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Clinical controversies: Pediatric tumors

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Abstract

Despite the claim in the published literature, the introduction of proton therapy for children is not analogous to the evolution of conformal photon irradiation relying on the understanding of the impact of altered dose distributions. The differences in radiobiological effect when comparing photons to protons means that we are comparing a known entity to an unknown entity: the dose-volume histogram for proton therapy might mean something substantially different than the dose-volume histogram for photon therapy. The multifaceted difference between the two modalities supports the argument for careful evaluation, follow-up and clinical trials with adverse event monitoring when using proton therapy in children. We review the current data on the outcome of proton therapy in a range of pediatric tumours and compare them to the often excellent results of photon therapy in the setting of multidisciplinary management of childhood cancer.

It is hoped that the apparent dosimetric advantage of proton therapy over photons will lead to improved indications for therapy, disease control and functional outcomes. While physical dose distribution is of clear importance, the multimodality management of children by an expert pediatric oncology team and the availability of ancillary measures that improve the quality of treatment delivery may be more important than the actual beam. In addition, current estimates of the benefit of proton therapy over photon therapy based on toxicity reduction will only be realized when survivorship has been achieved. Once substantive data proton therapy data become available, it will be necessary to demonstrate benefit in clinically relevant outcome measures in comparison to best existing photon outcome data. Such an effort will require improved funding and appreciation for late effects research. Only real clinical outcome data combined with better understanding of the radiobiological differences between protons and photons will help us to further reduce side effects in children and exploit the full curative potential of this relatively new modality.

Introduction

New methods of irradiation have been responsible for maintaining or increasing the role of radiation therapy in the treatment of children. Proton therapy is a recent advance in the field of radiation oncology. Similar to the implementation of 3-dimensional methods of photon irradiation more than 20 years ago, proton therapy promises to advance the role of radiation therapy in the treatment of children because its primary advantage is a reduction in dose to normal tissues, a goal of pediatric therapy and clinical trials. The lack of availability of proton therapy, the current environment of referral and care, and the general unknowns

associated with proton therapy physics and biology should be viewed as threats to the appropriate use of this modality and understanding its potential benefit in the treatment of children.

There are approximately 12,000 new cases of pediatric cancer each year in the United States (1), and about 3000 will require radiation therapy as part of frontline management, including those with advanced or incurable tumors. Most will require a 6-week treatment course; however, those treated for Hodgkin lymphoma, Wilms' tumor, and neuroblastoma will require fewer fractions and a shorter course. There are currently more than 10 proton centers in the United States. If each were to commit to the treatment of 300 children annually, their daily census would be fewer than 30 pediatric patients or the number of patients that might be treated in a single gantry room. This proposal does not account for the added complexity of the pediatric patient, including the use of general anesthesia, specialized localization and verification, the proportion of cases requiring craniospinal irradiation or other difficult treatment scenarios, or the requirement of multi-field treatment. However, it does point out that the number of proton centers currently built in the United States could manage all of the pediatric cases that require radiation therapy. The limited number of centers also represents an opportunity to concentrate care to increase experience, perform research, increase compliance and improve outcomes provided that they are integrated with pediatric oncology programs. Unfortunately, proton centers are not well-distributed in the country, and some may lack the appropriate environment of care to fit a long-term model of comprehensive care. There is no estimate available with regard to the need or availability of centers outside the US although certain countries, such as Japan, have a number of existing or planned centers that might accommodate their domestic proportion of pediatric patients.

Prior to the formation of the Children's Oncology Group (COG) in 2000 and the merger of the Intergroup Rhabdomyosarcoma Study Group (IRSG), Pediatric Oncology Group, Children's Cancer Study Group, and National Wilms' Tumor Study, the existing pediatric cooperative groups allowed proton therapy in clinical trials as early as 1997. The IRSG included proton therapy in a low-risk embryonal/botryoid rhabdomyosarcoma (RMS) protocol that opened in September 1997. From that time forward, proton therapy has been used for pediatric sarcoma studies, including those currently active in the COG for RMS and non-RMS soft-tissue sarcoma. The earliest use of proton therapy in pediatric brain tumor trials dates from 2000. Proton therapy was allowed in a study for children younger than 3 years with non-metastatic medulloblastoma, and in subsequent studies for ependymoma (2003), medulloblastoma (2004), and low-grade glioma (2005). With a few exceptions, all new and current studies for pediatric sarcoma and central nervous system (CNS) tumors allow proton therapy and adhere to the current National Cancer Institute (NCI) guidelines, including the 2012 guidelines for neuroblastoma. Guidelines for Wilms' tumor, Hodgkin lymphoma, and nasopharyngeal cancer are anticipated for the next series of clinical trials to complete the portfolio.

Because radiation therapy is an integral component of clinical trials within the COG, access to an approved treatment facility is a requirement for institutional membership. Furthermore, specific guidelines, benchmarks and quality assurance procedures required for NCI-sponsored clinical trials must be followed by the COG, including those developed for proton therapy; the COG has amended ongoing trials to meet these requirements. Nearly all existing proton therapy centers have been approved for proton therapy administered on COG protocols or are currently going through the approval process. This model is important for proton centers in other countries where pediatric accreditation should be a prerequisite for proton therapy in children.

It has been difficult for caregivers and parents to comply with the timelines, requirements, and quality assurance processes included in pediatric clinical trials to the extent that trial enrollment has suffered in the referral process for proton therapy. This problem is reflected in the survey results from the pediatric proton foundation, which showed that in 2010, 465 children and adolescents were treated with proton therapy; however, only a small fraction were enrolled on COG clinical trials (www.pediatricprotonfoundation.org) Figure 1.

The advantage of proton therapy over photon therapy is not yet supported by results from clinical trials. This may never happen unless the current trends evolve and those receiving treatment are enrolled on clinical trials with appropriate endpoints and statistical designs. Statements and articles suggesting that proton therapy has a “strong track record in treating pediatric patients” or that proton therapy is inappropriate for adult cancer but there are no questions about its benefit in children are ignorant, irksome, and detrimental to the clinical trials process that has been very successful in pediatric cancer care.

Pediatric radiation oncology is a subdivision of radiation oncology in which minor improvements may have a major impact on the risk of long-term effects. During the past decade and longer, technical improvements in photon therapy have significantly increased the conformity of the high-dose volume and reduced the dose to critical normal tissue structures such that common side effects of the past have become rare or, in some instances, nonexistent. In comparing proton therapy to other modalities of radiation therapy the following axioms should be considered: the competing risk for tumor recurrence often exceeds the risk of a treatment-related effect; catastrophic and irreversible side effects (incurable secondary cancer, vasculopathy, and deformity) almost always happen within the volume that receives the highest dose; cure is a lifelong achievement and therefore the specter of treatment-related side effects looms lifelong—no patient is ever followed long enough.

We review the use of proton therapy in the treatment of children with craniopharyngioma, medulloblastoma, ependymoma, Ewing sarcoma, neuroblastoma, and Hodgkin lymphoma, focusing on opportunity, a review of the literature, and suggestions for future evaluation.

Craniopharyngioma

There has been considerable interest in the treatment of craniopharyngioma, a brain tumor that arises in both adults and children. Because of morbidity from the tumor and treatment other than radiation therapy, there is heightened interest in reducing the effects of radiation therapy, which is required in most cases. Recent neuro-oncology and neuro-radiotherapy symposia have been replete with preliminary institutional experiences using proton therapy. Understanding pre-existing morbidity in this population is critical to the evaluation of proton therapy and its potential impact. Indeed, in a tumor such as craniopharyngioma, there may be little to gain through low-dose volume reductions, even though an association has been made between dose to normal tissues and cognitive effects.

