Review Article

Proton Radiotherapy for Childhood Tumors: an Overview of Early Clinical Results

Barbara Rombi[1]*, Shannon M MacDonald[2], Amichetti Maurizio[1], Nancy J Tarbell[2] and Torunn I Yock[2]

[1]ATreP (Provincial Agency for Proton Therapy) and APSS (Azienda Provinciale per i Servizi Sanitari) Trento, Italy
[2]Department of Radiation Oncology, Massachusetts General Hospital - Harvard Medical School, Boston, MA 02114, USA

Abstract

Radiation therapy (RT) is an important part of a multidisciplinary treatment for many pediatric tumors and has been integral to the improvement in disease control seen over the past few decades. However, long-term survivors experience late morbidity related to RT. Proton radiation therapy is an emerging type of radiotherapy that can mitigate the incidence of acute and late side effects by minimizing the dose of radiation to normal tissues with a significant reduction of integral dose compared with photons. Furthermore, true clinical advantages are now being measured and published in the medical literature, showing both excellent disease control rates and reduction of late effects. The purpose of this review is to summarize the early clinical outcomes after proton radiotherapy in childhood available in the literature.

**Keywords:** Proton radiation therapy in pediatrics; Pediatric tumors

Introduction

Tremendous progress in the field of pediatric oncology has been made over the past two decades, and currently over 70% of children diagnosed with cancer will be cured of their disease [1]. Radiotherapy is an integral component in the curative treatment of many childhood tumors. Unfortunately, radiation exposure is a major contributor to treatment related late morbidity for long-term survivors. Children are particularly susceptible to the late effects of radiation, even at low doses, as demonstrated in epidemiologic studies of exposed populations [2,3]. The reasons for this include the sensitivity of developing and growing tissues, the longer life expectancy resulting in a larger window of opportunity for expressing radiation damage, and the large number of long-term survivors. Several approaches have been used to decrease the morbidity of radiation delaying radiation using chemotherapy or surgery to avoid or reduce the dose of radiotherapy. Despite these approaches, many children require radiation and remain at high risk for developing a multitude of serious long-term sequelae.

There are multiple options for radiation delivery, including three dimensional conformal photon radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT), and proton beam radiotherapy (PT). Dosimetric studies continue to show the benefits of PT over these photons techniques and as a result, medical centers around the world are working to open more facilities and improve patient access. Proton radiation therapy is a high-precision form of irradiation which enables optimal coverage of the tumor while maximally avoiding non-target tissues. As a result of its physical favorable characteristics [4], PT can treat the target with high homogeneity and conformality while relatively sparing the surrounding organs at risk (OAR); this dosimetric advantage should translate to reduced toxicity and a decreased incidence of radiation-induced secondary malignancies.

Physics of Protons

Proton radiation therapy is a form of external radiation that uses charged particles produced by particle accelerators (e.g. a cyclotron or synchrotron). Proton beam has distinct physical advantages over photons in the way that delivers the majority of its dose in the target. As depicted in figure 1, high energy photons deposit the maximum dose within a few centimeters of the skin surface and continue to irradiate

tissues beyond the target delivering dose throughout the entire volume of the irradiated tissue and decreasing exponentially until exiting the body. For targets deeper than three cm, each photon beam will deliver more dose proximal to the target than in the target. For this reason, photon therapy is generally delivered with multiple beam directions. Protons enter the body and deliver a small and constant dose until near the end of range. This dose distribution is known as the Bragg peak, beyond which, no dose is delivered. Because a single mono-energetic Bragg peak is too narrow to cover the entire volume of most tumors, several beams are used to cover all the tumor with uniform dose

Figure 1: Comparison between spread out Bragg peak (SOBP) protons and 10 MeV photons.
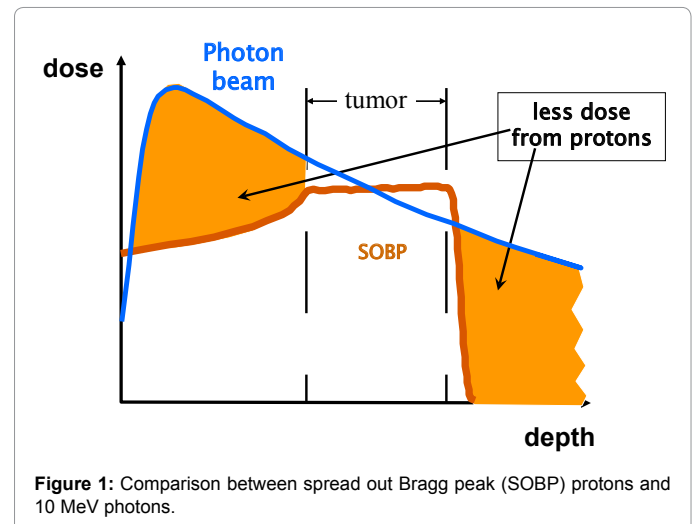
*Corresponding author: Barbara Rombi, Provincial Agency for Proton Therapy (ATreP) and APSS, Via F. Perini 18, 38122, Trento, Italy, Tel: +39/0461-39720, Fax: +39/0461-391648; E-mail: barbararombi@libero.it

