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Review Article

Are further studies needed to justify the use of proton therapy for paediatric cancers of the central nervous system? A review of current evidence

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ABSTRACT

Clinical implementation of proton therapy demonstrated its potential to overcome some limitations of the more traditional, photon-based radiotherapy, due to physical and radiobiological advantages of protons. However, questions concerning the long-term effects of protons on paediatric patients need outcome analysis of the reported literature in order to be answered. The current paper has analysed the available clinical trials and comparative studies (protons vs photons) for paediatric cancers of the central nervous system (CNS) analysing the reported outcomes and follow-up times in order to evaluate the safety of proton therapy for this patient group.

Based on the literature analysis, proton therapy for treatment of paediatric cancers of the CNS was found to provide survival and tumour control outcomes comparable, and frequently superior, to photon therapy. Furthermore, the use of protons was shown to decrease the incidence of severe acute and late toxicities, including reduced severity of endocrine, neurological, IQ and QoL deficits. Most commonly, the reported median follow-up time was up to 5 years. Only a few studies reported promising, longer follow-up results. Considering that these patients are likely to survive many of the malignancies reported on, the incidence of long term sequellae impacting growth, development and quality of life into adulthood, should be viewed longitudinally for completeness.

The evidence surrounding proton therapy in paediatric tumour management supports its effectiveness and potential benefits in reducing the incidence of late-onset toxicities and second malignancies. For stronger evidence, it is highly desired for future studies to improve current reporting by (1) highlighting the paediatric patient cohort's outcome (in mixed patient groups), (2) reporting the follow-up time, (3) clearly indicating the toxicity criteria used in their evaluation, and (4) identifying the risk group. With this suggested clarity of future reporting, meaningful data to support treatment choice may then be available.

Although progress has been achieved in the treatment of CNS tumours, significant morbidity and mortality are still associated with childhood brain cancers. Current therapeutic strategies include a combination of surgery, chemotherapy and radiotherapy. While all treatment methods impose a certain risk, traditional photon-based treatments carry a high risk of adverse events, especially in very young patients. The more optimal physical and radiobiological properties of protons as compared to photons, have justified their implementation in radiotherapy, with several studies reporting promising results in otherwise difficult-to-treat cancers. Paediatric brain cancers are no exception, given (1) the sensitive anatomical location of tumours requiring highly conformal targeting, (2) the need for better organ sparing to avoid both early as well as late effects and (3) possibly reducing the risk of second cancers with a better targeted radiotherapy.

There are still some questions concerning the long-term advantage of protons both from a tumour control and normal tissue toxicity perspectives [1].

The aim of the current paper was to collate the existing information on proton studies undertaken on paediatric CNS tumours and to analyse, based on the reported data, whether the current knowledge fully justifies the use of protons in this patient group,

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or if further, better designed studies are needed to demonstrate their advantage over photons.

Methods

A search strategy utilising the Medline database was created with the intent of including all articles reporting on proton therapy, paediatric cancers, CNS tumours and treatment outcomes. The final search strategy included the following limitations: limited to humans, English, published from 2000 onwards. No "clinical study" or "clinical trial" limitations were applied as the final article count dropped to 20, resulting in the exclusion of numerous relevant articles. The final search strategy yielded a total of 164 papers (Appendix A). Twenty-six duplications were removed. Paper selection was then conducted via referring to the title and abstract, and involved the exclusion of physics-based papers, planning-centric papers, carbon-ion only papers, non-CNS tumour papers, and papers with non-paediatric patient populations. After paper selection, and the inclusion of additional papers extracted from a review published in 2016 by Gondi, Yock & Mehta, the final article count was 74.

Literature analysis

The distribution of the type of papers included (top) in the final data extraction and the total the number of clinical studies published per year (bottom) are shown in Fig. 1.

Eight countries demonstrated research investigating proton therapy for use in the treatment of paediatric CNS tumours. The USA had the most papers published with a total of 30 clinical studies (see Fig. 2), followed by Switzerland and Germany. The number of papers per disease type is displayed in Fig. 3.

Discussion of findings

Clinical trials

Three clinical trials on CNS tumours were identified, all phase II [2–4], with only one trial involving a purely paediatric patient cohort (1–17 years), having also the lowest number of participants (8 patients) [2]. The other two trials had larger cohorts, however, both included an unspecified number of non-paediatric patients [3,4].