The limited opportunity to improve outcomes for these patients is highlighted in a report from France. The report (2) included assessment of quality of life, mood, and executive functioning after surgery and proton therapy in 29 children with craniopharyngioma. Even though the overall quality of life self-report was in the normal range, the proxy report was lower, and nearly half of the responding patients reported depression. A significant proportion (24–38%) had symptoms, according to tests of executive function.

Proton therapy in children with craniopharyngioma presents a unique clinical problem because these tumors are prone to cystic enlargement during treatment in response to irradiation (3–5). In one series (3), almost half of the treated children experienced cyst

enlargement during treatment based on planned week 3 and 5 magnetic resonance imaging (MRI) studies, most required cyst aspiration during radiation therapy and many required replanning largely dependent on the target volume margins.

Planning studies

Initial dosimetry studies comparing intensity-modulated proton therapy (IMPT) and photon therapy (IMRT) for craniopharyngioma reported no differences in target coverage for the 90% and 80% isodose volumes regardless of method. Comparing the 50% isodose volume, there was a divergence between the methods depending on the specific case; in some the conformity was better with IMRT. The differences were more pronounced and favored IMPT at the level of the 30% isodose volume and by integral dose. Organs at risk were equally spared by both methods; however, fewer proton beams were required to achieve the same results (6).

Three-dimensional conformal proton radiotherapy (3DPT), IMPT, and IMRT were compared in 10 patients with pediatric craniopharyngioma (prescribed dose 50.4Gy) in relation to the dose distribution to the neuronal stem cells, major blood vessels, and other normal brain structures (7). IMRT and IMPT were the most conformal. However, compared to IMRT, plans generated using 3DPT and IMPT methods delivered a lower integral dose to the hippocampus, dentate gyrus, and subventricular zone and a lower dose to the anterior cerebral, middle cerebral, anterior communicating, and carotid arteries with a lower integral dose to the infratentorial and supratentorial brain (without PTV), brainstem, and whole brain (without PTV). The significance of such dose reductions remains to be demonstrated.

In another series, after taking into account changes in cyst size, IMRT dose distributions were compared to 3DPT and IMPT plans in 14 children with craniopharyngioma (8). The conformity index and normal tissue dose values for the IMPT plans were better than IMRT and 3DPT plans. IMRT plans had a higher conformity and lower optic nerve doses than did 3DPT plans, while 3DPT plans had lower cochlear, optic chiasm, brain, and scanned body doses. With weekly MRI, the mean increase in planning target volume (PTV) was 11.3% over the course of treatment. IMPT was the most conformal method and spared the most normal tissue; however, it was highly sensitive to target volume changes, whereas the 3DPT method was not (8). The clinical significance of such differences is not clear particularly as most of the doses are within the conventional tolerance for the structures examined.

Modeling the potential benefit of protons versus photons for a mixture of pediatric brain tumours suggested a lesser decline in intelligence quotient (IQ) scores during the first 5 years after treatment with IMPT compared to IMRT due to a reduction in the volume of supratentorial brain exposed to the lowest doses (9). Newer dose effects models based on children treated with photons to estimate cognitive function after irradiation similarly predicted differences in cognitive function (54 Gy tumour dose) can be estimated (10). Math scores for a white female patient age 8 years and without CSF shunt would be 103 (IMRT) vs. 112 (3DPT) vs. 113 (IMPT) at 5 years based on treatment method. The difference would be considered clinically significant, even though both fall within the range of normal. Considering a 5-year-old male with a CSF shunt, the estimated math scores fall to 88 (IMRT) vs. 97 (3DPT) vs. 98 (IMPT) and those treated with photons begin to approach the abnormal range Figure 2).

Currently, such models are only indicative of a potential benefit and require validation. This type of modeling is useful, for it reveals the critical findings from the photon era—that late effects result from patient and treatment factors other than radiation therapy—and sets the threshold for the quality of data required from proton therapy studies to validate photon models and the expected benefit of proton therapy.

Clinical outcome

Actual clinical outcome data is limited. Luu et al. (11) reported on 16 children and young adults treated for craniopharyngioma using proton therapy and cumulative doses of 50.4–59.4 CGE. Although there were few acute effects, long-term complications included stroke in at least one patient. Long-term outcomes are currently only available for the combination of protons and photons (12). Actuarial 5- and 10-year local control rates were 93% and 85% with no observed late effects in the 10 young adults, but 1 of 5 children developed mental deficiency.

Medulloblastoma

There has been longstanding interest in the treatment of medulloblastoma using proton therapy as it is the most common malignant pediatric CNS tumor. Although identified as ideally suited for proton therapy, concerns abound regarding the physical and biological differences of protons versus photons (13, 14).

Overall, the view on the use of proton therapy is positive and the ability to spare extra-CNS tissue is remarkable Figure 3). An early dosimetry study compared megavoltage photon spinal irradiation with protons (15). Six MV photons exposed more than 60% of the prescribed dose to 44% of the heart, whereas proton therapy minimized irradiation of the heart, liver, thyroid (in most cases), and gonads.

Comparison of conventional photon, intensity-modulated photon, and proton craniospinal irradiation plans for a single patient, demonstrated 90% of the cochlea would receive 101.2%, 33.4%, and 2.4% of the prescribed dose using the respective delivery methods and a reduction from 72.2% to 29.5% to 0.5% for 50% of the heart volume (16).

Cochleae Sparing in Medulloblastoma Treatment

Proton therapy was able to spare the cochleae and hypothalamus better than photons from the posterior fossa boost treated to 30.6 Gy (17). Doses to normal tissue volumes as a percentage of the prescribed dose was (cochlea) 34% for protons, 87% for IMRT, and 89% for 3-dimensional conformal radiotherapy (3DCRT), and (hypothalamus) 21% for protons, 81% for IMRT and 91% for 3DCRT. However, cochlea sparing in 23 children treated with proton therapy did not result in reduced ototoxicity and did not correlate with predicted dose to the auditory apparatus for proton-treated patients, suggesting a lower-limit threshold for the effect of radiation on the cochlea. The rate of high-grade ototoxicity after one year was only 5% despite a mean cumulative cisplatin dose of 303 mg/m^2 (range, 298–330 mg/m^2).

Cognitive Sparing in Medulloblastoma Treatment

All standard and high-risk patients with medulloblastoma older than 3 years of age continue to receive whole-brain irradiation as the initial component of therapy; therefore, when comparing the cognitive sparing possibilities for different treatment methods or modalities the modeled benefit requires inclusion of the effect of the whole-brain dose and is limited to the boost component of therapy. It follows that patients treated with the lowest craniospinal (whole-brain) doses and those who receive primary site irradiation with a limited clinical target volume margin should have the greatest potential benefit from advanced methods of irradiation including proton therapy.

Modeling studies suggest a reduction in the mean dose (from the boost) to the hippocampus and subventricular zone from 88.3% to 77.1% to 42.3% comparing intensity-modulated arc therapy (IMAT), IMRT, and IMPT, respectively with predicted risks for developing memory deficits of 47%, 44%, 41%, and 33% corresponding to opposing fields, IMAT,

IMRT, and IMPT, respectively, and craniospinal doses of 23.4 Gy (18). This was also predicted as a potential reduction in cognitive loss (IQ) comparing IMPT with photon techniques based on photon models (9). Figure 4 shows simulated gains based on mean dose models for the brain comparing IMRT and IMPT using simulated data and previously published models (19) for the supratentorial brain volume. Simulated whole-brain irradiation to 30 Gy estimated a 25.1% risk of a subnormal (<90 points) IQ using photons and only 15.7% or 16.3% risk when proton therapy was used to treat only the "supratentorial subsites at risk" in favorable and unfavorable patients, respectively (20). Normal tissue complication probability modeling using published partial-brain cognitive effects estimates did not show significant gains for proton therapy until age was incorporated. When age was included in the model, ages 4–8 years appeared to benefit most from proton therapy.

