TREATING PEDIATRIC CANCERS WITH PROTON THERAPY:
HISTORY AND INDICATIONS

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PROTOM
proton therapy technologies

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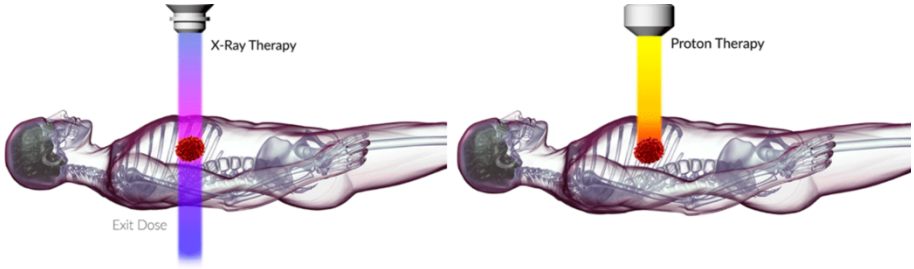
INTRODUCTION

Proton therapy, or proton beam therapy, is a type of radiation therapy used in the treatment of cancer. Unlike photon-based forms of external beam radiotherapy, proton therapy enables an intense dose distribution pattern, depositing radiation in the precise dimensions of a tumor while eliminating the exit dose and damage to adjacent normal tissue.

Figure 1: Traditional radiation treatment has a relatively high entrance dose and exit dose. Proton therapy has a lower entrance dose and no exit dose.



Because of its unique dose-deposition characteristics, proton therapy is indicated for treating tumors near critical organs and brain tissue, and for the treatment of pediatric tumors.

Over the last 40 years, the 5-year survival rate for children diagnosed with cancer has skyrocketed from 10% to nearly 90%. Yet, because of the radiosensitive nature of developing tissue, approximately 60% of survivors suffer from late effects, such as growth deficiencies and secondary cancers.[1] Proton therapy has given pediatric oncologists a promising option in the complicated matter of treatment planning for child patients.

Children tolerate proton therapy well because it is non-invasive and painless, and it typically results in fewer side effects. Most importantly, proton therapy may reduce the risk of late effects, including secondary malignancies, which is of particular concern for pediatric cancer survivors.

HISTORY OF ACCEPTANCE

The idea of using protons in the treatment of cancers has been in existence since 1946,[2] with the first patient being treated with protons in 1954 at the Berkeley Radiation Laboratory. A limited number of physics laboratories offered proton therapy over the next few decades, as advancements in imaging, accelerator, and treatment-delivery technology made proton therapy more viable for routine medical applications. The pediatric population was not excluded from treatment with protons during this time. In fact, the Mass General Department of Radiation Oncology has been treating children with fractionated proton radiotherapy since 1974.[3]

[1] National Cancer Institute. Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/ Accessed: August 2018
[2] R. Wilson, R. Radiological Use of Fast Protons. *Radiology*. 47(5):487-91 (1946). doi: 10.1148/47.5.487
[3] H.D. Suit, J.S. Loeffler, Evolution of Radiation Oncology at Massachusetts General Hospital. Springer: 2011. p 71-78. doi: 10.1007/978-1-4419-6744-2

PENCIL BEAM SCANNING

The development of pencil beam or spot-scanning technology in proton therapy has contributed to a more widespread acceptance of proton therapy as a radiation therapy modality, particularly in the pediatric population.

Pencil beam scanning is the most precise form of proton therapy. Using an electronically guided scanning system and magnets, pencil beam scanning delivers proton therapy treatment via a proton beam that is just millimeters wide. With pencil beam scanning, beam position and depth are able to be controlled, allowing for highly precise deposition of radiation to be delivered in all three dimensions of the tumor. The technology's precision reduces neutron contamination generated by proton scatter and scatter produced from beam shaping devices required with non-scanned proton beams, thereby reducing the risk of secondary malignancies.[4]

Not coincidentally, the development of pencil beam scanning technology corresponds with the rise of pediatric-specific proton therapy treatment programs.

ASTRO'S POLICY MODEL

The American Society for Radiation Oncology's model policy for proton therapy[5] offers guidelines for which cancer diagnoses private insurers and Medicare should cover, based on the organization's evidence-based standards.

ASTRO considers proton therapy reasonable in instances when photon-based radiotherapy will not adequately spare surrounding normal tissue and when it is of added clinical benefit to the patient.[6] The inclusion of pediatric solid tumors on this list of six criteria represents an important milestone in the acceptance of proton therapy in pediatric oncology. It means that the premier radiation oncology society in the U.S. considers solid tumors in children among the highest priority for proton therapy.