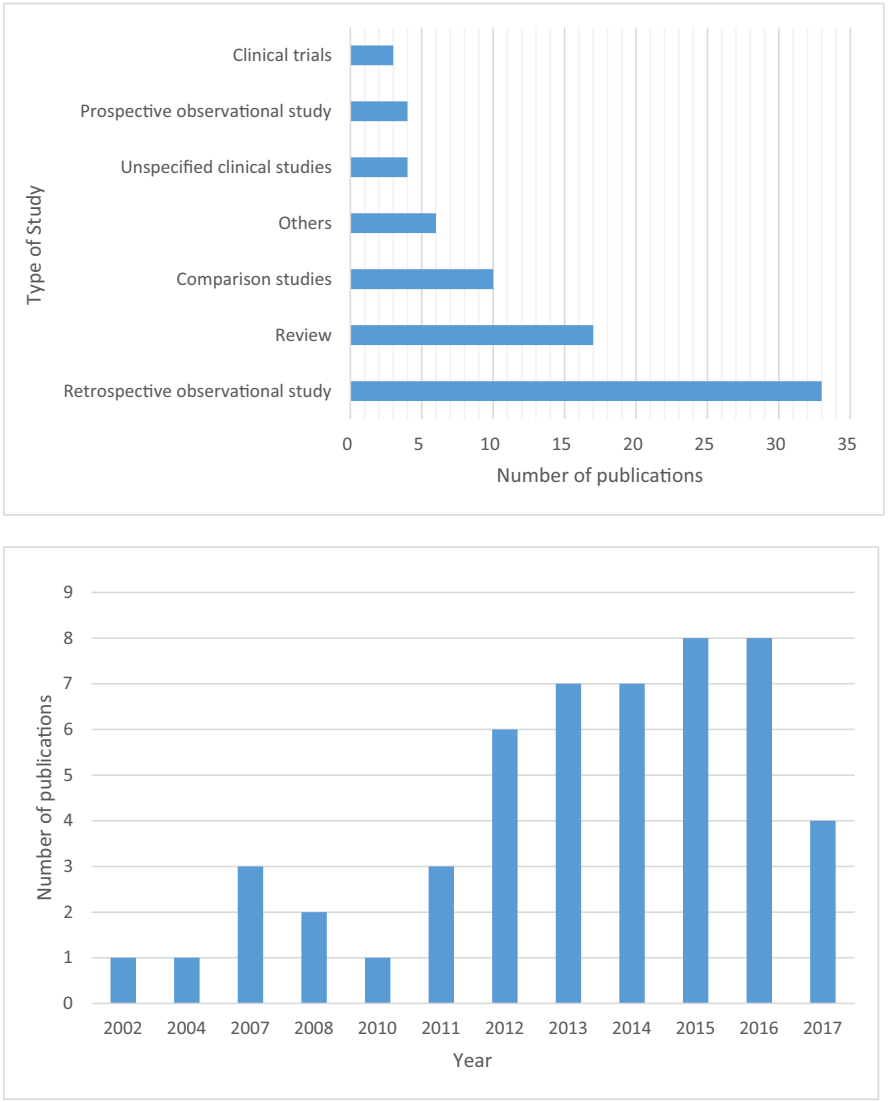

Fig. 1. Top: Number of publications per study type. Bottom: Number of clinical studies published per year.

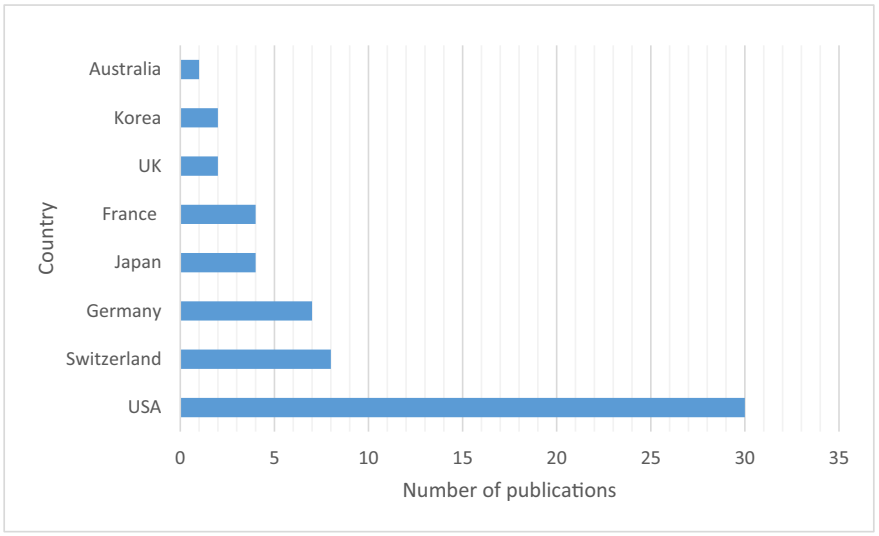

Fig. 2. Number of clinical studies published per country (publications involving more than one country were included multiple times, counting towards all involved countries).

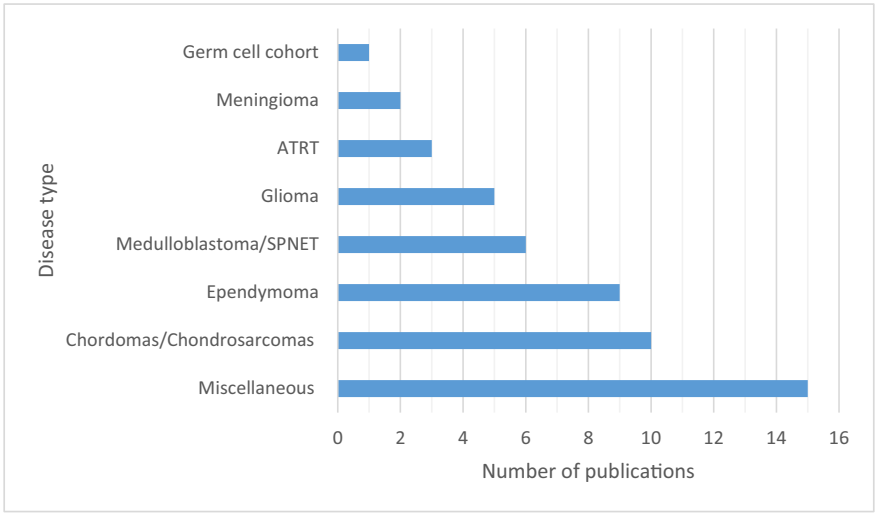

Fig. 3. Number of publications per disease type. Abbreviations: ATRT = atypical teratoid/rhabdoid tumour; SPNET = supratentorial primitive neuroectodermal tumour.

