinivas Chilukuri, MD, MBBS, Apollo Proton Cancer Centre, 4/661, Dr Vikram Sarabai Instronic Estate 7th St, Dr. Vasi Estate, Phase II, Tharamani, Chennai, Tamil Nadu 600096, India; Twitter: @DrSrinivas_C; e-mail: drsrinivas_c@apollohospitals.com.

AUTHOR CONTRIBUTIONS

Conception and design: Srinivas Chilukuri, Nagarjuna Burela, Pankaj Kumar Panda, Dayananda Sharma Shamurailatpam, Thirumalai Raja, Rakesh Jalali

Provision of study material or patients: Thirumalai Raja

Collection and assembly of data: Srinivas Chilukuri, Nagarjuna Burela, Ramya Uppuluri, D. Indumathi, Sapna Nangia, Pankaj Kumar Panda, Dayananda Sharma Shamurailatpam, Revathi Raj, Rakesh Jalali

Data analysis and interpretation: Srinivas Chilukuri, Nagarjuna Burela, Pankaj Kumar Panda, Dayananda Sharma Shamurailatpam, Thirumalai Raja
Manuscript writing: All authors
Final approval of manuscript: All authors
Agree to be accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/site/misc/authors.html.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Srinivas Chilukuri
Employment: Apollo Proton Cancer Centre
Leadership: Optimus Oncology Private Ltd
Stocks and Other Ownership Interests: Optimus Oncology Private Ltd
Honoraria: AstraZeneca
Consulting or Advisory Role: Varian Medical Systems
Speakers' Bureau: AstraZeneca

Nagarjuna Burela
Employment: Apollo Proton Cancer Centre

Sapna Nangia
Consulting or Advisory Role: Varian International India Ltd

Pankaj Kumar Panda
Employment: Apollo Proton Cancer Centre, Apollo Hospitals Enterprise Ltd
Travel, Accommodations, Expenses: Reliance Life Sciences

Rakesh Jalali
Employment: Apollo Proton Cancer Centre, Apollo Hospitals Enterprise Ltd

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

We acknowledge the contributions of all the colleagues in the department of radiation oncology, medical physics including the radiation therapists, nursing staff, and administrative staff for rendering services during the treatment and analyzing these data. We also acknowledge all the referring physicians and pediatricians globally for putting their trust in us and maintaining the continuum of care.

REFERENCES

1. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572-1582, 2006
2. Armstrong GT, Kawashima T, Leisenring W, et al: Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 32:1218-1227, 2014
3. Diller L, Chow EJ, Gurney JG, et al: Chronic disease in the Childhood Cancer Survivor Study cohort: A review of published findings. J Clin Oncol 27:2339-2355, 2009
4. Meshref M, ElShazly N, Nasr M, et al: Effect of different doses of prophylactic cranial irradiation in childhood lymphoblastic leukemia on CNS relapse, late cognitive decline and learning disabilities. J Cancer Ther Res 2:10, 2013 doi:10.7243/2049-7962-2-10
5. Packer RJ, Goldwein J, Nicholson HS, et al: Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. J Clin Oncol 17:2127-2136, 1999
6. Casey DL, Kushner BH, Cheung NV, et al: Reduced-dose radiation therapy to the primary site is effective for high-risk neuroblastoma: Results from a prospective trial. Int J Radiat Oncol Biol Phys 104:409-414, 2019
7. Jalali R, Gupta T, Goda JS, et al: Efficacy of stereotactic conformal radiotherapy vs conventional radiotherapy on benign and low-grade brain tumors: A randomized clinical trial. JAMA Oncol 3:1368-1376, 2017
8. Kahalley LS, Peterson R, Ris MD, et al: Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. J Clin Oncol 38:454-461, 2020
9. Eaton BR, Esiashvili N, Kim S, et al: Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. Neuro-oncol 18:881-887, 2016
10. Chung CS, Yock TI, Nelson K, et al: Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 87:46-52, 2013
11. Sardaro A, Carbonara R, Petruzzelli MF, et al: Proton therapy in the most common pediatric non-central nervous system malignancies: An overview of clinical and dosimetric outcomes. Ital J Pediatr 45:170, 2019
12. Yock TI, Bhat S, Szymonifka J, et al: Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. Radiother Oncol 113:89-94, 2014
13. Carbonara R, Di Rito A, Monti A, et al: Proton versus photon radiotherapy for pediatric central nervous system malignancies: A systematic review and meta-analysis of dosimetric comparison studies. J Oncol 2019:5879723, 2019
14. Yock TI, Yeap BY, Ebb DH, et al: Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: A phase 2 single-arm study. Lancet Oncol 17:287-298, 2016
15. Cotter SE, Herrup DA, Friedmann A, et al: Proton radiotherapy for pediatric bladder/prostate rhabdomyosarcoma: Clinical outcomes and dosimetry compared to intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 81:1367-1373, 2011
16. Breneman JC, Donaldson SS, Constine L, et al: The Children's Oncology Group radiation oncology discipline: 15 years of contributions to the treatment of childhood cancer. Int J Radiat Oncol Biol Phys 101:860-874, 2018
17. Weber DC, Habrand JL, Hoppe BS, et al: Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN. Radiother Oncol 128:44-55, 2018
18. Indelicato DJ, Merchant T, Laperriere N, et al: Consensus report from the Stockholm pediatric proton therapy conference. Int J Radiat Oncol Biol Phys 96:387-392, 2016
19. Tonse R, Noufal MP, Deopujari CE, et al: India's first proton beam therapy pediatric patient. Neurol India 68:189-191, 2020
20. Tonse R, Chilikuri S, Shamurailatpam D, et al: Introduction of image-guided pencil beam for skull base tumors in India: A report of two cases and a brief review of the literature. Neurol India 68:42-44, 2020