area named spread out Bragg peak (SOBP). Therefore, with protons less normal tissues are irradiated and the integral dose is minimized, decreasing the dose to non-target tissues by more than one-half [5]. Protons are also capable of depositing their maximal dose at depths much greater than photons. Biologically, protons are not known to have an advantage over photons and dose is prescribed in Gy (RBE) taking into account a relative biological effectiveness of protons of 1.1 compared to photons [6]. Cancer control by PT is predicted to be identical to photon RT, unless the physical advantages of protons are utilized for dose escalation or hypo-fractionation.

Pediatric Clinical Outcomes with Protons

Tumors of the central nervous system

Approximately 20% of pediatric cancers occur within the central nervous system (CNS). Treatment options for childhood CNS tumors include radiation therapy, surgery and chemotherapy, often given in combination. Fortunately, approximately 70% of children survive at least 5 years [7]. Although outcomes have improved, the greatest challenge for long-term childhood cancer survivors remain the balance between cure and long-term morbidity. In particular, brain radiotherapy continues to pose a challenge to radiation oncologists because of the negative effects in neurocognitive, neuroendocrine function, and hearing loss. Neurocognitive damage is demonstrated by a development of deficits in several areas including mathematic ability, language, attention, memory, sleep-wake rhythm and Intelligence Quotient (IQ) [8]. Negative neurocognitive effects are the result of several factors including the brain tumor itself disrupting neurocognitive functioning, hydrocephalus, operative approaches and peri-operative complications. Chemotherapies can also have an effect on neurocognitive functioning, and additionally, host factors such as age at the time of treatment, gender, irradiated brain volume and dose delivered [9,10]. A recent prospective study from Massachusetts General Hospital (MGH) which evaluated the health-related quality of life (HRQoL) of children with brain tumors treated with PT and followed annually thereafter, demonstrated the effect of disease type and intensity of treatment on HRQoL, in particular in the anxiety, communication, and worry domains [11]. Viswanathan et al. [12] analyzed the endocrine sequelae developed in 31 children with brain tumors (the most common types were craniopharyngioma, medulloblastoma and glioma) treated with PT or with combined proton and photon radiotherapy. Before irradiation, a surgical approach was performed in 28 patients, and 22 received chemotherapy before or with radiotherapy. The authors observed that endocrine dysfunction developed faster in the group who received a component of photon radiotherapy than in those receiving PT only.

Low-grade gliomas: Low-grade gliomas (LGG) account for approximately 10% of childhood malignancies and are frequently amenable to surgical resection. However, deep seated tumors in the region of the hypothalamus, optic chiasm and brainstem as well as more peripheral tumors in areas of critical function are generally not removed surgically because of the high risk of morbidity. These tumors can respond to chemotherapy which is often the first line of treatment for children under 7-10 years of age and is often effective in delaying the need for radiotherapy. However, radiation therapy is considered definitive and used when tumors progress after chemotherapy or in older children. Radiotherapy can achieve 10-years event-free survival (EFS) rates of 74.3% and an overall survival (OS) of 95.9% [13].

Hug et al. [14] evaluated the safety and efficacy of proton therapy for 27 patients with progressive or recurrent intracranial LGG, treated

between 1991 and 1997 at Loma Linda University Medical Center. Fifteen patients had diencephalic tumors, seven had cerebral and cerebellar hemispheres tumors and in five the tumor was located in the brainstem. Twenty-five out of 27 patients had progressive, unresectable or residual tumor after subtotal resection. The target dose was between 50.4 and 63 Cobalt Gray Equivalent (CGE), at 1.8 daily fractions. At a median follow-up of 3.3 years, local control (LC) and OS were 87% and 93% for diencephalic tumors, 71% and 86% for hemispheric tumors, 60% and 60% for brainstem tumors, respectively. All patients with local stable disease maintained their performance status.

Optic pathway gliomas are common site of low grade glial tumors that occur in childhood and with increased frequency in children with Neurofibromatosis Type 1 (NF1). The prechiasmatic location shows a less aggressive behavior and a better prognosis with survival rates at 10 years between 85 and 100% [15]. In these tumors an anterior surgical approach can be curative but at the cost of ipsilateral vision loss. When the tumor extends posteriorly along the optic nerve to involve the chiasm or optic structures, resections are avoided because it would cause complete blindness or other unacceptable side effects. For unresectable tumors radiation therapy plays a fundamental role in controlling these lesions [16]. However, tumors in NF1 patients are often more indolent and may be managed with watchful waiting or chemotherapy with close monitoring of visual outcomes. Due to their less aggressivity and their susceptibility to radiation-induced vascular injury [17], radiation is typically used as an option. Fuss et al. [18] compared the PT plans used to treat seven localized and extensive optic pathway gliomas, with 3DCRT and two laterals photon plans. PT plans showed similar high conformity to target volumes compared with 3D photon plans and a higher capability of sparing, in high- and low- dose areas, organs at risk (OAR) such as temporal lobes, frontal lobes, optic chiasm, contralateral optic nerves and pituitary gland. At a median follow-up of 37 months, all the patients were alive without evidence of local recurrence and all patients with useful vision during treatment maintained eyesight capacity.

