TREATING PEDIATRIC TUMORS WITH PROTON THERAPY
CURRENT PRACTICE, OPPORTUNITIES AND CHALLENGES
The largest consensus on the preference of proton over photon radiation therapy is in pediatric oncology. Counting 70-80% survival rates, finding solutions that positively impact quality of life outcomes has become a growing focal point among pediatric oncologists. This white paper presents clinical outcomes data that proton therapy provides an effective means to achieve this end.

PATIENT SELECTION

Proton beams’ physical and biological properties support an advantageous quality of dose distribution, resulting in improved therapeutic gains. The clinical interest lies in the comparative impact of proton beam therapy versus alternatives such as photon beam treatment, either as a curative solution or salvage remedy for cancerous and noncancerous conditions and their effect on survival, disease progression, safety, health-related quality of life and other patient outcomes. An increasing emphasis on evidence-based medicine makes it worthwhile to assess the available data that supports proton therapy over other techniques to better guide the physician and patient toward the most appropriate treatment.1

The current model policy developed by the American Society for Radiation Oncology (ASTRO) recommends basing patient selection on the added clinical benefit proton therapy offers. This comes down to considering proton therapy in such cases where sparing the surrounding normal tissue is crucial and cannot be adequately achieved with a photon-based approach. The policy provides several non-specific examples:

- The target volume is in close proximity to one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s).
- A decrease in the amount of dose inhomogeneity in a large treatment volume is required to avoid an excessive dose “hotspot” within the treated volume to lessen the risk of excessive early or late normal tissue toxicity.
- A photon-based technique would increase the probability of clinically meaningful normal tissue toxicity by exceeding an integral dose-based metric associated with toxicity. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.2

Fully leveraging proton therapy’s dosimetric advantages adds complexity to the treatment compared to other kinds of radiation therapy. A thorough comprehension by oncology professionals of the benefits and consequences is therefore indispensable.

PROTON THERAPY FOR PEDIATRIC TUMORS

A) OVERVIEW BENEFITS

WHAT CAN YOU GAIN?

Pediatric cancer survival has increased from about 30% in the late 1960s to 70-80% today. Given the better chances for cure, the reduction of acute complications, late ones in particular, has become a major focus when it comes to improving the therapies.3, 4, 5, 6, 7

Irreversible, long-term side effects of conventional radiation therapy for pediatric cancers have been well documented and include growth disorders, neurocognitive toxicity, ototoxicity with subsequent effects on learning and language development, renal, endocrine and gonadal dysfunctions.4, 8, 9, 10, 11, 12 Radiation-induced secondary malignancy is another very serious adverse effect that has been reported.13

As there is no exit dose when using proton radiation therapy, the dose to surrounding normal tissues can be significantly limited, reducing the acute toxicity which positively impacts the risk for these long-term side effects.

Cancers requiring craniospinal irradiation, for example, benefit from the absence of exit dose with proton therapy: dose to the heart, mediastinum, bowel, bladder and other tissues anterior to the vertebrae is eliminated, resulting in a reduction of acute thoracic, gastrointestinal and bladder side effects.1 For young patients at risk, proton therapy also considerably lengthens the latency period for the possible development of late sequelae.14 Furthermore, radiation induced secondary cancer numbers turn out significantly lower in comparison to conventional radiation therapy.15, 16

When it comes to cranioopharyngiomas, one of the primary benefits of protons over photons appears to be situated in large treatment volumes, particularly large, cystic lesions that extend beyond the sella and have a diameter over two to three cm.

B) DOSIMETRIC COMPARISON

There have been numerous comparative planning studies that demonstrate superior normal tissue sparing and decreased integral dose with proton therapy, which is relevant to the risk of long-term adverse effects and secondary cancers.15, 16

In the case of parameningeal rhabdomyosarcomas, Kozak et al. of the Massachusetts General Hospital (MGH) group published a dosimetric study comparing Intensity Modulated Radiation Therapy (IMRT) and proton radiation therapy in 2009. Both proton and IMRT plans provided acceptable and comparable target volume (CTV) coverage, with at least 99% of the CTV receiving 95% of the prescribed dose in all cases. Proton use, however, provided significant sparing of all examined normal tissues, except for ipsilateral cochlea and mastoid, while ipsilateral parotid gland sparing was of borderline statistical significance (p=0.05). More profound sparing of contralateral structures by protons resulted in greater dose asymmetry between ipsilateral and contralateral retina, optic nerves, cochlea, and mastoids.21