- Ocular tumors, including intraocular melanomas
- Tumors that approach or are located at the base of the skull
- Primary or metastatic tumors of the spine
- Primary hepatocellular cancer treated in a hypo-fractionated regimen
- Patients with genetic syndromes making total volume of radiation minimization crucial (e.g., NF-1 and retinoblastoma patients)
- **Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply**

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[4] E.J. Hall. Intensity-modulated radiation therapy, protons, and the risk of second cancers. *Int J Radiat Oncol Biol Phys.* 1;65(1):1-7 (2006). doi: 10.1016/j.ijrobp.2006.01.027

[5] ASTRO. ASTRO Policy Models: Proton Beam Therapy. https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf Accessed: August 2018

[6] ASTRO. ASTRO Policy Models: Proton Beam Therapy. https://www.astro.org/uploadedFiles/_MAIN_SITE/Daily_Practice/Reimbursement/Model_Policies/Content_Pieces/ASTROPBTModelPolicy.pdf Accessed: August 2018

INDICATIONS FOR THE USE OF PROTON THERAPY

Sparing normal tissue and improving quality of life is important for all patients. But because of the long natural life expectancy of pediatric patients — and the particularly radiosensitive nature of developing tissue — pediatric oncologists place heightened emphasis on late effects.

Childhood cancer survivors often overcome one enormous battle only to encounter another, months, years, or even decades after treatment has ended. Cosmetic, hormonal, neurocognitive, reproductive, and other physical impairments are prevalent among survivors. This is particularly true for pediatric patients whose disease sites occur near the brain stem, spinal cord, and other sensitive organs.

Of utmost concern are radiation-induced secondary cancers. The relationship between radiation therapy and secondary cancers has been clarified. For example, the Childhood Cancer Survivor Study[7] has assessed more than 14,000 childhood cancer survivors to determine how different treatment plans have affected their long-term health. This data demonstrates a correlation between radiotherapy and various secondary malignancies, including, but not limited to:

- Basal cell carcinoma[8]
- Breast cancer[9]
- Gastrointestinal cancer[10]
- Meningioma[11]
- Salivary gland cancer[12]
- Thyroid cancer[13]

BENEFITS OF PROTON THERAPY IN PEDIATRIC CANCER PATIENTS

A growing body of research suggests that proton therapy may spare pediatric patients from developmental, cognitive, and other complications associated with photon-based forms of external beam radiotherapy. This is especially promising for the prevention of secondary malignancies.

The following offers an overview of the most recent research regarding the decreased risks associated with proton therapy versus photon radiation therapy in pediatric cancer patients.

[7] St. Jude Children's Research Hospital. Childhood Cancer Survivor Study. https://ccss.stjude.org/ Accessed August 2018.
[8] T.C. Watt, P.D. Inskip, K. Stratton, et. al. Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 104(16):1240-50 (2012). doi: 10.1093/jnci/djs298
[9] C.S. Moskowitz, J.F. Chou, S.L. Wolden, et. al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol.* 20;32(21):2217-23 (2014). doi: 10.1200/JCO.2013.54.4601
[10] T.O. Henderson, K.C. Oeffinger, J. Whitton, et. al. Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. *Ann Intern Med.* 5;156(11):757-66, W-260 (2012). doi: 10.1093/jnci/djs298
[11] D.C. Bowers, C.S. Moskowitz, J.F. Chou. Morbidity and Mortality Associated With Meningioma After Cranial Radiotherapy: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. 10;35(14):1570-1576 (2017). doi: 10.1200/JCO.2016.70.1896.
[12] H. Boukheris, M. Stovall, E. Gilbert, et. al. Risk of salivary gland cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys.* 1;85(3):776-83 (2013). doi: 10.1016/j.ijrobp.2012.06.006
[13] H. Lene, S. Veiga, E. Holmberg, et. al. Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies. *Radiation Research* 185(5):473-484 (2016). doi: 10.1667/RR14213.1

STUDY EVIDENCE

SECONDARY CANCER

A number of studies suggest there is a decreased risk of secondary malignancies in childhood cancer survivors when treated with proton therapy instead of photon-based forms of radiotherapy.