Hug et al. [14] treated seven optic pathway tumor patients for progressive symptoms with PT at Loma Linda University Medical Center to a total mean dose of 55.2 CGE with 1.8 CGE daily fractions. In this patient's cohort, the LC obtained was 100%, while the useful vision has been maintained in four patients and improved in two. One patient with optic pathway glioma and NF1 developed Moyamoya disease.

Germ cell tumor: Germ cell tumors (GCT) of the CNS account for 3-5 % of childhood brain tumors. These tumors typically arise within the suprasellar region or the pineal gland, but can occur elsewhere in the brain [19]. GCTs are often localized, but spread may occur to the cerebral spinal fluid (CSF), ventricular surface, or spinal cord. GCTs are divided into two main histologic subgroups that are highly prognostic, pure germinomas and those with non-germinomatous components (NGGCT). In the past, craniospinal irradiation (CSI) alone was considered the standard treatment for all pure germinomas attaining excellent cure rates but with significant late side effects. Outcomes with whole ventricular radiation (WVRT) followed by a boost to the tumor bed were found to yield comparable results and is the new standard of care [20]. Chemotherapy followed by local irradiation showed promising results in early institutional trials, [21,22]. However, recent publications have demonstrated a high risk of ventricular relapse [23,24] and therefore WVRT remains a component of treatment when chemotherapy is also used. For patients with disseminated disease, CSI is standard. For NGGCT, a more aggressive approach using

chemotherapy followed by CSI has been most frequently used, but reduced volume radiation following chemotherapy is being explored.

MacDonald et al.[25] reported early clinical outcomes of twenty-two children with CNS GCT or NGGCT treated with WVRT and involved field (IF) boost, or CSI with IF boost or with IF only delivered with three dimensional conformal proton therapy (3DCPT). At a median follow-up of 28 months, there were no CNS recurrences; one patient had an intraabdominal recurrence presumably from seeding from his ventriculoperitoneal shunt. He was successfully salvaged with further therapy. Local control, progression free, and OS were 100%, 95%, and 100%, respectively. In this group of patients, treatment was well tolerated with minimal acute toxicity. Although it is too early to evaluate long-term toxicity, at a median follow-up of 28 months, no late complications attributed to non-target radiation dose have been documented. The authors also compared treatment plans for WVRT with IMRT, 3DCPT, and intensity-modulated proton therapy (IMPT) with pencil beam scanning. Comparable tumor volume coverage was achieved with IMRT, 3DCPT, and IMPT. Substantial normal tissue sparing was seen with the two proton therapy techniques over IMRT.

Medulloblastoma: Medulloblastoma represents about 20% of all pediatric CNS malignancy and arises in the cerebellum. The standard therapy for children with this disease is maximal safe tumor resection followed by CSI plus posterior fossa or tumor bed boost and platinum-based chemotherapy. The multimodal approach with conventional radiotherapy yields 5-year DFS rates in excess of 80% for patients with non-disseminated disease (standard risk) [26] and survival rates of 65-70% in high risk patients [27]. Using photon beams, craniospinal treatment results in irradiation of normal tissues anterior to the spine i.e. heart, lung, thyroid, bowel, and gonads in females due to the exit dose from the spinal field. PT offers a major potential advantage over photons because no appreciable dose is delivered to these structures. For the boost portion of the treatment, PT also reduces additional dose to the normal brain structures, especially middle ear, temporal lobes, and neuroendocrine structures [28,29]. This sparing can result in the clinical reduction of several late effects including endocrine dysfunction, growth bone deficiency, neurocognitive impairment, ototoxicity, and second malignancy [30].

Recently, early clinical outcomes for 45 standard risk and 14 high-risk medulloblastoma patients treated with protons from 2003 to 2009 were reported by Pulsifer et al. [31]. After maximal safe resection, all patients received CSI with protons radiotherapy to doses ranging from 18 to 36 Gy (RBE), plus additional dose to the tumor bed or posterior fossa for a total prescribed dose of 54 -55.8Gy (RBE). After a median follow-up of 28 months, OS and PFS at 3-years were comparable to photons treatment with 90% and 76% for average risk and 89% and 92% for high risk patients. Regarding late effects, relatively few patients (29%) required hormone replacement. Only 16% developed grade 3 or 4 ototoxicity compared to 25% reported in IMRT and conventional RT studies [32], likely due to lower mean dose to the cochlea achieved with protons. Neurocognitive outcomes remained overall, excellent.