A 2006 study by Merchant et al. modelled the effects of radiation dosimetry on the IQ of 39 pediatric patients with central nervous system (CNS) tumors. Comparing IQ after treatment with prospective evaluation, they found that partitioning dose distribution into two levels resulted in both levels having a significantly negative effect on longitudinal IQ across all five brain volumes (total brain, supratentorial brain, infratentorial brain, and left and right temporal lobes). A three-level partitioning (low, medium and high) showed exposure to the supratentorial brain to have the most
Yeung et al. evaluated the dosimetric characteristics of Intensity Modulated Proton Therapy (IMPT) optimization techniques and Pencil Beam Scanning (PBS) nozzle designs on pediatric craniopharyngiomas, publishing their results in 2013. Comparing a double-scatter (DS) with IMPT plans, they found that both achieved adequate target coverage, but the latter achieved a better conformity index of 0.78 versus 0.60 for DS. IMPT with multi-field optimization (MFO) performed better for the inhomogeneity than using single-field uniform dose (SFUD) or DS. MFO with a PBS dedicated nozzle (DN) achieved the best result: 0.023, where other plans reached values of 0.03 or higher. IMPT also achieved lower doses to the normal tissues, as compared to DS, with MFO-DN showing the best results again. Nozzle designs that provided small beam spots and sharp lateral penumbra allowed for better target coverage and reduced dose to normal tissue. MFO, in contrast to SFUD, required minimal use of range shifters in the case of shallow targets, preserving the penumbra and the dosimetric advantage. They concluded that IMPT achieved significantly better target coverage and dose sparing of normal tissue than DS for pediatric craniopharyngiomas and that MFO-DN proved to be the optimal delivery technique (figures 2A, 2B & 3).

In their 2014 article ‘Craniopharyngioma and Proton Therapy’, Bradley et al. assembled available data and found dosimetric studies suggesting that proton therapy affords a reduction in dose to critical structures compared to conventional photon radiation, including IMRT, for patients with craniopharyngioma (figure 1). They concluded that radiation dosimetry data from five brain volumes can be used to predict decline in longitudinal IQ and that the volume receiving the highest dose continues to be most impacted, despite measures to reduce radiation dose and treatment volume, which supports current volume reduction efforts.23

Figure 1: Radiation treatment plans comparing intensity modulated radiation therapy, double-scatter proton therapy, and intensity modulated proton therapy for a child with a craniopharyngioma.

Figure 2A: A dose-volume histogram (DVH) comparison between double-scatter proton therapy and intensity modulated proton therapy (IMPT) with single-field uniform dose (SFUD) optimization and range shifters. Target coverage was achieved with both plans, but IMPT resulted in a lower dose to the organs at risk. Three fields with the same beam angles were used for both plans.

Figure 2B: A DVH comparison between SFUD and multi-field optimization further reduced the dose to the organs at risk. Range shifters were not needed for the multi-field optimization technique for this case; the sharper penumbra resulted in better sparing, especially for the left hippocampal tail.
C) CLINICAL OUTCOMES - LITERATURE REVIEW

Significant clinical outcome data have been reported over the years.

* SURVIVAL AND CONTROL RATES

In 2004, Yuh et al. reported adverse effect reduction with craniospinal irradiation by proton beam for medulloblastoma. Based on their experiences at Loma Linda University Medical Center, California, they established a substantial reduction in dose to the cochlea and vertebral bodies and observed that the exit dose through thorax, abdomen and pelvis was virtually eliminated. Despite the concurrent chemotherapy, a clinically significant lymphocyte count reduction was not detected. Acute side effects were mild. At MGH, Krecjarek et al. confirmed these findings in 2007. In 2008, MacDonald et al. of MGH published the outcomes of 17 pediatric patients treated for ependymoma, showing an 89% overall survival rate and substantial sparing of cochlea, hypophalumus and temporal lobes as compared to IMRT. The same group's 2011 publication on 22 pediatric patients with CNS germ cell tumors mentions outstanding results: local control, progression-free survival, and overall survival rates of 100%, 95%, and 100% respectively. Any form of proton therapy showed substantially more normal tissue sparing than IMRT, indicating that the use of IMPT may lead to additional sparing of the brain and temporal lobes. The authors concluded that preliminary disease control with proton therapy compares favorably to the literature. Dosimetric comparisons demonstrate the advantage of proton use over IMRT for whole-ventricular irradiation. Superior dose distributions were achieved with fewer beam angles utilizing 3-Dimensional Conformal Proton Therapy (3D-CPT) and scanned protons. Compared to 3D-CPT, IMPT with PBS may even further improve dose distribution for this treatment.