Quality of Life

Prospective quality of life assessments during and after radiation therapy have been lacking in pediatric radiation oncology. 142 pediatric patients treated for brain tumors using proton therapy had health-related quality of life as part of the assessment and this included patients with medulloblastoma or requiring craniospinal irradiation who had among the lowest scores (21). However, parental reports were in the subnormal range at the outset of treatment and subsequently improved during the first 3 years after treatment. These findings support the contention that the burden of tumor and pre-irradiation morbidity will weigh heavily on these patients, even in the setting of improvements in radiation modalities.

Secondary Cancer Risk Reduction

Secondary cancer risk reduction after treatment for medulloblastoma has been predicted by a number of groups. A comprehensive analysis that included 10 patients (mean age, 8 years) planned for proton therapy using craniospinal irradiation doses of 23.4 Gy and 36 Gy estimated that the secondary cancer risks were highest for patients treated using photon arc-rotation or 3DCRT plans versus IMPT plans, even when secondary neutron weighting factors were applied (22). The risks were most notable after the age of 40 years. They also predicted a reduction in the long-term risks of pneumonitis, heart failure, xerostomia, blindness, hypothyroidism, and ototoxicity between different treatment modalities. The risk of second cancers from secondary neutrons was predicted to be highest in females (14.8% versus 8.5% for males) (23). The risk of a fatal secondary cancer from secondary neutrons was 5.3% for females and 3.4% for males not attributable solely to greater susceptibility to breast cancer. Lung cancer was the predominant form of secondary cancer in both sexes. These concerns have driven the consideration of intensity-modulated proton craniospinal irradiation (24), where collimation is not required and the volume receiving the highest dose may be further reduced. In an analysis of life-lost years estimated based on excess hazard for treatment using 3DCRT (25), volumetric modulated-arc therapy, and IMPT showed also that lung cancer, myocardial infarction, and stomach cancer contributed most to life-lost years, ranging from 1.90 years (3DCRT) to 0.28 years (IMPT). The incidence of secondary cancer in medulloblastoma comparing photons and protons (including IMPT) was estimated to be reduced by a factor of 8 (vs. IMRT) and 15 (vs. conventional photon) (26).

Other Toxicity Reductions

Proton therapy is predicted to reduce acute toxicity during craniospinal irradiation, including preservation of lymphocyte count during concomitant chemotherapy, and overall reduction in nausea, decreased appetite, and odynophagia (27). Considering rare and unusual complications, the incidence of cavernoma, estimated at 31% for a mean follow-up exceeding 7 years, may not be changed by using proton therapy because of the burden of whole brain irradiation (28). In contrast, prevention of cataract formation, especially in

patients younger than 10 years, might benefit greatly from proton craniospinal irradiation when the beams are angled 15–20 degrees to the posterior (29).

It is currently unclear how proton therapy might be used to address the problem of spinal growth impairment associated with craniospinal irradiation. The effect of radiation on spinal growth and development is a complex problem and depends on the age and sex of the patient in addition to radiation dose (30). In addition, not all spinal vertebrae respond equally to the effects of radiation dose (30). Although some have proposed that the spinal theca may be optimally irradiated to reduce growth impairment or other long-term sequelae (16), the multifocal nature of spinal growth and uncertainty about the effects of non-uniform irradiation might make realization of this goal difficult (31). At the present, approaches considering sparing the vertebral body in post-pubertal children and continued homogeneous irradiation of the entire vertebral element seem reasonable.

Concerned about the high costs of proton therapy, the health economic impact of adverse events in medulloblastoma survivors, including hearing loss, IQ loss, endocrine deficiencies (hypothyroidism and growth hormone [GH] deficiency), osteoporosis, cardiac disease, and secondary malignancies, using literature-based parameters were modeled (32). Proton therapy was predicted to lead to €23,600 ($28,945 at the 2012 exchange rate) cost savings and 0.68 additional quality-adjusted life-years where the predicted reductions in IQ loss and growth hormone deficiency (GHD) contributed most to the cost savings.

In summary, proton therapy to the craniospinal axis leads to significant reduction in dose to tissues outside the CNS, which should result in lesser non-neurological morbidity although the magnitude of benefit, in the context of other tumor and CNS related problems is uncertain. The use of proton boost is predicted to result in lesser adverse effect on cognitive function although this is additional to the currently unavoidable deficit from whole brain radiotherapy, surgery and the consequences of the tumour. As in other tumour types, the predicted benefit should be demonstrated in prospective studies.

Ependymoma

More than 20 years ago, the progression-free survival rate for a young child with ependymoma ranged from 26% at 3 years using postoperative chemotherapy to 36% at 10 years using postoperative craniospinal irradiation and post-irradiation chemotherapy (33). The poor outcome was attributed to the limited number of children who underwent gross total resection. Those who survived suffered severe side effects from radiation therapy, limiting the use of this modality in very young children, who characteristically make up the bulk of this patient population. Pioneering research performed at St. Jude Children's Research Hospital during the decade beginning in 1997 increased progression-free survival rates to 70% when measured at 7 years (34). A systematic approach to achieving gross total resection, including the routine use of second surgery, was combined with high-dose conformal RT and IMRT (54–59.4 Gy) to treat children as young as 12 months at the time of irradiation and the neurologic, endocrine, and cognitive effects have been limited or immeasurable (35–37).

This demonstrates how a new management approach may lead to an improvement in outcome, create new indications for an old treatment, and position radiation oncologists as gatekeepers to achieving surgical optimization for their patients. The standard treatment approach became second surgery and conformal postoperative irradiation. Proton therapy availability increased on the heels of the acceptance of conformal therapy for very young children with ependymoma, marking the intersection of a therapy seeking new indications with a tumor system for which radiation therapy is indicated nearly regardless of age (38). Indeed, children with ependymoma make up one of the largest groups currently receiving

proton therapy. Among the 465 children with 45 different diagnoses treated with proton therapy at US centers in 2010, 71 had ependymoma (www.pediatricprotonfoundation.org).

Seventeen children with ependymoma were treated at Massachusetts General Hospital between 2000 and 2006 and the local control, progression-free survival, and overall survival rates were 86%, 80%, and 89%, respectively at a median follow up of 26 months (38). Dose comparisons between proton and simulation photon plans showed an advantage for passively scattered proton therapy (3DPT) over IMRT. Similar excellent disease control rates have been reported from a larger series with longer follow-up (39). Comparative planning for ependymoma showed a dose advantage for protons at the level of the hypothalamus, cochleae, and supratentorial brain volumes (9) using proton spot scanning, superior to PT plans on the basis of high- and low-dose volume comparisons.

Proton therapy has become the radiation modality of choice for children with ependymoma and parents are willing to pursue proton therapy regardless of cost and, in some instances, without a team approach that might have included second surgery to achieve gross total resection prior to irradiation. The use of protons in the context of no improvement in tumour control or survival when minimal or no toxicity can be achieved with conformal photon therapy is questionable, especially in situations when striving for protons the overall team management approach is compromised. This is of particular concern with the so far unknown late effects associated with the uncertainties of proton RBE and the reported necrosis rates.

Figure 5 shows an example of a comparison of 3DPT and photon IMRT plan for posterior fossa ependymoma. The minor differences in dose distribution are not within a range of measurable change in radiation induced toxicity which with the use of highly conformal photon RT is largely non-existent and this includes cognitive function. The best estimates about the impact of brain dose are derived from children with medulloblastoma, for whom mean brain doses (craniospinal plus boost dose) of approximately 45 Gy, 37 Gy, 36 Gy, and 35 Gy are required to achieve a probability of a 50% risk of subnormal IQ, math, reading, or spelling score 5 years after irradiation (40). Photon IMRT plans generate a mean dose of approximately 10 Gy while the mean dose was 7–8 Gy with 3DPT, which are not clinically significant and the risk of subnormal cognitive test scores are predicted to be the same.

