Radiotherapy and Oncology 128 (2018) 44–55

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

EPTN, PTCOCG, PROS consensus

Proton therapy for pediatric malignancies: Fact, figures and costs. A joint consensus statement from the pediatric subcommittee of PTCOG, PROS and EPTN

Damien C. Weber [a,*], Jean Louis Habrand [b], Bradford S. Hoppe [c], Christine Hill Kayser [d], Nadia N. Laack [e], Johanes A. Langendijk [f], Shannon M. MacDonald [g], Susan L. McGovern [h], Luke Pater [i], John P. Perentesis [j], Juliette Thariat [b], Beate Timmerman [k], Torunn I. Yock [g], Anita Mahajan [e]

[a] Center for Proton Therapy, Paul Scherrer Institute, ETH Domain, Villigen PSI, Switzerland; [b] Centre de lutte contre le cancer François-Baclesse, Caen, France; [c] Department of Radiation Oncology, University of Florida College of Medicine, Gainesville; [d] Department of Radiation Oncology, University of Pennsylvania, Philadelphia; [e] Department of Radiation Oncology, Mayo Clinic, Rochester, USA; [f] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands; [g] Department of Radiation Oncology, Massachusetts General Hospital, Boston; [h] Department of Radiation Oncology, MD Anderson Cancer Center, Houston; [i] Department of Radiation Oncology, University of Cincinnati; [j] Cincinnati Children's Hospital Medical Center, University of Cincinnati, USA; [k] WPE, University Hospital Essen, Germany

ARTICLE INFO

Article history:
Received 31 March 2018
Received in revised form 11 May 2018
Accepted 15 May 2018
Available online 21 June 2018

Keywords:
Proton therapy
CNS tumors
Sarcoma
Children
Pediatric cancer
Lymphoma

ABSTRACT

Radiotherapy plays an important role in the management of childhood cancer, with the primary aim of achieving the highest likelihood of cure with the lowest risk of radiation-induced morbidity. Proton therapy (PT) provides an undisputable advantage by reducing the radiation 'bath' dose delivered to non-target structures/volume while optimally covering the tumor with tumoricidal dose. This treatment modality comes, however, with an additional costs compared to conventional radiotherapy that could put substantial financial pressure to the health care systems with societal implications.

In this review we assess the data available to the oncology community of PT delivered to children with cancer, discuss on the urgency to develop high-quality data. Additionally, we look at the advantage of combining systemic agents with protons and look at the cost-effectiveness data published so far.

Over 300,000 new cancers are diagnosed annually in patients younger than 19 ($156/10^6$ person-years) worldwide [1]. The specific cancer diagnoses vary greatly by age, race, sex and country (Fig. 1); however, the most common are CNS tumors, Hodgkin lymphoma, and sarcomas (Fig. 2). Through strong cooperative group structures, overall survival (OS) rates have improved over the past 50 years and now long-term survivorship and quality of life (QOL) have become relevant.

Radiotherapy (RT) is effective for local control (LC), progression-free survival (PFS) and OS for most pediatric solid tumors; however, children are vulnerable to RT related late-effects affecting normal organ function, growth, development and the development of second malignant neoplasms (SMNs). Technological advances in imaging and RT delivery have resulted in better tumor delineation, smaller target volumes and more conformal RT but, surrounding normal tissues remain at risk due to non-target radiation dose. Proton therapy (PT), by elimination and reduction of exit and entry dose, reduces the low and intermediate dose volumes without compromising tumoricidal dose. Further advances such as pencil beam scanning (PBS) and intensity modulated proton therapy can allows usually better dose conformality, lower normal tissue dose and lower neutron dose contamination. Strategic use of PT is projected to reduce acute and late effect risks, thereby, allowing a better QOL for cancer survivors.

Though many dosimetric and modeling studies support the theoretical benefits of PT, actual clinical results are only now starting to emerge. Existing challenges include the small patient numbers, late-effect latency, inconsistent objective toxicity measures, low incidence of significant late effects, costs associated with long term follow-up studies or registries. Habrand et al. summarize the available literature and demonstrate the dearth of comparison studies that objectively evaluate the practical benefit of PT in comparison to alternative approaches Table 1 [2].

This paper summarizes the potential applications, research opportunities, challenges and benefits of PT in pediatric cancer management.

* Corresponding author at: Center for Proton Therapy, ETH Domain, Paul Scherrer Institute, WPTA 144, CH-5232 Villigen West, Switzerland.
E-mail addresses: damien.weber@psi.ch, damiencharles.weber@uzh.ch (D.C. Weber).

https://doi.org/10.1016/j.radonc.2018.05.020
0167-8140/

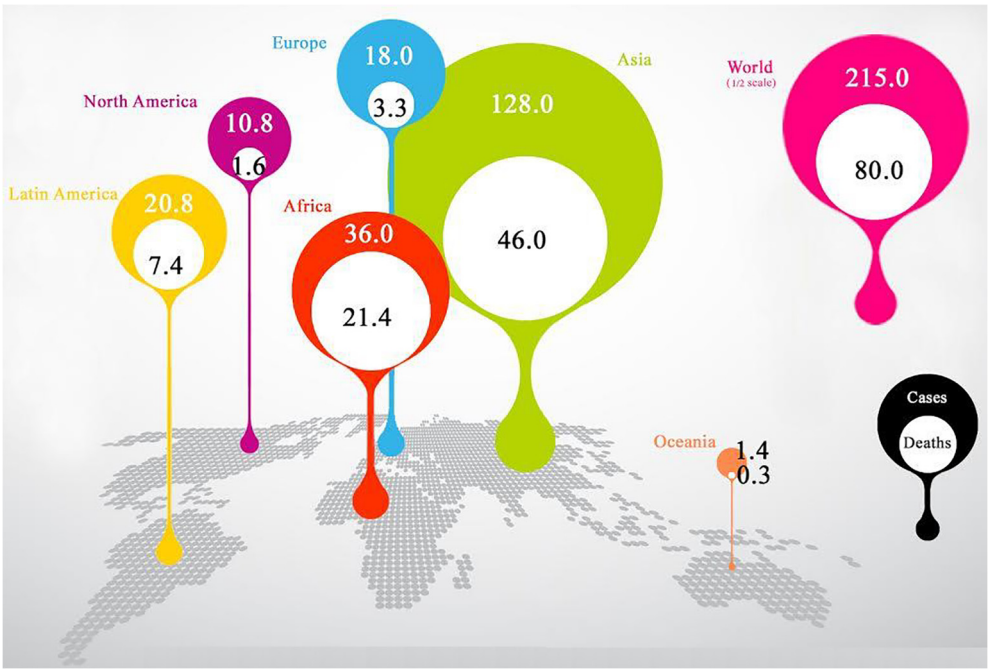

Fig. 1. Estimated numbers of cases and death in ages 0–14 years (2010s).

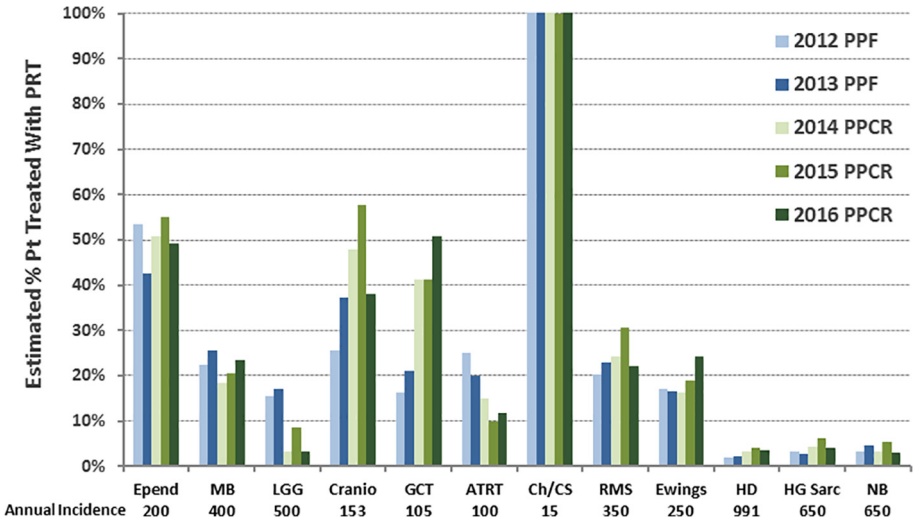

Fig. 2. Estimate of the proportion of total specific new pediatric cancer diagnosis treated at proton centers over five years in the US. 2012–2013 data from the Pediatric Proton Foundation (PPF) and 2014–2016 from the Pediatric Proton Consortium Registry (PPCR) assuming a 60% national participation.

Challenges in level I evidence generation

Despite many more publications examining outcomes and toxicities of PT in comparison to the number examining X-ray RT (XRT), the concern about efficacy and the extent clinical benefit by oncologists, bioethicists, and insurance companies are raised even for children since PT is usually associated with additional expense, treatment complexity and inconvenience. Phase III randomized trials comparing PT to XRT are on-going for adult lung, esophageal and prostate cancer, but the possibility of prospective trials for childhood malignancies remains challenging due to clinical equipoise and several other reasons listed below that cause challenges in clinical trial design and completion: First, which question should be addressed – disease related outcomes? Late effects from therapy? Dosimetrically, PT almost universally results in lower non-target tissue dose than XRT. The normal tissue dose difference may be enough to raise ethical concerns of patient randomization. Single and multi-institutional publications document the efficacy of PT, and though the majority of these do not provide level 1 evidence, none have raised concern that LC rates are lower with PT.

Second, is the long-term toxicity lowered by non-target tissue dose reduction? These question is premature because PT has been used consistently in children for the past decade – late effect risks may start manifesting now. It is likely that reports are forthcoming; however, the absence of robust XRT related late effects and QOL data limits historical comparisons. Third, perhaps the most important one, is that comparison of one radiation modality to another is meaningless without rigorous understanding of dosimetric parameters. The meaningful comparison is not XRT versus PT, but instead outcomes based on integral organ/patient doses with other dosimetric parameters. The future of research in pediatric radiation oncology will depend on this understanding, and on creative trial design that allows incorporation of various modalities with dose-related outcomes.

Table 1
Inter-comparisons between the impact on toxicity of modern photon and particle therapy, in pediatric malignancies. 2005–2015 clinical experience.