21. Odei B, Frandsen JE, Boothe D, et al: Patterns of care in proton radiation therapy for pediatric central nervous system malignancies. Int J Radiat Oncol Biol Phys 97:60-63, 2017
22. Chilukuri S, Jalali R, Panda PK: Survey on variations of knowledge and perception amongst radiation oncologists across India regarding proton beam therapy (PBT). Int J Part Ther 6:45-491, 2020 doi:10.14338/IJPT.19-PTCOG-6.4
23. Hess CB, Indelicato DJ, Paulino AC, et al: An update from the Pediatric Proton Consortium Registry. Front Oncol 8:165, 2018
24. Ladra MM, Szymonifka JD, Mahajan A, et al: Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. J Clin Oncol 32:3762-3770, 2014
25. Suneja G, Poorvu PD, Hill-Kayser C, et al: Acute toxicity of proton beam radiation for pediatric central nervous system malignancies. Pediatr Blood Cancer 60:1431-1436, 2013
26. Selo N, Bölling T, Ernst I, et al: Acute toxicity profile of radiotherapy in 690 children and adolescents: RiSK data. Radiother Oncol 97:119-126, 2010
27. Song S, Park HJ, Yoon JH, et al: Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors. Acta Oncol 53:1158-1164, 2014
28. Bujold A, Craig T, Jaffray D, et al: Image-guided radiotherapy: Has it influenced patient outcomes? Semin Radiat Oncol 22:50-61, 2012
29. Alcorn SR, Chen MJ, Claude L, et al: Practice patterns of photon and proton pediatric image guided radiation treatment: Results from an International Pediatric Research consortium. Pract Radiat Oncol 4:336-341, 2014
30. National Cancer Registry Programme: Three-Year Report of Population Based Cancer Registries 2012-2014: Incidence, Distribution, Trends in Incidence Rates and Projections of Burden of Cancer (Report of 27 PBCRs in India). Indian Council of Medical Research, Bengaluru, India. 2016.
31. Lundkvist J, Ekman M, Ericsson SR, et al: Proton therapy of cancer: Potential clinical advantages and cost-effectiveness. Acta Oncol 44:850-861, 2005
32. Lundkvist J, Ekman M, Ericsson SR, et al: Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. Cancer 103:793-801, 2005
33. Mailhot Vega R, Kim J, Hollander A, et al: Cost effectiveness of proton versus photon radiation therapy with respect to the risk of growth hormone deficiency in children. Cancer 121:1694-1702, 2015
34. Verma V, Mishra MV, Mehta MP: A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 122:1483-1501, 2016
35. Noticewala SS, Williamson CW, Murphy JD: Cost-effectiveness of proton therapy for parameningeal rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 96(2, supplement)E398, 2016
36. Chilukuri S, Panda PK, Jalali R: PITChing (professional organisations, innovative trial designs and collaborative approach) for evidence generation for proton therapy. Radiat Oncol 15:138, 2020