Amsbaugh et al. focused on the use of proton therapy for spinal ependymomas [2]. Highly encouraging local control (LC), progression-free survival (PFS) and overall survival (OS) rates were reported at 100% each during the follow-up time (mean of 26 months) [2]. In addition, no patients reported grade 3 + adverse events with Relative Biological Effectiveness (RBE) equivalent doses from 45 to 54 CGE (Cobalt Gray Equivalent). Following this study, optimal therapeutic approaches to spinal ependymomas are still being debated, though irradiation has been linked to improved local control for patients with subtotal resection or recurrences [2]. The small patient cohort and limited follow-up time, suggest that the findings of this clinical trial are not very substantial, and still require further investigation [2].

Patients included in the DeLaney et al. cohort had spine chordomas, chondrosarcomas and other sarcomas, and were treated with a combined proton and photon regimen [3]. Relatively high LC was reported in primary tumour patients, 85% at 8 years, with a risk of grade 3–4 late toxicities of 13% [3]. No late neurological toxicities were reported in patients receiving $\leq$ 72.0 Gy RBE. Patients received a large variety of treatment techniques. While some received Dural plaque brachytherapy during surgery, others were treated with external beam radiation including photons (delivered via 3D Conformal Radiotherapy (CRT) or Intensity Modulated Radiotherapy (IMRT)) and Proton Radiotherapy (3D PRT), delivered via 3D passive scattering. The results and discussion did not address the effect of the treatment delivery variation on patient outcomes or toxicities [3].

Yock et al. investigated medulloblastoma patients between the ages of 3 and 21 [4]. Some patients in this cohort received photon radiation only for part of their treatment due to cyclotron breakdown, however the data from these patients was not presented separately. Similar outcomes to conventional radiotherapy were found with 7-year PFS and OS rates of 75% and 81% [4]. Acceptable toxicities were reported, however grade 3 + toxicities were experienced in 8 out of 58 patients [4]. Endocrine deficits were reported in 61% of patients, alongside a 1.5 point overall decrease in IQ per year [4].

All of these papers involved USA researchers, and were conducted at different institutions [2–4]. The small number of studies, and the variation in the aims of current published trials indicates

the overall lack of high quality evidence for the use of proton therapy across paediatric CNS tumours. Additionally, all the above reports had follow-up times less than 10 years, indicating a scarcity of knowledge regarding long-term toxicities.

Prospective and retrospective comparative studies

Comparative studies between photons and protons offer an overview of the relative effectiveness of one treatment technique, while also offering indications concerning adverse events. Ten comparative studies were found based on literature research, including 2 prospective comparative studies [5,6], 6 retrospective comparative cohort studies [7–12], and 2 retrospective cohort planning analyses [13,14]. Anatomical locations that were covered included miscellaneous brain tumours in 4 studies [5–7,11], 1 report on medulloblastoma [8], 3 intracranial ependymoma papers [9,12,13], 1 study on chordomas and chondrosarcomas of the spine [10], and 1 germ cell tumour report [15]. Table 1 is a compilation of the comparative study results in order to offer a better overview of treatment outcome and toxicities.

The studies reported by Song et al. and Yock et al. had different methods of accruing their cohorts; both had prospective proton therapy cohorts, with either retrospective or cross-sectional photon cohort data collection [5,6].

Comparative studies with matching proton and photon cohorts often had a disproportionate number of patients in each group, and lack of matching for rarer diseases [5–9,11,12]. Proton cohorts frequently included a greater proportion of younger patients [9,12], with treatment occurring later in time [5,6,8,11,12]. These studies had paediatric cohort sizes ranging from $n = 15$ to $n = 43$, including both proton and photon therapy patients up to 21.9 years of age [5–9,11,12]. Radiation treatment technique also had variations across studies with photon therapy patients receiving either IMRT, 3DCRT or unstated treatments, whereas proton therapy patients received either passively scattered, scanning beam or unstated treatment methods [5–9,11,12]. One retrospective comparative cohort study looked at early adjuvant versus salvage treatment approaches in a mixed adult and paediatric population of chordomas and chondrosarcomas of the spine [10].

Studies comparing photon and proton cohorts reported median follow-up times ranging from 22 months to 6.2 years for protons and 7.0 years for photons [5–9,12]. Proton therapy patient survival outcomes were reported to be comparable to photon patient rates, at a range of 82–97% vs. 78.8–87.6% [8,9,12]. Recurrence free survival rates were also compared and reported to be higher for the proton cohorts (78.8–82% for proton patients vs. 60–76.5% for photon patients) [8,12].