Site	# Patients	Endpoint	Results	*P* value
Brain				
Gunther [161]	72	MRI changes	P < IMXRT	(.002)
Yock [162]	120	Psycho., QOL	P > XR	(.01)
Bishop [41]	52	Vision	P > IMXRT	(NS)
Neuro-endocrine				
Eaton [137]	77	Ant.pituitary, height	P > XR	(.01–.001)
Viswanathan [163]	31	Ant.pituitary	P > XR+P	(.01)
Bishop [41]	52	Panhypo., obesity	P > XR	(NS)
Acute				
Song [164]	43	Hemato & Digestive	P > XR	(.01)
Grant [8]	24	HN Mucosa	P > XR	(.05)
Rieber [165]	83	Skin & Mucosa	C = P + XR	(NS)
Body				
Sethi [166]	86	K2	P > XR	(.01)
Chung [100]	75	K2	P = XR	(NS)
Lung				
Green [167]	303	Restrictive syndrome	P < XR	(.001)
Head & neck				
Böling [168]	133	Salivary	P < XR	(.02)

Abbreviations: >: better; <worse; Ant.: anterior; C: carbon ions; HN: head and neck; Hemato: haematological; NP: not significant; Panhypo.: panhypopituitarism; Psycho.: psychological. Other abbreviations: see text.

CNS tumors

For CNS tumors, PT spares nearby critical structures, such as the hypothalamus, optic apparatus, hippocampus, and uninvolved brain while maintaining excellent outcomes [3,4]. For many children, this translates to avoidance of neurocognitive sequelae, hearing loss, neuroendocrine abnormalities, vascular disease and SMNs all resulting in the ability to function normally in society [5,6]. Craniospinal irradiation (CSI) has become an important indication for the use of PT [7]. In comparison to XRT, PT decreases dose to neck, thoracic, abdominal and pelvic structures, including the thyroid, esophagus, heart, lungs, bowel and gonads [8]. In addition, as the technology matures, complete vertebral body sparing with PT-CSI in young children may prevent growth retardation. Overall, the decreased exposure is expected to translate into lower rates of chronic organ damage and SMNs.

Medulloblastoma

Approximately 330 cases of medulloblastoma are diagnosed in the US in 0–19 year olds annually. CSI is a critical component in the definitive treatment of medulloblastoma and PT has become an important modality in the management of this disease. A recent single-arm phase II trial of 59 medulloblastoma patients from Massachusetts General Hospital found that CSI with PT resulted in no cases of long-term cardiac, lung, or gastrointestinal toxicity compared to a 25–50% incidence of these late effects in prior studies of patients treated with XRT [9]. Moreover, disease control was similar compared to historical studies with XRT. Interestingly, a recent evaluation of ototoxicity did not identify a significant difference between patients treated for medulloblastoma with IMXT and PT, though this is likely due to the use of cisplatinum [10]. Given the recent results from the Children's Oncology Group (COG) study ACNS0331 showing that decreasing CSI dose to 18 Gy in young standard-risk patients resulted in inferior survival [11], it is apparent that CSI dose reduction is not acceptable for all standard-risk patients but further evaluation with molecular risk stratification is ongoing [12]. At present, PT enables the greatest reduction in dose to organs at risk [13]. A future trial will explore the use of scanning beam PT for vertebral-body sparing CSI to decrease late effects on growth [14].

Ependymoma

Approximately 200 cases of ependymoma are diagnosed in the US annually with 40% occurring in children <3 years of age [15,16]. The majority arise in the posterior fossa with extension into the cervical canal. Metastatic disease is present in only 10–15% of patients at diagnosis but is more common at relapse [17,18]. Intracranial ependymomas are currently classified as WHO Grade II or III (classic/differentiated or anaplastic); however, molecular sub-classification is expected to offer better prognostication.

Standard treatment for ependymoma consists of maximal surgical resection followed by primary site RT [19,20]. The LC rate is 75–80% after a gross total resection (GTR) and adjuvant local PT which is similar to XRT outcomes [3,21]. RT escalation to 59.4 Gy has been advocated by several authors, administered with conventional fractionation or stereotactic hypofractionation [4,22]. PT, as with medulloblastoma, may be used for ependymoma when CSI is indicated for metastatic or recurrent disease. Past trials using chemotherapy without RT have led to dismal outcomes; however, a short course of chemotherapy after a sub-total resection can be considered to facilitate a second attempt for a GTR [23,24]. Clinical data of the use of PT for pediatric ependymoma are summarized in Table 2.

Glioma

Pediatric low grade glioma constitutes over 25% of all primary brain tumors in patients 0–19 years of age. PT is very relevant in the management of pediatric low grade glioma because survival for these patients is expected to be measured in decades. The reduction in the volume of irradiated brain with PT should translate into lower rates of chronic medical issues and improvements in sociodemographic outcomes [25]. Indeed, in a study of 54 pediatric brain tumor patients treated with focal PT or XRT, the IQ of patients treated with XRT declined by 1.57 points/year in comparison to a stable IQ in patients receiving PT ($p = 0.026$) [26]. This benefit may be particularly useful for younger patients who require RT, as young age at RT, especially less than 5 years old, consistently correlates with worse neurocognitive outcomes [27]. Early results demonstrate similar survival outcomes compared to XRT data; in a study of 32 patients treated with PT for PLGG glioma, 8y PFS and OS were 82.8% and 100%, respectively [28].

Table 2
Studies assessing the outcome of children with CNS tumors treated with proton therapy.

Author	Method	Med FU (mo) [range]	N	Med Dose Gy(RBE) [range]	PS/PBS	Chemo Y/N	Outcome
Ependymoma							
MacDonald [3]	R	26 [1.5–78]	17	55.8 [52.2–89.4]	PS	Y 24%	2.2y LC: 86% 2.2y OS: 89%
MacDonald [169]	R	46 [12–139]	70	55.8 [50.4–60]	PS	Y 30%	3y LC:83% 3y OS: 95%
Ares [170]	R	43.4 [8.5–114]	50	59.4 [54–60]	PBS	Y 86%	5y LC: 78% 5y OS: 84%
Sato [171]	R	31 [7–86]	38	55.8 [50.4–59.4]	PS	Y 16%	3y LC: 86% 3y OS: 97%
ATRT							
McGovern [172]	R	24 [4–55]	31	50.4 [9–50.4]	PS	Y	2y PFS: 48% 2y OS:69%
De Amorim [36]	R	27.5 [11.3–99.4]	10	50.4 [50.4–55.8]	PS	Y	9/10 AWD
Weber [38]	R	33.4 [9.7–69.2]	15	54.0	PBS	Y	2y PFS:66.0% 2y OS:64.6%
Craniopharyngioma							
Fitzek [39]	R	186 [122–212]	15*	56.9 [53.4–67.5]	PS**	N	10y LC: 85% 10y OS:72%
Laffond [40]	R	74	29	NS	PS**	N	Exec fxn sx: 25–38%
Bishop [41]	R	33.1 [10.5–65.6]	21	50.4	PBS	N	10y CFFS: 76% 3y OS:96%
Luu [42]	R	NR	16	50.4 [50.4–59.4]	PBS	N	15/16 pts controlled

Abbreviations: N: Number PS: passive scatter, PBS: pencil beam scanning, Chemo: chemotherapy, LC: local control, OS: overall survival, PFS: progression free survival, AWD; alive with disease, Exec fxn sx: executive function symptoms, CFFS: cyst failure free survival, NR: not reported ATRT: atypical teratoid rhabdoid tumor; AWD: alive without disease, R: retrospective analysis; CFFS: cystic failure-free survival; NS: not specified.

* 2/3 of cohort are adults.

** Proton/photon therapy.

Data to support PT for pediatric high grade glioma are limited, but may be useful for selected grade III tumors. Given the poor overall prognosis of glioblastoma of diffuse midline glioma (H3K27 mutant), PT has not been shown to have a strategic role at this time.

Atypical teratoid/rhabdoid tumor

Atypical teratoid/rhabdoid tumor (ATRT) is a brain tumor that affects infants (≤20% of CNS tumors) or children younger than 5 [29–32]. Despite aggressive regimens with maximal safe resection, chemotherapy and RT, the median survival remains low (6–11mo) [33,34]. RT does improve outcomes; however, oncologists are reluctant to use RT in these young patients [30–32,34,35]. PT may provide an acceptable approach since dose-comparative studies have shown that PT in comparison to IMXT substantially decreases the integral brain dose in these patients [36].

(Table 2) details the series reporting the outcome of young children (median age, 17–28 months), treated with PT. The reported 2-year OS range from to 55% to 66%. Of note focal or CSI has been administered to these patients. These data are encouraging and compared favorably to modern XRT series [37]. Of note, Weber et al. performed a proxy-QOL analysis which showed that PT did not negatively impact the QOL of these ATRT patients. The mean QOL scores in the physical and emotion domains were higher after PT when compared to those observed prior to irradiation [38].

Craniopharyngioma

Craniopharyngioma is the third most common brain tumor in children (100–150 cases/yr in the US). It is histologically benign with a good survivorship but with substantial neurocognitive and/or psychological morbidity. In an effort to mitigate risks associated with aggressive surgery, the recommended strategy is to perform maximal safe surgery with postoperative or salvage RT. Several different RT modalities, including IMXT, stereotactic RT and PT, have been used in the past.

Fitzek et al. published on 5 children (median age, 15.9 yr) and 10 adults (median age, 36.2 yr) treated with XRT and PT to a median dose of 56.9 Gy(RBE) [39]. After a median of 13.2 years, the 10 y OS and LC rates were 72% and 85%, respectively (Table 2). Life style and professional accomplishments of the entire cohort was satisfactory. The French group reported the QOL, executive functioning and mood disorders of 29 patients with craniopharyngioma (mean, 7.8 years) treated with PT and XRT [40]. 38% were depressed and >20% had executive function symptoms. Bishop et al. reported on 21 children (median, age 9.1 years) treated with PT or XRT to a median dose of 50.4 Gy(RBE). The 3-year OS was excellent (Table 2). LC and OS were equivalent between the PT and XRT cohorts [40,41]. Finally, Luu et al. reported on 16 patients (range 7–34 yr) who received PT (50.4–59.4 Gy(RBE)). LC was achieved in 15 patients and 75% of the patients survived [42].

In summary, the outcome of patients treated with XRT and PT seem to be equivalent but PT were frequently used to deliver higher doses but allows improved temporal lobe and hippocampal sparing (Table 2).

Germ cell tumor

Approximately 200 malignant CNS germ cell tumors are diagnosed annually in the US with >75% occurring in children and young adults [43]. These tumors typically arise in the suprasellar or pineal regions (5–10% in both areas), and rarely in other locations [44]. GCTs are divided into two highly prognostic histologic subgroups: pure germinomas (more common) and non-germinomatous germ cell tumor (NGGCT).

Pure germinoma has the most favorable prognosis and is treated successfully with RT alone or RT with chemotherapy [45–48]. Whole-ventricle RT to a dose of 24 Gy followed by a tumor bed boost to total 45–50 Gy is a very effective treatment for localized GCT. Larger field RT (24 Gy CSI, boost to 45 Gy) is recommended for patients with disseminated pure germinoma, still with an excellent prognosis. The use of 2–4 cycles of platinum-based

induction chemotherapy may allow a RT dose reduction, 21 Gy whole ventricular or CSI and boost to 30 Gy, using the same target volumes. A further reduction to 18 Gy large field is being evaluated in COG ACNS1223.

