Demographic profile and early clinical experience of treating children and young adults with image guided proton beam therapy in India

Srinivas Chilukuri[1], Nagarjuna Burela[1], RAMYA UPPULURI[2], Indumathi D[1], Ch Kartikeswar Patro[1], Rajesh Thiyagarajan[1], Noufal MP[1], Sapna Nangia[1], Arjunan Manikandan[1], Ganapathy Krishnan[1], Pankaj Panda[1], Utpal Gaikwad[1], Sham Sundar[1], Dayananda Sharma[1], REVATHI RAJ[3], T Raja[1], and Rakesh Jalali[1]

[1]Apollo Proton Cancer Centre
[2]Apollo Speciality Hospital
[3]APOLLO SPECIALITY HOSPITAL

June 24, 2020

Abstract

Background: We report demographic profile and our initial experience of treating children and young adults with image guided pencil beam scanning proton beam therapy (PBS-PBT) at our centre. Material and methods: All patients younger than 25 years, consecutively treated with PBT based on a multi-disciplinary tumor board decision were analyzed. Patients were treated under daily on-board kilovoltage x-ray and/or cone beam CT scan guidance. The demographic profile, treatment characteristics and the acute toxicities were reported. Patient and treatment related factors and their association with acute toxicities were analyzed using univariate and multivariate analysis. Results: Forty-seven patients {27 with central nervous system(CNS) and 20 with non-CNS tumors} with a median age of 9 years were evaluated. Most common diagnoses were ependymoma, rhabdomyosarcoma and glioma. Median dose delivered was 54.8CGE(40-70.4) to a median clinical target volume of 175cc (18.7-3083cc) with 34% requiring concurrent chemotherapy(CCT). Acute grade-2 and 3 dermatitis, mucositis, and hematological toxicity was noted in 45% and 2%; 34% and 0%; 38% and 30%; respectively. Grade-2 fatigue was noted in 26%. On univariate analysis, CCT(p=0.009) and cranio-spinal irradiation(p<0.001) were associated with grade-2 or more hematological toxicity in patients with CNS tumors. Among non-CNS tumors, clinical target volume more than 150cc was associated with grade-2 or more fatigue(p=0.017). Conclusions: The demographic pattern of patients treated with PBT at this new and only centre in the region was similar to previously published literature. Image guided PBS-PBT resulted in acceptable acute toxicities both among children with CNS and non-CNS tumors.

Demographic profile and early clinical experience of treating children and young adults with image guided proton beam therapy in India

Authors:

Srinivas Chilukuri, MD[1*], Nagarjuna Burela, DNB[1], Ramya Uppuluri, MD [2], Indumathi D, MD [3], Ch Kartikeswar Patro, Dip RP, MSc Phy[4], Rajesh Thiyagarajan, MSc [4], Noufal MP, MSc, PhD [4], Sapna Nangia, MD[1], Arjunan Manikandan, MSc, Dip.R.P[4], Ganapathy Krishnan, MSc, PhD [4], Pankaj Kumar Panda, BDS, MSc [1], Utpal Gaikwad, MD[1], Dayananda S Sharma, PhD [4], Sham Sundar C, DMRT, MD [1], Revathi Raj, MBBS, DCH, PLAB, MRCP, FRCPath [2], T Raja, MD, DM [5], Dr Rakesh Jalali, MD [1]

[1]Department of Radiation Oncology

Apollo Proton Cancer Centre

Chennai, India

[2]Department of Pediatric Hemato - Oncology,

Apollo Speciality Hospital,

Chennai, India

[3]Department of Anaesthsiology,

Apollo Proton Cancer Centre

Chennai, India

[4]Department of Medical Physics,

Apollo Proton Cancer Centre

Chennai, India

[5]Department of Medical Oncology,

Apollo Proton Cancer Centre

Chennai, India

[*]**Corresponding author:**

Name: Dr Srinivas Chilukuri

Address: 4/661, Dr Vikram Sarabai Instronic Estate 7th St, Dr. Vasi Estate, Phase II, Tharamani, Chennai, Tamil Nadu 600096

Phone: 044-2454 8888

E-mail: csrinivas1@gmail.com

Word Count : 1. Abstract: 246

2. Main text: 3027

Number of tables: 4

Number of figures: 2

Running title: Proton beam therapy in children and young adolescents

Key words: proton beam therapy, demography, acute toxicities, children, adolescent