Song et al. reported reduced incidences of haematological toxicities, reduced thrombocytopenia severity, and increased leucocyte and platelet recovery rate with the use of proton CSI, showing also reductions in liver and bowel doses [5]. Reductions in the incidence of diarrhoea were also reported with protons (0% incidence in the proton cohort vs. 23% incidence in the photon cohort) [5]. Kahalley et al. found no significant incidences of IQ decline in proton patients, compared to a 1.1 point IQ decline per year experienced by photon patients [11]. An overall lower IQ of 8.7 points was found with the use of photon therapy compared to proton therapy [11]. Larger declines in physical and psychosocial QoL domains were found for photon patients in Yock et al. [6]. Proton patients were found to have no difference in physical summary score domain when compared to the normal population [6]. In the overall health-related QoL, proton patients still scored lower than the normal population, but were found to have the same or favourable QoL scores when compared to other chronic diseases including diabetes, obesity and all cancers including leukaemia [6]. No second malignancies were reported in proton cohorts, with increased risk of second malignancy development associated with photon-based treatments [7,8].

Song et al. provided the best data collection with a prospective proton cohort and retrospective photon cohort; however, this study had the smallest number of patients (43) [5]. The largest paediatric cohort of 150 was reported by Kahalley et al., but no follow-up time was stated [11]. The most substantial study from an accrual perspective was that reported by Chung et al. including 119 paediatric patients from a 1592 patient cohort, with a median follow-up of 4.1 years [7].

The two comparative planning analyses studies aimed to compare dosimetric outcomes from IMRT, 3DCRT and IMPT treatment plans [13,14]. IMPT, particularly when using a 3 mm beam, was found to provide the best normal tissue sparing, reduction in dose to critical structures, dose homogeneity, and dose distribution compared to all other plans [13,14].

Endocrine and neurocognitive effects

With the increasing number of long-term survivors of childhood cancer, the sparing of endocrine and neurocognitive functions is becoming a critical aspect of treatment management. Of all studies that reported on proton therapy for paediatric CNS, a total of 10 articles offered data on endocrine outcomes [4,14–22]. The number of patients in each cohort ranged from 1 to 166, all containing purely paediatric patients $\leq$ 21 years of age [4,14–22]. Median follow-up times ranged from 24 months to 7.6 years [4,14–22]. The median proton doses used ranged from 44.0 to 68.3 Gy RBE [4,14–22].

Reported endocrine deficits ranged from grade 0 to 2 [16,19,21], however, most articles did not state the grade of reported endocrine changes [4,14,15,17,18,20,22]. A majority of reported endocrine deficits were that of growth hormone deficiency or hypothyroidism [4,14–17,20–22]. MacDonald et al. reported an associated decline in median height of 2.6 percentiles in 57 measured patients [14]. Additional reported endocrine deficits include adrenal/cortisol deficiency and sex hormone deficiency [4,21]. Doses larger than 40 Gy received by the hypothalamus and pituitary were found to correlate with the incidence of neuroendocrine deficits [4,18]. In Yock et al. 73% of patients receiving 40 Gy RBE or more to the hypothalamus reported neuroendocrine deficits, in comparison to 44% in patients receiving doses below 40 Gy RBE [4].

Neurocognitive changes were reported by 9 studies [4,11,14,15,18,21–24]. Patient cohort sizes ranged from 1 to 150 patients, with all patients being younger than 21.7 years of age [4,11,14,15,18,21–24]. Median follow-up times ranged from 24 months to 7.6 years [4,14,15,18,21–24]. Median proton doses ranged from 44.0 to 55.8 Gy RBE [4,11,14,15,18,21–24]. Most articles reported no significant declines in IQ scores from baseline to follow-up with the use of proton therapy [14,15,18,21,23]. However, increased risks of significant neurological declines were found to be associated with patients < 7 years of age, high doses to the left temporal lobe or hippocampus, infratentorial tumour location, medulloblastoma/PNET histology, larger tumour size, longer time since radiation therapy and posterior fossa boost history [11,18]. Despite reporting no significant change in overall Full Scale Intelligence Quotient (FSIQ) scores, Pulsifer et al. did report a significant decline in processing speed scores by a mean of 5.2 points [23]. In this study greater declines were associated with patients < 12 years old, patients with initial highest baseline FSIQ scores, whole brain patients, infratentorial tumours and CSI low dose groups [23]. Processing speed scores were associated with a reduced rate of skill acquisition as opposed to a loss of previous skills [23]. When proton and photon cohorts were compared, photon patients reported a lower IQ of 8.7 points compared to proton patients, however no significant difference in IQ changes were

Table 1
Compilation of comparative studies (protons vs photons) for paediatric CNS tumours (treatment planning comparison studies not included).