RT alone for NGGCT has resulted in poor outcomes (20–40% LC). Now combined modality treatment with 6 cycles of neoadjuvant of alternating carboplatin/etoposide and ifosfomide/etoposide, followed by RT with or without surgery is standard of care [49,50]. Patients who achieve a complete response after chemotherapy are then treated with CSI to 36 Gy followed by a primary tumor boost to 54 Gy. Those without a CR may benefit from a second-look surgery with resection if feasible.

Though clinical outcomes are still sparse for CNS Germ Cell Tumors, there does appear to be a dosimetric advantage of PT, particularly PBS for whole ventricular to reduce whole brain, temporal lobes, and non-chiasm optic structure doses [48]. Children treated with CSI should benefit in a similar way to patients treated with CSI for medulloblastoma. Patients with CNS germ cell tumors have an excellent prognosis and are likely to be cured of their disease with a prolonged OS and therefore should be highly likely to benefit from reduced RT dose uninvolved structures.

Non CNS tumors

Chordoma/chondrosarcoma

Chordomas are locally invasive tumors that usually occur at the skull base in children, though sacro-coccygeal tumors have been described [51–53]. These tumors are of notochordal origin and only occur in only 5% in the pediatric population [54,55]. The mean age at presentation in children is 10 years, but this tumor has been reported in a neonate [56]. Cranial nerve dysfunction (60%) and headache (40%) are the common presenting symptoms of skull base chordoma [57,58]. Bladder and bowel dysfunction, perineal or radicular pain and cauda equina syndrome are the most common presenting symptoms for sacral tumors. In general, OS rates of 57–81% have been reported for pediatric chordoma [54,55,57,59]. It appears that chordoma in children younger than 5 years have a worse prognosis than older children or adults, possibly due to a higher rate of metastasis, sacrococcygeal primaries and/or dedifferentiation [55,58,60–62].

Chondrosarcoma is less common tumor in children that occurs in the pelvis and long bones, with <10% arising in the head, neck or skull base regions [63]. As in adults, chordomas and chondrosarcoma are treated with surgery and usually postoperative RT.

Table 3 summarizes the series that report outcomes of 56 patients treated with carbon ions or PT with or without XRT [57,64,65]. The 5y OS with PT ranges from 68% to 89%, which compares favorably to XRT series [59,66]. Because these tumors are very radioresistant and require a high dose of RT, PT or carbon therapy are ideal modalities that allow excellent high-dose conformality with a substantial reduction in the overall integral dose to the patient.

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common childhood soft tissue sarcoma [67,68]. RT has proven to be an important component of the combined-modality treatment in rhabdomyosarcoma [69–71]. PT has been increasingly used in the last decade [72–74] and may offer considerable dosimetric advantages in parameningeal (Fig. 1) [75,76], orbital [76,77], paraspinal [78] and genitourinary sites [76,79].

Thus far, clinical outcomes for rhabdomyosarcoma with PT are similar to XRT reports: 5-year OS, LC and EFS for PT in localized RMS or metastatic embryonal rhabdomyosarcoma were 78%, 81%,

Table 3
Studies assessing the outcome of children with sarcomas treated with proton therapy.

Author	Method	Med FU (mo) [range]	N	Med Dose Gy(RBE) [range]	PS/PBS	Chemo Yes/no	Outcome
Chordoma/Chondrosarcoma							
Rombi [65]	R	46 [4.5–126.5]	26	74.0 Ch [73.8–75.6] 66.0 ChSa [54.0–72.0]	PBS	N	5y LC: 80–81% 5y OS: 75%-89%
Benk [57]	R	72.0 [419.0–120.2]	18	69.0 [56.8–75.6]	PS	N	5y DFS: 63% 5y OS: 68%
Combs [64]	R	9 [1–23]	10	60.0 [60.0–70.0]	CIT	N	LC: 100%*
Rhabdomyosarcoma							
Ladra [80]	P	47 [14–102]	57	50.4 [36–50.4]	PS	Y	3y LC: 81% 5y LC: 81% 3y OS: 81% 5y OS: 78%
Leiser [81]	R	55.5 [0.9–126.3]	83	54 [41.4–64.8]	PBS	Y	5y LC: 78.5% 5y OS: 80.6%
Weber [82]	R	41 (mean) [9–106]	39	54 [50.4–55.8]	PBS	Y	5y PFS: 72% 5y OS: 73%
Childs [83]	R	60 [24–130]	17	50.4 [50.4–56]	PS	Y	5y FFS: 59% 5y OS: 64%
Ewing Sarcoma							
Rombi [92]	R	38.4 [17.4–444.0]	30	54 [45.0–59.4]	PS	Y	3y LC: 86% 3y OS: 89%
Weber [87]	R	49.6 [9.2–131.7]	38	54.9 [45.0–69.9]	PBS	Y	5y LC: 82% 3y OS: 83%
Iwata [173]***	R	[12.0–160.0]	5	70.4 [70.4–73.6]	**	Y	1/5 recurrence

Abbreviations: N: Number PS: passive scatter, PBS: pencil beam scanning, Chemo: chemotherapy ChSa: chondrosarcoma; R: retrospective analysis; Ch: chordoma, ChSa, chondrosarcoma, LC: local control, OS: overall survival, DFS: disease free survival, CIT: carbon ion therapy.

* No actuarial survival estimates.

** Carbon ion therapy.

*** Adult and pediatric mix series.

and 69%, respectively [80] and for parameningeal rhabdomyosarcoma were 5-year OS, LC, EFS, PFS 64–73%, 67.5–77%, 60%, 72% and 59%, respectively [80–83]. Other adverse predictors for prognosis were young age [80], higher stage according to COG grouping and IRS stage [80,81], tumor size (>5 cm) [81], intracranial extensions [81] and delay in the initiation of PT [82]. The risk for late adverse events of any grade (18–35%) [80,81] after PT seemed to be lower when compared to long-term toxicity data for RMS treated with IMXT, ranging from 32% to 47% [84–86]. These results are summarized in Table 3.

In summary, data on treatment outcome and treatment related side effects in pediatric rhabdomyosarcoma after PT are promising. PT should be considered particularly in young patients and geometrically challenging scenarios though tissues within the high dose areas can lead to impaired growth and development especially in young children.

Ewing sarcoma

Ewing sarcoma is a rare malignant bone and/or soft tissue small blue round cell cancer with an approximate annual incidence of 200 cases in the US [87]. It is the second most prevalent bone tumor with a peak incidence between 10 and 15 years of age [88,89]. Induction chemotherapy followed by local consolidation (surgery or RT) is the standard of care with an expected 5y OS of 50–75% [90,91]. RT can be delivered with conventional RT, IMXT or particle therapy (i.e. PT or carbon ions). Table 3 summarizes studies reporting the efficacy of particles for Ewing sarcoma.

Rombi et al. reported the outcome of 30 Ewing sarcoma patients (median age, 10 years) treated to a median dose of 54 Gy(RBE). After a median follow-up time of 38.4 months, with 3yLC and OS rates of 86% and 89%, respectively. 20% of these patients presented grade 3 toxicities [92].

Weber et al. reported on 38 Ewing sarcoma patients (median age, 9.9 years) to a same median dose level of 54.9 Gy(RBE) with PBS PT only. Surgery was not performed on 53% of these patients. At a follow-up of 49.6 months, the 5y LC and OS rates were81.5% and 83%, respectively. Of note, all local recurrences occurred infield for non-extremity tumors. The 5y toxicity-free survival was 90.9%, only 2 grade 3 toxicities were observed in this series [87].

Overall, a very limited number (total, 50 patients) of Ewing sarcoma patients treated with particles have been reported in the literature. With a recent COG report noted inferior LC for unresectable pelvic tumors [93] higher doses possible with PT may be advantageous. Where tumors are typically adjacent to, dose-limiting structures such as small bowel and bladder. Carbon ion or PT may substantially decrease long term complications of RT for most unresectable tumors and may result in reduction in peri-operative morbidity for patients receiving combined therapy with surgery due to the significant reduction in bowel and bladder dose.

Osteosarcoma

Osteosarcoma is diagnosed in 400–450 pediatric patients per year in the United States and represents approximately 5% of childhood and adolescent/young adult cancers. The peak incidence coincides with the pubertal growth spurt with approximately 75% occurring in appendicular locations.

Neoadjuvant chemotherapy and aggressive surgery for localized disease yields a 10-year OS of 70% [94]. Some data suggest that RT can achieve LC in patients with unresectable disease or positive margins [95]. Other series that do not show benefit of RT neglect the effect of biases such as incomplete resection. Brady et al. reported on 204 children with head and neck sarcoma (44% osteosarcoma) treated from 1973 to 2013: 58% surgery, 12% RT and 30% both. Disease-specific survival rates were 86.0%, 67.9% and 75.3% respectively. No difference was found with RT alone vs surgery with RT [96].

Delaney et al. reported a 5y LC of 68% after PT (median 66 Gy, +/− XRT) for osteosarcoma after inadequate surgery. [97] RT was more effective for microscopic or minimal residual disease. A 5y LC and OS of 72% and 67%, respectively was noted in a subsequent report of 55 patients, median age 29 years (range, 2–76), treated with a median dose of 68 Gy using PT or mixed PT/XRT [98]. Risk factors for local failure were $\geq$ 2 grade disease and total treatment length. Grade 3–4 late toxicity was seen in 30% of patients [98].

Although the level of evidence for RT and PT is low, PT in young patients with unresected or inadequately resected osteosarcoma, often axial tumors adjacent to critical structures, can overcome the limitations of XRT by delivering a higher, tumoricidal, dose while delivering low dose to nearby critical structures. This may be even more relevant to young osteosarcoma patients, who may have germline mutations, associated with an increased vulnerability to secondary cancers [99].

Retinoblastoma

Retinoblastoma is the most common childhood tumor of the eye with an expected >95% 5y OS. Approximately 50–65% of cases are heritable retinoblastoma, a condition in which both RB1 tumor suppressor gene alleles are inactivated in the germline DNA. Children with heritable retinoblastoma often develop tumors in both eyes and are at increased risk of subsequent malignancies as well as treatment-related second malignancies. RT was recognized early as an effective eye-preserving therapy but due to increased risk of SMNs, has now been largely replaced by other eye-preserving therapies such as chemotherapy, laser, and cryo-ablation with RT being reserved for salvage of advanced and refractory disease.