Abbreviations:

CBCT	Cone Beam Computed Tomography
CGE	Cobalt Grey Equivalent
CNS	Central Nervous System
CSI	Cranio-Spinal Irradiation
CTV	Clinical Target Volume
IMRT	Intensity Modulated Radiation Therapy
IGRT	Image Guided Radiation Therapy
MFO	Multi Field Optimization
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PBT	Proton Beam Therapy
PBS	Pencil Beam Scanning

CBCT	Cone Beam Computed Tomography
PPCR	Proton Photon Cancer Registry
PSQA	Patient Specific Quality Assurance
PSPT	Passive Scattering Proton Therapy
QALY	Quality Adjusted Life Year
RMS	Rhabdomyosarcoma
SFO	Single Field Optimization
SMN	Secondary Malignant Neoplasms
SRT	Stereotactic Radiation Therapy
WVI	Whole Ventricular Irradiation

Abstract

Background:

We report demographic profile and our initial experience of treating children and young adults with image guided pencil beam scanning proton beam therapy (PBS-PBT) at our centre.

Material and methods:

Allpatientsyounger than 25years,consecutively treated with PBTbased on a multi-disciplinary tumor board decision were analyzed. Patients were treated under daily on-board kilovoltage x-ray and/or cone beam CT scan guidance. The demographic profile, treatment characteristics and the acute toxicities were reported. Patient and treatment related factors and their association with acute toxicities were analyzed using univariate and multivariate analysis.

Results:

Forty-seven patients {27 with central nervous system(CNS) and 20 with non-CNS tumors} with a median age of 9years were evaluated. Most common diagnoses were ependymoma, rhabdomyosarcoma and glioma. Median dose delivered was 54.8CGE(40-70.4) to a median clinical target volume of 175cc (18.7-3083cc) with 34% requiring concurrent chemotherapy(CCT). Acute grade-2 and 3 dermatitis, mucositis, and hematological toxicity was noted in 45% and 2%; 34% and 0%; 38% and 30%; respectively. Grade-2 fatigue was noted in 26%. On univariate analysis, CCT($p=0.009$) and cranio-spinal irradiation($p<0.001$) were associated with grade-2 or more hematological toxicityin patients with CNS tumors. Among non-CNS tumors, clinical target volume more than 150cc was associated with grade-2 or more fatigue($p=0.017$).

Conclusions:

The demographic pattern of patients treated with PBT at this new and only centre in the region was similar to previously published literature. Image guided PBS-PBT resulted in acceptable acute toxicities both among children with CNS and non-CNS tumors.

Demographic profile and early clinical experience of treating children and young adults with image guided proton beam therapy inIndia

Introduction:

De-intensification of cancer treatment in children and young adults has gathered considerable momentumas the long-term childhood cancer survivors are at an increased risk of serious health related issuesrelatedto treatment[1,2]. Since radiation is one of the major contributors to the late effects in children including growth defects, neuro-cognitive defects, endocrinopathies, cardiovascular effects, lymphedema and secondary malignant neoplasms (SMN) [3], there has been a widespread evaluation of radiation de-intensification in the last two decades for several haematological and solid tumors [4,5,6]. Radiation therapy however cannot be completely avoided in many clinical protocols and remain an integral component of management and the best possible conformal techniques of radiation should be employed in such situations.

Proton beam therapy (PBT) owing to its superior physical property results in significantly lower doses of radiation to the healthy normal structures thereby has a potential tomitigate both acute and late radiation related effects. This is especially impactful in children and young adults due to much larger tumor to body volumes (compared to adults) and also due to higher propensity to develop permanent radiation sequelae. Multiple prospective and retrospective studies have shown that the dosimetric benefit achieved results in favourable clinical outcomes[7-11].Despite the lack of randomized controlled trials demonstrating superiority of PBT over conformal photon-based techniques most collaborative group trials conducted in North America (Children's Oncology group) and Europe allow patients to be treated with PBT [12, 13]. In fact, it is the preferred treatment modality for a majority of leading pediatric oncologists of the worldfor most solid tumors requiring radiation therapy[14]. The concerns related to safety of the older generation passive scattering proton therapy (PSPT) such as neutron contamination, 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 biological uncertainties of PBT.