Both plans achieve cochlear doses less than 20 Gy (41), below the tolerance doses (42). In fact, the IMRT plan had superior cochlear sparing with the left and right cochlea with a mean dose of 1.4 Gy and 7.7 Gy, and the 3DPT 9–11 Gy and 8–9 Gy, respectively. The risk of hearing loss would be considered minimal whether proton therapy or photon therapy was used.

The mean dose to the hypothalamus using proton therapy was 0.4–0.8 Gy, and 7 Gy for photon IMRT with a higher risk of GH deficiency due to hypothalamic irradiation (43). On the basis of the potential risk for GH and other endocrine deficiencies, proton therapy may be an option with the requirement for GH testing prior to irradiation.

Parents of children who are long-term survivors of ependymoma treated in the conformal treatment era sometimes ask about proton therapy. They are curious about how it might have benefitted their normal child and then remember the promise of new technology and how they were attracted to cutting-edge photon treatment in the day. After asking their questions about proton therapy, these same parents of normally functioning long-term survivors return to their only concern—a negative MRI report and long-term tumor control. Late effects are often a distant concern.

In conclusion, apart from the potential to reduce the risk of hormone deficiencies, the parents and caregivers succumbed to the fear of the unknown—the very late occurring and rarely observed or reported late effect. The effect best characterized in responses at symposia as “you never know,” which suggests that any reduction in normal tissue dose should be pursued, no matter how small. And this is at the potential cost of other unknowns – the so far not entirely predictable late effects due to uncertainties of RBE with potential concern of late necrosis and the unknown long term tumour control of challenging technology subject to other uncertainties and not infrequently combined with a “stand alone” facility without full pediatric infrastructure.

Proton Therapy and Necrosis

Does proton therapy have a necrosis problem in children with brain tumors? The cumulative incidence of CNS necrosis in the modern photon era was recently documented for ependymoma (34) and CNS embryonal tumors, including medulloblastoma (44). The rates were 2.5% after 7 years and 3.7% after 5 years. The ependymoma necrosis rate was reported from a series of 153 children (median age, 2.9 years) treated with conformal radiation therapy at St. Jude Children’s Research Hospital between 1997 and 2007 using 54–59.4 Gy and a clinical target volume margin of 1 cm. The CNS embryonal tumor necrosis rate was also reported from a St. Jude series of children treated on successive protocols from 1996 to 2009 that included 236 children treated with craniospinal irradiation (23.4 Gy to 39.6 Gy) and focal boost treatment (cumulative dose, 55.8 Gy) using a 2 cm (prior to 2003) or 1 cm (2003–2009) clinical target volume margin. Both trials should be considered contemporary. Surgical morbidity and unique clinical features were attributed to necrosis in the ependymoma cohort; in the CNS embryonal tumor cohort, the volume of infratentorial brain receiving a radiation dose in excess of 50 Gy was predictive for necrosis. There were deaths from necrosis in both groups. An alarming report was presented at a recent symposium (45). The incidence of proton-related “radiation injury” was determined by the collective experience of three tertiary pediatric hospitals that referred 132 children for proton therapy to various institutions between 1995 and 2012. Eight cases of symptomatic injury were identified among the 132 children (crude rate, 6%). All patients (median age, 6 years) required treatment with corticosteroids, hyperbaric oxygen, or bevacizumab. It is unclear whether any of these patients died from radiation injury; however, among the 4 surviving radiation injury patients (median follow-up, 24 months), 2 were reported to have persistent neurologic deficits. The actuarial incidence might be higher with the use of cumulative incidence statistics.

In a recent series from St. Jude Children’s Research Hospital that included very young children with brain tumors treated prospectively with proton therapy after 4 months of postoperative induction chemotherapy including high-dose methotrexate, imaging changes consistent with radiation effects were reported in 8 of 18 patients. There were transient signal abnormalities and enhancement that appeared early (less than 12 weeks) after treatment and resolved within 2–3 months of their initial appearance. One patient had symptomatic progression and was treated with hyperbaric oxygen with eventual resolution of symptoms (46). The imaging changes appeared to coincide with the intersection of the distal aspect of the proton beams used in a multi-field arrangement.

The risk needs to be fully defined and this is best achieved by enrolling children on clinical trials that mandate toxicity reporting, such as the current collaborative proton therapy trial for craniopharyngioma at St. Jude Children’s Research Hospital and the University of Florida Proton Therapy Institute (47).

Ewing sarcoma

Ewing sarcoma is a highly radiosensitive and unique pediatric bone tumor that may arise in a variety of locations. Radiation therapy has been a mainstay for unresectable tumors, including those located in head and neck, thoracic, paraspinal, and pelvic sites. The combination of critical location, large tumor volume, young age, surgical intervention, and the use of concurrent chemotherapy are predictive of a spectrum of normal tissue effects both early and late.

There have been a number of comparative planning studies that have included patients with Ewing sarcoma, (17, 48). Planning scans of a patient with intrathoracic Ewing sarcoma were used to compare helical tomotherapy, rapid-arc and IMPT plans. The IMPT plans had sparing of organs at risk. With the following objectives and results by organ (goal, tomotherapy dose, proton therapy dose, arc therapy dose): vertebra (mean < 20 Gy, 17.6 Gy, 13.6 Gy, 22.2 Gy), right lung (mean < 15 Gy, 11.9 Gy, 0.9 Gy, 11.9 Gy), left uninvolved lung (mean < 15 Gy, 14.1 Gy, 6.4 Gy, 15.5 Gy), heart (mean < 30 Gy, 29.1 Gy, 3.8 Gy, 26.7 Gy), healthy tissue (minimal, 9.1 Gy, 2.5 Gy, 8.7 Gy) (48),. Similarly, in cases of pelvic sarcoma, including a single case of Ewing sarcoma, photon 3DCRT, electron therapy, and IMRT were inferior to standard proton therapy (3DPT). None of the ovarian volume was irradiated with more than 2 Gy, and the pelvic bones and vertebrae were spared in a superior manner. IMRT did show more reduction in the dose to the bladder.

Dose - volume comparison of photon and proton therapy for unresectable Ewing sarcoma of the pelvis in pediatric patients demonstrated lower mean integral dose for the 3D proton plans compared to IMRT plans with similar conformity index. The ipsilateral V2Gy of the femoral growth plate was 81% (range 6–100%) for IMRT versus 34% (range, 0–99%) for proton therapy. The contralateral values were 80% (0–100%) versus 18% (0–90%). Example of PT plan for a female patient with Ewing sarcoma is shown in Figure 6.

Thirty children with Ewing sarcoma were treated using proton therapy (median dose, 54 Gy) during a 6-year interval up to 2009 (49). Three-year event-free survival, local control, and overall survival rates were 60%, 86%, and 89%, respectively, which is similar to the outcome following photon RT. As expected, the use of protons did not reduce the risk of chemotherapy-induced hematologic malignancies, which were reported in 4 of the survivors. The use of protons also offers the potential for dose escalation for high-risk sarcoma, including those arising adjacent to critical normal tissue volumes not possible with photons (50). This may be especially true for paraspinal tumors with relatively high radiosensitivity located near the spinal cord (51).

In conclusion, protons offer the possibility of significant reduction of normal tissue doses concurrently with tumour control results similar to those obtained with photon RT. However, despite the improvements in normal tissue dose distributions, local radiation effects in the high-dose volume persist, including radiation recall, radiation myositis, and alopecia (52).