PT has the potential to reduce the incidence of in-field SMNs by reducing radiation exposure to nearby surrounding bone and soft tissues [100]. Current practice trends, however, are influenced largely by second malignancy data from historic RT techniques, thus the majority of patients receiving and RT are now are locally advanced, chemo-refractory and/or status post other focal therapies. Patients with locally advanced and refractory retinoblastoma treated in both the series by Agarwal et al. and Mouw et al., had a >60% enucleation-free survival with PT (Table 4) [101,102]. The report by Mouw et al. also details outcomes for early stage patients who received focal PT. Enucleation-free survival was >90% in those patients suggesting that PT remains a potent therapy for retinoblastoma. Follow-up is limited but the data suggest PT should be reconsidered at earlier stages of disease if long-term outcomes in reduction in late toxicity are confirmed.

Lymphoma

Approximately 800 cases of Hodgkin's lymphoma are diagnosed annually in the United States in patients 18 and younger. Adolescents with Hodgkin lymphoma experience excellent cure rates and are expected to live several decades [68]. Unfortunately, they have a high risk of developing late grade 3 toxicities, including SMNs and cardiovascular complications which generally exhibit a linear dose–response relationship to RT [103,104]. A recent summary of dosimetric studies has demonstrated reductions in dose to organs at risk with PT compared with 3D-RT and IMXT [105]. These dose reductions are expected to translate into a lower risk of SMNs and cardiovascular complications, thereby improving survivorship health outcomes [106]. Late toxicity is generally not seen for 10–15 years after treatment so long-term data are not yet available. Early studies have confirmed the efficacy of PT in Hodgkin's lymphoma; indeed, a large collaborative study among several

Table 4
Studies assessing the outcome of children with other tumors treated with proton therapy.

Author [ref]	Method	Med FU (mo) [range]	N	Med Dose Gy(RBE) [range]	PS/PBS	Chemo Y/N	Outcome
Retinoblastoma							
Agarwal [102]	R	3	16	36 [36–45]	PS	Y	ENS: 63% No in-field SMN
Mouw [101]	R	8	60	44 [40–46.8]	PS	Y	ENS:80% No in-field SMN
Lymphoma							
Hoppe [107]	R	32	138 (mix)	21 ped 30.6 adult	PS/US	Y	3y PFS: 96% adults 3y PFS: 87% peds No G3 toxicity
Nanda [110]	R	24	59 (mix)	30.6 CGE	PS/US	Y	No G 2/3 pneumonitis
Wray [109]	R	36	22 (peds)	21 CGE	PS/US	Y	3 yr PFS: 86%; No G3 toxicity
Neuroblastoma							
Fuji [124]	R	NR	5	36 [21.6–41.4]	PS	Y	NR
Hattangadi [125]	R	38 [11–70]	9 [7–1 site, 2–2 sites]	22 [10.8–36]*	PS	Y	LC: 100% 5/9 NED 7/9 alive
Hill-Kayser [126]	P	16 [5–27]	13pt [8–1 site, 5 – ≥2 sites]	21.6 [21.6–36.0]	PS	Y	LC: 100% 11/13 alive
Oshiro [127]	R	21 [5–348]	14 [9–1 site, 5 – ≥2 sites]	30.6 [19.8–45.5]	PS	Y	LC:100% 8/14 alive

Abbreviations: N: Number PS: passive scatter, PBS: pencil beam scanning, Chemo: chemotherapy, P: prospective, R: retrospective, ENS: enucleation free survival, SMN: second malignant neoplasm, NR: not reported, TBI: total body irradiation, IORT: intra-operative radiotherapy.
* Only proton dose noted in table: 1pt 12 Gy TBI + 10.8 GyRBE; 1pt 5 Gy IORT + 23.4 GyRBE.

institutions reported a 3y event free survival of 92% for all patients and 87% for pediatric patients [107–109]. These studies have not shown any significant grade 3 toxicities or clinically significant pneumonitis [110,111] (Table 4). Currently, pediatric Hodgkin's lymphoma trials, including the COG AHOD 1331 and Euronet PHL-2 study, allow PT. Unfortunately, insurance coverage remains a problem and can prevent these children from receiving a treatment that could potentially impact their late toxicities and QOL as well as limits ability to generate data needed to demonstrate the expected reduction in late toxicity [112].

Neuroblastoma

Neuroblastoma is diagnosed in approximately 800 children in the US annually and is the most common solid extracranial tumor. The median age at diagnosis of 18 months with 90% before age 10 years. Metastatic disease is noted in >70% of cases at diagnosis. Age and stage at presentation remain the most important prognostic factors. In general >75% of patients <2 years and those with INSS stages 1 and 2 have OS rates >90% [113–117].

RT to the primary and selected metastatic sites is needed for definitive treatment of neuroblastoma and for palliation for refractory disease [118–120]. RT planning for neuroblastoma is challenging due to the patient's age, neighboring structures and possible need multiple site treatment. Parallel-opposed fields have been used to cover the surgical bed with a margin; however, with advanced techniques conformal approaches are now used to reduce normal tissue doses including the kidney(s), liver, spinal cord, pancreas, bowel, heart and vertebra for abdominal disease.

Dosimetric comparisons of PT and XRT have suggested an improved therapeutic index for normal tissues [121–124]. Clinical results of PT for neuroblastoma are summarized in Table 4 [124–127]. In general, tumor control and patterns of failure are as expected. PT appears to result in fewer acute toxicities, with improved organ preservation and lower SMN risks. Hill-Kayser et al. conclude that a customized approach is needed and sometimes IMXT is better for ipsilateral renal sparing than 3D PT. PBS will likely provide a better solution for these cases. PT for metastatic site consolidation can be considered for dosimetric benefits or patient safety/convenience/efficiency if the primary site is treated with PT.

Wilms tumors

Wilms tumor is the most common childhood renal malignancy. Approximately 500 cases are diagnosed annually in the US and the 5-year OS is 90% [68]. RT is used for LC in patients with incomplete resection, higher stage, unfavorable histology, lung metastases and high-risk chromosomal aberrations [128,129]. Classically "flank radiation" is delivered anterior/posterior XRT fields encompassing the initial tumor, involved lymph nodes, 1 cm margin, and adjacent vertebral bodies.

Hillbrand et al. reported 40–60% mean liver and kidney dose reduction with PT for Wilms tumor. In addition, SMNs with PBS-PT were predicted to decrease relative to IMXT and PS-PT [122]. Vogel et al. assessed RT plans for 11 patients comparing standard AP-PA fields to PBS-PT for given CTVs. PBS-PT resulted in a significant dose reduction to the contralateral kidney, bowel and liver [130]. Given the ability of PT to minimize normal tissue exposures, there is interest to investigate its use for Wilms tumor; however, concerns of increased abdominal failures remain [131]. In patients with no diffuse abdominal spill, a clinical trial of PT evaluating LC and incidence and pattern of failure would be helpful.

Costs and CEA

The global cost of cancer care has increased substantially in the last decade and has been estimated to be as high as $ 895 billion USD in 2008 [148]. It is foreseen that growth in cancer spending is unsustainable in the long-term [149]. One of the main drivers of cancer costs is the delivery of costly new treatments [150], the other being the aging population. The costs associated with the latest cancer drugs have skyrocketed and account for 12% cancer care [151]. PT is also an expensive anti-cancer treatment, with a cost factor of approximately of 2.5, when compared to modern XRT techniques [152]. Interestingly, only 0.05% of all US care health is used for technology assessment [153].

Innovative cancer management should reduce overall health-related costs, improve HR-QOL, reduce toxicities, or improve patient's outcome. PT aims to modify the last three factors and possibly the first. Because resources are scarce, it is of paramount importance to consider the cost-effectiveness (CE) of PT. The CE of PT for medulloblastoma has been evaluated in two hypothetical cohorts of children receiving PT and XRT [154,155]. The model included the risks of IQ loss, hearing loss, hypothyroidism, growth hormone (GH) deficiency, osteoporosis, cardiac disease and SMNs. Study parameters for modeling with PT were: (1) a 52% reduction in SMNs and (2) a 33% reduction in cardiac and non-cardiac mortality and (3) 88% risk reduction for hearing loss, hormone insufficiencies, osteoporosis and IQ loss [6]. The author reporteda gain of 0.68 QALY/child with an estimated ICER of € −34,622 EUR. According to this model, for childhood MB, PT is cost-effective and cost-saving.

The CE of PT with cochlear dose reduction in childhood MB has been also assessed in a Japanese study [156] Table 1. Both groups were prescribed RT dose based on disease risk with the same ototoxic chemotherapy regimens resulting in the same treatment efficacy. The cochlear dose was reduced by 37% and 21% with PT for the standard- and high-risk groups, respectively. The utilities associated with irreversible hearing loss were assumed to be 0.80, 0.64 and 0.79 using three different QOL indexes. The costs associated with hearing aids (for 5 years) were $ 2087 USD Table 2. Th authors estimated a 99.5% probability of PT being cost-effective.

Another CE analysis was performed by the Boston group, assessing the value of PT *vs.* XRT with respect of GH deficiency [157]. The same methodology was used as the former analyses (i.e. using a Markov model) and longitudinal data were used to inform risk parameters for the cohort-simulation model. The annual costs of GH replacement were estimated to be $ 10,000 based on 2012 figures and CE was assumed at a level of $50,000/QALY. For hypothalamic doses $\geq$10–15 Gy RBE, regardless of patient age (4 *vs.* 12 years), PT was found to be cost saving. As such, PT was felt to be above the cost-neutral threshold when hypothalamic dose could be lowered independent of the tumor type. The corollary conclusion is that PT would probably not be as CE if the critical structure was direct vicinity of the tumor.

In summary, PT may be cost-effective for pediatric CNS tumor management. More CE analyses are urgently needed to evaluate the benefit of PT for non-CNS pediatric tumor management.

Global pediatric radiation oncology: PROS and proton therapy access

Despite the overwhelming dosimetric evidence of advantages of PT for many pediatric diseases demonstrated in this paper, as pediatric radiation oncologists we recognize that PT is not appropriate for all pediatric patients. Children with incurable malignancies who will not live long enough to see the benefits can be very effectively treated with XRT. In some cases, a family may not be able to relocate, treatment is urgently needed or insurance coverage is lacking. We are continuing to make major improvements in XRT, including MR-linacs, VMAT and MR-guided HDR brachytherapy.

The Paediatric Radiation Oncology Society (PROS) is the only international society devoted to this unique sub-specialty. PROS has over 150 members from 37 nations including many members from Low- and Middle-Income Countries. Whereas some of our members treat the majority of pediatric patients with PT, many members come from underserved areas where Cobalt teletherapy units can provide goodconformal therapy. The mission of PROS is to set a worldwide standard of excellence in radiation oncology for children and adolescents with cancer. While we endorse and encourage the use of PT for children, we also strive to deliver safe and effective treatment for all children who need RT.