Our multi-room PBT facility with fully rotating gantries capable of delivering contemporary image guided PBS PBT is the first proton therapy centre in the Indian subcontinent. The patient treatments began in Jan 2019 [15,16] and since then our centre has been the only referral centre 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 socio-economic, cultural and educational back grounds and very little is known regarding their preference and adoption of this relatively new and cost-intensive technology. We hereby report the demographic profile and our initial experience of treating children and young adults with image guided PBS PBT.

Materials and Method

For allpatients treated with PBTat our centre, the baseline characteristics, imaging features, pathology including molecular information, multimodality treatment, proton therapy technique, plan parameters, quality assurance metrics, set-up and delivery parameters, treatment response and their subsequent follow-up information are being routinely captured in a prospectively maintained registry. The present work focusses on reporting baseline characteristics, diagnosis, treatment delivery parameters, treatment related acute toxicity and follow-up information of all children and young adults <25 years of age consecutively treatedpatients treated at our centre.

Initial work-up and selection

Decision to offer PBTin each of the patients was taken after a thorough evaluation and discussion in 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 treatmentrequiring relatively high doses of radiation orwithtumors located adjacent toradiosensitive structures making them prone to late radiation sequelae or had required magna-field irradiation were recommended PBT. Patients requiring whole organ irradiation were not chosen for PBT except in patients receiving craniospinal irradiation (CSI). In certain cases, a dosimetric plan was generated before a decision to treat with PBT was taken.

A few days prior to the day of simulation, younger children (<10 years old), were encouraged to visit the treatment facility to view treatments of other children to familiarize the procedure and reduce anxiety.All patients underwent a simulation procedure (with or without sedation) consisting of immobilization and multimodality imaging (CT and MRI of the site to be treated) nearly a week before the decided day of starting treatment.

PBT planning

Planning process consisted of target, 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 multi-field optimization technique (SFO or MFO) or a combination of both (referred to as Hybrid plans) which were robust to range and setup uncertainties up to acceptable

thresholds. A pre-treatment patient specific quality assurance (PSQA) was carried out to verify the approved plan before the treatment was implemented. Each day pre-treatment imaging with KV-X rays and/or CBCT was carried out to verify the patient position and to ensure the precision of treatment on a daily basis. Patients were followed up atleast weekly to assess the treatment toxicities (NCI CTC version 4.0). Repeat check scans(CT or MRI) weredone periodically (once in 1-2 weeks as decided by the treating team) orif required during the treatment (on the basis of clinical or CBCT information). Patients received concurrent chemotherapy as per the treatment plan. All patients underwent response assessment imaging 4-12 weeks following treatment and were followed up regularly.Data was analysed using SPSS version 22. Relevant treatment and tumor related factors and their association with acute toxicities wereanalysed using Chi-square test and multivariate analysis of variance. When multiple clinical target volumes (CTV) were irradiated to different doses, CTV that was prescribed a lower dose was considered for analysis.

Results

47 patients with a median age of 9 years (2-25 years)were treated at our institution with image guided PBS PBT till the cut-off period. During this period this patient population constituted 28% of the total patients treated with PBT at our centre. Table-1 describes the baseline characteristics of the patients. 27 patients were diagnosed with a CNS tumor, and the rest with a non-CNS tumor [Fig-1a and 1b].The most common diagnosis was ependymoma followed by rhabdomyosarcoma (RMS) and glioma. 23 patients who had recurrent disease were referred for PBT of which 7 patientswere for re-irradiation.13 children (80% of children younger than 6 years and 2 children between 6-8 years) required atleast one procedure of sedation during either simulation and/or treatment[Fig 2a and 2b]. Of these, only 7 required sedation during the entire treatment (all of them were <4 years except one autistic child who was 8 years old).

Treatment related characteristics have been described in Table-2. Among patients who received CSI, 3 patients were younger than 6 years, 7 were between 7-15 years and 3 were >15 years. One 15-year-old girl with an intracranial germinoma received whole ventricular irradiation (WVI).On analysis of the technique of PBT planning, MFO was used in 21 patients (of which 17 were non-CNS tumors), SFO was used in 11 patients (all of them being CNS tumors) and hybrid planswere used in 15 patients (including all 13 patients of CSI). Median number of fractions received was 30 (23-33) for CNS patients to a median dose of 54CGE(40-55.8Gy) and 32 (17-35) for non-CNS patients to a median dose of 59.4CGE (30.6-70.4). One patient of recurrent para-meningeal RMS received hyperfractionation with 52.8CGE in 40 fractions with a twice daily fractionation.