- A study of 26 pediatric cancer patients by Tamura et al. found the risk of secondary cancer from proton therapy to be statistically lower in thoracic and abdominal regions than it would have been if treated by intensity-modulated X-ray therapy.[14]
- Miralbell et al. found that proton beams reduced the expected incidence of radiation-induced secondary cancers for a parameningeal rhabdomyosarcoma pediatric patient by a factor of ≥2 and for a medulloblastoma pediatric patient by a factor of 8 to 15 when compared with either intensity-modulated or conventional X-ray plans.[15]
- Paganetti et al. found that in optic glioma and vertebral body Ewing's sarcoma pediatric patients, lifetime attributable risks for developing a secondary malignancy from proton therapy was lower at least by a factor of 2 and up to a factor of 10 when compared to intensity-modulated photon therapy.[16]
- In a study of six pediatric medulloblastoma patients, Stokkevag et al. found that both double-scattering protons and intensity-modulated proton therapy achieved a significantly better dose conformity compared to the photon and electron irradiation techniques resulting in a six times lower overall risk of radiation-induced cancer.[17]
- In a study of 86 pediatric retinoblastoma patients, Roshan et al. show that proton therapy may significantly reduce the risk of secondary malignancy.[18]

COGNITIVE FUNCTION

Proton therapy may spare pediatric patients from some of the neurocognitive effects of traditional irradiation.

- Kahalley et al. studied intelligence quotient (IQ) scores in 150 childhood brain tumor survivors. While those treated with radiation therapy experienced an IQ decline of 1.1 points per year, those treated with proton therapy experienced no change in IQ over time.[19]
- In a study of modeling changes in cognitive function in 40 child brain tumor survivors, Merchant et al. found clinically significant higher IQ scores in former medulloblastoma

[14] M. Tamura, H. Sakurai, M. Mizumoto, et. al. Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients. *J Radiat Res*. 58 (3): 363-371 (2017). doi: 10.1093/jrr/rrw088

[15] R. Miralbell, A. Lomax, L. Cella. et. al. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. *Int J Radiat Oncol Biol Phys* 54 (3): 824 – 829 (2002). doi: 10.1016/S0360-3016(02)02982-6

[16] H. Paganetti, B.S. Athar, M. Moteabbed, et al. Assessment of radiation-induced second cancer risks in proton therapy and IMRT for organs inside the primary radiation field. *Phys Med Biol* 57: 6047–61 (2012) doi: 10.1088/0031-9155/57/19/6047

[17] C.H. Stokkevag, G.M. Engeseth, K.S. Ytre-Hauge, et al. Estimated risk of radiation-induced cancer following paediatric cranio-spinal irradiation with electron, photon and proton therapy. *Acta Oncol* 53:1048–57 (2014). doi: 10.3109/0284186X.2014.92842

[18] V. Roshan, B.S. Sethi, A. Helen, et. al Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer*. 120(1):126-33 (2014). doi: 10.1002/cncr.28387

[19] L.S. Kahalley, M. Douglas Ris, D.R. Grosshans, et al. Comparing Intelligence Quotient Change After Treatment With Proton Versus Photon Radiation Therapy for Pediatric Brain Tumors. *J Clin Oncol 34:*1043-1049 (2016). doi: 10.1200/JCO.2015.62.1383

and craniopharyngioma patients, and clinically significant higher academic reading scores in optic pathway glioma patients.[20]

HEARING LOSS

- Fortin et al. found hearing loss probability to be systematically less for pediatric brain tumor patients treated with protons over photon radiation therapy.[21]

ENDOCRINE DYSFUNCTION

- In a study of 77 pediatric medulloblastoma patients, Eaton et al. found that, compared to those receiving photon radiation, patients receiving proton therapy had a reduced risk for hypothyroidism, sex hormone deficiency, requirement for endocrine replacement therapy, and a greater height standard deviation score.[22]

CARDIAC MORTALITY

- Zhang et al. found decreased lifetime attributable risks of cardiac mortality when treated with proton craniospinal irradiation over photon CSI in a study of 17 pediatric medulloblastoma patients.[23]

The search for evidence-based indications for proton therapy in pediatric oncology continues. As of July 2018, 110 active proton therapy clinical trials for pediatric patients listed on clinicaltrials.gov.

[20] T.E. Merchant, C. Hua, H. Shukla, et. al. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer*. 51(1):110-7 (2008). doi: 10.1002/pbc.21530

[21] D. Fortin, A. Ng, D.S.C. Tsang, et al. Predicting IQ and the Risk of Hearing Loss Following Proton Versus Photon Radiation Therapy for Pediatric Brain Tumor Patients. *Int J Radiat Oncol Biol Phys* 96(2):E684 - E685 (2016) doi: 10.1016/j.ijrobp.2016.06.2341

[22] B.R. Eaton, N. Esiashvili, S. Kim, et. al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol*. 18(6):881-7 (2016). doi: 10.1093/neuonc/nov302.

[23] R. Zhang, R.M. Howell, P, J. Taddei, et. al. A comparative study on the risks of radiogenic second cancers and cardiac mortality in a set of pediatric medulloblastoma patients treated with photon or proton craniospinal irradiation. *Radiother Oncol*. 113(1):84-8 (2014). doi: 10.1016/j.radonc.2014.07.003.

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