Discussion

In this paper, we have reviewed the data on proton therapy delivered to a number of cancers occurring in children and adolescents. Moreover, we discussed the important issue of access to this costly treatment modality and the cost-effectiveness of protons. Notwithstanding these two important questions, health professionals are left with the conundrum of how to decide on the selection of an appropriate treatment selection for a given child or adolescent with cancer. Of note, a model-based approach for selecting patients who are expected to benefit from PT compared to XRT has been initiated in the Netherlands [132]. In this approach, three criteria should be met: (1) the target dose of PT and XRT should be bio-equivalent; (2) the dose to relevant organs-at-risk should be lower with PT (ΔDose), and (3) ΔDose should translate to a clinically relevant RT related toxicity risk reduction, also referred to as ΔNTCP. To translate ΔDose to ΔNTCP, preferably multivariable NTCP-models are needed, describing the relationship between the 3D-dose distributions in organs-at-risk and toxicity risks. High quality multivariable NTCP-models are increasingly available for adult patients but are lacking for most organs-at-risk in the pediatric population.

Though, a model-based selection in pediatric patients is not feasible with the same level of objectivity a PT and XRT plan comparison with defined threshold dose volume parameters is relevant and will provide more objective data. Comparison plans could be generated for all patients; however, many times one can predict the outcome and the time required for developing XRT plans for comparison may be used otherwise. After some experience, plan comparisons are more useful for uncommon circumstances or specific reasons. Because of the high vulnerability of children to effects of ionizing radiation, the ALARA-principle is used in routine clinical practice. Multivariable NTCP-models, however, also provide essential information for RT planning optimization; therefore, comprehensive prospective data registration programs should have high priority for pediatric radiation oncology. These will enable linking 3D dose distributions to outcome in terms of toxicities and SMN induction. The European Particle Therapy Network (EPTN) is currently working on a prospective data registration program in Europe.

Additionally, normal tissue sparing with PT affords the opportunity for effective strategies for RT sensitization and enhanced tumor killing with chemo-RT combinations.

In adult malignancies, improved outcomes result from combinations of RT and systemic therapies compared with RT alone in multiple clinical trials across select histologies [133]. Combined systemic chemotherapy with XRT or PT is standard practice in pediatric cancer management. PT guidelines have been incorporated into COG clinical studies [134].

Most pediatric studies employing concurrent systemic and RT aggregate PT and XRT patients, because of the small number of patients receiving PT. These data support superior outcomes with concurrent RT and systemic chemotherapy in multiple diagnoses. The use of concurrent and adjuvant chemotherapy for pediatric standard-risk medulloblastoma permitted reduction of CSI dose from 36 Gy to 23.4 Gy with equivalent event free survival [135,136]. A recent study of 88 children treated with PT (45 patients) or XRT (43 patients) for standard-risk medulloblastoma revealed equivalent LC and OS, supporting the role of concurrent chemoradiotherapy for both XRT and PT [137]. In high-risk medulloblastoma, a single arm pilot study of concurrent carboplatin with CSI exhibited EFS of 71%, better than historical controls [138].

Concurrent use of RT and chemotherapy is a critical component of therapy for significant groups of patients with RMS, particularly with residual disease after surgery, nodal involvement or alveolar

histology. Parameningeal RMS (PM-RMS) is a frequent treatment scenario that is not amenable to complete surgical resection, and with high risk for RT related toxicities. Recent reports of children with PM-RMS treated with PT and standard concurrent chemotherapy revealed LC and OS comparable to historical controls and with favorable rates of late effects compared to reported XRT cohorts [76,83]. COG and other collaborative consortia have also demonstrated tolerability of concurrent RT with systemic multiagent chemotherapy in other childhood malignancies including EWS, WT, NB, nasopharyngeal carcinoma and other malignancies.

Key consensus proposals have been advanced to systematically exploit the significant opportunities for the development of new drug- and immunotherapy-RT combinations, particularly with the advent of precision RT approaches, including PT [133,139,140]. Challenges remain, however, for the systematic and rational development of drug- and immunotherapy-PT combinations and should be target areas for future research. A major area for investigation is the incomplete understanding of the biological mechanisms underpinning PT and heavy ion cytotoxicity [141,142]. Several recent reports suggest that PT is more efficient than XRT in the generation of apoptosis and cytotoxicity against RT-resistant stem-like cancer cells derived from patients with glioblastoma and non-small cell lung cancer [143,144]. In parallel, a better understanding is needed of factors influencing the cytotoxicity and relative biological effectiveness (RBE) of PT, including the influence of linear energy transfer considerations, dose-per-fraction, tumor heterogeneity and architecture, and differential sensitivity of different tumor types, and other variables [145,146]. Notably, PT may provide advantages in combined immunotherapy applications, as PT technology is associated with reduced marrow and normal hematopoietic and immune stem cell toxicity and sparing of lymphocytes. A better understanding of effects of PT on the immune microenvironment of tumors will also provide an enhanced foundation for the refinement of PT-immunotherapy combination studies.

Finally, it is imperative that treatment centers work together to accelerate the pace of research in pediatric cancer. While it is ideal to follow every patient on a large prospective group studies, it is simply not feasible because of tight research funding budgets and the diversity of malignancies. Registries are an ideal method to capture outcomes of every willing patient. Registries are not limited by specific disease type and are minimal risk studies with less oversight and monitoring; therefore, requiring a more affordable infrastructure.

Children treated with PT where data need to be collected, analyzed and published are an ideal group for observational registries because of the relative rarity of pediatric cancer and PT. The Pediatric Proton Consortium Registry (PPCR) was established to accelerate outcomes research in this patient population. 2000 patients have enrolled at 14 US PT centers as of early 2018. [147] The PPCR and other registries will provide a real-world view of clinical practice in PT, patient outcomes, safety, and can establish a platform for comparative effectiveness studies with XRT cohorts.

Importantly, registries require some funding and participating institutional commitment. It is clear that a comprehensive database will provide better data and more robust research, but can be more expensive to run. With more details, data entry, chart review and follow up are more time consuming and labor intensive as patient numbers increase. New methods including web-based input and automatized medical record data extraction provide promise for the future to reduce the time, effort and expense of registry management. In summary, registries are ideal to maximize learning from patients' experiences while requiring fewer research community resources; however, they still require research funding and resource investment.

Conclusions

Many studies still suggest that the predominant cause for early death among cancer survivors remains the primary tumor; however, it is also known survivors have many treatment related sequelae that impair their QOL in many domains. Through almost all dosimetric and model based evaluation, clinical outcomes for PT should be favorable with an improved QOL, organ function, development with a reduction in the risk of SMNs. Several decades of follow up data are required to provide objective data on the benefits of PT, as shown by existing study cohorts [158–160]. As highlighted in this review, the model base-approach seems promising for PT selection for cancer children when the primary aim is to reduce side effects. PT may be more efficient that XRT in cancer cell kill and it could be potentially interesting to combine this modality with systemic treatment.

With the use of strategic databases, appropriate baseline testing for organs at risk, diligent follow up and collaborations, there will be more data that will be collected that can help identify appropriate PT expectations and allow more precise modeling for prediction of late effects for patients and their families. Finally, PT remains a costly treatment and more emphasis should be put in assessing the cost-benefit of this treatment and making protons more affordable and available to the pediatric population.

Conflicts of interest notification

The author & co-authors have no potential Conflict of Interest.

References

[1] Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, et al. International incidence of childhood cancer, 2001–10: a population-based registry study. Lancet Oncol 2017;18:719–31.
[2] Habrand JL, Stefan D, Bolle S. D. L, Helfre S, Alapetite C. The impact of particle therapy in pediatric tumors with emphasis on clinical toxicity. Ped Blood. Cancer 2017;64:365–433.
[3] MacDonald SM, Safai S, Trofimov A, Wolfgang J, Fullerton B, Yeap BY, et al. Proton radiotherapy for childhood ependymoma: initial clinical outcomes and dose comparisons. Int J Radiat Oncol Biol Phys 2008;71:979–86.
[4] Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol 2009;10:258–66.
[5] Reynolds MR, Haydon DH, Caird J, Leonard JR. Radiation-Induced Moyamoya Syndrome after Proton Beam Therapy in the Pediatric Patient: A Case Series. Pediatr Neurosurg 2016;51:297–301.
[6] Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer 2008;51:110–7.
[7] Mahajan A. Proton Craniospinal Radiation Therapy: Rationale and Clinical Evidence. Int J Particle Therapy 2014;1:399–407.
[8] St Clair WH, Adams JA, Bues M, Fullerton BC, La Shell S, Kooy HM, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 2004;58:727–34.
[9] 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;17:287–98.
[10] Paulino AC, Mahajan A, Ye R, Grosshans DR, Fatih Okcu M, Su J, et al. Ototoxicity and cochlear sparing in children with medulloblastoma: Proton vs. photon radiotherapy. Radiother Oncol 2018.
[11] Michalski JM, Janss A, Vezina G, Gajjar A, Pollack I, Merchant TE, et al. Results of COG ACNS0331: A Phase III Trial of Involved-Field Radiotherapy (IFRT) and Low Dose Craniospinal Irradiation (LD-CSI) with Chemotherapy in Average-Risk Medulloblastoma: A Report from the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2016;96:937–8.
[12] Taylor MD, Northcott PA, Korshunov A, Remke M, Cho YJ, Clifford SC, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol 2012;123:465–72.
[13] Yoon M, Shin DH, Kim J, Kim JW, Kim DW, Park SY, et al. Craniospinal irradiation techniques: a dosimetric comparison of proton beams with standard and advanced photon radiotherapy. Int J Radiat Oncol Biol Phys 2011;81:637–46.
[14] Giantsoudi D, Seco J, Eaton BR, Simeone FJ, Kooy H, Yock TI, et al. Evaluating Intensity Modulated Proton Therapy Relative to Passive Scattering Proton