Lin et al. [28] reported cochlea and temporal lobe brain sparing of PT over photon radiotherapy in 9 patients treated for posterior fossa tumors. The sensory-neural hearing loss has been reported in 84-100% of brain cancer patients treated with cranial photons RT and cisplatin chemotherapy [33] after 6-12 months from RT and it is a chemotherapy and radiation therapy dose dependant phenomenon. Dosimetric advantages of PT are confirmed in the study of St. Clair et al. [34] which compared treatments plans from standard photon therapy to IMRT and PT for CSI plus posterior fossa boost in a patient with medulloblastoma. In particular, for spinal axis irradiation, protons were superior to IMRT and 3DCRT resulting in decreased dose to non-target normal tissues, (heart, lungs, stomach, kidneys, and colon). For the posterior fossa boost, protons were superior to both photons techniques sparing dose to the cochlea, pituitary, hypothalamus and temporomandibular joints.

Yuh et al. [35] treated three high-risk medulloblastoma patients with CSI to a total dose of 36 CGE plus the posterior fossa boost to 18 CGE. All patients tolerated very well the treatment with improved morbidity-free survival consequent to the greater volume of OAR spared by PT. Despite the use of concurrent chemotherapy, they had only minor acute side effects.

Ependymoma: Ependymoma accounts for 8-10% of intracranial pediatric malignancies with two thirds arising in the posterior fossa and the remaining in the supratentorial region. The standard treatment approach is maximal resection followed by local radiation therapy that offers progression-free survival rates of 70-80% after complete resection [36].

MacDonald et al. [37] reported outcomes for 17 patients treated with PT from 2000 to 2006. Thirteen patients had gross total resection and four had subtotal resection before PT. The median prescribed total dose was 55.8 CGE. The treatment was well tolerated without significant acute side effects; after a median follow-up of 26 month, OS, PFS and LC were 89%, 80% 86%, respectively. Subtotal resection was significantly associated with inferior outcomes. The same authors compared four beam conformal PT plan with six field IMRT plans and three field IMPT plans. Although similar tumor coverage was achieved with all techniques, PT and IMPT provided greater normal tissue sparing (i.e. whole brain tissue, temporal lobes, hypothalamus) with significantly fewer beam angles.

Amsbaugh et al. [38] have recently published the preliminary outcomes of eight pediatric spine ependymoma patients treated with PT at MD Anderson Cancer Center; they have obtained LC, EFS and OS rates of 100% after a mean follow up of 26 months and mild acute toxicities.

Craniopharyngioma: Craniopharyngiomas represent 6-8% of all pediatric brain tumors. They are benign, usually slow growing tumors with a cystic component that during radiation therapy could change in volume affecting treatment planning and delivery. Seventy percent are located on retrochiasmatic region where gross total resection is difficult to achieve without undue morbidity. Treatment options include surgery, radiotherapy, or limited surgery followed by radiotherapy. Maximal resection improves LC rates but can be difficult to achieve without significant morbidity due to the infiltration of nearby critical structures. Winkfield et al. [39] obtained excellent control survival rates with 10 year OS and LC of 94% and 69%, respectively. Recurrence rates after surgical resection alone (GTR) or limited surgery (STR) and radiotherapy were 36% and 5% respectively.

In a ten-year period (1991-2000), Luu et al. [40] reported on 16 craniopharyngioma patients treated with post-operative PT. The total dose delivered was between 50.4 and 59.4 CGE with standard fractionation and a mean follow-up of 60.2 months. LC and OS were 93% and 80%, respectively. They found that repeated resections were significantly associated with reduction of OS at 5 years from 100% for a single procedure up to 60% with multiple resections. Seventy five percent of patients had no late toxicity. One patient developed panhypopituitarism at 36 months after salvage therapy, another patient had a cerebrovascular accident at 36 months after combined primary

treatment, and the last one developed a meningioma in the previous radiation photon port, but outside of the proton port. Winkfield et al. [41] reported the outcome of 17 patients treated with PT and scanned with CT or MRI during treatment to monitor changes in cyst size. Six patients required a change of the treatment plan due to cyst growth (n=5) or shrinkage (n=1) and the need to change the field size in order to encompass the whole cyst. At a median follow-up of 40.5 months local and disease control was 100% .The authors concluded that those patients with a cystic component should be monitored with imaging during treatment (proton or photon based) so that treatments may be adapted in order to assure full tumor coverage [42].

Fitzek et al. [43] reported on a mixed pediatric and adult craniopharyngioma population treated with either protons alone (n=5) or a combination of protons and photons (n=10). Median dose prescribed to pediatric patients was 55.6 CGE. Median observation period of surviving patients was 13.1 years from radiotherapy. None of the pediatric patients (n=5) had experienced recurrence of the tumor.