Study details and aims	Disease/Site	Treatment and dose	Outcomes	Toxicities
Sato et al. 2017 *Retrospective comparative cohort study* 79 paediatric patients Median age = 3.7 years (Range: 0.4–18.7 years)	Localised intracranial ependymoma *Diagnosis:* *IMRT:* Grade II (differentiated): 7 (18%); Grade III (anaplastic): 31 (82%) (4/31 patients = Grade II focal anaplasia); *PRT:* Grade II (differentiated): 8 (20%); Grade III (anaplastic): 33 (80%) *Location:* 54 infratentorial (61% IMRT, 76% PT)	All patients had surgical procedures, attempt to achieve maximal safe resection. 15 patients received chemo pre-RT; *Median RT dose:* - IMRT: 54 Gy (50.4–59.4 Gy) - PRT: 55.8 Gy (50.4–59.4 Gy) 1.8 Gy per day, 5 days per week	*Median follow-up:* PRT = 2.6 years (range: 0.6–7.2 years), IMRT = 4.9 years (range: 1.1–11.7 years); 3-year OS: 88% 3-year OS, IMRT vs. PRT: 81% vs. 97%; Recurrence: 21/38 (55%) IMRT patients, 7/41 (17%) PRT patients; 3-year PFS IMRT vs. PRT = 60% vs. 82%	8 patients (10%) = vasculopathy Median age at diagnosis: 6 years (Range: 2.7–9.1 years) 6 patients (3 = IMRT, 3 = PRT) (8%) = radiation necrosis 1 patient = stroke (20 months after IMRT) - presented with: acute onset of hemiparesis 1 patient = cavernoma (50 months after IMRT) - presented with: seizures
Eaton et al. 2016 *Retrospective multi-institutional comparative cohort study: clinical outcome* 88 paediatric patients *Proton:* Median = 6.2 years (Range = 3.3–21.9 years) *Photon:* Median = 8.2 years (Range = 3.4–19.5 years)	Standard risk medulloblastoma *Histology:* Proton group: Classic: 34 patients (75.6%) Anaplastic: 6 (13.3%) Other: 5 (11.1%) Photon group: Classic: 37 patients (86%) Anaplastic: 3 (7%) Other: 3 (7%)	All patients = maximal safe resection + CSI & involved field/posterior fossa boost + chemo; PRT = 45 patients XRT = 43 patients - IF/PF boost for patients NOT on concurrent COG protocol *RT boost location:* Tumour bed: 50 patients Posterior fossa: 24 patients PF > TB: 12 patients Median CSI dose = 23.4 Gy (Range = 18–27 Gy); Median boost dose = 30.6 Gy (Range = 27–37.8 Gy); Total dose of 54–55.8 Gy	*Median follow-up time:* 6.2 years (5.1–6.6) for PRT, 7.0 years (5.8–8.9) for XRT. 6-year OS, PRTs vs. XRT: 82.0 vs. 87.6% 6-year RFS, PRT vs. XRT: 78.8% vs. 76.5%; No significant difference in OS & RFS between the two modalities. 16/77 (20.8%) patients receiving $\geq$ 23.4 Gy CSI-recurrence 4/11 (36.4%) patients receiving 18 Gy CSI-recurrence No compromise of tumour control with PRT.	No proton patients developed second malignancy No early/late toxicities reported.
Kahalley et al. 2016 *Retrospective comparative cohort study: IQ changes* 150 patients $\leq$ 18 years *Age at RT:* Photon: 8.1 years (Range: 1.2–18.0) PT: 9.2 (Range: 1.7–18.2)	Brain tumours *Histology:* Glioma = 28 patients Medulloblastoma/PNET = 62 Ependymoma = 17 Germ cell tumour = 20 Other = 23 *Location:* Infratentorial: 68 patients Supratentorial: 80	Majority of patients had craniotomy. RT: 60 patients = XRT; 90 patients = PRT; CSI: XRT = 31 (51.7%), PRT = 51 (56.75); All CSI patients = tumour bed + margin boost. *Total RT dose:* XRT = Median 54.0 Gy (30.6–59.4 Gy) PRT = Median 54.0 Gy (30.0–60.0 Gy) *CSI dose:* XRT = Median 23.4 Gy (21.0–39.6 Gy) PRT: Median 23.4 Gy (21.0–	N/A	*CSI subgroup:* IQ stable (PBRT, XRT); XRT lower IQ by 12.5 points vs. PRT. *Focal subgroup:* PRT = IQ stable XRT = significant decline, 1.57 points/ year; *Overall:* PRT = no change in IQ over time XRT = IQ decline by 1.1 points per year XRT = lower IQ by 8.7 points vs. PBRT; No association between PRT and IQ decline/ impairment; Lower IQ scores associated with: XRT, Black/Hispanic race or ethnicity, younger age at RT, infratentorial, medulloblastoma/PNET histology, larger tumour diameter.