Therapy for Increased Vertebral Column Sparing in Craniospinal Irradiation in Growing Pediatric Patients. Int J Radiat Oncol Biol Phys 2017;98:37–46.
[15] Merchant TE. Current management of childhood ependymoma. Oncology (Williston Park) 2002;16. 629–42, 44; discussion 45–6, 48.
[16] Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000;50:7–33.
[17] Dhall G, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer 2008;50:1169–75.
[18] Smyth MD, Horn BN, Russo C, Berger MS. Intracranial ependymomas of childhood: current management strategies. Pediatr Neurosurg 2000;33:138–50.
[19] Merchant TE, Fouladi M. Ependymoma: new therapeutic approaches including radiation and chemotherapy. J Neurooncol 2005;75:287–99.
[20] van Veelen-Vincent ML, Pierre-Kahn A, Kalifa C, Sainte-Rose C, Zerah M, Thorne J, et al. Ependymoma in childhood: prognostic factors, extent of surgery, and adjuvant therapy. J Neurosurg 2002;97:827–35.
[21] Merchant TE. Three-dimensional conformal radiation therapy for ependymoma. Childs Nerv Syst 2009;25:1261–8.
[22] Massimino M, Miceli R, Giangaspero F, Boschetti L, Modena P, Antonelli M, et al. Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma. Neuro Oncol 2016;18:1451–60.
[23] Foreman NK, Love S, Gill SS, Coakham HB. Second-look surgery for incompletely resected fourth ventricle ependymomas: technical case report. Neurosurgery. 1997;40:856-60; discussion 60.
[24] ClinicalTrials.gov. Observation or radiation therapy and/or chemotherapy and second surgery in treating children who have undergone surgery for ependymoma. Sponsored by the National Cancer Institute. Available at: <https://clinicaltrials.gov/ct2/show/NCT00027846>; 2016 [accessed 11.17.16].
[25] Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the childhood cancer survivor study. J Natl Cancer Inst 2009;101:946–58.
[26] Kahalley LS, Ris MD, Grosshans DR, Okcu MF, Paulino AC, Chintagumpala M, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. J Clin Oncol 2016;34:1043–9.
[27] Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 2009;27:3691–7.
[28] Greenberger BA, Pulsifer MB, Ebb DH, MacDonald SM, Jones RM, Butler WE, et al. Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys 2014;89:1060–8.
[29] Rickert CH, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 2001;17:503–11.
[30] Packer RJ, Biegel JA, Blaney S, Finlay J, Geyer JR, Heideman R, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: report on workshop. J Pediatr Hematol Oncol 2002;24:337–42.
[31] Tekautz TM, Fuller CE, Blaney S, Fouladi M, Broniscer A, Merchant TE, et al. Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. J Clin Oncol 2005;23:1491–9.
[32] Chi SN, Zimmerman MA, Yao X, Cohen KJ, Burger P, Biegel JA, et al. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol 2009;27:385–9.
[33] Burger PC, Yu IT, Tihan T, Friedman HS, Strother DR, Kepner JL, et al. Atypical teratoid/rhabdoid tumor of the central nervous system: a highly malignant tumor of infancy and childhood frequently mistaken for medulloblastoma: a pediatric oncology group study. Am J Surg Pathol 1998;22:1083–92.
[34] Weiss E, Behring B, Behnke J, Christen HJ, Pekrun A, Hess CF. Treatment of primary malignant rhabdoid tumor of the brain: report of three cases and review of the literature. Int J Radiat Oncol Biol Phys 1998;41:1013–9.
[35] Squire SE, Chan MD, Marcus KJ. Atypical teratoid/rhabdoid tumor: the controversy behind radiation therapy. J Neurooncol 2007;81:97–111.
[36] De Amorim Bernstein K, Sethi R, Trofimov A, Zeng C, Fullerton B, Yeap BY, et al. Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. Int J Radiat Oncol Biol Phys 2013;86:114–20.
[37] Elsayad K, Kriz J, Samhouri L, Haverkamp U, Straeter R, Stummer W, et al. Long-term survival following additive radiotherapy in patients with atypical teratoid rhabdoid tumors. Strahlenther Onkol 2016;192:569–81.
[38] Weber DC, Ares C, Malyapa R, Albertini F, Calaminus G, Kliebsch U, et al. Tumor control and QoL outcomes of very young children with atypical teratoid/rhabdoid tumor treated with focal only chemo-radiation therapy using pencil beam scanning proton therapy. J Neurooncol 2015;121:389–97.
[39] Fitzek MM, Linggood RM, Adams J, Munzenrider JE. Combined proton and photon irradiation for craniopharyngioma: long-term results of the early cohort of patients treated at harvard cyclotron laboratory and massachusetts general hospital. Int J Radiat Oncol Biol Phys 2006;64:1348–54.
[40] Laffond C, Dellatolas G, Alapetite C, Puget S, Grill J, Habrand JL, et al. Quality-of-life, mood and executive functioning after childhood craniopharyngioma treated with surgery and proton beam therapy. Brain Inj 2012;26:270–81.
[41] Bishop AJ, Greenfield B, Mahajan A, Paulino AC, Okcu MF, Allen PK, et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. Int J Radiat Oncol Biol Phys 2014;90:354–61.
[42] Luu QT, Loredo LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. Cancer J 2006;12:155–9.
[43] Ostrom QT, Gittleman H, Liao P, Vecchione-Koval T, Wolinsky Y, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro Oncol 2017;19:v1–v88.
[44] Jellinger K. Primary intracranial germ cell tumours. Acta Neuropathol 1973;25:291–306.
[45] Maity A, Shu HK, Janss A, Belasco JB, Rorke L, Phillips PC, et al. Craniospinal radiation in the treatment of biopsy-proven intracranial germinomas: twenty-five years' experience in a single center. Int J Radiat Oncol Biol Phys 2004;58:1165–70.
[46] Huh SJ, Shin KH, Kim IH, Ahn YC, Ha SW, Park CI. Radiotherapy of intracranial germinomas. Radiother Oncol 1996;38:19–23.
[47] Ogawa K, Shikama N, Toita T, Nakamura K, Uno T, Onishi H, et al. Long-term results of radiotherapy for intracranial germinoma: a multi-institutional retrospective review of 126 patients. Int J Radiat Oncol Biol Phys 2004;58:705–13.
[48] MacDonald SM, Trofimov A, Safai S, Adams J, Fullerton B, Ebb D, et al. Proton radiotherapy for pediatric central nervous system germ cell tumors: early clinical outcomes. Int J Radiat Oncol Biol Phys 2011;79:121–9.
[49] Robertson PL, DaRosso RC, Allen JC. Improved prognosis of intracranial non-germinoma germ cell tumors with multimodality therapy. J Neuro Oncol 1997;32:71–80.
[50] Kim JW, Kim WC, Cho JH, Kim DS, Shim KW, Lyu CJ, et al. A multimodal approach including craniospinal irradiation improves the treatment outcome of high-risk intracranial nongerminomatous germ cell tumors. Int J Radiat Oncol Biol Phys 2012;84:625–31.
[51] Richards AT, Stricke L, Spitz L. Sacrococcygeal chordomas in children. J Pediatr Surg 1973;8:911–4.
[52] Cable DG, Moir C. Pediatric sacrococcygeal chordomas: a rare tumor to be differentiated from sacrococcygeal teratoma. J Pediatr Surg 1997;32:759–61.
[53] Al-Adra D, Bennett A, Gill R, Lees G. Pediatric metastatic sacrococcygeal chordoma treated with surgery. Eur J Pediatr Surg 2011;21:196–8.
[54] Hoch BL, Nielsen GP, Liebsch NJ, Rosenberg AE. Base of skull chordomas in children and adolescents: a clinicopathologic study of 73 cases. Am J Surg Pathol 2006;30:811–8.
[55] Borba LA, Al-Mefty O, Mrak RE, Suen J. Cranial chordomas in children and adolescents. J Neurosurg 1996;84:584–91.
[56] Probst EN, Zanella FE, Vortmeyer AO. Congenital clivus chordoma. AJNR Am J Neuroradiol 1993;14:537–9.
[57] Benk V, Liebsch NJ, Munzenrider JE, Efird J, McManus P, Suit H. Base of skull and cervical spine chordomas in children treated by high-dose irradiation. Int J Radiat Oncol Biol Phys 1995;31:577–81.
[58] Matsumoto J, Towbin RB, Ball Jr WS. Cranial chordomas in infancy and childhood. a report of two cases and review of the literature. Pediatr Radiol 1989;20:28–32.
[59] Ridenour 3rd RV, Ahrens WA, Folpe AL, Miller DV. Clinical and histopathologic features of chordomas in children and young adults. Pediatr Dev Pathol 2010;13:9–17.
[60] Coffin CM, Swanson PE, Wick MR, Dehner LP. Chordoma in childhood and adolescence. A clinicopathologic analysis of 12 cases. Arch Pathol Lab Med 1993;117:927–33.
[61] Kaneko Y, Sato Y, Iwaki T, Shin RW, Tateishi J, Fukui M. Chordoma in early childhood: a clinicopathological study. Neurosurgery 1991;29:442–6.
[62] Hug EB, Sweeney RA, Nurre PM, Holloway KC, Slater JD, Munzenrider JE. Proton radiotherapy in management of pediatric base of skull tumors. Int J Radiat Oncol Biol Phys 2002;52:1017–24.
[63] Gadwal SR, Fanburg-Smith JC, Gannon FH, Thompson LD. Primary chondrosarcoma of the head and neck in pediatric patients: a clinicopathologic study of 14 cases with a review of the literature. Cancer 2000;88:2181–8.
[64] Combs SE, Kessel KA, Herfarth K, Jensen A, Oertel S, Blattmann C, et al. Treatment of pediatric patients and young adults with particle therapy at the Heidelberg Ion Therapy Center (HIT): establishment of workflow and initial clinical data. Radiat Oncol 2012;7:170.
[65] Rombi B, Ares C, Hug EB, Schneider R, Goitein G, Staab A, et al. Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at paul scherrer institute. Int J Radiat Oncol Biol Phys 2013;86:578–84.
[66] Choi GH, Yang MS, Yoon DH, Shin HC, Kim KN, Yi S, et al. Pediatric cervical chordoma: report of two cases and a review of the current literature. Childs Nerv Syst 2010;26:835–40.
[67] Kaatsch P, Spix C. German Childhood Cancer Registry – Annual Report 2015 (1980–2014). Institute of Medical Biostatistics, Epidemiology, and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University Mainz. Available from: <http://wwwkinderkrebsregisterde/dkkr-gb/latest-publications/annual-reports/annual-report-2015html?L=1>; 2015 [accessed 20.11.17].
[68] Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014;64:83–103.