Median number of CBCT's per patient for CNS tumors was 16 (4-29), whereas for patients with non-CNS tumors it was 20 (7-33). 6 patients underwent an adaptive re-planning based on the check CT scans and/or CBCT imaging. 16 patients (34%) also received concurrent chemotherapy as 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 0.95Kg (0.1-10.5kg corresponding to 0.15-10.9% of body weight). 17 patients gained weight during the treatment with a median of 0.9kg (0.1-5.3Kg or 0.5-21.7%). Table 3 depicts acute toxicities noted in CNS and non-CNS tumors. Most common acute toxicity noted irrespective of the site of irradiation was radiation dermatitis. 21 patients (45%) had grade 2 dermatitis and only 1 patient (2%) had grade 3 dermatitis (13-year child with nasopharyngeal carcinoma who received 70Gyto bilateral neck). 18 patients (38%) had grade> 2 and 14 patients (30%) had grade> 3 hematological toxicities of which 12 patients (26%) had grade > 3 neutropenia. None of the patients developed grade 3 mucositis or dysphagia which mandated a need for feeding tube during treatment.

On univariate analysis (Chi-square test) of patients with CNS tumors, concurrent chemotherapy (p=0.009), CSI (p<0.001)and volume of CTVwere associated with > 2 grade hematological toxicity[Table 4]. On multivariate analysis both concurrent chemotherapy (p=) and CSI (p) were independently associated with> 2 grade hematological toxicity.

Among non-CNS tumors, on univariate analysis CTV>150cc was significantly associated with > 2grade fatigue (p=0.017), head neck irradiation (p=0.01) was associated with> 2 grade mucositis and concurrent chemotherapy(p=0.02) was associated with grade > 2 hematological toxicity. The same were found significant on multivariate analysis. (p=0.05, p=0.03 and p=0.01 respectively)

Follow-up and earlyoutcomes

With a median follow up of 6 months (2-14 months), 4 patients had progressed (after a median time of 3 months) of which 3 patients progressed in the irradiated volume whereas 1 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 on follow-up and have no clinical or radiological signs of progression.

Discussion

Given the paucity of data from this part of the world, we demonstrated that image guided PBS PBT in our setting can be safely delivered with acceptable acute toxicities in children and young adults. 28% of the patients treated at our centre with PBT belonged to this age group. Despite a wide variation in socio-political and cultural backgrounds of patients and physicians, the demographic profile of patients treated at our centre was comparable to other established PBT centres. A survey among 253 radiation oncologists in India, there was a significant variation in perception and knowledge regarding PBT [17]. According to this survey, although 90% of the respondents believed PBT has a definite role in pediatric tumors, 69% believed that there is a need for randomized trials in pediatric population.

Due to potential benefits of PBT, increasing number of children are being treated with this modality. The use of PBT for children in the United States has increased nearly 10-fold in the last 15 years [18]. A study based on US national cancer database showed that the patients treated with PBT are more likely to be from higher socioeconomic strata, have a residence >200 miles from the treating centre, younger (<10 years), and have a diagnosis of bone or soft-tissue sarcoma, ependymoma, or medulloblastoma[18]. The demographic pattern of patients treated at our centre was very similar to the patient profile across several established proton therapy centres of North America and Europe and that of the pediatric proton photon cancer registry (PPCR) [19]. The common sites for use of proton therapy at our centre were CNS, head neck and skull base as was noted in the PPCR. The most common histologies treated at our centre were pediatric sarcoma (including RMS, Ewing's and Non-RMS sarcomas), ependymoma, glioma and medulloblastoma. 77% of our patients travelled more than 500km and 70% of them belonged to metropolitan cities.