Table 1 (*continued*)

Study details and aims	Disease/Site	Treatment and dose	Outcomes	Toxicities
		39.6 Gy) *Tumour bed boost dose:* XRT = Median 55.8 Gy (44.4–55.8 Gy) PRT = Median 54.0 (30.0–55.8)		
Gunther et al. 2015 *Retrospective comparative cohort study: imaging changes related to PRT/IMRT* 72 paediatric patients; *Mean age:* PRT: 4.4 years (7.8–224.8 months); IMRT: 6.9 years (9.8–198.3 months)	Non-metastatic intracranial ependymoma *Histology:* Anaplastic ependymoma: 59 patients Ependymoma: 13 patients	Post-operative RT: PRT: 37 patients IMRT: 35 patients Median RT dose: PRT: 59.4 Gy (Range: 53.0–59.4) IMRT: 54.0 Gy (Range: 50.4–59.4)	4-year OS, PRT: 87.5% 4-year OS, IMRT: 78.8% 4-year disease-specific survival: PRT: 90%, IMRT: 78.8%	*Median follow-up:* 40.6 months (Range: 7.3–140.7 months) Toxicities – 22 patients: 7/22 patients grade 1 (1 IMRT, 6 PRT) 9/22 patients grade 2 (5 IMRT, 4 PRT) 4/22 patients grade 3 (4 PRT) 2/22 patients grade 4 (2 PRT) OBS: PRT patients younger treatment age (33.7 vs. 73.3 months)
Song et al 2014. *Comparative study: incidence of acute haematological and gastrointestinal toxicities* *Proton: Prospective cohort study* 30 patients < 18 years old Median: 10 years (Range: 2–18 years) *Photon: Retrospective cohort study* 13 patients < 18 years old Median: 11 years (Range: 3–18 years)	Malignant brain tumour: Medulloblastoma: Photons: 4 Protons: 9 Mixed germ cell tumours: Photons: 3 Protons: 5 Germinoma: Photons: 1 Protons: 6 Non-germinomatous germ cell tumours: Photons: 1 Protons: 3 Other histology: Photons: 2 Protons: 6	Proton CSI or Photon CSI −72%: curative (prophylactic) −28%: recurrence; Brain PTV = bilateral fields Spinal PTV: ≥2 abutting posterior-anterior (PA) fields; *Proton CSI:* Mean dose: 32.1 CGE (Range: 23.4–39.6 CGE); Mean **total** dose: 51.8 CGE (30.6–61.2 CGE); Dose per #: 1.8 CGE; Photon CSI: Mean dose: 29.4 Gy (19.8–39.6 Gy); Mean **total** dose: 53.2 Gy (39.6–60.6 Gy); Dose per # : 3 patients = 1.5 Gy, Remaining patients = 1.8 Gy	*Median follow-up:* 22 months (Range: 2–118 months) 2 patients died: recurrent disease, leptomeningeal seeding No CSI fluid space relapse (both groups).	Volume irradiated (%) & mean dose (Gy OR CGE) for liver & bowel: significantly reduced in PRT CSI patients; - Liver: XRT CSI patients = 61%, 9.7 Gy vs. PRT CSI patients = 8%, 0.7 CGE - Bowel: XRT CSI patients = 59%, 11.9 Gy vs. PRT CSI 14%, 1.1 CGE; Reduced thrombocytopenia severity and increased leukocyte and platelet count recovery rate in Proton group; Diarrhoea: 23% XRT, 0% PRT patients. Increased incidence of dysphagia in PRT patients (not statistically significant): Grade 1: 1 XRT patient, 10 PRT patients.
Yock et al. 2014 *Comparative study: comparison of health-related quality of life* *Proton: Prospective cohort study* 57 paediatric patients (Median = 7.0, Range = 2.0–14.0); *Photon: Cross-sectional data* 63 paediatric patients (Median = 7.7, Range = 2.3–18.0)	Diagnosis *Protons:* Medulloblastoma/PNET: 33.3% Ependymoma/high grade glioma: 26.3% Low-grade glioma: 10.5% Other low-grade neoplasm: 17.5% Germ cell tumour/germinoma: 12.3% *Photons:* Medulloblastoma/PNET: 46.0% Ependymoma/high grade glioma: 19.1% Low-grade glioma: 19.1% Other low-grade neoplasm: 4.8% Germ cell tumour/germinoma: 11.1%	*Surgery:* Proton group: No surgery/biopsy only: 17.5% Definitive surgery: 82.5%; Photon group: No surgery/biopsy only: 15.9% Definitive surgery: 84.1%; *Chemotherapy:* Proton group: 52.6% Photon: 69.8%; *Radiation:* Proton therapy: 57 patients Photon therapy: 63 patients; Proton therapy: < 50 Gy = 10.5% 50–54 Gy = 71.9% > 54 Gy = 17.5% Photon therapy: < 50 Gy = 23.8% 50–54 Gy = 71.4% > 54 Gy = 4.8%	N/A	*Parent proxy HRQoL scores reported median 3 years for proton cohort, 2.9 years for photon cohort:* Mean total core score Proton group: 75.9 Mean total core score Photon group: 65.4 Normative population: 80.9 Proton group = 10.3, 10.5 points higher than Photon group in PhSE and PsSD Proton: 5.0 points lower than normative healthy population Photon: 15.5 points lower than normative healthy population

(*continued on next page*)

Table 1 (*continued*)