The combined effect of surgery and radiation can have a profound effect on the long term quality of life (QoL). Laffond et al. [44] report on the QoL of 29 pediatric craniopharyngioma treated with both surgery and PT at a mean follow-up of six years. They found that 38% of patients developed depression and some adverse effects on measures of executive function, and a majority of families felt very concerned by the disease.

Other pediatric malignancies outside cns

Skull base tumor: Chordomas and Chondrosarcomas are uncommon tumors, diagnosed rarely in children. Chordomas are slow-growing tumors that can metastasize, but more frequently pose a significant challenge to LC because of their location.. They are always in close proximity to many critical structures, such as brainstem or other parts of the brain, cranial nerves, arteries, spinal cord, and/or optic pathways [45]. Because of the physical properties of protons and the ability to dose escalate in these areas; patients are often referred for PT.

Chondrosarcoma, although less aggressive, is also challenging to manage in the pediatric population [46]. Maximum safe tumor resection is considered the treatment of choice followed by high dose radiotherapy. PT has repeatedly demonstrated its ability to control this disease safely and more effectively than photon techniques at doses of 70-76 Gy (RBE) [47,48]. The most relevant data from the literature regarding clinical results after radiotherapy (protons or mixed photons and protons) for the treatment of chordomas and chondorsarcomas in pediatric patients are summarized in table 1 [49-52]. In the most recent study by Rombi et al. [52] 26 patients were treated with spot-scanning PT achieving 5-year LC of 81% and 80%, and 5-year OS rates of 89% and 75%, for chordomas and chondrosarcomas, respectively. Furthermore, there were relatively few (19%) late complications and no high grade (≤ grade 2) late toxicities were noted. The late effects included two patients who developed otitis media requiring drainage; one patient developed unilateral hearing impairment; four patients were diagnosed with partial hypopituitarism requiring hormonal replacement and one patient with symptomatic nasal mucosal crusting required surgical debridement. No secondary malignancies were observed during the follow-up.

Although all of these proton studies show good chance of long-term disease-free survival and acceptable risks of late effects, the cohorts of patients are still considered quite small and longer follow-up is necessary to evaluate the long-term disease control and late effect profile.

Retinoblastoma: Retinoblastoma (RB) is the most frequent ocular tumor in childhood with an incidence of about 1:15000-30000 live births. Radiation therapy is commonly used to preserve visual function and in organ preservation techniques. It is typically used for more advanced tumors of the eye that are not amenable to cryotherapy or to transpupillary thermotherapy, such as in larger tumors, those involving the macula, or those with vitreous seeding. It is also prescribed in the post operative setting for high-risk features. Although the rate of LC with photon radiation therapy is good, late effects are common and can include cataract development, optic neuropathy, neurocognitive deficit, neuro-endocrine dysfunction, severe growth abnormalities of the facial bones, lacrimal gland dysfunction, and radiation-induced malignancy. Second malignancy is the most serious concern for children with the hereditary form of RB. The risk of a second tumor in patients treated with radiotherapy for hereditary RB is as high as 38% at 50 years [53].

Based on this scenario, PT for children with RB should be considered because reducing the integral dose to the normal tissue as showed in dosimetric studies [54,55] could result in decreased risks of second malignancy, cosmetic and functional sequelae. There are minimal clinical outcome studies to date on retinoblastoma but a number of centers are starting to generate a critical mass and outcomes will be reported shortly. Chang et al. [56] evaluated the clinical results of three RB patients treated with PT after no response to other treatment modalities showing tumor regression although two of them which had

Author/Institution	#	Tumor Site (#)	Histology	RT Type (# pt)	Dose in CGE	5y-LC (%)	5y-OS (%)	F/U in months (range)
Benk (MGH)[49]	18	SB (15) C-spine (3)	All CH	P + Ph (18)	Median, 69.0	63%	68%*	Median, 72 (19-120)
Habrand (CPO)[50]	30	SB (16) C-spine (1) Both (13)	27 CH 3 CS	P + Ph (29) P (1)	Mean, 69.1 Mean, 65.3	77% (CH) 100% (CS)	81% (CH) 100% (CS)	Mean, 26.5 (5-102)
Hug (LLUMC)[51]	13	SB	10 CH 3 CS	P (6) P + Ph (4) P + Ph (3)	Median, 73.7 Median, 70.0	60% (CH) § 100% (CS) §	60% (CH)** 100% (CS) §	Mean, 40 (13-92)
Rombi (PSI)[52]	26	SB (17) Axial Skel (9)	19 CH 7 CS	P (All)	Mean, 74.0 Mean, 66.0	81%(CH) 80% (CS)	89% (CH) 75% (CS)	Mean, 46 (5-126)

*: patients with cervical spine chordoma had a significant worse survival than other skull base patients (*p*= 0.008);
**: overall survival of the males was significantly superior to female patients (*p*=0.002);
§ :at last follow up
Abbreviations: **#**: number of; RT: radiotherapy; pt: patients; LC: local control; OS: overall survival; F/U: follow up; SB: skull base; CH: chordoma; CS: chondrosarcoma; Skel: skeleton; P: protons; Ph: photons; y: year.