Therapeutic ratio in radiation therapy is the relationship between the tumor control probability and normal tissue complications. Advances inconventional radiation therapysuch as IMRT, image guided radiation therapy (IGRT) and stereotactic radiation therapy (SRT) have significantly improved this ratio in the last two decades.Several dosimetric studies have consistently shown that PBT can improve the therapeutic ratio even further due to significant reductions in the total radiation dose received by the normal tissues despite the fact that most literature is based onthe previous generation passive scattering proton therapy (PSPT) without image guidance. This dosimetric benefit can potentially mitigate the risk of major late toxicities such as hearing loss, neuro-cognitive impairment, endocrinopathies, vision impairment, cardiovascular toxicities, gonadal dysfunction, growth defects/deformities, pneumonitis, nephropathy, late bowel complications, xerostomia, lymphedema and SMN [20, 21, 22].In a phase 3 setting, reduction in the dose to pituitary hypothalamic axis and hippocampus has shown to limit neuro-cognitive decline and endocrine dysfunction [23] and these results can be extrapolated to several other contexts.

Apart from the potential to minimize toxicities due to sharp dose gradients, protons atleast theoretically areradiobiologically more effective than photons (10-70% higher radiobiological effectiveness) [24]. However, in reality there is no conclusive clinical evidence to prove that the increased radiobiological effectiveness leads to improvement in local control, but there is evidence to show thatmodern PBT plans are dosimetrically superior for most indications.

Our study demonstrated very low incidence of grade 3 acute toxicities despite a median dose of 54CGE for CNS, 59.4CGE for non-CNS tumors, 28% of our patients received CSI, and nearly 70% of patients of non-CNS tumors were in the head neck region. Acute toxicities noted in our study were comparable to other reported studies [25-28].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, CTV>150cc was associated with grade > 2 fatigue. Treatment related fatigue, which is multi-factorial, has been under-reported across several studies especially in children. In a study of 57 RMS patients treated with PBT, although grade 1 fatigue was not reported, 14% children had grade 2 fatigue [25] whereas in another study where 48 children were treated with PBT for CNS tumors, 77% of children had grade 1-2 fatigue[26]. Expectedly our study also showed that CSI and concurrent chemotherapy was associated with grade> 2 hematological toxicity. Although PBT can potentially spare the vertebral bone marrow, 77% of our patients who underwent CSI were of <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 hematological toxicity.

Image guidance has shown to improve radiation therapy outcomes for several [29]tumor sites and is practiced widely across all age groups including the pediatric population [30].Incorporation of on-board CBCT imaging on PBT equipment, has significantly improved the treatment precision and efficiency. Since PBS is extremely depth sensitive,small deformations of the tissues in the beam path could lead to significant dose perturbations and therefore frequent volumetric imaging is crucial.At our centre, our on-treatment imaging protocol included 1-2 weekly check CT scans to quantify the dose perturbations apart from the routine use of on-board CBCT. In our study, 6 patients required adaptive re-planning during the treatment. Threepatientshada significant weight-loss leading to loss of tissue in the proton beam path. Increase in post-operative collection, significant deformation of bowel due to gaseous distension and frequent setup errors due to non-reproducibility of spinal curvature led to adaptive re-planning in 3 patients (one each). All these deformations which triggered a re-plan were picked upduring the on-board CBCT.None of the fivepatients with craniopharyngioma requiredadaptive re-planning. Based on these results, our on-treatment imaging protocol was amended for most tumor sites to include check CT's only if the CBCT showed significant deformations. A detailed imaging audit of the first 150 patients will be published elsewhere.

Despite the increased adoption of PBT in Europe and North America, the cost and access to PBTare the biggest hurdles to its widespread dissemination.In India where nearly up to 4.4% of all cancers are seen in children younger than 15 years[31] there would be a significant demand for this modality. Unfortunately,since approximately 70% of healthcare is delivered by the private sector in India and the penetration of health insurance is limited, most patients have to pay for healthcare services out of pocket. Only 13% of children in this studyhad the treatment funded through insurance. 60% received partial financial support from our institution and 20% received additional crowdfunding support towards the treatment.