[69] Hiniker SM, Donaldson SS. Recent advances in understanding and managing rhabdomyosarcoma. F1000prime reports. 2015;7:59.
[70] Yang L, Takimoto T, Fujimoto J. Prognostic model for predicting overall survival in children and adolescents with rhabdomyosarcoma. BMC Cancer 2014;14:654.
[71] Merks JH, De Salvo GL, Bergeron C, Bisogno G, De Paoli A, Ferrari A, et al. Parameningeal rhabdomyosarcoma in pediatric age: results of a pooled analysis from North American and European cooperative groups. Ann Oncol 2014;25:231–6.
[72] Timmermann B, Schuck A, Niggli F, Weiss M, Lomax AJ, Pedroni E, et al. Spot-scanning proton therapy for malignant soft tissue tumors in childhood: first experiences at the Paul Scherrer Institute. Int J Radiat Oncol Biol Phys 2007;67:497–504.
[73] Frisch S, Timmermann B. The evolving role of proton beam therapy for sarcomas. Clin oncol (R Coll Radiol ((Great Britain)) 2017;29:500–6.
[74] [74] Timmermann B, Schuck A, Niggli F, Weiss M, Lomax A, Goitein G. ["Spot-scanning" proton therapy for rhabdomyosarcomas of early childhood. First experiences at PSI]. Strahlentherapie und Onkologie: Organ der Deutschen Rontgengesellschaft [et al]. 2006;182:653–9.
[75] Kozak KR, Adams J, Krejcarek SJ, Tarbell NJ, Yock TI. A dosimetric comparison of proton and intensity-modulated photon radiotherapy for pediatric parameningeal rhabdomyosarcomas. Int J Radiat Oncol Biol Phys 2009;74:179–86.
[76] Ladra MM, Edgington SK, Mahajan A, Grosshans D, Szymonifka J, Khan F, et al. A dosimetric comparison of proton and intensity modulated radiation therapy in pediatric rhabdomyosarcoma patients enrolled on a prospective phase II proton study. Radiother Oncol: Journal Eur Soc Ther Radiol Oncol 2014;113:77–83.
[77] Yock T, Schneider R, Friedmann A, Adams J, Fullerton B, Tarbell N. Proton radiotherapy for orbital rhabdomyosarcoma: clinical outcome and a dosimetric comparison with photons. Int J Radiat Oncol Biol Phys 2005;63:1161–8.
[78] Weber DC, Trofimov AV, Delaney TF, Bortfeld T. A treatment planning comparison of intensity modulated photon and proton therapy for paraspinal sarcomas. Int J Radiat Oncoly Biol Phys 2004;58:1596–606.
[79] Cotter SE, Herrup DA, Friedmann A, Macdonald SM, Pieretti RV, Robinson G, 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.
[80] Ladra MM, Szymonifka JD, Mahajan A, Friedmann AM, Yong Yeap B, Goebel CP, et al. Preliminary results of a phase II trial of proton radiotherapy for pediatric rhabdomyosarcoma. J Clin Oncol 2014;32:3762–70.
[81] Leiser D, Calaminus G, Malyapa R, Bojaxhiu B, Albertini F, Kliebsch U, et al. Tumour control and Quality of Life in children with rhabdomyosarcoma treated with pencil beam scanning proton therapy. Radiother Oncol: J Eur Soc Ther Radiol Oncol 2016.
[82] Weber DC, Ares C, Albertini F, Frei-Welte M, Niggli FK, Schneider R, et al. Pencil beam scanning proton therapy for pediatric parameningeal rhabdomyosarcomas: clinical outcome of patients treated at the Paul Scherrer Institute. Pediatr Blood Cancer 2016;63:1731–6.
[83] Childs SK, Kozak KR, Friedmann AM, Yeap BY, Adams J, MacDonald SM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. Int J Radiat Oncol Biol Phys 2012;82:635–42.
[84] Curtis AE, Okcu MF, Chintagumpala M, Teh BS, Paulino AC. Local control after intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2009;73:173–7.
[85] Wolden SL, Wexler LH, Kraus DH, Laquaglia MP, Lis E, Meyers PA. Intensity-modulated radiotherapy for head-and-neck rhabdomyosarcoma. Int J Radiat Oncol Biol Phys 2005;61:1432–8.
[86] Combs SE, Behnisch W, Kulozik AE, Huber PE, Debus J, Schulz-Ertner D. Intensity Modulated Radiotherapy (IMRT) and Fractionated Stereotactic Radiotherapy (FSRT) for children with head-and-neck-rhabdomyosarcoma. BMC Cancer 2007;7:177.
[87] Weber DC, Murray FR, Correia D, Bolsi A, Frei-Welte M, Pica A, et al. Pencil beam scanned protons for the treatment of patients with Ewing sarcoma. Pediatr Blood Cancer 2017;64.
[88] Stiller CA, Bielack SS, Jundt G, Steliarova-Foucher E. Bone tumours in European children and adolescents, 1978–1997. Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2124–35.
[89] Sundaresan N, Rosen G, Boriani S. Primary malignant tumors of the spine. Orthop Clin North Am 2009;40:21–36.
[90] Rodriguez-Galindo C, Liu T, Krasin MJ, Wu J, Billups CA, Daw NC, et al. Analysis of prognostic factors in ewing sarcoma family of tumors: review of St.Jude Children's Research Hospital studies. Cancer 2007;110:375–84.
[91] Granowetter L, Womer R, Devidas M, Krailo M, Wang C, Bernstein M, et al. Dose-intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol 2009;27:2536–41.
[92] Rombi B, DeLaney TF, MacDonald SM, Huang MS, Ebb DH, Liebsch NJ, et al. Proton radiotherapy for pediatric Ewing's sarcoma: initial clinical outcomes. Int J Radiat Oncol Biol Phys 2012;82:1142–8.
[93] Ahmed SK, Randall RL, DuBois SG, Harmsen WS, Krailo M, Marcus KJ, et al. Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group. Int J Radiat Oncol Biol Phys 2017;99:1286–94.
[94] Hundsdoerfer P, Albrecht M, Ruhl U, Fengler R, Kulozik AE, Henze G. Long-term outcome after polychemotherapy and intensive local radiation therapy of high-grade osteosarcoma. Eur J Cancer 2009;45:2447–51.
[95] Kager L, Zoubek A, Dominkus M, Lang S, Bodmer N, Jundt G, et al. Osteosarcoma in very young children: experience of the Cooperative Osteosarcoma Study Group. Cancer 2010;116:5316–24.
[96] Brady JS, Chung SY, Marchiano E, Eloy JA, Baredes S, Park RCW. Pediatric head and neck bone sarcomas: An analysis of 204 cases. Int J Pediatr Otorhinolaryngol 2017;100:71–6.
[97] DeLaney TF, Park L, Goldberg SI, Hug EB, Liebsch NJ, Munzenrider JE, et al. Radiotherapy for local control of osteosarcoma. Int J Radiat Oncol Biol Phys 2005;61:492–8.
[98] Ciernik IF, Niemierko A, Harmon DC, Kobayashi W, Chen YL, Yock TI, et al. Proton-based radiotherapy for unresectable or incompletely resected osteosarcoma. Cancer 2011;117:4522–30.
[99] Leroy R, Benahmed N, Hulstaert F, Van Damme N, De Ruysscher D. Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers. Int J Radiat Oncol Biol Phys. 2016;95:267–78.
[100] 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.
[101] Mouw KW, Sethi RV, Yeap BY, MacDonald SM, Chen YL, Tarbell NJ, et al. Proton radiation therapy for the treatment of retinoblastoma. Int J Radiat Oncol Biol Phys 2014;90:863–9.
[102] Agarwal A, Thaker NG, Bouchra T, Allen PK, Grosshans DR, Herzog CE, et al. The Evolution of Radiation Therapy for Retinoblastoma: The MD Anderson Cancer Center Experience. Int J Particle Therapy 2016;2:190–498.
[103] Inskip PD, Sigurdson AJ, Veiga L, Bhatti P, Ronckers C, Rajaraman P, et al. Radiation-Related New Primary Solid Cancers in the Childhood Cancer Survivor Study: Comparative Radiation Dose Response and Modification of Treatment Effects. Int J Radiat Oncol Biol Phys 2016;94:800–7.
[104] van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CP, Krol AD, Hauptmann M, et al. Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma. J Clin Oncol 2016;34:235–43.
[105] Tseng YD, Cutter DJ, Plastaras JP, Parikh RR, Cahlon O, Chuong MD, et al. Evidence-based Review on the Use of Proton Therapy in Lymphoma From the Particle Therapy Cooperative Group (PTCOG) Lymphoma Subcommittee. Int J Radiat Oncol Biol Phys 2017;99:825–42.
[106] Maraldo MV, Brodin NP, Aznar MC, Vogelius IR, Munck af Rosenschold P, Petersen PM PM, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. Ann Oncol 2013;24:2113–8.
[107] Hoppe BS, Tsai H, Larson G, Laramore GE, Vargas C, Tseng YD, et al. Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry. Acta Oncol 2016;55:1378–80.
[108] Hoppe BS, Hill-Kayser CE, Tseng YD, Flampouri S, Elmongy HM, Cahlon O, et al. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. Ann Oncol 2017;28:2179–84.
[109] Wray J, Flampouri S, Slayton W, Joyce M, Sandler E, Morris CG, et al. Proton Therapy for Pediatric Hodgkin Lymphoma. Pediatr Blood Cancer 2016;63:1522–6.
[110] Nanda R, Flampouri S, Mendenhall NP, Indelicato DJ, Jones LM, Seeram VK, et al. Pulmonary Toxicity Following Proton Therapy for Thoracic Lymphoma. Int J Radiat Oncol Biol Phys 2017;99:494–7.
[111] Hoppe BS, Flampouri S, Zaiden R, Slayton W, Sandler E, Ozdemir S, et al. Involved-node proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. Int J Radiat Oncol Biol Phys 2014;89:1053–9.
[112] Ojerholm E, Hill-Kayser CE. Reply to comment on: Insurance coverage decisions for pediatric proton therapy. Pediatr Blood Cancer 2017.
[113] Evans AE, Baum E, Chard R. Do infants with stage IV-S neuroblastoma need treatment? Arch Dis Child 1981;56:271–4.
[114] Evans AE, D'Angio GJ, Propert K, Anderson J, Hann HW. Prognostic factor in neuroblastoma. Cancer 1987;59:1853–9.
[115] Carlsen NL, Christensen IJ, Schroeder H, Bro PV, Erichsen G, Hamborg-Pedersen B, et al. Prognostic factors in neuroblastomas treated in Denmark from 1943 to 1980. A statistical estimate of prognosis based on 253 cases. Cancer 1980;1986(58):2726–35.
[116] Brodeur GM, Seeger RC, Schwab M, Varmus HE, Bishop JM. Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. Science 1984;224:1121–4.
[117] Caron H, van Sluis P, de Kraker J, Bokkerink J, Egeler M, Laureys G, et al. Allelic loss of chromosome 1p as a predictor of unfavorable outcome in patients with neuroblastoma. N Engl J Med. 1996;334:225–30.
[118] Haase GM, O'Leary MC, Ramsay NK, Romansky SG, Stram DO, Seeger RC, et al. Aggressive surgery combined with intensive chemotherapy improves survival in poor-risk neuroblastoma. J Pediatr Surg. 1991;26:1119–23. discussion 23-4.
[119] Matthay KK, Atkinson JB, Stram DO, Selch M, Reynolds CP, Seeger RC. Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: a Childrens Cancer Group pilot study. J Clin Oncol. 1993;11:2226–33.
[120] Halperin EC. Hepatic metastasis from neuroblastoma. South Med J 1987;80:1370–3.
[121] Hug EB, Nevinny-Stickel M, Fuss M, Miller DW, Schaefer RA, Slater JD. Conformal proton radiation treatment for retroperitoneal neuroblastoma: introduction of a novel technique. Med Pediatr Oncol 2001;37:36–41.