Ten pediatric and adolescent patients with skull base chordoma and chondrosarcoma were reported to be treated with proton spot-scanning and intensity modulated techniques by Rutz et al. of the Paul Scherrer Institute, Switzerland. In 2008, there were no treatment failures and no severe late toxicities.

That same year, the Habrand et al. group of the Centre de Protonthérapie in Orsay, France, investigated a cohort of 30 children with skull base and cervical chordomas and chondrosarcomas. The 5-year overall survival and progression-free survival rates were both 100% for chondrosarcoma and 81% and 77% for chordoma. Acute toxicity ranged between 0 and 2 and late toxicity of radiation therapy was severe in one patient, who displayed grade 3 auditory toxicity, but minor or mild in the rest of the population, showing seven patients with grade 2 pituitary dysfunction.

Colter et al. reported in 2010 the clinical outcomes of seven children with bladder/prostate rhabdomyosarcoma (RMS) that received proton treatment. Proton radiation therapy led to a significant decrease in mean organ dose to the bladder (25.1 Gy(RBE) vs. 33.2 Gy; p=0.03), testes (0.0 Gy(RBE) vs. 0.6 Gy; p=0.016), femoral heads (1.6 Gy(RBE) vs. 10.6 Gy; p=0.016), growth plates (21.7 Gy(RBE) vs. 32.4 Gy; p=0.016), and pelvic bones (8.8 Gy(RBE) vs. 13.5 Gy; p=0.016) compared to IMRT.

Another retrospective study was published by Chung et al. in 2013, comparing 558 patients treated with proton radiation and 558 matched patients treated with photon therapy in the Surveillance, Epidemiology, and End Results (SEER) Program cancer registry. Second malignancies occurred in 29 proton patients (5.2%) and 42 photon patients (7.5%). After adjusting for sex, age at treatment, primary site and year of diagnosis, the authors concluded that proton radiation therapy was not associated with an increased risk of second malignancy compared with photon therapy (adjusted hazard ratio: 0.52 [95% confidence interval, 0.32-0.85], P = 0.009).

In 2014, Ladra and Yock published an in-depth review on proton radiation therapy for pediatric sarcoma. They reviewed both institutional and dosimetric data from various proton centers of proton treatment for rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, osteosarcoma, Ewing sarcoma, chordoma and chondrosarcoma. They concluded that there is sufficient data to suggest that in most pediatric cancers, sarcoma or any other categories, proton beam radiation delivers plans with superior dosimetric properties, specifically a reduced integral dose as well as a reduced dose to organs at risk. Next to attributing dosimetric superiority to proton beam treatment, it stated that initial clinical data regarding protons and soft tissue sarcoma appeared to show either equivalence or improvement in outcomes when compared to historical photon controls, and that toxicity may also be reduced.

Also in 2014, Sreeraman and Indelicato published a review of the use of proton therapy for the treatment of children with CNS malignancies, and came to similar conclusions. They presented a dosimetric study that demonstrated the capacity of protons to allow more normal tissue sparing and decrease the risk of late toxicities. The review included recent economic and risk models, making the link with the decrease in late toxicities and the increase in quality adjusted life years and cost effectiveness. They also compared outcomes with a historical photon cohort, showing equivalent or improved local control, progression-free survival and overall survival rates. Based on these findings, the authors put proton therapy forward as the best treatment modality to achieve the goals of reducing toxicity while maintaining treatment efficacy.

In 2015, a Japanese group at the University of Tsukuba, Ibaraki Prefecture, came out with the results of treating six pediatric ependymoma patients with proton therapy. A median follow-up after 24.5 months revealed all patients alive and a local recurrence in the treatment field in only one patient.