Table 1: Summary of studies using PT in pediatric Chordomas and Chondrosarcoma.

diffuse infiltrating subretinal seeding or extensively advanced tumor, developed multiple recurrences requiring enucleation.

Soft tissue sarcoma: In soft tissue sarcoma (STS), the multimodal approach widely accepted consists of combined surgery, chemotherapy +/- radiotherapy. If complete resection is not possible, radiation therapy can be administered to achieve LC, but with increased risk of late sequelae. For these patients, PT plays a potential role to reduce acute and late side effects.

Timmermann et al. [57] treated 16 different types of malignant STS with PT. The total dose range was between 50.4 and 61.2 CGE; the median follow-up was 18.6 months. In this report was found that the worst acute side effect during the treatment was the bone marrow toxicity (grade 4 in three patients and grade 3 in four patients) attributed to chemotherapy. Only nine out of 16 patients were followed up for sufficient time to be analyzed for late sequelae. Two paraspinal sarcoma patients developed skin hyperpigmentation, one parameningeal sarcoma developed dental caries, and one alveolar orbital rhabdomyosarcoma (RMS) developed mild myopia and orbital bone asymmetry. No neurological sequelae were noticed. Two-year PFS and OS were 71.6% and 69.3% respectively. Four patients had a local failure and eventually died of disease and two of them had non RMS-like tumor. PT achieved similar LC rates and morbidity with respect to conventional photon radiotherapy.

Ewing's sarcoma: Currently, 60-70% of patients with localized Ewing's sarcoma survive more than 5 years [58]. Because Ewing's sarcoma is highly responsive to radiation therapy, and it often occurs in difficult to resect locations, radiotherapy is a mainstay of treatment and is employed in approximately 60% of Ewing's patients [59]. Radiation is used in the post-operative setting for patients with close or positive resection margins and sometimes in the setting of a poor response to neoadjuvant chemotherapy [60]. Radiation is typically used instead of surgery for children with unresectable tumors or in cases where surgery would be too morbid.

Rombi et al. [61] reported on 30 pediatric Ewing's sarcoma patients treated between April 2003 and April 2009 at MGH, with PT at median prescribed dose of 54 Gy (RBE). Proton dosimetry in a patient with Ewing's sarcoma of the pelvis and of the base of skull is shown figure 2. At a median follow-up of 38.4 months, 3-year actuarial EFS, LC, and OS were 60%, 86%, and 89%, respectively. Regarding late effects, 16% of patients developed scoliosis/kyphosis (three mild, one moderate, one severe) but all of them had been treated with surgical laminectomy prior to radiation. Permanent skin changes were noted in 20% of patients but none were high grade. None of the patients developed a second solid tumor, but four patients developed secondary hematological tumors (three acute myeloid leukemia and one myelodysplastic syndrome), potentially attributable to the leukemogenic effects of the drugs used (including high cumulative doses of etoposide and anthracyclines).

Rhabdomyosarcoma

Orbital site: Rhabdomyosarcoma is the most common primary orbital malignancy in childhood and comprises 10% of all pediatric RMSs. Although orbital RMS is the most favorable tumor site with a 5-year survival rate greater than 85%, late adverse effects after conventional XRT are frequent and include cataract, orbital hypoplasia, corneal ulcers, xerophthalmia, vitreous hemorrhage, and hypopituitarism [62,63].

Yock et al. [64] reported outcomes for seven orbital RMS patients treated with PT and standard chemotherapy. The median dose was 46.6
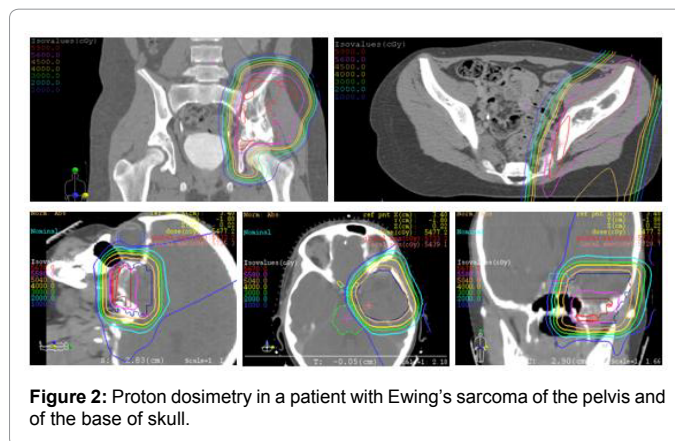

Figure 2: Proton dosimetry in a patient with Ewing's sarcoma of the pelvis and of the base of skull.