Retroperitoneal Neuroblastoma

Based on the known complexity of neuroblastoma target volumes and the proximity of normal tissue structures including the liver and kidneys, proton therapy was used after chemotherapy and delayed resection in a 4-year-old boy to administer 34.2 CGE to the residual disease. The use of proton therapy achieved normal tissue sparing to the extent that 50% of the ipsilateral kidney received less than 16 CGE, and doses to the 50% and 20% isodose volumes were less than 1 CGE and 10 CGE, respectively. Similar gains were noted in reducing the dose to the liver (80% of the liver received less than 27 CGE). (53)

In a similar comparison of photon and proton therapy plans (54) using IMRT, 3DPT and IMPT with primary beams configured in a parallel-opposed arrangement, both proton therapy methods reduced mean liver and kidney dose by 40–60%. 3DPT also reduced the predicted risk of secondary cancer by 30% and IMPT by 50% compared to IMRT. When secondary neutrons associated with collimation used for the passively scattered method were included in the model, the reduction in secondary cancer risk was limited to IMPT.

Nine children with advanced (International Neuroblastoma Staging System stage III or IV) neuroblastoma were treated at Massachusetts General Hospital using PT (55). At a median follow-up of 38 months there were no local failures; 4 children developed distant metastases, and two subsequently died. The plans were comparable in target volume coverage: but PT achieved sparing of the liver, lungs, heart, and kidneys, the heart, stomach, and bowel.

Proton therapy was recently approved for the treatment of neuroblastoma in the COG and may be especially useful for cases that require dose escalation and for sparing renal parenchyma. Patients for whom the lung is subtended as part of the irradiated volume will not be eligible for proton therapy. There remain concerns about tissue heterogeneity and organ motion in these patients.

Hodgkin Lymphoma

The advent of proton therapy for the treatment of Hodgkin lymphoma in children coincides with the need to properly define the extent of disease and response to chemotherapy in patients destined to receive radiation therapy. Reducing the incidence of cardiotoxity and secondary cancers in a truly vulnerable population makes proton therapy a logical next step. Indeed, as some move to further exclude the use of radiation therapy in children with Hodgkin lymphoma because the competing risks of secondary cancer and debilitating late effects exceed the incidence of disease recurrence (56), balance can be achieved only through the rational reduction in the targeted volume and advancement of newer methods (57, 58). The Hodgkin lymphoma committee in the COG is set to meet these goals, as it has completed its first trial for high-risk Hodgkin lymphoma that includes 3-dimensional targeting. In future trials, clinical risk factors will be used to stratify patients for treatment, functional imaging ([^{18}F] fluorodeoxyglucose positron emission tomography) will be used to determine treatment intensity, and the radiotherapy target volume will evolve from involved-field RT to involved-node RT, which will reduce breast and cardiac dose in patients regardless of the chosen modality. Proton therapy will be permitted on future trials to further reduce treatment toxicity in selected patients, acknowledging some of the difficulties associated with proton therapy at thoracic and mediastinal sites (59) (Figure 7).

Summary

When a new and unproven method of irradiation promises a reduction in toxicity and the promise leads to the referral of a child for treatment when he might otherwise have received a lesser form of therapy, perhaps the normal requirements of proof, in this case toxicity reduction, might be abandoned. Such was the case more than 15 years ago when 3DCRT was introduced as a treatment for very young children with brain tumors. The proof of benefit was difficult at that time owing to the paucity of quantitative data about the effects of irradiation from an earlier time; however, no one could argue that reducing dose to normal tissue would be detrimental provided that the volume at risk was encompassed by the prescription dose. The introduction of proton therapy for children is not analogous to the evolution of conformal photon irradiation and understanding the impact of altered dose distributions. The differences in radiobiological effect when comparing photons to protons means that we are comparing a known entity to an unknown entity: the dose-volume

histogram for proton therapy might mean something substantially different than the dose-volume histogram for photon therapy. The multifaceted difference between the two modalities supports the argument for careful evaluation, follow-up and clinical trials with adverse event monitoring when using proton therapy in children.

For the sake of our patients, we hope for an advantage of proton therapy over photons that will lead to improved indications for therapy, disease control and functional outcomes. Considering that multimodality management of children with an expert pediatric oncology team and the availability of ancillary measures that improve the quality of treatment delivery may be more important than the actual beam, it should be further stressed that our estimates of the benefit of proton therapy over photon therapy based on toxicity reduction will only be realized when survivorship has been achieved. We will have to rely on photon outcomes data for comparison once substantive data become available for proton therapy and hope for more funding and appreciation for late effects research, and a better understanding of the radiobiological differences between protons and photons to further reduce side effects in children and exploit the full curative potential of this relatively new modality.

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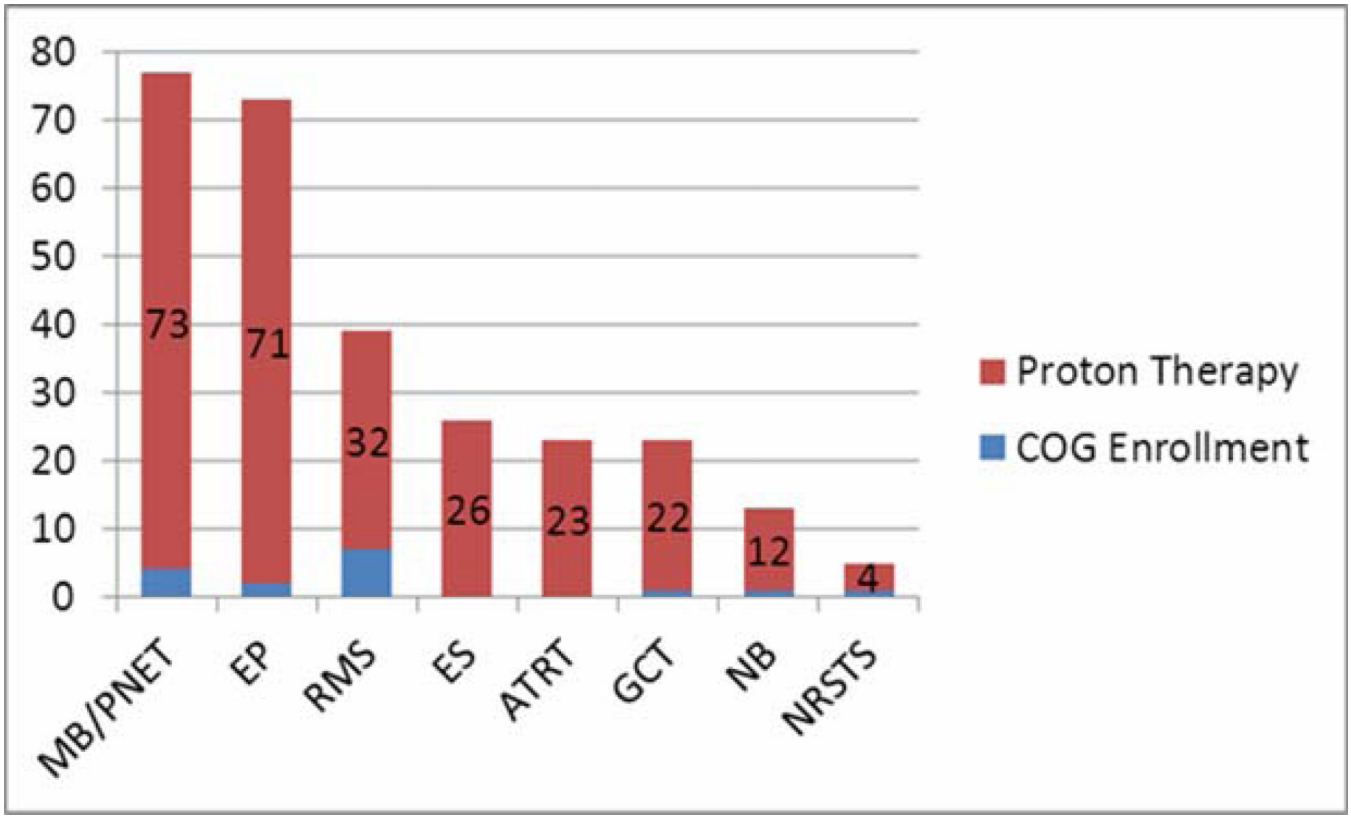

Figure 1.
Children treated with proton therapy in 2010 (adapted from presentation at www.pediatricprotonfoundation.org).
Legend: MB/PNET, medulloblastoma/primitive neuroectodermal tumor; EP, ependymoma; RMS, rhabdomyosarcoma; ES, Ewing sarcoma; ATRT, atypical teratoid rhabdoid tumor; CGT, CNS germ cell tumor; NB, neuroblastoma; NRSTS, non-RMS soft tissue sarcoma.