Study details and aims	Disease/Site	Treatment and dose	Outcomes	Toxicities
Chung et al. 2013 *Retrospective cohort study* *Comparative analysis* 44 paediatric proton patients and 44 matched paediatric photon patients (Age < 18 years during RT); 31 unmatched pediatric proton patients; Total cohort (including adults) = 1034	*Paediatric patients:* *Diseases:* Matched cohort: Sarcoma = 1 (clavicle), Lymphoma = 1 (arm), CNS tumours = 42 (Acoustic neuroma = 1, Chordoma = 3, Chondrosarcoma = 1, Glioma = 4, Meningioma = 2, Sarcoma = 1, Astrocytoma = 9, Medulloblastoma = 13, Ependymoma = 4, Pineoblastoma = 1, Teratoid/rhabdoid = 1, Ganglioglioma = 1, Rhabdomyosarcoma = 1)	No information about chemotherapy regimens known (both cohorts) Median proton dose: Matched paediatric proton patients = 40 Gy Unmatched paediatric proton patients = 45 Gy From 1973-2001: Most proton patients received some photon radiation (20% of total treatment) combined with proton radiation	N/A	*Median follow up:* Matched paediatric proton patients = 4.1 years, unmatched paediatric proton patients = 5.9 years. *Paediatric cohort:* No secondary cancer development in any matched proton/photon paediatric patients No secondary cancer development in any unmatched paediatric proton patients

Abbreviations: CGE = CR = complete response; CSI = cranio-spinal irradiation; LC = local control; OS = overall survival; PFS = progression-free survival; PhSD: physical summary domain; PR = partial response; PRT = proton therapy; PsSD: psychosocial summary domain; QoL = quality of life; STR = supratentorial; XRT = photon radiotherapy; # = dose fraction.

found between the two cohorts [11]. Two case reports had neurological follow-ups reporting adequate development, and the ability to attend regular schooling [22,24]. Yock et al. reported an overall FSIQ of 1.5 point decrease per year at a median follow-up of 5.2 years with the use of proton therapy [4]. Declines were related to decreases in processing speed, and verbal comprehension index [4].

In summary, overall proton therapy appears to offer a reduction in late neurocognitive declines, and was frequently found to offer superior tissue sparing to photon therapy. However, limited comparative studies and follow-up times are points of weakness in this conclusion.

Limitations of research analysis

In most studies, cohorts included a mix of adult and paediatric patients, without specifying the exact number of paediatric patients. In paediatric only cohorts, most papers had no distinction between higher risk patients (e.g. < 3 years of age) and the main paediatric cohort. In addition, the classification of paediatric patients varied between articles, with some including patients up to 21 years of age.

There were large variations among patients with previous treatments, with differences in surgery extent and the number of chemotherapy regimens administered. Doses across studies, including those targeting a specific tumour type, also had large variations.

The number of studies looking at specific tumours in a paediatric population was often limited, as was the number of patients per study. Some reports focused more on toxicities, others on tumour control. Follow-up times, critical in the evaluation of treatment effectiveness on paediatric patients, were not always reported. Median follow-up times were also limited (most studies specified the 2–5 years outcome), though a number of reports had longer follow-up times (Fig. 4).

Discussion and conclusions

Photon therapy is considered a standard treatment for solid malignancies including those of the central nervous system. Advances in technology resulted in techniques that allow more conformal radiation delivery to the target and better normal tissue sparing. Techniques such as IMRT and volumetric arc therapy (VMAT) are more commonly used in paediatric patients than hadron therapy. In order to compare photon therapy versus protons, clinical outcome and long-term toxicities deriving from the two treatment approaches need to be paralleled. The relative advantage of protons versus photons depends on the quality of data reported for protons as well as photon therapy. However, there is scarcity of consistent data on both sides, as some of the latest results from photon studies (IMRT/VMAT) are yet to be reported and published.

One of the most deliberated aspect of radiotherapy concerns late and very late effects. The risk of second cancers (i.e. very late effects) is a critical aspect in paediatric cohorts previously treated with radiation. There is epidemiological and radiobiological evidence supporting the risk of second cancers after photon treatment [25] and, at the same time, scientific consent on the unlikelihood of higher risks from protons [26]. Furthermore, a comparative study between proton therapy, IMRT and VMAT for paediatric patients with brain tumours regarding the risk of radiation-induced second cancers revealed that IMRT and VMAT presented similar and the highest lifetime attributable risks (0.05–4.9%), while proton therapy was associated with the lowest risk of second malignancies (0.01–2.8%) [27]. To date, several risk-assessment reports are based

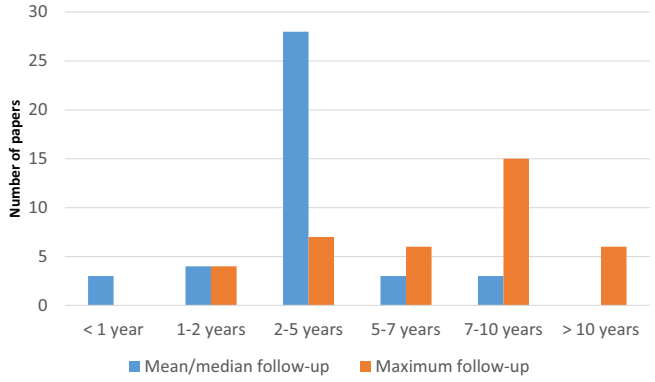

Fig. 4. Mean/median and maximum follow-up time after proton therapy reported by studies on paediatric CNS tumours.

on models, due to lack of high-quality studies and long-term follow-up data. For more decisive results, all radiotherapy studies should be accompanied by late effect investigations regardless of the techniques employed.