The Swiss group examined 43 juvenile uveal melanoma (JUM) patients treated by proton and compared it with matched adult cohort treated by photon beam. The results published in 2014 showed that the metastatic rate at 10 years was significantly lower in juvenile UM patients than in adult controls –11% versus 34% (p<0.01) – with an associated relative survival rate of 93% versus 65% (p= 0.02). The authors concluded that, clinically, juvenile and adult eyes react similarly to proton radiation therapy, with patients having a comparable eye retention probability and maintaining a useful level of vision in most cases. This is the largest case-control study of proton therapy in juvenile eyes to date. It further validates proton radiation therapy as an appropriate conservative treatment for UM in patients younger than 21 years.

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<th>Author</th>
<th>Histology</th>
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<td>Habrand et al, 2008</td>
<td>chordoma/chondrosarcoma chordoma</td>
<td>photon+proton 29 chordoma patients 3 chordrosarcoma patients 1 chordoma patient Institut Curie Orsay</td>
<td>5-year overall survival 100%</td>
<td>target volume dosimetry equivalent between IMRT and PT for all 7 patients. PT led to significant decrease in mean organ dose to bladder, testes, femoral heads, growth plates and pelvic bones compared to IMRT.</td>
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<td>Cotter et al, 2010</td>
<td>rhabdomyosarcoma (bladder/prostate)</td>
<td>Surgery+proton+chemo 7 patients MGH</td>
<td>57 RMS patients 11 osteosarcoma patients 30 Ewing patients</td>
<td>proton 3-year local control &amp; overall survival RMS, 82% &amp; 81%; 5-year local control &amp; overall survival, 72% &amp; 67%; sufficient data to suggest that in most pediatric cancers proton beam radiation delivers plans with superior dosimetric properties, a reduced integral dose and reduced dose to OAR</td>
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<td>Ladra et al, 2014</td>
<td>Sarcomas</td>
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The second study seeks to determine the feasibility and safety of treating patients with craniofacial angiofibroma with limited surgery and a 5 mm clinical target volume margin in combination with proton therapy. The primary endpoint is to measure progression-free and overall survival distributions. Reducing the clinical target volume margin to 5 mm and using proton therapy, with the goal of reducing side effects from irradiation, will not increase the rate of tumor progression compared to proton therapy with a similar or larger clinical target volume margin. The third study will investigate and compare treatments including surgery, chemotherapy and radiation therapy for standard- and high-risk patients of Ewing sarcoma family of tumors (ESFT) and desmoplastic small round cell tumors (DSRCT). Study number four is designed to investigate a stratified treatment approach for clinical risk and molecular subgroups. Patients will be placed in a study group in accordance with different biomarkers plus clinical risks. All patients are then treated with risk-adapted radiation therapy and adjuvant chemotherapy. Progression-free survival distribution is the primary endpoint.

The last clinical trial studies how well a combined chemotherapy and radiation therapy approach works in treating young patients with newly diagnosed CNS tumors.

Chemotherapy gives the brain more time to develop before radiation is given. Most patients treated in this trial will also receive proton therapy radiation. Past attempts to delay or avoid using radiation therapy in very young children with brain tumors to avoid side effects showed that the tumor is likely to come back within a year from diagnosis. Recent research protocols suggest that using radiation therapy soon after initial surgery results in better cure rates, with the latest radiation therapy modalities reducing anticipated side effects. Progression-free survival, DNA methylation in peripheral blood or tissue, and event-free survival are the primary outcome measures for this study.

+ SECONDARY CANCER RISKS

The cohort study MGH presented at ASTRO 2008 is one of the few putting forward the advantages of proton therapy when it comes to radiation induced secondary cancers. The study found a 6.4% rate of second malignancy in 1,450 patients treated with protons at their institution from 1974 to 2001. They compared these numbers with the 12% from a matched cohort in photons from the SEER database. None of the 15 pediatric patients in this protons cohort developed secondary cancer.

Another article published by Sethi et al. in 2014 examined the long-term outcomes of proton therapy for intra-ocular tumors. The Harvard University group did a retrospective review on 86 retinoblastoma survivors, 55 of which received proton therapy treatment; the others photon beam. A comparison was drawn on the 10-year cumulative incidence of radiation-induced or in-field secondary malignancies, limited to 0% for proton therapy while rising to 14% when it came to photon beam.