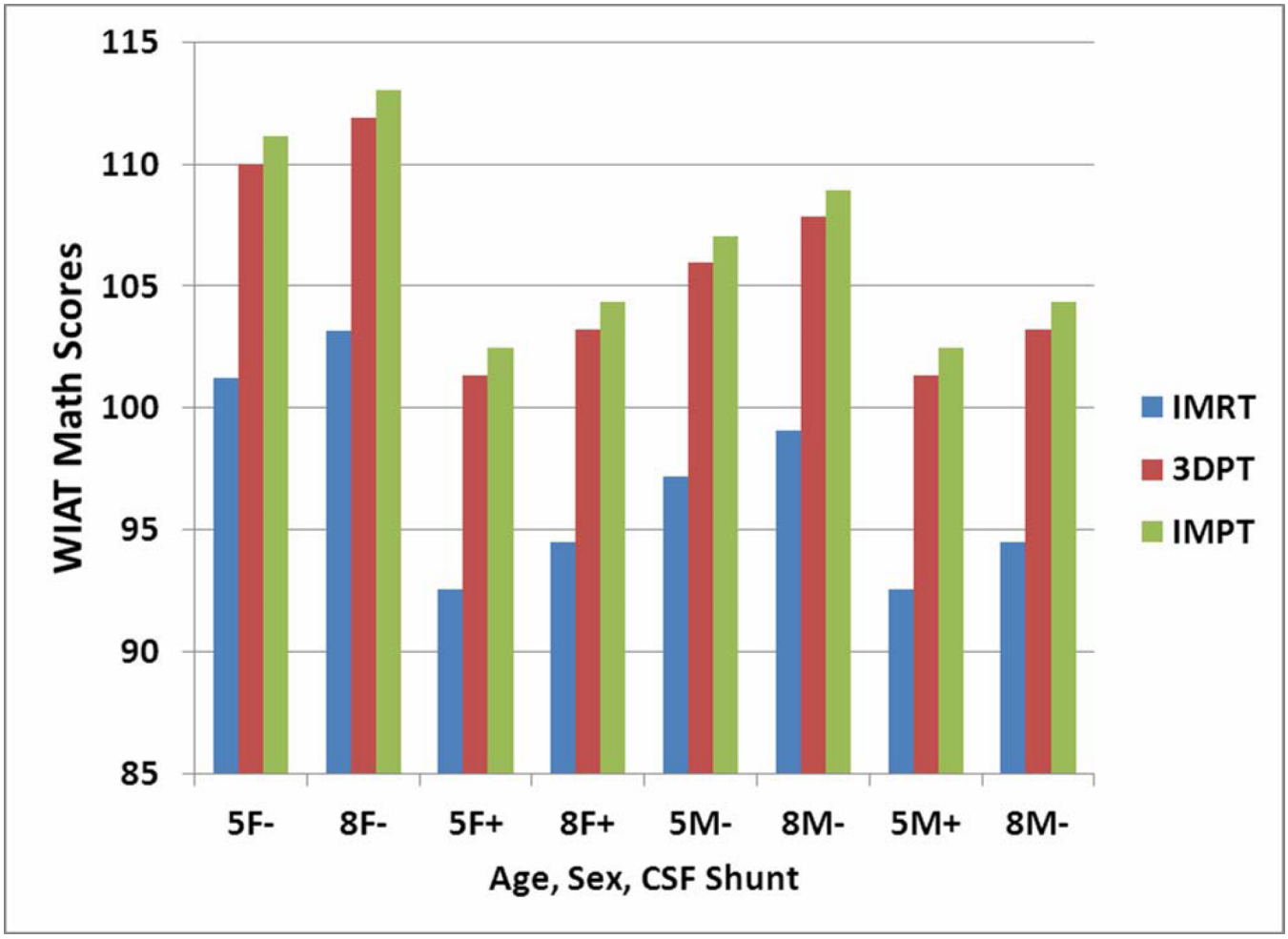

Figure 2.

Wechsler Individual Achievement Test (WIAT) mathematics scores estimated 5 years after treatment for children with craniopharyngioma using whole-brain integral dose data from the MD Anderson Cancer Center comparative dosimetry study (Boehling 2012) and St. Jude Children's Research Hospital cognitive effects models (Merchant 2011).

Legend: CSF, cerebrospinal fluid; IMRT, intensity-modulated radiation (photon) therapy; 3DPT, 3-dimensional (passively-scattered) proton therapy; IMPT, intensity-modulated proton therapy.

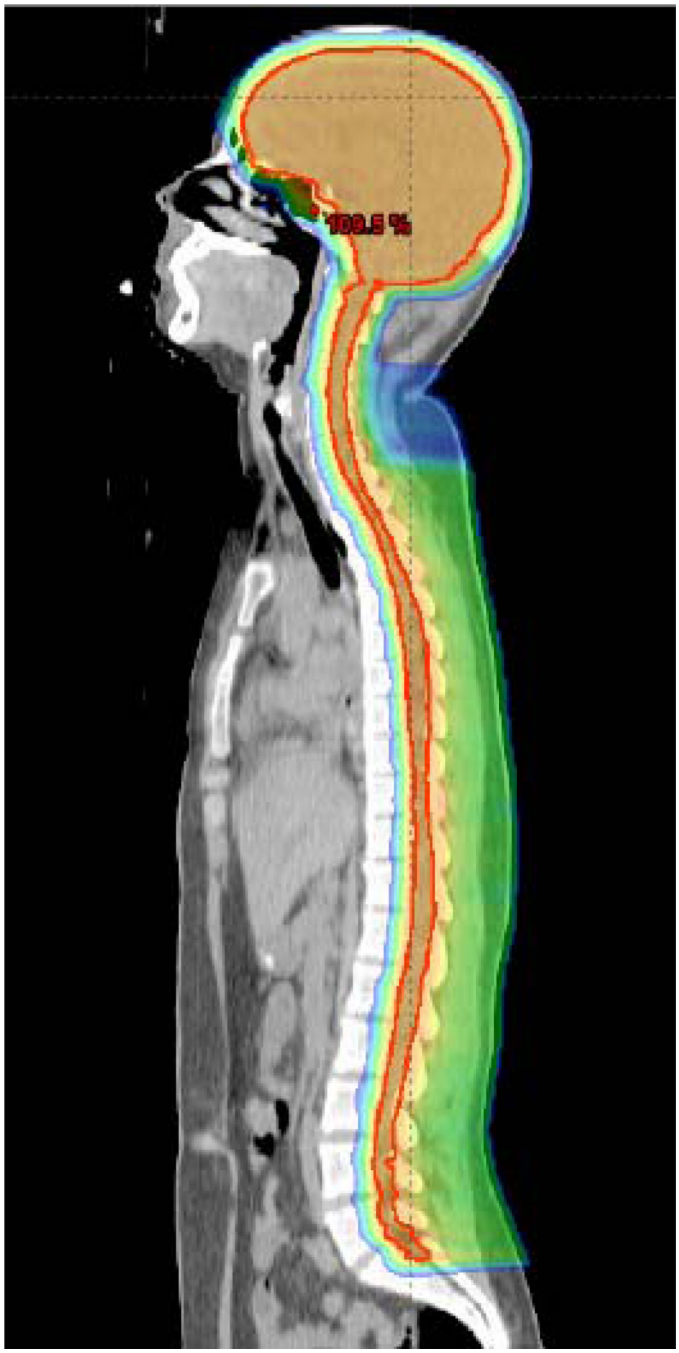

Figure 3.
Craniospinal dose distribution planned for a pediatric case of medulloblastoma using intensity-modulated proton therapy.