CGE with conventional fractionation and the median follow-up was 6.3 years. None of the patients developed cataract, keratitis, chronic conjunctivitis, endocrine dysfunction or painful dry eye syndrome. Excellent vision was retained in all patients with intact orbits, however two patients required chronic eye lubrication. Two patients developed mild and moderate orbital hypoplasia and five patients an enophthalmous. All the patients remained disease-free except one that had a local failure and was successfully salvaged with stereotactic radiotherapy. Compared with historical results of photon RT, PT improved the rate of clinical late effects and reduced the need of growth hormone replacement.

Parameningeal site: Kozak et al. [65] compared the IMRT plans of 10 parameningeal (PM) RMS patients treated with PT. Based on Intergroup Rhabdomyosarcoma study classification (IRS), eight patients had grade 3 and 2 patients grade 4 tumors. The median prescribed dose to CTV was 47.7 Gy. For both techniques acceptable and comparable target volume coverage was obtained. PT reduced volumes of all normal tissues irradiated as for example orbital globes, lens, retina, optic nerves, chiasm, whole brain, brainstem, temporal lobe, pituitary, hypothalamus, parotid and lacrimal glands, except for ipsilateral cochlea and ipsilateral mastoid bone. In conclusion, because of increased normal tissue sparing compared to IMRT, PT was found to be dosimetrically superior to IMRT. Para Childs et al. [66] evaluated the clinical outcome and late side effect profile of PT in the treatment of children with PM RMS. Seventeen consecutive children were treated with PT at MGH between 1996 and 2005. Median patient age at diagnosis was 3.4 years. Embryonal (n=11), alveolar (n=4), and undifferentiated (n=2) histologies were represented. Ten patients (59%) had intracranial extension. Median prescribed dose was 50.4 cobalt gray equivalents (GyRBE) (range, 50.4–56.0 GyRBE) delivered in 1.8–2.0-GyRBE daily fractions. Median follow-up was 5 years for survivors. The 5-year failure-free survival was 59%, 5-year OS 64%. Among the 7 patients who failed, sites of first recurrence were local only (n=2), regional only (n = 2), distant only (n=2), and local and distant (n=1). Late effects related to PT in the 10 recurrence-free patients include failure to maintain height velocity (n=3), endocrinopathies (n=2), mild facial hypoplasia (n=7), failure of permanent tooth eruption (n=3), dental caries (n=5), and chronic nasal/sinus congestion (n=2). They concluded that although tumor control and survival are comparable to the historical controls with similar poor prognostic factors, rates of late effects from PT compare favorably to published reports of photon-treated cohorts.

Bladder/ prostate site: Cotter et al. [67] reported the clinical

outcomes of 7 children with bladder/prostate RMS treated with PT. The study also compared proton treatment plans with matched IMRT plans, with an emphasis on dose savings to reproductive and skeletal structures. Seven male patients were treated with PT for bladder/prostate RMS at the MGH between 2002 and 2008 with a median age of 30 months and with median follow-up of 27 months. Four patients underwent a gross total resection prior to radiation, and all patients received concurrent chemotherapy. Radiation doses ranged from 36 to 50.4 CGE. Five of 7 patients were without evidence of disease and with intact bladders at study completion. Although the target volume dosimetry was equivalent between the two modalities for all patients, PT achieved a significant decrease in mean organ dose to the bladder, testes, femoral heads, growth plates, and pelvic bones compared to IMRT.

Abdominal tumors: The most common childhood solid abdominal tumor is neuroblastoma (NBL) and approximately one-half of children diagnosed present with high-risk disease. A multidisciplinary aggressive therapeutic approach can improve survival rates to 60-70% at five years [68].

Hattangadi et al. [69] analyzed nine patients with high-risk (International Neuroblastoma Staging System [INSS] stage III or IV) NBL treated from 2005 to 2010 at MGH. All patients received induction chemotherapy, surgical resection of residual disease, and adjuvant PT to primary tumor sites. IMRT, PT, and IMPT plans were generated and compared for a representative case of adjuvant radiation therapy to the primary tumor bed followed by boost. Median age at diagnosis was 2 years (range, 10 months-4 years). At a median follow-up of 38 months (range 11-70), there were no locoregional failures. Four patients failed distantly, and of these, two died of disease. No patients experienced ≥ grade 2 late effects. While comparable target coverage was achieved with all three modalities, PT obtained substantial normal tissue sparing compared with IMRT. IMPT allowed additional sparing of the kidneys, lungs, and heart as shown in Figure 3.
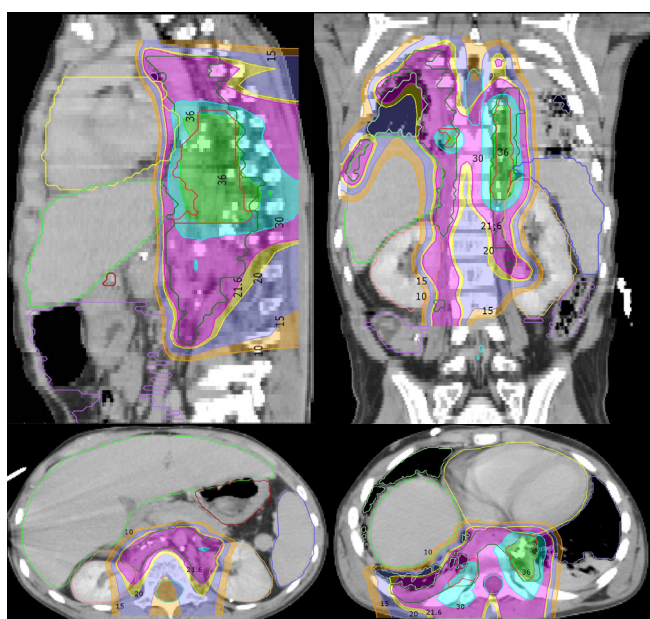