D) REFERENCE TO ONGOING STUDIES

Ethical concerns deter many experts from performing Phase III randomized studies of protons versus photons when it comes to children with malignancies. However, no less than twelve studies are being conducted across the United States. MGH leads five studies. One of these is a Phase II investigation of proton therapy for partial brain irradiation that aims to assess long term neurocognitive, neuroendocrine, and ototoxicity outcomes. Another aims to define and report the acute and late effects associated with proton radiation treatment, as well as quality of life outcomes. Researchers will help delineate the positive and negative effects of radiation treatment on patients’ quality of life, highlight points of success, and expose areas in need of improvement. There is also a trial designed to assess the short- and long-term side effects of proton radiation for pediatric bone and non-rhabdomyosarcoma soft tissue sarcomas. Collaborating with many sites such as MD Anderson Cancer Center, University of Florida, University of Pennsylvania and University of Washington, the Pediatric Proton Consortium Registry (PPCR) has been established with the goal to enroll children treated with proton radiation in the United States in order to describe the population that currently receives protons and better evaluate its benefits over other therapies. Data collected from this study will facilitate collaborative research. The last study is to determine if using proton beam radiation therapy instead of photon beam can reduce side effects for rhabdomyosarcoma.

The University of Florida is the principal investigator for a large perspective cohort study measuring late effects of proton therapy on pediatric patients with CNS tumors. In addition, there are five studies being conducted at the University of Florida in conjunction with St Jude Children’s Research Hospital, Tennessee. The first investigates treatments for low, intermediate and high risk rhabdomyosarcoma (RMS) using multi-modality risk-adapted therapy with standard or intensified dose chemotherapy, radiation and surgical resection. Event-free survival is the primary endpoint. The study also aims to measure local failure rate and toxicity.
Dr. Indelicato observes various clinical advantages from proton radiation therapy. "In some tumors, it allows us to improve the cure rate through dose escalation, while in other settings, clinical benefits lie in reduced radiation toxicity. In cases where the late radiation effects are fatal, such as cardiac death in Hodgkin lymphoma patients, we may alternately see improved survival through toxicity reduction." Dr. Indelicato believes that multidisciplinary pediatric oncology teams worldwide now recognize the value of proton therapy as a legitimate advancement in the treatment of tumors across diverse sites in children.

**THE FUTURE**

Dr. Indelicato has high expectations for proton therapy, both short and long term. "Improvements in CT and MRI based image guidance are imminent and will bring proton therapy on par with the image guidance on linear accelerators. Proton delivery will become increasingly efficient. In the future, I expect the cost of facilities to decrease without compromising any of their capabilities. We might identify unique radiobiologic characteristics of protons that we can use to our advantage. Intensified Modulated Proton Therapy offers the promise of increased conformality, but we still have a lot to learn about its limitations. As proton facilities become more integrated with academic medical systems, we will see an acceleration of high quality research."

**E) THE EXPERT’S PERSPECTIVE**

**THE PRESENT**

When asked about proton therapy’s role in pediatrics today, Dr. Indelicato answers that two primary approaches are applied. "In some cases, we leverage the conformity of proton therapy to deliver a higher dose to the tumor and keep the adjacent normal tissue dose unchanged. The expectation is that by delivering a higher dose to the tumor we can cure some of the more radio-resistant tumors that lie adjacent to healthy tissue, such as a pediatric base-of-skull chordoma or pelvic osteosarcoma," Dr. Indelicato explains. "The other approach is to keep radiation dose to the tumor constant but use the proton dose distribution to reduce radiation to adjacent organs and therefore reduce toxicity. In this approach, we expect to see the same level of tumor control, but less side effects. Examples of malignancies benefiting from this approach would be a parameningeal rhabdomyosarcoma or a pelvic osteosarcoma. Today, the majority of pediatric tumors are treated with protons according to the latter rationale. In reality, a broad spectrum exists between these two approaches and in some tumors, one might be able to escalate the tumor dose and simultaneously decrease exposure to surrounding normal tissues."

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27. HN-Kayser, CE, Both, S, et al. ‘Proton therapy: ever shifting settings, clinical benefits lie in reduced radiation toxicity. In cases where the late radiation effects are fatal, such as cardiac death in Hodgkin lymphoma patients, we may alternately see improved survival through toxicity reduction.’ Dr. Indelicato believes that multidisciplinary pediatric oncology teams worldwide now recognize the value of proton therapy as a legitimate advancement in the treatment of tumors across diverse sites in children.

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