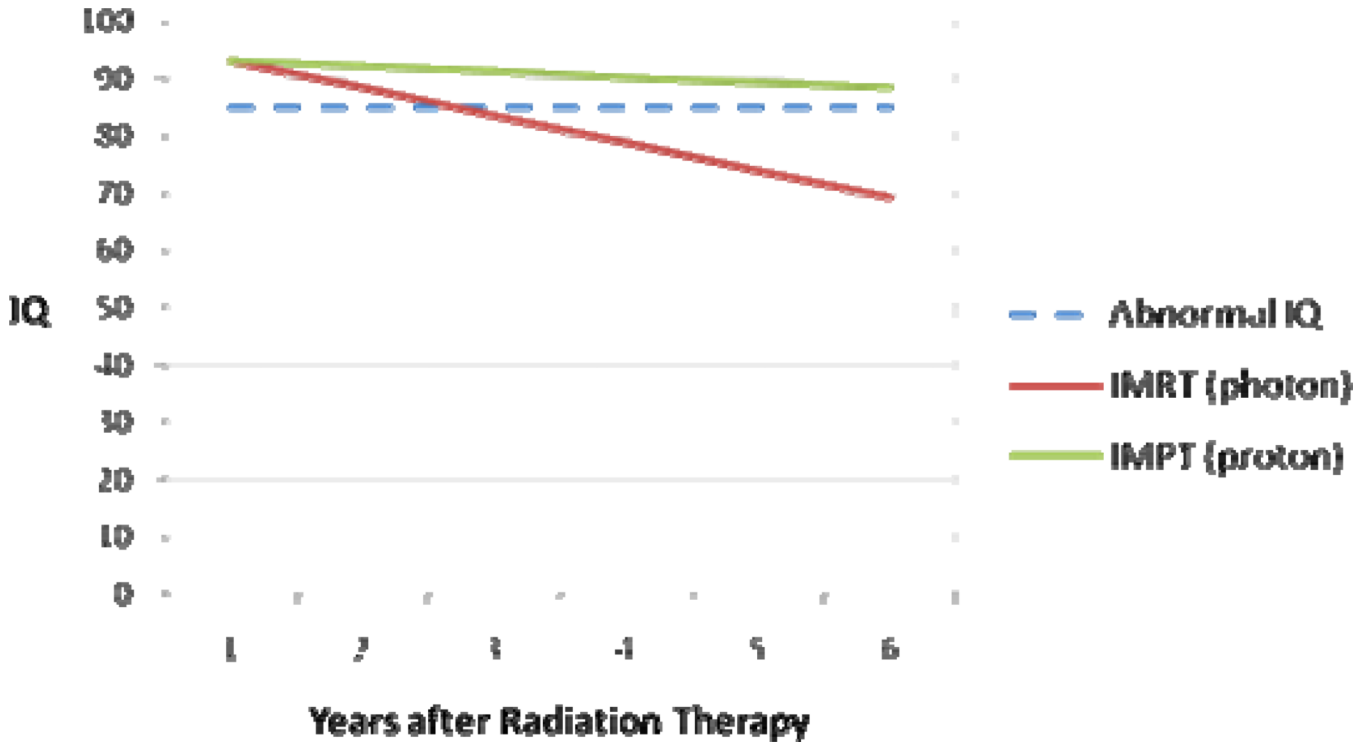

Figure 4.
Simulated intensity-modulated photon therapy (IMRT) and intensity-modulated photon therapy (IMPT) mean brain dose data and published cognitive models (Merchant et al., Int J Radiat Oncol Biol Phys 65:210:2006).

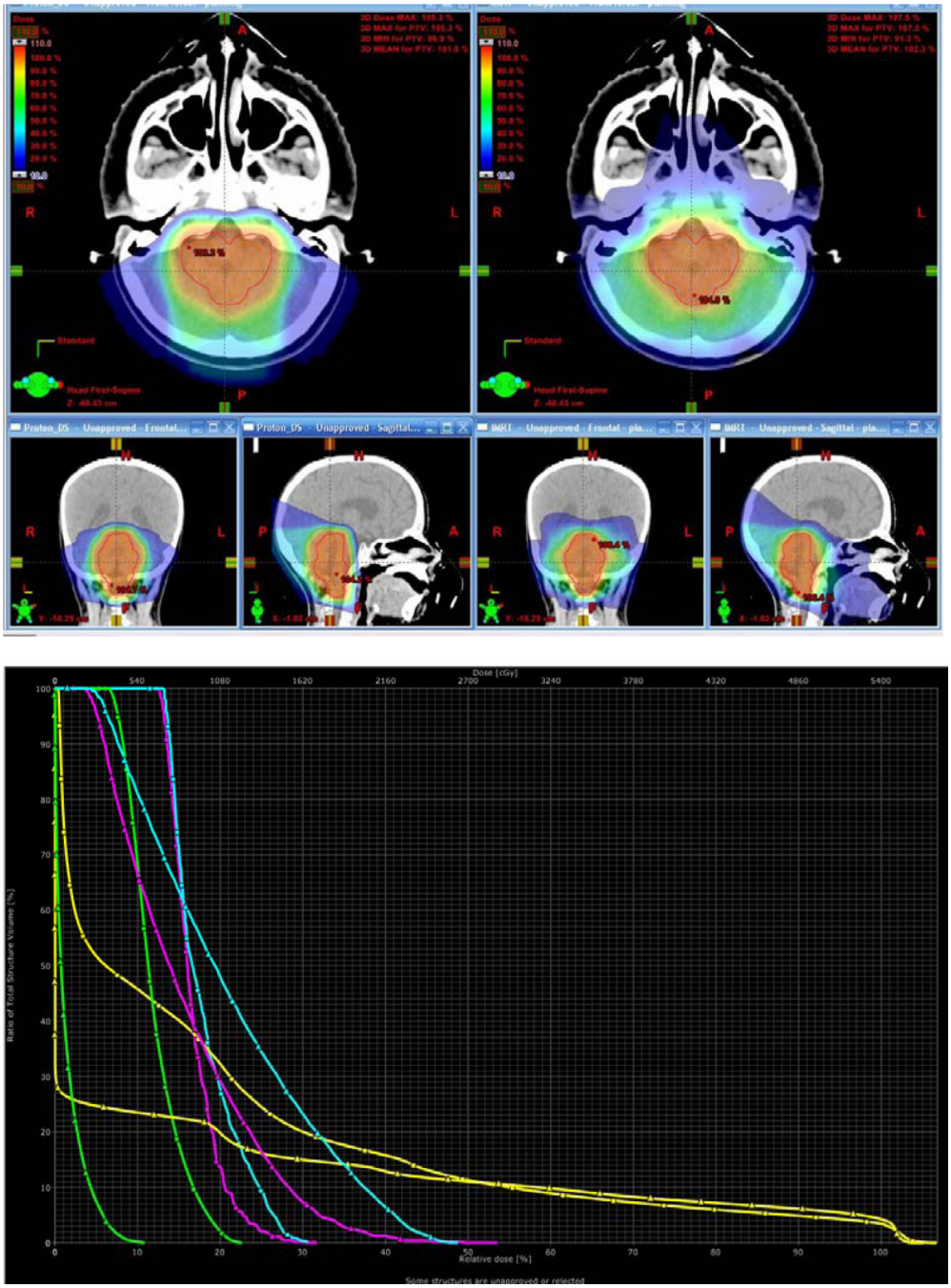

Figure 5.
Double-scattered proton therapy (left) and intensity-modulated photon therapy (right) treatment plans for a child with infratentorial ependymoma.
Legend: Whole-brain dose volume histograms (yellow); cochlear dose volume histograms (light blue=photon, magenta-proton); hypothalamus (green).