Although the upfront cost of proton therapy is higher, studies have shown that it is more cost effective than other conventional radiation techniques for certain pediatric tumors.[32-36]A study evaluating cost effectiveness of PBT in medulloblastoma revealed a 52% reduction in risk of SMN, a 33% reduction in cardiovascular and non-cardiovascular mortality, an 88% reduction in risk of hearing loss, endocrinopathies, osteoporosis and IQ decline with gain of 0.68 QALY/child with an estimated incremental cost-effectiveness ratio of -23,600 Euros [32]. 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 and there is a need for generating relevant evidence based on local factors.Unfortunately there are several challenges inevidence generation for PBT across the world. Active engagement by professional organizations, innovative clinical trial designs and a collaborative approach between various stake-holders have been proposed as possible solutions to overcome some of these challenges [37]

This study was aimed to report the demographic features and our initial experience with treating children and young adults with PBT at our centre. Although the data was prospectively collected in consecutive patients, there were a few limitations to this study. The median follow-up period was only 6 months and

hence we wereonly able to report acute toxicities. We intend to report detailed dosimetric and clinical outcomes of relatively homogenous groups of patients after a sufficiently longer follow-up period. Also, so far we were unable to collect quality of life or detailed neuro-cognitive assessments, however we would be prospectively collecting the same in the future.

Conclusion

This study reports demographic features of the consecutive 47 patients treated at a new proton therapy centre in the initial 14 months. This study also showed that PBT can bedelivered safely with acceptable acute toxicitiesfor judiciously selected children and young adults with CNS and non-CNS tumors. A longer follow-up is needed to evaluate its efficacy with respect to disease outcomes and late toxicities.

Conflicts of interest: No

References

1. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006;355(15):1572-1582.
2. Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 2014;32(12):1218–27.
3. Diller L, Chow EJ, Gurney JG, Hudson MM, Kadin-Lottick NS, Kawashima TI, et al. Chronic disease in the childhood cancer survivor study cohort: a review of published findings. J Clin Oncol 2009;27(14):2339–55.
4. Meshref M, ElShazly N, Nasr M and AbdElhai R. Effect of different doses of prophylactic cranial irradiation in childhood lymphoblastic leukemia on CNS relapse, late cognitive decline and learning disabilities. journal of Cancer Therapeutics and Research 2013, 2:10.
5. Packer RJ, Goldwein J, Nicholson HS, Vezina LG, Allen JC, Ris MD, 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. 1999;17(7):2127-2136.
6. Casey DL, Kushner BH, Cheung N KV, Roberts SS, LaQuaglia MP, Wolden SL, 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. 2019;104(2):409-414.
7. Kahalley LS, Peterson R, Ris MD, Janzen L, Okcu MF, Grosshans DR, Ramaswamy V, et al. Superior Intellectual Outcomes After Proton Radiotherapy Compared with Photon Radiotherapy for Pediatric Medulloblastoma. J Clin Oncol. 2020;38:454-61.
8. Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. Neuro Oncol 2016;18:88;1–7.
9. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiat Oncol Biol Phys 2013;87:46–52.
10. Sardaro A, Carbonara R, Petruzzelli MF, Turi B, Moschetta M, Scardapane A, et al. Proton therapy in the most common pediatric non-central nervous system malignancies: an overview of clinical and dosimetric outcomes. Ital J Pediatr 2019;45(1):170.
11. Yock TI, Bhat S, Szymonifka J, et al. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. Radiother Oncol 2014;113:89–94.
12. Breneman JC, Donaldson SS, Constine L, Merchant T, Marcus K, Paulino A, et al. The Children's Oncology Group Radiation Oncology Discipline: 15 Years of Contribution to the Treatment of Childhood Cancer. Int J Radiat Oncol Biol Phys 2018;101(4):860-874.
13. Weber DC, Habrand JL, Hoppe BS, Kayser CH, Laack NN, Langendijk JA, 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* . 2018;128(1):44-55.
14. Indelicato D, Merchant T, Leperriere N, Lassen Y, Vennarini S, Wolden S, et al. Consensus report from the Stockholm pediatric proton therapy conference. Int J Radiat Oncol Biol Phys 2016;96(2):387-392.
15. Tonse R, Noufal MP, Deopujari CE, Jalali R. India's first proton beam therapy pediatric patient.