Without doubt, clinical trials are indispensable prerequisites to establish the optimal treatment regimen for a particular malignancy. Phase III trials usually accrue a large number of patients to achieve a high statistical power in establishing adverse event rates. However, there are no phase III trial reports on proton therapy for paediatric CNS tumours to clearly elucidate the immediate and also the long-term biological effects of these particles. Some might even argue, that knowing the physics of proton therapy (dose distribution and range) which positions the protons above photons, randomised clinical trials for paediatric patients would actually be unethical. Moreover, given that some CNS tumours are rare, designing clinical trials in rare diseases brings additional challenges and limitations due to the small cohort. The small sample size increases the extent of inter-individual variability, increasing therefore the level of heterogeneity within the group. This factor leads to a decreased study power, affecting the verity of the findings. Also, data collection can be easily biased by the geographic dispersion of patients, inadequate recruitment (i.e. not meeting all criteria), difficulty in choosing clinical outcome, poor follow-up and/or data recording [28].

Funding required to conduct clinical trials for proton therapy (adults and children) also represents a significant barrier. Proton therapy is a more expensive radiation therapy compared to current photon therapy techniques by a factor of between 2.5 and 3.2 [29,30] when looking at per treatment costs. These costs would only increase should every patient be included in a clinical trial. Additional and/or significant funding to conduct clinical proton therapy trials is required that may not be readily available, making the data acquisition even more complex, especially as long term follow ups are required to ascertain cost effectiveness overall (i.e. including management of long-term effects and reducing risks of second cancers) and not just per treatment costs [31–33].

This, combined with ethical issues linked to clinical trials with children (as mentioned above, due to treatment planning dosimetry clearly showing that radiation doses would be consistently lower compared to photon treatments and due to increased radiation sensitivity of children) means, that much of the data on PT cost-effectiveness comes from modelling studies such as performed by Lundkvist et al. [34] who evaluated cost effectiveness of proton radiation therapy for children with medulloblastoma using a Markov cohort-simulation model accounting for hearing loss, IQ loss, hypothyroidism, GHD, osteoporosis, cardiac disease, and secondary malignancies. Their results indicated €23,600 cost savings and 0.68 additional quality-adjusted life-years per patient when comparing proton therapy with photon therapy. The results were confirmed by other studies using risk estimates and data on capital investments showing that protons are cost effective for paediatric medulloblastoma patients when compared to photon therapy [35]. Looking at the endocrine dysfunction, Mailhot Vega et al. [36] published the first evidence-based guide to identify children with CNS tumours who may benefit the most from proton therapy. They showed that while protons may be more cost effective than photons in situations when the hypothalamus can be spared, this will not be the case when tumours are adjacent to this organ due to possible high doses delivered to sensitive structures. These examples underline the fact that cost-effectiveness in regard to adverse events and long-term toxicities should be evaluated on an individual basis or precise tumour location, rather than on general terms, adding more challenges to the evaluation of health economics aspects.

Report by Ollendorf et al. [37], who surveyed all available clinical proton therapy data by 2014, stated "incremental" (i.e. small) net health benefit in paediatric cancers. Similarly, Weber et al [30] conclude that: "*PT may be cost-effective for paediatric CNS tumor management. More CE analyses are urgently needed to evaluate the benefit of PT for non-CNS paediatric tumor management*". This in turn requires more funding to be allocated to clinical trials and data acquisition.

More information on cost effectiveness of proton therapy (in adults and children) can be found in recent extensive reviews by Verma et al. [33,37], Weber et al. [30] and in the report by Ollendorf et al. [37].

It can be concluded, however, that based on the above literature analysis, proton therapy for the treatment of paediatric cancers of the central nervous system was found to provide survival and tumour control outcomes comparable, and frequently superior, to photon therapy. Furthermore, the use of protons was shown to decrease the incidence of severe acute and late toxicities, including reduced severity of endocrine, neurological, IQ and QoL deficits.

As with any relatively new treatment technique, reliable reports on long-term adverse events after proton therapy need adequate follow-up times. While most commonly, the reported median follow-up time was up to 5 years, there are studies that reported promising, longer follow-up results. Given patients are likely to survive many of the malignancies reported on, the incidence of long term sequellae impacting growth, development and quality of life into adulthood, should be viewed longitudinally for completeness.

Therefore: *Are further studies needed to justify the use of proton therapy for paediatric cancers of the central nervous system?* So far, the evidence surrounding proton therapy in paediatric tumour management supports its effectiveness and potential benefits in reducing the incidence of late-onset toxicities and second malignancies. While the high costs and limited availability of proton therapy justifies comparative studies with other radiotherapy techniques, randomization should not be an option due to ethical reasons.

Yet, for a clearer overview, it would be highly beneficial for future studies to overcome the limitations of current reports by (1) highlighting the paediatric patient cohort's outcome (in mixed patient groups), (2) reporting the follow-up time, (3) clearly indicating the toxicity criteria used in their evaluation, and (4) identifying the risk group. With this suggested clarity of future reporting, meaningful data to support treatment choice may then be available.

Conflict of interests statement

All authors certify that they have seen and approved the final version of the manuscript being submitted. They also warrant that

the article is the authors' original work, has not received prior publication and is not under consideration for publication elsewhere.

All authors declare that there was no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.009.

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