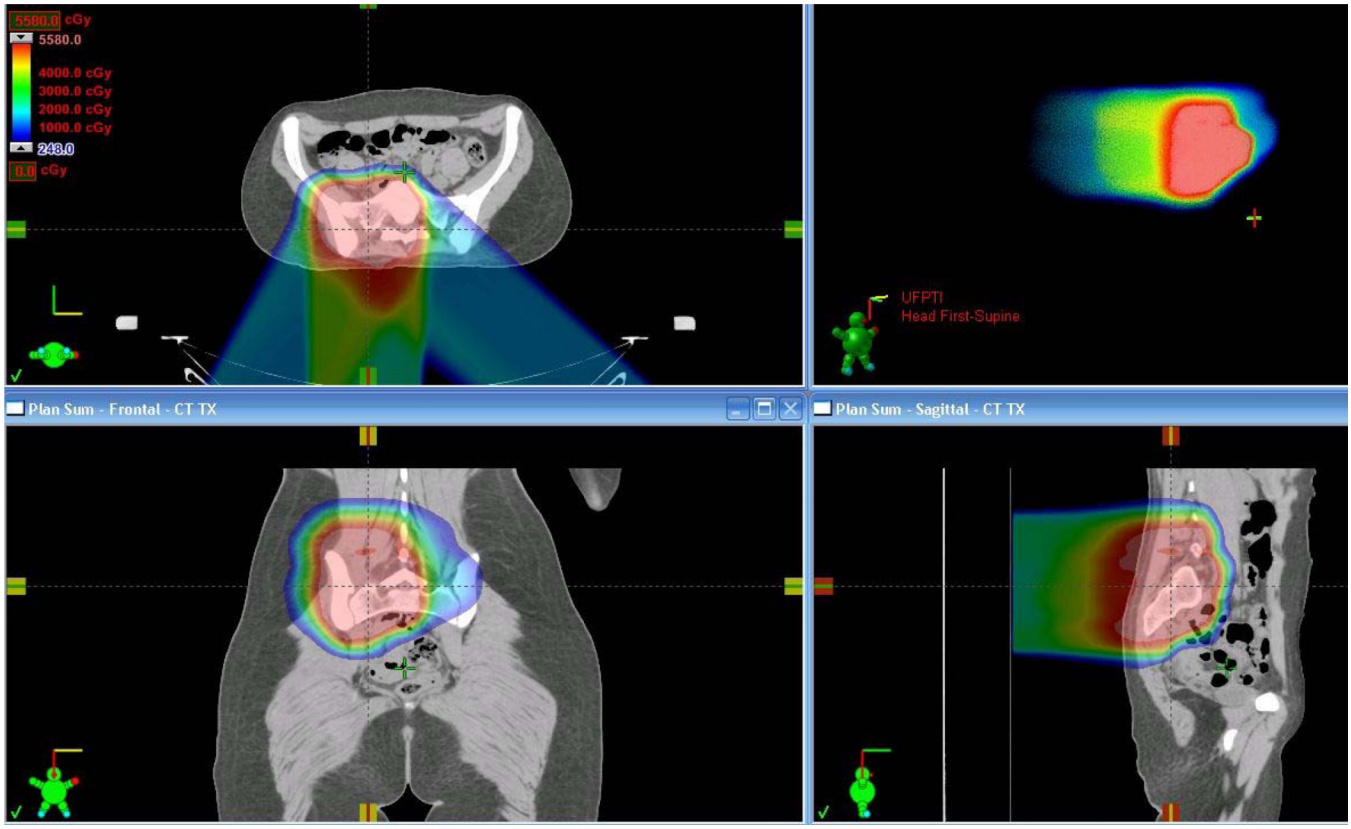

Figure 6.
Double-scattered proton therapy plan for a pelvic Ewing sarcoma in a female patient.

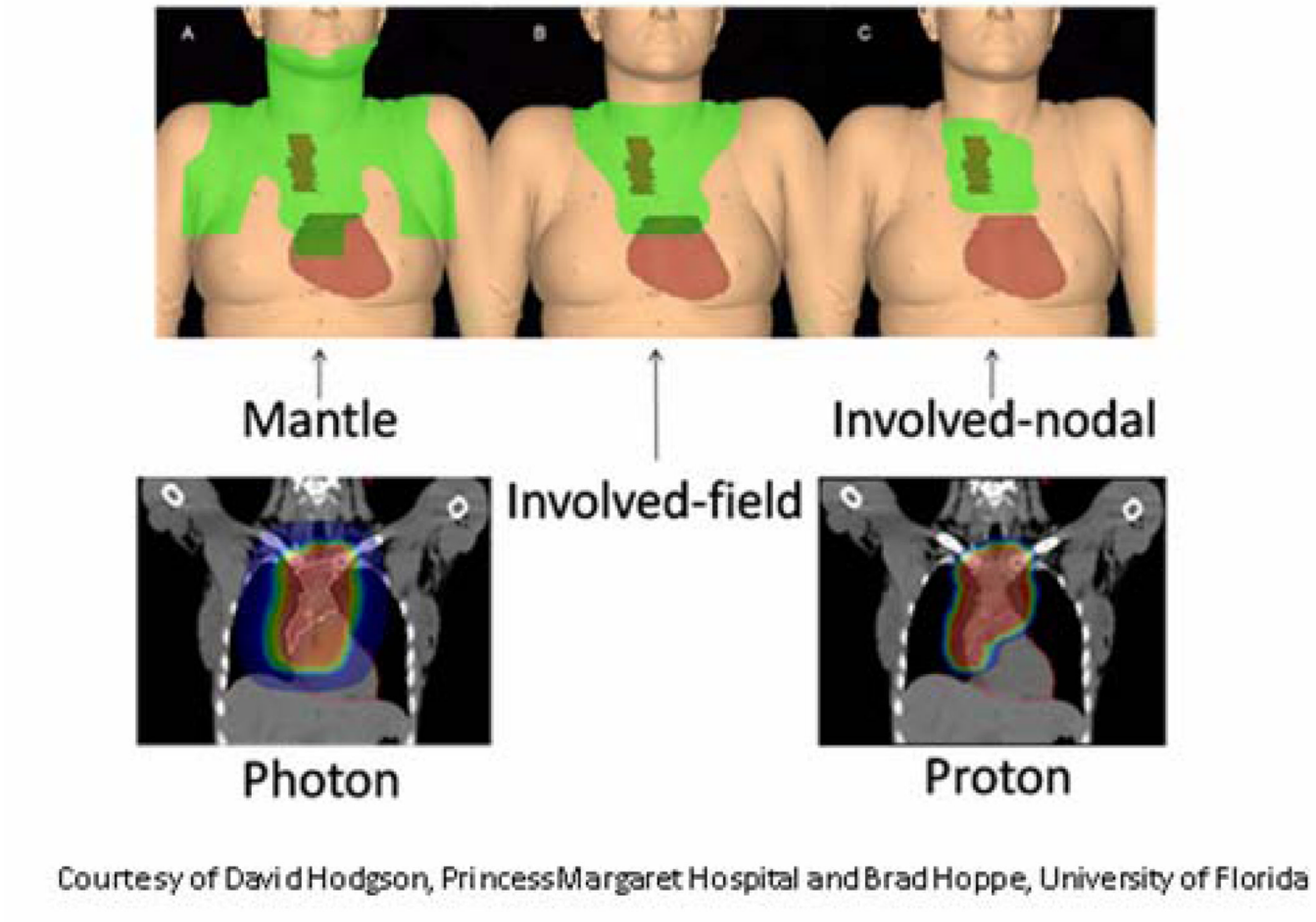

Figure 7.
Examples of conventional (mantle), involved-field, and involved-nodal treatment volumes for Hodgkin Lymphoma and photon and proton therapy dose distributions.