Figure 3: Sagittal, coronal and axial CT images from protontherapy plan for a case of advanced thoraco-abdominal neuroblastoma.

Hug et al. [70] reported the case of a 4 year-old child with right adrenal gland NBL treated with PT to total dose of 25.2 CGE to CTV plus 9 CGE to boost volume (residual tumor). The patient tolerated well the treatment without any acute toxicity except mild erythema in posterior paraspinal region. The use of a single posterior or two postero-lateral oblique fields permitted good sparing of intrabdominal organs including kidneys, bowel and liver.

Risk of Radiation Induced Second Malignancy

Secondary malignancy is a major concern in younger populations due to the protracted latency period and greater susceptibility to second cancer formation (10–20 years). This is of particular concern with the use of IMRT that has the potential to increase whole body radiation exposure. IMRT employs multiple treatment fields, has longer treatment time with an increase of the leakage from the treatment 'head' exposing a greater volume of normal tissue to low dose radiation than conventional 3-D conformal treatment.

Miralbell et al. [71] mathematically modeled the reduction of second malignancy risk performing a dosimetric study in two pediatric patients, one with a PM RMS, the other with a medulloblastoma. The study determined that PT had the potential to reduce the risk of second malignancy by a factor > 2 in the PMRMS patient and by a factor of 8-15 in the medulloblastoma patient, as compared with either IMRT or conventional RT. Most proton centers currently use passive scattering techniques, whereby the narrow proton beam is allowed to impinge on a scattering foil such that a broad field of useful clinical size is produced. Field-shaping apertures and range compensators are then employed to tailor the beam to the shape of the target. Scattering foils, field-shaping apertures and range compensators are all sources of secondary neutron production with consequent risk of radiation exposure. Therefore, patients will potentially be at risk for a radiation-induced tumor from this small amount of neutron contamination. Hall et al. [72] postulated that the whole body neutron production by the passive scattering method results in a greater incidence of secondary malignancy than IMRT. This risk was, however, emphasized by the use of older proton facility data which overestimate the neutron production from the aperture, and lack of acknowledgement of the decreased integral dose provided with protons [73]. Pencil-beam scanning, which generates less neutrons scattered, may significantly decrease the rates of secondary malignancy.

Simulations of CSI with both passively scattered and scanned-beam proton therapies reveal that the risk of secondary cancer is lower than conventional and intensity modulated photon therapies even when neutrons are taken into account [74].

Limitations of Proton Beam Therapy

Currently, the major limitation of PT in pediatric patients is that many proton centers are not hospital-based and unable to accommodate children who require daily anesthesia. Only recently PT has become available in dedicated clinical centers devoted to treatment and furnished by modern delivery systems (i.e. gantry rooms) and not in physical laboratories for limited periods of time during the year.

Another problem is the high cost of PT centers which range from US $25 million to $150 million, depending on the unit and number of treatment gantries installed. The issue of whether the cost of proton therapy is justified has only recently been raised, but if it is like other technologies, the high capital and maintenance costs are likely to come down in the future are innovations progress. Additionally, if one

chooses appropriate patients (such as children with curable tumors) and factors in the benefits to the patients of fewer and less serious late effects of treatment, the treatments are likely to prove cost effective in the long run [75].

Conclusion

Multiple radiation options exist for pediatric patients, including 3D conformal photon radiotherapy, IMRT, and now, proton beam radiotherapy. The dosimetric advantages of protons which substantially decrease the radiation dose to normal tissues, promise important clinical benefits in childhood cancer survivors, by maintaining tumor control, while decreasing the deleterious late effects of radiation therapy as well as the incidence of radiation induced secondary malignancies. The medical literature is now populated with several manuscripts on the early clinical outcomes showing the real benefits of PT with regards to improved quality of life, and health outcomes. As new centers become more readily available around the world, pediatric patients with solid tumors should take precedence in receiving PT as solid tumors in childhood are more curable than adult tumors and the side effects in children due to dose to non target tissues are far graver. Additional studies with longer follow-up time will be coming soon to even better document the ameliorated long-term morbidity and the risk of secondary tumors after proton therapy.

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