Neurol India 2020;68(1):189-191.
16. Tonse R, Chilukuri S, Shamurailatpam D, Jalali R. Introduction of image guided pencil beam scanning proton therapy for skull base tumors in India: A report of two cases and a brief review of literature. Neurol India 2020;68(1):42-44.
17. Chilukuri S, Jalali R, Panda PK. Survey on variations of knowledge and perception amongst radiation oncologists across India regarding proton beam therapy. Int J Particle Therapy 2020;6(4):PTC58-0527.
18. Odei B, Frandsen JE, Boothe D, Ermoian RP, Poppe MM. Patterns of Care in Proton radiation therapy for pediatric central nervous system malignancies. Int J Radiat Oncol Biol Phys 2017;97(1):60–3.
19. Hess CB, Indelicato DJ, Paulino AC, Hartsell WF, Hill-Kayser CE, Perkins SM, et al. An update from the Pediatric Proton Consortium Registry. Front Oncol 2018;8:165.
20. Carbonara R, Di Rito A, Monti A, Rubini G, Sardaro A. Proton versus photon radiotherapy for pediatric central nervous system malignancies: A systematic review and meta-Analysis of dosimetric comparison studies. J Oncol 2019:5879723.
21. Yock TI, Yeap BY, Ebb DH, Weyman E, Eaton BR, Sherry NA, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol. 2016;17:287-298.
22. 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 2011;81:1367–73.
23. Jalali R, Gupta T, Goda JS, Goswami S, Shah N, Dutta D, et al. Efficacy of stereotactic conformal radiotherapy vs conventional radiotherapy on benign and low-grade brain tumors: a Randomized clinical trial. JAMA Oncol 2017;3(10)1368-1376.
24. Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as function of biological endpoint, dose, and linear energy transfer. *Phys Med Biol* 2014;59(22):R419-72.
25. Ladra MM, Szymonifka JD, Mahajan A, Friedmann AM, Yeap BY, Goebel CP, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma.J Clin Oncol 2014;32(33):3762-3770.
26. Suneja G, Poorvu PD, Hill-Kayser C, Lustig RA. Acute toxicity of proton beam radiation for pediatric central nervous system malignancies. Pediatr Blood Cancer 2013;60(9):1431–6.
27. Selo N, Bölling T, Ernst I, Pape H, Martini C, Rübe C, et al. Acute toxicity profile of radiotherapy in 690 children and adolescents: RiSK data. Radiother Oncol 2010;97(1):119–26.
28. 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 2014;53:1158–64.
29. Bujold A, Craig T, Jaffray D, Dawson LA. Image-guided radiotherapy: Has it influenced patient outcomes? Semin Radiat Oncol 2012;22:50-61.
30. Alcorn SR, Chen MJ, Claude L,Dieckmann K, Ermoian RP,Ford EC, et al. Practice patterns of photon and proton pediatric image guided radiation treatment: results from an International Pediatric Research consortium. *Pract Radiat Oncol* . 2014;4(5):336-341.
31. Three Year Report of the Population Based Cancer Registries 2012-2014: Report of 27 PBCRs; National Cancer Registry Programme, Indian Council Medical Research, Bangalore. 2016.
32. Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncol 2005;44(8):850-861.
33. Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. Cancer 2005;103(4):793–801.
34. 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 2015;121:1694–702.
35. Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 2016;122(10):1483–501.
36. Noticewala SS, Williamson CW, Murphy JD. Cost-effectiveness of proton therapy for parameningeal rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2016;96(2)supplement:e398.

37. Chilukuri S, Panda PK, Jalali R. PITChing(professional organizations, innovative clinical trial design and collaborative approach) for evidence generation for proton therapy. RadiatOncol2020;15:138 https://doi.org/10.1186/s13014-020-01538-y

KEY WORDS: proton beam therapy, demography, acute toxicities, children, adolescent

TABLES

TABLE 1 Baseline characteristics

TABLE 2 Treatment characteristics

CSI-craniospinal irradiation, CTV-clinical target volume, CGE-cobalt grey equivalent, SFO-single field optimisation, MFO-multifield optimisation, QA-quality assurance, CBCT-cone beam computed tomography

TABLE 3 Acute Toxicities CNS vs Non-CNS

TABLE 4 Univariate analyses (Chi square test)

CTV-Clinical Target Volume, PBT-Proton Beam therapy, CCT-Concurrent chemotherapy, CSI-Craniospinal irradiation,

*Any mucositis, bowel or esophageal toxicity

FIGURE

FIGURE 1 Pie diagram of site-wise diagnosis (A) CNS (B)Non-CNS

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

Hosted file

`Tables 1_20th June edited.docx` available at https://authorea.com/users/336399/articles/462115-demographic-profile-and-early-clinical-experience-of-treating-children-and-young-adults-with-image-guided-proton-beam-therapy-in-india