[122] Hillbrand M, Georg D, Gadner H, Potter R, Dieckmann K. Abdominal cancer during early childhood: a dosimetric comparison of proton beams to standard and advanced photon radiotherapy. Radiother Oncol 2008;89:141–9.
[123] Rombi B, Vennarini S, Vinante L, Ravanelli D, Amichetti M. Proton radiotherapy for pediatric tumors: review of first clinical results. Ital J Pediatr 2014;40:74.
[124] Fuji H, Schneider U, Ishida Y, Konno M, Yamashita H, Kase Y, et al. Assessment of organ dose reduction and secondary cancer risk associated with the use of proton beam therapy and intensity modulated radiation therapy in treatment of neuroblastomas. Radiat Oncol 2013;8:255.
[125] Hattangadi JA, Rombi B, Yock TI, Broussard G, Friedmann AM, Huang M, et al. Proton radiotherapy for high-risk pediatric neuroblastoma: early outcomes and dose comparison. Int J Radiat Oncol Biol Phys 2012;83:1015–22.
[126] Hill-Kayser C, Tochner Z, Both S, Lustig R, Reilly A, Balamuth N, et al. Proton versus photon radiation therapy for patients with high-risk neuroblastoma: the need for a customized approach. Pediatr Blood Cancer 2013;60:1606–11.
[127] Oshiro Y, Mizumoto M, Okumura T, Sugahara S, Fukushima T, Ishikawa H, et al. Clinical results of proton beam therapy for advanced neuroblastoma. Radiat Oncol 2013;8:142.
[128] Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey ML, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol 2005;23:7312–21.
[129] Chagtai T, Zill C, Dainese L, Wegert J, Savola S, Popov S, et al. Gain of 1q As a Prognostic Biomarker in Wilms Tumors (WTs) Treated With Preoperative Chemotherapy in the International Society of Paediatric Oncology (SIOP) WT 2001 Trial: A SIOP Renal Tumours Biology Consortium Study. J Clin Oncol 2016;34:3195–203.
[130] Vogel J, Lin H, Both S, Tochner Z, Balis F, Hill-Kayser C. Pencil beam scanning proton therapy for treatment of the retroperitoneum after nephrectomy for Wilms tumor: A dosimetric comparison study. Pediatr Blood Cancer 2017;64:39–45.
[131] Kalapurakal JA, Li SM, Breslow NE, Beckwith JB, Ritchey ML, Shamberger RC, et al. Intraoperative spillage of favorable histology wilms tumor cells: influence of irradiation and chemotherapy regimens on abdominal recurrence. A report from the National Wilms Tumor Study Group. Int J Radiat Oncol Biol Phys 2010;76:201–6.
[132] Sullivan R, Peppercorn J, Sikora K, Zalcberg J, Meropol NJ, Amir E, et al. Delivering affordable cancer care in high-income countries. Lancet Oncol 2011;12:933–80.
[133] Trogdon JG, Tangka FK, Ekwueme DU, Guy Jr GP, Nwaise I, Orenstein D. State-level projections of cancer-related medical care costs: 2010 to 2020. Am J Manag Care 2012;18:525–32.
[134] Truffer CJ, Keehan S, Smith S, Cylus J, Sisko A, Poisal JA, et al. Health spending projections through 2019: the recession's impact continues. Health Aff (Millwood) 2010;29:522–9.
[135] Goozner M. Strategies to reduce cancer-care costs. J Natl Cancer Inst 2013;105:247–8.
[136] Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. Clin Oncol (R Coll Radiol) 2003;15:S37–50.
[137] Emanuel EJ, Fuchs VR, Garber AM. Essential elements of a technology and outcomes assessment initiative. JAMA 2007;298:1323–5.
[138] Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. Acta Oncol 2005;44:850–61.
[139] Lundkvist J, Ekman M, Ericsson SR, Jonsson B, Glimelius B. Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. Cancer 2005;103:793–801.
[140] Hirano E, Fuji H, Onoe T, Kumar V, Shirato H, Kawabuchi K. Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood. J Radiat Res 2013.
[141] Mailhot Vega R, Kim J, Hollander A, Hattangadi-Gluth J, Michalski J, Tarbell NJ, 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.
[142] Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. Radiother Oncol 2013;107:267–73.
[143] Lawrence TS, Feng M. Protons for prostate cancer: the dream versus the reality. J Natl Cancer Inst. 2013;105:7–8.
[144] 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.
[145] Thomas PR, Deutsch M, Kepner JL, Boyett JM, Krischer J, Aronin P, et al. Low-stage medulloblastoma: final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol 2000;18:3004–11.
[146] Packer RJ. Childhood medulloblastoma: progress and future challenges. Brain Dev 1999;21:75–81.
[147] Eaton BR, Esiashvili N, Kim S, Weyman EA, Thornton LT, Mazewski C, et al. Clinical outcomes among children with standard-risk medulloblastoma treated with proton and photon radiation therapy: a comparison of disease control and overall survival. Int J Radiat Oncol Biol Phys 2016;94:133–8.
[148] Jakacki RI, Burger PC, Zhou T, Holmes EJ, Kocak M, Onar A, et al. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. J Clin Oncol 2012;30:2648–53.
[149] Sharma RA, Plummer R, Stock JK, Greenhalgh TA, Ataman O, Kelly S, et al. Clinical development of new drug-radiotherapy combinations. Nat Rev Clin Oncol 2016;13:627–42.
[150] Marciscano AE, Walker JM, McGee HM, Kim MM, Kunos CA, Monjazeb AM, et al. Incorporating Radiation Oncology into Immunotherapy: proceedings from the ASTRO-SITC-NCI immunotherapy workshop. J Immunother Cancer 2018;6:6.
[151] Schlaff CD, Krauze A, Belard A, O'Connell JJ, Camphausen KA. Bringing the heavy: carbon ion therapy in the radiobiological and clinical context. Radiat Oncol 2014;9:88.
[152] Girdhani S, Sachs R, Hlatky L. Biological effects of proton radiation: what we know and don't know. Radiat Res 2013;179:257–72.
[153] Alan Mitteer R, Wang Y, Shah J, Gordon S, Fager M, Butter PP, et al. Proton beam radiation induces DNA damage and cell apoptosis in glioma stem cells through reactive oxygen species. Sci Rep 2015;5:13961.
[154] Zhang X, Lin SH, Fang B, Gillin M, Mohan R, Chang JY. Therapy-resistant cancer stem cells have differing sensitivity to photon versus proton beam radiation. J Thorac Oncol 2013;8:1484–91.
[155] McNamara AL, Schuemann J, Paganetti H. A phenomenological relative biological effectiveness (RBE) model for proton therapy based on all published in vitro cell survival data. Phys Med Biol 2015;60:8399–416.
[156] Mohan R, Peeler CR, Guan F, Bronk L, Cao W, Grosshans DR. Radiobiological issues in proton therapy. Acta Oncol 2017;56:1367–73.
[157] Kasper HB, Raeke L, Indelicato DJ, Symecko H, Hartsell W, Mahajan A, et al. The pediatric proton consortium registry: a multi-institutional collaboration in U.S. proton centers. Int J Particle Therapy 2014;1:323–33.
[158] Armstrong GT, Liu W, Leisenring W, Yasui Y, Hammond S, Bhatia S, et al. Occurrence of multiple subsequent neoplasms in long-term survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2011;29:3056–64.
[159] Armstrong GT, Stovall M, Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study. Radiat Res 2010;174:840–50.
[160] Brinkman TM, Merchant TE, Li Z, Brennan R, Wilson M, Hoehn ME, et al. Cognitive function and social attainment in adult survivors of retinoblastoma: a report from the St.Jude Lifetime Cohort Study. Cancer 2015;121:123–31.
[161] Gunther JR, Sato M, Chintagumpala M, Ketonen L, Jones JY, Allen PK, et al. Imaging changes in pediatric intracranial ependymoma patients treated with proton beam radiation therapy compared to intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2015;93:54–63.
[162] Yock TI, Bhat S, Szymonifka J, Yeap BY, Delahaye J, Donaldson SS, et al. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. Radiother Oncol 2014;113:89–94.
[163] Viswanathan V, Pradhan KR, Eugster EA. Pituitary hormone dysfunction after proton beam radiation therapy in children with brain tumors. Endocr Pract 2011;17:891–6.
[164] Song S, Park HJ, Yoon JH, Kim DW, Park J, Shin D, 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.
[165] Rieber JG, Kessel KA, Witt O, Behnisch W, Kulozik AE, Debus J, et al. Treatment tolerance of particle therapy in pediatric patients. Acta Oncol 2015;54:1049–55.
[166] Sethi RV, Shih HA, Yeap BY, Mouw KW, Petersen R, Kim DY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer 2014;120:126–33.
[167] Green DM, Merchant TE, Billups CA, Stokes DC, Broniscer A, Bartels U, et al. Pulmonary function after treatment for embryonal brain tumors on SJMB03 that included craniospinal irradiation. Int J Radiat Oncol Biol Phys 2015;93:47–53.
[168] Bolling T, Weege J, Eich HT, Timmermann B, Meyer FM, Rube C, et al. Acute and late side effects to salivary glands and oral mucosa after head and neck radiotherapy in children and adolescents. results of the "registry for the evaluation of side effects after radiotherapy in childhood and adolescence". Head Neck 2015;37:1137–41.
[169] Macdonald SM, Sethi R, Lavally B, Yeap BY, Marcus KJ, Caruso P, et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. Neuro Oncol 2013;15:1552–9.
[170] Ares C, Albertini F, Frei-Welte M, Bolsi A, Grotzer MA, Goitein G, et al. Pencil beam scanning proton therapy for pediatric intracranial ependymoma. J Neurooncol 2016;128:137–45.
[171] Sato M, Gunther JR, Mahajan A, Jo E, Paulino AC, Adesina AM, et al. Progression-free survival of children with localized ependymoma treated with intensity-modulated radiation therapy or proton-beam radiation therapy. Cancer 2017;123:2570–8.
[172] McGovern SL, Okcu MF, Munsell MF, Kumbalasseriyil N, Grosshans DR, McAleer MF, et al. Outcomes and acute toxicities of proton therapy for pediatric atypical teratoid/rhabdoid tumor of the central nervous system. Int J Radiat Oncol Biol Phys 2014;90:1143–52.
[173] Iwata S, Yonemoto T, Ishii T, Kumagai K, Imai R, Hagiwara Y, et al. Efficacy of carbon-ion radiotherapy and high-dose chemotherapy for patients with unresectable Ewing's sarcoma family of tumors. Int J Clin Oncol 2013;18:1114–8.